National Institute for Health and Care Excellence

Final version

Cirrhosis in over 16s

Assessment and management

NICE guideline NG50

Appendices I–Q

July 2016

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

ISBN
978-1-4731-1997-0

Contents

Appendices

Appendix I: Economic evidence tables

I.1 Risk factors and risk assessment tools

None.

I.2 Diagnostic tests

Study	Canavan 2013[119]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov decision model **Approach to analysis:** • Simulated population monitored for cirrhosis and progressing to possible HCC or transplant • 3 month cycle length • 7 strategies compared, 3 of which are relevant to this question • States: fibrosis, compensated cirrhosis, decompensated cirrhosis, operable HCC, non-operable HCC, RFT/resection, recurrent HCC, transplant, palliative treatment	**Population:** Chronic hepatitis C patients without fibrosis **Cohort settings:** Start age: 34 years Male: NR **Intervention 1:** No testing; Investigations only conducted after patients have become symptomatic **Intervention 2:** Annual biopsy, followed by HCC screening at 6-month intervals once cirrhosis is confirmed **Intervention 3:** Annual transient	**Total costs (mean per patient):** Intervention 1: £4,500 Intervention 2: £16,250 Intervention 3: £8,000 Incremental (2−1): £11,750 (95% CI: NR; p=NR) Incremental (3−1): £3,500 (95% CI: NR; p=NR) Incremental (3−2): –£8,250 (95% CI: NR; p=NR) **Currency & cost year:** 2013 UK pounds **Cost components incorporated:** Liver biopsy, TE, AFP and ultrasound, CT scan, ablation,	**QALYs (mean per patient):** Intervention 1: 18.20 Intervention 2: 17.20 Intervention 3: 18.75 Incremental (2−1): –1.00 (95% CI: NR; p=NR) Incremental (3−1): 0.55 (95% CI: NR; p=NR) Incremental (3−2): 1.55 (95% CI: NR; p=NR)	Annual liver biopsy is dominated by both alternatives (more expensive and less effective) **ICER (Intervention 3 versus Intervention 1):** £6557 per QALY gained (pa) 95% CI:NR **Analysis of uncertainty:** Univariate sensitivity analysis; ICER most sensitive to rate of developing cirrhosis from F3 fibrosis but TE still considered cost-effective using a £30,000 threshold. Changes in other parameters do not change the cost-effectiveness conclusions.

Perspective: UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	elastography followed by HCC screening at 6-month intervals once cirrhosis is confirmed	resection, transplant, compensated cirrhosis, decompensated cirrhosis, HCC, annual palliative care costs		
Data sources				
Health outcomes: TE diagnostic accuracy obtained from a 2011 meta-analysis, liver biopsy diagnostic accuracy obtained from 2 studies (no meta-analyses). **Quality-of-life weights:** QALY values obtained from 8 sources that used the EQ-5D questionnaire. **Cost sources:** NHS reference costs, UK NHS hospital trust sources, NIHR HTA studies.				
Comments				
Source of funding: MRC Population Health Science Fellowship. **Limitations:** Quality of life estimates do not come from a meta-analysis but from single studies. Liver biopsy unit costs low compared to current UK NHS costs. The model did not include the polymerase inhibitor drug treatment as a parameter.				
Overall applicability[(a)]: directly applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; AFP: alpha-fetoprotein; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HCC: hepatocellular carcinoma; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; TE: transient elastography

(a) Directly applicable/partially applicable/not applicable

(b) Minor limitations/potentially serious limitations/very serious limitations

Study	**Steadman 2013[709]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost analysis (cost per additional correct diagnosis) **Study design:** Decision tree **Approach to analysis:** Proportion of true and false outcomes of testing using the 2 strategies were calculated based on their diagnostic accuracy. **Perspective:** Canadian	**Population:** Meta-analysis of published diagnostic accuracy studies. Five patient subgroups: HBV (8 studies), HCV (14), NAFLD (6) (also reported cholestatic liver disease, post-liver transplantation)	**Total costs (mean per patient):** Intervention 1: £56 Intervention 2: £261 Incremental (2−1): £205 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Canadian dollars (presented here as 2010 UK pounds[(a)])	**Correct diagnoses (per 1000 patient):** <u>Intervention 1:</u> Hepatitis B: 820 Hepatitis C: 898 NAFLD: 947 <u>Intervention 2:</u> Hepatitis B: 1,000[(b)] Hepatitis C: 1,000[(b)] NAFLD: 1,000[(b)]	**Cost per additional correct diagnosis (Intervention 2 versus Intervention 1):** Hepatitis B: £1,136 (95% CI: £276–2,927) Hepatitis C: £2,001 (95% CI: £284–7,317) NAFLD: £3,841 (95% CI: £288–NA) **Analysis of uncertainty:** Changes in sensitivity, specificity and prevalence have a significant effect on the resulting cost per correct diagnosis

healthcare provider **Time horizon:** NA **Discounting:** Costs: NA; Outcomes: NA	**Intervention 1:** Transient elastography **Intervention 2:** Liver biopsy	**Cost components incorporated:** Only test costs considered	Incremental (2–1): Hepatitis B: 180 Hepatitis C: 102 NAFLD: 53 (95% CI: NR; p=NR)	

Data sources
Health outcomes: Pooled diagnostic accuracy data was obtained from 57 studies (78% were considered of high quality by the authors). **Cost sources:** Liver biopsy costs were obtained from a single Canadian study, transient elastography costs were estimated through a micro costing process.
Comments
Source of funding: Alberta Health. **Limitations:** Differences in healthcare system may make results less applicable to UK, no health outcomes following diagnosis were considered in the model. TE diagnostic accuracy estimates were informed by observational data. **Other:** The study reported results in all 4 categories of the METAVIR classification scale. For the purpose of the report only F=4 is presented here.
Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; da: deterministic analysis; HBV: hepatitis B; HCV: hepatitis C; NA: not applicable; NAFLD: non-alcoholic fatty liver disease
(a) Converted using 2010 purchasing power parities[567]
(b) The economic model assumed that the sensitivity and specificity of liver biopsy is equal to 1 (reference standard)
(c) Directly applicable/partially applicable/not applicable
(d) Minor limitations/potentially serious limitations/very serious limitations

Study	**Stevenson[711]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Discrete event simulation model **Approach to analysis:** Progression of liver disease/cirrhosis following cirrhosis diagnosis with regular monitoring for varices,	**Population:** Patients with suspected liver fibrosis related to alcohol consumption. **Cohort settings:** Start age: NR Male: NA **Intervention 1:** Percutaneous liver biopsy for all patients (assumed current practice) **Intervention 2:**	**Total costs (mean per patient):** Details in Table 30, Chapter 6 **Currency & cost year:** 2012 UK pounds **Cost components**	**QALYs (mean per patient):** Details in Table 30, Chapter 6	**ICER (Intervention 2 versus Intervention 1):** Details in Table 30, Chapter 6. Biopsy only is the most effective strategy that is cost-effective at a threshold of £20,000. **Analysis of uncertainty:** There is high uncertainty in the results. This was explored with the identification of 36

ascites, hepatic encephalopathy and HCC **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	Triage with TE (threshold: 11.5), biopsy all those in whom cirrhosis is indicated **Intervention 3:** Triage with FibroTest (threshold: 0.70), biopsy all those in whom cirrhosis is indicated **Intervention 4:** Triage with ELF (threshold: 0.431), biopsy all those in whom cirrhosis is indicated **Intervention 5:** TE (threshold: 11.5) for all patients, diagnosis on basis of Fibroscan alone **Intervention 6:** ELF (threshold: 0.431) for all patients, diagnosis on basis of ELF alone	**incorporated:** Test costs, screening for varices, prophylaxis treatment, variceal bleeding treatment, electroencephalo-grams, lifestyle advice costs		scenarios for every strategy which were based on the combination of changes in 4 key parameters: liver biopsy diagnostic accuracy, liver biopsy type (percutaneous or transjugular), NILT diagnostic accuracy, disutility level of liver biopsy.
Data sources				
Health outcomes: diagnostic accuracy data obtained from multiple published sources and were not pooled. **Quality-of-life weights:** published literature and clinical assumptions. **Cost sources:** published literature figures and clinical input.				
Comments				
Source of funding: UK National Institute for Health Research **Limitations:** Most of the quality of life values are taken from hepatitis C patients. For some health states, QALYs are based on assumptions. Quality of life and test accuracy estimates do not come from a meta-analysis but from single studies, there is inconsistency between the trial data used in the model, for some tests small patient numbers lead to high uncertainty over the test accuracy, ELF did not report sensitivity and specificity for detecting only cirrhosis results not subjected to probabilistic sensitivity analysis. **Other**: 10 strategies compared of which 6 are relevant and reported here.				
Overall applicability[(a)]: partially applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life year; NILT: non-invasive liver test

(a) Directly applicable/partially applicable/not applicable

(b) Minor limitations/potentially serious limitations/very serious limitations

I.3 Severity risk tools

None.

I.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Study	Cucchetti 2012[178]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov decision model **Approach to analysis:** • Cycle length NR (assumed to be 6 months) • Model states: compensated cirrhosis, decompensated cirrhosis, surveillance, HCC diagnosis, HCC treatment, survival, death **Perspective:** Italian NHS **Time horizon:** 10 years **Discounting:** Costs: 3%; Outcomes: NR	**Population:** Data obtained from 918 patients from 11 medical institutions **Cohort settings:** Start age: 67 years Male: NR **Intervention 1:** Annual surveillance including liver function tests, AFP and ultrasound, CT scan performed to confirm positive diagnoses **Intervention 2:** Semi-annual surveillance including liver function tests, AFP and ultrasound, CT scan performed to confirm positive diagnoses **Treatment options for both groups:** Hepatic resection, liver transplant, percutaneous ablation, TACE	**Total costs (mean per patient):** Compensated cirrhosis: Intervention 1: £14,514 Intervention 2: £16,893 Incremental (2−1): £2,379 (95% CI: NR; p=NR) Decompensated cirrhosis: Intervention 1: £20,606 Intervention 2: £23,068 Incremental (2−1): £2,462 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Euros (presented here as 2010 UK pounds[(a)]) **Cost components incorporated:** Costs of surveillance and treatment of HCC	**QALYs (mean per patient):** Compensated cirrhosis: Intervention 1: 5.09 Intervention 2: 5.20 Incremental (2−1): 0.11 (95% CI: NR; p=NR) Decompensated cirrhosis: Intervention 1: unclear[(a)] Intervention 2: unclear[(b)] Incremental (2−1): 0.06 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Compensated cirrhosis: £21,230 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Decompensated cirrhosis: £40,540 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** In patients with compensated cirrhosis, a 7% and above annual HCC incidence (base case 5%) or a 1.6 and above risk ratio for survival gain (base case 1.4) make semi-annual surveillance a cost-effective option at a threshold of £20,000 per QALY gained. In patients with decompensated cirrhosis no plausible changes in the annual HCC incidence or the risk ratio for survival gain reduced the ICER to below £20,000 per QALY gained.
Data sources				
Health outcomes: Data on transition probabilities and ranges regarding treatment modality and survival were extracted from the ITA.LI.CA database. **Quality-of-life weights:** Utility values were taken from 4 sources: 1 systematic review and 3 single studies. **Cost sources:** Unit costs were extracted from data on payments from the Italian NHS.				

Comments
Source of funding: NR. **Limitations:** Differences in healthcare system may make results less applicable to UK; the study claimed to use a societal perspective in terms of costs; no discounting applied to health effects. Unclear source of resource use for health states, only deterministic sensitivity analyses were conducted, no probabilistic analysis.
Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: AFP: alpha-foetoprotein; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years; TACE: trans-arterial chemoembolisation

(a) Converted using 2010 purchasing power parities[567]

(b) Directly applicable/partially applicable/not applicable

(c) Minor limitations/potentially serious limitations/very serious limitations

(d) Reported as 19.66 and 29.51 QALMs for interventions 1 and 2 respectively but at least 1 of these was misreported as the incremental difference between them should have been 0.73 QALMs (0.06 QALYs)

Study	**Thompson Coon 2008[733]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov model and decision tree **Approach to analysis:** • One-month cycle length • Four aetiologies reported (ALD, HBV, HCV, mixed aetiologies)[(a)] • Health states include: no HCC, occult HCC (S,M,L), known HCC (S,M,L), transplant and resection in 4 discrete model sections: surveillance programme, transplant waiting list, curative treatment, palliative treatment	**Population:** People with compensated cirrhosis aged 70 years or less **Cohort settings:** ALD: Start age: 53.3 Male: 70.1% Hepatitis C: Start age: 54 Male: 58.1% **Intervention 1:** No surveillance **Intervention 2:** Annual	**Total costs (mean per patient)[(b)]:** ALD Intervention 1: £26,100 Intervention 2: £27,400 Intervention 5: £28,200 Intervention 7: £29,200 Incremental 2–1: £1,300 Incremental 5–2: £800 Incremental 7–5: £1,000 Hepatitis C Intervention 1: £27,600 Intervention 2: £29,500 Intervention 5: £30,600 Intervention 7: £31,600 Incremental 2–1: £1,900 Incremental 5–2: £1,100	**QALYs (mean per patient)[(b)]:** ALD disease Intervention 1: 9.359 Intervention 2: 9.410 Intervention 5: 9.433 Intervention 7: 9.445 Incremental 2–1: 0.051 Incremental 5–2: 0.023 Incremental 7–5: 0.012 Hepatitis C Intervention 1: 8.087 Intervention 2: 8.172 Intervention 5: 8.212 Intervention 7: 8.232 Incremental 2–1: 0.085	**ICER:** ALD Intervention 2 versus 1: £25,490 Intervention 5 versus 2: £34,783 Intervention 7 versus 5: £83,333 Hepatitis C Intervention 2 versus 1: £22,353 Intervention 5 versus 2: £27,500 Intervention 7 versus 5: £50,000 Interventions 3, 4 and 6 are extendedly dominated in both cases (that is, a combination of other interventions are both cheaper and more effective) More details in Section 8.4.1 of the full guideline document.

Perspective: UK NHS **Time horizon**: Lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	AFP **Intervention 3:** Annual ultrasound **Intervention 4:** Annual AFP+ultrasound **Intervention 5:** Semi-annual AFP **Intervention 6:** Semi-annual ultrasound **Intervention 7:** Semi-annual AFP+ultrasound	Incremental 7−5: £1,000 **Currency & cost year:** 2004 UK pounds **Cost components incorporated:** HCC surveillance (AFP, CT scan, ultrasound, MRI, outpatient appointment), HCC treatment (PEI, RFA, TACE, transplant), management costs for patients (with compensated cirrhosis, decompensated cirrhosis, HCC state, liver transplant, post-transplant, resection, post resection, palliative care, false positive, incidental diagnosis)	Incremental 5−2: 0.040 Incremental 7−5: 0.020	**Analysis of uncertainty (probabilistic sensitivity analysis):** ALD: At the £20,000 threshold, 'no surveillance' is likely to be the only cost-effective strategy (80% likelihood). At around £30,000 interventions 2, 5 and 7 are all equally likely to be the preferable option. Hepatitis C: At the £20,000 threshold, 'no surveillance' is likely to be considered cost-effective (75% likelihood). At £30,000 semi-annual AFP is preferred to no surveillance.
Data sources				
Health outcomes: Obtained through literature searches, focusing on large, recent studies of UK patients diagnosed with cirrhosis. **Quality-of-life weights:** Majority of utilities extracted from 2 studies that used EQ-5D; 3 utility values were based on authors' assumptions. **Cost sources:** Resource use data based on published sources and authors' assumptions, unit costs based on UK sources and authors' assumptions.				
Comments				
Source of funding: UK NHS HTA programme. **Limitations:** Some quality of life values are based on authors' assumptions. Only HCC-related costs are considered; not including costs related to other cirrhosis complications (such as ascites, hepatic encephalopathy).				
Overall applicability[(c)]: directly applicable **Overall quality[(d)]:** minor limitations				

Abbreviations: AFP: alpha-foetoprotein; ALD: alcohol-related liver disease; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], ICER: incremental cost-effectiveness ratio; negative values mean worse than death); L: large; M: medium; MRI: magnetic resonance imaging NR: not reported; pa: probabilistic analysis; PEI: percutaneous ethanol injection; QALYs: quality-adjusted life years; RFA: radiofrequency ablation; S: small; TACE: transarterial chemoembolisation

(a) Only ALD, HCV patient groups relevant to this review question and therefore presented here

(b) Interventions 3, 4, 6 were not reported as they were dominated in the incremental analysis

(c) Directly applicable/partially applicable/not applicable

(d) Minor limitations/potentially serious limitations/very serious limitations

I.5 Surveillance for the detection of varices

None.

I.6 Prophylaxis of variceal haemorrhage

Study	Norberto 2007[553]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA **Study design:** RCT **Approach to analysis:** Cost data including treatment medications, endoscopic treatment, follow-up endoscopies and visits, complications, readmissions for bleeding were collected during the trial **Perspective:** Italian acute hospital **Follow-up**: 14.6 months **Treatment effect duration:** 14.6 months **Discounting:** Costs: NR; Outcomes: NR	**Population:** 62 subjects were selected from the patients referred for liver transplantation **Cohort settings:** Mean age: 52.6 years Male: NR **Intervention 1:** Beta-blocker therapy – propranolol 20 mg twice a day, increasing by 20 mg/day until a 25% reduction of the baseline heart rate was obtained **Intervention 2:** Band ligation procedure – oesophagogastroduodenoscopy prior to the procedure, 1 day hospital stay, subsequent sessions every 2 weeks until varices eradicated	**Total costs (mean per patient):** Intervention 1: £920 Intervention 2: £2,770 Incremental (2−1): £1,850 (95% CI: NR; p=0.001) **Currency & cost year:** US dollars. Study did not mention cost year; 2007 was used for conversion (costs presented as 2007 British pounds)[(a)] **Cost components incorporated:** Initial treatment (including medications and endoscopy); follow-up (including appointments and endoscopy); hospitalisation due to complications, bleeding or re-bleeding	**Variceal bleeding:** Intervention 1: 9.7% patients Intervention 2: 6.5% patients Incremental (2−1): −3.2% patients (95% CI: NR; p=1) **Bleeding-related mortality:** Intervention 1: 6.5% Intervention 2: 3.2% Incremental (2−1): −3.2% (95% CI: NR; p=1)	**ICER (BB versus BL):** £57,812 per bleeding episode averted (or per death averted) **Analysis of uncertainty:** No sensitivity analysis conducted. Difference in costs was significant (p<0.001), but none of the 7 health outcomes had significant differences
Data sources				
Health outcomes: From RCT. **Quality-of-life weights:** NR. **Cost sources:** Resource use was captured through the trial records. Costs were taken from Italian Health Ministry cost assignments.				
Comments				
Source of funding: NR **Limitations:** It does not report QALYs, health outcomes and costs are not discounted. In addition, the study had a relatively short time horizon, no sensitivity analysis was performed.				

Overall applicability[(b)]: partially applicable	**Overall quality[(c)]:** potentially serious limitations

Abbreviations: RCT: randomised control trial; BB: beta-blocker therapy; BL: band ligation therapy; CCA: cost-consequences analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported

(a) Converted using 2007 purchasing power parities[567]

(b) Directly applicable/partially applicable/not applicable

(c) Minor limitations/potentially serious limitations/very serious limitations

I.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

None.

I.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large volume paracentesis (LVP) for ascites

Study	**Gines 2002[285]**			
Study details	**Population & interventions**	**Costs[(a)]**	**Health outcomes[(c)]**	**Cost-effectiveness**
Economic analysis: CCA **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Multicentre RCT (US and Spain), collecting total resource use (procedures) and applying Spanish unit costs **Perspective:** Spain acute hospital **Follow-up:** 2 years **Treatment effect duration:** 2 years **Discounting:** Costs: NR;	**Population:** Patients with refractory ascites (not responding to low sodium diet) **Patient characteristics:** n=70 Mean age: TIPS group: 59 (SE: ±2); LVP group: 56 (SE: ±2) Male: TIPS group: 68%; LVP group: 74% **Intervention 1:** LVP with albumin (repeated as necessary) **Intervention 2:**	**Total costs (mean per patient):** Intervention 1: £1820 Intervention 2: £3924 Incremental (2−1): £2104 (95% CI NR; p=NR) **Currency & cost year:** 2000 US dollars (presented here as 2000 UK pounds)[(b)] **Cost components incorporated:** Initial procedure (LVP, TIPS, additional stents); follow-up (TIPS correction or repeat, LVP, angioplasty)	**Death:** RR: 1.11 (95% CI: NR; p=0.6); ARD: 57 more per 1000 **Ascites re-accumulation:** Patients with ≥1 episode: RR: 0.59 (95% CI: 0.40, 0.85; p=0.003); ARD: 343 fewer per 1000 Total episodes: RR: 0.18 (95% CI: NR, p: NR); ARD: 8029 fewer episodes per 1000 people **Renal failure:** Patients with ≥1 episode: RR: 0.53 (95% CI: 0.27, 1.02); ARD: 229 fewer per 1000 **Spontaneous bacterial peritonitis:**	**ICERs:** Death: LVP dominates TIPS Ascites re-accumulation: £6,137 per patient with ascites averted; £262 per re-accumulation averted Renal failure: £9205 per patient SBP: £36,820 per patient Hepatic encephalopathy: LVP dominates TIPS **Analysis of uncertainty:** No sensitivity analysis was undertaken. Differences in the outcomes of ascites re-accumulation and renal failure were

Study	Gines 2002[285]			
Outcomes: NR	TIPS (with repeated TIPS and additional LVP if necessary)		Patients with ≥1 episode: RR: 0.5 (95% CI: 0.10, 2.56); ARD: 57 fewer per 1000 **Hepatic encephalopathy:** Patients with ≥1 episode: RR: 1.17 (0.95% CI: 0.87, 1.58); ARD: 114 more episodes per 1000 patients	significant (at a level of p=0.05); differences in death, SBP and hepatic encephalopathy were not (though significantly more patients in the TIPS group had severe hepatic encephalopathy).
Data sources				
Health outcomes: Within-trial. **Cost sources:** Resource use (number of procedures) was captured through the trial records. Unit costs from the Spanish hospital were applied to the combined resource use.				
Comments				
Source of funding: Supported by grants from the Fondo de Investigacion Sanitaria (Spain), Veterans Administration (USA) and National Institutes of Health (USA) **Limitations:** Study was partially conducted in US – differences in healthcare system may make results less applicable to UK; discounting does not appear to have been used; no quality-of-life data collected. Clinical outcomes and resource usage based on a single RCT; unit costs derived from a single Spanish hospital; costs associated with some complications were not included, unclear whether costs of hospitals stays were included; no sensitivity analysis conducted. **Other:** Total costs were reported as TIPS: £5,797; LVP: £4,023, apparently due to miscalculation in the paper. Costs given above were recalculated using figures given in Table 6 of the study.				
Overall applicability[(d)]: partially applicable **Overall quality**[(e)]: potentially serious limitations				

Abbreviations: ARD: absolute risk difference; CCA: cost-consequences analysis; LVP: large-volume paracentesis; NR: not reported; RCT: randomised control trial; RR: risk ratio; SBP: spontaneous bacterial peritonitis; SE: standard error; TIPS: transjugular intrahepatic portosystemic shunt

(a) The study presented Spanish and US costs; the Spanish costs are presented here as more applicable to the UK

(b) Converted using 2000 purchasing power parities[567]

(c) See also the clinical evidence table for Gines 2002 in Appendix H

(d) Directly applicable/partially applicable/not applicable

(e) Minor limitations/potentially serious limitations/very serious limitations

I.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

None.

I.10 Volume replacers in hepatorenal syndrome

None.

I.11 Management of an episode of acute hepatic encephalopathy

None.

Appendix J: GRADE tables

J.1 Risk factors and risk assessment tools

Table 1: Prognostic factor: Alcohol consumption

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
MEN <1 drink/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HR[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	HR 7.76 (3.35–18.0)	LOW
WOMEN <1 drink/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HR[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported separately for men and women	Not reported	HR 1.32 (0.51–3.42)	VERY LOW

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
WOMEN 1–7 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HR[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported separately for men and women	Not reported	HR 1.19 (0.54–2.62)	VERY LOW
MEN 8–21 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	HR 2.34 (1.18–4.64)	LOW
WOMEN 8–21 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	HR 5.33 (2.63–10.8)	LOW
MEN 22–35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	HR 10.4 (5.4–20.03)	LOW
WOMEN 22–35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	HR 10.8 (4.28–27.1)	LOW
MEN >35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	Not reported	HR 20.4 (10.8–38.53)	LOW
WOMEN >35 drinks/week versus 1–7 drinks/week in men (reference) for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported separately for men and women	None	HR 14.1 (4.45–44.6)	LOW
'Model 1' (alcohol abuse definition 1) versus non abusers for predicting death or hospitalisation with cirrhosis (adjusted ORs[c])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	Not reported	OR 0.71 (0.17–2.92)	VERY LOW
'Model 2' (alcohol abuse definition 2) versus non abusers for predicting death or hospitalisation with cirrhosis (adjusted ORs[c])										
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	Not reported	OR 1.55 (0.36–6.78)	VERY LOW
0.1–1.4 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	1/11,304 (0.009%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	HR 0.21 (0.27–1.59)	LOW
1.5–4.9 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	5/18,406 (0.03%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	HR 0.69 (0.24–1.98)	LOW

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
5.0–14.9 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	10/17,783 (0.06%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	HR 1.27 (0.54–3.01)	LOW
15.0–29.9 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	9/8,106 (0.11%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	HR 1.86 (0.76–4.59)	LOW
≥30 g/day versus 0 g/day for predicting death due to cirrhosis (adjusted HRs[d])										
Fuchs 1995	Cohort study	Serious	No inconsistency	No indirectness	None[b]	None	15/4,521 (0.33%) versus 12/25,535 (0.05%)	12/25,535 (0.05%)	HR 2.55 (1.06–6.11)	MODERATE
Association of alcohol intake with death from cirrhosis[e]										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Blackwelder 1980	Cohort study	Very serious	No inconsistency	No indirectness	CIs not reported	None	Total n=8008 Events per alcohol intake level (ml/day): 0: 6 events 1–10:1 event 11–30:2 events 31+: 7 events	Not reported	Standardised coefficient from multivariate analysis = 0.341 (t=3.11, estimated coefficient divided by its standard error, p<0.01)	LOW
MEN current abstainers versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	7/350 (2.00%) versus 27/9165 (0.29%)		HR 10.00 (4.32–23.15)	LOW
WOMEN current abstainers versus 2–4 drinking days/week in women (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	2/370 (0.54%) versus 15/9481 (0.16%)		HR 4.03 (0.91–17.85)	VERY LOW
MEN <1 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	14/2946 (0.48%) versus 27/9165 (0.29)		HR 1.34 (0.67–2.68)	VERY LOW
WOMEN <1 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	16/7682 (0.21%) versus 15/9481 (0.16%)		HR 1.45 (0.71–2.96)	VERY LOW
MEN 1 drinking day/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	8/2401 (0.33%) versus 27/9165 (0.29%)		HR 1.30 (0.59–2.86)	VERY LOW
WOMEN 1 drinking day/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	5/4345 (0.12%) versus 15/9481 (0.16%)		HR 0.81 (0.29–2.26)	VERY LOW

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
MEN 5–6 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	30/4495 (0.67%) versus 27/9165 (0.29%)		HR 1.43 (0.84–2.43)	VERY LOW
WOMEN 5–6 drinking days/week versus 2–4 drinking days/week in women (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	17/3147 (0.54%) versus 15/9481 (0.16%)		HR 2.30 (1.14–4.64)	LOW
MEN 7 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	171/7276 (2.35%) versus 27/9165 (0.29%)		HR 3.65 (2.39–5.57)	LOW
WOMEN 7 drinking days/week versus 2–4 drinking days/week in men (reference) for predicting diagnosis of alcohol-induced cirrhosis (adjusted HRs[f])										

Quality assessment							Number of patients/events		Adjusted effects	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Askgaard 2015	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	30/3931 (0.76%) versus 15/9481 (0.16%)		HR 1.73 (0.85–3.52)	VERY LOW

[a] *Methods multivariable analysis, key covariates included: age, smoking habits, number of years in school education, percentage wine of total alcohol intake*
[b] *If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded*
[c] *Methods multivariable analysis, key covariates included: BMI, triglycerides, 2 definitions of alcohol abuse*
[d] *Methods multivariable analysis, key covariates included: age, smoking status, BMI, regular aspirin use, regular vigorous exercise, high plasma cholesterol level*
[e] *Methods multivariable analysis, key covariates included: age, cigarettes smoked per day, systolic blood pressure, serum cholesterol, relative weight*
[f] *Methods multivariable analysis, key covariates included: age, smoking, education, and waist circumference*

Table 2: Prognostic factor: BMI

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
BMI <20 versus 20–24 for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	HR 2.2(1.3–3.9)	LOW
BMI >30 versus 20–24 for predicting death or discharge with alcohol-induced cirrhosis (adjusted HRs[a])										
Becker 2002	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	HR 2.2 (1.5–3.4)	LOW
BMI overweight 25—<30 versus normal <25 (adjusted HRs[c])										
Ioannou 2003	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	35/3774 versus 34/5752	HR1.08 (0.6–1.9)	LOW
BMI obese ≥30 versus normal <25 (adjusted HRs[c])										

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
Ioannou 2003	Cohort study	Serious	No inconsistency	No indirectness	Serious[b]	None	Not reported	20/1939 versus 34/5752	HR1.65 (0.9–3.1)	LOW
'Model 1' (alcohol abuse definition 1) elevated BMI[f] versus non-obese for predicting death or hospitalisation with cirrhosis (adjusted ORs[d])										
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	OR1.27 (1.09–1.48)	LOW
'Model 2' (alcohol abuse definition 1) elevated BMI[f] versus non-obese for predicting death or hospitalisation with cirrhosis (adjusted ORs[d])										
Schult 2011	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	OR1.26 (1.08–1.47)	LOW
BMI <22.5 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs[e])										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	414/237,619 (0.17%) versus 402/331,480 (0.12%)	(0.12%)	HR 1.36 (1.23–1.50)	LOW

Quality assessment							Number of patients/events		Effect	
Study	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Median risk for no risk factor**	**Effect and CI**	**Quality**
BMI 25 to <27.5 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	343/266,795 (0.13%) versus 402/331,480 (0.12%)	(0.12%)	HR 1.05 (0.94–1.17)	VERY LOW
BMI 27.5 to <30 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	Serious[b]	None	236/173,498 (0.14%) versus 402/331,480 (0.12%)	(0.12%)	HR 1.11 (0.97–1.26)	VERY LOW
BMI 30 to <35 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	283/156,733 (0.18%) versus 402/331,480 (0.12%)	(0.12%)	HR 1.49 (1.33–1.68)	LOW
BMI ≥35 versus 22.5 to <25 for predicting death or hospitalisation with cirrhosis (adjusted HRs)										

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
Liu 2010A	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	133/64,537 (0.21%) versus 402/331,480 (0.12%)	(0.12%)	HR 1.77 (1.49–2.10)	LOW

[a] *Methods multivariable analysis, key covariates included: age, smoking habits, number of years in school education, percentage wine of total alcohol intake*
[b] *If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded*
[c] *Methods multivariable analysis, key covariates included: BMI, triglycerides, 2 definitions of alcohol abuse*
[d] *Methods multivariable analysis, key covariates included: age, alcohol consumption, sex, race, education, household income, geographic location in the United States. Adjusted HR reported in this review also adjusted for presence of diabetes*
[e] *Methods multivariable analysis, key covariates included: age, region, socioeconomic status, alcohol consumption, smoking, physical activity*
[f] *Elevated BMI presumed to be >30 but unclear as reported in paper*

Table 3: Prognostic factor: Diabetes

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
Diabetes versus no diabetes (in people with BMI 22.5 to <25) for predicting death or hospitalisation with cirrhosis (adjusted HRs[a])										

Quality assessment							Number of patients/events		Effect	
Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Median risk for no risk factor	Effect and CI	Quality
Liu 2010	Cohort study	Very serious	No inconsistency	No indirectness	None[b]	None	Not reported	Not reported	HR 4.29 (2.74 to 6.73)	LOW

[a] *Adjusted for age, region, socioeconomic status, physical activity, and alcohol consumption and smoking as appropriate*
[b] *If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded*

J.2 Diagnostic tests

None

J.3 Severity risk tools

None

J.4 Surveillance for the detection of hepatocellular carcinoma (HCC)

Table 4: Clinical evidence profile: Surveillance versus no surveillance

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Surveillance	No surveillance	Relative (95% CI)	Absolute	Quality	Importance

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Surveillance	No surveillance	Relative (95% CI)	Absolute	Quality	Importance
Survival (follow-up median 9 months reported by one study, follow-up in other study not reported; assessed with: adjusted hazard ratio [HR >1 indicates an advantage to the surveillance group][1])												
2	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	–	–	Not pooled	Not pooled	VERY LOW	CRITICAL
Survival (follow-up 5-7 years from recruitment estimated; assessed with: adjusted odds ratio [OR >1 indicates an advantage to the surveillance group][4])												
1	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	–	–	OR 1.13 (0.64 to 2.01)	[5]	VERY LOW	CRITICAL
Detection of HCC at a very early stage (single nodule ≤2 cm) (assessed with: adjusted odds ratio [OR >1 indicates an advantage to the surveillance group][6])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 5.4 (2.35 to 12.4)	[5]	LOW	IMPORTANT
Detection of HCC at a non-advanced stage (single nodule ≤5 cm or 3 nodules each ≤3 cm without vascular and lymphonodal invasion and metastases) (assessed with: adjusted odds ratio [OR >1 indicates an advantage to the surveillance group][6])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 3.1 (1.85 to 5.2)	[5]	LOW	IMPORTANT
Detection of HCC at an advanced stage (according to Milano criteria) – surveillance versus incidental diagnosis (assessed with: adjusted odds ratio [OR <1 indicates an advantage to the surveillance group][7])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 0.29 (0.17 to 0.49)	[5]	LOW	IMPORTANT
Detection of HCC at an advanced stage (according to Milano criteria) – surveillance versus symptom diagnosis (assessed with: adjusted odds ratio [OR <1 indicates an advantage to the surveillance group][7])												
1	Observational studies	No serious risk of	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 0.18 (0.09 to 0.37)	[5]	LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Surveillance	No surveillance	Relative (95% CI)	Absolute	Quality	Importance
		bias										

1 Study 1 adjusted for the following confounders: gender, Child-Pugh score, number of tumoural nodules (1/>1), AFP value, AFP (normal/increased), type of treatment (treated/not treated) and modality of diagnosis (follow-up/incidental). Study 2 adjusted for the following confounders: Child-Pugh status, tumour characteristics, treatment applied for HCC
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias (main reasons for risk of bias include no adjustment for lead time bias or no adjustment for all the key confounders)
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
4 Adjusted for factors found to be statistically significant in the univariate analysis: degree of liver function, screening, tumour size, and prognosis (curative versus palliative). In this analysis, screening was not statistically significant (not an independent predictor of survival)
5 Control group risk not reported for calculation of absolute effect
6 Adjustment for the confounding factors (age, gender, surveillance, aetiologies, AFP levels, cirrhosis)
7 Adjusted for centre of enrolment, age, sex, aetiology of cirrhosis, Child-Pugh class, AFP level and type of diagnosis

Table 5: Clinical evidence profile: Yearly versus 6-monthly surveillance

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Yearly surveillance	6-monthly surveillance	Relative (95% CI)	Absolute	Quality	Importance
Survival (assessed with: adjusted hazard ratio [HR >1 indicates an advantage to the 6-monthly surveillance group][1])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	–	–	HR 1.39 (1.06 to 1.82)	[3]	VERY LOW	CRITICAL
Detection of HCC beyond a very early stage (solitary nodule >2 cm or multinodular tumour with/without vascular invasion and/or metastases) (assessed with: adjusted odds ratio [OR >1 indicates an advantage to the 6-monthly surveillance group][4])												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	–	–	OR 5.99 (2.57 to 13.98)	[3]	LOW	IMPORTANT

1 Adjusted variables: age, platelet count, AFP, Child-Pugh class and oesophageal varices
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

3 Control group risk not reported for calculation of absolute effect
4 Adjusted variables included those associated with a tumour beyond the very early stage: surveillance interval aetiology, ALT, AFP, and Child-Pugh class

Table 6: Clinical evidence profile: 3-monthly versus 6-monthly surveillance

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	3-monthly surveillance	6-monthly surveillance	Relative (95% CI)	Absolute	Quality	Importance
Survival (follow-up median 47 months; assessed with: Hazard ratio [HR <1 indicates an advantage to the 3-monthly surveillance group])												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	–	14.2%2	HR 0.87 (0.64 to 1.19)	17 fewer per 1000 (from 49 fewer to 25 more)3	MODERATE	CRITICAL
HCC occurrence (follow-up median 47 months)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	53/640 (8.3%)	11%	RR 0.75 (0.54 to 1.06)	27 fewer per 1000 (from 51 fewer to 7 more)	MODERATE	IMPORTANT
Diameter of the largest HCC nodule ≤30 mm (follow-up median 47 months; assessed with: positive outcome, RR<1 indicates an advantage to the 6-monthly group)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	42/640 (6.6%)	7.7%	RR 0.85 (0.57 to 1.27)	12 fewer per 1000 (from 33 fewer to 21 more)	LOW	
Diameter of the largest HCC nodule >30 mm (follow-up median 47 months; assessed with: negative outcome, RR<1 indicates an advantage to the 3-monthly group)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	11/640 (1.7%)	3.3%	RR 0.52 (0.25 to 1.07)	16 fewer per 1000 (from 25 fewer to 2 more)	MODERATE	IMPORTANT
Number of lesions – Uninodular (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	3-monthly surveillance	6-monthly surveillance	Relative (95% CI)	Absolute	Quality	Importance
Survival (follow-up median 47 months; assessed with: Hazard ratio [HR <1 indicates an advantage to the 3-monthly surveillance group])												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[1]	None	31/640 (4.8%)	6.4%	RR 0.75 (0.48 to 1.19)	16 fewer per 1000 (from 33 fewer to 12 more)	LOW	IMPORTANT
Number of lesions – 2 or 3 nodules (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[4]	None	15/640 (2.3%)	1.9%	RR 1.25 (0.59 to 2.64)	5 more per 1000 (from 8 fewer to 31 more)	VERY LOW	IMPORTANT
Number of lesions – >3 nodules (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/640 (0.63%)	1.1%	RR 0.57 (0.17 to 1.94)	5 fewer per 1000 (from 9 fewer to 10 more)	VERY LOW	IMPORTANT
Number of lesions – Infiltrative (follow-up median 47 months; assessed with: RR<1 indicates less events in the 3-monthly group)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[1]	None	3/640 (0.47%)	1.6%	RR 0.3 (0.08 to 1.08)	11 fewer per 1000 (from 15 fewer to 1 more)	LOW	IMPORTANT
HCC stage (within Milan criteria: one nodule ≤50 mm or 2 or 3 nodules ≤30 mm) (follow-up median 47 months; assessed with: positive outcome, RR<1 indicates an advantage to the 6-monthly group)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	42/640 (6.6%)	7.8%	RR 0.84 (0.56 to 1.24)	12 fewer per 1000 (from 34 fewer to 19 more)	MODERATE	IMPORTANT
HCC stage (beyond Milan criteria: one nodule ≤50 mm or 2 or 3 nodules ≤30 mm) (follow-up median 47 months; assessed with: negative outcome, RR<1 indicates an advantage to the												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	3-monthly surveillance	6-monthly surveillance	Relative (95% CI)	Absolute		
Survival (follow-up median 47 months; assessed with: Hazard ratio [HR <1 indicates an advantage to the 3-monthly surveillance group])												
3-monthly group)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[1]	None	11/640 (1.7%)	3.1%	RR 0.55 (0.26 to 1.13)	14 fewer per 1000 (from 23 fewer to 4 more)	LOW	IMPORTANT
Liver transplant (follow-up median 47 months)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[4]	None	17/640 (2.7%)	2%	RR 1.3 (0.64 to 2.66)	6 more per 1000 (from 7 fewer to 33 more)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
2 Survival at 60 months in the control group was 85.8%
3 Based on survival rate of control group at 60 months
4 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and by 2 increments if the majority of the evidence was at very high risk of bias

J.5 Surveillance for the detection of varices

None

J.6 Prophylaxis of variceal haemorrhage

Table 7: Clinical evidence profile: Non-selective beta-blockers versus placebo or no intervention: medium or large varices

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Large non-selective beta-blockers versus placebo	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
2	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	Serious[2]	None	-	33.8%3	HR 1.2 (0.78 to 1.84)	52 more per 1000 (from 63 fewer to 194 more)	LOW	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Variceal bleeding (follow-up median 24 months4)												
3	Randomised trials	No serious risk of bias	Serious[5]	Serious[6]	Very serious[2]	None	15/136 (11%)	36.4%	RR 0.28 (0.06 to 1.3)	262 fewer per 1000 (from 342 fewer to 109 more)	VERY LOW	CRITICAL
Upper gastrointestinal bleeding (follow-up median 24 months[4])												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	40/227 (17.6%)	35.2%	RR 0.55 (0.39 to 0.78)	158 fewer per 1000 (from 77 fewer to 215 fewer)	MODERATE	IMPORTANT
Bleeding-related mortality (follow-up median 21 months[4])												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	20/199 (10.1%)	14.9%	RR 0.67 (0.39 to 1.13)	49 fewer per 1000 (from 91 fewer to 19 more)	MODERATE	IMPORTANT

[1] *I squared value 36%. Heterogeneity by visual inspection of the forest plots (different directions of effect). Cannot perform predefined subgroups. Random effects model used*

[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

[3] *Calculated from the median control group rate at the end of the study*

[4] *Median of the mean follow-up times of the individual studies where reported*

[5] *Statistical heterogeneity. Cannot investigate predefined subgroups. Random effects model used*

[6] *Reported as a dichotomous outcome not time-to-event*

Table 8: Clinical evidence profile: Non-selective beta-blockers versus placebo or no intervention: small varices

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Small non-selective beta-blockers versus placebo	Control	Relative (95% CI)	Absolute	Quality	Importance
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Mortality (follow-up mean 25 months)												
1	Randomised trials	Serious [1]	No serious inconsistency	Serious[2]	Very serious[3]	None	3/77 (3.9%)	2.7%	RR 1.42 (0.24 to 8.27)	11 more per 1000 (from 21 fewer to 196 more)	VERY LOW	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Variceal bleeding (follow-up median 24 months[4])												
3	Randomised trials	Serious [1]	Serious[5]	Serious[2]	Very serious[3]	None	6/118 (5.1%)	6.9%	RR 1.24 (0.31 to	17 more per 1000 (from 48 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Small non-selective beta-blockers versus placebo	Control	Relative (95% CI)	Absolute		
									5)	276 more)		
Upper gastrointestinal bleeding (follow-up median 24.5 months[4])												
2	Randomised trials	Serious [1]	Serious[6]	No serious indirectness	Very serious[3]	None	4/92 (4.3%)	9.5%	RR 0.9 (0.04 to 20.15)	10 fewer per 1000 (from 91 fewer to 1000 more)	VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Reported as a dichotomous outcome not time-to-event

[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

[4] Median of the mean follow-up times of the individual studies where reported

[5] I squared value 13%. Heterogeneity by visual inspection of the forest plots (different directions of effect). Cannot perform predefined subgroups. Random effects model used

[6] Statistical heterogeneity. Cannot investigate predefined subgroups. Random effects model used

Table 9: Clinical evidence profile: Band ligation versus no intervention: medium or large varices

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Large varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Large varices: banding ligation versus no intervention**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Survival												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	47.2%2	HR 0.5 (0.33 to 0.75)	199 fewer per 1000 (from 91 fewer to 282 fewer)	MODERATE	CRITICAL
Mortality (follow-up 14–25 months)												
2	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	Serious[4]	None	16/87 (18.4%)	31.1%	RR 0.57 (0.33 to 0.97)	134 fewer per 1000 (from 9 fewer to 208 fewer)	VERY LOW	CRITICAL
Free from variceal bleeding												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	40.8%2	HR 0.39 (0.25 to 0.63)	223 fewer per 1000 (from 127 fewer to 285 fewer)	MODERATE	CRITICAL
Variceal bleeding (follow-up 14–25 months)												
2	Randomised trials	Serious[1]	Serious[5]	Serious[3]	Serious[4]	None	18/87 (20.7%)	46.7%	RR 0.4 (0.17 to 0.93)	280 fewer per 1000 (from 33 fewer to 388 fewer)	VERY LOW	CRITICAL
Upper gastrointestinal bleeding (follow-up median 20.6 months[6])												
5	Randomised trials	Serious[1]	Serious[5]	No serious indirectness	Serious[4]	None	48/224 (21.4%)	39.4%	RR 0.49 (0.31 to 0.76)	201 fewer per 1000 (from 95 fewer to 272 fewer)	VERY LOW	IMPORTANT
Bleeding-related mortality (follow-up 25 months[6])												
3	Randomised	Very	No serious	No serious	No serious	None	10/151	15.2%	RR 0.36	97 fewer per	LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Large varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute	Quality	Importance
	trials	serious[1]	inconsistency	indirectness	imprecision		(6.6%)		(0.18 to 0.71)	1000 (from 44 fewer to 125 fewer)		

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

[2] *Calculated from the median control group rate at the end of the study*

[3] *Reported as a dichotomous outcome not time-to-event*

[4] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

[5] *Statistical heterogeneity. Cannot investigate predefined subgroups. Random effects model used*

[6] *Median of the mean follow-up times of the individual studies where reported*

Table 10: Clinical evidence profile: Band ligation versus no intervention: small varices

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Small varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute	Quality	Importance
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Small varices: banding ligation versus no intervention	Control	Relative (95% CI)	Absolute	Quality	Importance
Upper gastrointestinal bleeding (follow-up mean 20.6 months)												
1	Randomised trials	Serious [1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/14 (7.1%)	0%	See comment	70 more per 1000 (from 100 fewer to 240 more)[3]	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

[3] *Manual calculation of absolute risk difference due to zero events in the control arm*

Table 11: Clinical evidence profile: Band ligation versus non-selective beta-blockers: medium or large varices

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Large varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute	Quality	Importance
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
7	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	-	33.3%[2]	HR 1.03 (0.8 to 1.34)	8 more per 1000 (from 56 fewer to	MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Large varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute		
										86 more)		
Mortality (follow-up median 14.5 months[3])												
12	Randomised trials	Serious[4]	No serious inconsistency	Serious[5]	Serious[1]	None	56/381 (14.7%)	14%	RR 0.83 (0.61 to 1.13)	24 fewer per 1000 (from 55 fewer to 18 more)	VERY LOW	CRITICAL
Free from variceal bleeding												
7	Randomised trials	No serious risk of bias	Serious[6]	No serious indirectness	Very serious[1]	None	-	27.3%2	HR 0.68 (0.35 to 1.31)	78 fewer per 1000 (from 167 fewer to 68 more)	VERY LOW	CRITICAL
Variceal bleeding (follow-up median 16.5 months[3])												
10	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[5]	No serious imprecision	None	21/276 (7.6%)	14.5%	RR 0.44 (0.27 to 0.71)	81 fewer per 1000 (from 42 fewer to 106 fewer)	MODERATE	CRITICAL
Upper gastrointestinal bleeding (follow-up median 19 months[3])												
20	Randomised trials	No serious risk of bias	Serious[7]	No serious indirectness	Serious[1]	None	102/785 (13%)	15.9%	RR 0.71 (0.54 to 0.92)	46 fewer per 1000 (from 13 fewer to 73 fewer)	LOW	IMPORTANT
Bleeding-related mortality (follow-up median 19 months[3])												
15	Randomised	No	No serious	No serious	Serious[1]	None	26/621	6.5%	RR 0.67	21 fewer	MODERATE	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Large varices: banding ligation versus non-selective beta-blockers	Control	Relative (95% CI)	Absolute		
	trials	serious risk of bias	inconsistency	indirectness			(4.2%)		(0.42 to 1.08)	per 1000 (from 38 fewer to 5 more)		
Hospitalisation (follow-up 0.5–18 months)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[1]	None	5/45 (11.1%)	27.3%	RR 0.41 (0.16 to 1.06)	161 fewer per 1000 (from 229 fewer to 16 more)	LOW	IMPORTANT
Adverse events – lethargy												
2	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/86 (0%)	28.8%	OR 0.09 (0.04 to 0.22)	253 fewer per 1000 (from 206 fewer to 272 fewer)	MODERATE	IMPORTANT

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

[2] *Calculated from the median control group rate at the end of the study*

[3] *Median of the mean follow-up times of the individual studies where reported*

[4] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

[5] *Reported as a dichotomous outcome not time-to-event*

[6] *Statistical heterogeneity and heterogeneity from visual inspection of forest plot. Cannot investigate predefined subgroups. Random effects model used*

[7] *I squared value 13%. Heterogeneity by visual inspection of the forest plots (CIs do not overlap).Predefined subgroup analyses performed but no statistical difference between subgroups. Random effects model used*

Table 12: Clinical evidence profile: Band ligation versus non-selective beta-blockers: small varices

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Small varices: banding ligation versus non-selective beta-blockers**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Survival												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL
Free from variceal bleeding												
0	No evidence available	-	-	-	-	None	-	-	-	-	-	CRITICAL

J.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Table 13: Clinical evidence profile: IV ceftriaxone 2 g versus oral ciprofloxacin 500 mg twice daily

Quality assessment							**Number of patients**		**Effect**			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**IV ceftriaxone 2 g**	**Oral ciprofloxacin 500 mg twice daily**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Bacterial infections (follow-up mean 7 days)												
1	Randomised	Serious[1]	No serious	No serious	No serious	None	2/66	20.6%	RR 0.13	179 fewer	MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV ceftriaxone 2 g	Oral ciprofloxacin 500 mg twice daily	Relative (95% CI)	Absolute		
	trials		inconsistency	indirectness	imprecision		(3%)		(0.03 to 0.56)	per 1000 (from 91 fewer to 200 fewer)		
Health-related quality of life												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

Table 14: Clinical evidence profile: IV ceftriaxone 1 g versus oral norfloxacin 400 mg twice daily

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV ceftriaxone 1 g	Oral norfloxacin 400 mg twice daily	Relative (95% CI)	Absolute		
Bacterial infections (follow-up mean 10 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	6/54 (11.1%)	26.3%	RR 0.42 (0.18 to 1.01)	153 fewer per 1000 (from 216 fewer to 3 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	No evidence	–	–	–	–	None	–	–	–	–	–	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV ceftriaxone 1 g	Oral norfloxacin 400 mg twice daily	Relative (95% CI)	Absolute		
	available											
All-cause mortality (follow-up mean 10 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	8/54 (14.8%)	10.5%	RR 1.41 (0.52 to 3.79)	43 more per 1000 (from 50 fewer to 293 more)	VERY LOW	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1/2 increments because the majority of the evidence had indirect outcomes*
[3] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 15: Clinical evidence profile: Oral norfloxacin 800 mg versus oral ofloxacin 400 mg

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral norfloxacin 800 mg	Oral ofloxacin 400 mg	Relative (95% CI)	Absolute		
Bacterial infections (follow-up mean 10 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	26/183 (14.2%)	14.8%	RR 0.96 (0.58 to 1.58)	6 fewer per 1000 (from 62 fewer to 86 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 16: Clinical evidence profile: Oral norfloxacin 800 mg + IV ceftriaxone (combination) versus oral norfloxacin 800 mg (monotherapy)

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral norfloxacin 800 mg + IV ceftriaxone	Oral norfloxacin 800 mg	Relative (95% CI)	Absolute	Quality	Importance
Bacterial infections (follow-up mean 3 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	3/24 (12.5%)	18.2%	RR 0.69 (0.17 to 2.73)	56 fewer per 1000 (from 151 fewer to 315 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	No evidence available	–	–	–	–	None	–	–	–	–	–	CRITICAL
All-cause mortality (follow-up mean 3 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	1/24 (4.2%)	9.1%	RR 0.46 (0.04 to 4.71)	49 fewer per 1000 (from 87 fewer to 338 more)	VERY LOW	CRITICAL
Length of hospital stay (days, follow-up mean 3 weeks; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	24	22	-	MD 0 higher (4.07 lower to 4.07 higher)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1/2 increment(s) because the majority of the evidence had indirect outcomes*
[3] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

J.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 17: Clinical evidence profile: TIPS versus LVP

Quality assessment							Number of patients		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**TIPS versus LVP – ascites re-accumulation**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Ascites re-accumulation (follow-up 12 months)												
4	Randomised trials	No serious risk of bias	Serious[4]	No serious indirectness	Serious[2]	None	75/150 (50%)	88.4%	RR 0.57 (0.40 to 0.82)	382 fewer per 1000 (from 160 fewer to 533 fewer)	LOW	CRITICAL
Quality of life – physical score (follow-up 12 months; measured with: SF-36 score; scale not reported, better indicated by lower values)												
1	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[2]	None	52	57	-	MD 3.36 lower (7.53 lower to 0.81 higher)	LOW	CRITICAL
Quality of life – mental score (follow-up 12 months; measured with: SF-36 score; scale not reported, better indicated by lower values)												
1	Randomised trials	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[2]	None	52	57	-	MD 2.13 lower (5.45 lower to 1.19 higher)	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**TIPS versus LVP – ascites re-accumulation**	**Control**	**Relative (95% CI)**	**Absolute**		
Transplant-free survival												
5	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	Serious[2]	None	-	65.3%3	HR 0.58 (0.35 to 0.96)	194 fewer per 1000 (from 15 fewer to 343 fewer)	LOW	CRITICAL
Spontaneous bacterial peritonitis												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/87 (6.9%)	7.5%	RR 1.05 (0.35 to 3.1)	4 more per 1000 (from 49 fewer to 157 more)	LOW	IMPORTANT
Acute renal failure												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	12/87 (13.8%)	26%	RR 0.64 (0.35 to 1.18)	94 fewer per 1000 (from 169 fewer to 47 more)	MODERATE	IMPORTANT
Hepatic encephalopathy												
5	Randomised trials	No serious risk of bias	Serious[6]	No serious indirectness	Serious[2]	None	104/179 (58.1%)	34.9%	RR 1.64 (1.14 to 2.36)	227 more per 1000 (from 50 more to 483 more)	LOW	IMPORTANT

[1] *Downgraded by 1 increment because of heterogeneity, I^2=74%, p=0.002, unexplained by subgroup analysis*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[3] *Calculated from the median control group rate at the end of the study*
[4] *Downgraded by 1 increment because heterogeneity, I^2=79%, p=0.003, unexplained by subgroup analysis*
[5] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[6] *Downgraded by 1 increment because of heterogeneity, I^2=58%, p=0.05, unexplained by subgroup analysis*

J.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 18: Clinical evidence profile: Antibiotic prophylaxis versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Antibiotic prophylaxis versus placebo or no treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
Spontaneous bacterial peritonitis (follow-up median 6 months)												
6	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/242 (2.9%)	18.7%	RR 0.22 (0.11 to 0.46)	146 fewer per 1000 (from 101 fewer to 166 fewer)	MODERATE	CRITICAL
All-cause mortality (time-to-event) (follow-up 6 to 12 months)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	28%	HR 0.40 (0.22 to 0.73)	157 fewer per 1000 (from 67 fewer to 210 fewer)	HIGH	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Antibiotic prophylaxis versus placebo or no treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality (dichotomous) – mortality at ~1 month follow-up (follow-up mean 25.5 days)												
1	Randomised trials	Serious[1]	No serious inconsistency	Very serious[4,5]	Very serious[2]	None	2/29 (6.9%)	16.7%	RR 0.39 (0.08 to 1.85)	102 fewer per 1000 (from 154 fewer to 142 more)	VERY LOW	CRITICAL
All-cause mortality (dichotomous) – mortality at ~4 months' follow-up (follow-up mean 132 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[4]	Very serious[2]	None	8/53 (15.1%)	18.5%	RR 0.82 (0.35 to 1.91)	33 fewer per 1000 (from 120 fewer to 168 more)	VERY LOW	CRITICAL
All-cause mortality (dichotomous) – mortality at 6 months' follow-up (follow-up mean 6 months)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Very serious[4,5]	Very serious[2]	None	4/26 (15.4%)	22.2%	RR 0.76 (0.24 to 2.43)	53 fewer per 1000 (from 169 fewer to 317 more)	VERY LOW	CRITICAL
Adverse event: renal failure (follow-up mean 12 months)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	14/85 (16.5%)	33.2%	RR 0.54 (0.31 to 0.96)	153 fewer per 1000	LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Antibiotic prophylaxis versus placebo or no treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
										(from 13 fewer to 229 fewer)		
Adverse event: liver failure (follow-up mean 8.5 months)												
4	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	12/164 (7.3%)	3.5%	RR 1.43 (0.54 to 3.79)	15 more per 1000 (from 16 fewer to 98 more)	VERY LOW	IMPORTANT
Length of hospital stay (follow-up mean 3.4 months; better indicated by lower values)												
2	Randomised trials	Serious[1]	Serious[6]	No serious indirectness	Serious[2]	None	60	63	-	MD 3.12 lower (14.15 lower to 7.92 higher)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[3] *Calculated from median control group rate at 6 to 12 months*
[4] *The majority of the evidence had indirect outcomes*
[5] *The majority of the evidence had an indirect population*
[6] *Downgraded by 1/2 increments because the confidence intervals across studies showed minimal or no overlap and heterogeneity, I^2=50%, p=0.04, unexplained by subgroup analysis*

J.10 Volume replacers in hepatorenal syndrome

None

J.11 Management of an episode of acute hepatic encephalopathy

J.11.1 Non-absorbable disaccharides versus single therapy

Table 19: Clinical evidence summary: Non-absorbable disaccharides versus neomycin

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	Neomycin	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/8 (12.5%)	10%	RR 1.25 (0.09 to 17.02)	25 more per 1000 (from 91 fewer to 1000 more)	VERY LOW	CRITICAL
Clinical-biochemical improvement (improvement of 1 grade in mental state (Conn's grading 0–4), a reduction of 30 s in time taken to perform the NCT and ammonia reduction of 50ug%)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	7/8 (87.5%)	70%	RR 1.25 (0.77 to 2.03)	175 more per 1000 (from 161 fewer to 721 more)	LOW	CRITICAL
Side effects												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/8 (0%)	0%	Not pooled	Not pooled	MODERATE	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 20: Clinical evidence summary: Non-absorbable disaccharides versus Rifaximin

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	Rifaximin	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/8 (12.5%)	10%	RR 1.25 (0.09 to 17.02)	25 more per 1000 (from 91 fewer to 1000 more)	VERY LOW	CRITICAL
Clinical-biochemical improvement (improvement of 1 grade in mental state (Conn's grading 0–4), a reduction of 30 s in time taken to perform the NCT and ammonia reduction of 50ug%)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	7/8 (87.5%)	70%	RR 1.25 (0.77 to 2.03)	175 more per 1000 (from 161 fewer to 721 more)	LOW	CRITICAL
Side effects												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/8 (0%)	0%	Not pooled	Not pooled	MODERATE	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Non-absorbable disaccharides**	**Rifaximin**	**Relative (95% CI)**	**Absolute**		
Mortality (considered unrelated to medication; at 28 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	2/53 (3.8%)	2%	RR 1.89 (0.18 to 20.17)	18 more per 1000 (from 16 fewer to 383 more)	LOW	CRITICAL
Unchanged/failure (hepatic encephalopathy clinical syndrome not improved and blood ammonia levels not decreased/increase in blood ammonia, increase in PSE index and/or a shift to a higher stage of hepatic encephalopathy)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	10/53 (18.9%)	18%	RR 1.05 (0.46 to 2.36)	9 more per 1000 (from 97 fewer to 245 more)	LOW	CRITICAL
Improvement in hepatic encephalopathy grade (at 7 days)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[1]	None	16/22 (72.7%)	81.3%	RR 0.9 (0.66 to 1.21)	81 fewer per 1000 (from 276 fewer to 171 more)	LOW	CRITICAL
Improvement in hepatic encephalopathy index (taking into account hepatic encephalopathy grade, NCT, blood ammonia and severity of flapping tremor; at 7 days)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[1]	None	21/22 (95.5%)	84.4%	RR 1.13 (0.95 to 1.35)	110 more per 1000 (from 42 fewer to 295 more)	LOW	CRITICAL
Adverse events												
2	Randomised trials	No serious risk of bias	Serious[3]	No serious indirectness	Very serious[1]	None	3/75 (4%)	4.6%	RR 0.8 (0.19 to 3.39)	9 fewer per 1000 (from 37 fewer to 110 more)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[2] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[3] *The point estimate varies widely across studies, unexplained by subgroup analysis*

Table 21: Clinical evidence summary: Non-absorbable disaccharides versus Branch chain amino acids (BCAA)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Non-absorbable disaccharides**	**BCAA**	**Relative (95% CI)**	**Absolute**		
Mortality (up to 10 days after mental recovery)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/17 (29.4%)	23.5%	RR 1.25 (0.4 to 3.87)	59 more per 1000 (from 141 fewer to 674 more)	LOW	CRITICAL
Time of arousal (hours, better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	17	17	-	MD 3.9 higher (11.43 lower to 19.23 higher)	MODERATE	IMPORTANT
Complete mental recovery (study 1 defines as consciousness regained and returned to grade 0 hepatic encephalopathy; study 2 defines as come out of coma by day 7)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	18/33 (54.5%)	82.2%	RR 0.67 (0.47 to 0.94)	271 fewer per 1000 (from 49 fewer to 436 fewer)	MODERATE	CRITICAL

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 22: Clinical evidence summary: Non-absorbable disaccharides versus PEG

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	PEG 3350	Relative (95% CI)	Absolute		
Mortality (at 24 hours)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	2/25 (8%)	4%	RR 2 (0.19 to 20.67)	40 more per 1000 (from 32 fewer to 787 more)	LOW	CRITICAL
Hepatic encephalopathy resolution (defined as an improvement to grade 0, or two days at grade 1 after an initial improvement of at least 1 grade)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[1]	None	-	0%	HR 0.57 (0.31 to 1.05)	-[3]	LOW	CRITICAL
Improvement of 1 or more in hepatic encephalopathy grade (hepatic encephalopathy spectral analysis (SA) score; at 24 hours)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[1]	None	13/25 (52%)	91.3 %	RR 0.57 (0.38 to 0.85)	393 fewer per 1000 (from 137 fewer to 566 fewer)	LOW	CRITICAL
Length of hospital stay (days) (better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	25	25	-	MD 4 higher (0.85 lower to 8.85 higher)	LOW	IMPORTANT
Adverse events (at 24 hours)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/25 (20%)	12%	RR 1.67 (0.45 to 6.24)	80 more per 1000 (from 66 fewer to 629 more)	LOW	IMPORTANT

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[2] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[3] *Not possible to calculate control risk*

Table 23: Clinical evidence summary: Non-absorbable disaccharides versus probiotics

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	Pro-biotics	Relative (95% CI)	Absolute	Quality	Importance
Improvement in hepatic encephalopathy symptoms (at day 10)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	14/19 (73.7%)	79%	RR 0.93 (0.65 to 1.33)	55 fewer per 1000 (from 277 fewer to 261 more)	VERY LOW	CRITICAL
Adverse events (at 20 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8/15 (53.3%)	6.3%	RR 8.53 (1.21 to 60.33)	474 more per 1000 (from 13 more to 1000 more)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 24: Clinical evidence summary: Non-absorbable disaccharides versus sodium benzoate

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	Sodium benzoate	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	7/36 (19.4%)	21.1%	RR 0.92 (0.37 to 2.29)	17 fewer per 1000 (from 133 fewer to 272 more)	LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	Sodium benzoate	Relative (95% CI)	Absolute		
Complete response (recovery to normal mental status with no evidence of asterixis)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	29/36 (80.6%)	79%	RR 1.02 (0.81 to 1.28)	16 more per 1000 (from 150 fewer to 221 more)	MODERATE	CRITICAL
Continued in grade 1+ mental status despite therapy for 21 days												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	1/36 (2.8%)	7.9%	RR 0.35 (0.04 to 3.23)	51 fewer per 1000 (from 76 fewer to 176 more)	LOW	CRITICAL
Complications during treatment												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30/36 (83.3%)	92.1%	RR 0.9 (0.76 to 1.08)	92 fewer per 1000 (from 221 fewer to 74 more)	HIGH	IMPORTANT

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

J.11.2 Combination therapy (1 intervention + non-absorbable disaccharides) versus non-absorbable disaccharides

Table 25: Clinical evidence summary: Rifaximin + non-absorbable disaccharides versus non-absorbable disaccharides

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rifaximin+non-absorbable disaccharides	Non-absorbable disaccharides	Relative (95% CI)	Absolute		
Mortality												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	15/63 (23.8%)	49.1%	RR 0.48 (0.29 to 0.81)	255 fewer per 1000 (from 93 fewer to 349 fewer)	MODERATE	CRITICAL
Complete reversal of hepatic encephalopathy (according to West Haven criteria; at 10 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	48/63 (76.2%)	50.9%	RR 1.5 (1.12 to 2)	255 more per 1000 (from 61 more to 509 more)	MODERATE	CRITICAL
Length of hospital stay (better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	63	57	-	MD 2.4 lower (3.86 to 0.94 lower)	MODERATE	IMPORTANT
Side effects related to study medications												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	12/63 (19%)	17.5%	RR 1.09 (0.51 to 2.32)	16 more per 1000 (from 86 fewer to 231 more)	LOW	IMPORTANT

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 26: Clinical evidence summary: BCAA + non-absorbable disaccharides versus non-absorbable disaccharides

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	BCAA+non-absorbable disaccharides	Non-absorbable disaccharides	Relative (95% CI)	Absolute		
Mortality (at 16 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	11/32 (34.4%)	30.3%	RR 1.13 (0.56 to 2.3)	39 more per 1000 (from 133 fewer to 394 more)	LOW	CRITICAL
Wake up (study 1 defines as woke up to hepatic encephalopathy grade 0 or I by Fogarty classification at 16 days; study 2 defines as came out of coma by day 7)												
2	Randomised trials	Serious[2]	Serious[3]	No serious indirectness	Serious[1]	None	33/48 (68.8%)	57%	RR 1.24 (0.91 to 1.69)	137 more per 1000 (from 51 fewer to 393 more)	VERY LOW	CRITICAL
Treatment failures other than death (hepatic encephalopathy deeper than grade I [Fogarty classification] despite other improvements; at 16 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/32 (12.5%)	18.2%	RR 0.69 (0.21 to 2.21)	56 fewer per 1000 (from 144 fewer to 220 more)	LOW	CRITICAL

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[2] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[3] *Downgraded by 1 or 2 increments because: the point estimate varies widely across studies, unexplained by subgroup analysis*

Table 27: Clinical evidence summary: Flumazenil + non-absorbable disaccharides versus non-absorbable disaccharides

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Flumazenil	Placebo (concurrent lactulose)	Relative (95% CI)	Absolute	Quality	Importance
Mortality (during the observation period, 3 hour treatment + 5 hour observation)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/28 (0%)	4.8%	OR 0.1 (0 to 5.09)	43 fewer per 1000	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Flumazenil	Placebo (concurrent lactulose)	Relative (95% CI)	Absolute		
										(from 48 fewer to 156 more)		
Clinically relevant response (improvement of at least 2 points in PSE score, PSE score on a 0–16 scale, at 8 hours)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/28 (25%)	0%	Peto OR 7.39 (1.49 to 36.61)	250 more per 1000 (from 80 more to 420 more)	LOW	CRITICAL
Adverse events (at 8 hours)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	4/28 (14.3%)	0%	Peto OR 6.47 (0.84 to 49.99)	140 more per 1000 (from 0 to 290 more)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

J.11.3 Combination therapy (2 interventions + non-absorbable disaccharides) versus combination therapy (1 intervention + non-absorbable disaccharides)

Table 28: Clinical evidence summary: Flumazenil + BCAA + non-absorbable disaccharides versus BCAA + non-absorbable disaccharides

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Flumazenil	Placebo (concurrent lactulose and BCAA)	Relative (95% CI)	Absolute		

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Flumazenil**	**Placebo (concurrent lactulose and BCAA)**	**Relative (95% CI)**	**Absolute**		
Mortality (at 24 hours)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/28 (21.4%)	19.2%	RR 1.11 (0.39 to 3.22)	21 more per 1000 (from 117 fewer to 426 more)	VERY LOW	CRITICAL
Improvement in neurological status (increase in Glasgow coma score by 3 points; at 24 hours)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	22/28 (78.6%)	53.9%	RR 1.46 (0.97 to 2.19)	248 more per 1000 (from 16 fewer to 641 more)	VERY LOW	CRITICAL
Side effects (at 24 hours)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/28 (0%)	0%	Not pooled	Not pooled	LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 29: Clinical evidence summary: LOLA + metronidazole + non-absorbable disaccharides versus metronidazole + non-absorbable disaccharides

Quality assessment	Number of patients	Effect	Quality	Importance

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LOLA (lactulose+ metronidazole)	Placebo (lactulose+ metronidazole)	Relative (95% CI)	Absolute		
Mortality (inpatient stay)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	Very serious[2]	None	6/100 (6%)	10.8%	RR 0.55 (0.21 to 1.42)	49 fewer per 1000 (from 85 fewer to 45 more)	VERY LOW	CRITICAL
Complete improvement defined as improvement of 2 grades from baseline (day 3)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	45/54 (83.3%)	46.3%	RR 1.8 (1.32 to 2.46)	370 more per 1000 (from 148 more to 676 more)	HIGH	CRITICAL
Achieved hepatic encephalopathy grade 0 (at 5 days)												
1	Randomised trials	Very serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	37/40 (92.5%)	77.5%	RR 1.19 (0.99 to 1.44)	147 more per 1000 (from 8 fewer to 341 more)	VERY LOW	CRITICAL
Adverse events												
2	Randomised trials	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/100 (1%)	0%	Peto OR 7.39 (0.15 to 372.38)	10 more per 1000 (from 20 fewer to 40 more)	VERY LOW	IMPORTANT

[1] *The majority of the evidence had indirect outcomes*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[3] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

J.11.4 Single therapy versus placebo

Table 30: Clinical evidence summary: Non-absorbable disaccharides versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Non-absorbable disaccharides	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/10 (0%)	60%	OR 0.03 (0 to 0.4)	557 fewer per 1000 (from 225 fewer to 600 fewer)	LOW	CRITICAL
Therapeutic response (assessed with: defined as (i) sustained improvement of 1 grade in mental state during ≤48 hours or (ii) improvement of more than 2 grades in mental state)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10/10 (100%)	20%	RR 3.82 (0.95 to 15.36)	564 more per 1000 (from 10 fewer to 1000 more)	VERY LOW	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 31: Clinical evidence summary: BCAA versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	BCAA	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality (at 5 days)												
1	Randomised	Serious[1]	No serious	No serious	Serious[2]	None	10/25	20%	RR 2 (0.8 to	200 more	LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**BCAA**	**Placebo**	**Relative (95% CI)**	**Absolute**		
	trials		inconsistency	indirectness			(40%)		5.02)	per 1000 (from 40 fewer to 804 more)		
Positive response to treatment (at 5 days)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	10/20 (50%)	50%	RR 1 (0.55 to 1.83)	0 fewer per 1000 (from 225 fewer to 415 more)	VERY LOW	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 32: Clinical evidence summary: Neomycin (+BCAA in grades III and IV) versus placebo (+BCAA in grades III and IV)

Quality assessment							Number of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Neomycin**	**Placebo (concurrent BCAA in grade III/IV)**	**Relative (95% CI)**	**Absolute**		
Mortality (at day 5)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	2/20 (10%)	10.5%	RR 0.95 (0.15 to 6.08)	5 fewer per 1000 (from 89 fewer to 533 more)	VERY LOW	CRITICAL
Time until regression to grade 0 hepatic encephalopathy (better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	20	19	-	MD 13.36 lower (27.47 lower to	LOW	CRITICAL

Quality assessment							Number of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Neomycin	Placebo (concurrent BCAA in grade III/IV)	Relative (95% CI)	Absolute	Quality	Importance
										0.75 higher)		

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

J.11.5 Single therapy versus single therapy

Table 33: Clinical evidence summary: BCAA versus neomycin

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	BCAA	Neomycin	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
3	Randomised trials	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	18/68 (26.5%)	40%	RR 0.57 (0.36 to 0.89)	172 fewer per 1000 (from 44 fewer to 256 fewer)	VERY LOW	CRITICAL
Full improvement to grade 0 hepatic encephalopathy												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	5/9 (55.6%)	25%	RR 2.22 (0.58 to 8.44)	305 more per 1000 (from 105 fewer to 1000 more)	VERY LOW	CRITICAL
Improvement to grade 0 or 1 hepatic encephalopathy												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**BCAA**	**Neomycin**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	8/9 (88.9%)	75%	RR 1.19 (0.75 to 1.88)	143 more per 1000 (from 188 fewer to 660 more)	LOW	CRITICAL
Time to recovery (hours) (better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	14	14	-	MD 37.4 lower (56.1 to 18.7 lower)	MODERATE	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 or 2 increments because: the point estimate varies widely across studies, unexplained by subgroup analysis*
[3] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

J.11.6 Combination therapy (1 intervention + non-absorbable disaccharides) versus single therapy

Table 34: Clinical evidence summary: BCAA+non-absorbable disaccharides versus BCAA

Quality assessment							Number of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**BCAA+non-absorbable disaccharides**	**BCAA**	**Relative (95% CI)**	**Absolute**		
Came out of coma (at 7 days)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	16/16 (100%)	93.8%	RR 1.06 (0.9 to 1.26)	56 more per 1000 (from 94 fewer to 244 more)	VERY LOW	CRITICAL

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

J.11.7 MARS versus Standard Medical Therapy

Table 35: Clinical evidence summary: MARS versus Standard Medical Therapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MARS**	**Standard medical therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Mortality (at 5 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/39 (12.8%)	16.1%	RR 0.79 (0.25 to 2.5)	34 fewer per 1000 (from 121 fewer to 241 more)	LOW	CRITICAL
Responder (improvement of hepatic encephalopathy by 2 grades at any time; at 5 days)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[1]	None	24/39 (61.5%)	40%	RR 1.54 (0.93 to 2.55)	216 more per 1000 (from 28 fewer to 620 more)	LOW	CRITICAL
Serious adverse events (at 5 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	20/39 (51.3%)	25.8%	RR 1.99 (1.02 to 3.89)	255 more per 1000 (from 5 more to 746 more)	MODERATE	IMPORTANT

[1] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[2] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

Appendix K: Forest plots

K.1 Risk factors and risk assessment tools

K.1.1 Risk factors

Prognostic factor: Alcohol

Figure 1: Prognostic factor: Alcohol consumption (Askgaard 2015)

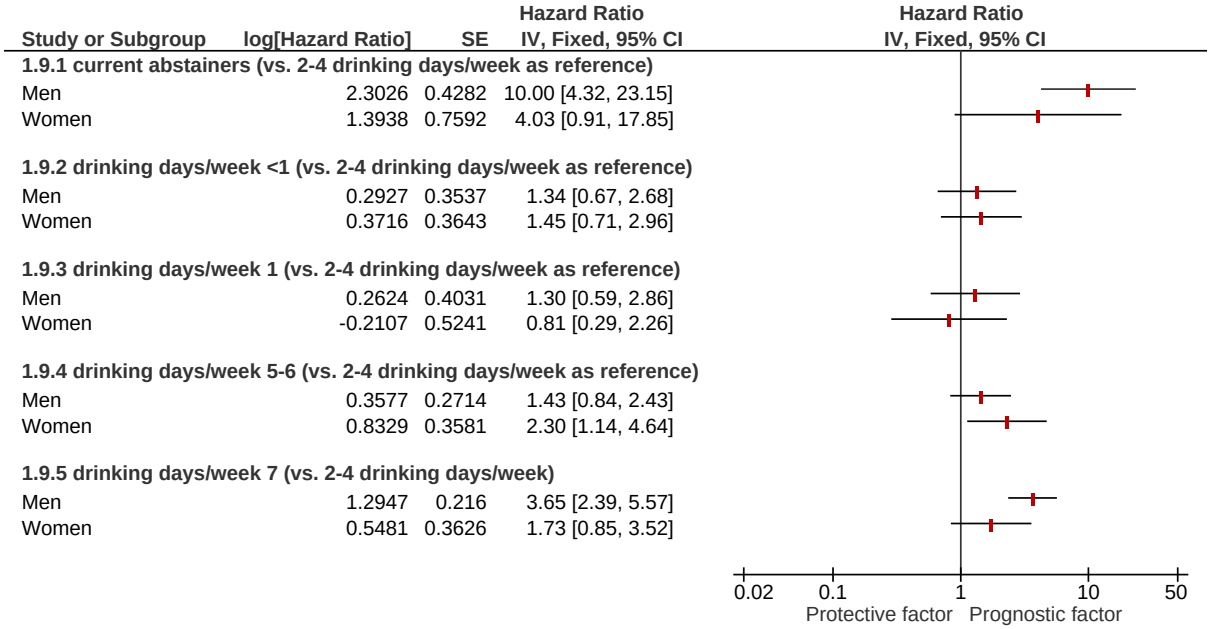


Figure 2: Prognostic factor: Alcohol consumption (Becker 2002)

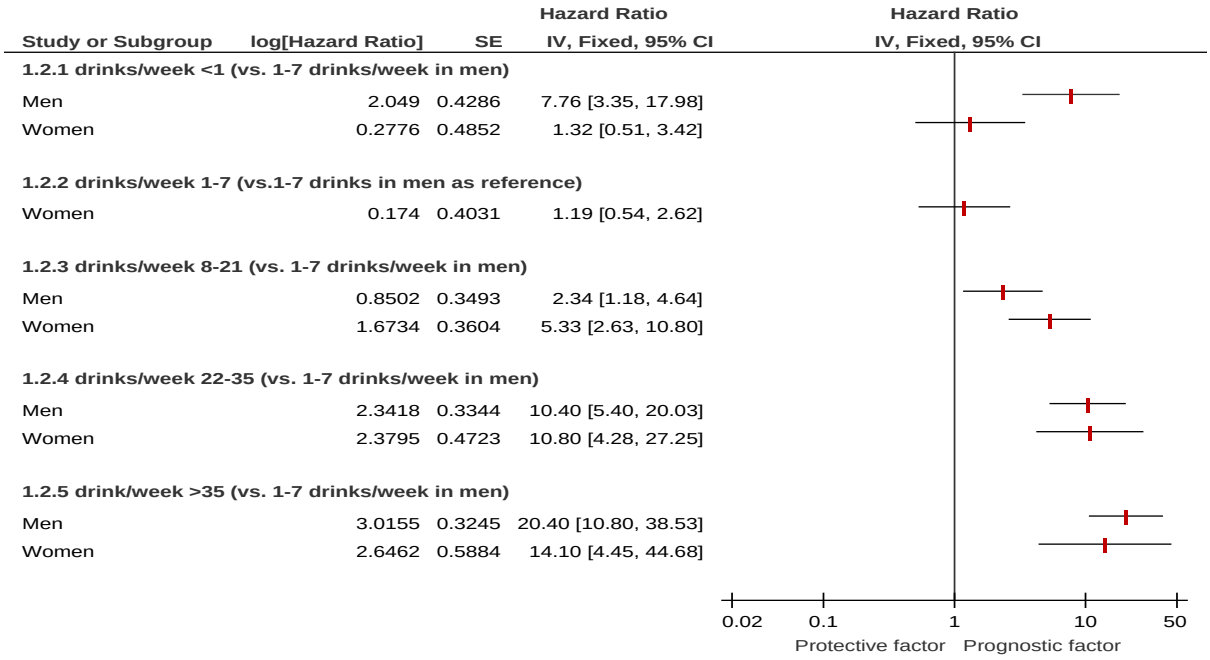


Figure 3: Prognostic factor: Alcohol consumption (Fuchs 1995)

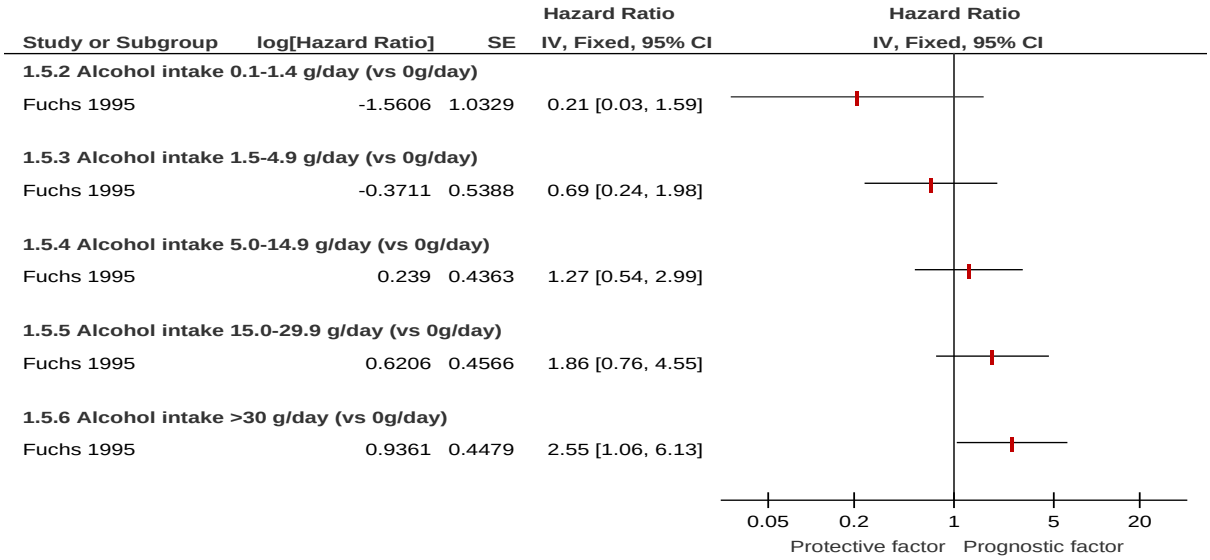
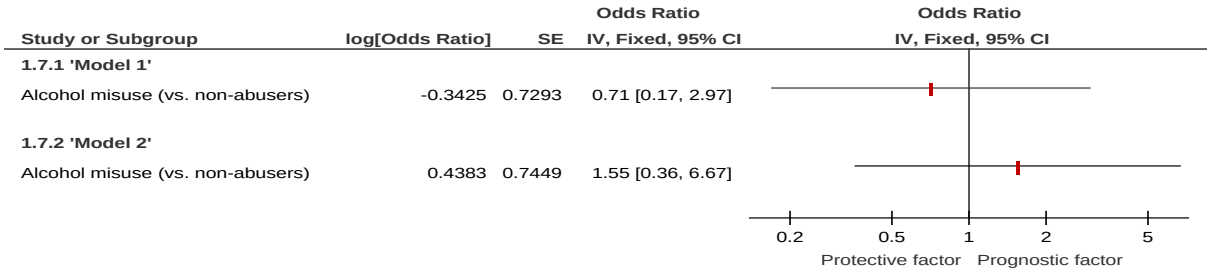
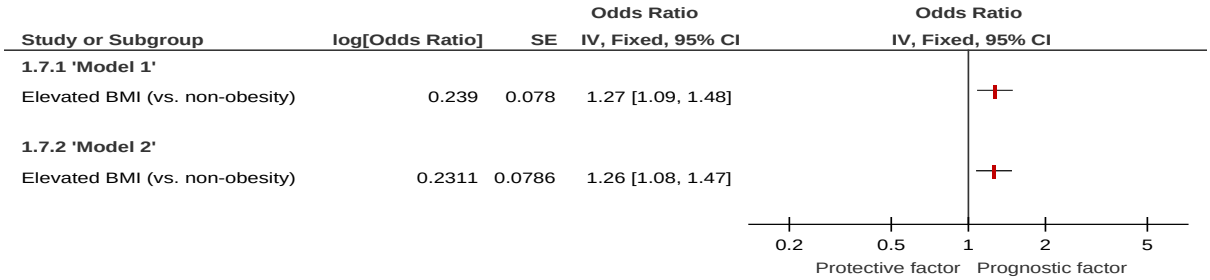


Figure 4: Prognostic factor: Alcohol consumption (Schult 2011)



Prognostic Factor: BMI

Figure 5: Prognostic factor: BMI (Schult 2011)



Note: elevated BMI presumed to be >30 but unclear as reported in paper

Figure 6: Prognostic factor: BMI (Becker 2002)

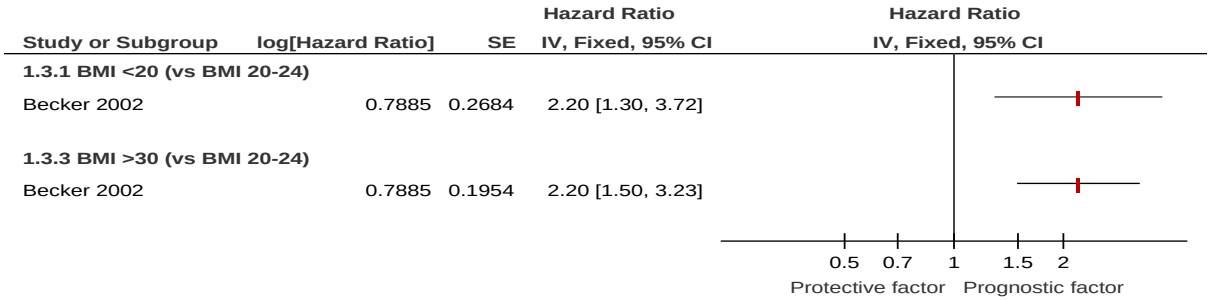


Figure 7: Prognostic factor: BMI (Liu 2010A)

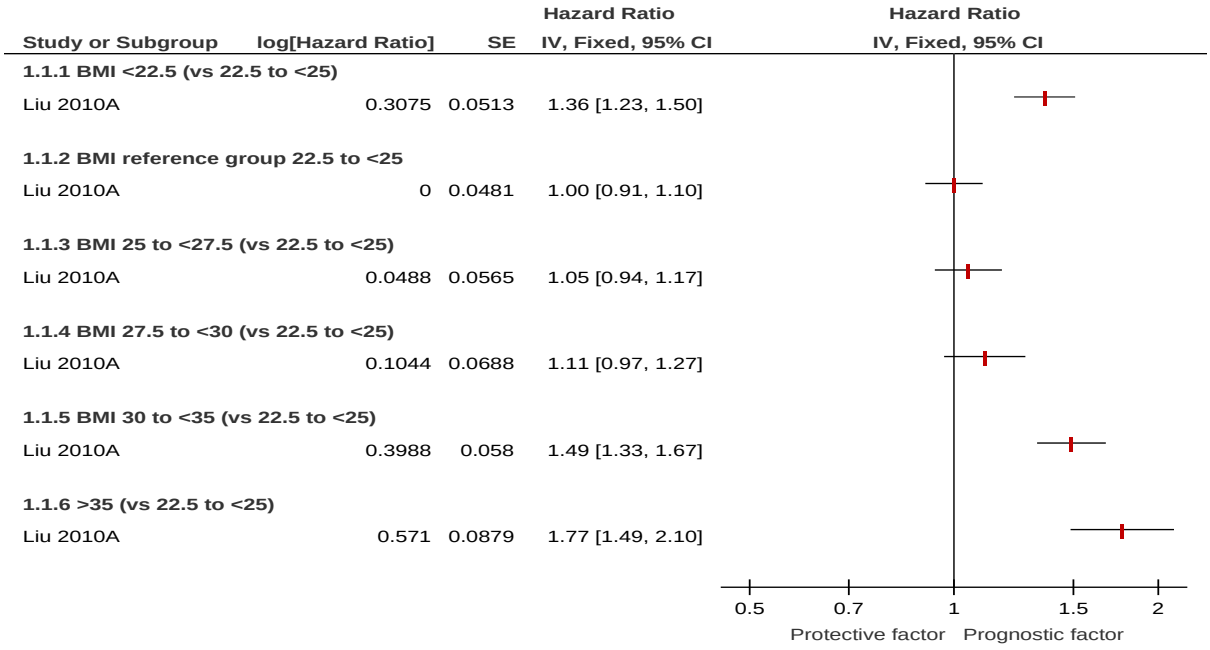
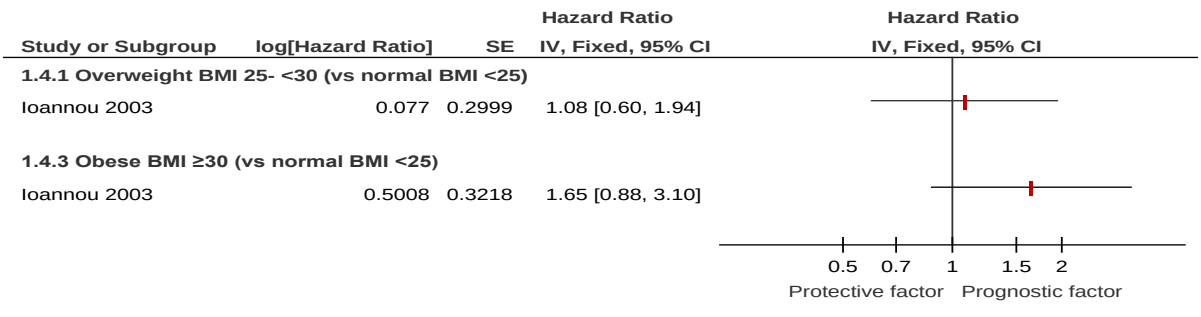
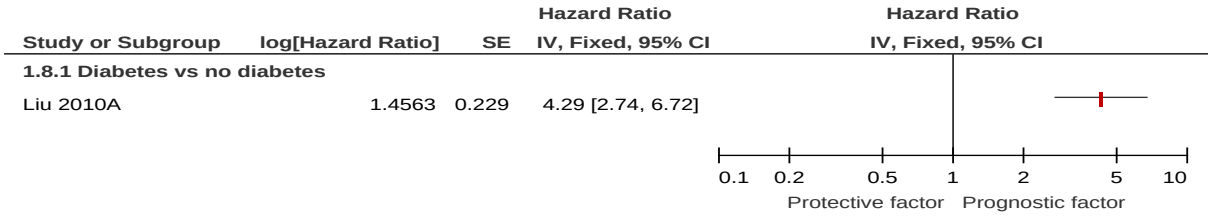


Figure 8: Prognostic factor: BMI (Ioannou 2003)



Prognostic Factor: Diabetes

Figure 9: Prognostic factor: Diabetes (Liu 2010)



K.1.2 Risk tools

No relevant clinical studies were identified.

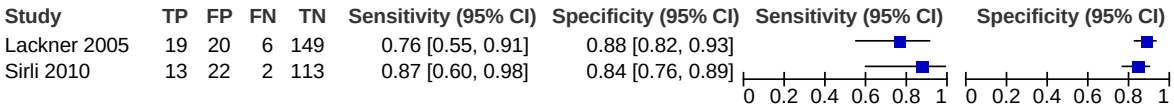
K.2 Diagnostic tests

K.2.1 Hepatitis C

K.2.1.1 Individual blood tests

Coupled sensitivity/specificity forest plots

Figure 10: Platelets



AUC plots

Figure 11: Platelets

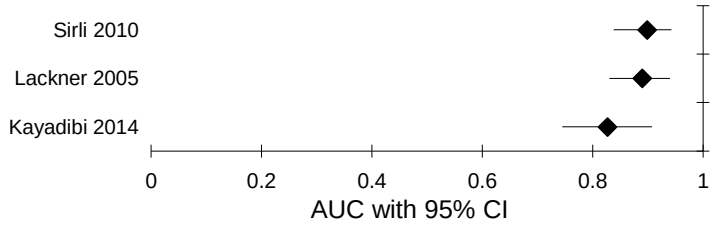


Figure 12: AST

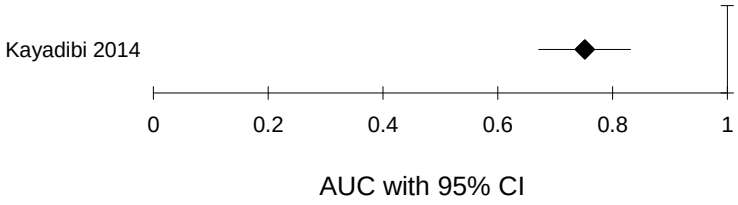
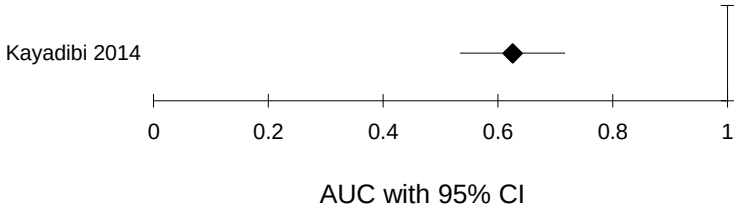


Figure 13: ALT



K.2.1.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

Figure 14: AST/ALT ratio

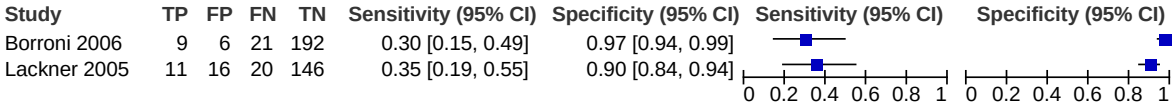
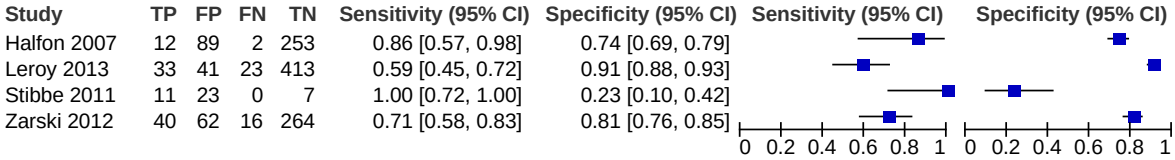


Figure 15: FibroTest



FibroTest data that could not be combined in the analysis:

Friedrich-Rust 2010[260]: cut-off 0.73, sensitivity: 67%, specificity: 81%;

Leroy 2014[446]: cut-off 0.74, sensitivity: 59%, specificity: 91%

Figure 16: FibroTest sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region

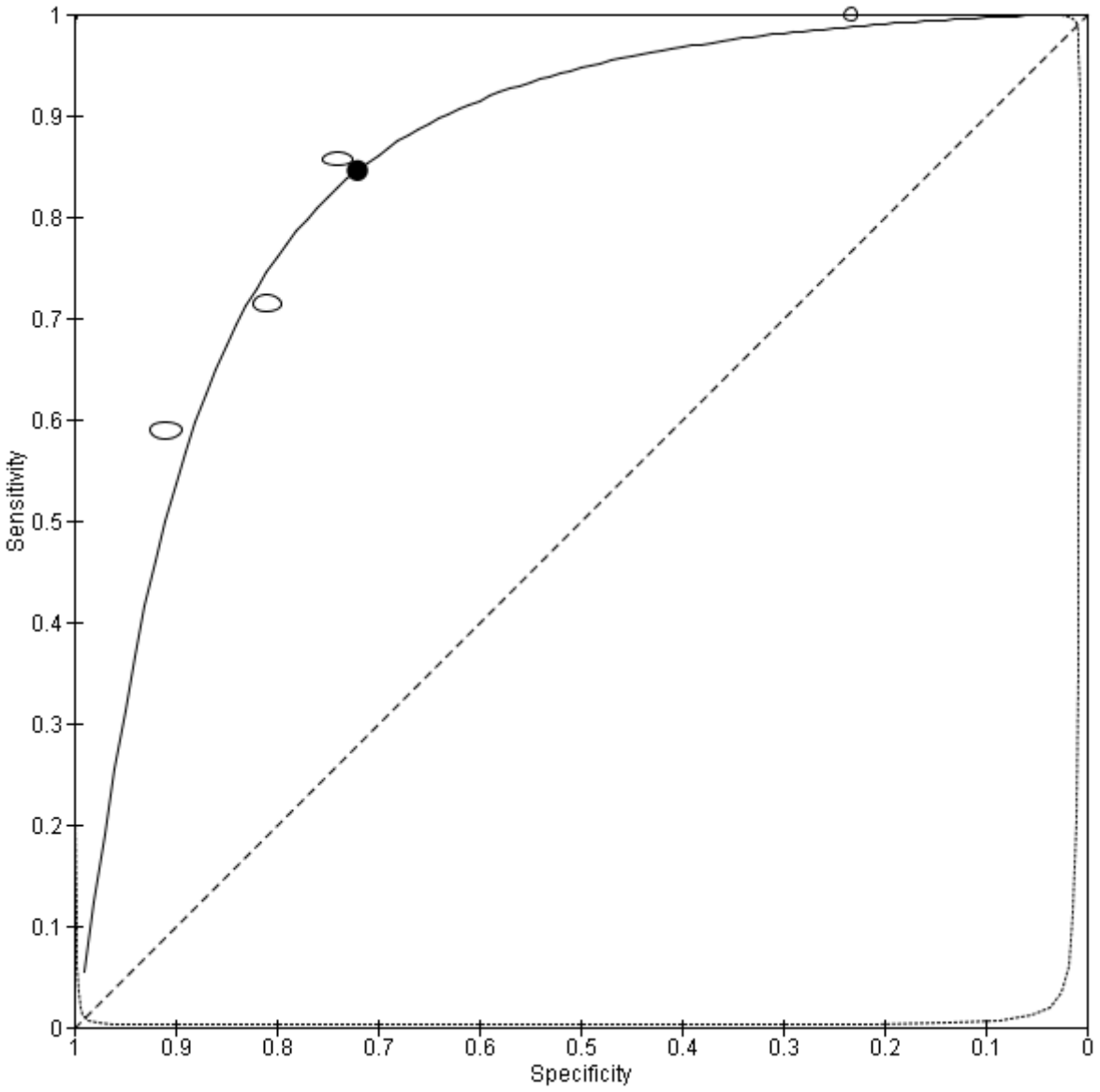


Figure 17: ELF

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cantanzaro 2013	34	11	9	108	0.79 [0.64, 0.90]	0.91 [0.84, 0.95]
Fernandes 2015	7	25	1	87	0.88 [0.47, 1.00]	0.78 [0.69, 0.85]
Guechot 2012	63	109	13	327	0.83 [0.73, 0.91]	0.75 [0.71, 0.79]

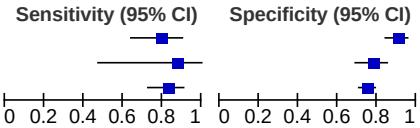
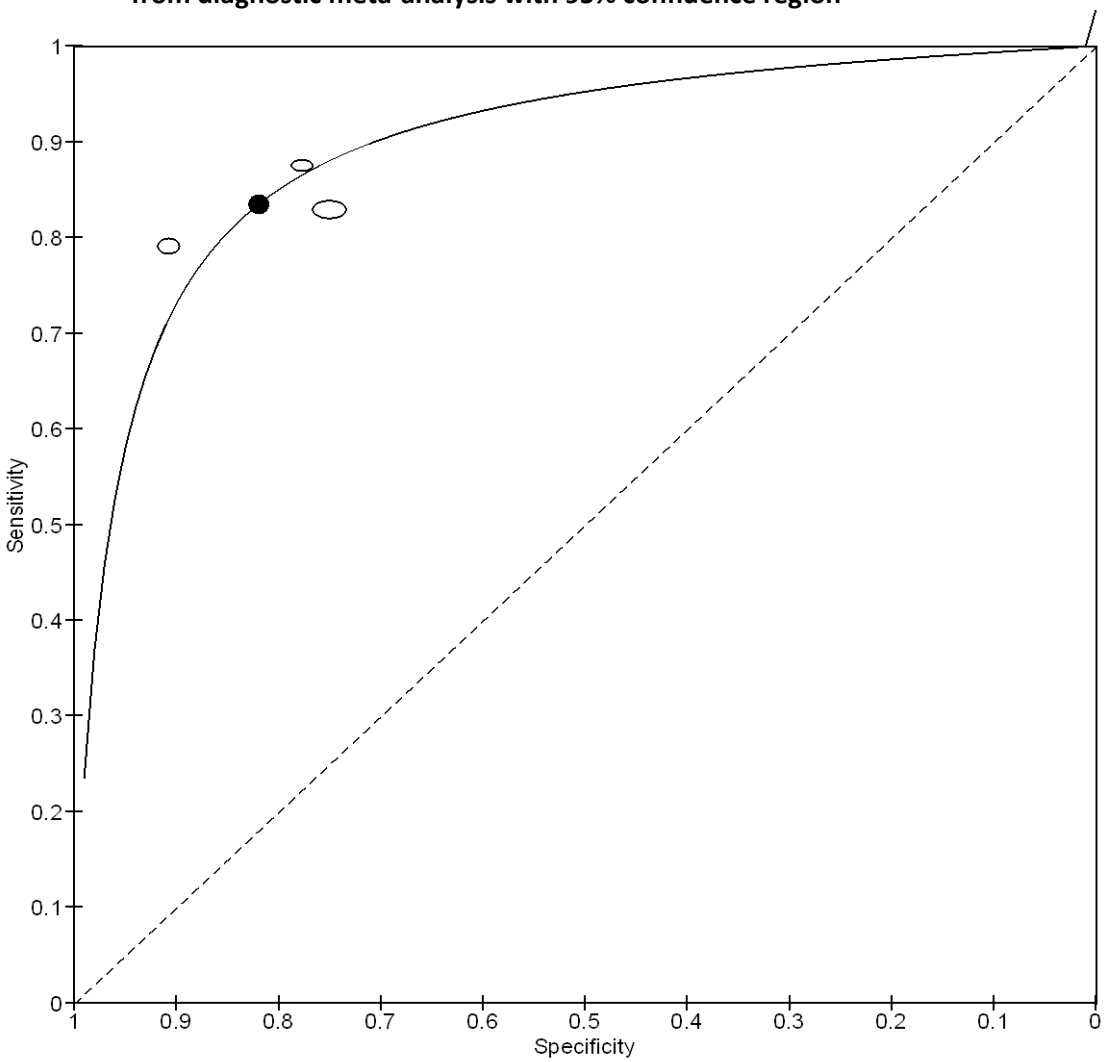


Figure 18: ELF sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region



ELF data that could not be combined in the analysis:

Friedrich-rust 2010[260]: cut-off 10.31, sensitivity: 89%, specificity: 63%

Figure 19: APRI (low threshold)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bota 2011a	24	47	6	135	0.80 [0.61, 0.92]	0.74 [0.67, 0.80]
Cantanzaro 2013	32	15	11	104	0.74 [0.59, 0.86]	0.87 [0.80, 0.93]
Chrysanthos 2006	35	64	23	162	0.60 [0.47, 0.73]	0.72 [0.65, 0.77]
Halfon 2007	14	58	0	284	1.00 [0.77, 1.00]	0.83 [0.79, 0.87]
Lackner 2005	30	49	2	114	0.94 [0.79, 0.99]	0.70 [0.62, 0.77]
Martinez 2011	102	57	22	159	0.82 [0.74, 0.89]	0.74 [0.67, 0.79]
Sirli 2010	14	23	1	112	0.93 [0.68, 1.00]	0.83 [0.76, 0.89]

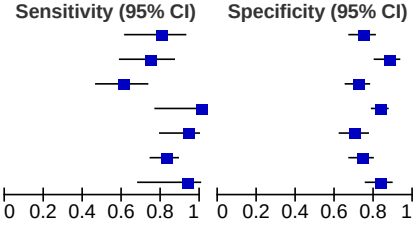
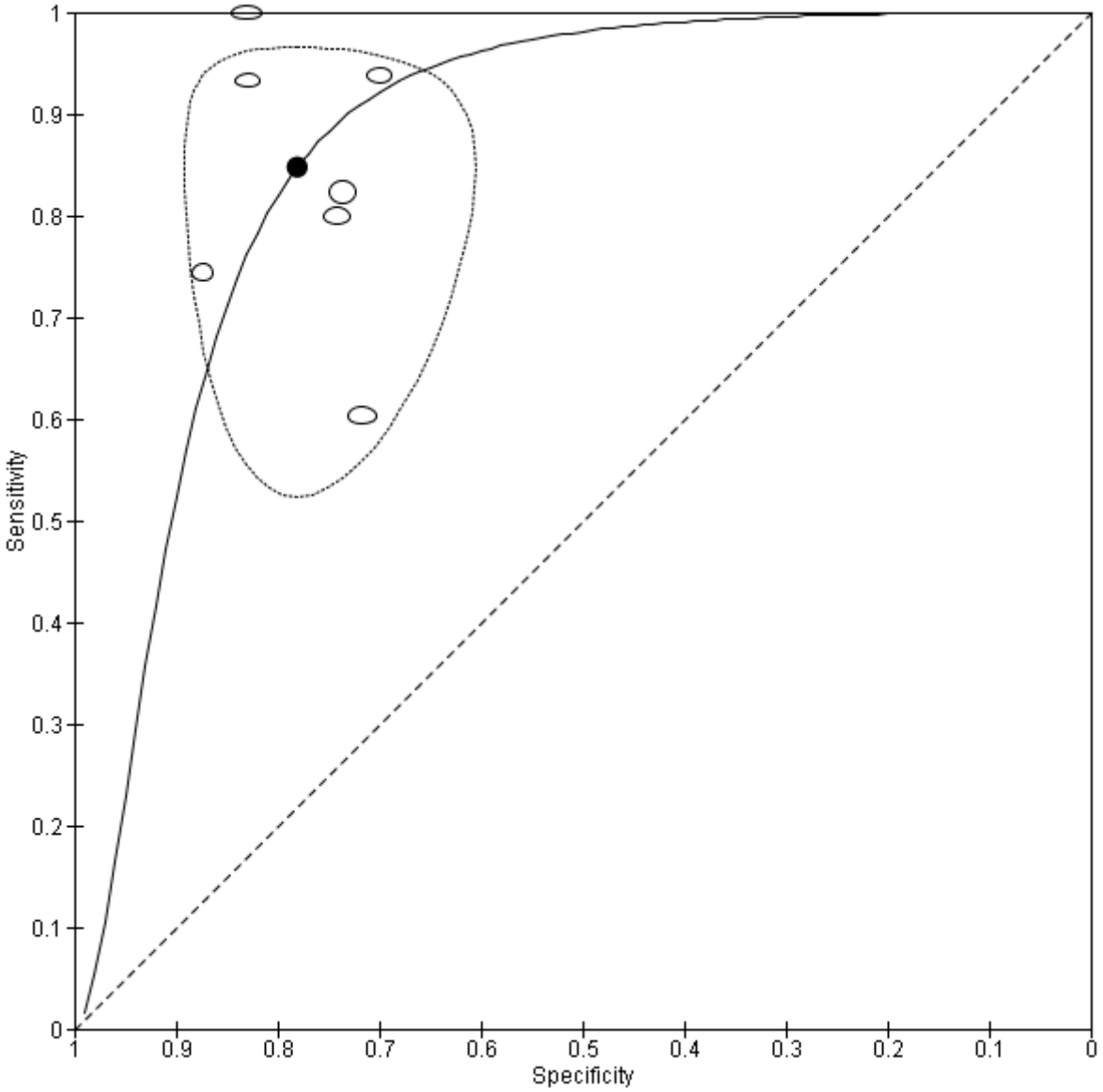


Figure 20: APRI (low threshold) sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region



APRI (low threshold) data that could not be combined in the analysis:

Shehab 2014[676]: cut-off 0.5, sensitivity: 100%, specificity: 12.8%

Figure 21: APRI (high threshold)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Borroni 2006	13	12	17	186	0.43 [0.25, 0.63]	0.94 [0.90, 0.97]
Chrysanthos 2006	22	20	36	206	0.38 [0.26, 0.52]	0.91 [0.87, 0.95]
Martinez 2011	61	20	63	196	0.49 [0.40, 0.58]	0.91 [0.86, 0.94]
Silva Junior 2014	6	3	3	39	0.67 [0.30, 0.93]	0.93 [0.81, 0.99]
Zarski 2012	4	1	52	325	0.07 [0.02, 0.17]	1.00 [0.98, 1.00]

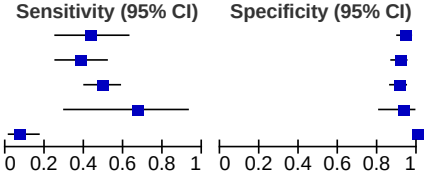
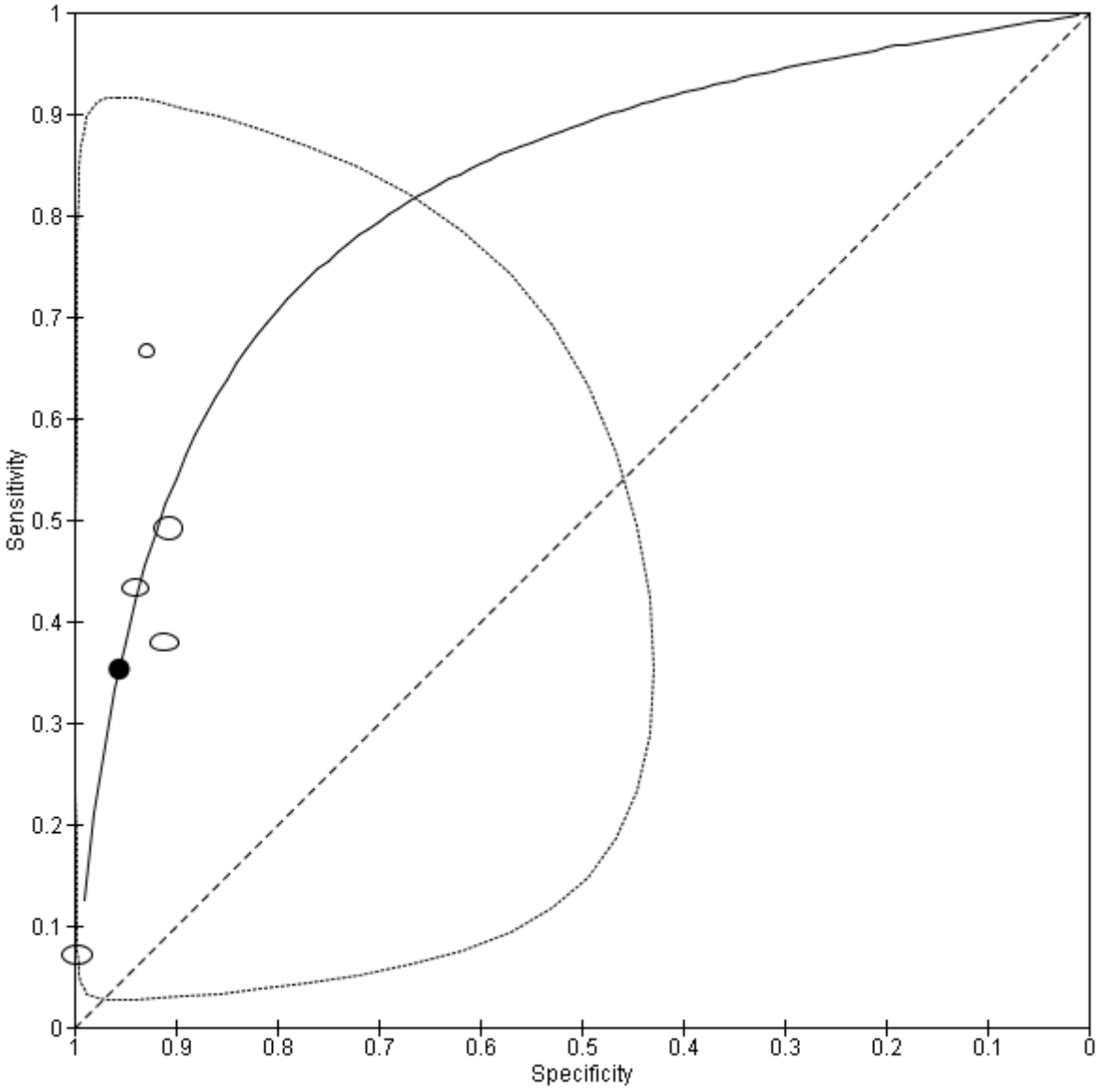


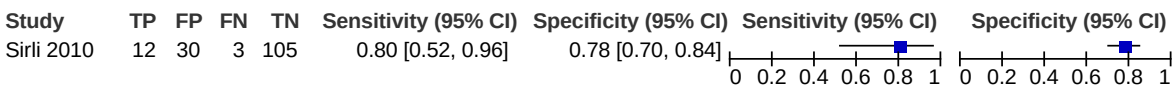
Figure 22: APRI (high threshold) sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region



APRI (high threshold) data that could not be combined in the analysis:

Shehab 2014[676]: cut-off 2.0, sensitivity: 15.4%, specificity: 96%

Figure 23: FIB-4



FIB-4 data that could not be combined in the analysis:

Shehab 2014[676]: cut-off 3.25, sensitivity: 28.2%, specificity: 93.5%

AUC plots

Figure 24: AST/ALT ratio

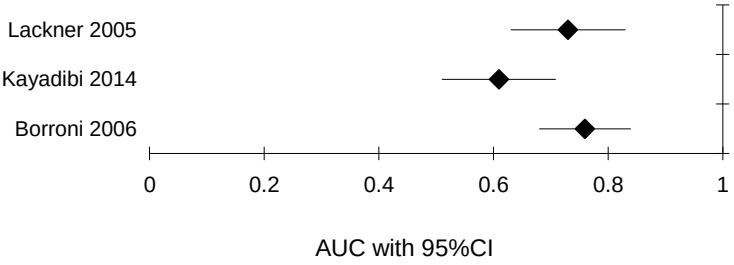


Figure 25: FibroTest

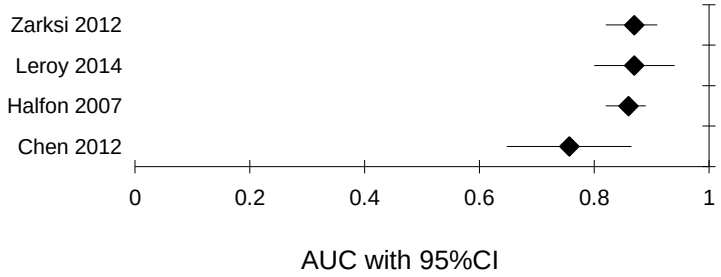


Figure 26: ELF

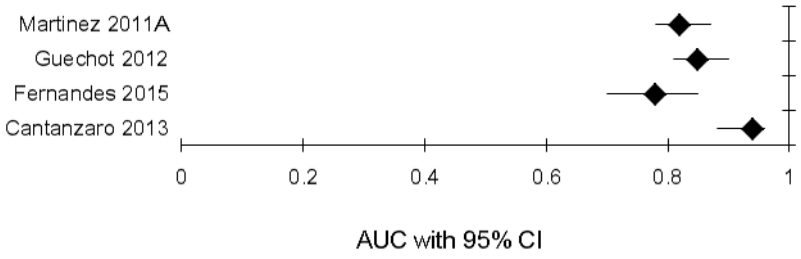


Figure 27: APRI

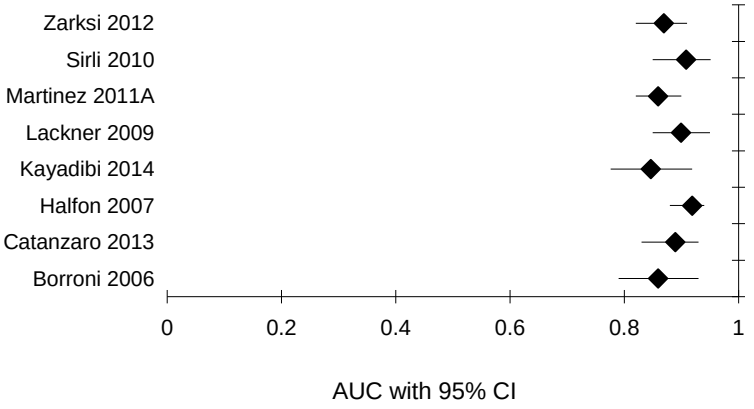
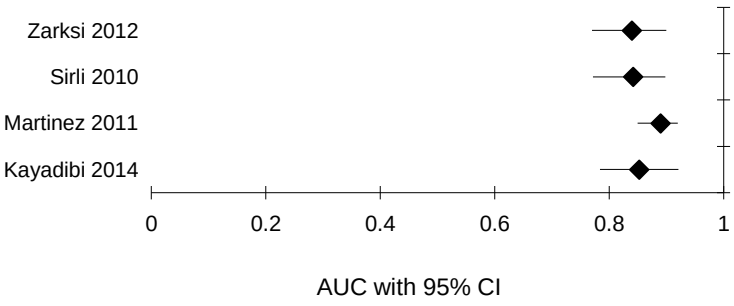


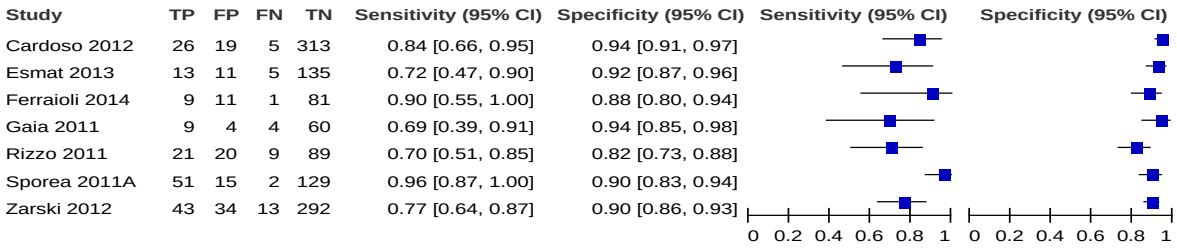
Figure 28: FIB-4



K.2.1.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 29: Transient elastography (low threshold)



TE (low threshold) data that could not be combined in the analysis:

Friedrich-rust 2010: cut-off 12.5 kPa, sensitivity: 78%, specificity: 84%

Figure 30: Transient elastography (low threshold) sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region

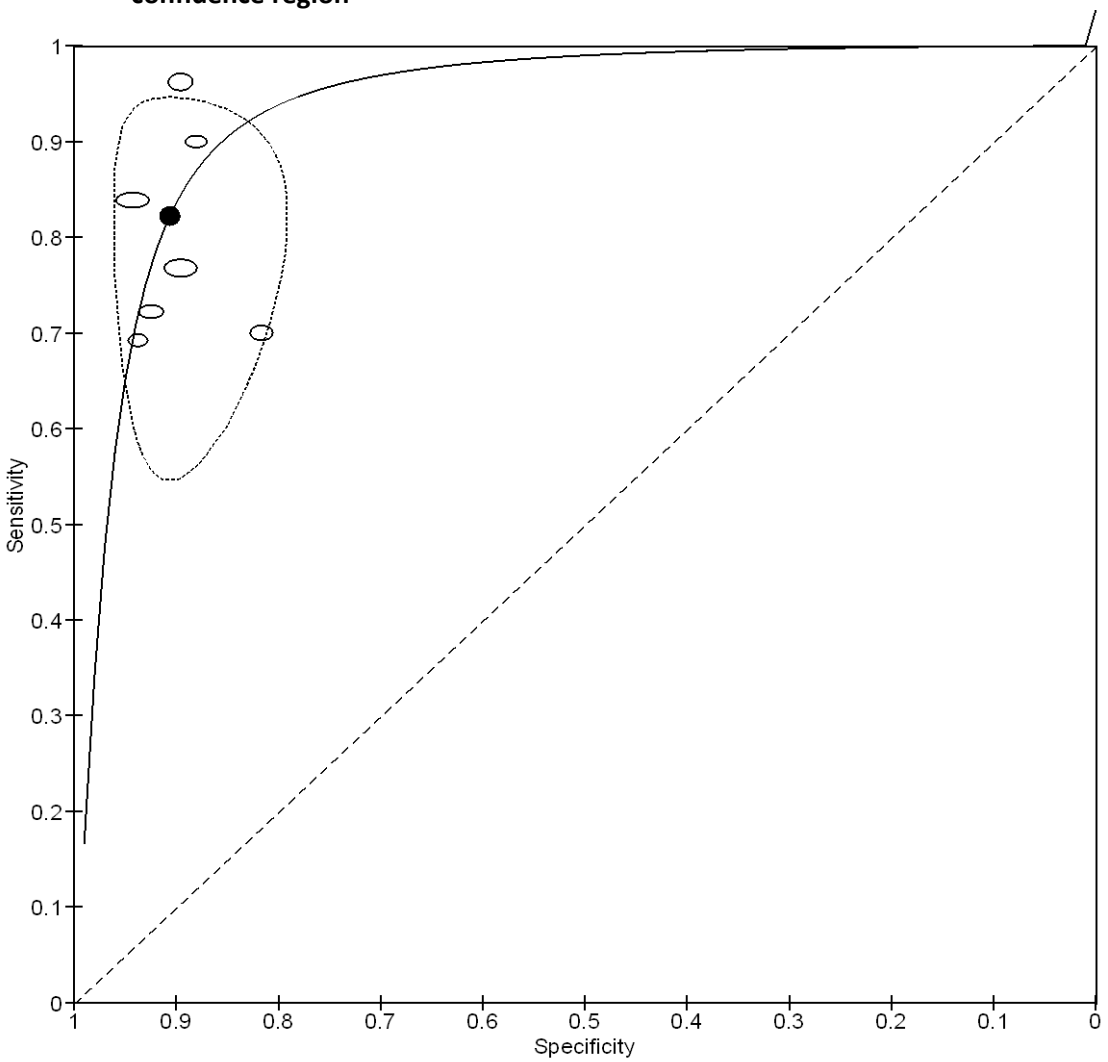


Figure 31: Transient elastography (medium threshold)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Arena 2008	27	10	2	111	0.93 [0.77, 0.99]	0.92 [0.85, 0.96]
Bota 2011a	28	5	2	177	0.93 [0.78, 0.99]	0.97 [0.94, 0.99]
Caviglia 2013	16	1	2	38	0.89 [0.65, 0.99]	0.97 [0.87, 1.00]
Lupsor Platon 2013	350	55	23	773	0.94 [0.91, 0.96]	0.93 [0.91, 0.95]
Sirli 2010	14	5	1	130	0.93 [0.68, 1.00]	0.96 [0.92, 0.99]
Sporea 2012A	40	8	2	62	0.95 [0.84, 0.99]	0.89 [0.79, 0.95]
Stibbe 2011	10	8	1	22	0.91 [0.59, 1.00]	0.73 [0.54, 0.88]

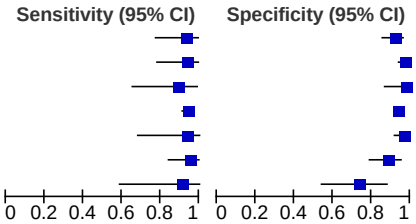


Figure 32: Transient elastography (medium threshold) sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region

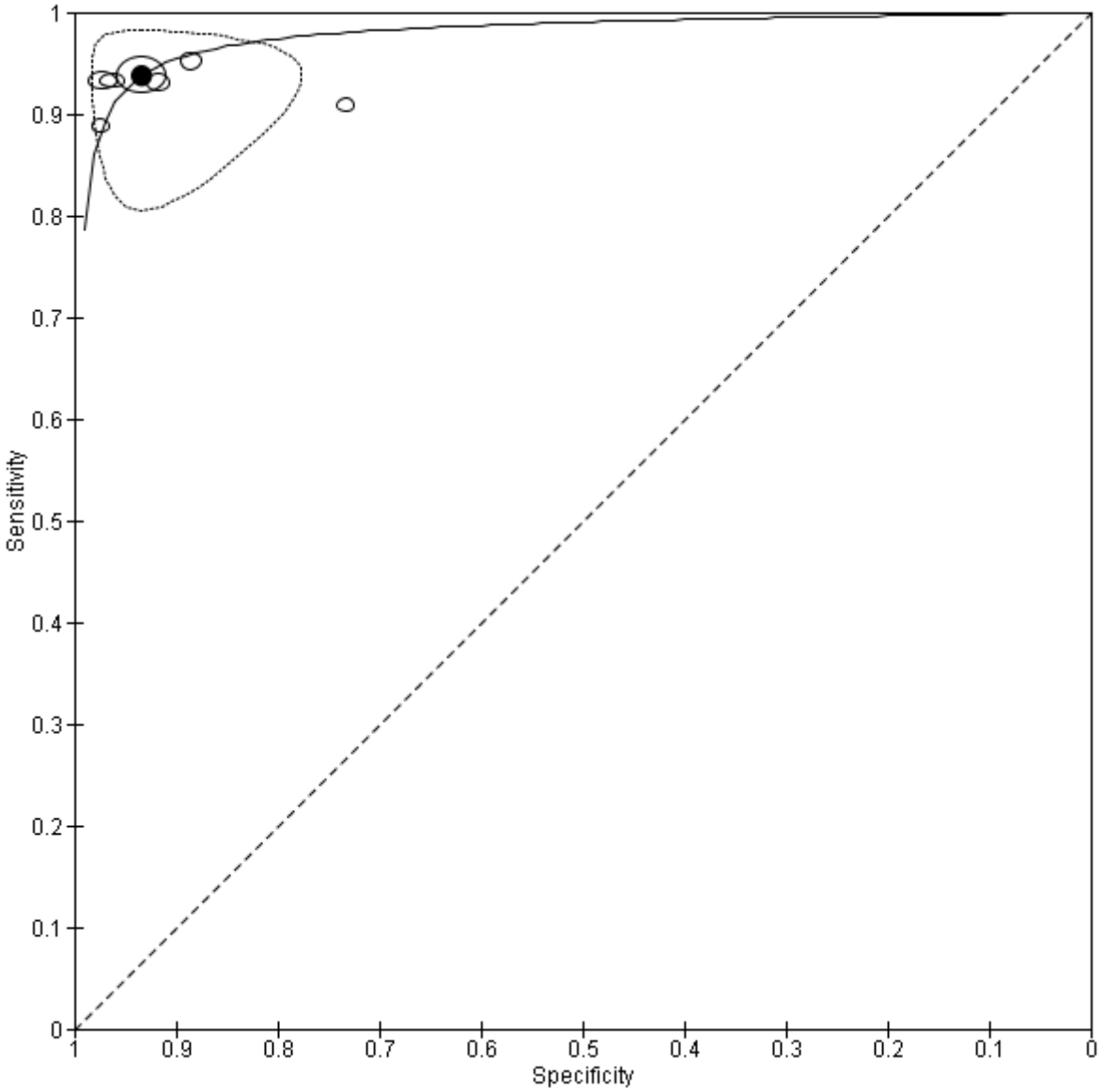


Figure 33: Transient elastography (high threshold)

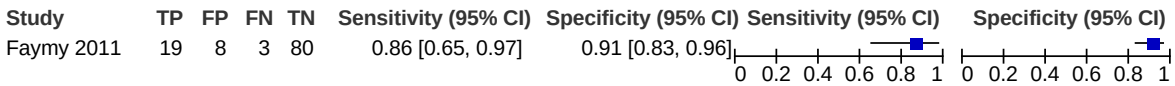


Figure 34: ARFI

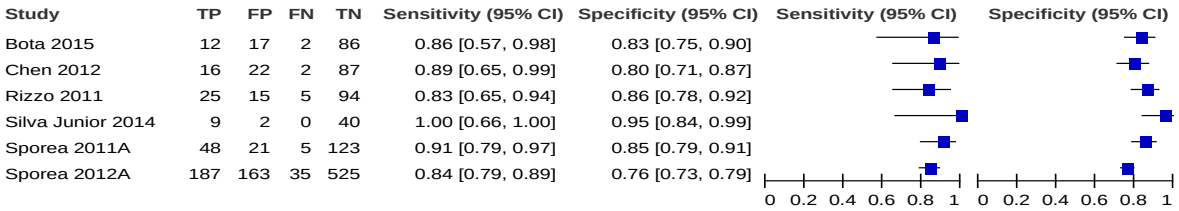


Figure 35: ARFI sROC with studies' results by size and the summary sensitivity and specificity value from diagnostic meta-analysis with 95% confidence region

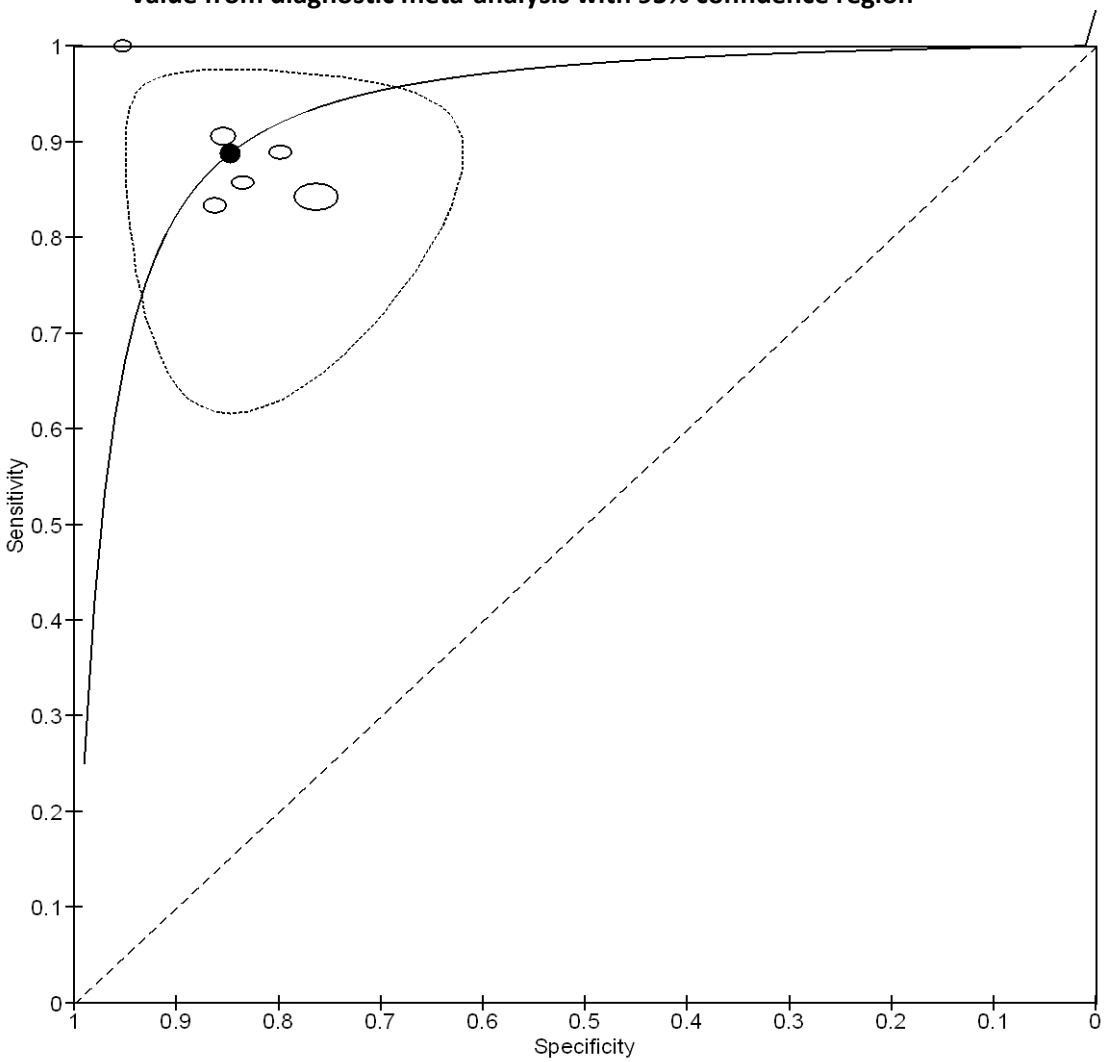
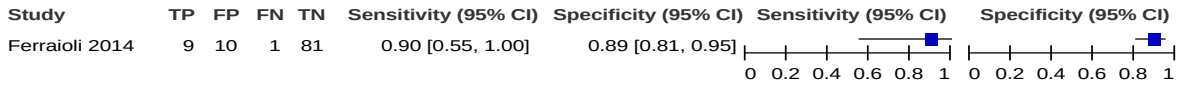


Figure 36: pSWE



AUC plots

Figure 37: Transient elastography

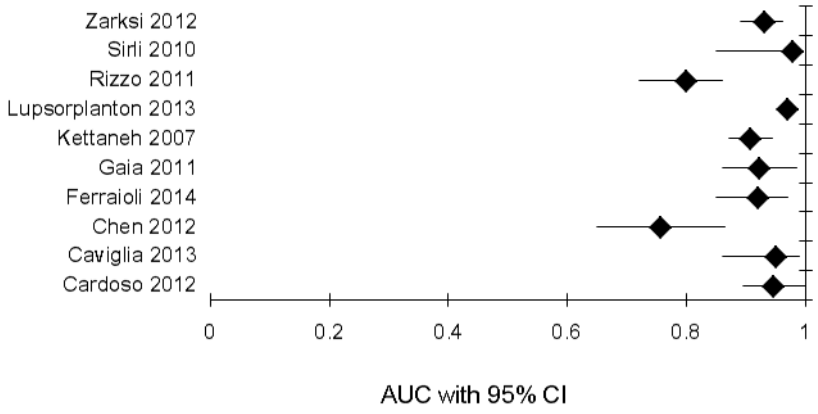


Figure 38: ARFI

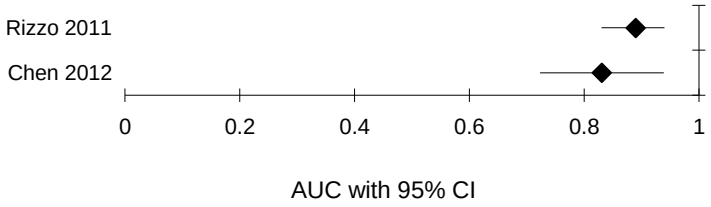
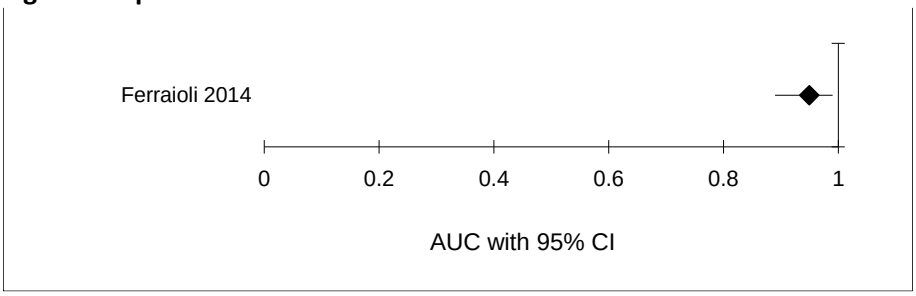


Figure 39: pSWE



K.2.1.4 Combinations of tests

Coupled sensitivity/specificity forest plots

Figure 40: Transient elastography and ARFI

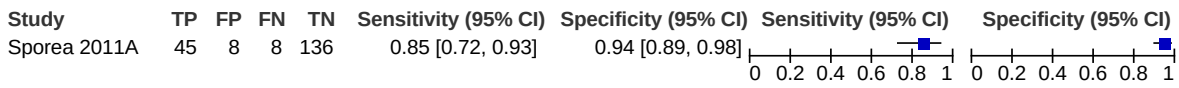


Figure 41: Transient elastography or ARFI

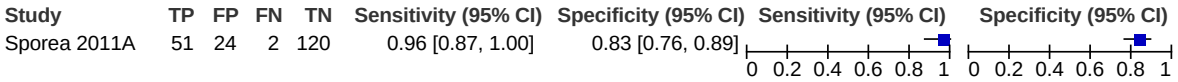


Figure 42: SAFE algorithm

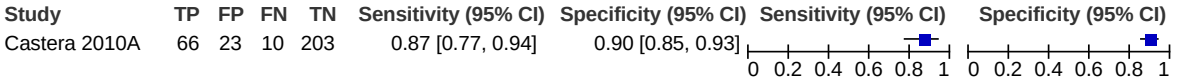
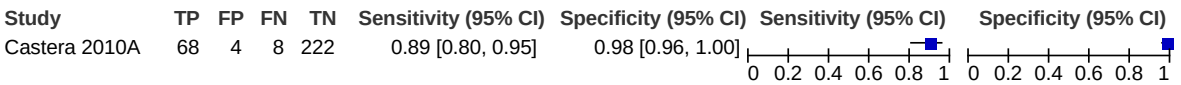


Figure 43: Castera algorithm



AUC plots

Figure 44: SAFE algorithm

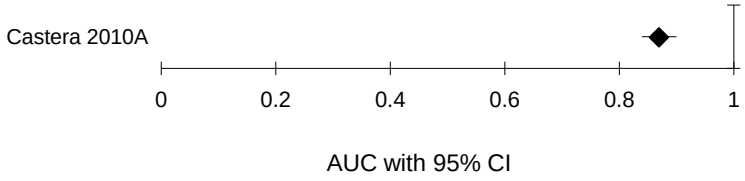
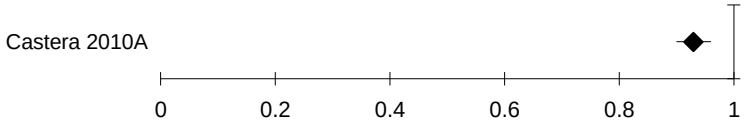


Figure 45: Castera algorithm



K.2.2 NAFLD

K.2.2.1 Individual blood tests

None reported

K.2.2.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

None reported

AUC plots

Figure 46: AST/ALT ratio

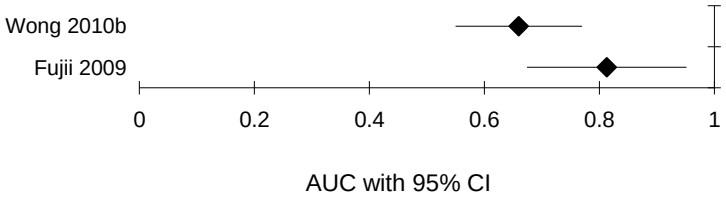


Figure 47: APRI

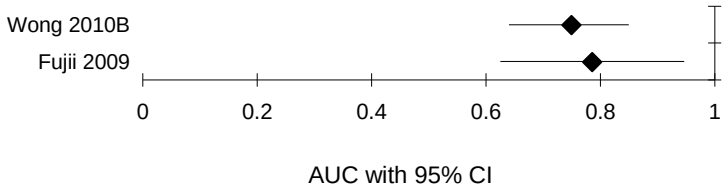
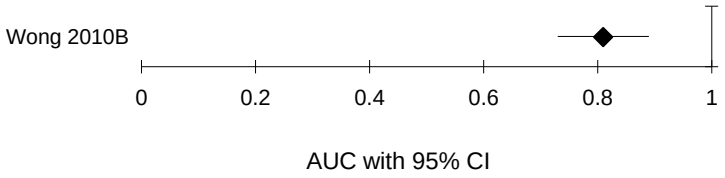


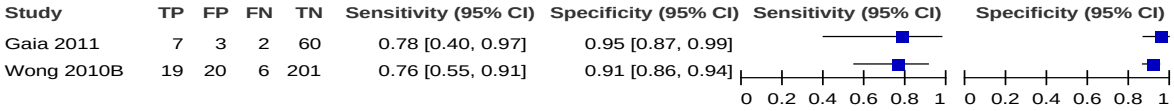
Figure 48: FIB-4



K.2.2.3 Imaging tests

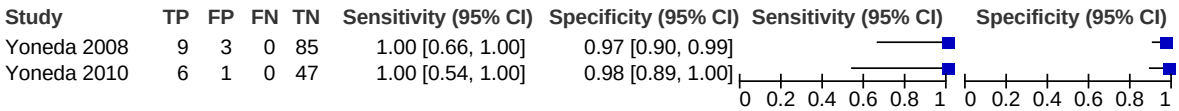
Coupled sensitivity/specificity forest plots

Figure 49: Transient elastography (low threshold)



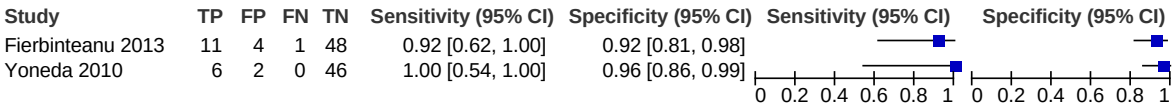
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gaia 2011	7	3	2	60	0.78 [0.40, 0.97]	0.95 [0.87, 0.99]
Wong 2010B	19	20	6	201	0.76 [0.55, 0.91]	0.91 [0.86, 0.94]

Figure 50: Transient elastography (high threshold)



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yoneda 2008	9	3	0	85	1.00 [0.66, 1.00]	0.97 [0.90, 0.99]
Yoneda 2010	6	1	0	47	1.00 [0.54, 1.00]	0.98 [0.89, 1.00]

Figure 51: ARFI



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fierbinteanu 2013	11	4	1	48	0.92 [0.62, 1.00]	0.92 [0.81, 0.98]
Yoneda 2010	6	2	0	46	1.00 [0.54, 1.00]	0.96 [0.86, 0.99]

AUC plots

Figure 52: Transient elastography

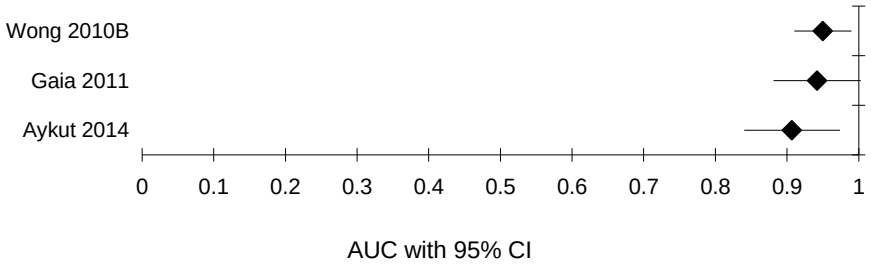
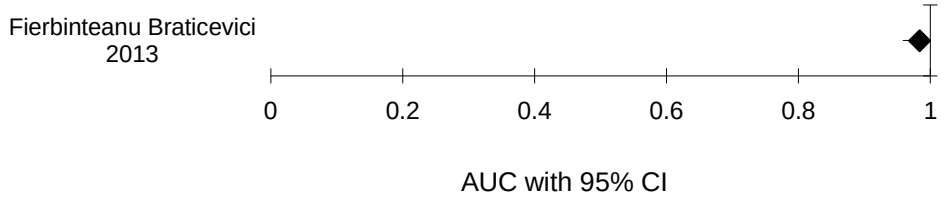


Figure 53: ARFI



K.2.2.4 Combinations of tests

None reported

K.2.3 ALD

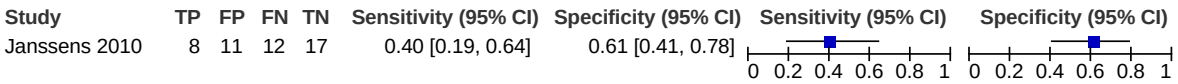
K.2.3.1 Individual blood tests

None reported

K.2.3.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

Figure 54: APRI (high threshold)



AUC plots

None reported

K.2.3.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 55: Transient elastography (low threshold)

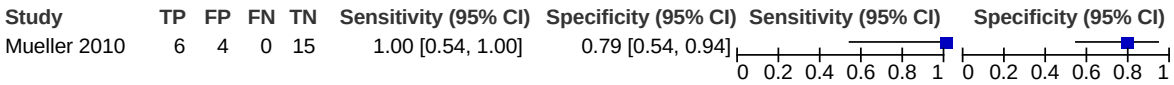
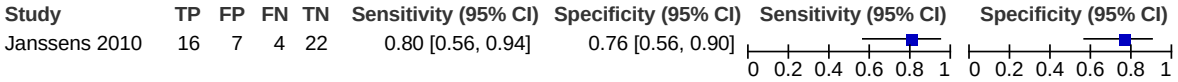
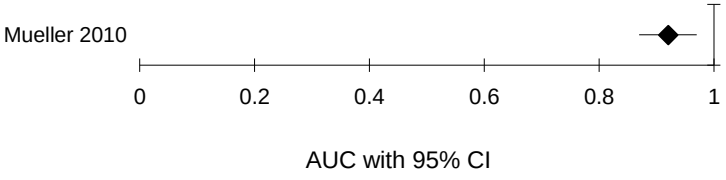


Figure 56: Transient elastography (high threshold)



AUC plots

Figure 57: Transient elastography



K.2.3.4 Combinations of tests

None reported

K.2.4 Primary biliary cholangitis

K.2.4.1 Individual blood tests

None reported

K.2.4.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

None reported

AUC plots

Figure 58: AST/ALT ratio

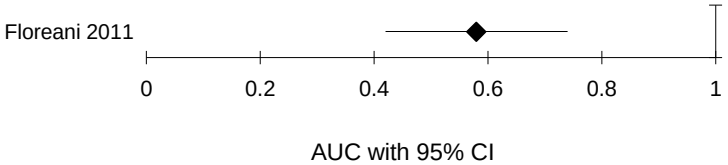


Figure 59: APRI

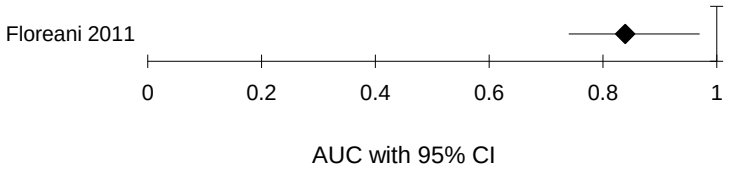
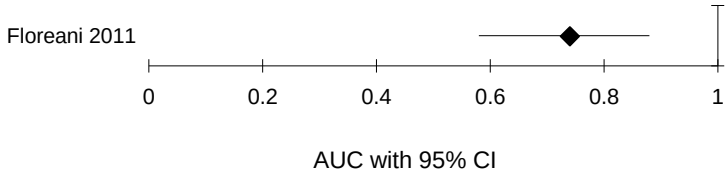


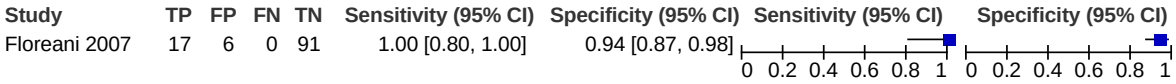
Figure 60: FIB-4



K.2.4.3 Imaging tests

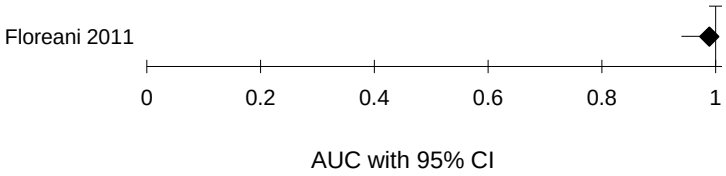
Coupled sensitivity/specificity forest plots

Figure 61: Transient elastography



AUC plots

Figure 62: Transient elastography



K.2.4.4 Combinations of tests

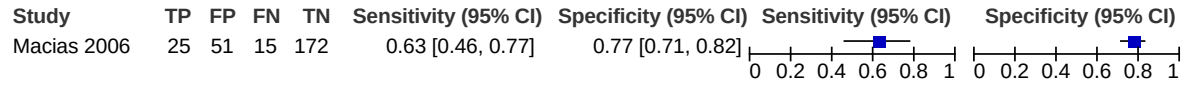
None reported

K.2.5 HIV/HCV

K.2.5.1 Individual blood tests

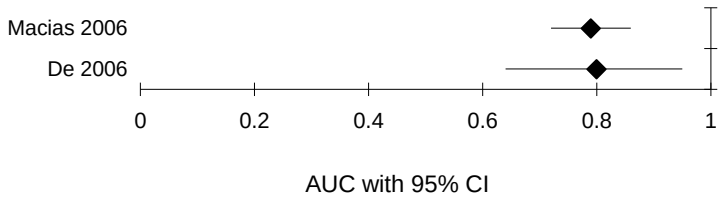
Coupled sensitivity/specificity forest plots

Figure 63: Platelets



AUC plots

Figure 64: Platelets



K.2.5.2 Blood fibrosis tests

Coupled sensitivity/specificity forest plots

Figure 65: AST/ALT ratio

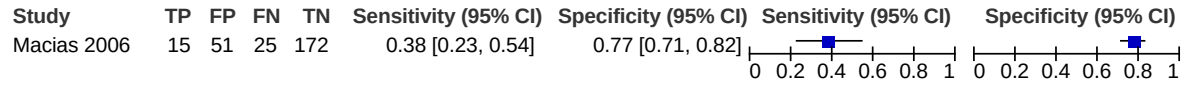


Figure 66: APRI (low threshold)

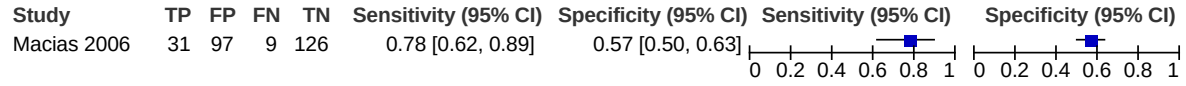
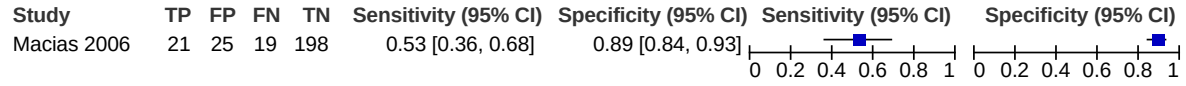


Figure 67: APRI (high threshold)



AUC plots

Figure 68: AST/ALT ratio

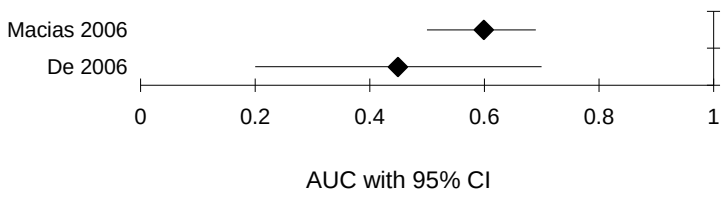


Figure 69: APRI

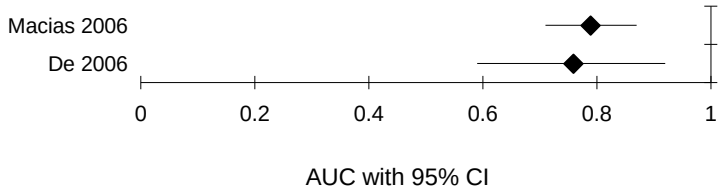
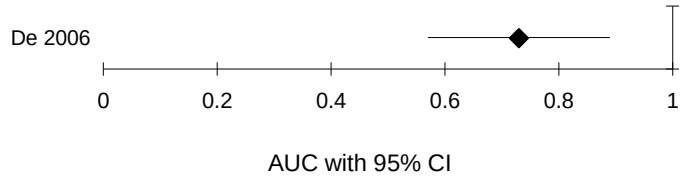


Figure 70: FIB-4



K.2.5.3 Imaging tests

Coupled sensitivity/specificity forest plots

Figure 71: Transient elastography (low threshold)

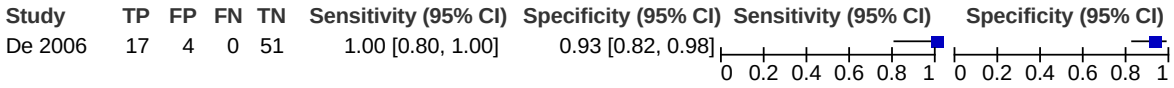
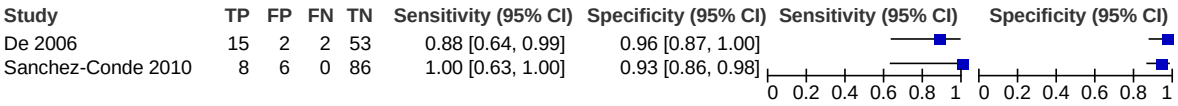
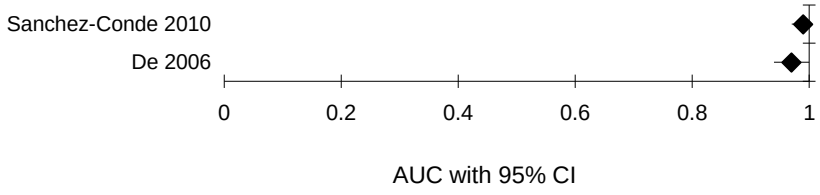


Figure 72: Transient elastography (medium threshold)



AUC plots

Figure 73: Transient elastography



K.2.5.4 Combinations of tests

None reported

K.3 Severity risk tools

K.3.1 Coupled sensitivity/specificity forest plots

Figure 74: Sensitivity and specificity of MELD for predicting 90-day mortality

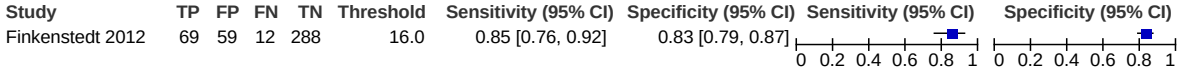


Figure 75: Sensitivity and specificity of transient elastography for predicting death and decompensation

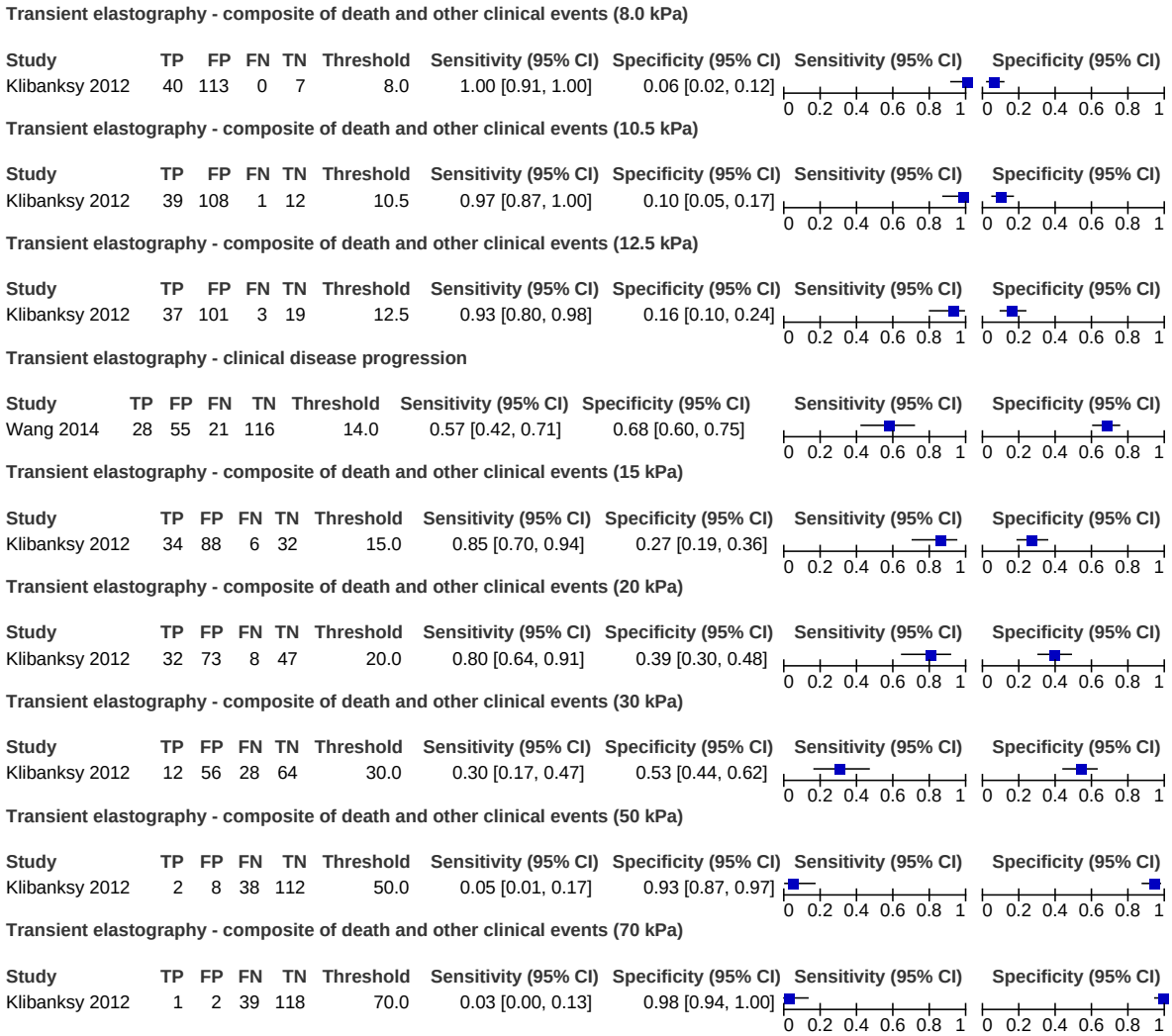


Figure 76: Sensitivity and specificity of transient elastography for predicting decompensation

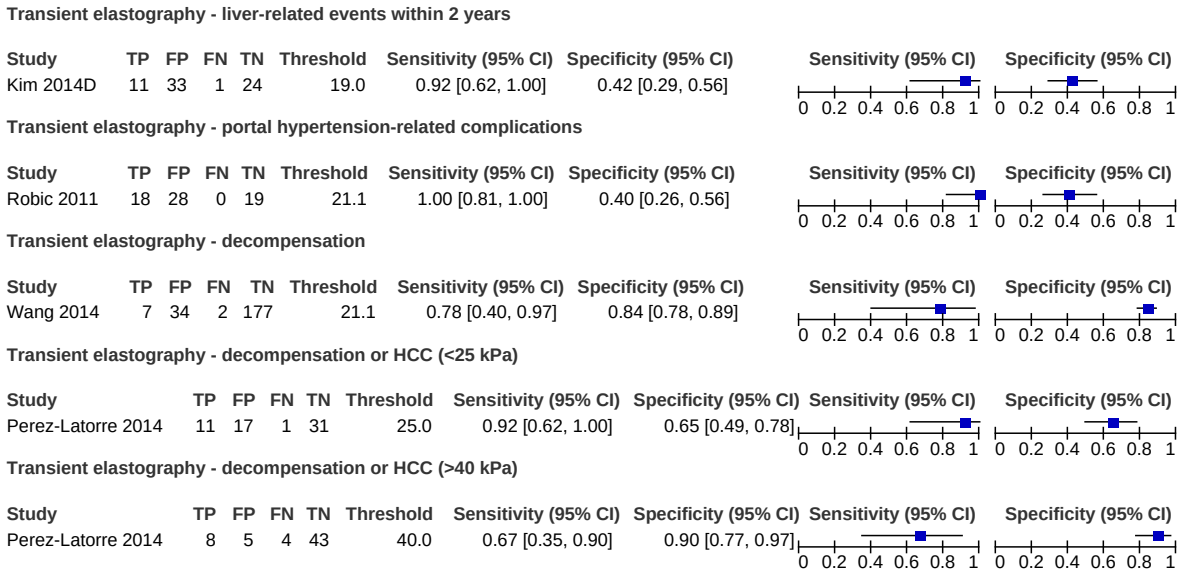


Figure 77: Sensitivity and specificity of transient elastography for predicting HCC

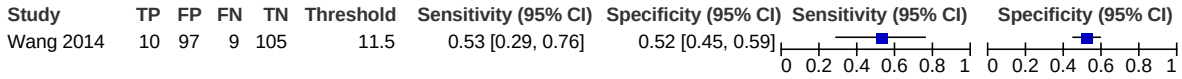


Figure 78: Sensitivity and specificity of transient elastography for predicting portal hypertension progression (hepatic decompensation, varices development and varices growth)

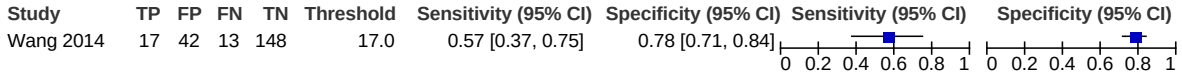
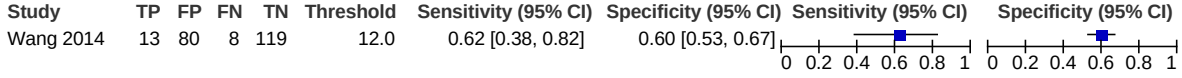


Figure 79: Sensitivity and specificity of transient elastography for predicting varices progression



K.3.2 AUC plots

Figure 80: Accuracy of Child Pugh in predicting 1-year mortality

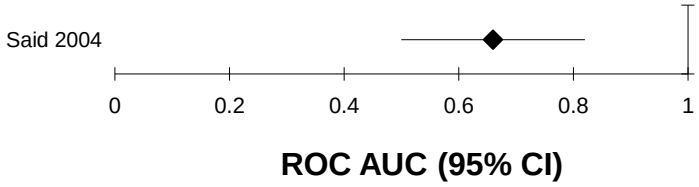


Figure 81: Accuracy of MELD in predicting 1-year mortality

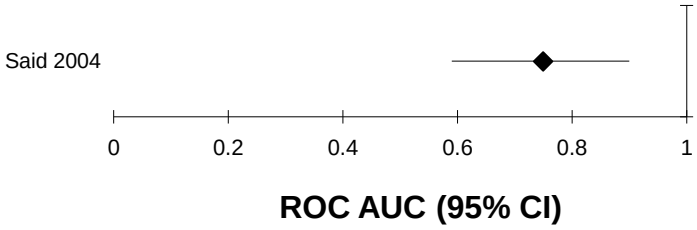


Figure 82: Accuracy of MELD in predicting 90-day mortality

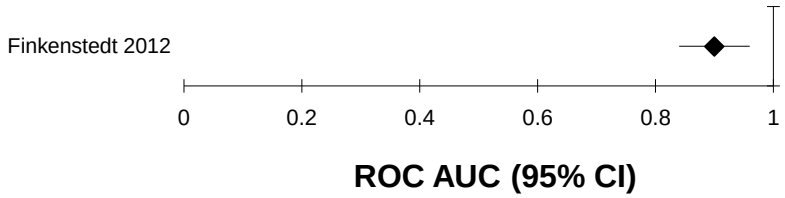


Figure 83: Accuracy of MELD in predicting death and decompensation

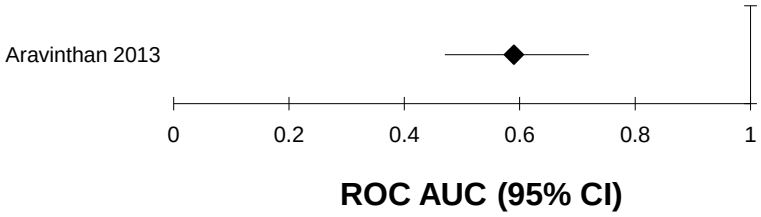


Figure 84: Accuracy of transient elastography in predicting death and decompensation

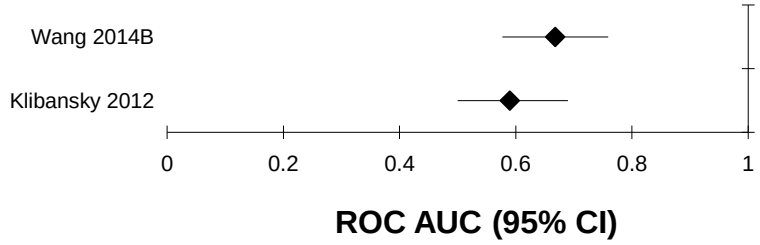
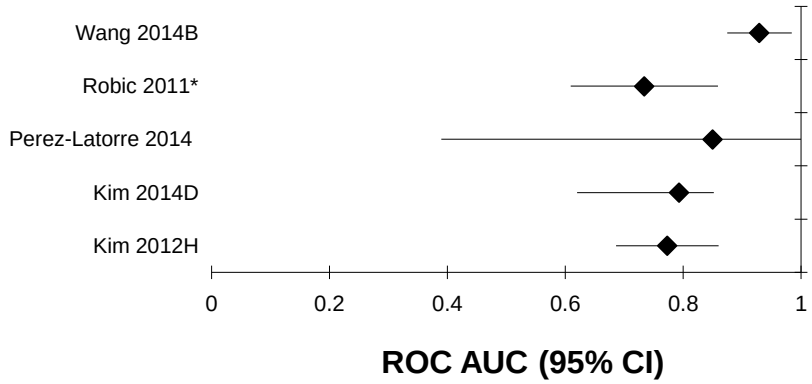


Figure 85: Accuracy of transient elastography in predicting decompensation



**variceal bleeding and/or ascites*

Figure 86: Accuracy of transient elastography in predicting decompensation or HCC

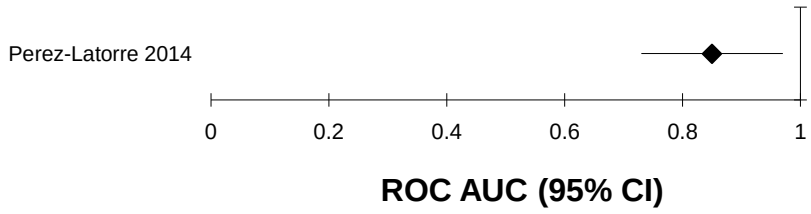


Figure 87: Accuracy of transient elastography in predicting HCC

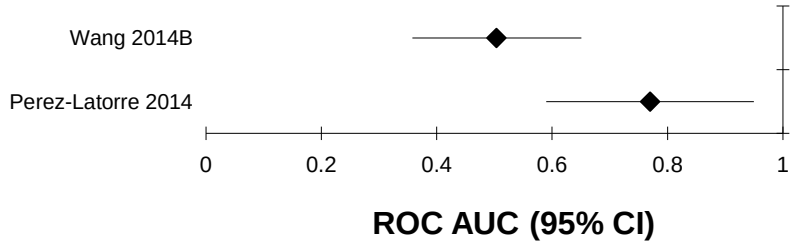


Figure 88: Accuracy of transient elastography in predicting decompensation and varices development

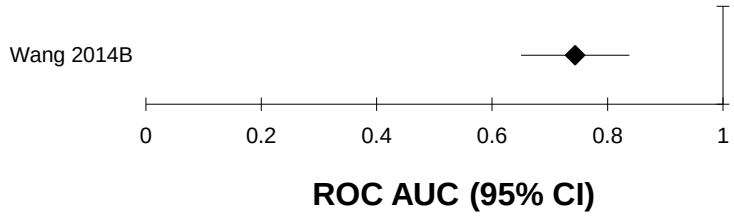
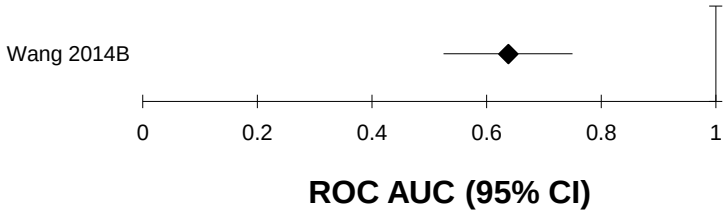


Figure 89: Accuracy of transient elastography in predicting varices progression



K.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

K.4.1 Surveillance versus no surveillance

Figure 90: Survival (adjusted HR >1 indicates an advantage to the surveillance group)

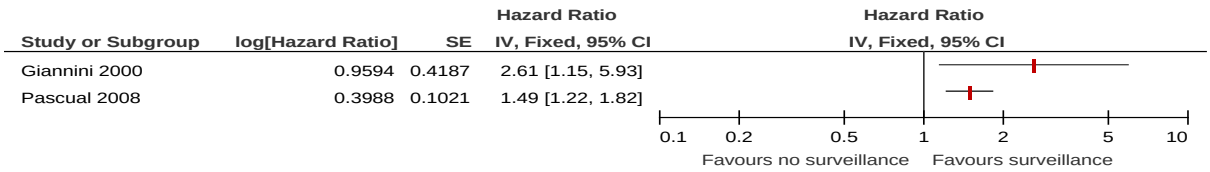


Figure 91: Survival (adjusted OR >1 indicates an advantage to the surveillance group)

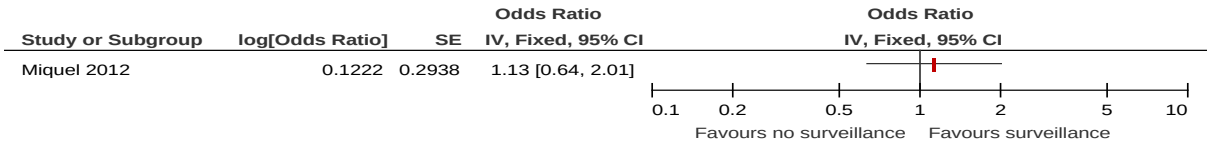


Figure 92: Detection of HCC at a very early stage (single nodule ≤2 cm; OR >1 indicates an advantage to the surveillance group)

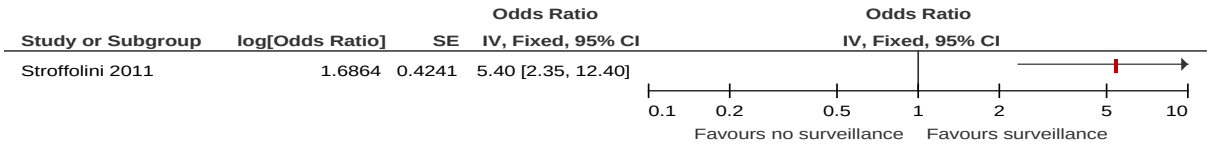


Figure 93: Detection of HCC at a non-advanced stage (single nodule ≤5 cm or 3 nodules each ≤3 cm without vascular and lymphonodal invasion and metastases; OR >1 indicates an advantage to the surveillance group)

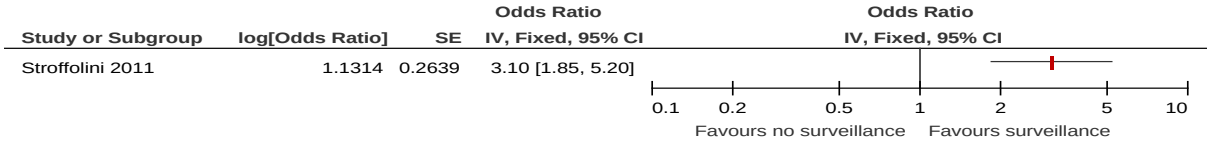
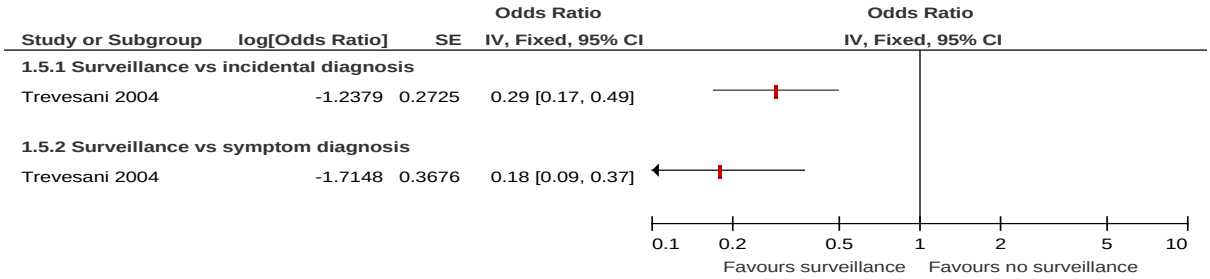


Figure 94: Detection of HCC at an advanced stage (according to Milano criteria; OR <1 indicates an advantage to the surveillance group)



K.4.2 Yearly surveillance versus 6-monthly surveillance

Figure 95: Survival (HR >1 indicates an advantage to the 6-monthly surveillance group)

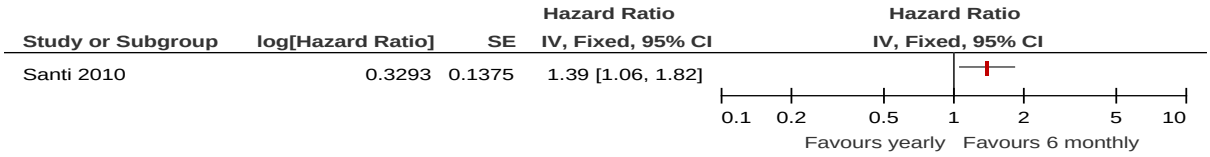
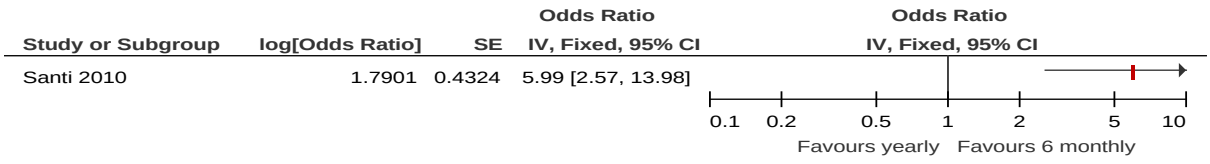


Figure 96: Detection of HCC beyond a very early stage (solitary nodule >2 cm or multinodular tumour with/without vascular invasion and/or metastases; OR >1 indicates an advantage to the 6-monthly surveillance group)



K.4.3 3-monthly surveillance versus 6-monthly surveillance

Figure 97: Survival (HR <1 indicates an advantage to the 3-monthly surveillance group)

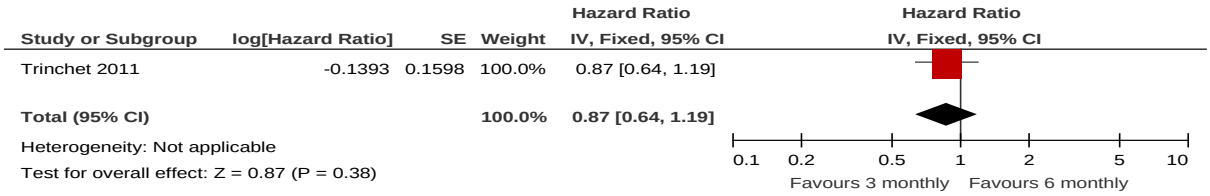


Figure 98: HCC occurrence

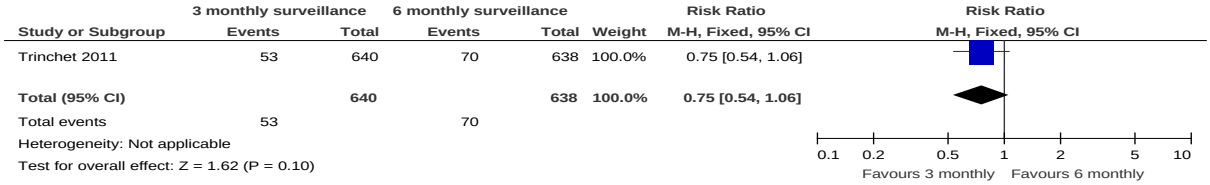


Figure 99: Diameter of the largest HCC nodule ≤30 mm (positive outcome, RR <1 indicates an advantage to the 6-monthly group)

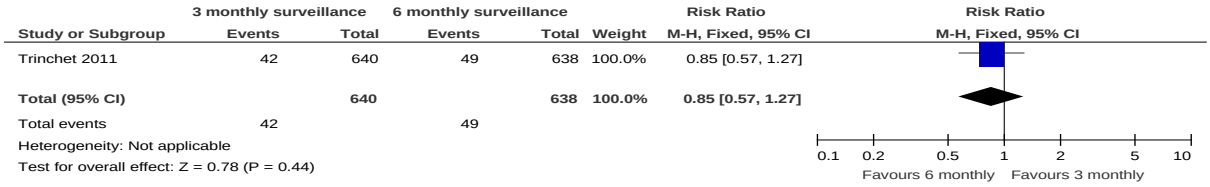


Figure 100: Diameter of the largest HCC nodule >30 mm (negative outcome, RR <1 indicates an advantage to the 3-monthly group)

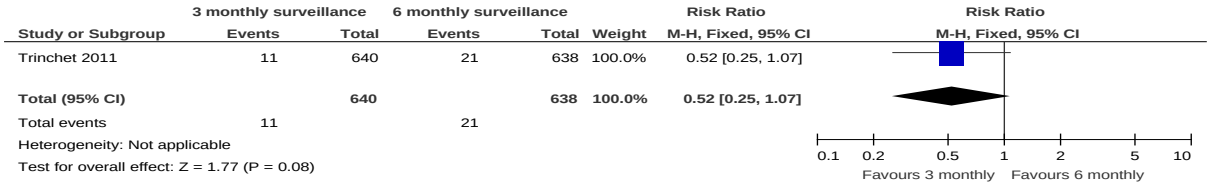


Figure 101: Number of lesions (RR <1 indicates fewer events in the 3-monthly group)

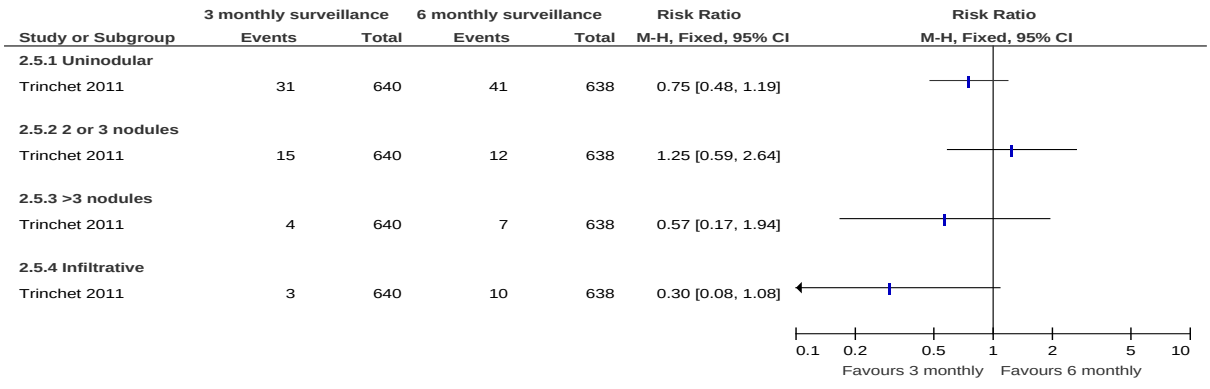


Figure 102: HCC stage (within Milan criteria: 1 nodule ≤50 mm or 2 or 3 nodules ≤30 mm; positive outcome, RR <1 indicates an advantage to the 6-monthly group)

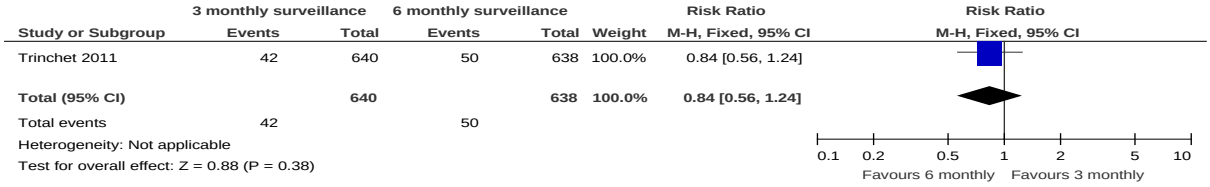


Figure 103: HCC stage (beyond Milan criteria: 1 nodule ≤50 mm or 2 or 3 nodules ≤30 mm; negative outcome, RR <1 indicates an advantage to the 3-monthly group)

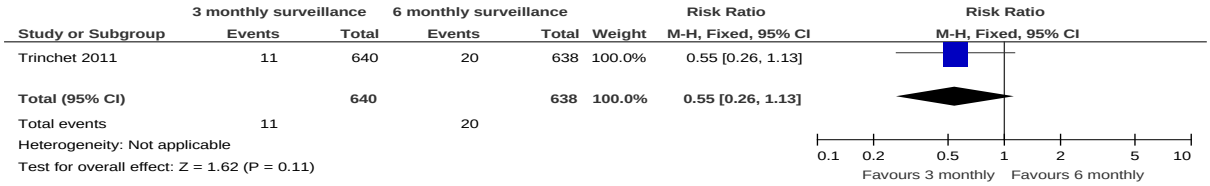
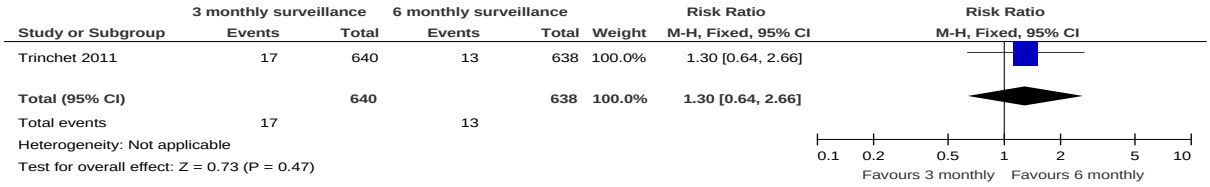


Figure 104: Liver transplant



K.5 Surveillance for the detection of varices

None

K.6 Prophylaxis of variceal haemorrhage

K.6.1 Non-selective beta-blockers versus placebo or no intervention

Size of varices (medium or large)

Figure 105: Survival

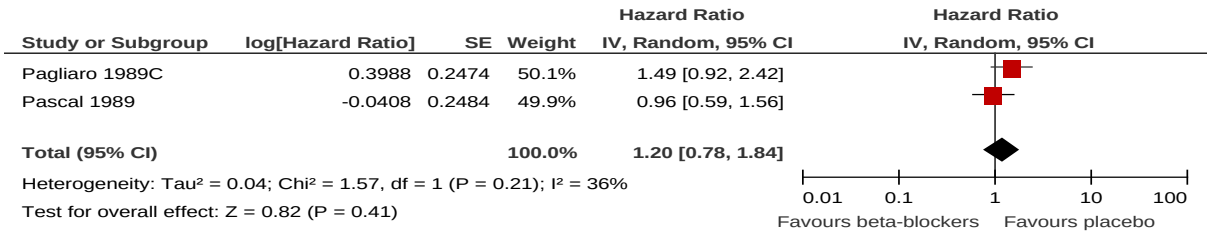


Figure 106: Variceal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andreani 1990	2	28	8	22	34.8%	0.20 [0.05, 0.83]
Conn 1991	0	25	9	22	18.8%	0.05 [0.00, 0.76]
Pagliaro 1989C	13	83	18	88	46.4%	0.77 [0.40, 1.46]
Total (95% CI)		**136**		**132**	**100.0%**	**0.28 [0.06, 1.30]**
Total events	15		35			

Heterogeneity: Tau² = 1.20; Chi² = 6.66, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 1.63 (P = 0.10)

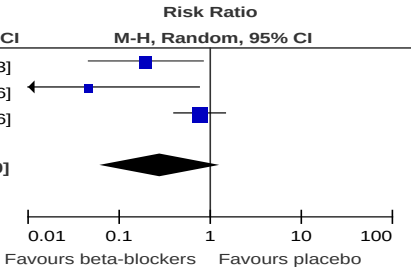


Figure 107: Upper gastrointestinal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andreani 1990	2	28	10	22	15.6%	0.16 [0.04, 0.64]
Pagliaro 1989C	18	83	31	88	41.8%	0.62 [0.37, 1.01]
Pascal 1989	20	116	30	111	42.6%	0.64 [0.39, 1.05]
Total (95% CI)		**227**		**221**	**100.0%**	**0.55 [0.39, 0.78]**
Total events	40		71			

Heterogeneity: Chi² = 3.54, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 3.42 (P = 0.0006)

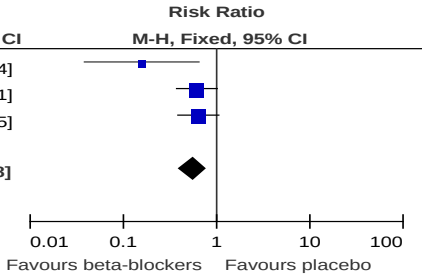
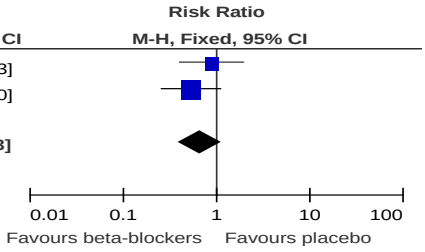


Figure 108: Bleeding-related mortality

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pagliaro 1989C	10	83	12	88	38.8%	0.88 [0.40, 1.93]
Pascal 1989	10	116	18	111	61.2%	0.53 [0.26, 1.10]
Total (95% CI)		**199**		**199**	**100.0%**	**0.67 [0.39, 1.13]**
Total events	20		30			

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



Size of varices (small)

Figure 109: Mortality

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2013	3	77	2	73	100.0%	1.42 [0.24, 8.27]
Total (95% CI)		**77**		**73**	**100.0%**	**1.42 [0.24, 8.27]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

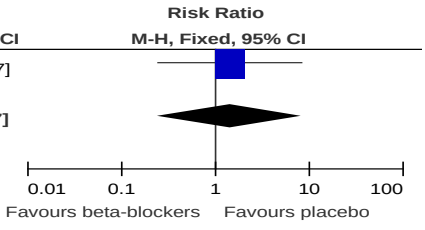


Figure 110: Variceal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andreani 1990	0	15	2	17	20.3%	0.23 [0.01, 4.35]
Conn 1991	2	26	2	29	44.4%	1.12 [0.17, 7.36]
Sarin 2013	4	77	1	73	35.3%	3.79 [0.43, 33.14]
Total (95% CI)		**118**		**119**	**100.0%**	**1.24 [0.31, 5.00]**
Total events	6		5			

Heterogeneity: Tau² = 0.21; Chi² = 2.31, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 0.30 (P = 0.76)

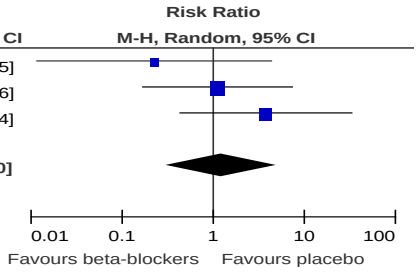
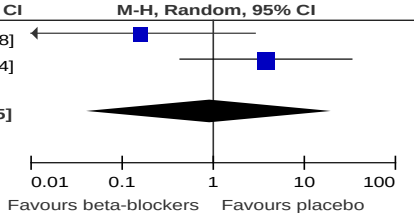


Figure 111: Upper gastrointestinal bleeding

Study or Subgroup	Beta-blockers Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andreani 1990	0	15	3	17	45.3%	0.16 [0.01, 2.88]
Sarin 2013	4	77	1	73	54.7%	3.79 [0.43, 33.14]
Total (95% CI)		**92**		**90**	**100.0%**	**0.90 [0.04, 20.15]**
Total events	4		4			

Heterogeneity: Tau² = 3.36; Chi² = 2.98, df = 1 (P = 0.08); I² = 66%
Test for overall effect: Z = 0.06 (P = 0.95)



K.6.2 Band ligation versus no intervention

Size of varices (medium or large)

Figure 112: Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Lay 1997	-0.8916	0.2729	57.5%	0.41 [0.24, 0.70]
Lo 1999	-0.4155	0.3176	42.5%	0.66 [0.35, 1.23]
Total (95% CI)			**100.0%**	**0.50 [0.33, 0.75]**

Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%
Test for overall effect: Z = 3.33 (P = 0.0009)

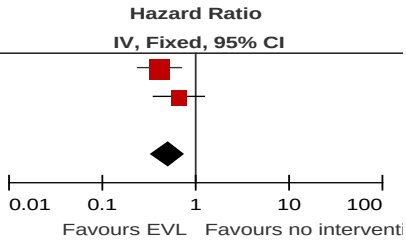


Figure 113: Mortality

Study or Subgroup	EVL Events	Total	no intervention Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 1996	4	35	8	33	29.8%	0.47 [0.16, 1.42]
Svoboda 1999	12	52	19	50	70.2%	0.61 [0.33, 1.12]
Total (95% CI)		**87**		**83**	**100.0%**	**0.57 [0.33, 0.97]**
Total events	16		27			

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

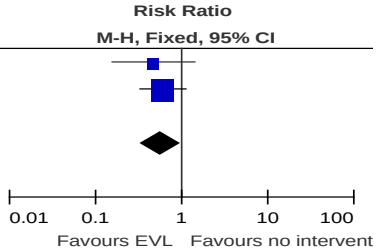


Figure 114: Free from variceal bleeding

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Lay 1997	-1.1087	0.2877	69.1%	0.33 [0.19, 0.58]
Lo 1999	-0.5276	0.4298	30.9%	0.59 [0.25, 1.37]
Total (95% CI)			**100.0%**	**0.39 [0.25, 0.63]**

Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 3.89 (P = 0.0001)

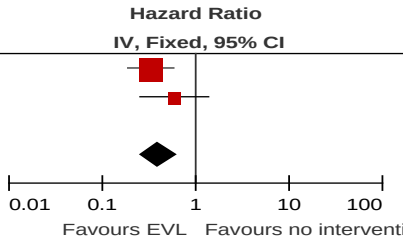


Figure 115: Variceal bleeding

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
Sarin 1996	3	35	13	33	33.1%	0.22 [0.07, 0.70]
Svoboda 1999	15	52	27	50	66.9%	0.53 [0.32, 0.88]
Total (95% CI)		**87**		**83**	**100.0%**	**0.40 [0.17, 0.93]**
Total events	18		40			

Heterogeneity: Tau² = 0.22; Chi² = 2.05, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.13 (P = 0.03)

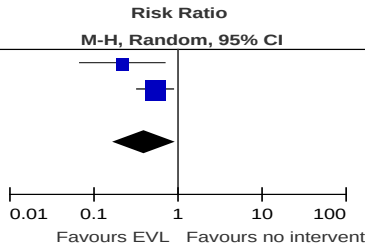


Figure 116: Upper gastrointestinal bleeding

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
Lay 1997	12	62	38	64	26.7%	0.33 [0.19, 0.56]
Lo 1999	14	64	22	63	25.7%	0.63 [0.35, 1.11]
Sarin 1996	3	35	13	33	11.3%	0.22 [0.07, 0.70]
Svoboda 1999	15	52	27	50	28.6%	0.53 [0.32, 0.88]
Triantos 2005	4	11	2	10	7.8%	1.82 [0.42, 7.87]
Total (95% CI)		**224**		**220**	**100.0%**	**0.49 [0.31, 0.76]**
Total events	48		102			

Heterogeneity: Tau² = 0.12; Chi² = 7.94, df = 4 (P = 0.09); I² = 50%
Test for overall effect: Z = 3.13 (P = 0.002)

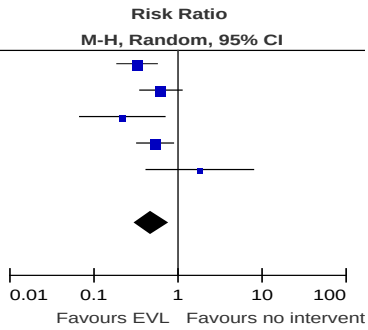
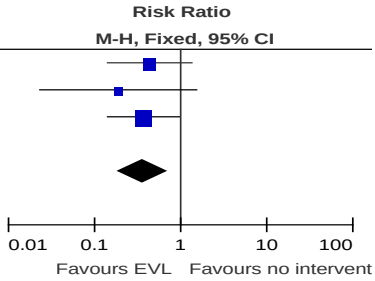


Figure 117: Bleeding-related mortality

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lo 1999	4	64	9	63	33.0%	0.44 [0.14, 1.35]
Sarin 1996	1	35	5	33	18.7%	0.19 [0.02, 1.53]
Svoboda 1999	5	52	13	50	48.2%	0.37 [0.14, 0.96]
Total (95% CI)		**151**		**146**	**100.0%**	**0.36 [0.18, 0.71]**
Total events	10		27			

Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.94 (P = 0.003)

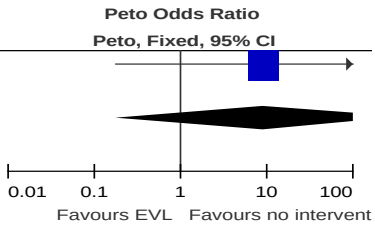


Size of varices (small)

Figure 118: Upper gastrointestinal bleeding

Study or Subgroup	EVL Events	EVL Total	no intervention Events	no intervention Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Triantos 2005	1	14	0	17	100.0%	9.15 [0.18, 469.98]
Total (95% CI)		**14**		**17**	**100.0%**	**9.15 [0.18, 469.98]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



K.6.3 Band ligation versus non-selective beta-blockers

Size of varices (medium or large)

Figure 119: Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Drastich 2005	-0.2107	1.0017	1.7%	0.81 [0.11, 5.77]
Lui 2002	0.0862	0.3941	11.3%	1.09 [0.50, 2.36]
Perez 2010	0.392	0.3537	14.0%	1.48 [0.74, 2.96]
Psilopoulos 2005	-0.2357	0.4302	9.5%	0.79 [0.34, 1.84]
Schepke 2004	0.2151	0.2431	29.6%	1.24 [0.77, 2.00]
Shah 2014	-0.4308	0.3945	11.2%	0.65 [0.30, 1.41]
Tripathi 2009	-0.1054	0.2774	22.7%	0.90 [0.52, 1.55]
Total (95% CI)			**100.0%**	**1.03 [0.80, 1.34]**

Heterogeneity: Chi² = 3.69, df = 6 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

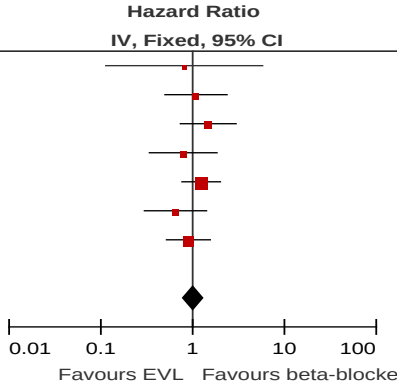


Figure 120: Mortality

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelfattah 2006	4	51	5	52	6.9%	0.82 [0.23, 2.87]
Abulfutuh 2003	13	44	24	66	26.7%	0.81 [0.47, 1.42]
Chen 1998	3	26	3	30	3.9%	1.15 [0.25, 5.23]
Gheorghe 2002	1	25	5	28	6.6%	0.22 [0.03, 1.79]
Jutabha 2005	0	31	4	31	6.3%	0.11 [0.01, 1.98]
Lay 2006	14	50	12	50	16.7%	1.17 [0.60, 2.27]
Mora 2000	0	12	1	12	2.1%	0.33 [0.01, 7.45]
Norberto 2007	3	31	3	31	4.2%	1.00 [0.22, 4.58]
Sarin 1999	5	46	5	44	7.1%	0.96 [0.30, 3.08]
Singh 2012	2	18	3	20	4.0%	0.74 [0.14, 3.94]
Song 2000	5	31	8	30	11.3%	0.60 [0.22, 1.64]
Thuluvath 2005	6	16	3	15	4.3%	1.88 [0.57, 6.19]
Total (95% CI)		**381**		**409**	**100.0%**	**0.83 [0.61, 1.13]**
Total events	56		76			

Heterogeneity: Chi² = 7.24, df = 11 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)

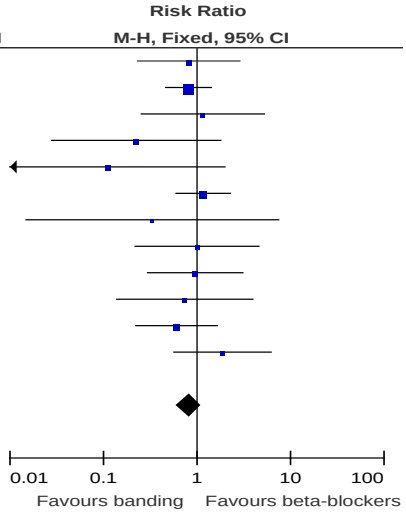


Figure 121: Free from variceal bleeding

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Drastich 2005	-0.4463	1.0063	7.9%	0.64 [0.09, 4.60]
Lui 2002	-0.7765	0.5928	14.4%	0.46 [0.14, 1.47]
Psilopoulos 2005	-1.5606	0.7701	11.1%	0.21 [0.05, 0.95]
Sarin 1999	-1.1087	0.4323	18.2%	0.33 [0.14, 0.77]
Schepke 2004	0.0488	0.3132	21.1%	1.05 [0.57, 1.94]
Shah 2014	-0.462	0.9033	9.1%	0.63 [0.11, 3.70]
Tripathi 2009	0.8755	0.4277	18.3%	2.40 [1.04, 5.55]
Total (95% CI)			**100.0%**	**0.68 [0.35, 1.31]**

Heterogeneity: Tau² = 0.45; Chi² = 15.55, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 1.16 (P = 0.25)

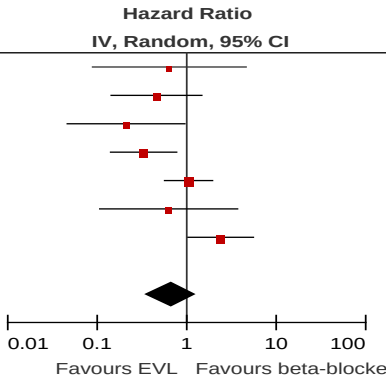


Figure 122: Variceal bleeding

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 1998	1	26	2	30	3.8%	0.58 [0.06, 6.00]
De 1999	2	15	1	15	2.0%	2.00 [0.20, 19.78]
Gheorghe 2002	3	25	13	28	25.0%	0.26 [0.08, 0.80]
Jutabha 2005	0	31	4	31	9.2%	0.11 [0.01, 1.98]
Lay 2006	5	50	8	50	16.3%	0.63 [0.22, 1.78]
Mora 2000	1	12	2	12	4.1%	0.50 [0.05, 4.81]
Norberto 2007	2	31	3	31	6.1%	0.67 [0.12, 3.72]
Perez 2010	2	39	9	36	19.1%	0.21 [0.05, 0.89]
Song 2000	3	31	6	30	12.4%	0.48 [0.13, 1.76]
Thuluvath 2005	2	16	1	15	2.1%	1.88 [0.19, 18.60]
Total (95% CI)		**276**		**278**	**100.0%**	**0.44 [0.27, 0.71]**
Total events	21		49			

Heterogeneity: Chi² = 6.72, df = 9 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)

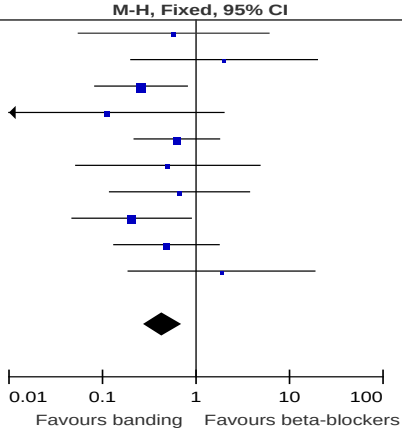


Figure 123: Upper gastrointestinal bleeding

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdelfattah 2006	4	51	13	52	5.5%	0.31 [0.11, 0.90]
Abulfutuh 2003	4	44	10	66	5.1%	0.60 [0.20, 1.79]
Chen 1998	1	26	2	30	1.3%	0.58 [0.06, 6.00]
De 1999	2	15	2	15	2.0%	1.00 [0.16, 6.20]
Drastich 2005	2	40	2	33	1.9%	0.82 [0.12, 5.54]
Gheorghe 2002	3	25	13	28	4.8%	0.26 [0.08, 0.80]
Jutabha 2005	0	31	4	31	0.8%	0.11 [0.01, 1.98]
Lay 2006	11	50	12	50	10.2%	0.92 [0.45, 1.88]
Lui 2002	3	44	9	66	4.1%	0.50 [0.14, 1.74]
Mora 2000	1	12	2	12	1.3%	0.50 [0.05, 4.81]
Norberto 2007	5	31	4	31	4.3%	1.25 [0.37, 4.22]
Perez 2010	5	39	9	36	6.1%	0.51 [0.19, 1.39]
Psilopoulos 2005	4	30	9	30	5.4%	0.44 [0.15, 1.29]
Sarin 1999	4	46	12	44	5.5%	0.32 [0.11, 0.91]
Schepke 2004	19	75	22	77	15.5%	0.89 [0.52, 1.50]
Shah 2014	6	86	7	82	5.6%	0.82 [0.29, 2.33]
Singh 2012	3	18	5	20	3.9%	0.67 [0.19, 2.40]
Song 2000	6	31	7	30	6.4%	0.83 [0.32, 2.18]
Thuluvath 2005	2	16	1	15	1.3%	1.88 [0.19, 18.60]
Tripathi 2009	17	75	8	77	9.0%	2.18 [1.00, 4.75]
Total (95% CI)		**785**		**825**	**100.0%**	**0.71 [0.54, 0.92]**
Total events	102		153			

Heterogeneity: Tau² = 0.05; Chi² = 21.96, df = 19 (P = 0.29); I² = 13%
Test for overall effect: Z = 2.56 (P = 0.01)

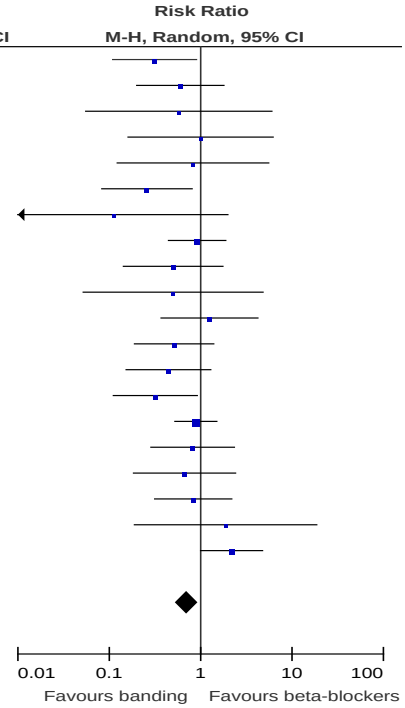


Figure 124: Bleeding-related mortality

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 1998	0	26	0	30		Not estimable
De 1999	0	15	0	15		Not estimable
Drastich 2005	1	40	1	33	2.7%	0.82 [0.05, 12.69]
Jutabha 2005	0	31	2	31	6.2%	0.20 [0.01, 4.00]
Lay 2006	1	50	2	50	5.0%	0.50 [0.05, 5.34]
Lui 2002	1	44	4	66	7.9%	0.38 [0.04, 3.24]
Norberto 2007	1	31	2	31	5.0%	0.50 [0.05, 5.23]
Perez 2010	2	39	3	36	7.7%	0.62 [0.11, 3.47]
Psilopoulos 2005	0	30	2	30	6.2%	0.20 [0.01, 4.00]
Sarin 1999	3	45	4	44	10.0%	0.73 [0.17, 3.09]
Schepke 2004	9	75	8	77	19.6%	1.16 [0.47, 2.83]
Shah 2014	4	86	4	82	10.2%	0.95 [0.25, 3.69]
Singh 2012	1	18	2	20	4.7%	0.56 [0.05, 5.62]
Thuluvath 2005	0	16	0	15		Not estimable
Tripathi 2009	3	75	6	77	14.7%	0.51 [0.13, 1.98]
Total (95% CI)		**621**		**637**	**100.0%**	**0.67 [0.42, 1.08]**
Total events	26		40			

Heterogeneity: Chi² = 3.54, df = 11 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

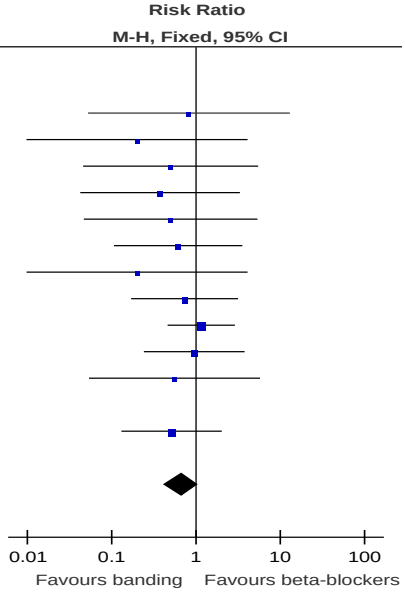


Figure 125: Hospitalisation

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 1999	5	45	12	44	100.0%	0.41 [0.16, 1.06]
Total (95% CI)		**45**		**44**	**100.0%**	**0.41 [0.16, 1.06]**
Total events	5		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

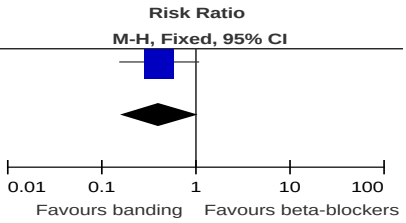
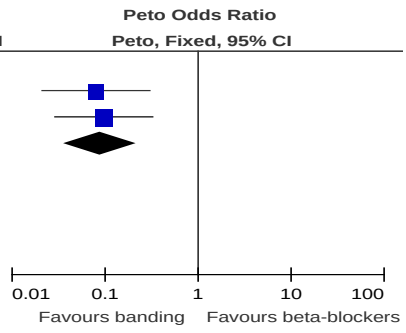


Figure 126: Adverse events: fatigue

Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.14.9 Lethargy						
Drastich 2005	0	40	10	33	45.2%	0.08 [0.02, 0.30]
Sarin 1999	0	46	12	44	54.8%	0.10 [0.03, 0.32]
Subtotal (95% CI)		**86**		**77**	**100.0%**	**0.09 [0.04, 0.22]**
Total events	0		22			

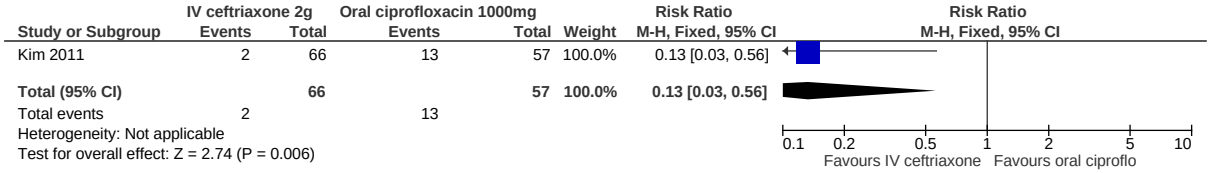
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 5.30 (P < 0.00001)



K.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

K.7.1 IV ceftriaxone 2 g versus oral ciprofloxacin 500 mg twice daily

Figure 127: Bacterial infections



K.7.2 IV ceftriaxone 1 g versus oral norfloxacin 400 mg twice daily

Figure 128: Bacterial infections

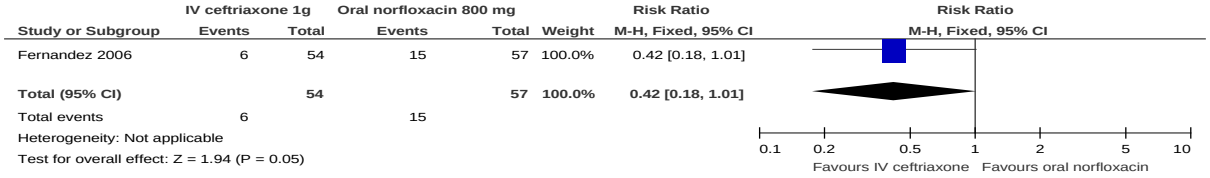
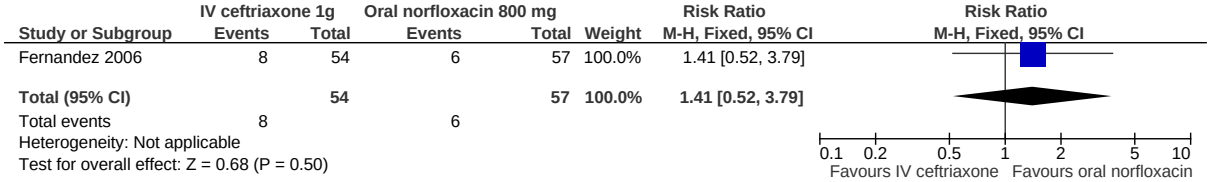
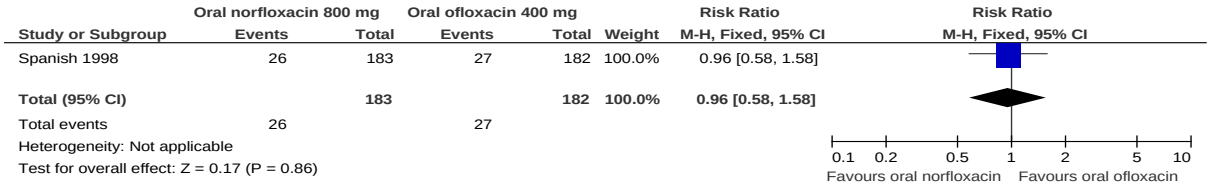


Figure 129: All-cause mortality (dichotomous)



K.7.3 Oral norfloxacin 800 mg versus oral ofloxacin 400 mg

Figure 130: Bacterial infections



K.7.4 Oral norfloxacin 800 mg and IV ceftriaxone 2 g (combination) versus oral norfloxacin 800 mg (monotherapy)

Figure 131: Bacterial infections

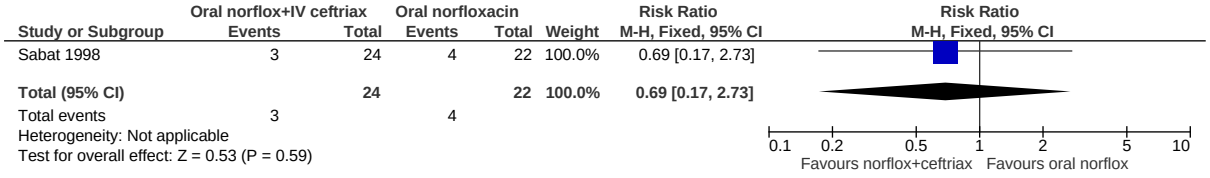


Figure 132: All-cause mortality (dichotomous)

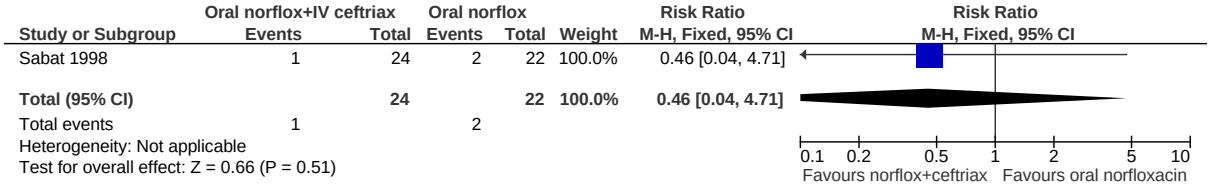
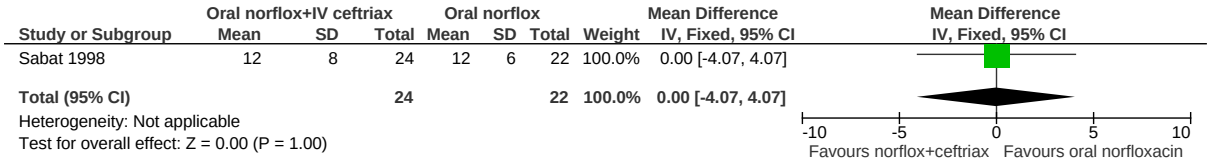
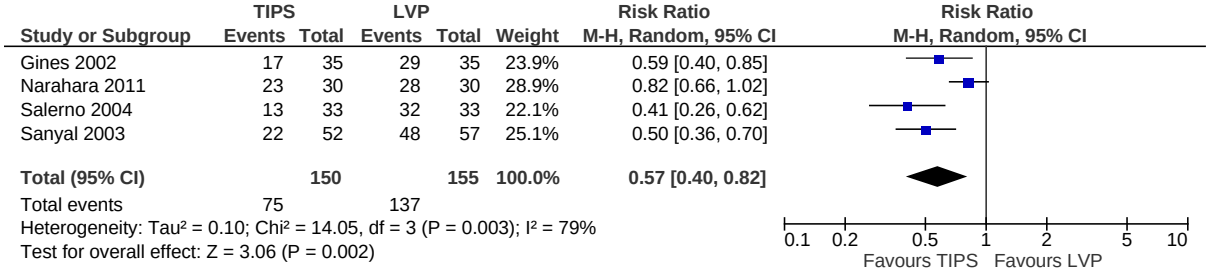


Figure 133: Length of hospital stay (days)



K.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Figure 134: Re-accumulation of ascites



Note: One study (Narahara 2011) defined complete response as the elimination of ascites – therefore the number of people that did not have a complete response were calculated as having recurrence of ascites

Figure 135: Health-related quality of life: SF-36 – physical and mental component

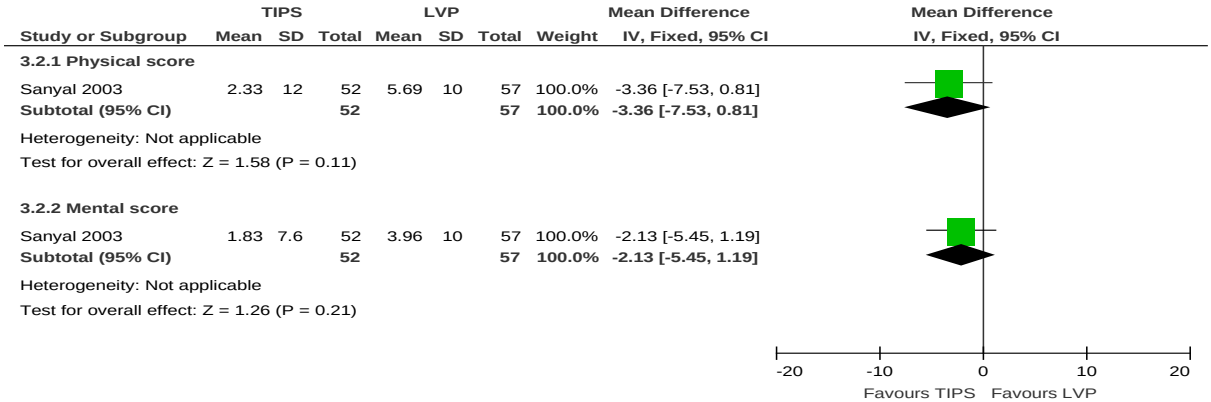
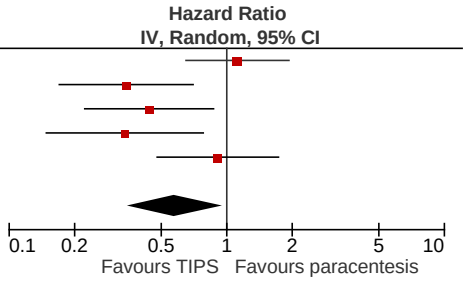


Figure 136: Transplant-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Gines 2002	0.1133	0.2777	22.9%	1.12 [0.65, 1.93]
Narahara 2011	-1.0642	0.3611	19.4%	0.35 [0.17, 0.70]
Rössle 2000	-0.821	0.3478	19.9%	0.44 [0.22, 0.87]
Salerno 2004	-1.0788	0.4237	17.0%	0.34 [0.15, 0.78]
Sanyal 2003	-0.0943	0.3278	20.8%	0.91 [0.48, 1.73]
Total (95% CI)			**100.0%**	**0.58 [0.35, 0.96]**

Heterogeneity: Tau² = 0.22; Chi² = 11.52, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 2.10 (P = 0.04)



Note: One study reported overall survival but no patients had transplantation (Narahara 2011)

Figure 137: Spontaneous bacterial peritonitis

Study or Subgroup	TIPS Events	TIPS Total	LVP Events	LVP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gines 2002	2	35	4	35	67.7%	0.50 [0.10, 2.56]
Sanyal 2003	4	52	2	57	32.3%	2.19 [0.42, 11.48]
Total (95% CI)		**87**		**92**	**100.0%**	**1.05 [0.35, 3.10]**
Total events	6		6			

Heterogeneity: Chi² = 1.55, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.08 (P = 0.93)

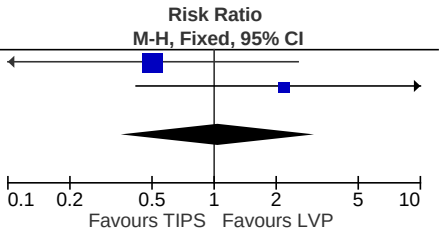


Figure 138: Renal failure

Study or Subgroup	TIPS Events	TIPS Total	LVP Events	LVP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gines 2002	9	35	17	35	89.9%	0.53 [0.27, 1.02]
Sanyal 2003	3	52	2	57	10.1%	1.64 [0.29, 9.45]
Total (95% CI)		**87**		**92**	**100.0%**	**0.64 [0.35, 1.18]**
Total events	12		19			

Heterogeneity: Chi² = 1.44, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 1.43 (P = 0.15)

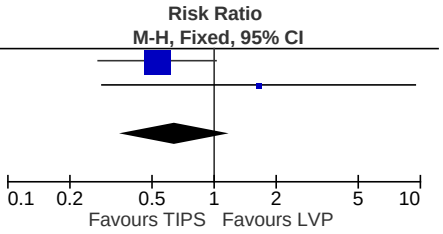
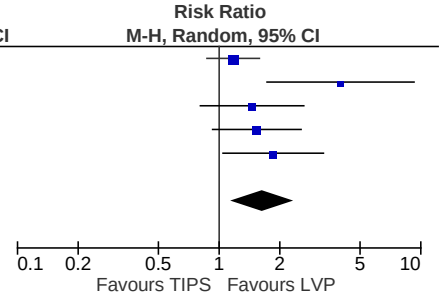


Figure 139: Hepatic encephalopathy

Study or Subgroup	TIPS Events	TIPS Total	LVP Events	LVP Total	Weight	Risk Ratio M-H, Random, 95% CI
Gines 2002	27	35	23	35	28.9%	1.17 [0.87, 1.58]
Narahara 2011	20	30	5	30	12.3%	4.00 [1.73, 9.26]
Rössle 2000	15	29	11	31	18.5%	1.46 [0.81, 2.63]
Salerno 2004	20	33	13	33	21.3%	1.54 [0.93, 2.55]
Sanyal 2003	22	52	13	57	19.0%	1.86 [1.05, 3.29]
Total (95% CI)		**179**		**186**	**100.0%**	**1.64 [1.14, 2.36]**
Total events	104		65			

Heterogeneity: Tau² = 0.10; Chi² = 9.61, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 2.67 (P = 0.007)



Hepatic encephalopathy (HE) was an exclusion criteria in all studies, however some studies reported new cases of hepatic encephalopathy, some worsening cases of hepatic encephalopathy and some relapse of hepatic encephalopathy

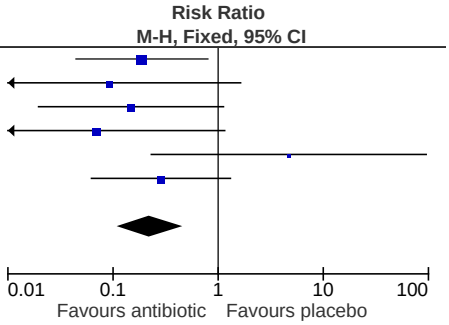
K.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

K.9.1 SBP

Figure 140: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez 2007	2	35	10	33	27.4%	0.19 [0.04, 0.80]
Grange 1998	0	53	5	54	14.5%	0.09 [0.01, 1.63]
Rolachon 1995	1	26	7	27	18.3%	0.15 [0.02, 1.12]
Soriano 1991	0	29	7	30	19.7%	0.07 [0.00, 1.15]
Tellez-Avila 2014	2	49	0	46	1.4%	4.70 [0.23, 95.36]
Terg 2008	2	50	7	50	18.7%	0.29 [0.06, 1.31]
Total (95% CI)		**242**		**240**	**100.0%**	**0.22 [0.11, 0.46]**
Total events	7		36			

Heterogeneity: Chi² = 5.28, df = 5 (P = 0.38); I² = 5%
Test for overall effect: Z = 4.04 (P < 0.0001)

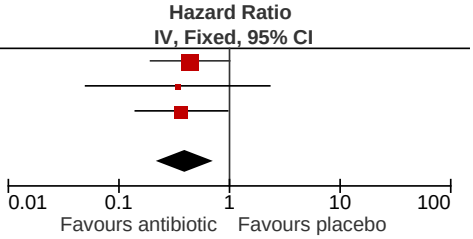


K.9.2 All-cause mortality (time-to-event)

Figure 141: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Fernandez 2007	-0.82	0.42	52.1%	0.44 [0.19, 1.00]
Tellez-Avila 2014	-1.0788	0.978	9.6%	0.34 [0.05, 2.31]
Terg 2008	-1	0.49	38.3%	0.37 [0.14, 0.96]
Total (95% CI)			**100.0%**	**0.40 [0.22, 0.73]**

Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.01 (P = 0.003)

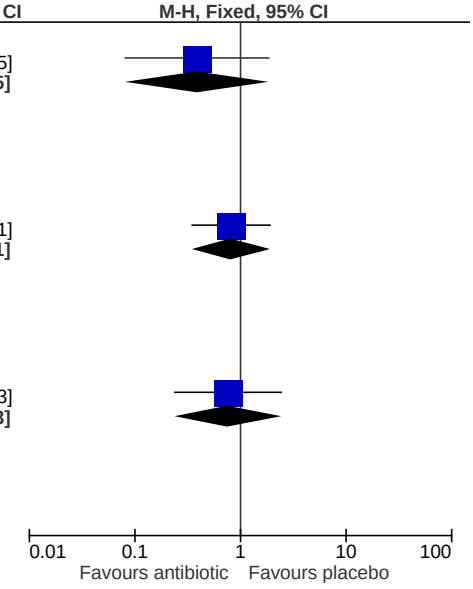


K.9.3 All-cause mortality (dichotomous)

Figure 142: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Mortality at ~1 month follow-up						
Soriano 1991	2	32	5	31	100.0%	0.39 [0.08, 1.85]
Subtotal (95% CI)		**32**		**31**	**100.0%**	**0.39 [0.08, 1.85]**
Total events	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.23)						
1.4.2 Mortality at ~4 months' follow-up						
Grange 1998	8	53	10	54	100.0%	0.82 [0.35, 1.91]
Subtotal (95% CI)		**53**		**54**	**100.0%**	**0.82 [0.35, 1.91]**
Total events	8		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.4.3 Mortality at 6 months' follow-up						
Rolachon 1995	4	28	6	32	100.0%	0.76 [0.24, 2.43]
Subtotal (95% CI)		**28**		**32**	**100.0%**	**0.76 [0.24, 2.43]**
Total events	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						

Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%

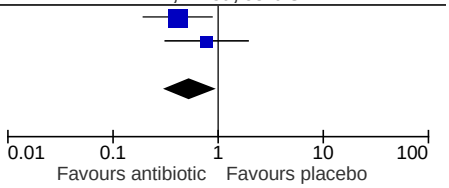


K.9.4 Adverse event: Renal failure

Figure 143: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez 2007	7	35	16	33	64.7%	0.41 [0.19, 0.87]
Terg 2008	7	50	9	50	35.3%	0.78 [0.31, 1.93]
Total (95% CI)		**85**		**83**	**100.0%**	**0.54 [0.31, 0.96]**
Total events	14		25			

Heterogeneity: Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 2.10 (P = 0.04)

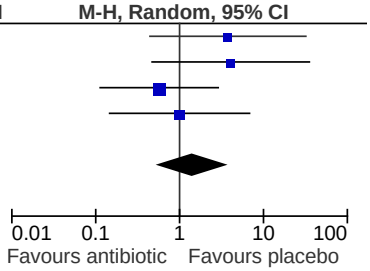


K.9.5 Adverse event: Liver failure

Figure 144: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Fernandez 2007	4	35	1	33	20.3%	3.77 [0.44, 32.03]
Grange 1998	4	53	1	54	19.9%	4.08 [0.47, 35.28]
Rolachon 1995	2	28	4	32	34.7%	0.57 [0.11, 2.89]
Terg 2008	2	50	2	50	25.0%	1.00 [0.15, 6.82]
Total (95% CI)		**166**		**169**	**100.0%**	**1.43 [0.54, 3.79]**
Total events	12		8			

Heterogeneity: Tau² = 0.03; Chi² = 3.09, df = 3 (P = 0.38); I² = 3%
Test for overall effect: Z = 0.71 (P = 0.48)

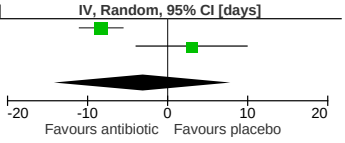


K.9.6 Length of hospital stay

Figure 145: Antibiotic prophylaxis versus placebo in people with cirrhosis and ascites

Study or Subgroup	Antibiotic Mean [days]	Antibiotic SD [days]	Antibiotic Total	Placebo Mean [days]	Placebo SD [days]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [days]
Rolachon 1995	9.3	4.5	28	17.6	6.2	32	54.1%	-8.30 [-11.02, -5.58]
Soriano 1991	27	15	32	24	13	31	45.9%	3.00 [-3.92, 9.92]
Total (95% CI)			**60**			**63**	**100.0%**	**-3.12 [-14.15, 7.92]**

Heterogeneity: Tau² = 56.64; Chi² = 8.86, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.55 (P = 0.58)



K.10 Volume replacers in hepatorenal syndrome

None

K.11 Management of an episode of acute hepatic encephalopathy

K.11.1 Non-absorbable disaccharides versus single therapy

K.11.1.1 Non-absorbable disaccharides versus neomycin

Figure 146: Mortality

Study or Subgroup	Non-absorb disaccharides Events	Non-absorb disaccharides Total	Neomycin Events	Neomycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Uribe 1981	1	8	1	10	100.0%	1.25 [0.09, 17.02]
Total (95% CI)		**8**		**10**	**100.0%**	**1.25 [0.09, 17.02]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)

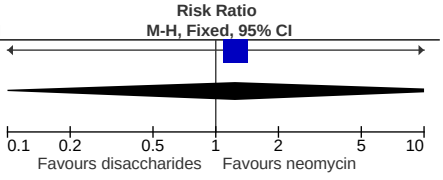


Figure 147: Clinical-biochemical improvement (improvement of 1 grade in mental state (Conn's grading 0–4), a reduction of 30 s in time taken to perform the NCT and ammonia reduction of 50ug%)

Study or Subgroup	Non-absorb disaccharides Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Uribe 1981	7	8	7	10	100.0%	1.25 [0.77, 2.03]
Total (95% CI)		**8**		**10**	**100.0%**	**1.25 [0.77, 2.03]**
Total events	7		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.37)

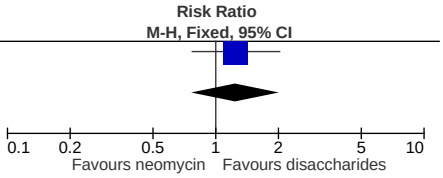
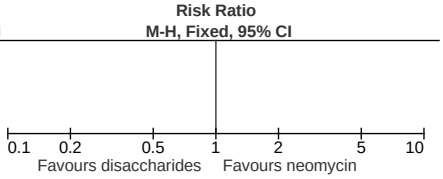


Figure 148: Side effects

Study or Subgroup	Non-absorb disaccharides Events	Total	Neomycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Uribe 1981	0	8	0	10		Not estimable
Total (95% CI)		**8**		**10**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



K.11.1.2 Non-absorbable disaccharides versus Rifaximin

Figure 149: Mortality (considered unrelated to medication; at 28 days)

Study or Subgroup	Non-absorb disacchrides Events	Total	Rifaximin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mas 2003	2	53	1	50	100.0%	1.89 [0.18, 20.17]
Total (95% CI)		**53**		**50**	**100.0%**	**1.89 [0.18, 20.17]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

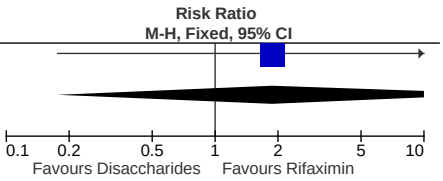


Figure 150: Unchanged/failure (hepatic encephalopathy clinical syndrome not improved and blood ammonia levels not decreased/increase in blood ammonia, increase in PSE index and/or a shift to a higher stage of hepatic encephalopathy)

Study or Subgroup	Non-absorb disacchrides Events	Total	Rifaximin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mas 2003	10	53	9	50	100.0%	1.05 [0.46, 2.36]
Total (95% CI)		**53**		**50**	**100.0%**	**1.05 [0.46, 2.36]**
Total events	10		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

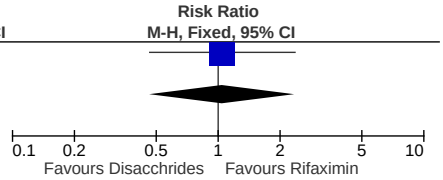


Figure 151: Improvement in hepatic encephalopathy grade (at 7 days)

Study or Subgroup	Non-absorb disacchrides Events	Total	Rifaximin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Paik 2005	16	22	26	32	100.0%	0.90 [0.66, 1.21]
Total (95% CI)		**22**		**32**	**100.0%**	**0.90 [0.66, 1.21]**
Total events	16		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

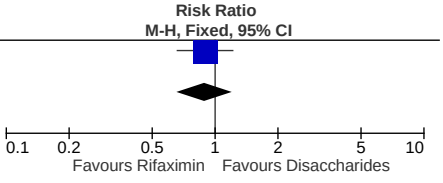


Figure 152: Improvement in hepatic encephalopathy index (taking into account hepatic encephalopathy grade, NCT, blood ammonia and severity of flapping tremor; at 7 days)

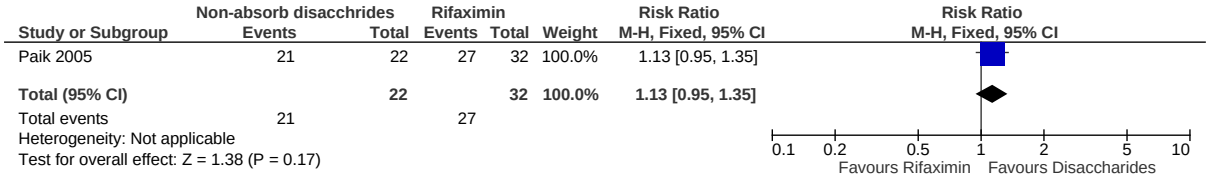
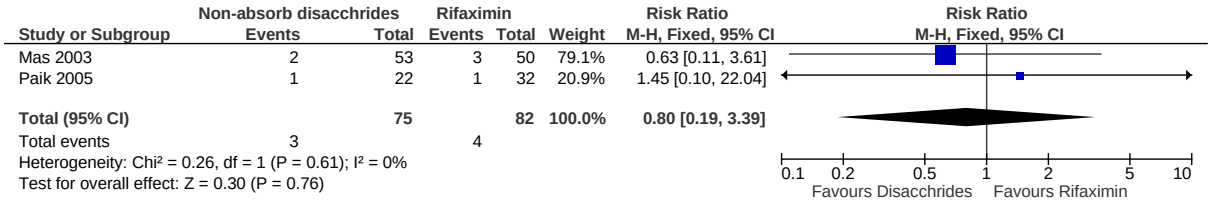


Figure 153: Adverse events



K.11.1.3 Non-absorbable disaccharides versus BCAA

Figure 154: Mortality (up to 10 days after mental recovery)

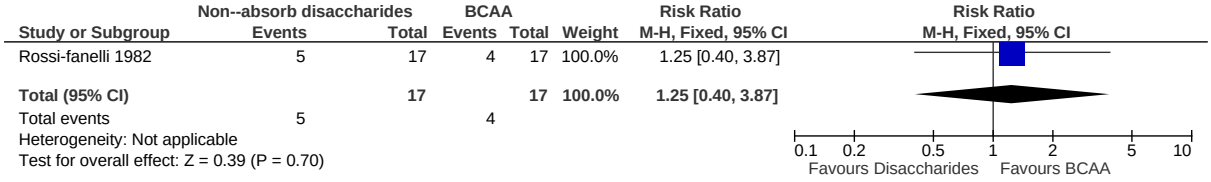


Figure 155: Complete mental recovery (study 1 defines as consciousness regained and returned to grade 0 hepatic encephalopathy; study 2 defines as come out of coma by day 7)

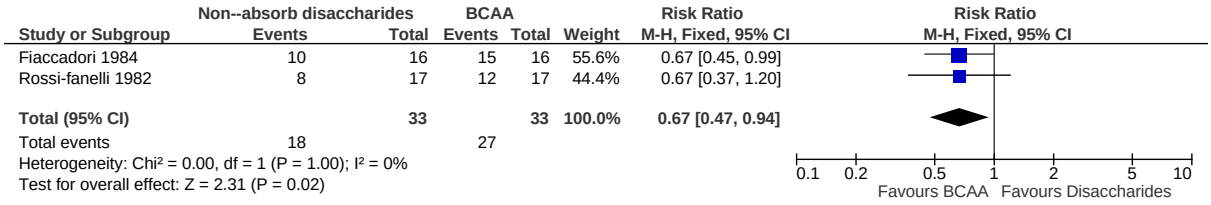
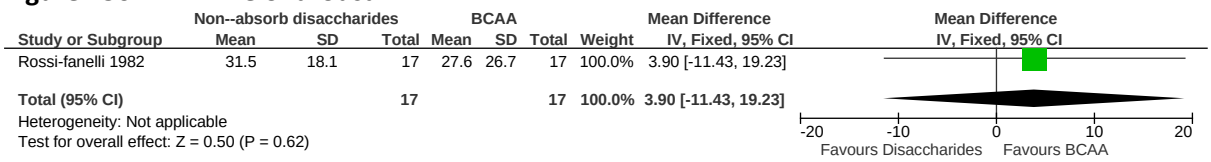


Figure 156: Time of arousal



K.11.1.4 Non-absorbable disaccharides versus PEG 3350

Figure 157: Mortality (at 24 hours)

Study or Subgroup	Non-absorb disaccharide Events	Total	PEG 3350 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rahimi 2014	2	25	1	25	100.0%	2.00 [0.19, 20.67]
Total (95% CI)		**25**		**25**	**100.0%**	**2.00 [0.19, 20.67]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

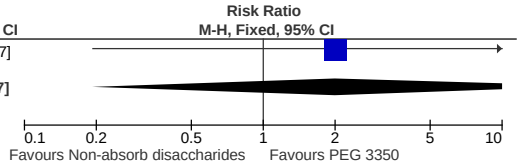


Figure 158: Hepatic encephalopathy resolution (defined as an improvement to grade 0, or two days at grade 1 after an initial improvement of at least 1 grade)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Rahimi 2014	-0.5621	0.3108	100.0%	0.57 [0.31, 1.05]
Total (95% CI)			**100.0%**	**0.57 [0.31, 1.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)

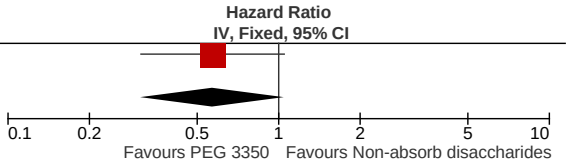


Figure 159: Improvement of 1 or more in hepatic encephalopathy grade (hepatic encephalopathy SA score; at 24 hours)

Study or Subgroup	Non-absorb disaccharides Events	Total	PEG 3350 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rahimi 2014	13	25	21	23	100.0%	0.57 [0.38, 0.85]
Total (95% CI)		**25**		**23**	**100.0%**	**0.57 [0.38, 0.85]**
Total events	13		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.78 (P = 0.005)

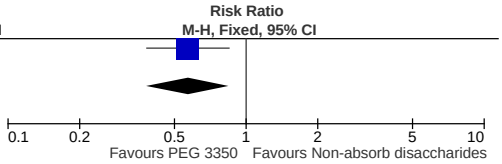


Figure 160: Length of hospital stay (days)

Study or Subgroup	Non-absorb disaccharides Mean	SD	Total	PEG 3350 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rahimi 2014	8	12	25	4	3	25	100.0%	4.00 [-0.85, 8.85]
Total (95% CI)			**25**			**25**	**100.0%**	**4.00 [-0.85, 8.85]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.11)

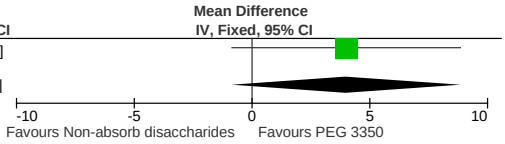
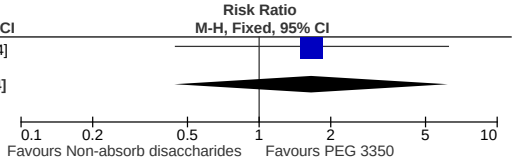


Figure 161: Adverse events (at 24 hours)

Study or Subgroup	Non-absorb disaccharides Events	Total	PEG 3350 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rahimi 2014	5	25	3	25	100.0%	1.67 [0.45, 6.24]
Total (95% CI)		**25**		**25**	**100.0%**	**1.67 [0.45, 6.24]**
Total events	5		3			

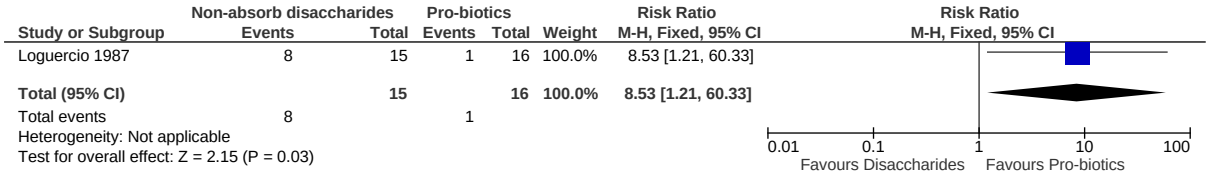
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)



K.11.1.5 Non-absorbable disaccharides versus probiotics

Figure 162: Improvement in hepatic encephalopathy symptoms (at day 10)

Figure 163: Adverse events (at 20 days)



K.11.1.6 Non-absorbable disaccharides versus sodium benzoate

Figure 164: Mortality

Figure 165: Complete response (recovery to normal mental status with no evidence of asterixis)

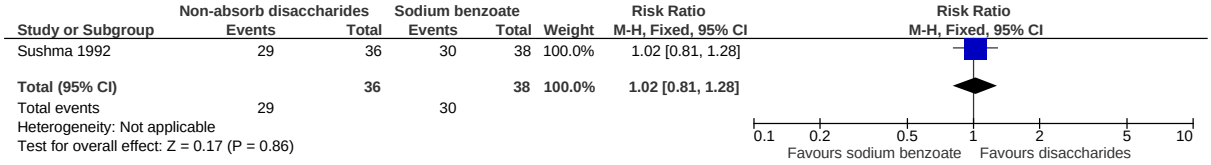


Figure 166: Continued in grade 1+ mental status despite therapy for 21 days

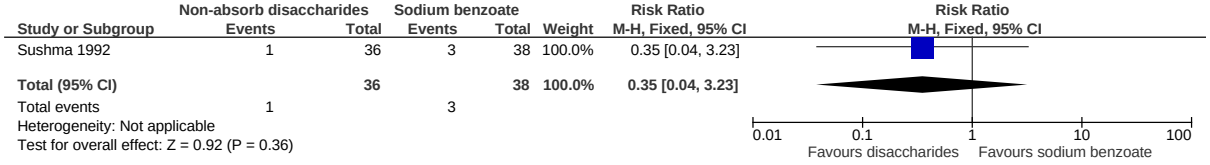
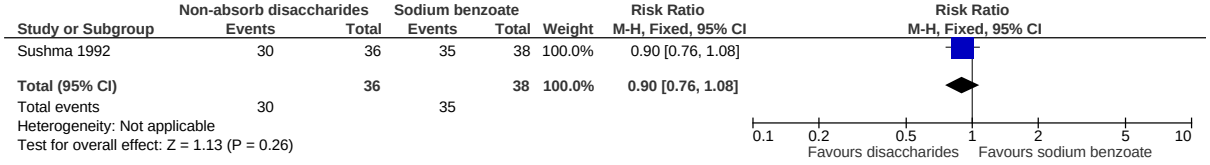


Figure 167: Complications during treatment



K.11.2 Combination therapy (1 intervention + non-absorbable disaccharides) versus non-absorbable disaccharides

K.11.2.1 Rifaximin + non-absorbable disaccharides versus non-absorbable disaccharides

Figure 168: Mortality

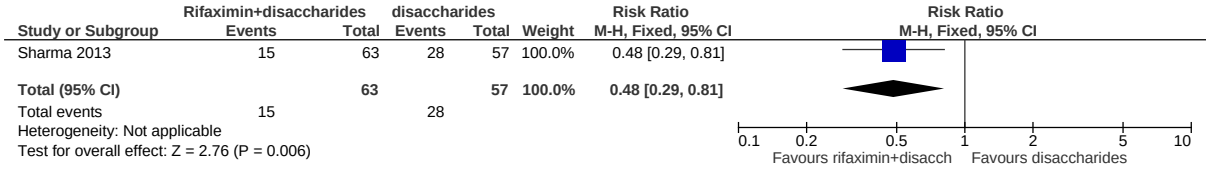


Figure 169: Complete reversal of hepatic encephalopathy (according to West Haven criteria; at 10 days)

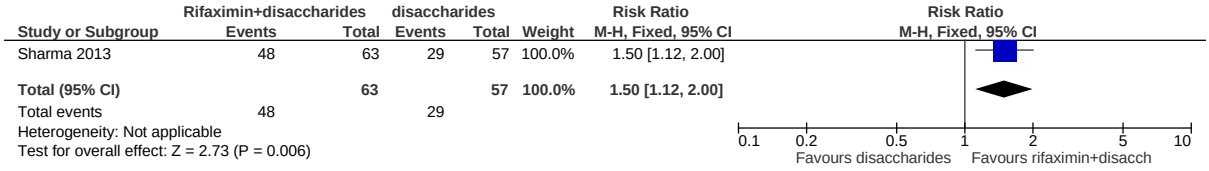


Figure 170: Length of hospital stay

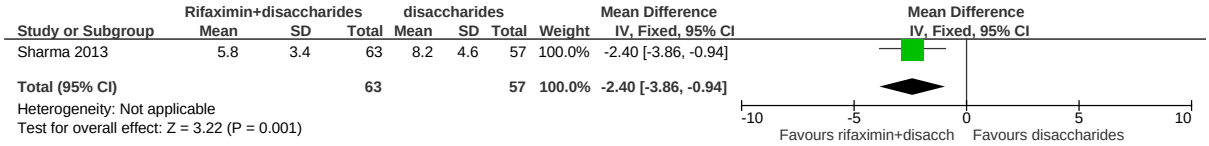
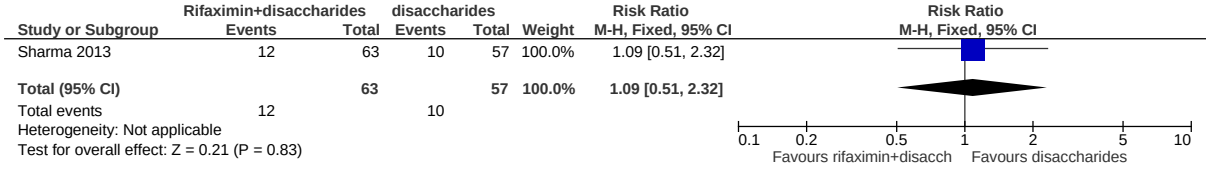


Figure 171: Side effects related to study medications



K.11.2.2 BCAA + non-absorbable disaccharides versus non-absorbable disaccharides

Figure 172: Mortality (at 16 days)

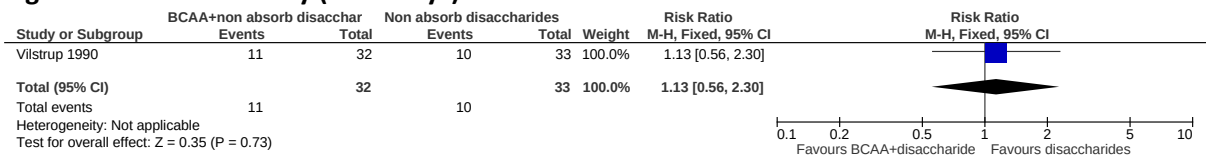


Figure 173: Wake up (study 1 defines as woke up to hepatic encephalopathy grade 0 or I by Fogarty classification at 16 days; study 2 defines as came out of coma by day 7)

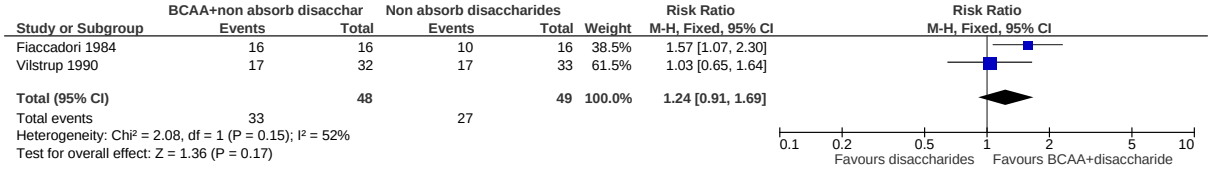
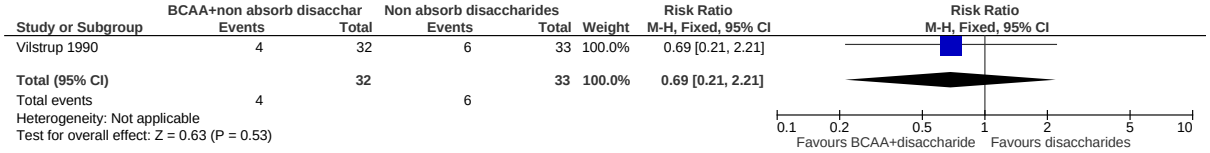


Figure 174: Treatment failures other than death (hepatic encephalopathy deeper than grade I by Fogarty classification despite other improvements; at 16 days)



K.11.2.3 Flumazenil + non-absorbable disaccharides versus non-absorbable disaccharides

Figure 175: Mortality (during the observation period, 3 hour treatment + 5 hour observation)

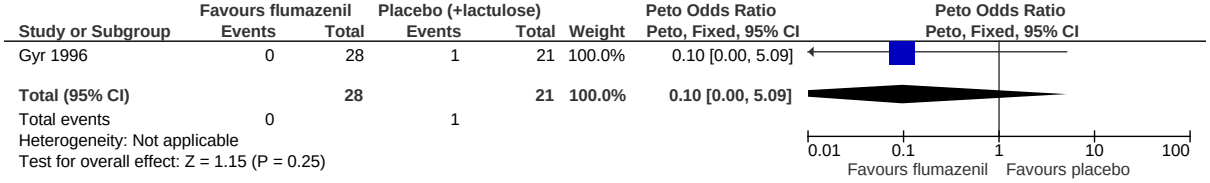


Figure 176: Clinically relevant response (improvement of at least 2 points in PSE score, PSE score on a 0–16 scale, at 8 hours)

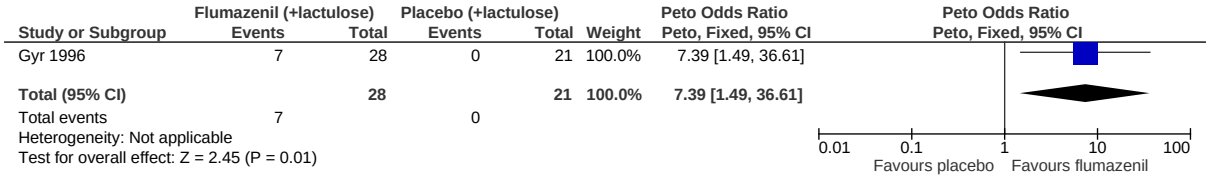
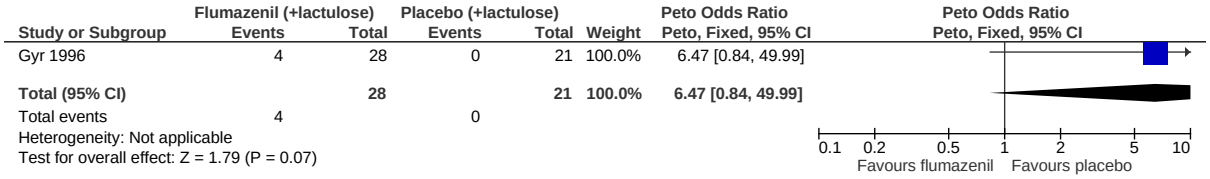


Figure 177: Adverse events (at 8 hours) – flushing, nausea and vomiting, nausea and irritability



K.11.3 Combination therapy (2 interventions + non-absorbable disaccharides) versus combination therapy (1 intervention + non-absorbable disaccharides)

K.11.3.1 Flumazenil + BCAA + non-absorbable disaccharides versus BCAA + non-absorbable disaccharides

Figure 178: Mortality at 24 hours

Study or Subgroup	Flumazanil (+lactulose+BCAA) Events	Total	Placebo (+lactulose+BCAA) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laccetti 2000	6	28	5	26	100.0%	1.11 [0.39, 3.22]
Total (95% CI)		**28**		**26**	**100.0%**	**1.11 [0.39, 3.22]**
Total events	6		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)

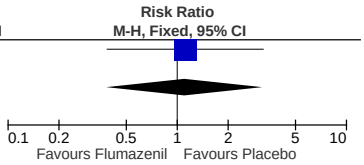


Figure 179: Improvement in neurological status (increase in Glasgow coma score by 3 points; at 24 hours

Study or Subgroup	Flumazanil (+lactulose+BCAA) Events	Total	Placebo (+lactulose+BCAA) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laccetti 2000	22	28	14	26	100.0%	1.46 [0.97, 2.19]
Total (95% CI)		**28**		**26**	**100.0%**	**1.46 [0.97, 2.19]**
Total events	22		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.83 (P = 0.07)

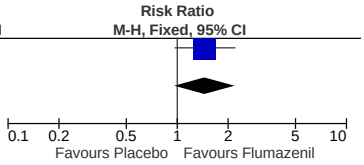
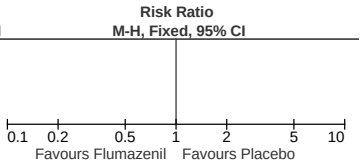


Figure 180: Side effects (at 24 hours)

Study or Subgroup	Flumazanil (+lactulose+BCAA) Events	Total	Placebo (+lactulose+BCAA) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laccetti 2000	0	28	0	26		Not estimable
Total (95% CI)		**28**		**26**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



K.11.3.2 LOLA + metronidazole + non-absorbable disaccharides versus metronidazole + non-absorbable disaccharides

Figure 181: Mortality during inpatient stay

Study or Subgroup	LOLA+lactulose+metronidaz Events	Total	lactulose+metronidazole Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abid 2011	4	60	7	60	63.6%	0.57 [0.18, 1.85]
Ahmed 2008	2	40	4	40	36.4%	0.50 [0.10, 2.58]
Total (95% CI)		**100**		**100**	**100.0%**	**0.55 [0.21, 1.42]**
Total events	6		11			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)

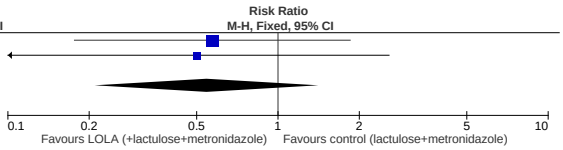


Figure 182: Complete improvement defined as improvement of 2 grades from baseline (day 3)

Study or Subgroup	LOLA+lactulose+metronidaz Events	Total	lactulose+metronidazole Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abid 2011	45	54	25	54	100.0%	1.80 [1.32, 2.46]
Total (95% CI)		**54**		**54**	**100.0%**	**1.80 [1.32, 2.46]**
Total events	45		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.70 (P = 0.0002)

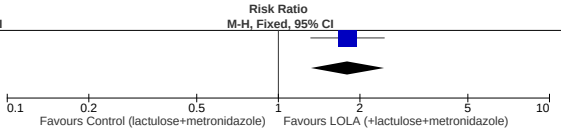


Figure 183: Achieved hepatic encephalopathy grade 0 (at 5 days)

Study or Subgroup	LOLA+lactulose+metronidaz Events	Total	lactulose+metronidazole Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmed 2008	37	40	31	40	100.0%	1.19 [0.99, 1.44]
Total (95% CI)		**40**		**40**	**100.0%**	**1.19 [0.99, 1.44]**
Total events	37		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

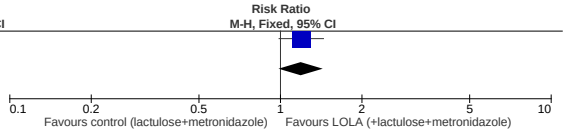
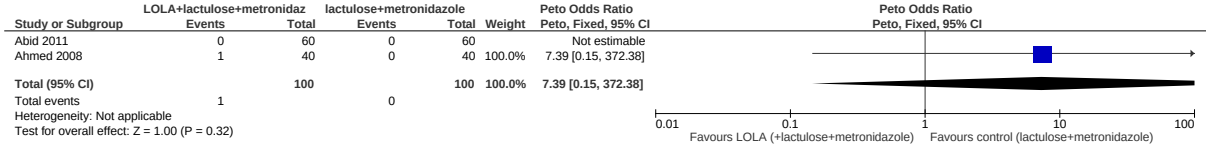


Figure 184: Adverse events



K.11.4 Single therapy versus placebo

K.11.4.1 Non-absorbable disaccharides versus placebo

Figure 185: Mortality (variable follow-up time and response dependent)

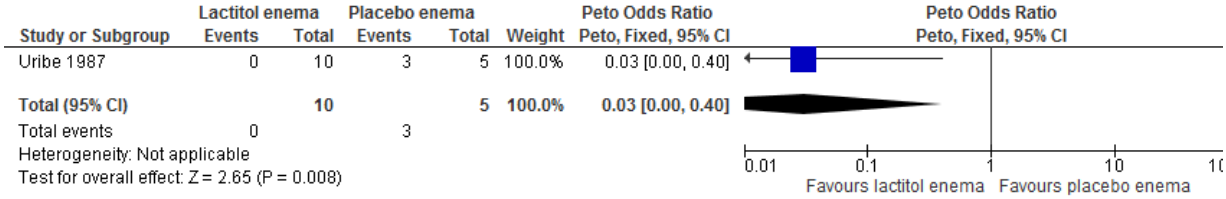
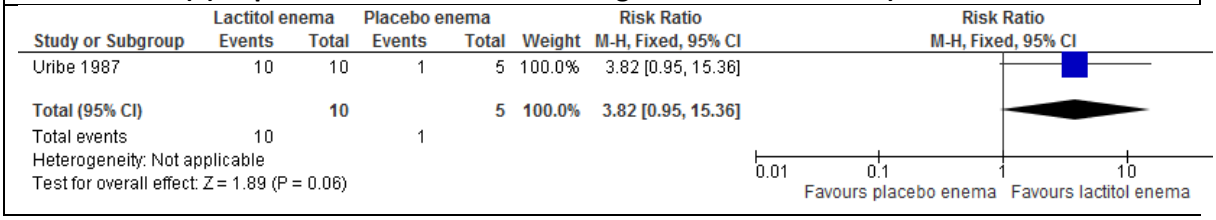


Figure 186: Therapeutic response (variable follow-up time and response dependent; defined as (i) sustained improvement of one grade in mental state during ≤48 hours or (ii) improvement of more than two grades in mental state)



K.11.4.2 BCAA versus placebo

Figure 187: Mortality (at 5 days)

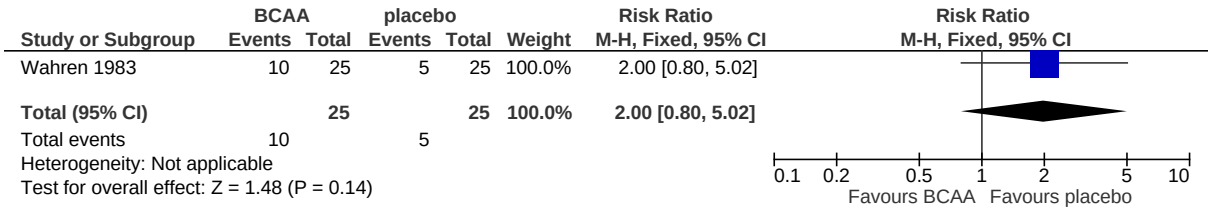
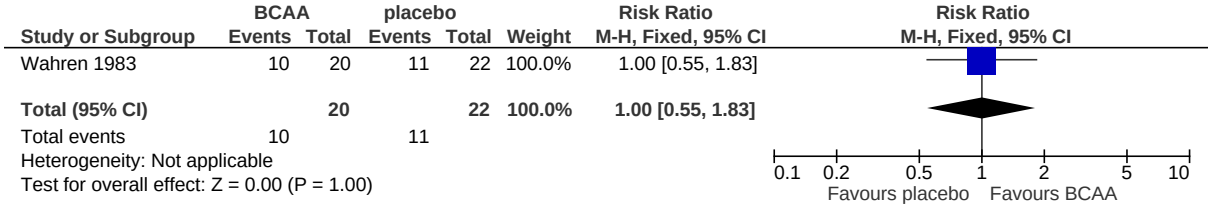


Figure 188: Positive response to treatment (at 5 days)



K.11.4.3 Neomycin (+BCAA in grades III and IV) versus placebo (+BCAA in grades III and IV)

Figure 189: Mortality (at 5 days)

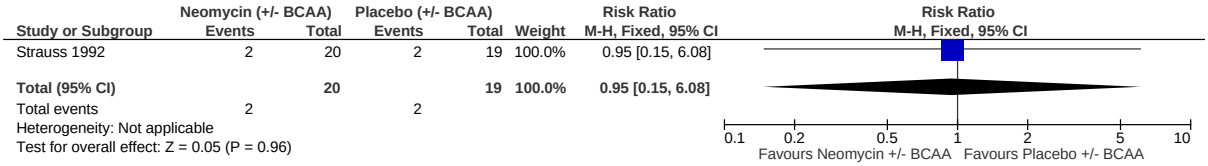
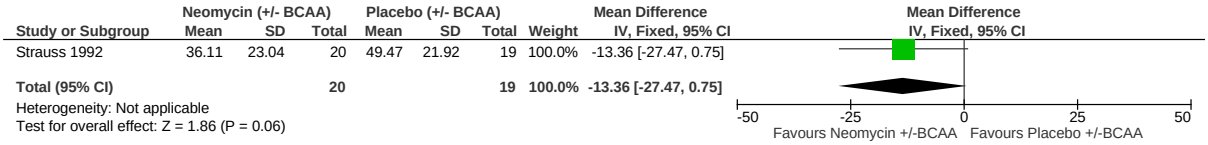


Figure 190: Time until regression to grade 0 hepatic encephalopathy



K.11.5 Single therapy versus single therapy

K.11.5.1 BCAA versus neomycin

Figure 191: Mortality

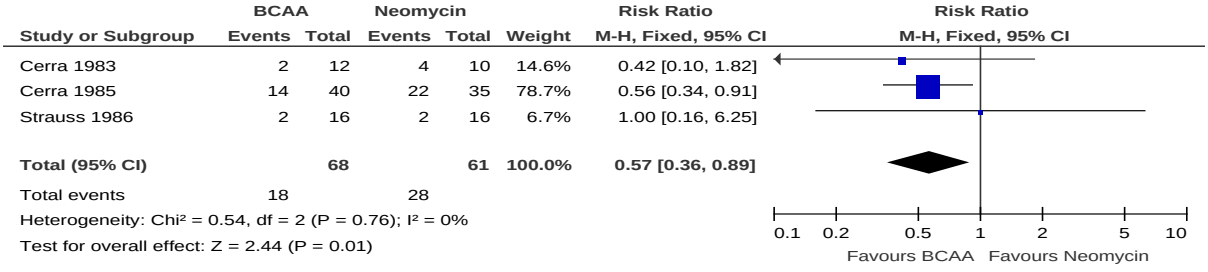


Figure 192: Improvement to grade 0 hepatic encephalopathy

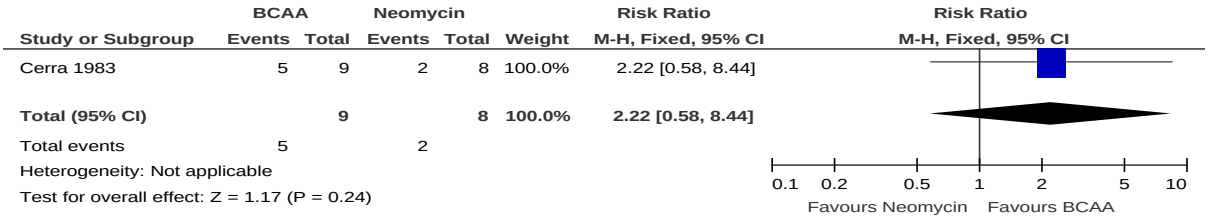


Figure 193: Improvement to grade 0 or 1 hepatic encephalopathy

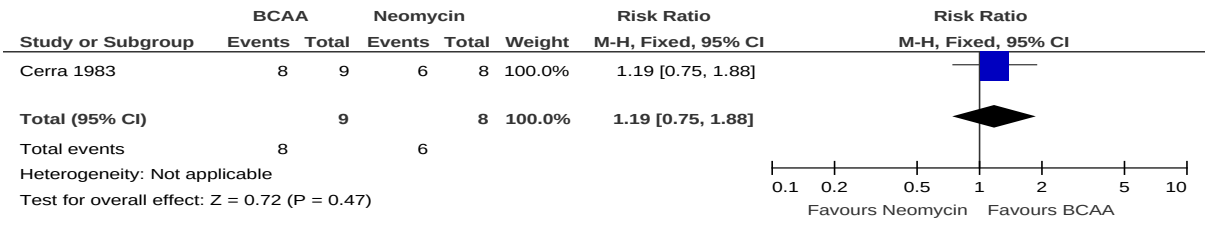
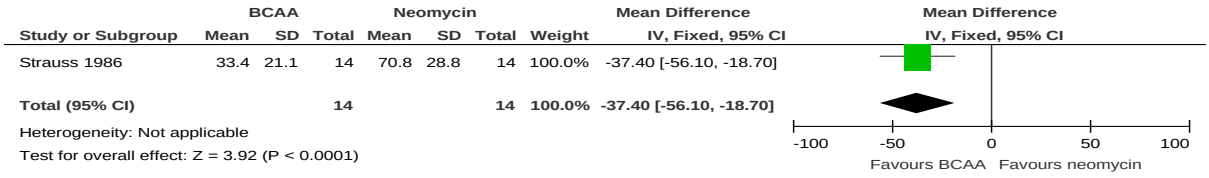


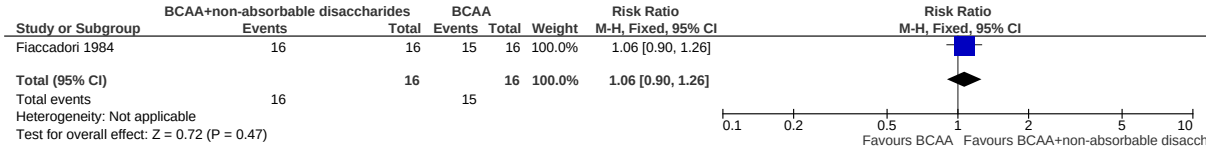
Figure 194: Time to recovery (hours)



K.11.6 Combination therapy (1 intervention + non-absorbable disaccharides) versus single therapy

K.11.6.1 BCAA + non-absorbable disaccharides versus BCAA

Figure 195: Came out of coma (at 7 days)



K.11.7 MARS versus standard medical therapy

K.11.7.1 MARS versus standard medical therapy

Figure 196: Mortality (at 5 days)

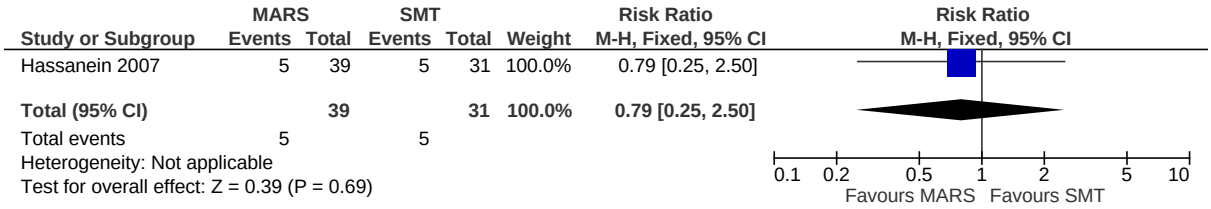


Figure 197: Responder (improvement of hepatic encephalopathy by 2 grades at any time; at 5 days)

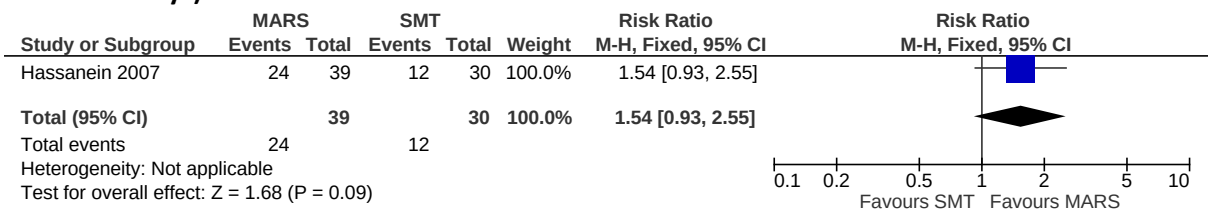
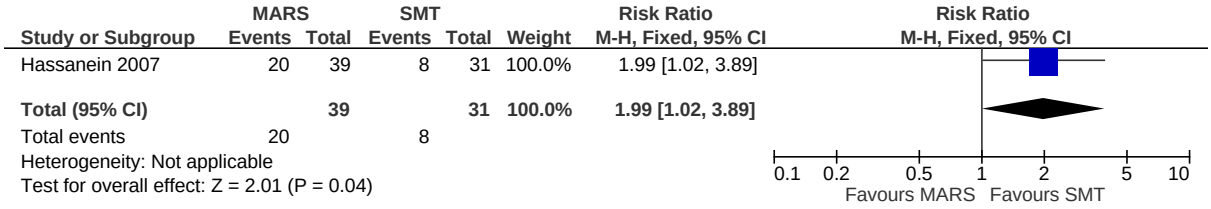


Figure 198: Serious adverse events (at 5 days)



Appendix L: Excluded clinical studies

L.1 Risk factors and risk assessment tools

Table 36: Studies excluded from the clinical review

Reference	Reason for exclusion
Anon 2006[3]	Conference abstract. Genetic test to predict cirrhosis likelihood in people with hepatitis C.
Becker 1996[63]	Data incorporated in another included study
Bellentani 1997[65]	Incorrect study design: cross-sectional study with retrospective assessment of alcohol consumption for prediction of current cirrhosis
Bellentani 1999[64]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Carulli 2015[123]	Study pertains to genetic risk factors not identified in protocol
Chen 2011[143]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Chen 2014D[144]	Conference abstract of descriptive case-control study; no longitudinal follow-up; not prognostic study
Corrao 1998[171]	Systematic review, checked for references
Craxi 1987[173]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Curto 2011[180]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Day 2001[187]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Delahall 1992[189]	Review paper
Delahooke 2000[196]	Review containing studies of incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Deleuran 2012[197]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse versus a control group)
Demeulenaere 1977A[199]	Review paper
Dhyani 2015[202]	Narrative review
Dragosics 1987[208]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Durbec 1981[213]	Incorrect study design (case-control study)
Dyal 2015[214]	Conference abstract of a systematic review; not enough information provided
Ebell 2003[215]	Incorrect study design (cross-sectional study, diagnosis of cirrhosis)
Everhart 2009[226]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Fattovich 1991[231]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Fernandez-Rodriguez 2013[238]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Freeman 2001[254]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)

Reference	Reason for exclusion
Freeman 2003A[255]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Garceau 1964[269]	Incorrect study design (examines previous alcohol intake and hepatitis status in current cirrhosis patients)
Garcia-Compean 2014[271]	Incorrect population (patients already have cirrhosis)
Ge 2015A[274]	Incorrect study design (looking at genetic polymorphisms contributing to susceptibility rather than clinical risk factors)
Goodgame 2003[296]	Review containing studies of incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Gordon 2015[297]	Incorrect study population (patients all already have chronic hepatitis C). Incorrect study design (looking at the association of other characteristics such as race, private health insurance cover and genotype with the risk of cirrhosis, rather than the risk of cirrhosis in people with hepatitis C compared to those without).
Gordon 1984[298]	Reports the future incidence of cirrhosis in people with various alcohol consumption levels, however does not report the relative risk adjusted for confounding factors
Harkisoen 2014[316]	Incorrect study design (not prognostic; cross-sectional design and population not followed up over time)
Hashemi 2015[317]	Incorrect study design (case-control study; no longitudinal follow-up) Incorrect study population (patients already had cirrhosis matched with healthy controls)
He 2015[320]	Systematic review looking at implications of genetic polymorphisms on alcoholic liver cirrhosis risk
Huang 2007[331]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Huang 2013[333]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Hui 2004A[335]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Huo 2000[341]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Huo 2000A[342]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Hsiang 2015[328]	Incorrect study population (patients already have cirrhosis)
Ieluzzi 2014[354]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Ikeda 1998[355]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B and C)
Iloeje 2006[358]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Innes 2013[366]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Ioannou 2005[368]	Additional analysis of a study already included in this review (Ioannou 2003)
Ioannou 2015[367]	Incorrect study design (case-control study; not prognostic; no longitudinal follow-up)
Jamal 2005[373]	Review paper checked for references
Jerkeman 2014[376]	Incorrect study design (cross-sectional study of associations of different

Reference	Reason for exclusion
	factors with cirrhosis; not prognostic; no longitudinal follow-up)
Kage 1997[384]	Assessing time to progression to cirrhosis in people with the risk factor (not relative risk in people with and without the risk factor)
Kamper-Jorgensen 2004[387]	Incorrect comparison (reference group [group without risk factor] had a level of drinking consistent with harmful drinking)
Khullar 2015[400]	Narrative review on diagnosis and treatment of hepatitis C
Klatsky 1981[413]	Reports the future incidence of cirrhosis in people with various alcohol consumption levels, however does not report the relative risk adjusted for confounding factors
Kramer 2005[421]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Lagging 2002[428]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Laspada 2013[426]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Lee 2013[443]	Risk assessment tool does not contain any risk factors stated in the protocol
Lee 2015[440]	Incorrect study population (patients with chronic hepatitis C). Incorrect intervention (comparing anti-hepatitis C treatment versus no treatment).
Levy 2015[447]	Incorrect study design (not prognostic study; no longitudinal follow-up; study aims to make associations between characteristics and alcoholic liver disease)
Marbet 1987[485]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Marcolongo 2009[486]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors)
Mathurin 2007[498]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Mcmahon 1990[503]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Mcmahon 2009[504]	Review paper discussing natural history of hepatitis B
Meikle 2015[509]	Incorrect comparison (study is looking at increase of susceptibility to cirrhosis in people who are already drinkers; no comparison to non-drinkers)
Mittal 2015[518]	Conference abstract of prognostic study but provides insufficient information for data extraction
Murakami 1999[531]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Naveau 1997[543]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Naveau 2010[542]	Narrative paper
Nyberg 2015[558]	Conference abstract of cross-sectional, descriptive study; no longitudinal follow-up; not prognostic study
Park 2014[580]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Parrish 1991[582]	Review article checked for references
Pequignot 1978[590]	Incorrect study design: case-control study recruiting a group with ascitic cirrhosis and a control group from the general population and

Reference	Reason for exclusion
	retrospective assessment of alcohol consumption
Petta 2015[592]	Incorrect study design (not prognostic but case-control study). Incorrect study population (all patients already have hepatitis C).
Poh 2015[598]	Incorrect study population (study population already being treated for hepatitis B; patients would only get treatment for hepatitis B if it is already known that they have cirrhosis)
Poynard 1997[603]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Poynard 2001[607]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Pradat 2010[612]	Narrative paper
Qian 2014[617]	Incorrect study design (looks at hepatitis B and cirrhosis as predictors of liver metastasis in colorectal cancer)
Rodriguez-Torres 2006[636]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Safdar 2004[645]	Review article checked for references
Sheen 1996[675]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Shen 2015[677]	Study pertains to genetic risk factors not identified in protocol
Skog 1984[694]	Incorrect study design (not primary research study)
Sorensen 1984[701]	Reports the future incidence of cirrhosis in people with various alcohol consumption levels, however does not report the relative risk adjusted for confounding factors
Sorensen 1989[700]	Review article checked for references
Takase 1993[718]	Incorrect study design (assesses the added effect of other risk factors in subjects with alcohol misuse)
Thein 2008[730]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Thein 2008A[729]	Meta-analysis containing studies of incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Trepo 2011[737]	Risk assessment tool does not contain any risk factors stated in the protocol (based on genetic factors and ELF score)
Tuyns 1984A[749]	Incorrect study design: case-control study recruiting a group with cirrhosis and a control group from the general population and retrospective assessment of alcohol consumption
Verbaan 1998[758]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis C)
Whitfield 2015[778]	Incorrect study design (case-control study; comparison between people with and without cirrhosis and their alcohol consumption)
Wu 2003[789]	Reports the incidence of cirrhosis in people with and without hepatitis B, but does not report the relative risk adjusted for confounders
Xiong 2015[791]	Incorrect study population (all patients have cirrhosis already). Incorrect study design (not longitudinal, prognostic study).
Yilmaz 2014B[800]	Incorrect study design (diagnostic study rather than prognostic; cross-sectional study without longitudinal follow-up)
Yu 1997[805]	Incorrect study design (assesses the added effect of other risk factors in subjects with hepatitis B)
Yu 2008[806]	Incorrect study design (assesses the added effect of other risk factors in

Reference	Reason for exclusion
	subjects with hepatitis B)

L.2 Diagnostic tests

Table 37: Studies excluded from the clinical review

Reference	Reason for exclusion
ABDELWAHAB 1993[7]	Population does not match protocol (schistosomal hepatic fibrosis without cirrhosis)
ABELWAHAB 1995[9]	Population does not match protocol (people presenting with splenomegaly)
ADAMS 2011[12]	Reference standard does not match protocol (biopsy length range 6–50 mm)
AFDHAL 2015[15]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
AHMED 2009[18]	Index test does not match protocol (α2-macroglobulin, haptoglobin, apolipoprotein A1 and APRI, but sensitivity and specificity of APRI only provided for the diagnosis of significant fibrosis and advanced fibrosis, not cirrhosis)
ALLAN 2014[25]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, length of biopsy not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
ANASTASIOU 2010[34]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, only subgroups into viral [hepatitis C [54]and hepatitis B], and non-viral [alcohol, autoimmune hepatitis and NASH]). Reference standard does not match protocol (included if biopsy >10 mm in length, mean 17 mm, median 1 fragment).
ANDERSON 2000[35]	Reference standard does not match protocol (fibrosis staging score not stated, length of biopsy not stated)
ASBACH 2010[41]	Reference standard does not match protocol (length of biopsy not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
AUBE 1999[45]	Reference standard does not match protocol (length of biopsy not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis, subgroups only provided for those with compensated alcohol and compensated viral disease).
AUBE 2004[46]	Reference standard does not match protocol (included if biopsy ≥10 mm in length). Study aims to identify Doppler US variables predicative of cirrhosis. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
BANERJEE 2014[54]	Population does not match protocol (steatohepatitis included those with both alcohol-related and non-alcoholic liver disease). Reference standard does not match protocol (threshold for diagnosing cirrhosis not reported).
BAVU 2011[61]	Reference standard does not match protocol (reference standard was a predicted fibrosis score based on serum markers, with liver biopsy only taken into account in 39/108 people).
BECKEBAUM 2010[62]	Population does not match protocol (fibrosis staging in liver transplant recipients, inclusion of different aetiological groups within the same analysis). Reference standard fibrosis scoring system does not match protocol.

Reference	Reason for exclusion
BEN 2009[66]	Diagnostic accuracy of serum fibrosis markers to predict significant fibrosis (METAVIR ≥F2) not cirrhosis.
BERZIGOTTI 2010[75]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
BOOZARI 2010[86]	Population does not match protocol (inclusion of different aetiological groups within the same analysis: 68.5% hepatitis C; 28.2% hepatitis B; 2.4% both).
BOTA 2013B[92]	Does not give diagnostic accuracy of ARFI for cirrhosis (only gives the number of people with discordance – a difference of at least 2 stages of fibrosis between METAVIR and ARFI)
BOTA 2015A[91]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (transient elastography).
BOTTERO 2009[94]	Reference standard does not match protocol (no minimum length stated, only 60% had a biopsy length ≥15 mm, mean 17.0 range 2–35 mm, mean portal tracts 12.3 range 3–25)
BOURLIERE 2006[96]	Reference standard does not match protocol (only 117⁄235 [50%] patients had a biopsy ≥15 mm, mean 16 [7.5] mm and mean number of portal tracts 9.4 [5]).
BOURLIERE 2008A[95]	Reference standard does not match protocol (only 282⁄467 [59%] patients had a biopsy >15 mm, mean 19.7 [8.4] mm and median number of portal tracts 9 [range 2–36].
BOURSIER 2009[102]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (reliable biopsy of ≥15 mm and/or ≥8 portal tracts only in 89.5%).
BOURSIER 2009A[100]	Systematic review (not all included studies had a liver biopsy criteria of ≥15 mm). Used for references to identify original papers with a liver biopsy criteria ≥15 mm.
BOURSIER 2012A[101]	Reference standard does not match protocol (only 79% patients had a biopsy >15 mm, mean 23(9))
BOURSIER 2013[103]	Reference standard does not match protocol (reliable liver biopsy was length ≥15 mm and/or portal tracts ≥8, biopsy reliable in only 93.8% of patients, median 24 [IQR 18–30] mm – subgroup analysis of TE accuracy in reliable and unreliable biopsies but data not shown).
CALES 2010[113]	Index test does not match protocol
CALES 2010A[112]	Validation study
CALES 2014[114]	Development and internal validation study for a combination of fibrometer and fibroscan
CALES 2014[114]	Reference standard does not match protocol (analysis of 2 datasets [overall 93.5% biopsies >15 mm and 8 portal tracts], reference standard biopsy length criteria does not meet protocol for one dataset, other dataset [Zarski 2012] already included in this review)
CALES 2015D[111]	Reference standard does not match protocol (reliable liver biopsy was length ≥15 mm and/or portal tracts ≥8, biopsy reliable in only 93.5% of patients)
CALVARUSO 2013[117]	Reference standard does not match protocol (length of biopsy not stated)
CARRION 2006[121]	Population does not match protocol (HCV recurrence after liver transplant). Reference standard does not match protocol (no minimum biopsy length stated).
CARTON 2011[122]	Reference standard does not match protocol (length of biopsy not

Reference	Reason for exclusion
	stated).
CASSINOTTO 2013[126]	Reference standard does not match protocol (no minimum biopsy length stated, median 25 mm range 10–51)
CASSINOTTO 2014[127]	Population does not match protocol (inclusion of different aetiological groups within the same analysis – subgroup analysis provided but only for mixed viral hepatitis and mixed alcoholic/NASH).
CASTERA 2005[130]	Reference standard does not match protocol (no minimum biopsy length stated, median length 17 mm and median number of fragments 2)
CASTERA 2009[129]	Reference standard does not match protocol (no minimum biopsy length stated, median length 19.5 mm and median number of fragments 2.9, length was ≥15 in 69% of patients)
CASTERA 2014A[128]	Reference standard does not match protocol (no minimum biopsy length, median length 19.5 mm and median number of portal tracts 14, length was ≥15 in 75% of patients, not reported if all have ≥6 portal tracts)
CHANG2008[136]	Reference standard does not match protocol (liver biopsy only performed in 79%). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 48% hepatitis B).
CHANTELOUP 2004[138]	Conference abstract, not a full paper. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
CHEN 2012A[147]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
CHOI 2013[150]	Reference standard does not match protocol (no minimum biopsy length). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
CHOONG 2012[153]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, 87% hepatitis B). Reference standard does not match protocol (length of biopsy not stated).
CHUNG 2013[158]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
COBBOLD 2010[160]	Article not available for copyright reasons
COCO 2007[161]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (range 12–54 mm).
COLLI 1994[163]	Index test does not match protocol (Doppler waveform of hepatic veins)
COLOMBO 2012[165]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
CORPECHOT 2006[169]	Reference standard does not match protocol (biopsy length median 17 mm [8–40 mm] and the median number of fragments was 2, number of portal tracts not reported)
CORPECHOT 2014[170]	Reference standard does not match protocol (included biopsies >8 mm, median 18 mm [8–42 mm], number of portal tracts not reported)
CRESPO 2012[175]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
CROSS 2010[176]	Reference standard does not match protocol (included biopsies >10 mm or >10 portal tracts, mean 15 mm [13–17mm], unknown if those <15 mm had at least 6 portal tracts)
CROSSON 2015[177]	HTA systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this HTA was checked for relevant studies but not updated itself.

Reference	Reason for exclusion
D'AMBROSIO[182]	Reference standard does not match protocol (inclusion criteria >10 mm and/or ≥12 portal tracts, median 30 mm [10–45mm], median number of portal tracts not reported – some biopsies <15 mm may not have contained enough portal tracts).
DE LÉDINGHEN 2012[191]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (inclusion criteria ≥11 mm, median 25 mm [IQR 20–30 mm], number of portal tracts unknown).
DEFFIEUX 2015[194]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length range 6–40 mm and portal tracts range 3–20).
DEGOS 2010[195]	Population does not match protocol (inclusion of different aetiological groups within the same analysis – subgroup analysis provided for HCV population but included people with HCV and HBV co-infection)
DI MARCO 2010[203]	Population does not match protocol (all patients have thalassaemia and some also have hepatitis C but results from all patients, regardless of aetiology, are combined)
DINESEN 2008[205]	Reference standard does not match protocol (length of biopsy not stated)
EL GUESIRY 2011[216]	Reference standard does not match protocol (length of biopsy not stated)
FERLITSCH 2010[235]	Conference abstract, not a full paper. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FERRAL 1992[242]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
FERRANTE 1968[243]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (details about biopsy, including length, not stated).
FERRIAOLI 2012[239]	Reference standard does not match protocol (no minimum biopsy length stated, mean 27[SD 8.0] mm, range 10–55 mm, >15 mm in 117/121 cases, number of portal tracts not reported)
FERRIAOLI 2012a[241]	Reference standard does not match protocol (no minimum biopsy length stated, median 25 [IQR 20-35] mm, but range not reported, number of portal tracts not reported)
FERRIAOLI 2013[240]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (no minimum biopsy length stated, mean 27 [SD 8.0] mm but range not reported).
FILLY2002[246]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
FORESTIER 2010[247]	Reference standard does not match protocol (length of biopsy not stated)
FOUAD 2012[248]	Reference standard does not match protocol (length of biopsy not stated)
FOUCHER 2006[249]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
FOUCHER2005[250]	Conference abstract, not a full paper. Population does not match protocol (inclusion of different aetiological groups within the same analysis).
FRAQUELLI 2007[252]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
FRAQUELLI 2014[251]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)

Reference	Reason for exclusion
FRIEDRICH-RUST 2007[258]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
FRIEDRICH-RUST 2009[261]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, HCV and HBV). Reference standard does not match protocol (not all patients had liver biopsy as the reference standard – 16/86 had proven cirrhosis but no biopsy and these patients included in the diagnostic accuracy calculation for cirrhosis F4).
FRIEDRICH-RUST 2010[257]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, Ludwig scoring system)
FRIEDRICH-RUST 2012[259]	Reference standard does not match protocol (inclusion criteria at least 10 mm or ≥6 portal tracts, range 10–60 mm, median number of portal tracts not reported – some biopsies <15 mm may not have contained enough portal tracts).
FRIEDRICH-RUST 2015[256]	Article not in English
FROSSARD 2013[262]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
GAIA 2015[265]	Diagnostic accuracy of transient elastography to predict advanced fibrosis (METAVIR ≥F3) not cirrhosis
GAIANI 1997[266]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
GANNE-CARRIE 2006[267]	Reference standard does not match protocol (median liver biopsy length 17 mm, range 5–40 mm, number of portal tracts not mentioned)
GARA 2013[268]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, mean length 13.4 [SD 6.8] and mean number of portal tracts 13 [SD 6]).
GE 2015[274]	Population does not match protocol (chronic hepatitis: 111 out of 120 people had hepatitis B)
GIANNINI 2003b[279]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
GIORGIO 1986[286]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
GOBEL 2015[292]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GODFREY 2012[293]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
GOERTZ 2010[294]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 37% hepatitis B).
GOMEZ-DOMINGUEZ 2008[295]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
GOSINK 1979[299]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
GOTO 2014[300]	Reference standard does not match protocol (minimum length of biopsy

Reference	Reason for exclusion
	not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
GRGUREVIC 2011[305]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, 19% hepatitis B)
GUZELBULUT 2011[310]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
HAKTANIR 2005[312]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Does not give diagnostic accuracy of Doppler Sonography for cirrhosis.
HAMBERG 1996[313]	Reference standard does not match protocol (fibrosis scoring system does not match protocol)
HAQUE 2010[315]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HEDIN 2000[321]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
HESS 1989[324]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HORNG 2002[326]	Incorrect study design. Does not compare index test to reference standard.
HSIEH 2009[329]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 19% hepatitis B).
HULTCRANTZ 1993[336]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
HUWART 2007[345]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
HUWART 2008[344]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
HUWART 2008A[346]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
IACOBELLIS 2005[348]	Reference standard does not match protocol (included if contained 5 or more portal tracts, average length not reported)
ICHIKAWA 2012[350]	Reference standard does not match protocol (no biopsy performed)
ICHIKAWA 2015[351]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (not all had liver biopsy).
ICHIKAWA 2015A[349]	Population does not match protocol (various aetiologies with fibrosis and healthy volunteers)
ICHINO 2010[352]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
ILIOPOULOS 2007[357]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)

Reference	Reason for exclusion
ILIOPOULOS 2008[356]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
IMBERT-BISMUT 2001[359]	Reference standard does not match protocol (included if biopsy ≥10 mm in length, number of portal tracts not mentioned)
IMPERIALE 2000[363]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
ISHIBASHI 2010[369]	Diagnostic test does not match protocol (ultrasound using microbubble transit time)
ISHIBASHI 2012[370]	Diagnostic test does not match protocol (ultrasound using microbubble transit time)
ISLAM 2005[371]	Reference standard does not match protocol (included if biopsy ≥10 mm in length and at least 4 portal tracts)
KAMPHUES 2010[388]	Population does not match protocol (post liver transplant)
KANEDA 2006[389]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
KAROUI 2012[393]	Non-English language publication
KHAN 2008[398]	Diagnosis of significant fibrosis and advanced fibrosis, not cirrhosis
KIM 2011[402]	Population does not match protocol (inclusion of people with hepatitis B (78%), hepatitis C and five living liver donors within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated).
KIRK 2009[412]	Reference standard does not match protocol (median biopsy length 12 mm, median portal tracts 11, range not stated)
KOBAYASHI 2015[415]	Systematic review protocol does not match protocol (minimum biopsy length for reference standard not an inclusion criteria)
KOIZUMI 2011[417]	Reference standard does not match protocol (included if biopsy ≥12 mm in length and if ≥5 portal tracts)
KRAMER 2014[420]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
KUMAR 2013[423]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
KURODA 2010[425]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
LADERO 2010[427]	Reference standard does not match protocol (included if biopsy ≥10 mm in length, subgroup analysis of biopsies >15 mm but data not shown, 84.1% had biopsy ≥15 mm).
LEE 2010[438]	Reference standard does not match protocol (included if biopsy ≥10 mm in length). Population does not match protocol (inclusion of different aetiological groups within the same analysis, 77% hepatitis B).
LEE 2010A[444]	Population does not match protocol (inclusion of people with hepatitis B (76%) and hepatitis C within the same analysis)
LI 2014[450]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
LICHTINGHAGEN 2013[451]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
LUCIDARME 2009[466]	Assessing the influence of TE success rate and IQR/median ratio on the diagnostic accuracy (accuracy reported for IQR/median >21 and <21 but

Reference	Reason for exclusion
	overall values not reported)
LIM (2005)[453]	Diagnostic test does not match protocol (ultrasound using microbubble transit time)
LIU 2007A[454]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
LIU 2015B[456]	Systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this review was checked for relevant studies but not updated itself.
LIM 2011[452]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
LIU 2011A[455]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
LUO 2002[467]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported, included if ≥5 portal tracts)
LUPSOR 2008[470]	Presumed overlap in patients with more recent larger study already included in this review (Lupsorplanten 2013). Both recruited from the same centre and recruitment started in May 2007.
LUPSOR 2010[469]	Diagnostic accuracy of transient elastography for cirrhosis Brunt F4 not reported as no patients in the population were diagnosed as F4
LUTZ 2012[471]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
MACIAS-RODRIGUEZ 2011[474]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
MAHADEVA 2013[475]	Reference standard does not match protocol (no minimum biopsy criteria, median 13 (IQR 8–15) mm, number of portal tracts not stated)
MALIK 2010[481]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
MARMO 1993[488]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
MARTIN 2015[491]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
MARUYAMA 2009[493]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
MARUYAMA 2012A[492]	Diagnostic test does not match protocol (ultrasound using microbubble transit time). Reference standard does not match protocol (length of biopsy not stated).
MATHIESEN 2002[497]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
MAZUZAKI 2008[495]	Population does not match protocol (inclusion of hepatocellular carcinoma patients within the same analysis)
MCPHERSON 2010[506]	Reference standard does not match protocol (no minimum biopsy criteria, mean 22(±8) mm, range not reported, number of portal tracts not reported)
MCPHERSON 2013[505]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)

Reference	Reason for exclusion
MEEK 1984[507]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
MOON 2013[523]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
MORIKAWA 2011[527]	Reference standard does not match protocol (median length of biopsy 18 mm, range 10–25)
MOROSAN 2014[528]	Reference standard does not match protocol (no minimum biopsy criteria stated and mean not reported)
MYERS 2010[532]	Reference standard does not match protocol (no minimum biopsy criteria stated, median 2.4 [IQR 1.7–2.8] mm, 87% of biopsies were at least 1.5 cm long, number of portal tracts not reported)
NAALEINI 2013[533]	Non-English language publication
NAGATA 2003[535]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (length of biopsy not stated).
NAHON 2006[537]	Reference standard does not match protocol (no minimum biopsy criteria, mean 15.8 (7.6) mm, range 4–50 mm, number of portal tracts not stated)
NAHON 2008[536]	Reference standard does not match protocol (median length of biopsy 14 mm, range 4–50)
NAVEAU 2005[547]	Reference standard does not match protocol (no minimum biopsy criteria, mean 15(0.5) mm, portal tracts 14.4(0.7), range not reported)
NAVEAU 2009[545]	Reference standard does not match protocol (no minimum biopsy criteria, mean 15(5) mm, portal tracts 14.4(0.7), range not reported)
NAVEAU 2014[546]	Reference standard does not match protocol (inclusion criteria at least 10 mm or 10 portal tracts, average not stated, some biopsies could be <15 mm and not have 6 portal tracts)
NAVEAU 2014[544]	Reference standard does not match protocol (no minimum biopsy criteria, mean 12 [SEM 0.4] mm, number of portal tracts not reported)
NGUYEN-KHAC 2008[549]	Reference standard does not match protocol (no minimum biopsy criteria, mean 12.2 (3) mm and 7.8 (2.7) portal tracts, range not reported)
NISHIURA 2005[550]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (details about biopsy, including length, not stated).
NITTA 2009[551]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
NUDO 2008[555]	Reference standard does not match protocol (Batts and Ludwig fibrosis scoring system in hepatitis C population)
NUNES 2005[556]	Reference standard does not match protocol (no minimum biopsy criteria, average 14.5 mm)
OCHI 2012[559]	Reference standard does not match protocol (included if biopsy ≥12 mm)
OGAWA 2012[562]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
ONG 2003[564]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
OSAKI 2010[569]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
PAPAGEORGIOU 2011[575]	Study does not report any outcomes that can be combined in the analysis (only ROC AUC for of transient elastography in hepatitis C population, no

Reference	Reason for exclusion
	CIs reported)
PARISE 2006[577]	Reference standard does not match protocol (Ludwig fibrosis scoring system)
PARK 2000[578]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, minimum length of biopsy not stated in inclusion criteria and average not reported)
PAVLOV 2015[586]	Review protocol only
PAVLOV 2015[585]	Systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this review was checked for relevant studies but not updated itself.
PEDERSEN 2008[587]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Index test does not match protocol (hepatic vein Doppler waveform). Reference standard does not match protocol (length of biopsy not stated).
PETTA 2011[591]	Diagnostic accuracy of transient elastography for significant (≥F2) and severe (≥F3) fibrosis, but not for diagnosis of cirrhosis
PFEIFER 2014[593]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
POUSTCHI 2013[602]	Population does not match protocol (people with beta thatassemia and chronic hepatitis C)
POYNARD 2007B[605]	Diagnostic accuracy of FibroTest adjusted for liver biopsy size (inclusion criterium for biopsy length does not match protocol)
POYNARD 2011A[609]	Retrospective review of data from 3 studies (reference standard biopsy length criteria does not meet protocol with the exception of Zarski study already included in this review)
POYNARD 2012D[606]	FibroTest for assessing liver fibrosis progression, not diagnosis of cirrhosis
POYNARD 2012[608]	Retrospective review of data from 3 studies (reference standard biopsy length criteria does not meet protocol with the exception of Zarski study already included in this review)
PROCOPET 2015[614]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (inclusion of different aetiological groups within the same analysis).
RATZIU 2006[620]	Reference standard does not match protocol (no minimum biopsy length in inclusion criteria, mean (SE): group 1: 20 (0.5) mm and 16.3 (0.6) portal tracts, group 2: 17.8 (0.7) mm and 13.6 (0.6) portal tracts, ranges not reported). Sensitivity analysis performed for biopsies ≥25 mm, but only for the diagnosis of significant fibrosis not cirrhosis.
REIBERGER 2012[623]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
RESINO 2010[626]	Reference standard does not match protocol (only states 'only 5 out of 297 biopsies yielded insufficient liver tissue for pathological diagnosis', minimum size not stated)
RICCI 2013[628]	Population does not match protocol (inclusion of people with hepatitis B and hepatitis C within the same analysis). Reference standard does not match protocol (no minimum biopsy length stated).
RUNGE 2014[641]	Aim to compare interobserver agreement of MR elastography (used data from the primary study KIM 2011A)
SAID 2010[646]	Reference standard does not match protocol (biopsy length range 10–35 mm and 2–25 portal tracts).

Reference	Reason for exclusion
SANDRIN 2003[653]	Study does not report any outcomes that can be combined in the analysis (only ROC AUC for of transient elastography in hepatitis C population, no CIs reported)
SANFORD 1985[654]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
SAMIR 2015[651]	Reference standard does not match protocol (minimum length of biopsy was 10 mm, range 10–53 mm and minimum number of portal tracts was 3)
SASSO 2012[660]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
SCHWABL[666]	Unable to access full text article
SEBASTIANI 2006[669]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
SEBASTIANI 2011[667]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
SEBASTIANI 2012[668]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and range not reported)
SHEN 2006[678]	Reference standard does not match protocol (included if biopsy ≥10 mm, number of portal tracts not stated)
SHETH 1998[681]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
SCHNEIDER 2005[664]	Index test does not match protocol (Doppler ultrasound variables: splenic artery pulsatile index, hepatic vein dampening index, portal vein flow, portal vein undulations)
SHARMA 2014[674]	Reference standard does not match protocol (minimum length of biopsy not stated [only stated 'adequate' specimens] in inclusion criteria and range not reported)
SINGH 2015[690]	Systematic review protocol did not match review protocol. The systematic review did not exclude studies based on the liver biopsy length.
SPOREA2010A[706]	Population does not match protocol (inclusion of people with hepatitis B and hepatitis C within the same analysis)
STEVENSON 2012[711]	HTA systematic review protocol did not match review protocol. Only included the ALD population and included studies assessing all stages of fibrosis, not just cirrhosis. The systematic review did not exclude studies based on the liver biopsy length. Therefore, this HTA was checked for relevant studies but not updated itself.
SU 2014[714]	Systematic review. Unable to obtain full paper.
SUGIMOTO 2010[715]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
TAKAHASHI 2010[717]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, mean 18.2 mm and 6.8 portal tracts, range not reported).
TATSUMI 2008[721]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
TAWADA 2013[723]	Reference standard does not match protocol (biopsy length range 11–28 mm, number of portal tracts not stated). Population does not match protocol (inclusion of different aetiological groups within the same analysis).

Reference	Reason for exclusion
TOSHIMA 2015[735]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (histology on hepatectomy or living donor liver transplantation).
TSOCHATZIS 2014[745]	Systematic review. Reference standard does not match protocol (accuracy of index tests for diagnosis of fibrosis stage ≥F2).
VALLET-PRICHARD 2007[752]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
VENKATESH 2015[756]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported). Population does not match protocol (some patients were undergoing MRI and biopsy for investigation of liver masses).
VERVEER 2012[762]	Study does not report any outcomes that can be combined in the analysis (only ROC AUC for of transient elastography in hepatitis C population, no CIs reported)
WAHL2012[766]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, mean 22.1 [SEM 2.2]).
WAI2003[767]	Development study for APRI (training and validation set). Reference standard biopsy length not stated.
WANG 2009[772]	Reference standard does not match protocol (included if biopsy ≥10 mm in length, biopsy length range 10–28 mm, number of portal tracts not stated)
WANG 2010[773]	Reference standard does not match protocol (length of biopsy not stated). Population does not match protocol (presumed inclusion of different aetiological groups within the same analysis, aetiologies not stated).
WANG2011[776]	Population does not match protocol (inclusion of different aetiological groups within the same analysis). Reference standard does not match protocol (only states 'all patients had adequate size biopsies', minimum size not stated).
WONG 2008a[787]	Population does not match protocol (inclusion of different aetiological groups within the same analysis)
WONG 2013A[786]	Diagnostic accuracy of cirrhosis not reported, only of significant fibrosis
YAKOOB 2015[793]	Reference standard does not match protocol (<50% of biopsies were >15 mm and 6 portal tracts)
YONEDA 2015[801]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
YOON 2012[802]	Reference standard does not match protocol (included if biopsy ≥10 mm in length). Population does not match protocol (inclusion of different aetiological groups, including 64% hepatitis B within the same analysis).
ZHANG 2014[812]	Reference standard does not match protocol (fibrosis scoring system does not match protocol, Ludwig scoring system)
ZHENG2003[816]	Population does not match protocol (inclusion of different aetiological groups within the same analysis, 92.4% hepatitis B). Reference standard does not match protocol (fibrosis scoring system does not match protocol and biopsy size not stated).
ZIOL 2005[819]	Population does not match protocol (included patients with mixed aetiologies, included 251 patients with HCV but 13 had a human immunodeficiency virus co-infection, 5 had a hepatitis B virus co-infection, 18 had a current daily alcohol intake of at least 60 g/day, and 2

Reference	Reason for exclusion
	had undergone a liver transplantation)

Table 38: Studies identified by the GDG which were picked up in the search but excluded from the clinical review during the first sift, prior to ordering full papers

Reference	Reason for exclusion
BARDOUJACQUET 2013[57]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
BOURSIER 2011[99]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, overall 93.5% biopsies >15 mm and 8 portal tracts)
BOURSIER 2014[97]	Incorrect study design – prognostic study (prognostic accuracy of blood fibrosis tests for the prediction of future liver related complications or death, not diagnostic accuracy for current cirrhosis)
CARL 2012[120]	Conference abstract only. Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
DOLMAN 2013[206]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, average length 23 mm IQR 16–29 mm, mean portal tracts 15 range 3–53, 84% of biopsies were greater than 15 mm)
FERNANDEZ 2012[237]	Conference abstract only. Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported).
KIM 2009[404]	Article not in English. Reference standard does not match protocol (fibrosis scoring system does not match protocol, Batts-Ludwig scoring system). Included in Stevenson HTA.
LANNERSTEDT 2013[431]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria and average not reported)
LEMOINE 2008[445]	Reference standard does not match protocol (minimum length of biopsy not stated in inclusion criteria, average length 14 mm, range not reported)
MELIN 2005[510]	Article not in English. Reference standard biopsy length not stated. Not identified in search due to incorrect referencing. Included in Stevenson HTA (data obtained direct from manufacturers).

L.3 Severity risk tools

Table 39: Studies excluded from the clinical review

Reference	Reason for exclusion
Addario 2006[13]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Albers 1989[20]	Population does not match protocol (some patients had decompensated cirrhosis at baseline). No prognostic accuracy data reported.
Alhasani 2014[19]	Population does not match protocol: people with HCC (86.9% cirrhosis) but with mixed aetiology (26.8% HBV)
Attia 2008a[44]	Population does not match protocol (57% Child-Pugh C at baseline)

Reference	Reason for exclusion
Berzigotti 2011[74]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Beuers 1991[76]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Bhise 2007[78]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Botta 2003[93]	Population does not match protocol (some patients had ascites at baseline)
Boursier 2009b[98]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Chan 2015[134]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Chawla 2011[140]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Choi 2009[149]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Cholongitas 2005[151]	Review paper checked for references
Chon 2012a[152]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Christensen 1984[156]	Population does not match protocol (27% of patients had minimal hepatic encephalopathy at baseline)
Christensen 2004[155]	Review paper checked for references
Christensen 2014[157]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Colecchia 2014[162]	Severity risk tool does not match protocol (prognostic accuracy of spleen stiffness)
Corpechot 2012[168]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Prognostic accuracy measures not reported.
Corpechot 2014[170]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Crespo 2014[174]	Population does not match protocol (post-transplant patients)
De ledinghen 2013[190]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Dultz 2013[211]	Unclear if subjects compensated at baseline. Prognostic accuracy measures not reported.
Dultz 2015[210]	Population does not match protocol (199 out of 272 patients were decompensated at baseline). Prognostic accuracy measures not reported.
Forestier 2010[247]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Gianni 2002[278]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Giannini 2004[277]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Giannini 2005[280]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Gotzberger 2012[301]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Hassan 2013[318]	Population does not match protocol (some patients had decompensated

Reference	Reason for exclusion
	cirrhosis at baseline)
Huo 2005[340]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Huo 2005a[343]	Unclear if patients were compensated at baseline
Huo 2008a[339]	Population does not match protocol (some patients classified as Child-Pugh C at baseline, therefore decompensated)
Huo 2010[338]	Severity risk tool does not match protocol (prognostic accuracy of different creatinine cut-off levels to calculate MELD score). Population does not match protocol (presumed some patients had decompensated cirrhosis at baseline as diagnosis of cirrhosis could be made based on the presence of ascites).
Infante-rivard 1987[365]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Jung 2011[382]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Kamath 2001[386]	Populations do not match protocol (some patients had decompensated cirrhosis at baseline)
Kang 2014[390]	Systematic review checked for references
Karagiannakis 2014[392]	Populations do not match protocol (48.9% patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Kim 1999[406]	Populations do not match protocol (some patients had decompensated cirrhosis at baseline). No prognostic accuracy data.
Kim 2012c[403]	Population does not match protocol (some patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Kim 2012i[405]	Population does not match protocol (recruited patients with F3 and F4 fibrosis stages, not all patients had cirrhosis at baseline)
Koo 2013[418]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Lee 2014c[439]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Longheval 2003[460]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Lv 2009[472]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Macias 2013a[473]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Mallaiyappan 2013[482]	Population does not match protocol (patients had decompensated cirrhosis at baseline)
Masuzaki 2009[496]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Mayo 2008[499]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Mishra 2007a[516]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Montagnese 2015[520]	Population does not match protocol (cirrhosis with previous decompensation)
Montano 2014[521]	Review paper checked for references
Moreno 2013a[525]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)

Reference	Reason for exclusion
Nunes 2010[557]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Pang 2014[574]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Park 2015[579]	Unable to access full text article
Pasqualetti 1992[583]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Prognostic accuracy measures not reported.
Poynard 2011[610]	Systematic review. One included study assessed the prognostic accuracy of transient elastography but in the wrong population (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline).
Poynard 2014[611]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Data presented for those with cirrhosis at baseline (EPIC cohort) for prognostic accuracy of FibroTest but not transient elastography.
Reichel 2000[624]	Population does not match protocol (some patients Child-Pugh C at baseline)
Ripoll 2005[631]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Ripoll 2007[632]	Population does not match protocol (9% of subjects had HCC at baseline)
Ripoll 2012a[633]	Population does not match protocol (29% of subjects had HCC at baseline)
Ripoll 2014[634]	Unable to access full text article
Ripoll 2015[635]	Prognostic accuracy only reported for albumin in the people with compensated cirrhosis
Ruiz-del-arbol 2013[640]	Population does not match protocol (some patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Singh 2013[689]	Systematic review. Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline or some patients had decompensated cirrhosis at baseline). Prognostic accuracy measures not reported.
Somsouk 2009[699]	Prognostic accuracy measures not reported. Population does not match protocol (some patients had decompensated cirrhosis at baseline).
Stokes 2014[712]	Prognostic accuracy measures not reported
Strauber 2014[707]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Testa 1999[728]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Tsochatzis 2014b[744]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Tuma 2010[746]	Prognostic accuracy measures not reported
Urbain 1995[750]	Population does not match protocol (some patients Child-Pugh C at baseline). Prognostic accuracy measures not reported. Severity risk tool does not match protocol (prognostic accuracy of thallium-201 per rectal scintigraphy).
Vandam 1999[753]	Population does not match protocol (included patients who died of primary biliary cirrhosis)
Vergniol 2011[760]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)

Reference	Reason for exclusion
Vergniol 2014[759]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Verma 2006[761]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Wang 2007[775]	Population does not match protocol (47% of patients had ascites at baseline)
Wang 2012a[774]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Wang 2013a[769]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline). Prognostic accuracy measures not reported.
Weinmann 2015[777]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
WONG 2014C[785]	Population does not match protocol (recruited patients with various fibrosis stages, not all patients had cirrhosis at baseline)
Xie 2013[790]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Yang 2012[797]	Population does not match protocol (all patients had decompensated cirrhosis at baseline)
Zhang 2012b[813]	Population does not match protocol (patients had decompensated cirrhosis at baseline)
Zheng 2011[815]	Population does not match protocol (patients had acute-on-chronic liver failure at baseline)
Zipprich 2010[821]	Population does not match protocol (some patients had decompensated cirrhosis at baseline)
Zipprich 2012a[820]	Severity risk tool does not match protocol (prognostic accuracy of HVPG alone)

L.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Table 40: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdelgawad 2015[8]	Incorrect intervention/comparison: study looks at diagnostic accuracy not surveillance
Ando 2006[36]	Intervention does not match protocol: surveillance consisted of combinations of ultrasound, AFP, des-ɣ-carboxyprothrombin and CT. Population does not match protocol: chronic liver disease irrespective of cirrhosis (unclear proportion with cirrhosis).
Berretta 2011[73]	Population does not match protocol: people with HCC and chronic liver disease but with mixed aetiology (23.1% HBV)
Bischof 2014[80]	Incorrect study design (commentary of Singal 2014)
Biselli 2015[81]	Incorrect intervention/comparison: study looks at diagnostic accuracy not surveillance
Bolondi 2001[85]	Population does not match protocol: people with HCC and chronic liver disease but with mixed aetiology (17.6% HBV)
Borzio 2013 [87]	Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed)

Reference	Reason for exclusion
Chandna 2015[135]	Conference abstract; no relevant comparison
Chang 2015[137]	Incorrect intervention/comparison: study looks at diagnostic test accuracy not surveillance
Chen 2003[145]	Population does not match protocol: surveillance versus no surveillance in HBV carriers, at risk of HCC irrespective of cirrhosis (unclear proportion with cirrhosis). Intervention does not match protocol: surveillance group had 6-monthly surveillance testing using alpha-fetoprotein only, not ultrasound.
Chou 2015[154]	Systematic review; incorrect intervention/comparison: study looks at diagnostic accuracy instead of surveillance frequency
Colombo 2007[164]	Review article and retrospective analysis (non-systematic)
Cucchetti 2014[179]	Non-randomised study comparing 12-monthly versus 6-monthly surveillance (multivariate analysis not performed)
El-Serag 2011[218]	Intervention does not match protocol: surveillance was ultrasound or alpha-fetoprotein. Population does not match protocol: chronic liver disease irrespective of cirrhosis (cirrhosis 40.5%).
Eltabbakh 2015[223]	Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed)
Elzayadi 2010[219]	Population does not match protocol: people with HCC and chronic liver disease but with mixed aetiology (20% HBV). Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed).
Fasani 1999[229]	Non-randomised study comparing 12-monthly versus 6-monthly surveillance (multivariate analysis not performed)
Gaba 2013[264]	Population does not match protocol: recruited people with HCC but unclear if they all had cirrhosis. Intervention does not match protocol: surveillance defined as a history of more than one imaging investigation (type of imaging not specified).
Gebo 2002[275]	Systematic review. Protocol included studies in people with all chronic liver disease not just cirrhosis. Protocol did not restrict surveillance to ultrasound with or without alpha-fetoprotein.
Han 2013[314]	Population does not match protocol: people with HCC (84.3% cirrhosis) but with mixed aetiology (72.3% HBV)
Hucke 2011[334]	Comparison does not match protocol: comparison of outcomes between two time periods before and after introduction of the EASL HCC surveillance guidelines. Non-randomised study (multivariate analysis not performed).
Hung 2015[337]	Incorrect intervention: study looks at screening rather than surveillance. Incorrect population: not just patients with cirrhosis.
Izzo 1997[372]	No comparator group: incidence of HCC in patients undergoing 3-monthly surveillance. Population does not match protocol: people with viral hepatitis irrespective of cirrhosis.
Jan 2005[374]	Incorrect study design: conference abstract. Population does not match protocol: people without cirrhosis (surveillance versus no surveillance).
Jou 2010[381]	Intervention does not match protocol: surveillance versus no surveillance but surveillance method and frequency unclear ("an imaging exam for the detection of HCC in the year before diagnosis")
Kalman 2014[385]	Incorrect intervention: investigated any imaging not just ultrasound
Kansagara 2014[391]	Systematic review. Protocol included studies in people with all chronic liver disease not just cirrhosis. Surveillance method of included studies

Reference	Reason for exclusion
	was ultrasound or other methods such as alpha-fetoprotein alone or an alternative scanning method.
Kemp 2005[394]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 19% hepatitis B.
Kim 2003[407]	Population does not match protocol: people with cirrhosis, mixed aetiologies with predominantly hepatitis B (58%), surveillance every 3 months versus 6 months
Khalili 2015[396]	Correct intervention but interval not relevant: effectiveness of ultrasound surveillance of ≤12 months was compared to >12 months
Kohli 2014[416]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 31% hepatitis B
Kuo 2010[424]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 55.6% hepatitis B or hepatitis B co-infection
Leykum 2007[448]	Population does not match protocol: population was people with HCV but not all people had cirrhosis. Co-infection with HBV in 40%.
Liu 2015B[456]	Incorrect intervention: study uses CT scan instead of ultrasound
Manini 2014[484]	Descriptive study, not comparing between intervals of surveillance
Marks 2015[487]	Incorrect intervention: study uses MRI instead of ultrasound
Marrero 2002[489]	Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed)
McGowan 2015[502]	No comparison: practice and knowledge of GPs' adherence to recommendations
Noda 2010[552]	Population does not match protocol: chronic liver disease irrespective of cirrhosis (cirrhosis 68.8%). Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed).
Onodera 1994[565]	Population does not match protocol: people with HCC but unclear if all people had cirrhosis and the proportion of people with HBV not clear. Non-randomised study (multivariate analysis not performed).
Panda 2014[572]	Narrative review
Prapruttam 2014[613]	Incorrect population: many patients with Hepatitis B and not necessarily cirrhosis. No comparison – just descriptive.
Sangio 2004[655]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 25.9% hepatitis B
Santago 2003[656]	Population does not match protocol: people with haemophilia and HCV but not all people had cirrhosis
Saquib 2015[658]	Incorrect population: asymptomatic patients, not having cirrhosis
Sherman 1991[680]	Incorrect study design: abstract
SHERMAN 2014[679]	Incorrect study design (review, non-systematic)
Shoreibah 2014[682]	Review article
Silveira 2008[684]	Intervention does not match protocol (surveillance test that prompted further investigation was not ultrasound in all cases due to variations in patient and physician preference)
Singal 2014 [686]	Systematic review. Protocol included studies in people with all chronic liver disease not just cirrhosis.
Singal 2015[687]	No comparison: study investigates reasons for inconsistent surveillance in a hospital in Dallas, USA
Solmi 1996[698]	Population does not match protocol: people with HCC and chronic liver disease but only 70.6% had cirrhosis

Reference	Reason for exclusion
Stravitz 2008[713]	Comparison does not match protocol: standard surveillance versus substandard surveillance (standard surveillance consisted of ultrasound or another imaging at least once in the year prior to HCC diagnosis)
Tanaka 2006[719]	Population does not match protocol: people with HCC and HCV but only 79.4% had cirrhosis
Taura 2005[722]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 18.5% hepatitis B or hepatitis B co-infection. Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed). Surveillance was based on ultrasound or alpha-fetoprotein results.
Thompson 2007[732]	Systematic review: protocol only included RCTs and not observational studies. No RCTs identified for comparison of surveillance versus no surveillance in people with cirrhosis.
Tomiyama 2013[734]	Incorrect study design: prognostic study assessing the risk factors for the development of HCC in people with primary biliary cholangitis (all received the same HCC surveillance frequency with no comparator group)
Toyoda 2006[736]	Population does not match protocol: presumed mixed population, not only people with cirrhosis. Co-infection with HBV in 21%, no surveillance versus surveillance.
Trevisani 2002[738]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 26.8% hepatitis B
Trevisani 2007[739]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 20.8% hepatitis B
Trinchet 2007[741]	Conference abstract
TRIVEDI 2015[743]	Incorrect study design: prognostic study assessing the risk factors for the development of HCC in people with primary biliary cholangitis (all received the same HCC surveillance frequency with no comparator group)
Vanvlier 2005[755]	Population does not match protocol: people with cirrhosis, mixed aetiologies with 17% hepatitis B. Surveillance method for the surveillance group was not reported.
Villalvazo 2015[763]	Conference abstract; intervention does not match review protocol
Wang 2011[770]	Conference abstract. Population does not match protocol: people with HBV and HCV but not all had cirrhosis.
Wang 2013[771]	Population does not match protocol: people with HBV and HCV but not all had cirrhosis (31.9% with cirrhosis and 34.9% hepatitis B)
Wang 2015A[768]	Conference abstract; incorrect population – mainly patients with hepatitis B that are excluded from review protocol
Wong 2013[788]	Population does not match protocol: mixed aetiologies with 22.7% hepatitis B. Surveillance method for the surveillance group was CT or ultrasound.
Yang 1997[794]	Population does not match protocol: people with HBV
Yang 2011[795]	Surveillance method for the surveillance group was CT, MRI or ultrasound. Population does not match protocol: cirrhosis 83%.
YEH 2014[799]	Population does not match protocol: people at risk for HCC but not all people had cirrhosis
Yuen 2003[808]	Review (non-systematic)
Zapata 2010[809]	Population does not match protocol: people with chronic liver disease but unclear if they all had cirrhosis and proportion of HBV unclear. Non-randomised study comparing surveillance with no surveillance (multivariate analysis not performed).

Reference	Reason for exclusion
Zhang 1997[810]	Incorrect study design: abstract
Zhang 2004[811]	Population does not match protocol: people with HBV

L.5 Surveillance for the detection of varices

Table 41: Studies excluded from the clinical review

Reference	Reason for exclusion
Amarapurkar 2013[33]	Conference abstract. Incorrect study design: adherence to guidelines in India.
Barritt 2009[58]	Incorrect study design: adherence to guidelines for screening for gastroesophageal varices in the US
Cales 1990[115]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
Cestari 1996[133]	Review article (non-systematic)
Chasalani 1999[139]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
Dagradi 1972[184]	Population does not match protocol: varices at baseline. Incorrect study design: not comparing different frequencies of surveillance.
D' Ambrosio 2011[181]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
De Franchis 2010[188]	EASL guidelines on the diagnosis of portal hypertension and its treatment
Debernardi 2014[193]	Population does not match protocol: treatment with endoscopic control following oesophageal variceal eradication by band ligation
Elia 2012[221]	Conference abstract. Population does not match protocol: assessment of frequency of endoscopic control after variceal obliteration.
Ferruzzi 2011[245]	Conference abstract. Population does not match protocol: assessment of frequency of endoscopic control after variceal obliteration.
Garcia-Tsao 2007[272]	AASLD guidelines on the prevention and management of varices
Giannini 2005[276]	Incorrect study design: prognostic study assessing the risk factors for the development of varices
Giraldez 2003[287]	Incorrect study design: prognostic study assessing the risk factors for variceal haemorrhage
Hsu 2013[330]	Incorrect study design: prognostic study assessing the risk factors for variceal bleeding
Jensen 2002[375]	Incorrect study design: review (non-systematic)
Khambaty 2014[397]	Incorrect study population: patients already had varices. Incorrect study design: aims to characterise compliance rates with surveillance; does not define 'timely surveillance'.
Krystallis 2012[422]	Incorrect study design: review (non-systematic)
Moodley 2010[522]	Incorrect study design: adherence to guidelines for screening and treatment of varices
Ooi 2013[566]	Conference abstract. Incorrect study design: prevalence of endoscopic screening and outcomes.
Riley 1999[630]	Review article: does not address review question
Saab 2003[642]	Incorrect study design: cost-effectiveness model
Sacher- Huvelin 2015[644]	Incorrect study design: study compares 2 endoscopy methods in terms of diagnostic test accuracy

Reference	Reason for exclusion
Sort 2014[704]	Incorrect study design: study looks at diagnostic test accuracy rather than comparing different frequencies of surveillance
Spiegel 2003[705]	Incorrect study design: cost-effectiveness model
Zoli 1990[822]	Incorrect study design: not comparing different frequencies of surveillance

L.6 Prophylaxis of variceal haemorrhage

Table 42: Studies excluded from the clinical review

Study	Exclusion reason
Agrawal 2002[16]	Conference abstract
Anon 1995[2]	Conference abstract
Anon 2012[4]	Review
Banares 1999[52]	Not review population. No relevant outcomes.
Bendtsen 1991[67]	No relevant outcomes
Berges 1983[69]	Not in English
Bhardwaj 2013[77]	Conference abstract
Bosch 1988[90]	Conference abstract
Bosch 1990[89]	Conference abstract
Bosch 2005[88]	Commentary on Merkel 2004 (assessed for eligibility in this review)
Burroughs 1992[108]	Commentary on Sorensen 1991
Cales 1999[116]	Not review population. Patients with no or small oesophageal varices at endoscopy.
Chen 1993[148]	Not in English
Chen 1999[141]	Conference abstract
Chen 2000[142]	Conference abstract
Deschenes 2000[200]	Commentary on Sarin 1999 (included in this review)
Drastich 2005[209]	Not in English
Elder 1992[220]	Review article
Elta 1991[222]	Commentary on Andreani 1990 (included in this review)
Feng 2012[233]	Not in English
Ferrarese 2014[244]	Conference abstract
Funakoshi 2012[263]	Systematic review: same studies included in the Cochrane review which has already been included
Gawrieh 2005[273]	Commentary on Schepke 2004 (included in this review)
Gluud 2007[289]	Systematic review: same studies included in the Cochrane review which has already been included
Grace 1988[303]	Conference abstract
Grace 1990[304]	Conference abstract
Hayes 1990[319]	Systematic review: methods are not adequate/unclear
Huang 2007[332]	Not in English
Ideo 1998[353]	Not review intervention (nadolol)
Imperiale 1992[362]	Commentary on Poynard 1991 (assessed for eligibility in this review)
Imperiale 2001[360]	Systematic review: methods are not adequate/unclear
Imperiale 2007[361]	Cost-effectiveness analysis. No relevant clinical outcomes.

Khuroo 2005[401]	Systematic review: same studies included in the Cochrane review which has already been included
Korula 1991[419]	Commentary on Groszmann 1990 (assessed for eligibility in this review)
Lebrec 1988[436]	Not review intervention (nadolol)
Lebrec 1990[437]	Systematic review: methods are not adequate/unclear
Lebrec 1993[433]	Systematic review: methods are not adequate/unclear
Lebrec 1994[434]	Review article
Li 2011[449]	Systematic review: same studies included in the Cochrane review which has already been included
Lo 2004[458]	Not review intervention (nadolol). Included in Cochrane review but excluded from this review.
Lopez-Acosta 2002[464]	Conference abstract
Manera 2012[483]	Conference abstract
Merkel 2003[511]	Conference abstract (full text article assessed for eligibility Merkel 2004)
Merkel 2004[512]	Not review intervention (nadolol)
Mishra 2007[517]	Conference abstract
Omar 1998[563]	Conference abstract
Pagliaro 1986[571]	Not full paper (letter to the editor). Full paper included in this review (Pagliaro 1989).
Pagliaro 1992[570]	Systematic review: methods are not adequate/unclear
Pedrosa 1992[589]	Systematic review: methods are not adequate/unclear
Plevris 1994[597]	Not review population. Patients with and without varices.
Poynard 1991[604]	Systematic review: methods are not adequate/unclear
Psilopoulos 2002[615]	Preliminary report (study included in this review)
Ricca Rosellini 1991[627]	Systematic review: methods are not adequate/unclear
Romero 2011[638]	Conference abstract
Saab 2003[642]	Not RCT: decision analytic model
Salami 2011[647]	Conference abstract
Sarin 2000[659]	Review
Sorensen 1991[702]	Population is people with all sizes of varices and no subgroup analyses to match the population strata of this protocol
Shah 2012[672]	Conference abstract
Sussman 2003[716]	Commentary on Lui 2002 (assessed for eligibility in this review)
Teran 1997[725]	Not RCT (cost-effectiveness model)
Tripathi 2007[742]	Systematic review: same studies included in the Cochrane review which has already been included
Vlachogiannakos 2000[764]	Review

L.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Table 43: Studies excluded from the clinical review

Study	Exclusion reason
Ali 2014[24]	Not relevant intervention, comparison and population (patients in remission from recurrent hepatic encephalopathy
Ahmed 2014[17]	Purpose of study is treatment of SBP, not prevention of bacterial

Study	Exclusion reason
	infections
Albillos 2004[22]	Not review population (not upper gastrointestinal bleeding). Incorrect interventions (antibiotic compared to placebo).
Alvarez 2005[32]	Not review population (not variceal bleeding)
Bernard 1998[70]	Not review population (not upper gastrointestinal bleeding)
Bernard 1999[71]	Incorrect interventions (antibiotic compared to placebo)
Casper 2015[125]	Protocol only; incorrect study population (patients with cirrhosis and ascites)
Dever 2015[201]	Narrative review
Fagiuoli 2014[227]	Consensus conference recommendations; no data
Gulberg 1999[309]	Incorrect interventions (study comparing dosages for the same antibiotic)
Jindal 2014[379]	Conference abstract of population not matching the study protocol
Jindal 2014A[380]	Not review population (patients have spontaneous bacterial peritonitis)
Lata 2005[432]	Drug unlicensed in UK
Londono 2015[459]	Conference summary
Loomba 2009[463]	Not review population (not variceal bleeding). Incorrect interventions (antibiotic compared to placebo).
Piano 2014[595]	Poster without abstract or any information
Rao 2014[618]	Conference abstract of observational study
Saab 2009[643]	Not review population (not variceal bleeding). Incorrect interventions.
Schubert 1991[665]	Commentary
Soares-weiser 2002[695]	This is the original Cochrane review which has since been updated (Chavez-Tapia 2010) and included
Soares-weiser 2003[696]	Incorrect interventions (antibiotic compared to placebo)
Soriano 1992[703]	Incorrect interventions (antibiotic compared to placebo)
Tellez-avila 2013[724]	Incorrect interventions (antibiotic compared to placebo). Not review population (not upper gastrointestinal bleeding).
Thevenot 2015[731]	Incorrect study population (people with cirrhosis and sepsis)
Tuncer 2003[747]	Purpose of study is treatment of SBP, not prevention of bacterial infections

L.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 44: Studies excluded from the clinical review

Study	Exclusion reason
Abou-Assi 2004[11]	Incorrect study design: abstract
Adebayo 2015[14]	Incorrect intervention and comparison: trial looking at new pump system versus large volume paracentesis
Albillos 2005[21]	Systematic review: same studies in this systematic review as in the Cochrane review which has already been included
Bai 2014[49]	Systematic review: same studies in this systematic review as in the Cochrane review which has already been included

Campbell 2005[118]	Incorrect study design. Secondary analysis of Sanyal 2003 study (included).
Chen 2014[146]	Systematic review: most of studies in this review were in the Cochrane review which has already been included
D'Amico 2005[183]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included
Deltenre 2005[198]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included
Engelmann 2015[225]	Incorrect comparison: trial looking at new pump system versus large volume paracentesis and TIPS; Poster of study protocol only, no data yet
Gines 1991[283]	Incorrect interventions: peritoneovenous shunting
Gines 1995[281]	Incorrect interventions: LVP compared to shunt with titanium tip
Gough 1993[302]	Not review population: malignant ascites
Lebrec 1996[435]	TIPS intervention not performed according to current UK practice
Luo 2015[468]	Incorrect study population: participants all have portal vein thrombosis. Incorrect comparison: trial is looking at prevention of bleeding.
Qi 2015A[616]	Systematic review looking at treatments for bleeding rather than ascites
Salerno 2007[650]	Systematic review: same studies included in this systematic review as in the Cochrane review which has already been included

L.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 45: Studies excluded from the clinical review

Study	Exclusion reason
Ahmed 2014[17]	Not review population (management of patients with SBP). Inappropriate comparison.
Ali 2014[24]	Not relevant intervention, comparison and population (use of antibiotics to prevent occurrence of hepatic encephalopathy in patients with cirrhosis)
Alvarez 2005[32]	Inappropriate comparison (head-to-head trial). Study population includes more than 15% of patients who previously had SBP.
Bauer 2002[60]	Inappropriate comparison (head-to-head trial). Study population includes more than 15% of patients who previously had SBP.
Bernard 1998[70]	Systematic review. Relevant included papers in Cochrane review. Study population includes more than 15% of patients who previously had SBP.
Casper 2015[125]	Relevant RCT but protocol only; results will not be published before the guideline
Casper 2015A[124]	Relevant RCT but conference abstract of protocol only; results will not be published before the guideline
Das 1998[185]	Cost analyses, not from a unique RCT
Dever 2015[201]	Narrative review
Fagiuoli 2014[227]	Consensus conference recommendations; no data
Frazee 2005[253]	Systematic review. Relevant included papers in Cochrane review.
Gines 2010[282]	Systematic review. Relevant included papers in Cochrane review.
Gines 1990[284]	Study population includes more than 15% of patients who previously had SBP
Inadomi 1997[364]	Cost analyses, not from a unique RCT
Jindal 2014[379]	Conference abstract; study population not matching the review protocol

Study	Exclusion reason
Jindal 2014A[380]	Conference abstract; study population already has SBP
Londono 2015[459]	Conference summary
Lontos 2008[461]	Published as an abstract
Lontos 2014[462]	Inappropriate comparison. Unable to obtain full paper.
Loomba 2009[463]	Systematic review. Relevant included papers in Cochrane review.
Mostafa 2014[529]	Inappropriate comparison. Incorrect interventions.
Navasa 1996[541]	Inappropriate comparison
Navasa 2005[540]	Published as an abstract
Novella 1997[554]	People with variceal bleeding (includes significant proportion of patients with upper GI haemorrhage). Inappropriate comparison (not versus placebo or no treatment).
Piano 2014[595]	Poster without abstract or any information
Rao 2014[618]	Conference abstract of observational study (RCTs only in this review)
Saab 2009[643]	Systematic review. Included papers in Cochrane review. People with previous SBP (meta-analysis includes studies on secondary prophylaxis).
Sandhu 2005[652]	Incorrect interventions. Inappropriate comparison.
Segarra-Newnham 2010[670]	Systematic review. Included papers in Cochrane review. No meta-analysis of results performed.
Singh 1995[688]	Study population includes more than 15% of patients who previously had SBP
Singh 2013[691]	Incorrect interventions. Inappropriate comparison.
Terg 2000[726]	Not review population (management of patients with SBP)
Thevenot 2015[731]	Incorrect study population (people with cirrhosis and sepsis)

L.10 Volume replacers in hepatorenal syndrome

Table 46: Studies excluded from the clinical review

Study	Exclusion reason
Altman 1998[31]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome). Not receiving vasoconstrictors.
Angeli 2008[38]	Incorrect study design (non-systematic review)
Angeli 2013[37]	Incorrect study design (non-systematic review)
Arroyo 2003[40]	Incorrect study design (non-systematic review)
Bagshaw 2010[48]	Incorrect study design (non-systematic review)
Barada 2004[56]	Incorrect study design (non-systematic review)
Boyer 2012[104]	Incorrect interventions (IV terlipressin versus placebo in people with type I hepatorenal syndrome also receiving IV albumin)
Boyer 2012A[105]	Incorrect interventions (IV terlipressin versus placebo in people with type I hepatorenal syndrome also receiving IV albumin)
Boyer 2015[106]	Incorrect comparison: trial looking at effect of vasopressin rather than volume replacer
Burroughs 2003[109]	Incorrect study design (non-systematic review)
Cavallin 2015[132]	Incorrect comparison: both groups received the same volume replacer plus vasopressins
Cavallin 2015A[131]	Incorrect intervention: narrative review looking at vasopressins rather

Study	Exclusion reason
	than volume replacers
Clewell 1994[159]	Incorrect interventions (prostaglandins)
Davenport 2012[186]	Incorrect study design (non-systematic review)
Fassio 1992[230]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Fernandez 2005[236]	Population does not match protocol (people with cirrhosis and SBP, not hepatorenal syndrome)
Garcia-Compean 2002[270]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Gines 2010[282]	Systematic review: study designs inappropriate
Hadengue 1995[311]	Incorrect interventions (terlipressin)
Junge 2010[383]	Conference abstract. Could not obtain full details of study.
Landoni 2013[429]	Systematic review is not relevant to review question or unclear PICO
Lee 2009[441]	Systematic review: study designs inappropriate
Lee 2012[442]	Incorrect study design (non-systematic review)
Liu 2014[457]	Not in English
Lu 1999[465]	Incorrect interventions
Moreau 2006[524]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Mudireddy 2013[530]	Systematic review: study designs inappropriate
Nadim 2012[534]	Systematic review: study designs inappropriate
Phillips 2003[594]	Conference abstract. Could not obtain full details of study.
Planas 1990[596]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Reddy 2012[622]	Incorrect study design (non-systematic review)
Rena 2010[625]	Incorrect study design (non-systematic review)
Salerno 1991[648]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Sanyal 2008[657]	Inappropriate comparison. Both groups receiving albumin.
Schepke 2007[661]	Incorrect study design (non-systematic review)
Schewior 2008[662]	Conference abstract. Could not obtain full details.
Schmidt 2006[663]	Incorrect study design (non-systematic review)
Singla 2011[692]	Incorrect study design
Skagen 2010[693]	Systematic review is not relevant to review question or unclear PICO
Sola-Vera 2003[697]	Population does not match protocol (people with cirrhosis and ascites undergoing paracentesis, not hepatorenal syndrome)
Tandon 2007[720]	Systematic review is not relevant to review question or unclear PICO
Turban 2007[748]	Incorrect study design (non-systematic review)
Whittman 2007[779]	Inappropriate comparison
Wong 2015[783]	Incorrect comparison: trial looking at effect of vasopressin rather than volume replacer
Wong 2001[782]	Incorrect study design (non-systematic review)
Wong 2007[784]	Incorrect study design (non-systematic review)
Yang 2001[798]	Not in English
Yang 2014[796]	Not in English

Study	Exclusion reason
Yu 2013[804]	Inappropriate comparison
Zhang 2009[814]	Not in English

L.11 Management of an episode of acute hepatic encephalopathy

Table 47: Studies excluded from the clinical review

Reference	Reason for exclusion
Abid 2005[10]	Conference abstract
Alexander 1992[23]	Not review population (no hepatic encephalopathy)
Als-Nielsen 2001[26]	Review paper checked for references
Als-Nielsen 2003[30]	Cochrane review checked for references
Als-Nielsen 2004[28]	Review paper checked for references
Als-Nielsen 2004[29]	Review paper checked for references
Als-Nielsen 2004[27]	Review paper checked for references
Anon 1976[1]	Review paper checked for references
Atterbury 1976[42]	Conference abstract
Atterbury 1978[43]	Twenty episodes of acute hepatic encephalopathy occurred in people in a trial of the same comparison (lactulose versus neomycin) for chronic hepatic encephalopathy (so these patients were already undergoing treatment)
Avery 1972[47]	Review (non-systematic)
Bai 2013[50]	Review paper checked for references
Bajaj 2015[51]	Prevention of recurrence of overt hepatic encephalopathy episodes
Banares 2013[53]	Incorrect population (looking at the improvement of acute hepatic encephalopathy in people with acute-on-chronic liver failure – deterioration of liver function which included HRS and circulatory failure as well as acute hepatic encephalopathy)
Bansky 1989[55]	Not a comparative study. All subjects received flumazenil.
Bass 2004[59]	Conference abstract
Berenguer 1971[68]	Not in English
Bircher 1966[79]	People with chronic hepatic encephalopathy
Blanc 1994[82]	Non-English language paper
Blanco 2011[83]	Conference abstract
Block 2010[84]	Primary or secondary prevention of hepatic encephalopathy. Incorrect line of therapy.
Bucci 1993[107]	Incorrect population. Unclear if patients had acute or chronic hepatic encephalopathy.
Cadranel 1995[110]	For the 8 episodes of hepatic encephalopathy randomised to the placebo arm, if there was no improvement after 10 minutes infusion, flumazenil was given. This occurred for all 8 episodes and the effectiveness of flumazenil was assessed in both arms of the trial, in a before-and-after manner.
Corazza 1982[167]	Population is people with clinical evidence of grade 1 chronic hepatic encephalopathy
Conn 1977[166]	People with chronic hepatic encephalopathy. Crossover study.
Cowan 1986[172]	Conference abstract

Reference	Reason for exclusion
DeMarco 1984[192]	Comparison between paromomycin (a drug not licenced in the UK) and rifaximin
DuPont 2015[212]	Narrative review of therapeutic effects and mechanism of action of rifaximin (references checked)
Eltawil 2012[224]	Systematic review – not all acute hepatic encephalopathy (checked for references)
Falavigna 2007[228]	Cochrane review – checked for references
Feher 1997[232]	Not review population
Fera 1993[234]	People with minimal hepatic encephalopathy (sometimes called latent or subclinical)
Gluud 1983[288]	Conference abstract
Gluud 2015[291]	Systematic review – not all acute hepatic encephalopathy (checked for references)
Gluud 2015A[290]	Poster of unpublished systematic review; uncertain if studies included are acute or chronic hepatic encephalopathy
Grimm 1988[306]	Not a comparative study (all patients received flumazenil)
Groeneweg 1996[307]	Incorrect study design. An ancillary study of a RCT (Gyr 1996, included in this review).
Grungreiff 1993[308]	Not in English
Held 1987[323]	Not in English
Held 1988[322]	Not in English
Hirayama 1982[325]	Some (17.5%) of the participants did not have cirrhosis but had hepatic carcinoma
Howard 1993[327]	Letter – checked for references
Hwang 1988[347]	Not in English
Jiang 2008[378]	Review – checked for references
Jiang 2009[377]	Review paper checked for references
Kersh 1973[395]	Incorrect study design
Khokhar 2015[399]	Secondary prevention of recurrence of hepatic encephalopathy
Kimer 2014[408]	Review – checked for references
Kimer 2015[409]	Review protocol only
Kircheis 1992[410]	Not in English
Kircheis 2002[411]	Review paper checked for references
Klotz 1989[414]	Commentary
Lang 1995[430]	Not in English
Maharsh 2015[476]	Trial for prevention rather than treatment of acute hepatic encephalopathy Incorrect study population: patients with acute variceal bleed
Malaguarnera 2003[477]	Duration of intervention longer than 2 weeks
Malaguarnera 2005[479]	Duration of treatment longer than 2 weeks
Malaguarnera 2006[478]	Incorrect interventions
Malaguarnera 2009[480]	(BCAA + L-acetylcarnitine) is compared against BCAA only, and all participants received lactulose
Martí-carvajal 2014[490]	Cochrane review protocol
Massa 1993[494]	People with chronic hepatic encephalopathy
Mazariegos 1998[500]	Conference abstract

Reference	Reason for exclusion
Mcgee 2011[501]	Cochrane review – checked for references
Meier 1988[508]	Not a comparative study (all patients received flumazenil)
Michel 1984[514]	Incorrect interventions. Branched chain amino acids infusion is compared with aromatic amino acids infusion.
Michel 1985[513]	Incorrect interventions. Branched chain amino acids infusion compared with conventional amino acids infusion.
Miglio 1997[515]	Treatment period >14 days
Mohammad 2012[519]	Review – checked for references
Morgan 1982[526]	Crossover study (results also presented for first treatment only, but only for one arm of the study – metronidazole before neomycin but not for neomycin before metronidazole). Some patients on treatment for chronic hepatic encephalopathy symptoms before the start of the trial.
Neff 2006[548]	Incorrect line of therapy. The participants had suffered from hepatic encephalopathy related to poor compliance or ineffective therapy for hepatic encephalopathy prior to entering the study.
Orlandi 1981[568]	Recruits people with chronic hepatic encephalopathy and an acute episode, washout period of 15 days but unclear treatment for chronic hepatic encephalopathy prior to this (recruited both inpatients and outpatients, the mean duration of hepatic encephalopathy was 14.1 months). The mean duration of the current hepatic encephalopathy episode prior to trial treatment was 14–18 days, therefore the intervention was not first-line treatment of the acute episode.
Panella 1993[573]	Conference abstract
Parini 1992[576]	Comparison between paromomycin (a drug not licenced in the UK) and rifaximin
Patel 2015[584]	Conference abstract clinical trial protocol involving patients with chronic hepatic encephalopathy
Pedretti 1991[588]	People with chronic hepatic encephalopathy
Pomier-layrargues 1994[599]	Crossover study
Poo 2006[601]	Review paper checked for references
Poo 2007[600]	Conference abstract
Ratnaike 1975[619]	Not a comparative study (all patients received lactulose)
Raza 2004[621]	Lactulose enema with oral lactulose was compared against tap water enema with oral lactulose: same drug class compared
Rigali 2006[629]	Review (drug information update) – references checked
Romeiro 2013[637]	Incorrect interventions
Sen 2004[671]	Incorrect population (looking at the improvement of acute hepatic encephalopathy in people with acute-on-chronic liver failure – deterioration of liver function which included HRS and circulatory failure as well as acute hepatic encephalopathy)
Sharma 2013[673]	Commentary
Simmons 1970[685]	Incorrect line of therapy. Half the participants had hepatic encephalopathy for between 4 and 93 days prior to the start of the study (and unclear prior treatment, therefore treatment may not be first line). Type of hepatic encephalopathy defined as chronic in 4/26 patients (according to Zieve et al. 1960 criteria) and all patients pooled for analysis.
Stauch 1992[708]	Not in English
Sterling 1994[710]	Crossover study. Not full paper (summary/commentary).

Reference	Reason for exclusion
Testa 1985[727]	People with minimal hepatic encephalopathy (sometimes called latent or subclinical)
Trey 1970[740]	Mechanisms of action study
Uribe 1980[751]	Conference abstract
Van der rijt 1995[754]	Crossover study. Incorrect population – patients had acute or chronic underlying liver disease.
Venturini 2005[757]	Population does not match protocol – people with cirrhosis but without hepatic encephalopathy
Wahib 2014[765]	Unable to obtain full text article
Williams 2000[781]	Not a comparative study (all patients received rifaximin)
Xue 2010[792]	Commentary
Younsi 1991[803]	Not in English
Yuan 2008[807]	Cochrane review protocol
Zhu 1998[817]	Not in English
Zhu 2015[818]	Systematic review protocol – acute and chronic hepatic encephalopathy

Appendix M: Excluded health economic studies

M.1 Risk factors and risk assessment tools

None.

M.2 Diagnostic tests

Table 48: Studies excluded from the economic review

Reference	Reason for exclusion
Crossan 2015[177]	Population does not match protocol: diagnostic tests for cirrhosis were assessed for a population with mixed aetiology; protocol specifies testing of people with different aetiologies must be analysed separately.

M.3 Severity risk tools

None.

M.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Table 49: Studies excluded from the economic review

Reference	Reason for exclusion
Ruelas 2004[639]	Population does not match protocol: study included people without cirrhosis.

M.5 Surveillance for the detection of varices

None.

M.6 Prophylaxis of variceal haemorrhage

Table 50: Studies excluded from the economic review

Study	Exclusion reason
Dipascoli 2014[204]	Intervention does not match protocol: beta-blocker used was nadolol.

M.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

None.

M.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 51: Studies excluded from the economic review

Reference	Reason for exclusion
Parker 2013[581]	This study was assessed as not applicable due to the study design: it compared costs of the same patients before and after TIPS was carried out; no randomisation.

M.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

None.

M.10 Volume replacers in hepatorenal syndrome

None.

M.11 Management of an episode of acute hepatic encephalopathy

None.

Appendix N: Cost-effectiveness analysis: diagnostic tests and surveillance strategies for cirrhosis

N.1 Introduction

Diagnosing cirrhosis in people with liver disease is a crucial point in a patient's disease pathway as it triggers a more intensive clinical path that includes surveillance for the cirrhosis complications of hepatocellular carcinoma (HCC) and oesophageal varices. Failing to detect cirrhosis at an early stage can have detrimental clinical effects for patients. Amongst hepatologists and gastroenterologists, the only commonly agreed reference standard for the diagnosis of advanced fibrosis or cirrhosis is liver biopsy. By nature liver biopsy is an invasive test associated with adverse clinical events and disutility for some people. In addition, it is a resource-intensive procedure, conducted with the guidance of ultrasound, which usually requires a day-case admission and has a considerable cost.

With the rising popularity of blood biomarkers associated with liver function and the increasing use of imaging tests that can stage liver fibrosis, without carrying the disadvantages of liver biopsy, these non-invasive liver tests have found their way into current clinical practice. However, the availability of the tests and the way that these are embedded into clinical practice vary substantially across NHS providers. For these reasons the GDG prioritised original economic analysis to be conducted for the review questions that address objective diagnostic tests for the diagnosis of cirrhosis and who should be offered such a test.

The economic review identified 3 studies (Canavan 2013, Steadman 2013, Stevenson 2012) that reported cost-effectiveness results in patients with different stages of fibrosis. However these studies reported outcomes for mixed populations at different stages of liver disease; none of the studies reported outcomes for only people with cirrhosis. A recently published NIHR HTA was also identified (Crossan 2015) that reported results for a population of people with cirrhosis, but this looked only at a population with mixed liver disease aetiology (including patients with viral hepatitis, alcohol-related liver disease and non-alcoholic fatty liver disease together).

Other areas of uncertainty identified in the clinical review questions were the optimal frequencies of surveillance for HCC and for oesophageal varices in people with cirrhosis, as regular surveillance for these complications is believed to lead to clinical benefits for patients but the best frequencies are unclear. These 2 review questions were hence also examined using the same whole disease pathway model.

N.2 Methods

N.2.1 Model overview

N.2.1.1 Comparators

The NGC liver disease pathway model (LDPM) was developed for this guideline and for the NICE non-alcoholic fatty liver disease guideline. The model is composed of 3 modules, covering steatosis, fibrosis and cirrhosis, and follows the progression of people with liver disease through the course of their lifetime. For this economic analysis the cirrhosis module was used, and was adapted for separate populations with alcohol-related liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), hepatitis B (HBV) and hepatitis C (HCV).

For this analysis, 23 single tests, identified in the relevant clinical review, and 4 combinations of tests, were compared for 1 or more of the 4 populations of interest. These are summarised below. Several tests were not considered for modelling due to the absence of sensitivity and specificity data in the relevant papers (only area under the curve figures reported). For each aetiology population the diagnostic tests are also compared against the reference standard, liver biopsy.

Two further strategies were also considered which did not include any tests:

- no test, monitor all patients in the relevant population assuming they have cirrhosis
- no test, monitor no-one, assuming none have cirrhosis until later clinical presentation.

In the hepatitis C cohort, for modelling purposes, there was an additional no-testing strategy for which in addition to no monitoring there would also be no treatment given for hepatitis C.

Table 52: Tests included in the model by disease aetiology

Hepatitis B	Hepatitis C	Alcohol-related liver disease	Non-alcoholic fatty liver disease
FibroTest at 0.74	Platelet count	APRI at 1.5–2.5	TE at 10.0 – <13.0 kPa
Transient elastography (TE) at 11.0 kPa	FibroTest at a 0.56–0.75	TE at 11.0 – <13.0 kPa	TE at >15 kPa
APRI at 2.0	ELF at 9.3–10.44	TE at 15+ kPa	ARFI at 1.636–1.9
APRI at 1.0	APRI at 0.5 – <1.5		
	APRI at 1.5–2.5		
	FIB-4 at 2.3122		
	AST/ALT ratio at 1.0		
	TE at 9.0 – <13.0 kPa		
	TE at 13.0 – <15.0 kPa		
	TE at 15+ kPa		
	ARFI at 1.55–2.0		
	pSWE at optimal level		
	TE and ARFI (at 12.2 kPa and 1.8 m/s)		
	TE or ARFI (at 12.2 kPa and 1.8 m/s)		
	SAFE algorithm		
	Castera algorithm		

***APRI**: AST, ALT, platelet count; **ARFI**: acoustic radiation force impulse; **Castera algorithm**: combination of TE and FibroTest, liver biopsy as confirmation when needed; **ELF**: enhanced liver fibrosis test including a serum concentration of procollagen-III aminoterminal-propeptide, tissue inhibitor of matrix metalloproteinase-1 and hyaluronic acid; **FIB-4:** age, AST, ALT, platelets count; **FibroTest**: Alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, alanine transaminase; **pSWE:** point shear wave elastography; **SAFE algorithm**: sequential use of APRI, FibroTest and liver biopsy; **TE:** Transient elastography*

N.2.1.1.1 Combinations of more than 1 test

In planning the model structure, the inclusion of combinations of tests was considered. Four algorithms were identified in papers included for the hepatitis C population (at the bottom of Table 52 above) and these were included alongside the single tests. The GDG also considered using 2 of the single tests (excluding liver biopsy) consecutively. The GDG considered that combinations should include 1 blood test and 1 imaging test as these would be likely to give independent results. The most promising combination would be one using a blood test with high sensitivity (to maximise true

positives and minimise false negatives) followed by an imaging test with high specificity (to rule out true negatives). However, when viewing the diagnostic accuracy values found in the clinical review (see Section N.2.3.2 below) no such combination could be found. Consequently there was no reason to believe any combination of 2 tests would give more accurate results than the best single tests, but with an increased cost for using 2 tests instead of 1. Therefore no such combinations were modelled.

N.2.1.2 Population

The model considers people aged 50 years at the start of the model with one of the 4 major underlying causes of cirrhosis (hepatitis B, hepatitis C, alcohol-related liver disease, non-alcoholic fatty liver disease) who are therefore at risk of developing cirrhosis. Patients with different aetiologies are treated as separate patient cohorts in the model. Hepatitis B patients are further separated in 2 cohorts (positive or negative hepatitis B e Antigen, HBeAg). Hepatitis C patients are further separated by disease genotype (Genotypes 1–4).

N.2.1.3 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and the perspective of the UK NHS and personal social services. A sensitivity analysis will also be conducted using a discount rate of 1.5% for costs and health benefits. A lifetime horizon has been chosen to fully capture the adverse outcomes derived from incorrect diagnosis.

N.2.2 Approach to modelling

The model is based on 2 phases:

- **Decision tree:** Using the sensitivity and specificity, combined with data on the prevalence of cirrhosis in each of the target populations, the model identifies the proportion of people who receive a true positive (TP), true negative (TN), false positive (FP) or false negative (FN) diagnosis.
- **Markov model:** Once the diagnosis is made the people move into the second part of the model which involves a Markov model to fully evaluate long-term health and cost outcomes for people starting with each diagnosis. The model has 6-monthly cycles and continues until death or age 100 years.

Further information and technical details are provided below.

N.2.2.1 Model structure

Figure 199: Graphical depiction of the decision tree

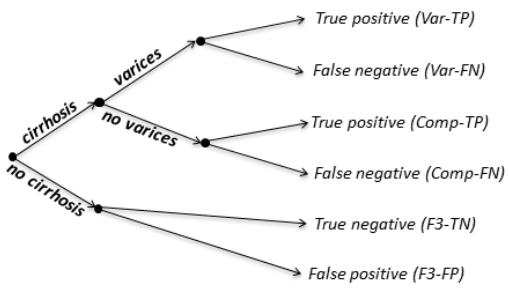
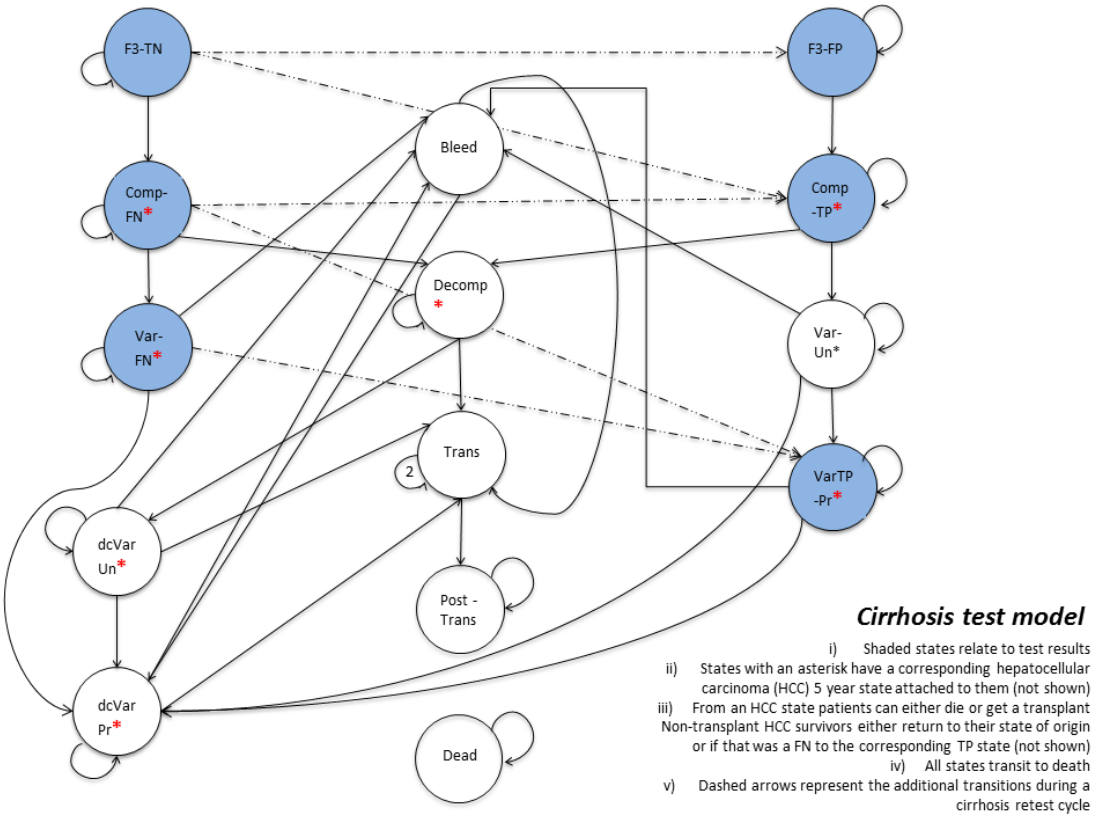


Figure 200: Graphical depiction of the Markov model



N.2.2.2 High-level model structure

Initially, a decision tree determines the proportion of people with cirrhosis who receive a correct diagnosis (true positive – TP) and an incorrect diagnosis (false negative – FN); and the proportion of people without cirrhosis who receive a correct diagnosis (true negative – TN) and an incorrect diagnosis (false positive – FP) depending on the diagnostic accuracy of every test. People diagnosed as not having cirrhosis were assumed to have advanced fibrosis (F3 on the METAVIR scale).

It is assumed that 27% of people with cirrhosis will already have medium or large varices at the time when they are first diagnosed with cirrhosis. People will receive endoscopic surveillance for oesophageal varices immediately following a positive diagnosis of cirrhosis. It is assumed that this is 100% successful at identifying medium or large varices.

Consequently, patients enter the Markov model through 6 health states:

- advanced fibrosis with a true negative diagnosis – (F3-TN)
- advanced fibrosis with a false positive diagnosis of cirrhosis– (F3-FP)
- compensated cirrhosis with a true positive diagnosis – (comp-TP)
- compensated cirrhosis with a false negative diagnosis of advanced fibrosis only – (comp-FN)
- compensated cirrhosis with oesophageal varices with a true positive diagnosis, hence immediately receiving prophylactic measures to prevent variceal bleeding – (VarTP-Pr)
- compensated cirrhosis with oesophageal varices with a false negative diagnosis of advanced fibrosis only, and hence not assessed or receiving treatment for varices – (Var-FN)

It is assumed that everyone with cirrhosis at the start of the model has compensated cirrhosis, as decompensated cirrhosis would have previously been identified by a clinician's observations without the need for the diagnostic tests examined here. Under GDG guidance, retesting for those with a

negative diagnosis was set at 2 years for all populations. The cost-effectiveness of decreasing the retesting frequency to 1 year was examined in sensitivity analyses for each population.

Overall, the model attempts to represent the natural history of the disease, from compensated cirrhosis without varices to the development of varices (which may lead to bleeding), HCC and other decompensation events, and finally to a post-liver transplant state or to death.

N.2.2.2.1 Surveillance for hepatocellular carcinoma (HCC)

Patients with cirrhosis run an increased risk of developing hepatocellular carcinoma. It is widely believed that a comprehensive HCC surveillance package can reduce the morbidity and mortality associated with HCC. However, there is a lot of uncertainty around the optimal surveillance frequency.

In the model, most of the health states depicted have a corresponding 5-year HCC state attached to them. Survivors from this cancer tunnel state that do not receive a liver transplant either return to their state of origin or are transferred to their corresponding true positive state in the cases where patients originally received an FN cirrhosis diagnosis. This is because it is assumed that if HCC is detected this would be directly attributed to cirrhosis and therefore patients would immediately receive a positive cirrhosis diagnosis without the need for further diagnostic testing.

As a model base case all patients diagnosed with cirrhosis will be monitored yearly for HCC. This was set after agreement with the GDG that this reflects common current practice in the NHS and in view of the GDG's opinion that having a no-surveillance strategy for HCC would not be appropriate. A 6-monthly surveillance strategy will also be tested for its cost-effectiveness compared with annual surveillance to contribute to the relevant clinical review question.

To apply the clinical benefit of HCC surveillance, figures from 2 different sources, identified by the clinical review (one included in the review: Santi 2010), were combined. A study by Zhang 2004 with a 5-year follow up on 18,816 hepatitis patients reported that 6-monthly surveillance (using alpha-fetoprotein [AFP] blood test plus ultrasound) was associated with a 37% reduction in HCC mortality in comparison to a no-monitor control group. This number was combined with an increased risk of death figure (1.39 hazard ratio) for patients under annual surveillance (AFP blood test plus imaging test) when compared to a 6-monthly surveillance strategy reported by Santi 2010 (649 patients of mixed disease aetiology). Therefore, for use in the model, 6-monthly and yearly surveillance were associated with a risk ratio of 0.63 and 0.88 respectively. These risk ratios were applied to the liver-associated mortality of every true positive HCC health state.

The costs of an AFP blood test and an ultrasound were added accordingly to the model as those tests were considered by the GDG to be the current HCC surveillance practice across the NHS.

Two relevant economic evaluations were identified in our systematic literature review: one that compared annual surveillance and 6-monthly surveillance in people with cirrhosis of mixed aetiology[178] and one that compared no surveillance, annual AFP, annual ultrasound, annual AFP plus ultrasound, 6-monthly AFP, 6-monthly ultrasound, and 6-monthly AFP plus ultrasound in people with cirrhosis with either alcohol-related liver disease or hepatitis C.[732,733]

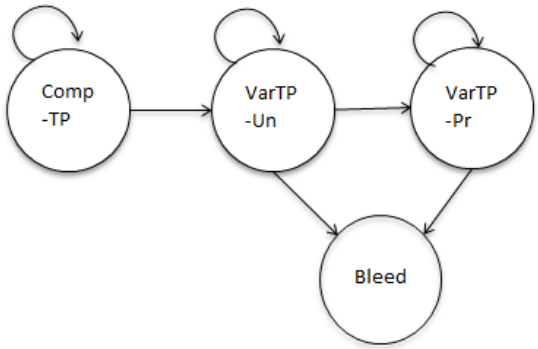
N.2.2.2.2 Surveillance for oesophageal varices

Variceal bleeding is one the most common complications of cirrhosis and is considered a decompensating event. Endoscopic surveillance for the development and the size estimation of oesophageal varices is believed to have a substantial patient benefit as those identified with medium and large varices receive a band ligation procedure that offers prophylactic benefits against variceal bleeding.

In the model base case, all patients diagnosed with cirrhosis will be monitored every 3 years for varices. This was set after agreement with the GDG that this reflects common current practice in the NHS. A 2-yearly and an annual surveillance strategy will also be tested for their cost-effectiveness compared to a 3-yearly strategy to contribute to the relevant clinical review question.

People who developed medium or large varices whilst in either compensated or decompensated cirrhosis states were represented in separate health states (depicted as Var and dcVar respectively in the model structure, Figure 200). As presented in Figure 201 below, people with cirrhosis are separated between those who have developed varices since their most recent endoscopy and so have not been yet been identified as having varices or offered a prophylactic band ligation (VarTP-Un, dcVar-Un) and those who have received an endoscopy since they have developed varices and so are assumed to have been correctly identified as having varices and consequently protected against bleeding by prophylactic band ligation (VarTP-Pr, dcVar-Pr). Similarly bleeding has been separated from the other decompensating events (ascites, hepatic encephalopathy, jaundice) and is represented as a separate state, which individuals are in for a single Markov cycle, after which if still alive they are transferred to a decompensated state, but with their varices now protected (dcVar-Pr). Prophylactic band ligation was taken to reduce the risk of bleeding by 50%, as found by a literature review provided by the GDG (Berzigotti 2013). The prevalence of varices (of any size) in people diagnosed with cirrhosis (40%) and annual rates of varices development in people with compensated or decompensated cirrhosis but without varices of 6% and 10% respectively were also sourced from this study. Those figures were adjusted accordingly to represent the proportion of people with cirrhosis with medium or large varices, which was set to 67% of the overall cohort of people with cirrhosis with varices of any size (assumption by Stevenson 2012).

Figure 201: Surveillance for varices structure



The cost of a diagnostic endoscopy is accordingly added to any Markov cycle during which surveillance for varices is conducted, depending on the frequency chosen. Under GDG guidance it was also assumed that if the endoscopy identified medium to large varices, a band ligation was offered immediately at the same visit. In the described scenario the cost of endoscopy was not applied to avoid double counting as band ligation is conducted endoscopically.

No relevant economic evaluations were identified in our systematic literature review.

N.2.2.3 Population cohorts

N.2.2.3.1 Non-alcoholic fatty liver disease (NAFLD)

This cohort has the simplest representation in the model. As for all populations, people with NAFLD diagnosed with cirrhosis will receive surveillance for HCC and varices. People with NAFLD will be offered lifestyle interventions and pharmacological treatment using pioglitazone or vitamin E regardless of whether they have advanced fibrosis (F3) or cirrhosis, and so diagnosis of cirrhosis will

not lead to any change in the treatment for the underlying NAFLD. Baseline probabilities are applied to model the progression of liver disease.

N.2.2.3.2 Alcohol-related liver disease (ALD)

All patients presenting with alcohol-related cirrhosis will need to undergo medically assisted withdrawal from alcohol as specified in NICE CG100 and CG115. Such treatment is not however different depending on whether the patient has cirrhosis or not and therefore is not represented in the current model. Instead, the model examines the effect of a positive cirrhosis test result on a patient's alcohol abstinence. A similar approach was also followed by 2 recently published NIHR HTAs on ALD cohorts (Crossan 2015, Stevenson 2012). Non-invasive liver tests were assumed to have a smaller effect compared to liver biopsy due to the latter's invasive nature. Figures on the abstinence effect of liver biopsy were sourced from Crossan 2015 (authors cite a published abstract) while the abstinence effect of non-invasive liver tests was based on authors' assumptions. Figures are tested in deterministic sensitivity analysis in the current model.

In addition, following assumptions made by the Stevenson 2012 HTA, we attached a different bleeding rate for abstainers and drinkers.

N.2.2.3.3 Hepatitis B (HBV)

Following guidance from the GDG, we assumed that all patients referred for a cirrhosis test are also receiving treatment with antiviral drugs. This was considered a rational assumption as for patients to be suspected for cirrhosis they must have been new referrals and therefore not been appropriately treated for the underlying cirrhosis cause before.

The GDG agreed that first-line treatment would be pegylated interferon alfa-2a for 1 year. Patients who do not respond to first-line treatment are switched to either tenofovir or entecavir from the second year onwards indefinitely. For modelling purposes we set 75% of the referrals for second-line treatment for tenofovir and the remaining 25% for entecavir as the GDG felt that this reflects current NHS practice. The rates by which patients respond to first-line treatment were different for patients with positive and negative e antigen. Relevant figures were sourced from the NICE Hepatitis B guideline (CG165). The therapeutic effect of the HBV antiviral drugs was applied through a relative risk ratio attached to the patient's mortality. The model also included a different progression rate from advanced fibrosis (F3) to cirrhosis for patients with positive and negative e antigen, an approach also adopted by the Crossan 2015 HTA.

N.2.2.3.4 Hepatitis C (HCV)

A new generation of polymerase inhibitor drugs for hepatitis C has been recently assessed by NICE in technology appraisals and are entering NHS practice. In order for the present economic model to reflect the most up-to-date NICE recommendations, 2 recently published drug combinations (part of TA330 and TA ID742) covering the 4 most prevalent UK HCV genotypes are included in the modelling of the cirrhosis patient pathway. Ombitasvir-paritaprevir-ritonavir is also an option for genotypes 1 and 4. We chose ledipasvir-sofosbuvir as that is at least as effective and with a similar price. Note that the economic results would not be altered by this choice of drug as both effectiveness and cost are very similar. People with HCV without cirrhosis are assumed to receive the appropriate pegylated interferon and ribavirin regimes since polymerase inhibitor drugs are not currently recommended for these patients.

With the introduction of the new antiviral treatments and their inclusion to the present model, the GDG has made a similar assumption as the one described for the HBV model cohort, that for patients to be suspected for cirrhosis they must be new referrals and therefore not appropriately treated before for the underlying cirrhosis cause (since antiviral treatments would dramatically decrease the

progression rate to cirrhosis). Therefore all of the patients in the model cohort will be treated with an antiviral agent.

The treatment effectiveness of the antiviral drugs is represented in the model by their sustained viral response (SVR). This figure is the rate of patients who have responded to treatment and therefore were 'cured' of the virus. The SVR was consequently applied to the probability of a patient progressing to the next state in the Markov model as patients that are free from the virus are assumed not to progress to more severe liver disease states. They were also assumed to only receive HCC surveillance and not varices surveillance; this was based on GDG guidance that there is still high uncertainty over the risk of HCC in 'cured' patients treated with the new drug combinations. SVRs per genotype where sourced from the evidence reports of TA330 and TA ID742.

Table 53: Sustained viral response per genotype

Genotype	People with **fibrosis**			People with **cirrhosis**		
	Drug combination	Duration	SVR	Drug combination	Duration	SVR
Genotype 1 – treatment naive	Ledipasvir-sofosbuvir	8 weeks	0.94	Ledipasvir-sofosbuvir	12 weeks	0.941
Genotype 2 – treatment naive	Pega-2a with ribavirin	24 weeks	0.815	Soforbuvir with ribavirin	12weeks	0.857
Genotype 3 – treatment naive	Pega-2a with ribavirin	24 weeks	0.712	Sofosbuvir with pega-2a & ribavirin	12 weeks	0.833
Genotype 4 – treatment naive	Pega-2a with ribavirin	48 weeks	0.436	Ledipasvir-sofosbuvir	12 weeks	0.941

In addition, under GDG guidance it was assumed that, for patients falsely identified as having cirrhosis, the drug effectiveness is identical as for the correctly diagnosed with cirrhosis patients. For patients falsely diagnosed as negative, the drug effectiveness of the fibrosis-HCV treatment options was adjusted to 50% in order to depict their lower efficacy in patients with cirrhosis.

N.2.2.4 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base case and 5,000 times for each sensitivity analysis – and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 54 and in the relevant input summary tables in Section N.2.3. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 54: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Specificity	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and Beta values were calculated as follows: Alpha=(True negatives) Beta=(Number of patients)-(True negatives)
Diagnostic odds ratio	Lognormal	Derived from the ln(DOR) and Se(ln(DOR))
Utility	Lognormal applied on utility decrements	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2
Costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. SE was set at deterministic cost/4. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = SE^2/Mean
Hepatitis B treatment effect – relative risk ratio	Log-normal	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2
Hepatitis C treatment effect – proportion of people who responded to treatment	Beta	Bounded between 0 and 1. Derived from the number of responders and non-responders. Alpha and Beta values were calculated as follows: Alpha = n responded to treatment Beta = n not responded to treatment
HCC surveillance - relative risk ratio	Log-normal	Mean = ln(mean cost) – $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96*2

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

N.2.2.4.1 Deterministic sensitivity analysis

Apart from assigning distributions to most of the model parameters, deterministic sensitivity analysis was also performed for a variety of variables.

Table 55: Summary of parameters tested in DSA

Parameter	Base case	DSA values
NAFLD		
NAFLD prevalence (50% lower/higher)	13%	6.5%, 19.5%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
Fibroscan unit cost (20% lower/higher)	£68	£54.4, £81.6
ARFI unit cost (20% lower/higher)	£51	£40.8, £61.2

Parameter	Base case	DSA values
Discount rate	3.5%	1.5%
TE>15 diagnostic accuracy (low CI)	Sens=99, Spec=96	Sens=66, Spec=90
ALD		
ALD prevalence (50% lower/higher)	34%	17%, 51%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
Abstinence after diagnosis with non-invasive liver test	Neg=0.31, Pos=0.52	Neg=0, Pos=0
TE at 11.0 - <13.0 diagnostic accuracy (low/high CI)	Sens=98, Spec=79	Sens=54, 100; Spec=54, 94
Fibroscan unit cost (20% lower/higher)	£68	£54.4, £81.6
Cirrhosis retesting	2 years	1 year
HBV (neg e antigen)		
HBV prevalence (50% lower/higher)	13%	6.5%, 19.5%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
TE at 11.0 diagnostic accuracy (low/high CI)	Sens=75, Spec=90	Sens=48, 93; Spec=85, 94
Fibroscan unit cost (20% lower/higher)	£68	£54.4, £81.6
Drug treatment effectiveness – second-line treatment (low/high CI)	0.65	0.06, 0.95
HCV (only genotype 3)		
HCV prevalence (50% lower/higher)	18%	9%, 27%
Medium to large varices at diagnosis (50% lower/higher)	27%	13.5%, 40.5%
TE at 13.0 - <15.0 diagnostic accuracy (high CI)	Sens=93, Spec=93	Sens=97; Spec=97
Fibroscan unit cost (20% lower)	£68	£54.4
HCV treatment	Yes	No
HCC surveillance in SVR patients	Yes	No
Drug treatment effectiveness – fibrosis patients	0.71	0.63, 0.79
Drug treatment effectiveness – cirrhosis patients	0.83	0.63, 0.95
Drug treatment cost (50%, 60% lower)	37,162.88	14,865, 18,581
HCC surveillance frequency		
Surveillance costs (20% lower)	£50.42	£40.3
HR comparing 6-monthly and annual surveillance (20% higher)	1.39	1.67
Varices surveillance frequency		
Surveillance costs (20% lower)	£205.66	£164.5
RR on bleeding probability (20% higher/lower)	0.50	0.40, 0.60

N.2.3 Model inputs

N.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated by clinical members of the GDG. A summary of the model inputs used in the base case (primary) analysis is provided in Table 56 and Table 57 below. Health state costs are presented separately in the relevant cost section. More details about sources, calculations and rationales for selection can be found in the sections following this summary table.

Table 56: Summary of base case model inputs

Input	Value	Source
Patient age at cirrhosis diagnosis	50 years	GDG assumption
Time horizon	Lifetime	NICE reference case
Discount rate	Costs = 3.5%; effects = 3.5%	NICE reference case

Table 57: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimates		Probability distribution	Distribution parameters
Prevalence of cirrhosis				
Hepatitis B (HBV)	0.13		95% CI 0.07–0.22	
Hepatitis C (HCV)	0.18		95% CI 0.14–0.22	
Alcohol-related liver disease (ALD)	0.34		95% CI 0.19–0.53	
Non-alcoholic fatty liver disease (NAFLD)	0.13		95% CI 0.09–0.20	
Diagnostic accuracy (HBV)	Sensitivity	Specificity	Lognormal distribution	
FibroTest at 0.74	0.47	0.91	DOR= 8.97	SE=0.74
TE at 11.0 kPa	0.75	0.90	DOR=26.37	SE=0.63
APRI at 2.0	0.20	0.84	DOR=1.28	SE=0.42
APRI at 1.0	0.67	0.81	DOR=8.38	SE=0.65
Diagnostic accuracy (HCV)	Sensitivity	Specificity	Lognormal distribution where applicable	
Platelet count	0.87	0.84	DOR=33.39	SE=0.79
FibroTest at 0.56–0.75	0.80	0.70	Sampled from the joint posterior distribution (WinBUGS iterations)	
ELF at 9.3–10.44	0.81	0.80	Sampled from the joint posterior distribution (WinBUGS iterations)	
APRI at 0.5 - <1.5	0.84	0.78	Sampled from the joint posterior distribution (WinBUGS iterations)	
APRI at 1.5–2.5	0.36	0.95	Sampled from the joint posterior distribution (WinBUGS iterations)	
FIB-4 at 2.3122	0.80	0.78	DOR=14.00	SE=0.68
AST/ALT ratio at 1.0	0.32	0.97	DOR=15.08	SE=0.57
TE at 9.0 - <13.0	0.82	0.90	Sampled from the joint posterior distribution (WinBUGS iterations)	
TE at 13.0 - <15.0	0.93	0.93	Sampled from the joint posterior distribution (WinBUGS iterations)	

Parameter description	Point estimates		Probability distribution	Distribution parameters
TE at 15+	0.86	0.91	DOR=60.75	SE=0.73
ARFI at 1.55–2.0	0.88	0.84	Sampled from the joint posterior distribution (WinBUGS iterations)	
pSWE (optimal cut-off)	0.90	0.89	DOR=69.75	SE=1.10
TE+ARFI (12.2 kPa and 1.8 m/s)	0.85	0.94	DOR=95.63	SE=0.53
TE or ARFI (12.2 kPa or 1.8 m/s)	0.96	0.83	DOR=127.50	SE=0.75
SAFE algorithm	0.86	0.90	DOR=52.58	SE=0.37
Castera algorithm	0.90	0.98	DOR=492.75	SE=0.61
Diagnostic accuracy (ALD)	Sensitivity	Specificity	Lognormal distribution	
APRI at 1.5–2.5	0.40	0.61	DOR=1.03	0.60
TE at 11.0 - <13.0	0.98	0.79	DOR=224.66	3.24
TE at 15+	0.80	0.76	DOR=12.57	0.71
Diagnostic accuracy (NAFLD)	Sensitivity	Specificity	Lognormal distribution	
TE at 10.0 - <13.0	0.78	0.95	DOR=70.00	1.00
TE at >15	0.99	0.96	DOR=2498.10	3.23
ARFI at 1.636–1.9	0.92	0.92	DOR=132.00	1.17
Utilities (NAFLD)				
Fibrosis F3	0.72		Lognormal	SE=utility decrement/4
Compensated cirrhosis	0.60		Lognormal	SE=utility decrement/4
Decompensated cirrhosis	0.54		Lognormal	SE=utility decrement/4
Varices	0.60		Lognormal	SE=utility decrement/4
Variceal bleeding	0.54		Lognormal	SE=utility decrement/4
Hepatocellular carcinoma	0.54		Lognormal	SE=utility decrement/4
Liver transplant	0.80		Lognormal	SE=utility decrement/4
Post liver transplant	0.85		Lognormal	SE=utility decrement/4
Utilities (HBV)				
Fibrosis F3	0.66		Lognormal	0.024
Compensated cirrhosis	0.55		Lognormal	0.037
Decompensated cirrhosis	0.49		Lognormal	0.064
Hepatocellular carcinoma	0.49		Lognormal	0.064
Varices	0.55		Lognormal	0.037
Variceal bleeding	0.49		Lognormal	0.064
Liver transplant	0.73		Lognormal	0.066
Post liver transplant	0.78		Lognormal	0.064
Utilities (HCV)				
Fibrosis F3	0.66		Lognormal	0.018
Compensated cirrhosis	0.55		Lognormal	0.037

Parameter description	Point estimates		Probability distribution	Distribution parameters
Decompensated cirrhosis	0.49		Lognormal	0.077
Hepatocellular carcinoma	0.49		Lognormal	0.077
Varices	0.55		Lognormal	0.037
Variceal bleeding	0.49		Lognormal	0.077
Liver transplant	0.51		Lognormal	0.081
Post liver transplant	0.52		Lognormal	0.069
Utilities (ALD)				
Fibrosis F3	0.62		Lognormal	SE=utility decrement/4
Compensated cirrhosis	0.52		Lognormal	SE=utility decrement/4
Decompensated cirrhosis	0.46		Lognormal	SE=utility decrement/4
Hepatocellular carcinoma	0.46		Lognormal	SE=utility decrement/4
Varices	0.52		Lognormal	SE=utility decrement/4
Variceal bleeding	0.46		Lognormal	SE=utility decrement/4
Liver transplant	0.69		Lognormal	SE=utility decrement/4
Post liver transplant	0.74		Lognormal	SE=utility decrement/4
Test costs (£)				
Transient elastography	68.00		Gamma	SE=mean/4
ARFI-VTq	50.96		Gamma	SE=mean/4
pSWE	50.96		Gamma	SE=mean/4
ELF	111.06		Gamma	SE=mean/4
FibroTest (one threshold)	44.83		Gamma	SE=mean/4
FIB-4 (one threshold)	4.52		Gamma	SE=mean/4
AST/ALT ratio	5.41		Gamma	SE=mean/4
APRI	4.16		Gamma	SE=mean/4
Platelets	2.71		Gamma	SE=mean/4
Liver biopsy	639.61		Gamma	SE=mean/4
SAFE algorithm	193.09		Gamma	SE=mean/4
Castera algorithm	248.42		Gamma	SE=mean/4
Other test costs (£)				
HBV-DNA test	66.37		Gamma	SE=mean/4
HCV-RNA test	79.43		Gamma	SE=mean/4
Full blood count	2.71		Gamma	SE=mean/4
INR	2.94		Gamma	SE=mean/4
Urea-electrolytes	3.00		Gamma	SE=mean/4
LFT	4.48		Gamma	SE=mean/4
Surveillance test costs (£)				

Parameter description	Point estimates		Probability distribution	Distribution parameters
Diagnostic endoscopy	205.66		Gamma	SE=mean/4
Ultrasound	49.00		Gamma	SE=mean/4
AFP	1.42		Gamma	SE=mean/4
Staff costs (£)				
GP consultation	67.00		Gamma	SE=mean/4
GP practice nurse consultation	17.67		Gamma	SE=mean/4
Hepatologist – first appointment	217.00		Gamma	SE=mean/4
Hepatologist – follow up	176.00		Gamma	SE=mean/4
Hospital nurse	19.33		Gamma	SE=mean/4
Hospital dietitian	12.33		Gamma	SE=mean/4
Hospital pharmacist	32.00		Gamma	SE=mean/4
Procedure and drug costs (£)				
Band Ligation	1325.83		Gamma	SE=mean/4
Variceal bleeding treatment	2653.29		Gamma	SE=mean/4
***Decompensation costs* (6-monthly)**				
Inpatient days	4568.89		Gamma	SE=mean/4
Procedures	1204.42		Gamma	SE=mean/4
Drugs	163.81		Gamma	SE=mean/4
HBV drug treatments				
Pega-2a Pegasys (per year)	6499.90		Fixed	
Entecavir (per year)	4419.66		Fixed	
Tenofovir (per year)	2486.75		Fixed	
HCV drug treatments				
Sofosbuvir (Sovaldi	11,660.98		Fixed	
ribavirin (Copegus)	246.65		Fixed	
Sofosbuvir/Ledipasvir (Harvoni)	12,993.33		Fixed	
Sofosbuvir/Ribavirin 12 weeks	36,092.87		Fixed	
Sofosbuvir/Ledipasvir 12 weeks	38,979.99		Fixed	
Sofosbuvir/Ledipasvir 8 weeks	25,986.66		Fixed	
Pega-2a/ribavirin 24 weeks	4359.88		Fixed	
Pega-2a/ribavirin 48 weeks	8719.75		Fixed	
Liver Transplant state costs (£) – 6-monthly				
HBV				
Liver transplant – year 1	34,854.82		Gamma	SE=mean 4
Liver transplant – year 2	11,943.02		Gamma	SE=mean 4
Post liver transplant	7454.69		Gamma	SE=mean 4
HCV				
Liver transplant – year 1	24,294.20		Gamma	SE=mean 4
Liver transplant – year 2	6428.52		Gamma	SE=mean 4
Post liver transplant	941.37		Gamma	SE=mean 4
ALD				
Liver transplant – year 1	29,574.51		Gamma	SE=mean 4

Parameter description	Point estimates		Probability distribution	Distribution parameters
Liver transplant – year 2	9185.77		Gamma	SE=mean 4
Post liver transplant	4198.03		Gamma	SE=mean 4
NAFLD				
Liver transplant – year 1	29,574.51		Gamma	SE=mean 4
Liver transplant – year 2	9185.77		Gamma	SE=mean 4
Post liver transplant	4198.03		Gamma	SE=mean 4

Abbreviations: AFP: alpha-fetoprotein blood test; APRI: aspartate aminotransferase to platelet ratio index; ARFI: acoustic radiation force impulse imaging; AST/ALT: aspartate aminotransferase to alanine aminotransferase; Castera algorithm: combination of transient elastography, FibroTest and liver biopsy; ELF: enhanced liver fibrosis test; INR: international normalized ratio; LFT: liver function blood test; SAFE algorithm: combination of FibroTest, APRI and liver biopsy; TE: transient elastography

N.2.3.2 Diagnostic accuracy

The characteristics of liver biopsy, when serving as a reference standard, were carefully specified in the diagnostic review protocol. Therefore, after agreement with the GDG, only studies reporting a liver biopsy with at least 6 portal tracts and a length of 15 mm or more were considered in the review of the literature. When there were not enough studies (fewer than 3) around the diagnostic accuracy of a specific test for pooled sensitivity and specificity estimates, the corresponding 2×2 diagnostic table was selected from a single study that was believed to represent the best quality evidence. For the ALD cohort and transient elastography at a 11–<13 threshold, to represent the uncertainty around its diagnostic accuracy and because the log-normal distribution could not fit onto a test with a 100% sensitivity, its 2×2 table was adjusted by adding 0.1 patients in each of the four diagnostic outcomes. This brought down its sensitivity from 100 to 99. A similar approach was followed for the NAFLD cohort and transient elastography at a 15 threshold. Selection criteria for the chosen sources are presented in Table 58 below.

Table 58: Source selection when <3 studies identified

Aetiology	Test	Source	Reason
HCV	Platelet count	Sirli 2010	Higher quality reference standard (compared to Lackner 2005)
HCV	AST/ALT ratio	Borroni 2006	Higher quality reference standard and larger patient cohort (compared to Lackner 2005)
NAFLD	TE (at 10.0 -<13.0)	Gaia 2011	Higher quality reference standard and more representative patient cohort (compared to Wong 2010b)
NAFLD	TE (at 15.0)	Yoneda 2008	Larger patient cohort and smaller time gap between TE and liver biopsy (compared to Yoneda 2010)
NAFLD	ARFI	Fierbinteanu 2013	Larger patient cohort and smaller time gap between TE and liver biopsy (compared to Yoneda 2010)

To account for uncertainty around diagnostic accuracies and correlation between sensitivity and specificity a joint distribution was used when making diagnostic accuracies probabilistic. First of all the diagnostic odds ratio (DOR) was calculated for the diagnostic test:

$$DOR = \frac{sensitivity}{1 - sensitivity} * \frac{specificity}{1 - specificity}$$

The standard error of the log DOR was calculated using the absolute values for the number of TP, TN, FP and FN:

$$SE(\ln(DOR)) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Using these equations a normal distribution was fitted around the log of the DOR.

Once the DOR is calculated the sensitivity can become a function of the DOR and the specificity:

$$sensitivity = 1 - \frac{specificity}{specificity + (1 - specificity) * DOR}$$

Finally a beta distribution was fitted around the specificity, therefore when probabilistic sensitivity analysis is conducted the specificity will change in accordance to the overall diagnostic uncertainty and its relationship with the sensitivity.

When reviewers identified more than 2 studies for a specific test, pooled diagnostic accuracy figures were estimated with the use of Bayesian methods. To account for uncertainty around these figures random samples were drawn from the original joint posterior distribution (WinBUGS iterations) for the purposes of probabilistic sensitivity analysis.

Diagnostic accuracy data for the HBV cohort were sourced from the NICE Hepatitis B guideline (CG165).

N.2.3.3 Baseline transition probabilities

Relevant transition rates were sought in the literature and were confirmed by the GDG as appropriate for use in the current model. All transition rates were transformed to 6-monthly transition probabilities.

N.2.3.3.1 Hepatitis B and hepatitis C

Table 59: HBV – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3 (HBeAg pos)	Compensated cirrhosis	0.019	Wright 2006
Fibrosis F3 (HBeAg neg)	Compensated cirrhosis	0.046	Dakin 2010
Compensated cirrhosis	Decompensated cirrhosis	0.025 (a)	Dakin 2010
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices	Bleeding	0.064	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.154	NIEC 1988
Compensated/decompensated cirrhosis/bleeding	HCC	0.012	Dakin 2010
Decompensated cirrhosis/ bleeding	Transplant	0.008	Wright 2006
HCC	Transplant	0.008	Wright 2006
Compensated cirrhosis	Death	0.026	Dakin 2010

From	To	Value	Source
Decompensated cirrhosis	Death	0.163	Dakin 2010
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010
Transplant	Death	0.111	Dakin 2010
Post-transplant	Death	0.029	Dakin 2010

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices

Table 60: HCV – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3	Compensated cirrhosis	0.019	Wright 2006
Compensated cirrhosis	Decompensated cirrhosis	0.020 (a)	Wright 2006
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices	Bleeding	0.065	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.154	NIEC 1988
Compensated/decompensated cirrhosis/bleeding	HCC	0.073	Wright 2006
Decompensated cirrhosis/HCC/bleeding	Transplant	0.010	Wright 2006
Compensated cirrhosis	Death	0.013	Dienstag 2011
Decompensated cirrhosis	Death	0.067	Wright 2006
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.245	Wright 2006
Transplant	Death	0.078	Wright 2006
Post-transplant	Death	0.0151	Wright 2006

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices

As presented in the above tables, the majority of the transition probabilities originated from the Wright 2006 UK HTA and an economic evaluation on HBV drugs conducted by Dakin et al 2010. For use in the current model those figures where sourced from the Crossan 2015 HTA. The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013 and were adjusted by assuming that two thirds of patients develop medium to large varices; this adjustment was applied to all subgroups evaluated in the model. Bleeding rates were obtained from a prospective study of 321 patients with cirrhosis and varices and no history of bleeding conducted by the North Italian Endoscopic Club (NIEC 1988). The HCC incidence rate was assumed to be constant across all patients with cirrhosis (compensated or decompensated), an approach also followed by the Crossan 2015 HTA. Bleeding mortality was sourced from Stevenson 2012 and it was

based on clinical judgement. The decompensation rates were adjusted for people with and without varices with a ±25% adjustment to the baseline rate that was based on GDG expert opinion. This adjustment was considered appropriate by the GDG and was applied to all the subgroups considered in the model.

N.2.3.3.2 NAFLD

Table 61: NAFLD – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3	Compensated cirrhosis	0.033	Singh 2015
Compensated cirrhosis	Decompensated cirrhosis	0.028 (a)	Hui 2003
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices	Bleeding	0.065	NIEC 1988
Decompensated cirrhosis with varices	Bleeding	0.154	NIEC 1988
Compensated/decompensated cirrhosis/bleeding	HCC	0.013	Ascha 2010
Decompensated cirrhosis/HCC/bleeding	Transplant	0.009	Average from HBV and HCV cohorts
F3	Death	0.003	Younossi 2011
Compensated cirrhosis	Death	0.009	Younossi 2011
Decompensated cirrhosis	Death	0.114	Average from HBV and HCV cohorts
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010 (from HBV cohort)
Transplant	Death	0.094	Average from HBV and HCV cohorts
Post-transplant	Death	0.022	Average from HBV and HCV cohorts

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices

As presented in the above table, for the progression of NAFLD patients to cirrhosis a transition probability was obtained from the Singh 2015 meta-analysis of studies with a paired biopsy study design. The decompensation rate was sourced from Hui 2003, a study observing the long-term outcomes of cirrhosis in non-alcoholic steatohepatitis (NASH) patients. The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013 and were adjusted by assuming that two thirds of patients develop medium to large varices. Bleeding rates were obtained from a prospective study of 321 patients with cirrhosis and varices and no history of bleeding conducted by the North Italian Endoscopic Club (NIEC 1988). Bleeding mortality was sourced from Stevenson 2012 and it was based on clinical judgement. The incidence of HCC was obtained from Ascha 2010, a study evaluating the incidence and risk factors of HCC in 195 NASH patients. It was assumed that this rate applied to both compensated and decompensated patients.

Due to the lack evidence in the remaining transition probabilities, those from the hepatitis cohorts were used after agreement with the GDG.

N.2.3.3.3 ALD

Table 62: ALD – 6-monthly transition probabilities

From	To	Value	Source
Fibrosis F3	Compensated cirrhosis	0.078	Pares 1986
Compensated cirrhosis	Decompensated cirrhosis	0.036 (a)	Fleming 2010
Compensated cirrhosis	Compensated cirrhosis with varices	0.020 (b)	Berzigotti 2013
Decompensated cirrhosis	Decompensated cirrhosis with varices	0.033 (c)	Berzigotti 2013
Compensated cirrhosis with varices (abstainers)	Bleeding	0.025	Stevenson 2012
Compensated cirrhosis with varices (drinkers)	Bleeding	0.078	Stevenson 2012
Decompensated cirrhosis with varices (abstainers)	Bleeding	0.059	GDG assumption
Decompensated cirrhosis with varices (drinkers)	Bleeding	0.189	GDG assumption
Compensated/decompensated cirrhosis/bleeding	HCC	0.042	Average from HBV and HCV cohorts
Decompensated cirrhosis/HCC/bleeding	Transplant	0.009	Average from HBV and HCV cohorts
Compensated cirrhosis	Death	0.019	Average from HBV and HCV cohorts
Decompensated cirrhosis	Death	0.114	Average from HBV and HCV cohorts
Bleeding	Death	0.163	Stevenson 2012
HCC	Death	0.337	Dakin 2010 (from HBV cohort)
Transplant	Death	0.094	Average from HBV and HCV cohorts
Post-transplant	Death	0.022	Average from HBV and HCV cohorts

(a) This value was adjusted by +25% in patients with varices and by -25% in patients without varices
(b) The original value of 0.0296 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices
(c) The original value of 0.0488 was adjusted by 2/3 as it was assumed that only this proportion of patients develop medium to large varices

As presented in the table above, progression to cirrhosis was obtained from Pares 1986, a study on the histological course of alcoholic hepatitis. The decompensation rate was sourced from an epidemiologic analysis of patients from the UK General practice research database conducted by Fleming 2010. The figures on the prevalence of varices in people with cirrhosis were sourced from a review conducted by Berzigotti 2013 and were adjusted by assuming that two thirds of patients develop medium to large varices. Bleeding rates were obtained from Stevenson 2012 where separate rates were reported for drinkers and abstainers (for abstainers this was based on clinical judgement). Those were adjusted for decompensated cirrhosis patients according to the proportional increase reported in NIEC 1988 that was used in the HBV, HCV and NAFLD model cohorts. The HCC incidence rate was assumed to be constant across all people with cirrhosis (compensated or decompensated), an approach also followed by the Crossan 2015 HTA. Bleeding mortality was sourced from Stevenson 2012 and it was based on clinical judgement. Due to the lack of evidence in the remaining transition probabilities, the mean between the HBV and HCV cohorts were used after agreement with the GDG.

N.2.3.4 Life expectancy and mortality rates

Life tables for England and Wales, published by the Office of National Statistics (ONS) based on 2011–2013 mortality data were used to establish population mortality rates for men and women for ages 45 to 100 years.[561] ONS 2013 mortality statistics for England and Wales by cause of death[560] were used to calculate the proportion of deaths for each 5-year age group which were due to liver related or non-liver related causes. These proportions were applied to the mortality rates to give the risk of death due to non-liver related causes for each annual age group for both men and women.

N.2.3.5 Utilities

N.2.3.5.1 Hepatitis B and hepatitis C

Quality of life figures were systematically sought in the literature (details in Appendix G) with priority given to studies in a UK population using EQ-5D with UK weights, in line with the NICE reference case. For both hepatitis B & C cohorts, utilities were sourced from a 2006 NIHR HTA study by Wright et al. on HCV patients. These were obtained through a separate observational study on 355 patients to whom an EQ-5D questionnaire was administered. For the health states of decompensated cirrhosis, HCC and transplant, utilities were sourced from Longworth et al. 2003, a UK transplantation study. Although HBV figures for the later health states were also available for a HBV population in the Longworth study, they were not used as there was a lack of consistency with the utilities reported by Wright 2006 that was highlighted by the GDG.

In addition, our search identified HBV-specific utilities in a non-UK population also used by the NICE Hepatitis B clinical guideline (CG165). They were not used however as they were considered too high for a population with advanced liver disease.

N.2.3.5.2 Alcohol-related liver disease

The systematic literature search identified a lack of quality of life evidence for this population. The GDG noted that this is mainly due to the fact that it is difficult for any quality of life instrument to isolate the effect of liver disease from the other effects of a patient's alcohol dependence.

For this reason the GDG suggested the use of utility values derived from alcohol-dependent patients as a baseline for the quality of life of patients with compensated cirrhosis (since this state is asymptomatic). After a comprehensive literature search, a study from Pettinati et al. 2009 was identified and used as a source for this value. The objective of the study was to quantify the effectiveness of extended-release naltrexone in alcohol-dependent patients through a randomised control trial. The SF-36 values of the trial's control group were transformed into quality of life utilities through the Ara & Brazier mapping algorithm (first regression model).[39]

To acquire utilities for the remaining model health states, using the baseline value from Pettinati et al. 2009 for the compensated cirrhosis state, we estimated the utilities for the other health states in this subgroup as the product of the baseline value by the proportional difference in utility in the Hepatitis B population for the health state compared to the compensated cirrhosis state. For example, in the Hepatitis B subgroup compensated cirrhosis has a utility of 0.55 while decompensated cirrhosis has a utility of 0.49. Therefore in the ALD subgroup the utility of decompensated cirrhosis is calculated as the utility of compensated cirrhosis in the ALD population (0.52) multiplied by the ratio of the 2 states in the Hepatitis B group (0.52 * 0.49/0.55).

N.2.3.5.3 Non-alcoholic fatty liver disease

The systematic literature review identified a variety of evidence for NAFLD patients. In the majority of this evidence authors did not report quality of life results per liver disease state (fibrosis, compensated cirrhosis, decompensated cirrhosis). In addition, a range of relevant literature could not be used due to the lack of available mapping algorithms for transformation to EQ-5D utilities. A

study conducted by David et al. 2009 reported a quality of life estimate specifically on non-NASH NAFLD patients (ADD VALUE), however this was considered too low by the NAFLD GDG and not appropriate to be used in the economic model.

As an alternative, the NAFLD GDG suggested using the utility attributed to patients with obesity as a baseline for quality of life of non-NASH NAFLD patients. This value was obtained from recent NICE public health guidance (PH53) that simulated the relation of BMI with quality of life in two-dimensional tables. To acquire utilities for the remaining model health states the same method used for the ALD subgroup was used (that is, using the proportional increments and decrements from the hepatitis B subgroup).

N.2.3.6 Resource use and cost

N.2.3.6.1 Diagnostic test costs

The majority of the unit costs were sourced from the 2 relevant published HTAs.[177,207] The cost of ARFI VTq was built on top of the ultrasound NHS tariff (NHS reference costs 2013–14) assuming an extra kit has to be acquired in order to perform an ARFI examination. The cost of the kit was sourced from the relevant NICE M-Tec assessment.[538] A machine lifespan of 5 years with 500 ultrasound or ARFI scans per year was assumed after GDG guidance. Point shear wave elastography cost was assumed to be similar to ARFI due to technology similarities and a lack of available evidence around it.

Table 63: Cirrhosis test unit costs

Test	Cost (£)	Source	Comment
Transient elastography	68.00	NHS hospital trust	Provided by GDG member
ARFI-VTq	50.96	Assumption	Built on top of ultrasound NHS tariff – see below
pSWE	50.96	Assumption	Assumed similar to VTq
ELF	111.06	Crossan 2015	
FibroTest (one threshold)	44.83	Crossan 2015	
FIB-4 (one threshold)	4.52	Crossan 2015	
AST/ALT ratio	5.41	Crossan 2015-Donnan 2009	Assumed to equal the cost of an LFT plus the cost of an extra biomarker
APRI	4.16	Crossan 2015	
Platelets	2.71	Donnan 2009	Part of FBC
Liver biopsy	639.61	NICE MTG027	
SAFE algorithm	193.09	Estimation	Based on the proportions of the cohort that received each of the tests included in the algorithm, figures sourced from the original paper
Castera algorithm	248.42	Estimation	Based on the proportions of the cohort that received each of the tests included in the algorithm, figures sourced from the original paper

(a) All values were inflated to 2013/14 prices

N.2.3.6.2 Surveillance for complications costs

Table 64: Unit costs of surveillance

Test	Cost (£)	Source	Comment
Diagnostic endoscopy	205.66	NHS reference costs 2013/14	FZ60Z, Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and

Test	Cost (£)	Source	Comment
			over
Ultrasound	49.00	NHS reference costs 2013/14	RA23Z, Ultrasound scan less than 20 minutes
AFP	1.42	Crossan 2015	

(a) All values were inflated to 2013/14 prices

N.2.3.6.3 Drugs

Unit costs were sourced from BNF 69. The dosages were either taken from the relevant NICE technology appraisals or were based on GDG guidance.

Table 65: Unit costs of drugs

Drug	Cost per 28 days (£)	Dose
Pega-2a (Pegasys ®)	497.76	180 mg weekly
Entecavir	339.04	500 mg daily
Tenofovir	190.76	245 mg daily
Sofosbuvir (Sovaldi ®)	11,660.98	400 mg daily
Sofosbuvir/Ledipasvir (Harvoni®)	12,993.33	400 mg daily
Ribavirin (Copegus®)	246.65	400 mg daily

Source: BNF 69

N.2.3.6.4 Health states

Health state costs were constructed with GDG guidance so they represent a reference patient pathway. These include staff, test, procedure and drug costs where relevant. When pegylated interferon was used as a drug treatment a more intensive management is assumed according to current clinical protocols. Staff costs were sourced from the NHS reference cost 2013/14 schedules and PSSRU 2014. A multi-speciality staff mix was also agreed with the GDG so that it better represents current care arrangements. Test costs where sourced from a relevant HTA (Donnan 2009). Complication costs related to cirrhosis were sourced from a HTA on HCV patients (Wright 2006) and were assumed to be relevant to all aetiologies. Under GDG guidance, complication costs of patients with ALD were assumed to be 50% higher than those in the other cohorts. Liver transplant costs for hepatitis B or C patients were sourced from Brown 2006 and Wright 2006. An average of those figures was used for the NAFLD and ALD aetiologies.

Table 66: Unit costs of staff

Drug	Cost	Details
Hepatologist – first appointment	217.00	Non-admitted face-to-face attendance (WF01B)
Hepatologist – follow up	176.00	Non-admitted face-to-face attendance (WF01A)
Hospital nurse	19.33	20 minute appointment, £58 per hour of face-to-face contact including qualifications
Hospital pharmacist	32.00	20 minutes, £96 per hour of direct patient time (including travel and qualifications)

Source: NHS reference costs 2013/14, PSSRU 2014

Table 67: 6-monthly health state costs (based on GDG guidance)

Input	Value (£)	Details
Dead	0	

Input	Value (£)	Details
HBV		
Fibrosis F3 during first-line treatment (includes drug costs)	4,192	7 appointments (50%hepatologist+25%nurse+25%pharmacist)+ combination of tests[(a)]
Fibrosis F3 during second-line treatment (includes drug costs)	1,662	1 appointment (50%hepatologist+25%nurse+25%pharmacist)+ combination of tests[(a)]
Fibrosis F3 (treated)	255	1 appointment (50%hepatologist+25%nurse+25%pharmacist)+ combination of tests [(a)]
Compensated cirrhosis during first-line treatment (includes drug costs)	4,192	7 appointments (50%hepatologist+25%nurse+25%pharmacist) + combination of tests [(a)]
Compensated cirrhosis during second-line treatment (includes drug costs)	1,662	1 appointment (50%hepatologist+25%nurse+25%pharmacist) + combination of tests[(a)]
Compensated cirrhosis (treated)	255	1 appointment (50%hepatologist+25%nurse+25%pharmacist + combination of tests[(a)]
Decompensated cirrhosis	6,929	4 hepatologist appointments+ combination of tests[(a)] + Complication costs
Bleeding	2,653	1 non-elective band ligation + 1.5 follow-up band ligations
HCC	6,929	Similar to those of decompensated cirrhosis state
HCV		
Fibrosis F3 – genotype 1 (includes drug costs)	26,380	2 appointments with nurse + 2 with pharmacist + combination of tests [(b)]
Fibrosis F3 – genotype 2/3 (includes drug costs)	5,693	7 appointments (50%hepatologist+25%nurse+25%pharmacist) + combination of tests [(b)]
Fibrosis F3 – genotype 4 (includes drug costs)	11,385	14 appointments (50%hepatologist+25%nurse+25%pharmacist) + combination of tests [(b)]
Fibrosis F3 (treated)	94.57	1 /2 appointment with hepatologist + combination of tests [(c)]
Compensated cirrhosis – genotype 1/4 (includes drug costs)	39,485	3 appointments with nurse + 2 with pharmacist + combination of tests[(b)]
Compensated cirrhosis – genotype 2 (includes drug costs)	36,631	4 appointments with nurse + 2 with pharmacist + combination of tests [(b)]
Compensated cirrhosis - genotype 3 (includes drug costs)	37,823	5 appointments with nurse + 4 with pharmacist + combination of tests [(b)]
Compensated cirrhosis - treated	189	1 appointment with hepatologist + combination of tests [(c)]
Decompensated cirrhosis	6,720	3 hepatologist appointments + combination of tests [(b)] + complication costs
Bleeding	2,653	1 non elective band ligation + 1.5 follow-up band ligations
HCC	6,720	Similar to those of decompensated cirrhosis state
ALD		
Fibrosis F3	186	1 appointment with hepatologist + combination of tests [(c)]
Compensated cirrhosis	186	1 appointment with hepatologist + combination of tests [(c)]

Input	Value (£)	Details
Decompensated cirrhosis	9,450	3 hepatologist appointments + combination of tests[(c)] +50% Increased complication costs
Bleeding	2,653	1 non elective band ligation + 1.5 follow-up band ligations
HCC	9,450	Similar to those of decompensated cirrhosis state
NAFLD		
Fibrosis F3	186	Same as compensated cirrhosis (NAFLD chair suggestion)
Compensated cirrhosis	186	1 appointment with hepatologist + combination of tests [(c)]
Decompensated cirrhosis	6,495	3 hepatologist appointments + combination of tests [(c)] + complication costs
Bleeding	2,653	1 non-elective band ligation + 1.5 follow-up band ligations
HCC	6,495	Similar to those of decompensated cirrhosis state
Liver transplant – year 1	29,575	Average of HBV-HCV cohort costs
Liver transplant – year 2	9,186	Average of HBV-HCV cohort costs
Post-transplant	4,198	Average of HBV-HCV cohort costs

(a) DNA+ full blood count + international normalized ratio + liver blood test
(b) RNA+ full blood count + international normalized ratio + liver blood test + urea & electrolytes
(c) Full blood count + international normalized ratio + liver blood test

N.2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohort's age as a respective risk factor for other-cause mortality.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities.

Where not already available, transition probabilities were calculated using an assumption of a fixed rate across each source-study follow-up.

Rates were converted into transition probabilities for the respective cycle length (6 months) before inputting into the Markov model. The probability of the event over the time horizon specified by the literature was converted into a rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (X months)
$$Transition\ Probability\ (P) = 1 - e^{-rt}$$	Where *r*=selected rate *t*=cycle length (6 months)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in each state of the model (6 months) was weighted by a utility value that is dependent on the time spent in the model and the treatment effect. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and resource costs accrued by patients in every health state was recorded. These subtotals were summed across all subgroups to ascertain the total number of patients in the population and the total QALYs and resource costs accrued for the population. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

N.2.5 Model validation

The model was developed in consultation with the NAFLD and Cirrhosis GDGs; model structures, inputs and results were presented to and discussed with the GDGs for clinical validation and interpretation.

The models were systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The models were peer reviewed by a second experienced health economist from the NGC; this included systematic checking of many of the model calculations.

N.2.6 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost-effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in terms of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$Net\ Monetary\ Benefit(X) = (QALYs(X) \times \lambda) - Costs(X)$	Cost-effective if: • Highest net benefit

Where: λ = threshold (£20,000 per QALY gained)	

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy. The NMB figure is followed by the test ranking and the 95% confidence intervals of the ranks. An additional figure that represented the percentage of simulations where every test ranked first was also calculated.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown.

N.2.7 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[539] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several diagnostic tests, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained. Where the differences in the NMBs between alternative options were considered small, ICERs were calculated to interpret the model results.

N.3 Results

Cost-effectiveness results of the cirrhosis diagnostic tests and the optimal surveillance frequency for HCC and oesophageal varices are presented in separate sections. For ALD, ICERs comparing all strategies to 'no test – no monitor' were also calculated due to the high uncertainty depicted in the confidence intervals. For the HCV cohort, diagnostic test results are only presented for genotypes 1 and 3 as those for genotypes 2 and 4 were consistent with these (top 3 test rankings are instead presented for all genotypes). To define the most cost-effective surveillance frequency for HCC and oesophageal varices, ICERs were calculated across the available options. Base case results below were obtained through the probabilistic analysis to take combined parameter uncertainty into account.

Table 68: Definitions of column categories

Header	Definition
Transplants	Number of transplants per patient
Unexpected HCCs	HCC episodes in patients with a false negative diagnosis
Expected HCCs	HCC episodes in patients with a true positive diagnosis
Bleedings	Number of bleeding events per patient
Liver deaths	Deaths occurred due to liver-associated mortality (applied to all health states apart from F3 fibrosis)
Decomp	Time spent in decompensated cirrhosis state
Var+dcVar – Unprotected	Time spent with non-band-ligated varices
Var+dcVar – Protected	Time spent with band-ligated varices

Header	Definition
Life years	Total life years per patient

N.3.1 Diagnostic tests – base cases

N.3.1.1 People with NAFLD

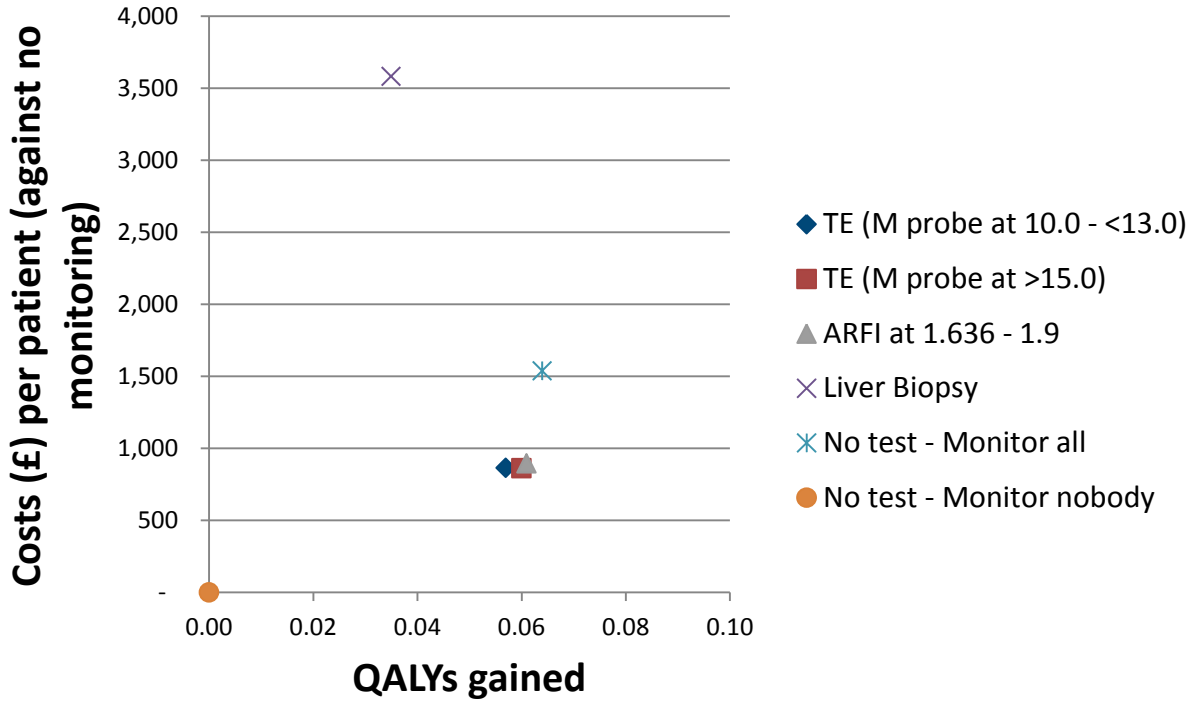
Table 69: Number of events & time spent in health states

	Events					Time spent (months)		
Test	Transplants	Unexpected HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
TE at 10.0 - <13.0	0.028	0.024	0.173	0.166	0.670	7.335	2.614	17.540
TE at >15.0	0.028	0.019	0.179	0.166	0.670	7.336	2.711	17.765
ARFI at 1.636–1.9	0.028	0.014	0.184	0.165	0.670	7.336	2.797	18.016
Liver biopsy	0.028	0.012	0.185	0.163	0.673	7.308	2.806	18.277
No test – monitor all	0.028	0.000	0.198	0.164	0.670	7.338	3.053	18.133
No test – no monitor	0.029	0.159	0.034	0.199	0.677	7.322	0.418	7.000

Table 70: Life years and results

Test	Life years (undiscounted)	Mean costs (£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic)
TE (at 10.0 - <13.0)	19.97	19,237	9.22	165,163	3	1	4	0.1192	3
TE (at >15.0)	19.98	19,229	9.22	165,224	1	1	4	0.5118	1
ARFI at 1.636–1.9	19.99	19,275	9.22	165,212	2	1	4	0.3562	2
Liver biopsy	19.90	22,087	9.19	161,811	6	6	6	0.0000	6
No test – monitor all	19.99	19,929	9.23	164,614	5	4	5	0.0000	5
No test – no monitor	19.77	18,310	9.16	164,818	4	2	5	0.0128	4

Figure 202: Cost-effectiveness plot: NAFLD



Across the 6 strategies compared, the non-invasive tests ranked on top with transient elastography at a <15.0 threshold ranking first having an NMB of £165,224. All 3 non-invasive strategies delivered similar QALY figures and slightly differed in the overall mean costs. The confidence intervals in the rankings only excluded liver biopsy and the 'no-test' strategies from ranking first, highlighting the uncertainty in the cost-effectiveness of the 3 non-invasive tests. In the probabilistic analysis transient elastography at <15.0 ranked first in 51% of the simulations followed by ARFI and TE at 10.0 < 13.0 (36% and 12% respectively). ICERs comparing all strategies against 'no test – no monitoring' ranged from £13,868 to £14,577 for the non-invasive strategies and at £98,051 for liver biopsy.

N.3.1.2 People with ALD

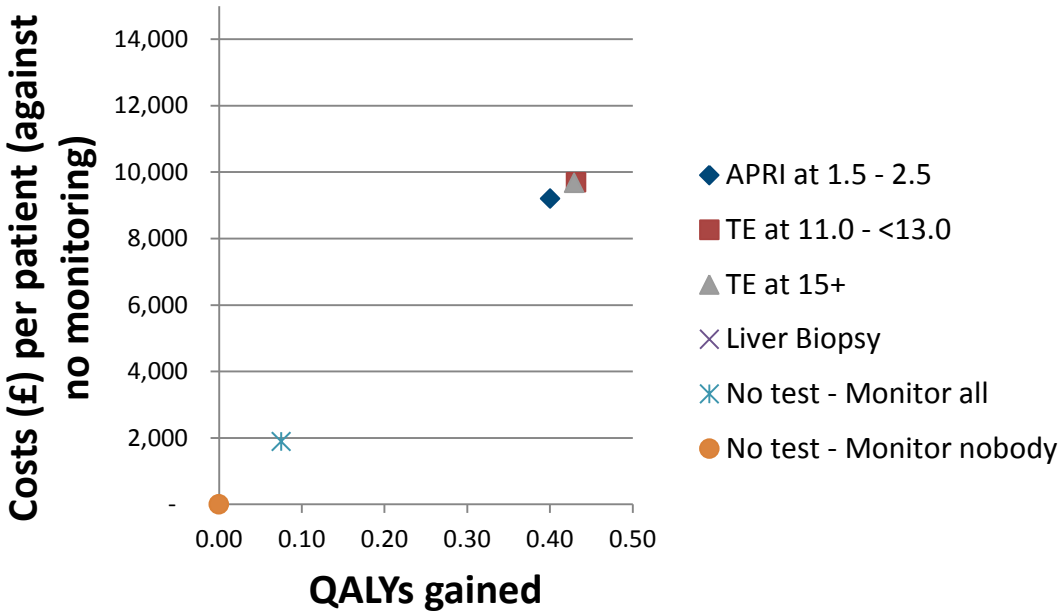
Table 71: Number of events & time spent in health states

	Events					Time spent (months)		
Test	**Transplants**	**Unexpected HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
APRI at 1.5–2.5	0.043	0.090	0.456	0.135	0.892	8.129	2.131	14.114
TE at 11.0 - <13.0	0.044	0.045	0.505	0.128	0.891	8.159	2.362	15.906
TE at 15+	0.044	0.048	0.502	0.128	0.891	8.157	2.343	15.816
Liver biopsy	0.046	0.040	0.525	0.126	0.886	8.584	2.446	17.508
No test – monitor all	0.033	0.000	0.492	0.162	0.911	6.485	2.262	12.703
No test – no monitor	0.032	0.388	0.094	0.195	0.914	6.449	0.342	5.295

Table 72: Life years and results

Test	**Life years (undiscounted)**	**Mean costs (£)**	**Mean QALYs**	**NMB (£) at £20,000/QALY**	**Rank**	**Rank 95% CIs**		**Prob (c/e)**	**Rank (deterministic)**
APRI at 1.5–2.5	12.26	38,483	5.30	67,504	5	2	5	0.0056	5
TE at 11.0 - <13.0	12.34	38,965	5.33	67,644	3	1	5	0.2062	3
TE at 15+	12.34	38,947	5.33	67,616	4	1	5	0.0548	4
Liver biopsy	12.63	42,562	5.42	65,870	6	4	6	0.0012	6
No test – monitor all	11.22	31,163	4.97	68,321	2	1	6	0.1272	2
No test – no monitor	11.00	29,278	4.90	68,697	1	1	6	0.6050	1

Figure 203: Cost-effectiveness plot: ALD



In the ALD cohort, testing for cirrhosis was not cost-effective at a £20,000 threshold with the 2 'no-test' strategies ranking higher. The 'no-monitor' strategy had the highest NMB value of £68,697 and the 'monitor-all' strategy followed with £68,321. The diagnostic test that ranked first was transient elastography at 11.0–<13.0 with an NMB of £67,644. All diagnostic test strategies delivered considerably higher QALY values compared to no testing (up to 0.5 more QALYs) but at increased mean costs. All strategies apart from liver biopsy had wide confidence intervals of their ranks ranging from first or second to fifth and depicting the high uncertainty in the results. ICERs comparing all strategies against 'no test – no monitoring' ranged from £22,438 to £22,977 for the non-invasive strategies and at £25,405 for liver biopsy.

N.3.1.3 People with HBV: HBV– antigen

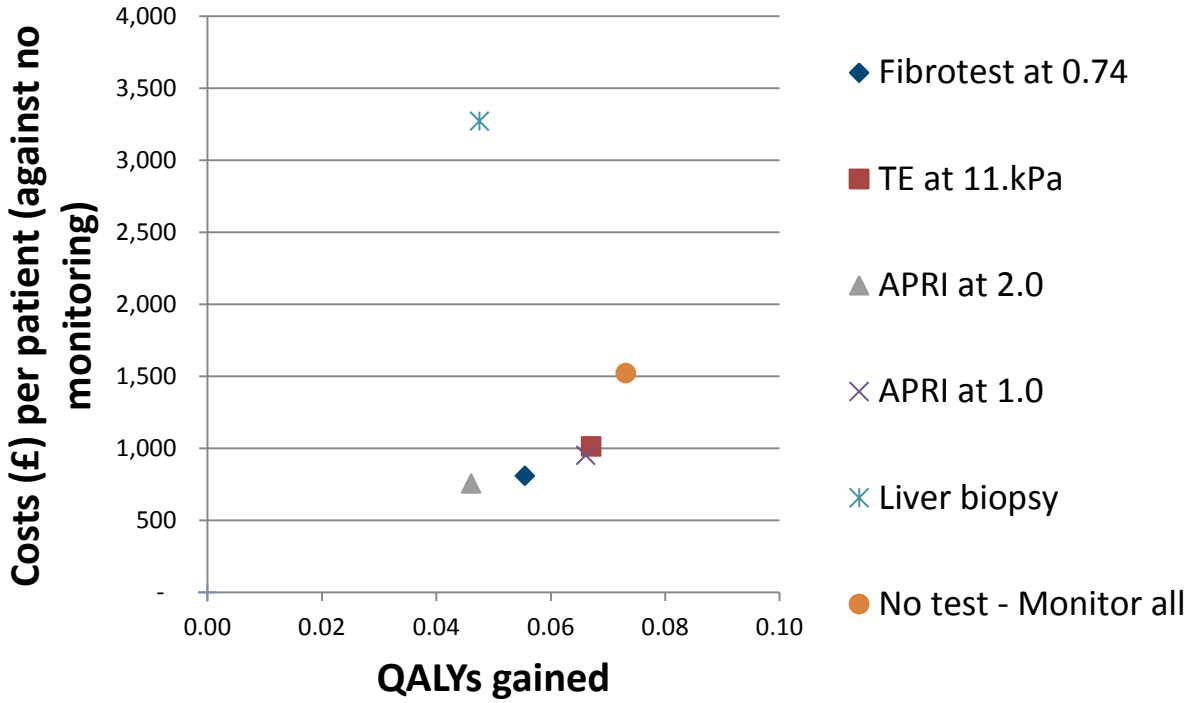
Table 73: Number of events & time spent in health states

	Events					Time spent (months)		
Test	Transplants	Unexpected HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar – Protected
FibroTest at 0.74	0.039	0.043	0.184	0.238	0.707	9.923	2.903	22.701
TE at 11.0 kPa	0.039	0.019	0.209	0.233	0.706	9.931	3.334	24.254
APRI at 2.0	0.039	0.054	0.172	0.243	0.707	9.919	2.715	21.153
APRI at 1.0	0.039	0.018	0.210	0.233	0.706	9.932	3.374	24.054
Liver biopsy	0.039	0.014	0.213	0.230	0.707	9.900	3.414	24.767
No test – monitor all	0.039	0.000	0.228	0.232	0.705	9.939	3.723	24.598
No test – no monitor	0.040	0.171	0.052	0.273	0.714	9.888	0.650	12.288

Table 74: Life years and results

Test	Life years (undiscounted)	Mean costs (£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic)
FibroTest at 0.74	19.23	63,375	8.33	103,210	3	1	5	0.226	2
TE at 11.0 kPa	19.27	63,583	8.34	103,237	2	1	5	0.1896	3
APRI at 2.0	19.20	63,317	8.32	103,070	4	2	5	0.003	4
APRI at 1.0	19.27	63,521	8.34	103,281	1	1	4	0.4458	1
Liver biopsy	19.21	65,820	8.32	100,612	7	7	7	0	7
No test – monitor all	19.29	64,096	8.35	102,849	6	3	6	0	6
No test – no monitor	19.03	62,552	8.27	102,904	5	1	6	0.1356	5

Figure 204: Cost-effectiveness plot: HBV– antigen



In the HBeAg-negative cohort, APRI at 1.0 ranked first with an NMB of £103,281. Transient elastography at 11.0 kPa and FibroTest at 0.74 followed with NMBs of £103,237 and £103,210 respectively. Transient elastography delivered similar QALYs to APRI at 1.0 but for an incremental cost of £62 per patient. FibroTest was less costly then transient elastography and APRI at 1.0 but less effective too. Liver biopsy ranked lowest across all strategies particularly due to its high overall mean costs. In the confidence intervals of the ranks, transient elastography, FibroTest, APRI at 1.0 and 'no test – no monitoring' could all rank first with APRI at 1.0 ranking first in 45% of the simulations followed by FibroTest (23%). ICERs comparing all strategies against 'no test – no monitoring' ranged from £14,406 to £16,439 for the non-invasive strategies and at £67,013 for liver biopsy.

N.3.1.4 People with HBV: HBV+ antigen

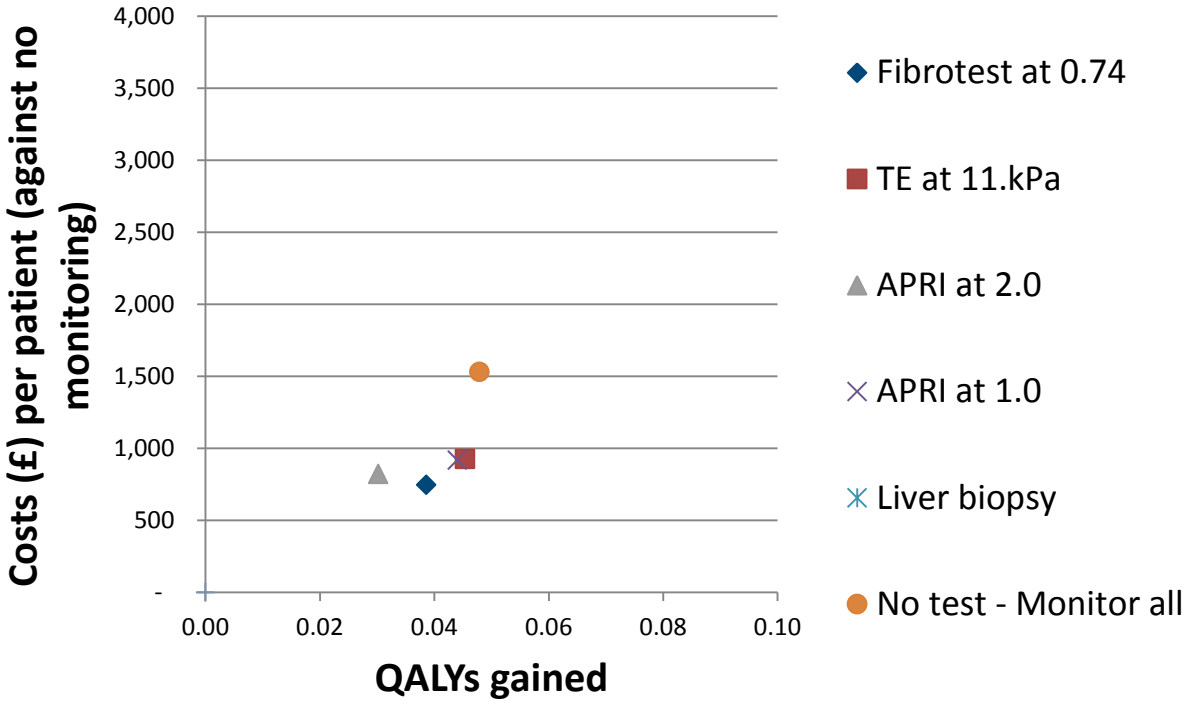
Table 75: Number of events & time spent in health states

	Events					Time spent (months)		
Test	Transplants	Unexpected HCCs	Expected HCCs	Bleedings	Liver deaths	Decomp	var+dcVar - Unprotected	var+dcVar - Protected
FibroTest at 0.74	0.034	0.029	0.148	0.202	0.477	8.172	2.296	19.284
TE at 11.0 kPa	0.034	0.013	0.165	0.198	0.477	8.177	2.602	20.480
APRI at 2.0	0.034	0.036	0.141	0.205	0.478	8.170	2.196	18.128
APRI at 1.0	0.034	0.011	0.167	0.198	0.477	8.178	2.637	20.315
Liver biopsy	0.034	0.010	0.167	0.195	0.482	8.144	2.634	20.912
No test – monitor all	0.034	0.000	0.178	0.197	0.476	8.183	2.854	20.817
No test – no monitoring	0.034	0.129	0.046	0.230	0.484	8.147	0.553	11.251

Table 76: Life years and results

Test	Life years (undiscounted)	Mean costs (£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic)
FibroTest at 0.74	24.16	42,758	10.06	158,366	1	1	5	0.2288	2
TE at 11.0 kPa	24.19	42,927	10.06	158,362	2	1	5	0.199	3
APRI at 2.0	24.14	42,827	10.05	158,155	5	3	5	0.0006	5
APRI at 1.0	24.18	42,916	10.06	158,358	3	1	5	0.2166	4
Liver biopsy	24.07	45,997	10.03	154,533	7	7	7	0	7
No test – monitor all	24.20	43,527	10.07	157,851	6	4	6	0	6
No test – no monitoring	24.02	42,013	10.02	158,328	4	1	6	0.355	1

Figure 205: Cost-effectiveness plot: HBV+ antigen



In the HBeAg-positive cohort, FibroTest at 0.74 ranked first. Transient elastography at 11.0 kPa and APRI at 1.0 followed as second and third options. NMB for FibroTest was £158,366 and for transient elastography at 11.0 kPa and APRI at 1.0 was £158,362 and £158,358 respectively. Liver biopsy ranked lowest across all strategies particularly due to its high mean costs. The top 4 options (transient elastography, FibroTest, APRI at 1.0 and 'no test – no monitoring') had NMBs sufficiently close that it is impossible to be sure which of these should be preferred in terms of cost-effectiveness. Each could rank first within the confidence intervals. In the probabilistic analysis, 'no test – no monitoring' ranked first in 36% of the simulations with transient elastography, FibroTest, APRI at 1.0 all ranking first in about 20% of the simulations, each highlighting the high uncertainty in the results. ICERs comparing all strategies against 'no test – no monitoring' ranged from £19,039 to £25,418 for the non-invasive strategies and at £423,351 for liver biopsy.

N.3.1.5 People with HCV: genotype 1

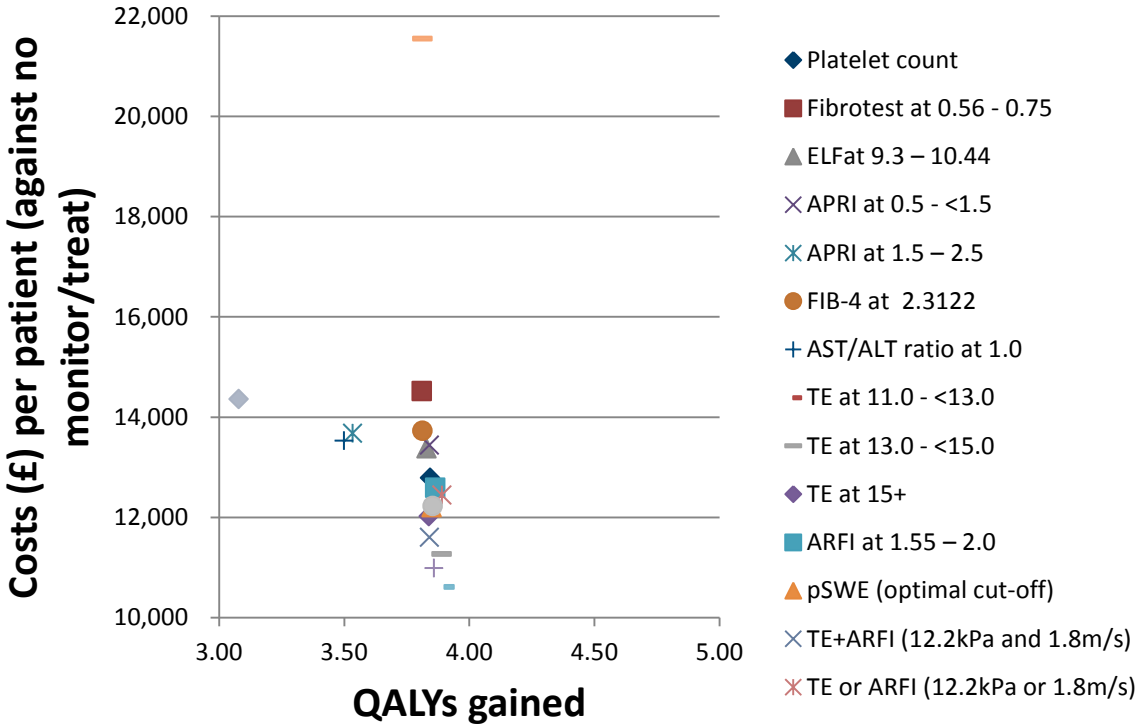
Table 77: Number of events & time spent in health states

	Events					Time spent (months)		
Test	**Transplants**	**Unexpected HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
Platelet count	0.002	0.008	0.039	0.004	0.047	0.093	0.034	0.295
FibroTest at 0.56–0.75	0.002	0.010	0.041	0.004	0.052	0.114	0.042	0.332
ELF at 9.3–10.44	0.002	0.009	0.039	0.004	0.049	0.100	0.036	0.307
APRI at 0.5 - <1.5	0.002	0.008	0.040	0.004	0.048	0.096	0.037	0.304
APRI at 1.5–2.5	0.004	0.042	0.027	0.011	0.077	0.215	0.028	0.443
FIB-4 at 2.3122	0.002	0.011	0.039	0.004	0.050	0.107	0.037	0.318
AST/ALT ratio at 1.0	0.004	0.046	0.026	0.012	0.081	0.231	0.027	0.461
TE at 11.0 - <13.0	0.002	0.010	0.038	0.004	0.048	0.092	0.030	0.285
TE at 13.0 - <15.0	0.002	0.005	0.040	0.003	0.043	0.073	0.029	0.260
TE at 15+	0.002	0.010	0.038	0.004	0.048	0.093	0.029	0.286
ARFI at 1.55–2.0	0.002	0.006	0.040	0.003	0.046	0.085	0.034	0.285
pSWE (optimal cut-off)	0.002	0.008	0.039	0.003	0.047	0.089	0.031	0.285
TE+ARFI (12.2 kPa and 1.8 m/s)	0.002	0.011	0.037	0.004	0.048	0.092	0.027	0.279
TE or ARFI (12.2 kPa or 1.8 m/s)	0.002	0.003	0.041	0.003	0.043	0.076	0.034	0.275
SAFE algorithm	0.002	0.008	0.038	0.003	0.046	0.087	0.030	0.281
Castera algorithm	0.002	0.009	0.038	0.003	0.046	0.085	0.025	0.265
Liver biopsy	0.002	0.003	0.040	0.002	0.043	0.064	0.025	0.239
No testing – monitor all	0.003	0.000	0.059	0.004	0.060	0.159	0.087	0.431
No testing – no monitoring	0.006	0.091	0.018	0.023	0.130	0.430	0.030	0.749
No testing – no monitoring or treatment	0.029	0.442	0.083	0.084	0.627	2.658	0.181	2.741

Table 78: Life years and results

Test	Life years (undiscounted)	Mean costs (£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic)
Platelet count	31.39	30,936	12.20	213,159	11	4	15	0	11
FibroTest at 0.56–0.75	31.30	32,666	12.17	210,760	15	9	17	0	15
ELF at 9.3–10.44	31.35	31,522	12.19	212,285	13	4	16	0.002	13
APRI at 0.5 - <1.5	31.38	31,589	12.20	212,445	12	7	15	0	12
APRI at 1.5–2.5	30.57	31,827	11.90	206,075	16	13	18	0	16
FIB-4 at 2.3122	31.31	31,877	12.17	211,589	14	8	16	0	14
AST/ALT ratio at 1.0	30.47	31,677	11.86	205,528	17	13	18	0	17
TE at 11.0 - <13.0	31.38	30,268	12.20	213,734	10	4	14	0.000	10
TE at 13.0 - <15.0	31.51	29,417	12.25	215,580	2	1	6	0.029	3
TE at 15+	31.38	30,170	12.20	213,822	8	3	15	0.001	7
ARFI at 1.55–2.0	31.45	30,737	12.23	213,769	9	3	13	0.000	9
pSWE (optimal cut-off)	31.41	30,348	12.21	213,868	7	2	15	0.001	5
TE+ARFI (12.2 kPa and 1.8 m/s)	31.38	29,747	12.20	214,276	5	2	14	0.000	4
TE or ARFI (12.2 kPa or 1.8 m/s)	31.51	30,589	12.25	214,444	4	3	11	0	6
SAFE algorithm	31.42	30,378	12.21	213,902	6	4	13	0	8
Castera algorithm	31.43	29,140	12.22	215,251	3	1	14	0.063	2
Liver biopsy	31.54	28,762	12.26	216,472	1	1	2	0.904	1
No testing–monitor all	31.25	39,699	12.17	203,774	18	16	19	0	18
No testing–no monitoring	29.30	32,505	11.44	196,274	19	18	19	0	19
No testing–no monitoring or treatment	19.92	18,149	8.36	149,055	20	20	20	0	20

Figure 206: Cost-effectiveness plot: HCV genotype 1



In the HCV genotype 1 cohort liver biopsy ranked first with a NMB value of £216,472. Transient elastography at 13.0–<15.0 and the Castera algorithm followed with £215,580 and £215,251 respectively. Liver biopsy dominated all the other strategies apart from 'no test – no monitoring or treatment' by having the highest QALY value and the second lowest mean costs. Transient elastography at 13.0–< 15.0 delivered slightly lower QALYs for an incremental cost of £656. From all strategies it was only liver biopsy and transient elastography at 13.0–<15.0 that could rank first according to the ranking confidence intervals with liver biopsy ranking first in 90% of the simulations. ICERs comparing liver biopsy and TE at 13.0-<15.0 to 'no testing – no monitoring or treatment' were £2,720 and £2,897 respectively.

N.3.1.6 People with HCV: genotype 3

Table 79: Number of events & time spent in health states

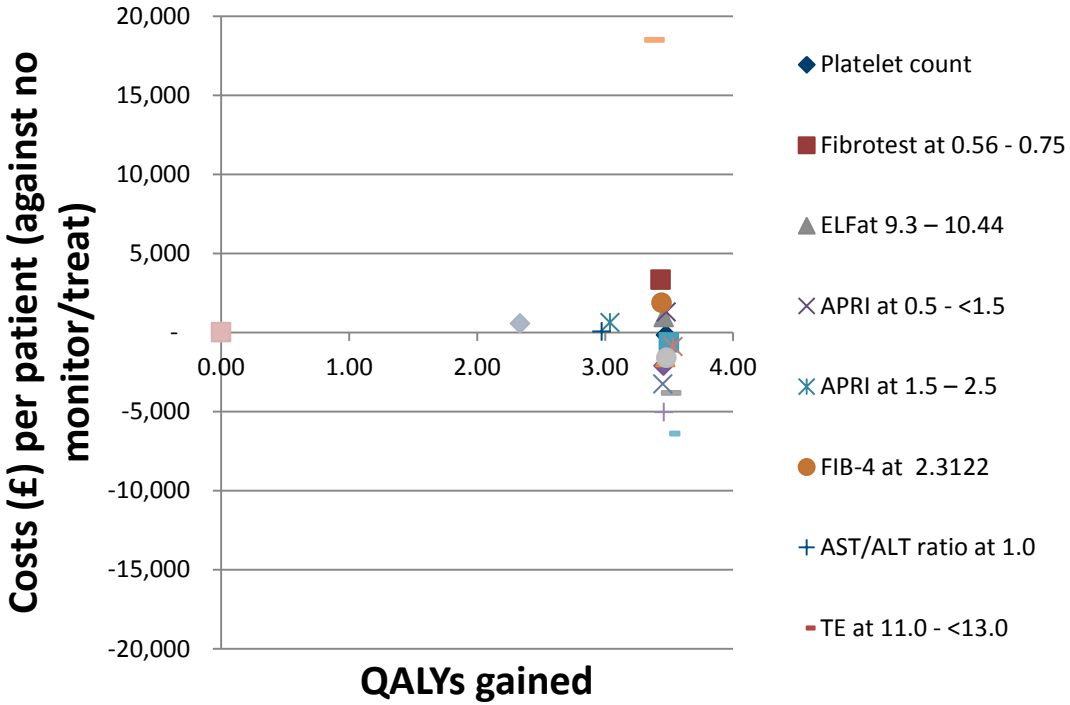
	Events					Time spent (months)		
Test	**Transplants**	**Unexpected HCCs**	**Expected HCCs**	**Bleedings**	**Liver deaths**	**Decomp**	**var+dcVar - Unprotected**	**var+dcVar - Protected**
Platelet count	0.005	0.016	0.075	0.009	0.098	0.308	0.126	0.872
FibroTest at 0.56–0.75	0.005	0.017	0.079	0.010	0.104	0.342	0.145	0.933
ELF at 9.3–10.44	0.005	0.017	0.076	0.009	0.100	0.320	0.131	0.889
APRI at 0.5 - <1.5	0.005	0.014	0.077	0.009	0.098	0.310	0.135	0.892
APRI at 1.5–2.5	0.007	0.075	0.056	0.018	0.150	0.534	0.094	0.942
FIB-4 at 2.3122	0.005	0.018	0.075	0.010	0.101	0.325	0.133	0.896
AST/ALT ratio at 1.0	0.008	0.085	0.054	0.020	0.159	0.576	0.089	0.960
TE at 11.0 - <13.0	0.005	0.021	0.073	0.009	0.100	0.315	0.116	0.850
TE at 13.0 - <15.0	0.005	0.014	0.076	0.008	0.096	0.290	0.116	0.838
TE at 15+	0.005	0.021	0.073	0.009	0.101	0.317	0.116	0.851
ARFI at 1.55–2.0	0.005	0.013	0.077	0.009	0.096	0.298	0.127	0.868
pSWE (optimal cut-off)	0.005	0.018	0.074	0.009	0.099	0.310	0.120	0.858
TE+ARFI (12.2 kPa and 1.8 m/s)	0.005	0.024	0.073	0.009	0.103	0.323	0.111	0.840
TE or ARFI (12.2 kPa or 1.8 m/s)	0.005	0.009	0.079	0.008	0.093	0.285	0.130	0.872
SAFE algorithm	0.005	0.018	0.074	0.009	0.098	0.306	0.118	0.851
Castera algorithm	0.005	0.025	0.073	0.009	0.104	0.325	0.106	0.830
Liver biopsy	0.005	0.016	0.077	0.007	0.100	0.289	0.107	0.816
No testing–monitor all	0.006	-	0.114	0.011	0.124	0.449	0.245	1.213
No testing–no monitoring	0.012	0.175	0.034	0.038	0.250	0.971	0.067	1.231
No testing–no monitoring or treatment	0.029	0.442	0.083	0.084	0.627	2.664	0.182	2.744

Table 80: Life years and results

Test	Life years (undiscounted)	Mean costs (£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic)
Platelet count	30.32	17,990	11.84	218,732	11	5	15	0	11
FibroTest at 0.56–0.75	30.20	21,494	11.79	214,391	15	9	17	0	15
ELF at 9.3–10.44	30.27	19,120	11.82	217,245	13	4	17	0.001	13
APRI at 0.5 - <1.5	30.33	19,453	11.84	217,316	12	8	15	0	12
APRI at 1.5–2.5	29.10	18,782	11.40	209,184	16	13	18	0	16
FIB-4 at 2.3122	30.23	20,040	11.80	215,996	14	9	16	0	14
AST/ALT ratio at 1.0	28.91	18,219	11.33	208,441	17	11	18	0	17
TE at 11.0 - <13.0	30.27	16,320	11.82	220,067	8	4	13	0	9
TE at 13.0 - <15.0	30.42	14,334	11.88	223,199	3	2	7	0.0066	3
TE at 15+	30.26	16,049	11.82	220,294	6	3	15	0	6
ARFI at 1.55–2.0	30.38	17,528	11.86	219,663	10	4	14	0	10
pSWE (optimal cut-off)	30.31	16,597	11.83	220,036	9	3	15	0	5
TE+ARFI (12.2 kPa and 1.8 m/s)	30.24	14,895	11.81	221,326	4	2	13	0	4
TE or ARFI (12.2 kPa or 1.8 m/s)	30.47	17,256	11.89	220,577	5	4	12	0	7
SAFE algorithm	30.33	16,546	11.84	220,227	7	4	12	0	8
Castera algorithm	30.25	13,110	11.82	223,277	2	1	13	0.027	2
Liver biopsy	30.38	11,759	11.87	225,611	1	1	2	0.9654	1
No testing–monitor all	29.99	36,657	11.75	198,272	18	17	19	0	18

Test	Life years (undiscounted)	Mean costs (£)	Mean QALYs	NMB (£) at £20,000/QALY	Rank	Rank 95% CIs		Prob (c/e)	Rank (deterministic)
No testing–no monitoring	27.03	18,724	10.69	195,174	19	18	19	0	19
No testing–no monitoring or treatment	19.92	18,164	8.36	149,001	20	20	20	0	20

Figure 207: Cost-effectiveness plot: HCV genotype 3



In the HCV genotype 3 cohort, liver biopsy ranked first with an NMB value of £225,611. Transient elastography at 13.0–<15.0 and the Castera algorithm followed with almost identical NMBs at £223,277 and £223,199 respectively. Liver biopsy dominated the Castera algorithm being more effective and less costly. Transient elastography at 13.0–<15.0 delivered marginally more QALYs but for a considerable incremental cost of £2,575. From all strategies it was

only liver biopsy and transient elastography at 13.0–<15.0 that could rank first according to the ranking confidence intervals with liver biopsy ranking first in 97% of the simulations. The 'no testing – no monitoring or treatment' strategy was dominated by liver biopsy and TE at 13.0-<15.0 in direct comparisons.

N.3.1.7 People with HCV: all genotypes

Table 81: HCV diagnostic tests – top 3 ranked in every genotype

Rank	Genotype 1	Genotype 2	Genotype 3	Genotype 4
First	Liver biopsy	Liver biopsy	Liver biopsy	Liver biopsy
Second	TE at 13.0<15.0	Castera algorithm	Castera algorithm	TE at 13.0<15.0
Third	Castera algorithm	TE at 13.0<15.0	TE at 13.0<15.0	TE or ARFI (12.2 kPa or 1.8 m/s)

N.3.2 Frequency of surveillance

N.3.2.1 Frequency of HCC surveillance

Table 82: ICERs comparing 6-monthly surveillance against annual surveillance

Aetiology	ICER	Cirrhosis test used
NAFLD	£23,220	TE at >15.0
ALD	£28,352	TE at 11.0 - <13.0
HBV -antigen	£26,063	TE at 11.0
HBV +antigen	£25,236	TE at 11.0
HCV genotype 1	£18,657	Liver biopsy
HCV genotype 3	£20,128	Liver biopsy

The cirrhosis test used in each case was that recommended by the GDG following its consideration of the results of Section N.3.1. Where more than 1 test was recommended, the most cost-effective of those tests was used.

Across all aetiologies 6-monthly surveillance for HCC was overall more costly and more effective compared to the annual strategy. At a £20,000 threshold, 6-monthly surveillance was cost-effective only in the HCV genotype 1 cohort (ICER at £18,657). The ICERs in the remaining cohorts ranged between £23,220 and £28,352.

N.3.2.2 Frequency of oesophageal varices surveillance

Table 83: ICERs comparing annual and 2-yearly surveillance against 3-yearly surveillance

Aetiology	Frequency	ICER	Cirrhosis test used for the comparison
NAFLD	2 years	Dominated	TE at >15.0
	1 year	£122,413	
ALD	2 years	£63,167	TE at 11.0 - <13.0
	1 year	£120,390	
HBV -antigen	2 years	£54,408	TE at 11.0
	1 year	Dominated	
HBV +antigen	2 years	£36,552	TE at 11.0
	1 year	£48,430	
HCV genotype 1	2 years	£75	Liver biopsy
	1 year	Dominated	
HCV genotype 3	2 years	Dominant	Liver biopsy
	1 year	Dominated	

The cirrhosis test used in each case was that recommended by the GDG following its consideration of the results of Section N.3.1. Where more than 1 test was recommended, the most cost-effective of those tests was used.

Surveillance for the presence of oesophageal varices every 2 years was not cost-effective for all cohorts but the two HCV. The ICER comparing 2-yearly with 3-yearly surveillance was below £20,000 for HCV genotype 1, dominating for genotype 3, but not cost-effective for NAFLD, ALD or HBV. Annual surveillance was not cost-effective for any aetiology at a £20,000 threshold.

N.3.3 Sensitivity analyses

N.3.3.1 NAFLD

Table 84: NAFLD model – Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	NAFLD prevalence 50% lower	NAFLD prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	Discount rate 1.5%	Fibroscan unit cost 20% higher	ARFI unit costs 20% lower	ARFI unit costs 20% higher	TE>15 diagnostic accuracy- low CI
TE at 10.0 - <13.0	3	3	3	3	3	3	3	3	2	2
TE at >15.0	1	1	1	1	1	1	2	1	1	3
ARFI at 1.636–1.9	2	2	2	2	2	2	1	2	3	1
Liver biopsy	6	6	6	6	6	6	6	6	6	6
No test – monitor all	5	5	4	5	5	5	5	5	5	5
No test – no monitoring	4	4	5	4	4	4	4	4	4	4
ICER – TE at >15.0 versus No test-monitor	£13,820	£16,673	£11,736	£12,045	£15,893	£12,482	£14,740	£13,820	£13,820	£16,985

Across all scenarios transient elastography at >15.0 ranked first apart from when its unit cost was increased 20% and when its diagnostic accuracy was set at the low CI value. ARFI ranked first in both the aforementioned scenarios showing the amount of uncertainty between the 2 tests. Liver biopsy and the 2 'no test' strategies remained last in all scenarios without a change in their rank.

N.3.3.2 ALD

Table 85: ALD model – Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	ALD prevalence 50% lower	ALD prevalence 50% higher	Medium to large varices at diagnosis 50% hieher	Medium to large varices at diagnosis 50% lower	No abstinence after diagnosis with non-invasive liver test	Fibroscan unit cost 20% higher	Fibroscan unit costs 20% lower	TE at 11.0 - <13.0 diagnostic accuracy- low CI	TE at 11.0 - <13.0 diagnostic accuracy- high CI
APRI at 1.5 - 2.5	5	5	5	5	5	5	5	5	4	5
TE at 11.0 - <13.0	3	3	3	3	3	3	3	3	5	3
TE at 15+	4	4	4	4	4	4	4	4	3	4
Liver biopsy	6	6	6	6	6	6	6	6	6	6
No test – monitor all	2	2	2	2	2	2	2	2	2	2
No test – no monitoring	1	1	1	1	1	1	1	1	1	1
ICER – TE at 11.0 - <13.0	£23,153	£23,804	£22,169	£22,192	£23,656	£25,996	£22,990	£22,861	£23,694	£22,668

The 'no test – no monitor' strategy remained first in all scenarios. Transient elastography at 11.0–<13.0 remained the diagnostic test ranking first in 9 out of the 10 tested scenarios. In the remaining scenarios transient elastography at >15.0 ranked higher when the diagnostic accuracy of transient elastography at 11.0–<13.0 was set at its low CI.

N.3.3.3 HBeAg-negative

Table 86: HBV- model – Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	HBV prevalence 50% lower	HBV prevalence 50% higher	Medium to large varices at diagnosis 50% hieher	Medium to large varices at diagnosis 50% lower	Fibroscan unit cost 20% higher	Fibroscan unit costs 20% lower	TE at 11 diagnostic accuracy- low CI	TE at 11 diagnostic accuracy- high CI	Second-line treatment effectiveness – low CI	Second-line treatment effectiveness – high CI

Tests	Base case (deterministic)	HBV prevalence 50% lower	HBV prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	Fibroscan unit cost 20% higher	Fibroscan unit costs 20% lower	TE at 11 diagnostic accuracy- low CI	TE at 11 diagnostic accuracy- high CI	Second-line treatment effectiveness – low CI	Second-line treatment effectiveness – high CI
FibroTest at 0.74	2	1	3	3	1	2	3	2	3	3	1
TE at 11.0 kPa	3	3	2	2	3	3	1	4	1	2	4
APRI at 2.0	4	5	4	4	4	4	4	3	4	4	5
APRI at 1.0	1	2	1	1	2	1	2	1	2	1	2
Liver biopsy	7	7	7	7	7	7	7	7	7	7	7
No test – monitor all	6	6	6	6	6	6	6	6	6	5	6
No test – no monitoring	5	4	5	5	5	5	5	5	5	6	3
ICER – TE at 11.0 kPa versus no test – no monitor	£17,018	£19,491	£14,997	£15,381	£18,795	£17,739	£16,296	£19,121	£15,685	£5,635	£20,185

APRI at a 1.0 threshold remained first in 6 out of 10 scenarios and came second in the 5 remaining ones. FibroTest ranked first in 3 scenarios and second or third in the remaining ones. Transient elastography ranked first in 2 scenarios (20% lower fibroscan unit costs or diagnostic accuracy of transient elastography at its high CI) and ranked from second to fourth in the remaining scenarios. No substantial ranking changes are observed in the other test strategies.

N.3.3.4 HCV genotype 3

Table 87: HCV genotype 3 model – Cost-effectiveness rank under different scenarios

Tests	Base case (deterministic)	HCV prevalence 50% lower	HCV prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	TE at 13 diagnostic accuracy- high CI	Fibroscan unit costs 20% lower	No HCV treatment	No HCC surveillance in SVR patients	Cirrhosis treatment effectiveness – low CI	Cirrhosis treatment effectiveness – high CI	Fib/cirr treatment effectiveness – low CI	Fib/cirr treatment effectiveness – high CI	Drug treatment cost 50% lower	HCV drug effectiveness for FNs - 75% lower
Platelet count	11	11	11	11	11	11	11	6	11	11	11	11	11	9	11
FibroTest at 0.56 - 0.75	15	15	15	15	15	15	15	16	15	17	15	15	15	15	15
ELF at 9.3 – 10.44	13	12	13	13	13	13	13	15	13	12	13	12	13	13	13
APRI at 0.5 - <1.5	12	13	12	12	12	12	12	10	12	13	12	13	12	12	12
APRI at 1.5 – 2.5	16	16	16	16	16	16	16	4	16	16	16	16	16	17	16
FIB-4 at 2.3122	14	14	14	14	14	14	14	11	14	14	14	14	14	14	14
AST/ALT ratio at 1.0	17	17	17	17	17	17	17	3	17	15	17	17	17	18	17
TE at 11.0 - <13.0	9	8	9	9	9	9	9	9	9	8	10	8	9	11	9
TE at 13.0 - <15.0	3	3	3	3	3	2	3	5	3	3	3	3	3	1	3
TE at 15+	6	5	6	6	6	6	6	8	6	5	7	5	7	6	7
ARFI at 1.55 – 2.0	10	10	10	10	10	10	10	12	10	10	9	10	10	8	10
pSWE (optimal cut-off)	5	6	5	5	5	5	5	7	5	6	6	6	5	5	5

Tests	Base case (deterministic)	HCV prevalence 50% lower	HCV prevalence 50% higher	Medium to large varices at diagnosis 50% higher	Medium to large varices at diagnosis 50% lower	TE at 13 diagnostic accuracy- high CI	Fibroscan unit costs 20% lower	No HCV treatment	No HCC surveillance in SVR patients	Cirrhosis treatment effectiveness – low CI	Cirrhosis treatment effectiveness – high CI	Fib/cirr treatment effectiveness – low CI	Fib/cirr treatment effectiveness – high CI	Drug treatment cost 50% lower	HCV drug effectiveness for FNs - 75% lower
TE+ARFI (12.2kPa and 1.8m/s)	4	4	4	4	4	4	4	14	4	4	5	4	4	7	4
TE or ARFI (12.2kPa or 1.8m/s)	7	9	7	7	7	7	7	13	7	9	4	9	6	3	6
SAFE algorithm	8	7	8	8	8	8	8	17	8	7	8	7	8	10	8
Castera algorithm	2	2	2	2	2	3	2	19	2	2	2	2	2	4	2
Liver Biopsy	1	1	1	1	1	1	1	20	1	1	1	1	1	2	1
No testing – monitor all	18	19	18	18	18	18	18	18	18	19	18	19	18	16	18
No testing – no monitoring	19	18	19	19	19	19	19	1.5	19	18	19	18	19	19	19
No testing – no monitoring or treatment	20	20	20	20	20	20	20	1.5	20	20	20	20	20	20	20
ICER – Liver biopsy versus no testing-no monitor	dominant	dominant	dominant	dominant	dominant	dominant	dominant	£323,402	dominant	dominant	dominant	dominant	dominant	dominant	dominant

In 13 out of the 15 scenarios liver biopsy remained the first ranked strategy. It came twentieth where HCV treatment was not provided and second where the drug treatment costs were reduced by 50%. The Castera algorithm remained second in 12 out of the 15 scenarios and third, fourth and nineteenth in the remaining 3 ones. Transient elastography at 11.0–<13.0 ranked third in 12 out of the 15 scenarios and first, second and fifth in the remaining 3 ones.

Rankings in the remaining test strategies did not differ substantially across the scenarios tested apart from the 'no HCV treatment' scenario which seemed to favour the 'no testing – no monitoring' strategy.

N.3.3.5 Frequency of cirrhosis testing

Table 88: ICERs comparing 2-yearly testing against annual testing

Aetiology	ICER	Cirrhosis test used
NAFLD	£1,060,920	TE at >15.0
ALD	£36,800	TE at 11.0 - <13.0
HBV -antigen	£99,587	TE at 11.0
HBV +antigen	£165,204	TE at 11.0
HCV genotype 1	£25,975	Liver biopsy
HCV genotype 3	£29,648	Liver biopsy

Annual testing was not found to be cost-effective at a £20,000 per QALY threshold. ICERs comparing annual and 2-yearly testing ranged from £25,975 to £1,060,920.

N.3.3.6 HCC surveillance frequencies

Table 89: ICERs comparing 6-monthly against annual surveillance

Aetiology	Base case (deterministic)	Surveillance costs – 20% lower	6-monthly surveillance effectiveness – 20% higher	Cirrhosis test used for the comparison
NAFLD	£22,472	£21,331	£20,254	TE at >15.0
ALD	£28,847	£28,492	£27,659	TE at 11.0 - <13.0
HBV -antigen	£27,290	£26,188	£26,342	TE at 11.0
HBV +antigen	£27,007	£25,377	£26,402	TE at 11.0
HCV genotype 1	£20,166	£18,252	£18,173	Liver biopsy
HCV genotype 3	£20,362	£19,008	£18,782	Liver biopsy

Lowering the HCC surveillance costs had a moderately small effect on the ICERs with only the HCV cohorts being lower than the 20,000 threshold. Increasing the effectiveness of 6-monthly surveillance had a slightly larger effect still making 6-monthly surveillance cost-effective only in the HCV cohorts.

N.3.3.7 Oesophageal varices surveillance frequencies

Table 90: ICERs compared to 3-year surveillance

Aetiology	Frequency	Base case (deterministic)	Surveillance costs – 20% lower	RR on bleeding probability – 20% higher	RR on bleeding probability – 20% lower	Cirrhosis test used for the comparison
NAFLD	2 years	£40,453	£31,999	£30,723	£54,982	TE at >15.0
	1 year	£58,416	£46,397	£44,981	£78,505	
ALD	2 years	£25,709	£19,569	£17,933	£37,327	TE at 11.0 - <13.0
	1 year	£131,314	£103,628	£101,829	£178,295	
HBV -antigen	2 years	£57,539	£45,108	£43,334	£78,777	TE at 11.0
	1 year	£85,246	£67,313	£65,312	£115,085	
HBV +antigen	2 years	£92,335	£71,865	£69,696	£126,221	TE at 11.0
	1 year	£145,652	£114,564	£111,959	£196,134	
HCV genotype 1	2 years	£39,891	£31,362	£29,463	£55,315	Liver biopsy
	1 year	£68,807	£54,582	£52,872	£92,484	
HCV genotype 3	2 years	£54,103	£42,827	£40,978	£73,566	Liver biopsy
	1 year	£77,311	£61,443	£59,762	£103,407	

Variation of the surveillance costs and the RR on the bleeding probability had little effect on the overall cost-effectiveness of more frequent surveillance for oesophageal varices. Increasing the frequency to 2 years was only cost-effective for the ALD cohort in 2 out of the 3 tested scenarios.

N.4 Conclusions

N.4.1 Evidence statements

- An original cost-utility analysis that compared 6 strategies to diagnose cirrhosis in people with NAFLD and advanced fibrosis with a retest frequency of 2 years found that transient elastography ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - ARFI
  - transient elastography (lower threshold)
  - no test – no surveillance
  - no test – surveillance for all
  - liver biopsy.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 6 strategies to diagnose cirrhosis in people with ALD, with a retest frequency of 2 years, found that:
  - The 'no test – no surveillance' strategy ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
    - no test – surveillance for all
    - transient elastography (low threshold)
    - transient elastography (high threshold)
    - APRI
    - liver biopsy.
  - When compared to the 'no test – no monitor' strategy, the 3 non-invasive tests had ICERs between £22,438 and £22,977 per QALY gained.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 7 strategies to diagnose cirrhosis in people with hepatitis B and HBeAg negative with a retest frequency of 2 years found that APRI ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - transient elastography
  - FibroTest
  - APRI (higher threshold)
  - no test – no surveillance
  - no test – surveillance for all
  - liver biopsy.

  This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis that compared 7 strategies to diagnose cirrhosis in people with hepatitis B and HBeAg positive with a retest frequency of 2 years found that FibroTest ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - no test – no surveillance
  - transient elastography
  - APRI (low threshold)

  - APRI (high threshold)
  - no test – surveillance for all
  - liver biopsy.

  This analysis was assessed as directly applicable with minor limitations.

- An original cost-utility analysis that compared 20 strategies to diagnose cirrhosis in people with hepatitis C with a retest frequency of 2 years found that liver biopsy ranked first compared to the following diagnostic strategies, using relevant thresholds for each test, with reference to a cost-effectiveness threshold of £20,000 per QALY gained:
  - Castera algorithm
  - transient elastography (medium threshold)
  - transient elastography and ARFI
  - transient elastography or ARFI
  - transient elastography (high threshold)
  - SAFE algorithm
  - point shear wave elastography
  - transient elastography (low threshold)
  - ARFI
  - platelet count
  - APRI
  - ELF
  - FIB-4
  - FibroTest
  - APRI
  - AST-ALT ratio
  - no testing – surveillance for all, treat HCV using medication for people with cirrhosis
  - no testing – no surveillance, treat HCV using medication for people with fibrosis
  - no testing – no surveillance, no treatment for HCV.

  This analysis was assessed as directly applicable with minor limitations.

- An original cost-utility analysis that compared 6-monthly with annual surveillance for HCC in people with cirrhosis at a cost-effectiveness threshold of £20,000 per QALY gained found that:
  - 6-monthly surveillance was cost-effective compared to annual surveillance for people with HCV genotype 1 (ICER: £18,657 per QALY gained).
  - 6-monthly surveillance was not cost-effective compared to annual surveillance for people with NAFLD, ALD, HBV or HCV genotype 1 (ICERs: £20,128–28,352).

  This analysis was assessed as directly applicable with minor limitations.

- An original cost-utility analysis that compared annual, 2-yearly and 3-yearly surveillance for the detection of varices in people with cirrhosis at a cost-effectiveness threshold of £20,000 per QALY gained found that:
  - Annual surveillance was not cost-effective compared to 3-yearly surveillance (ICERs: £48,430–122,413 per QALY gained or dominated).
  - 2-yearly surveillance was cost-effective compared to 3-yearly surveillance in people with C (ICERs: £75 per QALY gained or dominant).
  - 2-yearly surveillance was not cost-effective compared to 3-yearly surveillance in people with NAFLD and advanced fibrosis, ALD or hepatitis B (ICERs: £36,552–63,167 per QALY gained or dominated).

This analysis was assessed as directly applicable with minor limitations.

N.4.2 Summary of results

N.4.2.1 NAFLD

Transient elastography at a threshold of 15.0 kPa ranked first mainly due to having the highest diagnostic accuracy among the non-invasive tests. ARFI followed second being slightly less accurate but also having lower test unit costs. Transient elastography at 10.0 - <13.0 kPa ranked third having similar specificity to the other 2 tests but lower sensitivity. All 3 non-invasive tests had similarly wide confidence intervals (1 to 4).

In the deterministic sensitivity analysis, rankings were sensitive to increases in the transient elastography and ARFI unit costs and in the decrease of the diagnostic accuracy of transient elastography at 15.0 kPa. Therefore, no safe conclusion can be made over the most cost-effective option among the 3 comparators.

N.4.2.2 ALD

Testing people with alcohol-related liver disease for cirrhosis was not cost-effective compared to 'no test – no monitor' and 'no test – monitor all' at a cost-effectiveness threshold of £20,000 per QALY gained. However, it was cost-effective at a threshold of £30,000 per QALY gained: the ICERs for the 3 non-invasive liver tests were £22,438–£22,977). All 3 non-invasive tests had similarly wide confidence intervals (from first or second to fifth place).

In none of the deterministic sensitivity analysis scenarios did a test strategy rank higher than third. Ranking among the 3 non-invasive liver tests slightly varied across the different scenarios with transient elastography at 11.0–<13.0 remaining third in ranking for 9 out of the 10 tested scenarios.

N.4.2.3 HBV

For the HBeAg negative group, APRI at 1.0 ranked first, most probably due to its low test unit costs and its moderate diagnostic accuracy (second best after transient elastography). Transient elastography and FibroTest ranked second and third. APRI at 2.0 ranked last among the non-invasive liver tests mainly due to its considerably lower sensitivity. All non-invasive liver tests had similarly wide 95% confidence intervals.

In the HBeAg positive group, FibroTest ranked first with transient elastography and APRI at 1.0 ranking second and third. All non-invasive liver tests had similarly wide 95% confidence intervals. In the probabilistic analysis, the 3 tests also shared similar probabilities ranking first (20–23%).

Deterministic sensitivity analysis was only conducted for the HBeAg negative group. Rankings between the deterministic and the probabilistic analyses varied particularly for the FibroTest and transient elastography tests, highlighting how incorporating the uncertainty of the input parameters in the model affects the cost-effectiveness results. APRI at 1.0 ranked first or second in all scenarios. FibroTest and transient elastography followed with alternating first to fourth positions. The cost-effectiveness of APRI at 1.0 was sensitive to the decrease of HBV prevalence, the presence of varices at the point of cirrhosis diagnosis and changes to the cost and accuracy of transient elastography.

N.4.2.4 HCV

For all 4 genotypes, liver biopsy ranked first with substantially higher NMB values compared to the second options. This is mainly attributable to the fact that liver biopsy was assumed to have perfect sensitivity and specificity, and that cirrhosis misdiagnosis is associated with the incorrect administration of the highly costly polymerase inhibitor drugs. This led to the economic model

particularly favouring the test with the highest diagnostic accuracy irrespective of its unit cost. In genotypes 1 and 3 where detailed results are presented, liver biopsy ranked first in 90% and 97% of the simulations respectively. Transient elastography at 13.0–<15.0 and the Castera algorithm ranked second and third in genotypes 1–4 and the 'transient elastography or ARFI' strategy ranked third in genotype 4.

Deterministic sensitivity analysis was only conducted for the genotype 3 group. Liver biopsy remained first in all but 2 scenarios. These were the 'no HCV treatment' and the 'drug treatment cost - 50% lower' scenarios, also highlighting how crucial the drug treatment element is for the HCV diagnostic model.

N.4.2.5 Frequency of HCC surveillance

At a cost-effectiveness threshold of £20,000 per QALY gained, 6-monthly surveillance was cost-effective compared to annual surveillance only for the HCV genotype 1 group. Although this group had the fewest liver-related deaths, risk of HCC progression was particularly high in this group compared to other model cohorts, making more frequent surveillance cost-effective at the specified threshold. However, at a cost-effectiveness threshold of £30,000 per QALY gained, 6-monthly surveillance was cost-effective compared to annual surveillance for all groups: ICERs £18,657–28,352. Variation in the ICERs was mainly due to differences in cirrhosis prevalence, risk of progression to HCC, and competing risks of other complications in each aetiology.

In the deterministic sensitivity analysis, changes in the surveillance costs or the 6-monthly surveillance effectiveness reduced the ICERs by up to £2,000 per QALY gained. Such reductions made 6-monthly surveillance cost-effective at a £20,000 per QALY gained threshold only for the 2 HCV cohorts.

N.4.2.6 Frequency of oesophageal varices surveillance

Annual surveillance was not cost-effective compared to 3-yearly surveillance for any of the model cohorts with the ICERs either exceeding £45,000 per QALY gained or showing it being dominated by the 3-year frequency option (more costly and less effective). Two-yearly surveillance was cost-effective compared to 3-yearly surveillance at a cost-effectiveness threshold of £20,000 per QALY in the 2 HCV cohorts. In the deterministic sensitivity analysis, changes in the surveillance costs or the RR applied on the bleeding probability had considerable effect on the ICERs of the higher frequencies. However with the base case ICERs of the deterministic analysis being far beyond the £20,000 threshold, any reductions in the ICERs made 2-yearly surveillance cost-effective only for the ALD cohort.

N.4.3 Comparisons with published studies

N.4.3.1 Cirrhosis diagnostic tests

Three relevant studies identified in our literature review attempted to assess the cost-effectiveness of diagnostic tests for cirrhosis, with contrasting findings.

Canavan 2013[119] found TE to have an ICER of £6,557 when compared with no testing in chronic HCV patients. Liver biopsy was dominated by both these strategies. This is in contrast to the result of this model, however, the Canavan evaluation did not include the recently launched HCV treatments which particularly enhance the cost-effectiveness of highly accurate tests (such as liver biopsy) irrespective of their cost due to the very high treatment cost.

Steadman 2013[709] concluded that liver biopsy was more costly and more effective compared to TE with a cost per additional correct diagnosis between £1,136 and 3,841 in the HBV, HCV and NAFLD

groups. However, no safe conclusions or comparisons can be made based on these figures since important factors such as the follow-up costs and the health-related quality of life following correct or incorrect diagnoses were not included in this economic evaluation.

Stevenson 2012[711] compared 6 relevant diagnostic strategies and concluded that only liver biopsy was cost-effective at a cost-effectiveness threshold of £20,000 per QALY gained for people with ALD. This is in contrast with the results of this model which indicated that neither non-invasive liver tests nor liver biopsy were considered cost-effective at the £20,000 threshold. The 2 models followed similar perspectives so result differences are mainly attributable to dissimilarities in the model structure and the input parameters (such as the strict liver biopsy quality criterion for the study selection followed by the present analysis).

N.4.3.2 Frequency of HCC surveillance

Two relevant studies identified in our literature review attempted to assess the cost-effectiveness of HCC surveillance in different frequencies.

Cucchetti 2012[178] compared annual versus 6-monthly surveillance and concluded that 6-monthly is not cost-effective for either groups with compensated or decompensated cirrhosis at a cost-effectiveness threshold of £20,000 per QALY gained (ICERs of £21,230 and £40,540 respectively). These figures are similar to the ones in the present analysis, which produced ICERs ranging between £20,000 and £30,000 across the different groups.

Thompson Coon 2008[732,733] compared 7 relevant strategies (including annual and 6-monthly frequencies) and concluded that only the 'no surveillance' strategy was cost-effective at a cost-effectiveness threshold of £20,000 per QALY gained. ICERs for the non-dominated strategies varied from £25,490 to £83,333. When 6-monthly strategies were directly compared with the annual ones, ICERs were beyond £27,500. The latter results are also in line with those in the present analysis.

N.4.3.3 Frequency of varices surveillance

No relevant studies were identified in the literature.

Appendix O: Unit costs

O.1 Risk factors and risk assessment tools

None.

O.2 Diagnostic tests

See Table 63 in Appendix N.

O.3 Severity risk tools

Table 91: Unit costs of severity risk tools

Risk tool	Unit cost	Comments
Child-Pugh	£7.42[(a)]	Includes bilirubin, albumin, INR, ascites events, hepatic encephalopathy events
MELD	£10.42[(a)]	Includes creatinine, bilirubin, INR
Transient elastography	£68.00	Imaging technique

Sources: Donnan 2009, NHS hospital trust (GDG source)
(a) MELD and Child-Pugh are inflated to 2013–14 prices

O.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

See **Table 64** in Appendix N.

O.5 Surveillance for the detection of varices

See **Table 64** in Appendix N.

O.6 Prophylaxis of variceal haemorrhage

Table 92: Unit costs of variceal haemorrhage prophylaxis – band ligation

Treatment	Unit cost	Details
Band ligation	£1,326	£530 per procedure; assuming 2.5 procedures

Source: NHS Hospital trust; GDG assumption

Table 93: Unit costs of variceal haemorrhage prophylaxis – beta blockers

Treatment	Daily dose	Cost per day	Cost per year
Propranolol[(a)]	60–120 mg	£0.08–0.16	£28.37–56.74
Carvedilol[(b)]	6.25–12.5 mg	£0.05, £0.04	£17.86, £16.42

Sources: NHS Drug Tariff July 2015
(a) Starting dose 20 mg three times per day, adjusted up to 40 mg three times per day, according to drug response
(b) Starting dose 6.25 mg, adjusted up to 12.5 mg according to drug response; note that 12.5 mg tablets are cheaper than 6.25 mg tablets

O.7 Primary prevention of bacterial infections in cirrhosis and gastrointestinal bleeding

Table 94: Unit costs of antibiotics to treat bacterial infections

Antibiotic	Daily dose	Cost per day	Cost of 5-day course
Ceftriaxone (IV)	1 g	£9.58	£47.90
Ceftriaxone (IV)	2 g	£19.18	£95.90
Ciprofloxacin (oral)	500 mg ×2	£0.21	£1.05
Norfloxacin (oral)[a]	400 mg ×2[b]	£1.71	£8.57
Norfloxacin (oral)[a] + ceftriaxone (IV)	400 mg ×2 + 2 g	£20.89	£104.47
Ofloxacin (oral)	400 mg ×2	£4.36	£21.8

Sources: NHS Drug Tariff July 2015, BNF August 2014
(a) Norfloxacin is currently unavailable in the UK
(b) Note that the Spanish group study used 1x 400 mg dosage

O.8 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Table 95: Unit costs of TIPS and LVP procedures

Procedures	Unit cost	Details
TIPS	£2,904	Average procedure costs of 28 patients
LVP	£672	Cost per single procedure, includes 1 elective day case admission, 100 ml of 20% albumin, catheter system use

Sources: TIPS: Parker 2013; LVP: NHS reference costs 2013–14, Parker 2013, GDG

O.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Table 96: Unit costs of antibiotics used for the primary prevention of SBP

Antibiotic	Daily dose	Cost per day	Cost per year
Ciprofloxacin (oral)	500 mg	£0.11	£40
Ciprofloxacin (oral)	750 mg	£0.80[a]	£292[a]
Norfloxacin (oral)[b]	400 mg	£0.86	£313

Sources: NHS Drug Tariff 2015, BNF August 2014
(a) Or £0.11 per day (£40 per year) if one and a half 500 mg tablets are used instead
(b) Norfloxacin is not currently available in the UK

Table 97: Unit costs of managing SBP related complications

Cost type	Unit cost	Details
7 day hospital stay	£1,561	GB03D (excess days), Intermediate, Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with CC Score 5-7
Tazocin	£237.30	Piperacillin 4 g/tazobactam 500 mg IV every 8 hours for 5 days
Paracentecis	£78	
Ultrasound	£49	

Sources: NHS reference costs 2013–14, NHS Drug Tariff July 2015, Parker 2013, GDG

O.10 Volume replacers in hepatorenal syndrome

Table 98: Unit costs of IV volume replacers

IV fluid type	Unit cost for 100 ml bag	Unit cost for 250 ml bag	Unit cost for 500 ml bag	Unit cost for 1000 ml bag
IV albumin				
Albumin (4.5%)	–	£17.03	–	–
Albumin (5%)	–	–	£30.52	–
Albumin (20%)	£35–50	–	–	–
IV crystalloids				
Ringer's lactate solution	–	–	£1.25	–
0.9% sodium chloride (saline)	–	–	£0.63	£0.70
Hartmann's solution	–	–	£0.70	£0.85
Dextrose (5%)	–	–	£0.63	£0.70
IV polygels, plasma, colloids				
Plasmalyte 148ph 7.4	–	–	–	£0.92
Haemocel	–	–	–	–
Gelofusion/gelofusine	–	–	–	£4.80
Dextran 70 (RescueFlow)	–	£28.50	–	–
Mannitol (10%)	–	–	£3.20	–
Mannitol (20%)	–	£3.78	£5.80	–
Voluven	–	–	£7.50–12.50	–
Volulyte	–	–	£7.65–18.00	–

Sources: BNF July 2015, NICE CG174 Intravenous fluid therapy in adults in hospital, personal communication with NHS hospitals

O.11 Management of an episode of acute hepatic encephalopathy

Table 99: Unit costs of drugs used to manage acute hepatic encephalopathy

Drug	Cost per day[(a)]	Dosage
BCAA	–	No cost information
Flumazenil (IV)	£81.00	One 5 ml ampule, 6x per day
Lactulose (oral solution)	£0.32	10–30 ml, 2–3x per day (average 50 ml)
Lactitol	Not prescribable	
LOLA	£34.4	10 ml ampoules, 4× per day
Metronidazole	£0.22	One 400 mg tablet, 3× per day
MARS	–	No cost information
Neomycin sulphate	£0.50	One 500 mg tablet, 2× per day
Rifaximin	£9.26	One 550 mg tablet, 2× per day

Sources: NHS Drug Tariff July 2015, BNF July 2015, NHS hospital trust (GDG source)

(a) Costs would apply for the duration of acute care (up to 5 days)

Appendix P: Research recommendations

P.1 Risk factors and risk assessment tools

Research question: Development of a risk tool to identify people at risk of cirrhosis

Why this is important:

Liver disease in the UK stands out as a glaring exception to the huge improvements in health and life expectancy for chronic disorders such as strokes, heart disease and many cancers. Since 1970 mortality rates for liver disease have increased 400% and in those under the age of 65 have risen almost five-fold. As a result, liver disease now constitutes the third commonest cause of premature death in working age in men and the second in women. The UK has overtaken European countries such as France, Spain and Italy which previously had very high liver mortality.[780] Of those with cirrhosis 5–10% will go on to develop liver cancer, and the incidence is rising.[217] In England and Wales it is estimated that some 600,000 people have some form of liver disease, of whom 60,000 people have cirrhosis, leading to 57,682 hospital admissions and 10,948 deaths in 2012.[5] This represents an increase of 62% in liver disease and 40% in cirrhosis in 10 years. The underlying cause of liver disease is in the main alcohol but there is a rising incidence of obesity, many of whom will have fatty liver disease (1 in 20 in the UK). These patients will have ongoing inflammation and fibrosis (scaring) that will progress over 10–20 years to cirrhosis. Annual deaths from hepatitis C have quadrupled since 1996. The incidence of hepatitis B is rising with the changing population demographics in the UK. There are also patients with autoimmune liver disease who go unrecognised and undiagnosed in the community. Left untreated these patients will progress to end-stage cirrhosis. The resultant cost to the NHS is staggering with estimates in excess of £9 billion per year for alcohol- and obesity-related health problems alone.[780]

Part of the problem is that for much of the time, until presentation with jaundice or decompensation, the liver disease may remain asymptomatic and silent. The earlier liver disease and even cirrhosis is diagnosed, the better the opportunity to intervene, limiting disease progression but in many cases offering a cure. The prevention of progression to end stage liver disease, avoiding complications, reducing the need for investigation, hospitalisation and intervention would have the potential for very large savings for the NHS. The earlier the diagnosis, the greater the potential patient and financial benefit. This is why GPs need a guide or 'tool kit' to identify people who are at high risk of having, or developing, advanced liver fibrosis or cirrhosis.

One approach would be to identify a retrospective cohort of people with cirrhosis, and to look at their cirrhosis risk factors. One potential source might be the clinical practice research database (CPRD).[6] This is a longitudinal database consisting of anonymous computerised primary care records for over 13 million patients in the UK. For many of the practices it is possible to link the CPRD data with HES data.

Patients with any diagnostic code for cirrhosis, oesophageal varices or portal hypertension would be identified in a fixed time period. It would then be possible to go back into the patient records to see if there was any mention in their CPRD record of alcoholism, alcohol abuse, addiction or dependence, or 'problem drinking'. The alcohol history will be broken down to drinks per week (<1, 1–7, 8–21, 22–35, >35) and alcohol intake (0.1–1.4, 1.5–4.9, 5–14.9, 15–29.9, >30 g/day).

Other demographic and risk factors would be sought including age, sex, viral hepatitis, race and ethnicity, intravenous drug use or substance misuse. Other factors may include autoimmune disease, thyroid, rheumatoid disease, metabolic disease including hypertension, hypercholesterolaemia, BMI

and type 2 diabetes mellitus. Also biochemical parameters, including; electrolytes, LFTs, AST, albumin, total protein, globulin fraction, Ferritin, FBC, platelets and coagulation studies.

The proposed study should use multivariate analysis to find the risk factors associated with the outcome of cirrhosis. By weighting the risk factors according to their association with the outcome, a risk tool should be developed to predict an individual's risk of developing cirrhosis. The ultimate risk prediction tool will require validation in a separate cohort (an external validation study).

P.2 Prophylaxis of variceal haemorrhage

Research question: Do non-selective beta-blockers improve survival and prevent first variceal bleeds in people with cirrhosis that is associated with small oesophageal varices?

Why this is important:

Bleeding from oesophageal varices is a major complication of cirrhosis. Approximately half of patients with cirrhosis have oesophageal varices and one-third of all patients with varices will experience bleeding at some point. Despite improvements in the management of acute haemorrhage in recent decades, the 6-week mortality associated with variceal bleeding remains of the order of 10–20%. Risk of variceal bleeding increases with variceal size. Whether non-selective beta-blockers are of benefit as primary prophylaxis in people with cirrhosis and small oesophageal varices has not been adequately studied.

Criterion	Explanation
Population	Adults with cirrhosis and small oesophageal varices with no history of variceal haemorrhage.
Interventions	Oral non-selective beta-blocker (for example propranolol, carvedilol)
Comparison	Placebo
Outcomes	• Acute variceal bleeding • Mortality • Regression of varices • Progression to large varices • Side effects
Importance to patients or the population	Bleeding from oesophageal varices is a major complication of cirrhosis. Approximately 50% of people with cirrhosis have oesophageal varices and one-third of these will develop variceal haemorrhage at some point. Despite improvements in the management of acute bleeding in recent decades, the 6-week mortality associated with variceal bleeding remains of the order of 10–20%. Therefore, measures that might reduce the likelihood of such life-threatening bleeding are clearly important.
Relevance to NICE guidance	The NICE guideline on cirrhosis recommends that all patients with cirrhosis be offered surveillance for oesophageal varices and that those with large varices are offered primary prophylaxis. The results of the proposed trial will allow NICE to make a recommendation on the use of non-selective beta-blockers as primary prophylaxis of variceal bleeding in people with small varices.
Relevance to the NHS	Acute variceal bleeding is a frequent cause of emergency hospital admission and one which is usually associated with high financial cost related to prolonged hospital stay (often on an intensive care unit) and use of high-cost interventions such as emergency endoscopy and intravenous medical therapies.
National priorities	–
Current evidence base	Data are limited with regard to the appropriate primary prophylactic strategy in the population described above. Recent national societal guidelines also identify this as an area for future study.

Equality	Liver disease represents one of the few diseases nationally where the inequalities gap is increasing. This study would recruit adults with cirrhosis regardless of gender, socio-demographic status or aetiology of cirrhosis.
Study design	Double-blind placebo-controlled trial. A crossover trial would be inappropriate because of progressing liver disease.
Feasibility	Many hospitals in the UK already offer surveillance for varices to patients with cirrhosis, often on designated endoscopy lists, and patients could be easily identified prospectively via this route. Duration of follow-up would be around 2 years.
Other comments	Care would need to be taken to establish a universal definition of small varices as various definitions exist in the literature and this is a potential area of inter-observer variability.

P.3 Transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis (LVP) for ascites

Research question: What is the quality of life in people who have had a transjugular intrahepatic portosystemic shunt (TIPS)?

Why this is important:

Prior to TIPS, people may have had several problems resulting from portal hypertension, including variceal bleeding from veins in the stomach, oesophagus, or intestines, ascites or hydrothorax – all of which will have had a detriment effect on their quality of life. TIPS should alleviate these problems, but little is known about the consequential effect on quality of life and any effects that potential problems following TIPS (for example, hepatic encephalopathy, shunt blockages, infection or cardiac problems) have on each person. It is therefore important to assess what benefits TIPS has to the quality of life of people with advanced liver disease.

Criterion	Explanation
Population	Adults with portal hypertension due to advanced liver disease
Interventions	TIPS
Comparison	Adults with portal hypertension who do not have TIPS
Outcomes	• Improvements in quality of life • Benefits of having TIPS
Importance to patients or the population	Portal hypertension is a life-threatening problem of advanced liver disease with physical and psychological quality of life problems for anyone living with it. TIPS offers an effective treatment for portal hypertension but there is little evidence to prove that it has a positive quality of life impact.
Relevance to NICE guidance	The NICE guideline on cirrhosis recommends TIPS as a treatment for portal hypertension. The answer to this question will allow NICE to make a definitive statement on the quality of life affects this has.
Relevance to the NHS	Whilst procedures like TIPS are thought to be beneficial at reducing the impact of advanced liver disease it is vital to know that this symptom control has a beneficial quality of life impact.
National priorities	PHE Liver Disease Improvement Framework (Autumn 2015) DoH/NHS Living Longer Lives: Reducing Premature Mortality NHS Improving Quality - Patient safety and quality
Current evidence base	Data are limited with regard to the quality of life impact of TIPS. Current JLA/NIHR PSPs for liver disease may also identify this as an area for future study.
Equality	Liver disease represents one of the few diseases nationally where the inequalities gap is increasing. This study would recruit adults with portal hypertension regardless of gender, socio-demographic status or aetiology of portal hypertension.

Study design	Qualitative study
Feasibility	All services providing TIPS could include this as part of the preparation and follow-up of patients who had had TIPS with a comparison group that do not.
Other comments	Quality of life evidence is scarce throughout hepatology – this could be an example of why it is so important for all interventions, for example for symptom control.

P.4 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Research question: How frequently does antibiotic resistance occur, and how significant are antibiotic treatment-related complications when antibiotics are used for the primary prevention of spontaneous bacterial peritonitis in people at high risk of having, or developing, cirrhosis?

Why this is important:

Spontaneous bacterial peritonitis (SBP) is the most common serious infection in people with cirrhosis, occurring in 25% of people who develop ascites. It is associated with significant morbidity and mortality rates of 20–40%.

It occurs most commonly in patients with advancing liver disease; approximately 70% of cases occur in people with Child-Pugh class C cirrhosis. Bacterial overgrowth associated with portal hypertension, reduced bowel motility, impairment of the intestinal barrier and reduced host defences result in bacterial translocation from the gut via the mucosa, to the circulation and other extra-intestinal sites. People who have ascites with a low ascitic fluid protein concentration, that is, less than 15 g/litre, are at particularly high risk of developing a first episode of SBP.

People with SBP commonly present with general malaise, pyrexia, abdominal pain, diarrhoea, vomiting, confusion and jaundice although up to 30% of patients may be asymptomatic. Most infections are caused by *E. coli*, *Klebsiella* sp., *Proteus* sp., *Enterococcus faecalis* and *Pseudomonas*. Diagnostic paracentesis and blood cultures should be undertaken to confirm or refute the diagnosis, however immediate empirical antibiotic therapy is required to prevent deterioration which may lead to worsening ascites, hepatorenal syndrome, liver failure and death. Hospitalisation, intravenous antibiotic therapy and the supportive care required to manage SBP are associated with significant healthcare costs. Following a primary episode of SBP, recurrence is common and up to 70% of patients relapse within 1 year. Two-year survival is estimated at 20%.

Several oral antibiotics that have been investigated for the prophylaxis of SBP have shown benefits and a significant reduction in the incidence of SBP in people at high risk of having, or developing, cirrhosis. They are, however, associated with antibiotic resistance, adverse reactions and drug interactions which may be important although data are currently lacking.

This GDG found that primary, oral prophylactic antibiotic therapy with ciprofloxacin or norfloxacin is currently more cost-effective than to diagnose and treat SBP in high-risk patients. Treatment should be offered to patients with severe disease (Childs-Pugh B and C) and an ascitic protein concentration of less than 15 g/litre as an adjunct to the management of ascites.

There was however a paucity of good quality, recent evidence regarding the prevalence and consequences of antibacterial resistance which may occur during long-term oral antibiotic therapy when used for the prevention of spontaneous bacterial peritonitis. Antibiotic therapy with broad-spectrum agents suppresses susceptible host commensal organisms allowing resistant pathogens such as *Clostridium difficile* to proliferate, releasing toxins which may damage the gut wall, exacerbating symptoms of SBP and potentially leading to sepsis and death.

Resistant pathogens emerge in hospital and community treatment settings over time irrespective of the antibiotic prophylaxis used and are a major concern for patients and healthcare providers. Antibiotic therapies currently available may be rendered ineffective and conditions incurable. Presently Hospital Trusts face financial penalties when outbreaks of infection with *C. difficile* occur. Local antimicrobial therapy guidance and epidemiological resistance patterns may need to be considered. Due consideration also needs to be given to antimicrobial stewardship when prophylactic antibiotic therapy is prescribed. Public Health England (2013) and NICE (2015) have published guidance that recommends the prudent prescribing of antimicrobials to prevent the emergence of resistance.

Prospective, randomised trials specifically in this group, adequately powered to determine optimal treatment, are required. The incidence and consequences of resistance, depending on the antibiotic used, the dose, treatment schedule (continuous, intermittent or cyclical) and duration of therapy need to be determined.

Criterion	Explanation
Population	Adult patients with cirrhosis and ascites (Child-Pugh B and C) who are at high risk of developing SBP. Including: • Patients with an ascitic protein concentration below 15 g/litre. • Patients who have not previously had an episode of SBP. Excluding: • Patients who have active GI bleeding. • Patients on antibiotic therapy at the time of presentation. • Patients with other confounding pathologies, for example colitis, perforation.
Interventions	Prophylactic oral antibiotic therapy to prevent a primary episode of SBP, specifying the antibiotic, dose, frequency and duration of therapy in different subgroups.
Comparison	A placebo given for the same duration as the active treatment group or until the first episode of SBP occurs. An alternative suitable antibiotic as a head-to-head comparator. A crossover or sequential study could be considered.
Outcomes	• Frequency of antibiotic-related adverse effects, for example, *Clostridium difficile* diarrhoea, superinfection with other resistant organisms. • Time to and the frequency of detection of resistant microbes in stool samples. • Time to first episode of SBP or hospitalisation due to breakthrough infection. • Quality of life • All-cause mortality.
Importance to patients or the population	Patients with cirrhosis and ascites have a poor quality of life and a high risk of developing SBP requiring hospitalisation and IV antibiotics. Optimising prophylactic antibiotic therapy would improve quality of life whilst reducing the associated morbidity, mortality and healthcare costs. Judicious use of appropriate antibiotic regimes should minimise the occurrence of resistance and the ensuing adverse outcomes for individual patients, the population at large and healthcare providers.
Relevance to NICE guidance	This information will allow NICE to make a definitive statement about the overall safety and effectiveness of specific prophylactic antibiotic regimens used to prevent primary episodes of SBP. The results may be used to ensure compliance with NICE recommendations on antimicrobial stewardship.
Relevance to the NHS	Ensures optimal use of healthcare resources.
National	Public Health England Expert advisory committee on Antimicrobial Resistance and

priorities	Healthcare Associated infection: Antimicrobial Prescribing and Stewardship Competencies (2013)
Current evidence base	Limited (as reviewed for the NICE Cirrhosis guideline)
Equality	Patients need to be informed about the balance of risks of prophylactic antibiotic therapy versus the likelihood and consequences of developing SBP
Study design	RCT study or sequential (crossover) study (n≥100)
Feasibility	The study population should be hepatology clinic, out-patient attenders from various centres in England who would be considered suitable for antibiotic prophylaxis.
Other comments	Funding for the study (studies) may be limited for generic antibiotics, long established in use.

P.5 Volume replacement in hepatorenal syndrome

Research question: What is the most clinically and cost-effective volume replacer for patients with hepatorenal syndrome due to cirrhosis who are also receiving vasoactive drugs?

Why this is important:

Hepatorenal syndrome (HRS) develops in people with cirrhosis with ascites and is characterised by impaired renal function.[649] Terlipressin, a vasoconstrictor most active in the splanchnic circulation, is used to treat HRS but it is given with a plasma volume expander, which serves to maintain the blood volume and increase the blood oncotic pressure, reducing the movement of free fluid into the peritoneum. Human albumin solution is the recommended intravenous volume replacement during large volume paracentesis[72] and in patients with SBP, in combination with antibiotics, when the serum creatinine is greater than 1 mg/dL, blood urea nitrogen greater than 30 mg/dL, or total bilirubin greater than 4 mg/dL.[683] However, in HRS there are no clinical studies examining the benefits and harms associated with albumin compared with other volume replacers.

People with HRS have a low intravascular volume state and there is general agreement that they require volume expansion in combination with vasopressors. Whilst these people have intravascular depletion, the pathophysiology of decompensated cirrhosis is such that they are also fluid overloaded, but the majority of fluid is outside the vascular compartment. People with decompensated cirrhosis are, therefore, more prone to complications of fluid overload, such as pulmonary oedema if given intravenous fluids. The ideal volume expander to be used in HRS should be able to provide its effect with a minimum of infused fluid (that is, have a high oncotic pressure).

PICO question	Population: • Adults and young people (16 and over) with confirmed cirrhosis and hepatorenal syndrome. Hepatorenal syndrome is defined as reversible renal dysfunction occurring in patients with cirrhosis (with a serum creatinine >133 micromol/litre and an absence of other identifiable causes of renal failure). • People will also receive the vasoconstrictor terlipressin Intervention(s): • IV human albumin solution • IV crystalloid (Ringer's lactate solution, 0.9% sodium chloride [saline], Hartmann's solution, dextrose) • IV colloid expander (gelofusion/gelofusine, dextran, voluven) Comparison: • IV albumin versus IV crystalloids • IV albumin versus colloid expanders Outcome(s):

	Critical outcomes • Survival (time-to-event) or mortality at 3 months • Health-related quality of life (continuous) • Reversal of hepatorenal syndrome or improved renal function (dichotomous – as defined by the study) at 3 months (reduction of serum creatinine below 133 micromol/litre, creatinine clearance, renal function returning to functioning kidneys without the requirement for drugs) **Important outcomes** • Time to discharge from hospital (time to event) • Readmission to hospital (dichotomous) • Adverse events such as infection, heart failure and deterioration of renal function.

P.6 Management of an episode of acute hepatic encephalopathy

Research question: In people with cirrhosis and an acute episode of hepatic encephalopathy secondary to a clearly identified, potentially reversible precipitating factor, does management of the precipitating event alone improve the hepatic encephalopathy without specific treatment?

Why this is important:

Hepatic encephalopathy is a major complication of cirrhosis. Approximately 50% of people with cirrhosis will develop clinically apparent hepatic encephalopathy at some stage after diagnosis – the risk being around 5–25% within 5 years. Hospital admissions are common and inpatient stays often prolonged. The presence of hepatic encephalopathy is associated with a significant increase in mortality; survival after the first episode is 42% at 1 year and 23% at 3 years.

At present, treatment of hepatic encephalopathy is directed primarily at reducing the production and absorption of gut-derived neurotoxins, particularly ammonia, mainly through bowel cleansing, and the use of non-absorbable disaccharides, such as lactulose, although several other agents such as non-absorbable antibiotics are also used. However, in approximately 50% of people admitted with episodic hepatic encephalopathy there is a clearly defined precipitating factor (for example, infections, gastrointestinal bleeding or overuse of diuretics). Treatment is often challenging and some people may need to be cared for in an intensive care setting, at least initially. The identification and correction of any precipitating events is important as there is evidence that this alone may ameliorate hepatic encephalopathy without recourse to specific therapies. However, this has not been rigorously tested in a randomised clinical trial.

Criterion	Explanation
Population	Adults with cirrhosis and an acute episode of hepatic encephalopathy secondary to (a) clearly identifiable, potentially reversible precipitating factor(s)
Interventions	Management of the precipitating event
Comparison	Management of the precipitating event plus oral lactulose
Outcomes	**Primary outcomes:** • All-cause mortality • Liver-related mortality • Improvement of hepatic encephalopathy • Time course of resolution in hepatic encephalopathy • Serious adverse events **Secondary outcomes:**

	• Quality of life • Non-serious adverse events • Surrogate outcomes, for example psychometric test results, blood ammonia concentrations, electroencephalogram, critical flicker frequency
Importance to patients or the population	Hepatic encephalopathy is the most common complication of cirrhosis. The cumulated incidence of overt hepatic encephalopathy is as high as 40% and its development often results in emergency hospital admission. The survival probability after a first episode is 42% at 1 year and 23% at 3 years. Measures which improve the management of episodic hepatic encephalopathy during the acute admission will be of benefit to patients.
Relevance to NICE guidance	The NICE guideline on cirrhosis investigated the treatment options for people with cirrhosis with episodic hepatic encephalopathy and did not make a recommendation because of the paucity of relevant studies and the poor quality of the evidence overall. There was some evidence from one very old study (Strauss, 1992), supported by clinical experience, that when the development of an episode of hepatic encephalopathy is associated with an obvious precipitating event, treatment of this event results in amelioration of the hepatic encephalopathy without the need for specific anti-encephalopathy treatment. Thus, it is important to determine whether, in the presence of a reversible precipitating event, specific treatment is of benefit. The results of such a trial would allow NICE to determine if head-to-head treatment trials are required.
Relevance to the NHS	In the UK the presence of hepatic encephalopathy in people with cirrhosis is associated with a significantly increase in mortality (58% compared to 32%) and longer inpatient stays (8 days compared to 6.8 days) and for those who survive more visits to primary care practitioners (18.2 compared to 8.7.contacts per patient years). Studies from elsewhere have identified a substantial burden for caregivers and a significant financial burden on healthcare systems.
National priorities	–
Current evidence base	There are very few good quality studies on which to base recommendations in this field. The evidence base overall is poor and no recommendation about the efficacy and safety of treatment for episodic hepatic encephalopathy was made in the NICE guideline on cirrhosis.
Equality	The significant disparity in the provision of care for individuals with cirrhosis by region is well documented and the inequality gap appears to be widening. This multicentre study would recruit patients from all sections of society irrespective of age, gender, racial group and the aetiology of their liver disease.
Study design	Multicentre, double-blind randomised controlled study
Feasibility	People with cirrhosis presenting with episodic hepatic encephalopathy are already assessed to identify likely precipitating factors. Only those in whom there is a clearly defined, potentially reversible precipitant will be recruited. Individuals in whom no such event is identified will be managed as per local guidelines. The study period will be short (around 7 days) so even with stringent inclusion and exclusion criteria recruitment should not be problematic.
Other comments	• It is difficult to estimate the required population size. In the single-site study by Strauss (2004), 102 patients were admitted over a 5-year period of whom 39 (38%) developed hepatic encephalopathy secondary to a precipitating event. This accords with clinical experience. Treatment of the precipitant alone resulted in amelioration of the hepatic encephalopathy in 90%. There was evidence that use of neomycin, a non-absorbable antibiotic, was associated with more rapid improvement and this will be an important primary outcome in any proposed study. • A large number of events can precipitate hepatic encephalopathy and it is possible that the degree of its amelioration might vary depending on the precipitating event and its treatment. It is also possible that unless the randomization is stratified the distribution of patients by precipitating event might be unbalanced between the groups. For this reason it may be advisable to select only 2 or 3 different precipitating events for inclusion. Management regimens for some complications, for example gastrointestinal bleeding, mandate use of antibiotics and this may have an independent beneficial

	effect on hepatic encephalopathy. • People will need to be monitored intensively during the trial and clear rescue criteria and procedures will need to be put in place for those not showing improvement. • The choice of lactulose as the adjuvant treatment was based on recent international guidelines recommending that it be used as first-line therapy in patients with hepatic encephalopathy.

Appendix Q: NICE technical team

Name	Role
Elizabeth Adelanwa	Communications Lead
Martin Allaby	Clinical Adviser
Steven Barnes	Technical Lead
Simran Chawla	Public Involvement Programme (PIP) Lead
Caroline Keir	Guideline Commissioning Manager
Ross Maconachie	Health Economic Lead
Sarah Palombella	Editorial Lead
Jill Peacock	Guideline Coordinator
Joanna Perkin	Digital Editor
Carmel Thomason	Implementation Lead
Sarah Willett	Guideline Lead
Maroulla Whiteley	Costings Lead

References

1 Lactulose for hepatic encephalopathy. Medical Letter on Drugs and Therapeutics. 1976; 18(1):3-4

2 Propranolol doses not decrease the development of large esophageal varices in patients with cirrhosis A controlled study. Hepatology. 1995; 22(4 Pt.2):155A

3 Test predicts cirrhosis likelihood. AIDS Patient Care and STDs. 2006; 20(6):450

4 Bleeding from ruptured oesophageal varices. Prescrire International. 2012; 21(125):73-77

5 Liver disease: the NHS atlas of variation in healthcare for people with liver disease. 2013. Available from: http://www.rightcare.nhs.uk/index.php/atlas/liver-disease-nhs-atlas-of-variation-in-healthcare-for-people-with-liver-disease [Last accessed: 2015]

6 Clinical Practice Research Datalink (CPRD). 2015. Available from: http://www.cprd.com [Last accessed: 2015]

7 Abdel-Wahab MF, Esmat G, Farrag A, el-Boraey Y, Strickland GT. Ultrasonographic prediction of esophageal varices in Schistosomiasis mansoni. American Journal of Gastroenterology. 1993; 88(4):560-563

8 Abdelgawad IA. Clinical utility of simple non-invasive liver fibrosis indices for predicting hepatocellular carcinoma (HCC) among Egyptian patients. Journal of Clinical Pathology. 2015; 68(2):154-160

9 Abel Wahab MF, El-Kateeb AA, El-Wakeel MR, Maklouf MM, Younis TA, El-Deeb TM et al. Comparative study between different diagnostic techniques in huge splenomegaly cases in El-Minia Province. Journal of the Egyptian Public Health Association. 1995; 70(1-2):37-55

10 Abid S, Mumtaz K, Abbas Z, Hamid S, Jafri N, Ali SH et al. Efficacy of infusion of L-ornithine L-aspartate in cirrhotic patients with portosystemic encephalopathy: a placebo controlled study. Journal of Hepatology. 2005; 42(Suppl.2):84

11 Abou-Assi SG, Moghimi R, Habib A, Mihas AA, Heuman DM, SanyalA. Nutritional and metabolic improvement in cirrhotic patients with refractory ascites randomized to transjugular intrahepatic portosystemic shunts (TIPS) or total paracentesis (TP). Hepatology. 2004; 40(4 Suppl.1):226A

12 Adams LA, George J, Bugianesi E, Rossi E, De Boer WB, van der Poorten D et al. Complex non-invasive fibrosis models are more accurate than simple models in non-alcoholic fatty liver disease. Journal of Gastroenterology and Hepatology. 2011; 26(10):1536-1543

13 Addario L, Scaglione G, Tritto G, Di Costanzo GG, De Luca M, Lampasi F et al. Prognostic value of quantitative liver function tests in viral cirrhosis: A prospective study. European Journal of Gastroenterology and Hepatology. 2006; 18(7):713-720

14 Adebayo D, Bureau C, Valla D, Peck-Radosavljevic M, McCune A, Vargas V et al. Alfapump system versus large volume paracentesis in the treatment of refractory ascites. A multicenter randomised controlled study. Journal of Hepatology. 2015; 62(Suppl.2):S849-S850

15 Afdhal N, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR et al. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. Clinical Gastroenterology and Hepatology. 2015; 13(4):772-773

16 Agrawal SR, Gupta R, Sharma S, Sarin SK. Comparable efficacy of propranolol plus isosorbide mononitrate and endoscopic variceal ligation in the prevention of variceal bleeding. Gastrointestinal Endoscopy. 2002; 55(5):AB195

17 Ahmed AC, Chaudhary S, Khan IM. Comparison of intravenous ciprofloxacin and ceftriaxone in the management of spontaneous bacterial peritonitis in cirrhosis of liver at Mayo Hospital, Lahore. Pakistan Journal of Medical and Health Sciences. 2014; 8(1):82-84

18 Ahmed L, Salama H, Ahmed R, Hamdy S, Al-Akel W, Shafi SA et al. Non-invasive fibrosis seromarkers as a predictor of liver fibrosis in chronic hepatitis C and/or non-alcoholic steatohepatitis. Arab Journal of Gastroenterology. 2009; 10(1):14-20

19 Al Hasani F, Knoepfli M, Gemperli A, Kollar A, Banz V, Kettenbach J et al. Factors affecting screening for hepatocellular carcinoma. Annals of Hepatology. 2014; 13(2):204-210

20 Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scandinavian Journal of Gastroenterology. 1989; 24(3):269-276

21 Albillos A, Banares R, Gonzalez M, Catalina MV, Molinero LM. A meta-analysis of transjugular intrahepatic portosystemic shunt versus paracentesis for refractory ascites. Journal of Hepatology. 2005; 43(6):990-996

22 Albillos A, de la Hera A, Reyes E, Monserrat J, Munoz L, Nieto M et al. Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. Journal of Hepatology. 2004; 40(4):624-631

23 Alexander T, Thomas K, Cherian AM, Kanakasabapathy. Effect of three antibacterial drugs in lowering blood & stool ammonia production in hepatic encephalopathy. Indian Journal of Medical Research. 1992; 96:292-296

24 Ali B, Zaidi YA, Alam A, Anjum HS. Efficacy of Rifaximin in prevention of recurrence of hepatic encephalopathy in patients with cirrhosis of liver. Journal of the College of Physicians and Surgeons--Pakistan. 2014; 24(4):269-273

25 Allan RB, Thoirs KA. A comparison of liver surface and hepatic vein wall ultrasound as markers for fibrosis or cirrhosis of the liver. Radiography. 2014; 20(1):8-14

26 Als-Nielsen B, Kjaergard LL, Gluud C. Benzodiazepine receptor antagonists for acute and chronic hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2001;(4):CD002798. DOI:DOI: 10.1002/14651858.CD002798

27 Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ. 2004; 328(7447):1046

28 Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2004;(2):CD002798. DOI:10.1002/14651858.CD002798.pub2

29 Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2004;(2):CD003044. DOI:10.1002/14651858.CD003044.pub2

30 Als-Nielsen B, Koretz RL, Gluud LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2003;(1):CD001939. DOI:10.1002/14651858.CD001939

31 Altman C, Bernard B, Roulot D, Vitte RL, Ink O. Randomized comparative multicenter study of hydroxyethyl starch versus albumin as a plasma expander in cirrhotic patients with tense ascites treated with paracentesis. European Journal of Gastroenterology and Hepatology. 1998; 10(1):5-10

32 Alvarez RF, Mattos AA, Correa EB, Cotrim HP, Nascimento TV. Trimethoprim-sulfamethoxazole versus norfloxacin in the prophylaxis of spontaneous bacterial peritonitis in cirrhosis. Arquivos De Gastroenterologia. 2005; 42(4):256-262

33 Amarapurkar DN, Chandnani MR, Dharod MV, Baijal R, Kumar P, Patel N et al. Care of Patients with cirrhosis-How are we doing? Hepatology. 2013; 58(4 Suppl.1):345A-346A

34 Anastasiou J, Alisa A, Virtue S, Portmann B, Murray-Lyon I, Williams R. Noninvasive markers of fibrosis and inflammation in clinical practice: prospective comparison with liver biopsy. European Journal of Gastroenterology and Hepatology. 2010; 22(4):474-480

35 Anderson FH, Zeng L, Rock NR, Yoshida EM. An assessment of the clinical utility of serum ALT and AST in chronic hepatitis C. Hepatology Research. 2000; 18(1):63-71

36 Ando E, Kuromatsu R, Tanaka M, Takada A, Fukushima N, Sumie S et al. Surveillance program for early detection of hepatocellular carcinoma in Japan: results of specialized department of liver disease. Journal of Clinical Gastroenterology. 2006; 40(10):942-948

37 Angeli P. Terlipressin for the treatment of hepatorenal syndrome in patients with cirrhosis. Expert Opinion on Orphan Drugs. 2013; 1(3):241-248

38 Angeli P, Merkel C. Pathogenesis and management of hepatorenal syndrome in patients with cirrhosis. Journal of Hepatology. 2008; 48(Suppl.1):S93-103

39 Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value in Health. 2008; 11(7):1131-1143

40 Arroyo V, Colmenero J. Use of albumin in the management of patients with decompensated cirrhosis An independent verdict. Digestive and Liver Disease. 2003; 35(9):668-672

41 Asbach P, Klatt D, Schlosser B, Biermer M, Muche M, Rieger A et al. Viscoelasticity-based staging of hepatic fibrosis with multifrequency MR elastography. Radiology. 2010; 257(1):80-86

42 Atterbury CE, Bar MS, Bessoff J. A double blind comparison of lactulose (L) and neomycin (N) plus sorbitol (S) in the treatment of acute nitrogenous portalsystemic encephalopathy (PSE). Gastroenterology. 1976; 70(5 II):977

43 Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. American Journal of Digestive Diseases. 1978; 23(5):398-406

44 Attia KA, Ackoundou-N'guessan KC, N'dri-yoman AT, Mahassadi AK, Messou E, Bathaix YF et al. Child-Pugh-Turcott versus Meld score for predicting survival in a retrospective cohort of black African cirrhotic patients. World Journal of Gastroenterology. 2008; 14(2):286-291

45 Aube C, Oberti F, Korali N, Namour MA, Loisel D, Tanguy JY et al. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. Journal of Hepatology. 1999; 30(3):472-478

46 Aube C, Winkfield B, Oberti F, Vuillemin E, Rousselet MC, Caron C et al. New Doppler ultrasound signs improve the non-invasive diagnosis of cirrhosis or severe liver fibrosis. European Journal of Gastroenterology and Hepatology. 2004; 16(8):743-751

47 Avery GS, Davies EF, Brogden RN. Lactulose: a review of its therapeutic and pharmacological properties with particular reference to ammonia metabolism and its mode of action of portal systemic encephalopathy. Drugs. 1972; 4(1):7-48

48 Bagshaw SM, Bellomo R, Devarajan P, Johnson C, Karvellas CJ, Kutsiogiannis DJ et al. Review article: Acute kidney injury in critical illness. Canadian Journal of Anesthesia. 2010; 57(11):985-998

49 Bai M, Qi XS, Yang ZP, Yang M, Fan D, Han G. TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. World Journal of Gastroenterology. 2014; 20(10):2704-2714

50 Bai M, Yang Z, Qi XS, Fan D, Han G. l-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. Journal of Gastroenterology and Hepatology. 2013; 28(5):783-792

51 Bajaj JS, Barrett AC, Bortey E, Paterson C, Forbes WP. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. Alimentary Pharmacology and Therapeutics. 2015; 41(1):39-45

52 Banares R, Moitinho E, Piqueras B, Casado M, Garcia-Pagan JC, de Diego A et al. Carvedilol, a new nonselective beta-blocker with intrinsic anti- Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology. 1999; 30(1):79-83

53 Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013; 57(3):1153-1162

54 Banerjee R, Pavlides M, Tunnicliffe EM, Piechnik SK, Sarania N, Philips R et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. Journal of Hepatology. 2014; 60(1):69-77

55 Bansky G, Meier PJ, Riederer E, Walser H, Ziegler WH, Schmid M. Effects of the benzodiazepine receptor antagonist flumazenil in hepatic encephalopathy in humans. Gastroenterology. 1989; 97(3):744-750

56 Barada K. Hepatorenal syndrome: pathogenesis and novel pharmacological targets. Current Opinion in Pharmacology. 2004; 4(2):189-197

57 Bardou-Jacquet E, Legros L, Soro D, Latournerie M, Guillygomarc'h A, Le Lan C et al. Effect of alcohol consumption on liver stiffness measured by transient elastography. World Journal of Gastroenterology. 2013; 19(4):516-522

58 Barritt AS, Arguedas MR. Practice patterns in screening for varices: an American survey. Digestive and Liver Disease. 2009; 41(9):676-682

59 Bass N, Ahmed A, Johnson L, Gardner J. Rifaximin treatment is beneficial for mild hepatic encephalopathy. Hepatology. 2004; 40(Suppl.4):646

60 Bauer TM, Follo A, Navasa M, Vila J, Planas R, Clemente G et al. Daily norfloxacin is more effective than weekly rufloxacin in prevention of spontaneous bacterial peritonitis recurrence. Digestive Diseases and Sciences. 2002; 47(6):1356-1361

61 Bavu E, Gennisson JL, Couade M, Bercoff J, Mallet V, Fink M et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. Ultrasound in Medicine and Biology. 2011; 37(9):1361-1373

62 Beckebaum S, Iacob S, Klein CG, Dechene A, Varghese J, Baba HA et al. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. Transplantation. 2010; 89(8):983-993

63 Becker U, Deis A, Sorensen TIA, Gronbaek M, Borch-Johnsen K, Muller C et al. Prediction of risk of liver disease by alcohol intake, sex, and age: A prospective population study. Hepatology. 1996; 23(5):1025-1029

64 Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Croce LS, Mazzoran L et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: Report from the Dionysos study. Gut. 1999; 44(6):874-880

65 Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut. 1997; 41(6):845-850

66 Ben Jazia E, Kaabia N, Benabdelkader A, Khalifa M, Harrabi I, Braham A et al. Noninvasive fibrosis markers for the prediction of significant fibrosis in patients with chronic hepatitis C virus infection in Tunisia. Infectious Diseases in Clinical Practice. 2009; 17(6):385-387

67 Bendtsen F, Henriksen JH, Sorensen TI. Long-term effects of oral propranolol on splanchnic and systemic haemodynamics in patients with cirrhosis and oesophageal varices. Scandinavian Journal of Gastroenterology. 1991; 26(9):933-939

68 Berenguer J, Sala T, Barrios J, Rodrigo M, Garrido G, Carrasquer J et al. Controlled study of lactulose in hepatic encephalopathy. Medicina Española. 1971; 66:266-273

69 Berges W, Erckenbrecht J, Teschke R, Wienbeck M. Prevention of bleeding esophageal varices by use of beta blockers. Deutsche Medizinische Wochenschrift. 1983; 08(36):1376-1377

70 Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with ascites: a meta-analysis. Digestion. 1998; 59(Suppl.2):54-57

71 Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology. 1999; 29(6):1655-1661

72 Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology. 2012; 55(4):1172-1181

73 Berretta M, Garlassi E, Cacopardo B, Cappellani A, Guaraldi G, Cocchi S et al. Hepatocellular carcinoma in HIV-infected patients: check early, treat hard. Oncologist. 2011; 16(9):1258-1269

74 Berzigotti A, Rossi V, Tiani C, Pierpaoli L, Zappoli P, Riili A et al. Prognostic value of a single HVPG measurement and Doppler-ultrasound evaluation in patients with cirrhosis and portal hypertension. Journal of Gastroenterology. 2011; 46(5):687-695

75 Berzigotti A, Abraldes JG, Tandon P, Erice E, Gilabert R, Garcia-Pagan JC et al. Ultrasonographic evaluation of liver surface and transient elastography in clinically doubtful cirrhosis. Journal of Hepatology. 2010; 52(6):846-853

76 Beuers U, Jager F, Wahllander A, Ansari H, Kirsch CM. Prognostic value of the intravenous 14C-aminopyrine breath test compared to the Child-Pugh score and serum bile acids in 84 cirrhotic patients. Digestion. 1991; 50(3-4):212-218

77 Bhardwaj A, Kedarisetty CK, Kumar M, Sarin SK. A prospective, double-blind, randomized placebo-controlled trial of carvedilol for early primary prophylaxis of esophageal varices in cirrhosis. Hepatology. 2013; 58(4 Suppl.1):294A

78 Bhise SB, Dias RJ, Mali KK. Prognostic value of the monoethylglycinexylidide test in alcoholic cirrhosis. Saudi Journal of Gastroenterology. 2007; 13(3):118-123

79 Bircher J, Muller J, Guggenheim P, Haemmerli UP. Treatment of chronic portal-systemic encephalopathy with lactulose. The Lancet. 1966; 1(7443):890-892

80 Bischof DA, Pawlik TM. Systematic review with meta-analysis: Surveillance for hepatocellular carcinoma with ultrasound and AFP is associated with improvements in tumour detection, receipt of curative therapy and overall survival in patients with cirrhosis. Evidence-Based Medicine. 2014; 19(6):225-226

81 Biselli M, Conti F, Gramenzi A, Frigerio M, Cucchetti A, Fatti G et al. A new approach to the use of alpha-fetoprotein as surveillance test for hepatocellular carcinoma in patients with cirrhosis. British Journal of Cancer. 2015; 112(1):69-76

82 Blanc P, Daures JP, Liautard J, Buttigieg R, Desprez D, Pageaux G et al. Treatment of acute hepatic encphalopathy by lactulose-neomycin combination versus placebo. A randomized controlled assay. Gastroenterologie Clinique Et Biologique. 1994; 18(12):1063-1068

83 Blanco CI, Vazquez-Elizondo G, Maldonado Garza HJ, Landeros CM, Bosques Padilla FJ. L-ornithine L-aspartate is as effective as nonabsorbable disaccharides in the management of acute hepatic encephalopathy. results of a randomized, double-blind, double-dummy, non-inferiority, clinical trial. Hepatology. 2011; 54(4 Suppl.):1255A-1256A

84 Block JP. Rifaximin improves the treatment of hepatic encephalopathy. Journal of Clinical Outcomes Management. 2010; 17(5):16-19

85 Bolondi L, Sofia S, Siringo S, Gaiani S, Cassali A, Zironi G et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut. 2001; 48(2):251-259

86 Boozari B, Potthoff A, Mederacke I, Hahn A, Reising A, Rifai K et al. Evaluation of sound speed for detection of liver fibrosis: prospective comparison with transient dynamic elastography and histology. Journal of Ultrasound in Medicine. 2010; 29(11):1581-1588

87 Borzio M, Fornari F, de Sio I, Andriulli A, Terracciano F, Parisi G et al. Adherence to American Association for the Study of Liver Diseases guidelines for the management of hepatocellular

carcinoma: results of an Italian field practice multicenter study. Future Oncology. 2013; 9(2):283-294

88 Bosch J. Is treatment with nadolol effective against the growth of small esophageal varices in patients with cirrhosis? Nature Clinical Practice Gastroenterology and Hepatology. 2005; 2(1):18-19

89 Bosch J, Groszmann R, Grace N, Navasa M, Conn HO, Rodes J. Propranolol in the prophylaxis of oesophageal variceal haemorrhage in patients with cirrhosis: a double-blind, multicenter controlled trial. Journal of Hepatology. 1990; 10(1):2

90 Bosch J, Groszmann R, Grace N, Navasa M, Mastai R, Conn HO et al. Propranolol in the prevention of the first hemorrhage from esophageal varices: results of a randomized, double-blin, cooperative clinical trial. Journal of Hepatology. 1988; 7(Suppl.1):S12

91 Bota S, Paternostro R, Etschmaier A, Schwarzer R, Salzl P, Mandorfer M et al. Performance of 2-D shear wave elastography in liver fibrosis assessment compared with serologic tests and transient elastography in clinical routine. Ultrasound in Medicine and Biology. 2015; 41(9):2340-2349

92 Bota S, Sporea I, Sirli R, Popescu A, Jurchis A. Factors which influence the accuracy of acoustic radiation force impulse (ARFI) elastography for the diagnosis of liver fibrosis in patients with chronic hepatitis C. Ultrasound in Medicine and Biology. 2013; 39(3):407-412

93 Botta F, Giannini E, Romagnoli P, Fasoli A, Malfatti F, Chiarbonello B et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: A European study. Gut. 2003; 52(1):134-139

94 Bottero J, Lacombe K, Guechot J, Serfaty L, Miailhes P, Bonnard P et al. Performance of 11 biomarkers for liver fibrosis assessment in HIV/HBV co-infected patients. Journal of Hepatology. 2009; 50(6):1074-1083

95 Bourliere M, Penaranda G, Ouzan D, Renou C, Botta-Fridlund D, Tran A et al. Optimized stepwise combination algorithms of non-invasive liver fibrosis scores including Hepascore in hepatitis C virus patients. Alimentary Pharmacology and Therapeutics. 2008; 28(4):458-467

96 Bourliere M, Penaranda G, Renou C, Botta-Fridlund D, Tran A, Portal I et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. Journal of Viral Hepatitis. 2006; 13(10):659-670

97 Boursier J, Brochard C, Bertrais S, Michalak S, Gallois Y, Fouchard-Hubert I et al. Combination of blood tests for significant fibrosis and cirrhosis improves the assessment of liver-prognosis in chronic hepatitis C. Alimentary Pharmacology and Therapeutics. 2014; 40(2):178-188

98 Boursier J, Cesbron E, Tropet A-L, Pilette C. Comparison and improvement of MELD and Child-Pugh score accuracies for the prediction of 6-month mortality in cirrhotic patients. Journal of Clinical Gastroenterology. 2009; 43(6):580-585

99 Boursier J, de Ledinghen V, Zarski JP, Rousselet MC, Sturm N, Foucher J et al. A new combination of blood test and fibroscan for accurate non-invasive diagnosis of liver fibrosis stages in chronic hepatitis C. American Journal of Gastroenterology. 2011; 106(7):1255-1263

100 Boursier J, Bacq Y, Halfon P, Leroy V, de Ledinghen V, de Muret A et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. European Journal of Gastroenterology and Hepatology. 2009; 21(1):28-38

101 Boursier J, de Ledinghen V, Zarski JP, Fouchard-Hubert I, Gallois Y, Oberti F et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology. 2012; 55(1):58-67

102 Boursier J, Vergniol J, Sawadogo A, Dakka T, Michalak S, Gallois Y et al. The combination of a blood test and Fibroscan improves the non-invasive diagnosis of liver fibrosis. Liver International. 2009; 29(10):1507-1515

103 Boursier J, Zarski JP, de Ledinghen V, Rousselet MC, Sturm N, Le Bail B et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology. 2013; 57(3):1182-1191

104 Boyer T, Medicis J, Pappas SC, Potenziano J, Jamil K. A randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin: The REVERSE trial design. Open Access Journal of Clinical Trials. 2012; 4:39-49

105 Boyer T, Medicis J, Pappas SC, Potenziano J, Jamil K. Erratum to: A randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin: The REVERSE trial design (Open Access Journal of Clinical Trials (2012), 4, (39-49)). Open Access Journal of Clinical Trials. 2012; 4:59

106 Boyer T, Sanyal AJ, Pappas SC, Wong F, Jamil K. Percentage change in serum creatinine (SCR) is a sensitive indicator of therapeutic response to terlipressin in hepatorenal syndrome type 1 (HRS-1). Journal of Hepatology. 2015; 62(Suppl.2):S379-S380

107 Bucci L, Palmieri GC. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy. Current Medical Research and Opinion. 1993; 13(2):109-118

108 Burroughs A. Should neither sclerotherapy nor propranolol be used prophylactically for oesophageal varices? HPB Surgery. 1992; 6(2):134-137

109 Burroughs A. Is the use of albumin of value in cirrhosis? The case not so in favour, or is there an alternative? Digestive and Liver Disease. 2003; 35(9):664-667

110 Cadranel JF, El-Younsi M, Pidoux B, Zylberberg P, Benhamou Y, Valla D et al. Flumazenil therapy for hepatic encephalopathy in cirrhotic patients: a double-blind pragmatic randomized, placebo study. European Journal of Gastroenterology and Hepatology. 1995; 7(4):325-329

111 Cales P, Boursier J, Oberti F, Bardou D, Zarski J-P, de Ledinghen V. Cirrhosis diagnosis and liver fibrosis staging: transient elastometry versus cirrhosis blood test. Journal of Clinical Gastroenterology. 2015; 49(6):512-519

112 Cales P, Boursier J, Bertrais S, Oberti F, Gallois Y, Fouchard-Hubert I et al. Optimization and robustness of blood tests for liver fibrosis and cirrhosis. Clinical Biochemistry. 2010; 43(16-17):1315-1322

113 Cales P, Boursier J, Chaigneau J, Laine F, Sandrini J, Michalak S et al. Diagnosis of different liver fibrosis characteristics by blood tests in non-alcoholic fatty liver disease. Liver International. 2010; 30(9):1346-1354

114 Cales P, Boursier J, Ducancelle A, Oberti F, Hubert I, Hunault G et al. Improved fibrosis staging by elastometry and blood test in chronic hepatitis C. Liver International. 2014; 34(6):907-917

115 Cales P, Desmorat H, Vinel JP, Caucanas JP, Ravaud A, Gerin P et al. Incidence of large oesophageal varices in patients with cirrhosis: application to prophylaxis of first bleeding. Gut. 1990; 31(11):1298-1302

116 Cales P, Oberti F, Payen JL, Naveau S, Guyader D, Blanc P et al. Lack of effect of propranolol in the prevention of large oesophageal varices in patients with cirrhosis: a randomized trial. European Journal of Gastroenterology and Hepatology. 1999; 11(7):741-745

117 Calvaruso V, Di Marco V, Ferraro D, Petta S, Cali A, Grazia Bavetta M et al. Fibrosis evaluation by transient elastography in patients with long-term sustained HCV clearance. Hepatitis Monthly. 2013; 13(5):e7176

118 Campbell MS, Brensinger CM, Sanyal AJ, Gennings C, Wong F, Kowdley K et al. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. Hepatology. 2005; 42(3):635-640

119 Canavan C, Eisenburg J, Meng L, Corey K, Hur C. Ultrasound elastography for fibrosis surveillance is cost effective in patients with chronic hepatitis C virus in the UK. Digestive Diseases and Sciences. 2013; 58(9):2691-2704

120 Carl I, Addley J, McDougall NI, Cash WJ. Transient hepatic elastography reliably excludes cirrhosis in an unselected liver disease population. Journal of Hepatology. 2012; 56(Suppl.2):S409-S410

121 Carrion JA, Navasa M, Bosch J, Bruguera M, Gilabert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transplantation. 2006; 12(12):1791-1798

122 Carton JA, Collazos J, De La Fuente B, Garcia-Alcalde ML, Suarez-Zarracina T, Rodriguez-Guardado A et al. Factors associated with liver fibrosis in intravenous drug users coinfected with HIV and HCV. Antiviral Therapy. 2011; 16(1):27-35

123 Carulli L. Telomere shortening as genetic risk factor of liver cirrhosis. World Journal of Gastroenterology. 2015; 21(2):379-383

124 Casper M, Mengel M, Fuhrmann C, Herrmann E, Reichert M, Appenrodt B et al. Design of the INCA trial (impact of NOD2 genotypeguided antibiotic prevention on survival in patients with liver cirrhosis and ascites): Prospective, doubleblind, randomised clinical trial evaluating the impact of genotype-stratified care. Journal of Hepatology. 2015; 62(Suppl.2):S847-S848

125 Casper M, Mengel M, Fuhrmann C, Herrmann E, Appenrodt B, Schiedermaier P et al. The INCA trial (Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver Cirrhosis and Ascites): study protocol for a randomized controlled trial. Trials. 2015; 16:83

126 Cassinotto C, Lapuyade B, Ait-Ali A, Vergniol J, Gaye D, Foucher J et al. Liver fibrosis: noninvasive assessment with acoustic radiation force impulse elastography--comparison with FibroScan M and XL probes and FibroTest in patients with chronic liver disease. Radiology. 2013; 269(1):283-292

127 Cassinotto C, Lapuyade B, Mouries A, Hiriart JB, Vergniol J, Gaye D et al. Non-invasive assessment of liver fibrosis with impulse elastography: Comparison of Supersonic Shear Imaging with ARFI and FibroScan. Journal of Hepatology. 2014; 61(3):550-557

128 Castera L, Winnock M, Pambrun E, Paradis V, Perez P, Loko MA et al. Comparison of transient elastography (FibroScan), FibroTest, APRI and two algorithms combining these non-invasive tests for liver fibrosis staging in HIV/HCV coinfected patients: ANRS CO13 HEPAVIH and FIBROSTIC collaboration. HIV Medicine. 2014; 15(1):30-39

129 Castera L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. Journal of Hepatology. 2009; 50(1):59-68

130 Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005; 128(2):343-350

131 Cavallin M, Fasolato S, Marenco S, Piano S, Tonon M, Angeli P. The treatment of hepatorenal syndrome. Digestive Diseases. 2015; 33(4):548-554

132 Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. Hepatology. 2015; 62(2):567-574

133 Cestari R, Minelli L, Lanzini A, Missale G, Ravelli P, Salerni B. Digestive endoscopy and portal hypertension. North Italian Endoscopic Club. Italian Journal of Gastroenterology. 1996; 28(Suppl.2):18-33

134 Chan AWH, Chan RCK, Wong GLH, Wong VWS, Choi PC, Chan HLY et al. New simple prognostic score for primary biliary cirrhosis: Albumin-bilirubin score. Journal of Gastroenterology and Hepatology. 2015; 30(9):1391-1396

135 Chandna S, Naumovich CN, Poreddy S, Zucker SD. Identification of a subset of patients at high risk for recurrent hepatocellular carcinoma (HCC) post liver transplantation: Is universal surveillance necessary? Gastroenterology. 2015; 148(4 Suppl.1):S1035

136 Chang PE, Lui HF, Chau YP, Lim KH, Yap WM, Tan CK et al. Prospective evaluation of transient elastography for the diagnosis of hepatic fibrosis in Asians: comparison with liver biopsy and aspartate transaminase platelet ratio index. Alimentary Pharmacology and Therapeutics. 2008; 28(1):51-61

137 Chang T-S, Wu YC, Tung SY, Wei KL, Hsieh Y-Y, Huang HC et al. Alpha-Fetoprotein Measurement Benefits Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis. American Journal of Gastroenterology. 2015; 110(6):836-844

138 Chanteloup E, Foucher J, Castera L. FibroScan® is a new non invasive method for the detection of cirrhosis and its complications in patients with chronic liver diseases. Results of a prospective study in 456 patients. Annual Meeting of the American Association for the Study of Liver Desease (AASLD). 2004; 55

139 Chasalani N, Imperiale TF, Ismail A, Carey M, Wilcox CM, Madichetty H et al. Predictors of large esophageal varices in patients with cirrhosis. American Journal of Gastroenterology. 1999; 94(11):3285-3291

140 Chawla YK, Kashinath RC, Duseja A, Dhiman RK. Predicting Mortality Across a Broad Spectrum of Liver Disease-An Assessment of Model for End-Stage Liver Disease (MELD), Child-Turcotte-Pugh

(CTP), and Creatinine-Modified CTP Scores. Journal of Clinical and Experimental Hepatology. 2011; 1(3):161-168

141 Chen CY, Sheu MZ, Tsai TL, Su SY, Lin YL. Endoscopic variceal ligation (EVL)VL) with multiple band ligator for prophylaxis of first hemorrhage esophageal varices. Endoscopy. 1999; 31(Suppl 1):E35

142 Chen CY, Sheu MZ, Tsai TL, Su SY, Lin YL. Multiple band ligator for prophylaxis of first hemorrhage of esophageal varices. Journal of Gastroenterology and Hepatology. 2000; 15(Suppl.):B76

143 Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. Journal of Gastroenterology and Hepatology. 2011; 26(4):628-638

144 Chen G, Chitturi S, Kaye GL, Teoh NC, Farrell GC. Hazardous alcohol use is more strongly associated with cirrhosis complications than obesity and diabetes in patients with chronic hepatitis C: Preliminary results of a case-control study. Journal of Gastroenterology and Hepatology. 2014; 29(Suppl.2):154

145 Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. Journal of Medical Screening. 2003; 10(4):204-209

146 Chen RP, Zhu Ge XJ, Huang ZM, Ye XH, Hu CY, Lu GR et al. Prophylactic use of transjugular intrahepatic portosystemic shunt aids in the treatment of refractory ascites: metaregression and trial sequential meta-analysis. Journal of Clinical Gastroenterology. 2014; 48(3):290-299

147 Chen SH, Li YF, Lai HC, Kao JT, Peng CY, Chuang PH et al. Noninvasive assessment of liver fibrosis via spleen stiffness measurement using acoustic radiation force impulse sonoelastography in patients with chronic hepatitis B or C. Journal of Viral Hepatitis. 2012; 19(9):654-663

148 Chen WJ, Hu QL, Ao ZX, Liu GQ, Zhang LH, Wang YH. Clinical observation on therapteutic effects of propranolol for prevention and treatment of esophagous varices of portal hypertension. Chinese Journal of Clinical Hepatology. 1993; 9(1):34-35

149 Choi PC, Kim HJ, Choi WH, Park DI, Park JH, Cho YK et al. Model for end-stage liver disease, model for end-stage liver disease-sodium and Child-Turcotte-Pugh scores over time for the prediction of complications of liver cirrhosis. Liver International. 2009; 29(2):221-226

150 Choi YR, Lee JM, Yoon JH, Han JK, Choi BI. Comparison of magnetic resonance elastography and gadoxetate disodium-enhanced magnetic resonance imaging for the evaluation of hepatic fibrosis. Investigative Radiology. 2013; 48(8):607-613

151 Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs A. Systematic review: The model for end-stage liver disease - Should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Alimentary Pharmacology and Therapeutics. 2005; 22(11-12):1079-1089

152 Chon YE, Jung ES, Park JY, Kim DY, Ahn SH, Han KH et al. The accuracy of noninvasive methods in predicting the development of hepatocellular carcinoma and hepatic decompensation in patients with chronic hepatitis B. Journal of Clinical Gastroenterology. 2012; 46(6):518-525

153 Choong CC, Venkatesh SK, Siew EPY. Accuracy of routine clinical ultrasound for staging of liver fibrosis. Journal of Clinical Imaging Science. 2012; 2:58

154 Chou R, Cuevas C, Fu R, Devine B, Wasson N, Ginsburg A et al. Imaging Techniques for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. Annals of Internal Medicine. 2015; 162(10):697-711

155 Christensen E. Prognostic models including the Child-Pugh, MELD and Mayo risk scores--where are we and where should we go? Journal of Hepatology. 2004; 41(2):344-350

156 Christensen E, Schlichting P, Fauerholdt L. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. Hepatology. 1984; 4(3):430-435

157 Christensen K, Mossner BK, Hansen JF, Jarnbjer EF, Pedersen C, Christensen PB. Liver Stiffness Measurement among Patients with Chronic Hepatitis B and C: Results from a 5-Year Prospective Study. PloS One. 2014; 9(11):e111912

158 Chung JH, Ahn HS, Kim SG, Lee YN, Kim YS, Jeong SW et al. The usefulness of transient elastography, acoustic-radiation-force impulse elastography, and real-time elastography for the evaluation of liver fibrosis. Clinical and Molecular Hepatology. 2013; 19(2):156-164

159 Clewell JD, Walker-Renard P. Prostaglandins for the treatment of hepatorenal syndrome. Annals of Pharmacotherapy. 1994; 28(1):54-55

160 Cobbold JFL, Crossey MME, Colman P, Goldin RD, Murphy PS, Patel N et al. Optimal combinations of ultrasound-based and serum markers of disease severity in patients with chronic hepatitis C. Journal of Viral Hepatitis. 2010; 17(8):537-545

161 Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. Journal of Viral Hepatitis. 2007; 14(5):360-369

162 Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: A prospective study. Journal of Hepatology. 2014; 60(6):1158-1164

163 Colli A, Cocciolo M, Riva C, Martinez E, Prisco A, Pirola M et al. Abnormalities of Doppler waveform of the hepatic veins in patients with chronic liver disease: correlation with histologic findings. American Journal of Roentgenology. 1994; 162(4):833-837

164 Colombo M. Screening. Hepatology Research. 2007; 37(Suppl.2):S146-S151

165 Colombo S, Buonocore M, Del Poggio A, Jamoletti C, Elia S, Mattiello M et al. Head-to-head comparison of transient elastography (TE), real-time tissue elastography (RTE), and acoustic radiation force impulse (ARFI) imaging in the diagnosis of liver fibrosis. Journal of Gastroenterology. 2012; 47(4):461-469

166 Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology. 1977; 72(4 Pt.1):573-583

167 Corazza GR, Tacconi C, Zoli G. Use of pyridoxine-alpha-ketoglutarate (PAK) in hepatic encephalopathy. International Journal of Clinical Pharmacology Research. 1982; 2(4 Suppl 1):7-13

168 Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouilleres O et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012; 56(1):198-208

169 Corpechot C, El Naggar A, Poujol-Robert A, Ziol M, Wendum D, Chazouilleres O et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. Hepatology. 2006; 43(5):1118-1124

170 Corpechot C, Gaouar F, El Naggar A, Kemgang A, Wendum D, Poupon R et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. Gastroenterology. 2014; 146(4):970-976

171 Corrao G, Bagnardi V, Zambon A, Torchio P. Meta-analysis of alcohol intake in relation to risk of liver cirrhosis. Alcohol and Alcoholism. 1998; 33(4):381-392

172 Cowan GSJ. Disease-specific amino acid infusion (F080) in hepatic encephalopathy: a prospective, randomized, double-blind, controlled trial. Journal of Parenteral and Enteral Nutrition. 1986; 10(2):247

173 Craxi A, Colombo P, D'Amico G, Di Blasi F, Di Marco V, Magrin S et al. Hepatitis B infection and liver cirrhosis: a reappraisal from the Mediterranean area. Annali Dell'Istituto Superiore Di Sanita. 1987; 24(2):257-265

174 Crespo G, Lens S, Gambato M, Carrion JA, Marino Z, Lombard M et al. Liver stiffness 1 year after transplantation predicts clinical outcomes in patients with recurrent hepatitis C. American Journal of Transplantation. 2014; 14(2):375-383

175 Crespo G, Fernandez-Varo G, Marino Z, Casals G, Miquel R, Martinez SM et al. ARFI, FibroScan, ELF, and their combinations in the assessment of liver fibrosis: a prospective study. Journal of Hepatology. 2012; 57(2):281-287

176 Cross TJS, Calvaruso V, Maimone S, Carey I, Chang TP, Pleguezuelo M et al. Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. Journal of Viral Hepatitis. 2010; 17(8):546-554

177 Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodriguez-Peralvarez M et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technology Assessment. 2015; 19(9):1-410

178 Cucchetti A, Trevisani F, Cescon M, Ercolani G, Farinati F, Poggio PD et al. Cost-effectiveness of semi-annual surveillance for hepatocellular carcinoma in cirrhotic patients of the Italian Liver Cancer population. Journal of Hepatology. 2012; 56(5):1089-1096

179 Cucchetti A, Trevisani F, Pecorelli A, Erroi V, Farinati F, Ciccarese F et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. Journal of Hepatology. 2014; 61(2):333-341

180 Curto TM, Lagier R, Lok AS, Everhart JE, Rowland CM, Sninsky JJ et al. Predicting cirrhosis and clinical outcomes in patients with advanced chronic hepatitis C with a panel of genetic markers (CRS7). Pharmacogenetics and Genomics. 2011; 21(12):851-860

181 D'Ambrosio R, Aghemo A, Rumi MG, Primignani M, Dell'Era A, Lampertico P et al. The course of esophageal varices in patients with hepatitis C cirrhosis responding to interferon/ribavirin therapy. Antiviral Therapy. 2011; 16(5):677-684

182 D'Ambrosio R, Aghemo A, Fraquelli M, Rumi MG, Donato MF, Paradis V et al. The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. Journal of Hepatology. 2013; 59(2):251-256

183 D'Amico G, Luca A, Morabito A, Miraglia R, D'Amico M. Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis. Gastroenterology. 2005; 129(4):1282-1293

184 Dagradi AE. The natural history of esophageal varices in patients with alcoholic liver cirrhosis. An endoscopic and clinical study. American Journal of Gastroenterology. 1972; 57(6):520-540

185 Das A. A cost analysis of long term antibiotic prophylaxis for spontaneous bacterial peritonitis in cirrhosis. American Journal of Gastroenterology. 1998; 93(10):1895-1900

186 Davenport A, Ahmad J, Al-Khafaji A, Kellum JA, Genyk YS, Nadim MK. Medical management of hepatorenal syndrome. Nephrology Dialysis Transplantation. 2012; 27(1):34-41

187 Day CP. Heavy drinking greatly increases the risk of cirrhosis in patients with HCV hepatitis. Gut. 2001; 49(6):750-751

188 de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. Journal of Hepatology. 2010; 53(4):762-768

189 De La Hall MP. Genetic and acquired factors that influence individual susceptibility to alcohol-associated liver disease. Journal of Gastroenterology and Hepatology. 1992; 7(4):417-426

190 de Ledinghen V, Vergniol J, Barthe C, Foucher J, Chermak F, Le Bail B et al. Non-invasive tests for fibrosis and liver stiffness predict 5-year survival of patients chronically infected with hepatitis B virus. Alimentary Pharmacology and Therapeutics. 2013; 37(10):979-988

191 de Ledinghen V, Wong VW-S, Vergniol J, Wong GL-H, Foucher J, Chu SH et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan. Journal of Hepatology. 2012; 56(4):833-839

192 De Marco F, Santamaria AP, D'Arienzo A. Rifaximin in collateral treatment of portal-systemic encephalopathy: A preliminary report. Current Therapeutic Research - Clinical and Experimental. 1984; 36(4):668-674

193 Debernardi VW, Elia C, Stradella D, Bruno M, Fadda M, de Angelis C et al. Prospective randomized trial: endoscopic follow up 3 vs 6 months after esophageal variceal eradication by band ligation in cirrhosis. European Journal of Internal Medicine. 2014; 25(7):674-679

194 Deffieux T, Gennisson JL, Bousquet L, Corouge M, Cosconea S, Amroun D et al. Investigating liver stiffness and viscosity for fibrosis, steatosis and activity staging using shear wave elastography. Journal of Hepatology. 2015; 62(2):317-324

195 Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). Journal of Hepatology. 2010; 53(6):1013-1021

196 Delahooke TE, Hayes P. Are cirrhosis and its complications inevitable in hepatitis C virus infection? Scottish Medical Journal. 2000; 45(2):35-37

197 Deleuran T, Gronbaek H, Vilstrup H, Jepsen P. Cirrhosis and mortality risks of biopsy-verified alcoholic pure steatosis and steatohepatitis: a nationwide registry-based study. Alimentary Pharmacology and Therapeutics. 2012; 35(11):1336-1342

198 Deltenre P, Mathurin P, Dharancy S, Moreau R, Bulois P, Henrion J et al. Transjugular intrahepatic portosystemic shunt in refractory ascites: a meta-analysis. Liver International. 2005; 25(2):349-356

199 Demeulenaere L, Van WL. Liver cirrhosis in alcoholics. Journal of the Royal College of Physicians of London. 1977; 12(1):11-14

200 Deschenes M, Barkun AN. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. Gastrointestinal Endoscopy. 2000; 51(5):630-633

201 Dever JB, Sheikh MY. Review article: spontaneous bacterial peritonitis - bacteriology, diagnosis, treatment, risk factors and prevention. Alimentary Pharmacology and Therapeutics. 2015; 41(11):1116-1131

202 Dhyani M, Anvari A, Samir AE. Ultrasound elastography: liver. Abdominal Imaging. 2015; 40(4):698-708

203 Di Marco V, Bronte F, Cabibi D, Calvaruso V, Alaimo G, Borsellino Z et al. Noninvasive assessment of liver fibrosis in thalassaemia major patients by transient elastography (TE) - lack of interference by iron deposition. British Journal of Haematology. 2010; 148(3):476-479

204 Di Pascoli L, Buja A, Bolognesi M, Montagnese S, Gatta A, Gregori D et al. Cost-effectiveness analysis of beta-blockers vs endoscopic surveillance in patients with cirrhosis and small varices. World Journal of Gastroenterology. 2014; 20(30):10464-10469

205 Dinesen L, Caspary WF, Chapman RW, Dietrich CF, Sarrazin C, Braden B. 13C-methacetin-breath test compared to also noninvasive biochemical blood tests in predicting hepatic fibrosis and cirrhosis in chronic hepatitis C. Digestive and Liver Disease. 2008; 40(9):743-748

206 Dolman GE, Nieboer D, Steyerberg EW, Harris S, Ferguson A, Zaitoun AM et al. The performance of transient elastography compared to clinical acumen and routine tests - what is the incremental diagnostic value? Liver International. 2013; 33(2):172-179

207 Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). Health Technology Assessment. England 2009; 13(25):1-156

208 Dragosics B, Ferenci P, Hitchman E, Denk H. Long-term follow-up study of asymptomatic HBsAg-positive voluntary blood donors in Austria: A clinical and histologic evaluation of 242 cases. Hepatology. 1987; 7(2):302-306

209 Drastich P, Spicak J, Petrtyl J, Bruha R, Lata J, Pribramska V et al. Endoscopic ligation of the esophageal varices compared with beta-blockers for prophylaxis of the first bleeding in patients with liver cirrhosis. Ceska a Slovenska Gastroenterologie a Hepatologie. 2005; 59(3):116-121

210 Dultz G, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. Alimentary Pharmacology and Therapeutics. 2015; 41(5):459-466

211 Dultz G, Seelhof M, Herrmann E, Welker M-W, Friedrich-Rust M, Teuber G et al. Baseline MELD score predicts hepatic decompensation during antiviral therapy in patients with chronic hepatitis C and advanced cirrhosis. PloS One. 2013; 8(8):e71262

212 DuPont HL. Therapeutic effects and mechanisms of action of rifaximin in gastrointestinal diseases. Mayo Clinic Proceedings. 2015; 90(8):1116-1124

213 Durbec JP, Bidart JM, Sarles H. Risks of chronic pancreatitis, hepatocirrhosis and pancreas cancer. Role of alcohol consumption, results of 3 retrospective studies (cases-controls). Materia Medica Polona. 1981; 13(1):10-14

214 Dyal HK, Aguilar M, Bhuket T, Liu B, Holt EW, Torres SA et al. Concurrent obesity, diabetes, and nonalcoholic fatty liver disease is associated with an increased risk of progression to advanced fibrosis among patients with chronic hepatitis c virus infection: A systematic review. Gastroenterology. 2015; 148(4 Suppl.1):S404-S405

215 Ebell MH. Probability of cirrhosis in patients with hepatitis C. American Family Physician. 2003; 68(9):1831-1833

216 El Guesiry D, Moez P, Hossam N, Kassem M. Usefulness of non-invasive serum markers for predicting liver fibrosis in Egyptian patients with chronic HCV infection. Egyptian Journal of Immunology. 2011; 18(2):1-12

217 El-Serag HB. Hepatocellular carcinoma. New England Journal of Medicine. 2011; 365(1118):1127

218 El-Serag HB, Kramer JR, Chen GJ, Duan Z, Richardson PA, Davila JA. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA. Gut. 2011; 60(7):992-997

219 El-Zayadi AR, Badran HM, Shawky S, Emara S, El-Bareedy A, Sobhi M. Effect of surveillance for hepatocellular carcinoma on tumor staging and treatment decisions in Egyptian patients. Hepatology International. 2010; 4(2):500-506

220 Elder CA, Restino MS. Beta-adrenergic antagonists for primary prevention of gastrointestinal hemorrhage in patients with cirrhosis and esophageal varices. Clinical Pharmacy. 1992; 11(4):337-341

221 Elia C, Debernardi VW, Ferruzzi G, Bruno M, Caronna S, Musso A et al. Follow up of esophageal varices at 3 vs 6 months after eradication by endoscopic banding in cirrhotic patients. Digestive and Liver Disease. 2012; 44(Suppl.2):S187

222 Elta GH. Prophylaxis for variceal bleeding. Gastroenterology. 1991; 100(6):1778-1780

223 Eltabbakh M, Zaghla H, Abdel-Razek W, Elshinnawy H, Ezzat S, Gomaa A et al. Utility and cost-effectiveness of screening for hepatocellular carcinoma in a resource-limited setting. Medical Oncology. 2015; 32(1):432

224 Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. World Journal of Gastroenterology. 2012; 18(8):767-777

225 Engelmann C, Brosteanu O, Tenckhoff H, Babatz J, Lammert F, Manns M et al. Alfapump system versus transjugular intrahepatic portosystemic shunt and paracentesis in the treatment of ascites. A multicentre randomised controlled study (agua-trial). Journal of Hepatology. 2015; 62(Suppl.2):S846-S847

226 Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology. 2009; 137(2):549-557

227 Fagiuoli S, Colli A, Bruno R, Burra P, Craxi A, Gaeta GB et al. Management of infections in cirrhotic patients: report of a consensus conference. Digestive and Liver Disease. 2014; 46(3):204-212

228 Falavigna M, Kieling C, Wolff FH, Medeiros Lídia RF, Cheinquer H. Antibiotics for hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2007;(1):CD006314. DOI:10.1002/14651858.CD006314

229 Fasani P, Sangiovanni A, De Fazio C, Borzio M, Bruno S, Ronchi G et al. High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. Hepatology. 1999; 29(6):1704-1707

230 Fassio E, Terg R, Landeira G, Abecasis R, Salemne M, Podesta A et al. Paracentesis with Dextran 70 vs. paracentesis with albumin in cirrhosis with tense ascites. Results of a randomized study. Journal of Hepatology. 1992; 14(2-3):310-316

231 Fattovich G, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A et al. Natural history and prognostic factors for chronic hepatitis type B. Gut. 1991; 32(3):294-298

232 Feher J, Lang I, Varga L, Tompos G. Effect of ornithine-aspartate infusion on elevated serum ammonia concentration in cirrhotic patients - results of a randomized, placebo-controlled double-blind multicentre trial. Medical Science Monitor. 1997; 3(5):669-673

233 Feng C, Huang F, Nie W, Liu X, Ren S. Comparison of endoscopic band ligation and propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Journal of Central South University. 2012; 37(5):513-516

234 Fera G. Rifaximin in the treatment of hepatic encephalopathy. European Journal of Clinical Research. 1993; 4(1):57-66

235 Ferlitsch A, Salzl P, Reiberger T, Homoncik M, Payer BA, Schwengerer B et al. Comparison of liver stiffness assessment by Fibroscan-« and Acoustic Radiation Force Impulse Imaging-« for the evaluation of liver fibrosis and cirrhosis. Zeitschrift Fur Gastroenterologie. 2010; 48(05):4

236 Fernandez J, Monteagudo J, Bargallo X, Jimenez W, Bosch J, Arroyo V et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology. 2005; 42(3):627-634

237 Fernandez M, Trepo E, Gustot T, Degre D, Verset L, Demetter P et al. Fibroscan (Transient Elastography) is the most reliable non-invasive method for the assessment of severe fibrosis and cirrhosis in alcoholic liver disease. Hepatology. 2012; 56(Suppl.1):821A-822A

238 Fernandez-Rodriguez A, Berenguer J, Jimenez-Sousa MA, Guzman-Fulgencio M, Micheloud D, Miralles P et al. Prediction of hepatic fibrosis in patients coinfected with HIV and hepatitis C virus based on genetic markers. Journal of Acquired Immune Deficiency Syndromes. 2013; 64(5):434-442

239 Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012; 56(6):2125-2133

240 Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Lissandrin R, Filice G et al. Performance of liver stiffness measurements by transient elastography in chronic hepatitis. World Journal of Gastroenterology. 2013; 19(1):49-56

241 Ferraioli G, Tinelli C, Malfitano A, Dal Bello B, Filice G, Filice C et al. Performance of real-time strain elastography, transient elastography, and aspartate-to-platelet ratio index in the assessment of fibrosis in chronic hepatitis C. American Journal of Roentgenology. 2012; 199(1):19-25

242 Ferral H, Male R, Cardiel M, Munoz L, Ferrari F. Cirrhosis: diagnosis by liver surface analysis with high-frequency ultrasound. Gastrointestinal Radiology. 1992; 17(1):74-78

243 Ferrante WA, Maxfield WS. Comparison of the diagnostic accuracy of liver scans, liver function tests and liver biopsies. Southern Medical Journal. 1968; 61(12):1255-1263

244 Ferrarese A, Germani G, Rodriguez-Castro KI, Nadal E, Zanetto A, Bortoluzzi I et al. Bleeding-unrelated mortality is not increased in patients with cirrhosis and ascites on treatment with beta-blockers: A meta-analysis. Digestive and Liver Disease. 2014; 46(Suppl.1):e31

245 Ferruzzi G, Debernardi VW, Elia C, Musso A, Bruno M, Saracco G et al. Follow up of esophageal varices at 3 vs 6 months after eradication by endoscopic banding in cirrhotic patients. A prospective randomized trial. Digestive and Liver Disease. 2011; 43(Suppl.2):S81-S82

246 Filly RA, Reddy SG, Nalbandian AB, Lu Y, Callen PW. Sonographic evaluation of liver nodularity: Inspection of deep versus superficial surfaces of the liver. Journal of Clinical Ultrasound. 2002; 30(7):399-407

247 Forestier J, Dumortier J, Guillaud O, Ecochard M, Roman S, Boillot O et al. Noninvasive diagnosis and prognosis of liver cirrhosis: a comparison of biological scores, elastometry, and metabolic liver function tests. European Journal of Gastroenterology and Hepatology. 2010; 22(5):532-540

248 Fouad SA, Esmat S, Omran D, Rashid L, Kobaisi MH. Noninvasive assessment of hepatic fibrosis in Egyptian patients with chronic hepatitis C virus infection. World Journal of Gastroenterology. 2012; 18(23):2988-2994

249 Foucher J, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut. 2006; 55(3):403-408

250 Foucher J, Vergniol L, Castera L, Chanteloup E, Darriet M, Couzigou P. Fibrosis evaluation in chronic liver diseases: comparison of FibroScan® with liver biopsy, FibroTest®, Forns score, APRI, hyaluronan, prothrombin time, and AST/ALT ratio. Annual Meeting of the European Association of the Study of the Liver. 2005;

251 Fraquelli M, Giunta M, Pozzi R, Rigamonti C, Della Valle S, Massironi S et al. Feasibility and reproducibility of spleen transient elastography and its role in combination with liver transient elastography for predicting the severity of chronic viral hepatitis. Journal of Viral Hepatitis. 2014; 21(2):90-98

252 Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut. 2007; 56(7):968-973

253 Frazee LA, Marinos AE, Rybarczyk AM, Fulton SA. Long-term prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis. Annals of Pharmacotherapy. 2005; 39(5):908-912

254 Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001; 34(4 Pt.1):809-816

255 Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. Journal of Viral Hepatitis. 2003; 10(4):285-293

256 Friedrich-Rust M, Lupsor M, de Knegt R, Dries V, Buggisch P, Gebel M et al. Point shear wave elastography by acoustic radiation force impulse quantification in comparison to transient elastography for the noninvasive assessment of liver fibrosis in chronic hepatitis C: a prospective international multicenter study. Ultraschall in Der Medizin. 2015; 36(3):239-247

257 Friedrich-Rust M, Muller C, Winckler A, Kriener S, Herrmann E, Holtmeier J et al. Assessment of liver fibrosis and steatosis in PBC with FibroScan, MRI, MR-spectroscopy, and serum markers. Journal of Clinical Gastroenterology. 2010; 44(1):58-65

258 Friedrich-Rust M, Ong MF, Herrmann E, Dries V, Samaras P, Zeuzem S et al. Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. American Journal of Roentgenology. 2007; 188(3):758-764

259 Friedrich-Rust M, Romen D, Vermehren J, Kriener S, Sadet D, Herrmann E et al. Acoustic radiation force impulse-imaging and transient elastography for non-invasive assessment of liver fibrosis and steatosis in NAFLD. European Journal of Radiology. 2012; 81(3):e325-e331

260 Friedrich-Rust M, Rosenberg W, Parkes J, Herrmann E, Zeuzem S, Sarrazin C. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. BMC Gastroenterology. 2010; 10:103

261 Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology. 2009; 252(2):595-604

262 Frossard JL, Giostra E, Rubbia-Brandt L, Hadengue A, Spahr L. The role of transient elastography in the detection of liver disease in patients with chronic pancreatitis. Liver International. 2013; 33(7):1121-1127

263 Funakoshi N, Duny Y, Valats JC, Segalas-Largey F, Flori N, Bismuth M et al. Meta-analysis: beta-blockers versus banding ligation for primary prophylaxis of esophageal variceal bleeding. Annals of Hepatology. 2012; 11(3):369-383

264 Gaba RC, Kallwitz ER, Parvinian A, Bui JT, Von Roenn NM, Berkes JL et al. Imaging surveillance and multidisciplinary review improves curative therapy access and survival in HCC patients. Annals of Hepatology. 2013; 12(5):766-773

265 Gaia S, Campion D, Evangelista A, Spandre M, Cosso L, Brunello F et al. Non-invasive score system for fibrosis in chronic hepatitis: proposal for a model based on biochemical, FibroScan and ultrasound data. Liver International. 2015; 35(8):2027-2035

266 Gaiani S, Gramantieri L, Venturoli N, Piscaglia F, Siringo S, D'Errico A et al. What is the criterion for differentiating chronic hepatitis from compensated cirrhosis? A prospective study comparing ultrasonography and percutaneous liver biopsy. Journal of Hepatology. 1997; 27(6):979-985

267 Ganne-Carrie N, Ziol M, de Ledinghen V, Douvin C, Marcellin P, Castera L et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology. 2006; 44(6):1511-1517

268 Gara N, Zhao X, Kleiner DE, Liang TJ, Hoofnagle JH, Ghany MG. Discordance among transient elastography, aspartate aminotransferase to platelet ratio index, and histologic assessments of liver fibrosis in patients with chronic hepatitis C. Clinical Gastroenterology and Hepatology. 2013; 11(3):303-308

269 Garceau AJ. The natural history of cirrhosis. II. The influence of alcohol and prior hepatitis on pathology and prognosis. New England Journal of Medicine. 1964; 271(23):1173-1179

270 Garcia-Compean D, Blanc P, Larrey D, Daures JP, Hirtz J, Mendoza E et al. Treatment of cirrhotic tense ascites with Dextran-40 versus albumin associated with large volume paracentesis: a randomized controlled trial. Annals of Hepatology. 2002; 1(1):29-35

271 Garcia-Compean D, Jaquez-Quintana JO, Lavalle-Gonzalez FJ, Gonzalez-Gonzalez JA, Maldonado Garza HJ, Villarreal-Perez JZ. Plasma cytokine levels imbalance in cirrhotic patients with impaired glucose tolerance and diabetes mellitus. A prospective study. Annals of Hepatology. 2014; 13(4):403-410

272 Garcia-Tsao G, Sanyal AJ, Grace N, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007; 46(3):922-938

273 Gawrieh S, Shaker R. Variceal band ligation versus propranolol for primary prophylaxis of variceal bleeding in cirrhosis. Current Gastroenterology Reports. 2005; 7(3):175-176

274 Ge J, Yu Y-Z, Li T, Guo Z-Y, Wu H, Tang S-C et al. IL-17A G197A gene polymorphism contributes to susceptibility for liver cirrhosis development from patients with chronic hepatitis B infection in chinese population. International Journal of Clinical and Experimental Medicine. 2015; 8(6):9793-9798

275 Gebo KA, Chander G, Jenckes MW, Ghanem KG, Herlong HF, Torbenson MS et al. Screening tests for hepatocellular carcinoma in patients with chronic hepatitis C: a systematic review. Hepatology. 2002; 36(5 Suppl.1):S84-S92

276 Giannini E, Botta F, Borro P, Dulbecco P, Testa E, Mansi C et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with cirrhosis: a validation study based on follow-up. Digestive and Liver Disease. 2005; 37(10):779-785

277 Giannini E, Botta F, Fumagalli A, Malfatti F, Testa E, Chiarbonello B et al. Can inclusion of serum creatinine values improve the Child-Turcotte-Pugh score and challenge the prognostic yield of the model for end-stage liver disease score in the short-term prognostic assessment of cirrhotic patients? Liver International. 2004; 24(5):465-470

278 Giannini E, Botta F, Testa E, Romagnoli P, Polegato S, Malfatti F et al. The 1-year and 3-month prognostic utility of the AST/ALT ratio and model for end-stage liver disease score in patients with viral liver cirrhosis. American Journal of Gastroenterology. 2002; 97(11):2855-2860

279 Giannini E, Risso D, Botta F, Chiarbonello B, Fasoli A, Malfatti F et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Archives of Internal Medicine. 2003; 163(2):218-224

280 Giannini E, Risso D, Caglieris S, Testa R. Longitudinal modifications of the MELD score have prognostic meaning in patients with liver cirrhosis. Journal of Clinical Gastroenterology. 2005; 39(10):912-914

281 Gines A, Planas R, Angeli P, Guarner C, Salerno F, Gines P et al. Treatment of patients with cirrhosis and refractory ascites using LeVeen shunt with titanium tip: comparison with therapeutic paracentesis. Hepatology. 1995; 22(1):124-131

282 Gines P, Angeli P, Lenz K, Moller S, Moore K, Moreau R et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of Hepatology. 2010; 53(3):397-417

283 Gines P, Arroyo V, Vargas V, Planas R, Casafont F, Panes J et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. New England Journal of Medicine. 1991; 325(12):829-835

284 Gines P, Rimola A, Planas R, Vargas V, Marco F, Almela M et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology. 1990; 12(4 Pt.1):716-724

285 Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology. 2002; 123(6):1839-1847

286 Giorgio A, Amoroso P, Lettieri G, Fico P, de Stefano G, Finelli L et al. Cirrhosis: value of caudate to right lobe ratio in diagnosis with US. Radiology. 1986; 161(2):443-445

287 Giraldez A, Sousa JM, Bozada JM, Cayuela A, Pascasio JM, Garcia I et al. Results of an upper endoscopy protocol in liver transplant candidates. Revista Espanola De Enfermedades Digestivas. 2003; 95(8):555-54

288 Gluud C, Dejgaard A, Hardt F, Kristensen M, Köhler O, Melgaard B et al. Preliminary treatment results with balanced amino acid infusion to patients with hepatic encephalopathy. Scandinavian Journal of Gastroenterology Supplement. 1983; 86:19

289 Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. American Journal of Gastroenterology. 2007; 102(12):2842-2849

290 Gluud LL, Vilstrup H, Morgan MY. The effect of treatment for hepatic encephalopathy with nonabsorbable disaccharides on morbidity and mortality in patients with cirrhosis: Systematic review and meta-analyses. Journal of Hepatology. 2015; 62(Suppl.2):S353

291 Gluud LL, Dam G, Les I, Cordoba J, Marchesini G, Borre M et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2015;(2):CD001939. DOI:10.1002/14651858.CD001939.pub3

292 Gobel T, Schadewaldt-Tummers J, Greiner L, Poremba C, Haussinger D, Erhardt A. Transient elastography improves detection of liver cirrhosis compared to routine screening tests. World Journal of Gastroenterology. 2015; 21(3):953-960

293 Godfrey EM, Patterson AJ, Priest AN, Davies S, Joubert I, Krishnan A et al. A comparison of MR elastography and 31P MR spectroscopy with histological staging of liver fibrosis. European Radiology. 2012; 22(12):2790-2797

294 Goertz RS, Zopf Y, Jugl V, Heide R, Janson C, Strobel D et al. Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis. Ultraschall in Der Medizin. 2010; 31(2):151-155

295 Gomez-Dominguez E, Mendoza J, Garcia-Buey L, Trapero M, Gisbert JP, Jones EA et al. Transient elastography to assess hepatic fibrosis in primary biliary cirrhosis. Alimentary Pharmacology and Therapeutics. 2008; 27(5):441-447

296 Goodgame B, Shaheen NJ, Galanko J, El-Serag HB. The risk of end stage liver disease and hepatocellular carcinoma among persons infected with hepatitis C virus: publication bias? American Journal of Gastroenterology. 2003; 98(11):2535-2542

297 Gordon SC, Lamerato LE, Rupp LB, Holmberg SD, Moorman AC, Spradling PR et al. Prevalence of cirrhosis in hepatitis C patients in the chronic hepatitis cohort study (CHeCS): a retrospective and prospective observational study. American Journal of Gastroenterology. 2015; 110(8):1169-1177

298 Gordon T, Kannel WB. Drinking and mortality. The Framingham Study. American Journal of Epidemiology. 1984; 120(1):97-107

299 Gosink BB, Lemon SK, Scheible W, Leopold GR. Accuracy of ultrasonography in diagnosis of hepatocellular disease. American Journal of Roentgenology. 1979; 133(1):19-23

300 Goto Y, Okuda K, Akasu G, Kinoshita H, Tanaka H. Noninvasive diagnosis of compensated cirrhosis using an analysis of the time-intensity curve portal vein slope gradient on contrast-enhanced ultrasonography. Surgery Today. 2014; 44(8):1496-1505

301 Gotzberger M, Singer J, Kaiser C, Gulberg V. Intrarenal resistance index as a prognostic parameter in patients with liver cirrhosis compared with other hepatic scoring systems. Digestion. 2012; 86(4):349-354

302 Gough IR, Balderson GA. Malignant ascites. A comparison of peritoneovenous shunting and nonoperative management. Cancer. 1993; 71(7):2377-2382

303 Grace N, Conn HO, Bosch J, Groszmann R, Rodes J, Wright SC et al. Propranolol in the prevention of first hemorrhage from esophageal varices (EVH): a multicenter controller trial. Hepatology. 1988; 8(5):1220

304 Grace N, Conn HO, Groszmann R, Richardson CR, Matloff DS, Garcia-Tsao G et al. Propranolol for prevention of first esophageal variceal hemorrhage (EVH): a lifetime commitment? Hepatology. 1990; 12(2):407

305 Grgurevic I, Cikara I, Horvat J, Lukic IK, Heinzl R, Banic M et al. Noninvasive assessment of liver fibrosis with acoustic radiation force impulse imaging: increased liver and splenic stiffness in patients with liver fibrosis and cirrhosis. Ultraschall in Der Medizin. 2011; 32(2):160-166

306 Grimm G, Ferenci P, Katzenschlager R, Madl C, Schneeweiss B, Laggner AN et al. Improvement of hepatic encephalopathy treated with flumazenil. The Lancet. 1988; 2(8625):1392-1394

307 Groeneweg M, Gyr K, Amrein R, Scollo-Lavizzari G, Williams R, Yoo JY et al. Effect of flumazenil on the electroencephalogram of patients with portosystemic encephalopathy. Results of a double blind, randomised, placebo-controlled multicentre trial. Electroencephalography and Clinical Neurophysiology. 1996; 98(1):29-34

308 Grungreiff K, Kleine F-D, Musil HE, Diete U, Franke D, Klauck S et al. Valine enriched branched-chain amino acids in the treatment of hepatic encephalopathy. Zeitschrift Fur Gastroenterologie. 1993; 31(4):235-241

309 Gulberg V, Deibert P, Ochs A, Rossle M, Gerbes A. Prevention of infectious complications after transjugular intrahepatic portosystemic shunt in cirrhotic patients with a single dose of ceftriaxone. Hepato-Gastroenterology. 1999; 46(26):1126-1130

310 Guzelbulut F, Cetinkaya ZA, Sezikli M, Yasar B, Ozkara S, Ovunc AOK. AST-platelet ratio index, Forns index and FIB-4 in the prediction of significant fibrosis and cirrhosis in patients with chronic hepatitis C. Turkish Journal of Gastroenterology. 2011; 22(3):279-285

311 Hadengue A, Gadano A, Giostra E, Negro F, Moreau R, Valla D et al. Terlipressin in the treatment of hepatorenal syndrome (HRS): a double blind cross-over study. Hepatology. 1995; 22(4 Pt.2):165A

312 Haktanir A, Cihan BS, Celenk C, Cihan S. Value of Doppler sonography in assessing the progression of chronic viral hepatitis and in the diagnosis and grading of cirrhosis. Journal of Ultrasound in Medicine. 2005; 24(3):311-321

313 Hamberg KJ, Carstensen B, Sorensen TI, Eghoje K. Accuracy of clinical diagnosis of cirrhosis among alcohol-abusing men. Journal of Clinical Epidemiology. 1996; 49(11):1295-1301

314 Han KH, Kim do Y, Park JY, Ahn SH, Kim J, Kim SU et al. Survival of hepatocellular carcinoma patients may be improved in surveillance interval not more than 6 months compared with more than 6 months: a 15-year prospective study. Journal of Clinical Gastroenterology. 2013; 47(6):538-544

315 Haque M, Robinson C, Owen D, Yoshida EM, Harris A. Comparison of acoustic radiation force impulse imaging (ARFI) to liver biopsy histologic scores in the evaluation of chronic liver disease: A pilot study. Annals of Hepatology. 2010; 9(3):289-293

316 Harkisoen S, Arends JE, van den Hoek JAR, Whelan J, van Erpecum KJ, Boland GJ et al. Historic and current hepatitis B viral DNA and quantitative HBsAg level are not associated with cirrhosis in non-Asian women with chronic hepatitis B. International Journal of Infectious Diseases. 2014; 29:133-138

317 Hashemi SJ, Hajiani E, Masjedizadeh A, Makvandi M, Shayesteh AA, Alavinejad SP et al. Occult hepatitis B infection in patients with cryptogenic liver cirrhosis in southwest of iran. Jundishapur Journal of Microbiology. 2015; 8(3):e16873

318 Hassan EA, Abd El-Rehim ASED. A revised scope in different prognostic models in cirrhotic patients: Current and future perspectives, an Egyptian experience. Arab Journal of Gastroenterology. 2013; 14(4):158-164

319 Hayes P, Davis JM, Lewis JA, Bouchier IA. Meta-analysis of value of propranolol in prevention of variceal haemorrhage. The Lancet. 1990; 336(8708):153-156

320 He L, Deng T, Luo HS. Genetic polymorphism in alcohol dehydrogenase 2 (ADH2) gene and alcoholic liver cirrhosis risk. International Journal of Clinical and Experimental Medicine. 2015; 8(5):7786-7793

321 Hedin K, Babic A, Fryden A. Liver guide for monitoring of chronic hepatitis C. AMIA Annual Symposium Proceedings. 2000;340-343

322 Held C. Metronidazole in hepatic encephalopathy (HE). Klinische Wochenschrift. 1988; 66(Suppl.13):63

323 Held C, Jennerjahn A. Metronidazol for hepatic encephalopathy. Zeitschrift Für Klinische Medizin. 1987; 42(7):625-627

324 Hess CF, Schmiedl U, Koelbel G, Knecht R, Kurtz B. Diagnosis of liver cirrhosis with US: receiver-operating characteristic analysis of multidimensional caudate lobe indexes. Radiology. 1989; 171(2):349-351

325 Hirayama C, Ichida F, Takahashi Y. A controlled clinical trial of nicotinohydroxamic acid and neomycin in advanced chronic liver disease. Digestion. 1982; 25(2):115-123

326 Horng MH, Sun YN, Lin XZ. Texture feature coding method for classification of liver sonography. Computerized Medical Imaging and Graphics. 2002; 26(1):33-42

327 Howard CD, Seifert CF. Flumazenil in the treatment of hepatic encephalopathy. Annals of Pharmacotherapy. 1993; 27(1):46-48

328 Hsiang JC, Gane EJ, Bai WW, Gerred SJ. Type 2 diabetes: a risk factor for liver mortality and complications in hepatitis B cirrhosis patients. Journal of Gastroenterology and Hepatology. 2015; 30(3):591-599

329 Hsieh WJ, Lin HC, Hwang SJ, Hou MC, Lee FY, Chang FY et al. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. American Journal of Gastroenterology. 1998; 93(6):962-966

330 Hsu C-S, Huang CJ, Kao JH, Lin HH, Chao YC, Fan Y et al. Interferon-based therapy decreases risks of hepatocellular carcinoma and complications of cirrhosis in chronic hepatitis C patients. PloS One. 2013; 8(7):e70458

331 Huang H, Shiffman ML, Friedman S, Venkatesh R, Bzowej N, Abar OT et al. A 7 gene signature identifies the risk of developing cirrhosis in patients with chronic hepatitis C. Hepatology. 2007; 46(2):297-306

332 Huang X, Lv B, Meng L, Xiang B. A meta-analysis on the efficacy of endoscopic variceal ligation and beta-adrenergic blocker for prophylaxis of first time esophageal variceal bleeding. Chinese Journal of Gastroenterology. 2007; 12(1):9-13

333 Huang YW, Wang TC, Lin SC, Chang HY, Chen DS, Hu JT et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: a nationwide cohort study. Clinical Infectious Diseases. 2013; 57(12):1695-1702

334 Hucke F, Sieghart W, Schoniger-Hekele M, Peck-Radosavljevic M, Muller C. Clinical characteristics of patients with hepatocellular carcinoma in Austria - is there a need for a structured screening program? Wiener Klinische Wochenschrift. 2011; 123(17-18):542-551

335 Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG et al. Erratum: Insulin resistance is associated with chronic hepatitis C and virus infection fibrosis progression (Gastroenterology (2002) 123 (1667-1676)). Gastroenterology. 2004; 126(2):634

336 Hultcrantz R, Gabrielsson N. Patients with persistent elevation of aminotransferases: investigation with ultrasonography, radionuclide imaging and liver biopsy. Journal of Internal Medicine. 1993; 233(1):7-12

337 Hung Y-C, Lin C-L, Liu C-J, Hung H, Lin S-M, Lee S-D et al. Development of risk scoring system for stratifying population for hepatocellular carcinoma screening. Hepatology. 2015; 61(6):1934-1944

338 Huo T, Hsu C-Y, Lin HC, Lee PC, Lee J-Y, Lee FY et al. Selecting an optimal cutoff value for creatinine in the model for end-stage liver disease equation. Clinical Transplantation. 2010; 24(2):157-163

339 Huo T, Lin HC, Huo SC, Lee PC, Wu J-C, Lee FY et al. Comparison of four model for end-stage liver disease-based prognostic systems for cirrhosis. Liver Transplantation. 2008; 14(6):837-844

340 Huo T, Lin HC, Wu J-C, Lee FY, Hou MC, Lee PC et al. Different model for end-stage liver disease score block distributions may have a variable ability for outcome prediction. Transplantation. 2005; 80(10):1414-1418

341 Huo T, Wu JC, Hwang SJ, Lai CR, Lee PC, Tsay SH et al. Factors predictive of liver cirrhosis in patients with chronic hepatitis B: a multivariate analysis in a longitudinal study. European Journal of Gastroenterology and Hepatology. 2000; 12(6):687-693

342 Huo T, Wu JC, Lee PC, Tsay SH, Chang FY, Lee SD. Diabetes mellitus as a risk factor of liver cirrhosis in patients with chronic hepatitis B virus infection. Journal of Clinical Gastroenterology. 2000; 30(3):250-254

343 Huo T, Wu J-C, Lin HC, Lee FY, Hou MC, Lee PC et al. Evaluation of the increase in model for end-stage liver disease (MELD) score over time as a prognostic predictor in patients with advanced cirrhosis: Risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. Journal of Hepatology. 2005; 42(6):826-832

344 Huwart L, Salameh N, ter Beek L, Vicaut E, Peeters F, Sinkus R et al. MR elastography of liver fibrosis: preliminary results comparing spin-echo and echo-planar imaging. European Radiology. 2008; 18(11):2535-2541

345 Huwart L, Sempoux C, Salameh N, Jamart J, Annet L, Sinkus R et al. Liver fibrosis: noninvasive assessment with MR elastography versus aspartate aminotransferase-to-platelet ratio index. Radiology. 2007; 245(2):458-466

346 Huwart L, Sempoux C, Vicaut E, Salameh N, Annet L, Danse E et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology. 2008; 135(1):32-40

347 Hwang SJ, Chan C-Y, Wu J-C, Lee S-D, Huan Y-S, Tsai Y-T. A randomized controlled trial for the evaluation of the efficacy of branched chain amino acid-enriched amino acid solution in the treatment of patients with hepatic encephalopathy. Chinese Journal of Gastroenterology. 1988; 5:185-192

348 Iacobellis A, Fusilli S, Mangia A, Clemente R, Festa V, Giacobbe A et al. Ultrasonographic and biochemical parameters in the non-invasive evaluation of liver fibrosis in hepatitis C virus chronic hepatitis. Alimentary Pharmacology and Therapeutics. 2005; 22(9):769-774

349 Ichikawa S, Motosugi U, Morisaka H, Sano K, Ichikawa T, Enomoto N et al. MRI-based staging of hepatic fibrosis: Comparison of intravoxel incoherent motion diffusion-weighted imaging with magnetic resonance elastography. Journal of Magnetic Resonance Imaging. 2015; 42(1):204-210

350 Ichikawa S, Motosugi U, Ichikawa T, Sano K, Morisaka H, Enomoto N et al. Magnetic resonance elastography for staging liver fibrosis in chronic hepatitis C. Magnetic Resonance in Medical Sciences. 2012; 11(4):291-297

351 Ichikawa S, Motosugi U, Morisaka H, Sano K, Ichikawa T, Tatsumi A et al. Comparison of the diagnostic accuracies of magnetic resonance elastography and transient elastography for hepatic fibrosis. Magnetic Resonance Imaging. 2015; 33(1):26-30

352 Ichino N, Osakabe K, Nishikawa T, Sugiyama H, Kato M, Kitahara S et al. A new index for non-invasive assessment of liver fibrosis. World Journal of Gastroenterology. 2010; 16(38):4809-4816

353 Ideo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: a prospective, randomized study. Hepatology. 1988; 8(1):6-9

354 Ieluzzi D, Covolo L, Donato F, Fattovich G. Progression to cirrhosis, hepatocellular carcinoma and liver-related mortality in chronic hepatitis B patients in Italy. Digestive and Liver Disease. 2014; 46(5):427-432

355 Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. Journal of Hepatology. 1998; 28(6):930-938

356 Iliopoulos P, Vlychou M, Karatza C, Yarmenitis SD, Repanti M, Tsamis I et al. Ultrasonography in differentiation between chronic viral hepatitis and compensated early stage cirrhosis. World Journal of Gastroenterology. 2008; 14(13):2072-2079

357 Iliopoulos P, Vlychou M, Margaritis V, Tsamis I, Tepetes K, Petsas T et al. Gray and color Doppler ultrasonography in differentiation between chronic viral hepatitis and compensated early stage cirrhosis. Journal of Gastrointestinal and Liver Diseases. 2007; 16(3):279-286

358 Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006; 130(3):678-686

359 Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. The Lancet. 2001; 357(9262):1069-1075

360 Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. Hepatology. 2001; 33(4):802-807

361 Imperiale TF, Klein RW, Chalasani N. Cost-effectiveness analysis of variceal ligation vs beta-blockers for primary prevention of variceal bleeding. Hepatology. 2007; 45(4):870-878

362 Imperiale TF, McCullough AJ. Prophylactic beta-blocker therapy: clinical implications of an aggregate analysis. Hepatology. 1992; 15(2):354-356

363 Imperiale TF, Said AT, Cummings OW, Born LJ. Need for validation of clinical decision aids: use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. American Journal of Gastroenterology. 2000; 95(9):2328-2332

364 Inadomi J, Sonnenberg A. Cost-analysis of prophylactic antibiotics in spontaneous bacterial peritonitis. Gastroenterology. 1997; 113(4):1289-1294

365 Infante-Rivard C, Esnaola S, Villeneuve J-P. Clinical and statistical validity of conventional prognostic factors in predicting short-term surfival among cirrhotics. Hepatology. 1987; 7(4):660-664

366 Innes HA, Hutchinson SJ, Barclay S, Cadzow E, Dillon J, Fraser A et al. Quantifying the fraction of cirrhosis attributable to alcohol among chronic hepatitis C virus patients: implications for treatment cost-effectiveness. Hepatology. 2013; 57(2):451-460

367 Ioannou GN, Bryson CL, Weiss NS, Boyko EJ. Associations between lipodystrophy or antiretroviral medications and cirrhosis in patients with HIV infection or HIV/HCV coinfection. European Journal of Gastroenterology and Hepatology. 2015; 27(5):577-584

368 Ioannou GN, Weiss NS, Boyko EJ, Kowdley K, Kahn SE, Carithers RL et al. Is central obesity associated with cirrhosis-related death or hospitalization? A population-based, cohort study. Clinical Gastroenterology and Hepatology. 2005; 3(1):67-74

369 Ishibashi H, Maruyama H, Takahashi M, Fujiwara K, Imazeki F, Yokosuka O. Assessment of hepatic fibrosis by analysis of the dynamic behaviour of microbubbles during contrast ultrasonography. Liver International. 2010; 30(9):1355-1363

370 Ishibashi H, Maruyama H, Takahashi M, Shimada T, Kamesaki H, Fujiwara K et al. Demonstration of intrahepatic accumulated microbubble on ultrasound represents the grade of hepatic fibrosis. European Radiology. 2012; 22(5):1083-1090

371 Islam S, Antonsson L, Westin J, Lagging M. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scandinavian Journal of Gastroenterology. 2005; 40(7):867-872

372 Izzo F, Cremona F, Ruffolo F, Palaia R, Parisi V, Curley S. Detection of hepatocellular cancer during screening of 1125 patients with chronic hepatitis virus infection. Journal of Chemotherapy. 1997; 9(2):151-152

373 Jamal MM, Saadi Z, Morgan TR. Alcohol and hepatitis C. Digestive Diseases. 2005; 23(3-4):285-296

374 Jan CF, You SL, Sun CA, Chen TI, Yang HI, Lu SN. A community-based randomized trial on hepatocellular carcinoma screening using abdominal ultrasonography and alha-fetoprotein in Taiwan. Journal of Hepatology. 2005; 44(2 Suppl.):S4

375 Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology. 2002; 122(6):1620-1630

376 Jerkeman A, Westin J, Lagging M, Norkrans G, Lidman C, Frimand J et al. Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy--factors associated with advanced fibrosis. Scandinavian Journal of Infectious Diseases. 2014; 46(5):340-347

377 Jiang Q, Jiang XH, Zheng MH, Chen YP. L-Ornithine-l-aspartate in the management of hepatic encephalopathy: a meta-analysis. Journal of Gastroenterology and Hepatology. 2009; 24(1):9-14

378 Jiang Q, Jiang XH, Zheng Mh, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. European Journal of Gastroenterology and Hepatology. 2008; 20(11):1064-1070

379 Jindal A, Maiwal R, Vashishta C, Kumar M, Kumar Chandan KN, Bhatia V et al. A randomized, comparative open label study of imipenem versus cefepime in difficult to treat spontaneous bacterial peritonitis. Indian Journal of Gastroenterology. 2014; 33(1 Suppl.1):A22

380 Jindal A, Sarin SK. A randomized trial of 'imipenem versus cefepime' in difficult to treat spontaneous bacterial peritonitis (SBP) and to evaluate the risk factors for treatment failure. Hepatology. 2014; 60(Suppl.1):279A

381 Jou JH, Chen PH, Jazwinski A, Bouneva I, Smith AD, Muir AJ. Rates of surveillance and management of hepatocellular carcinoma in patients evaluated at a liver transplant center. Digestive Diseases and Sciences. 2010; 55(12):3591-3596

382 Jung KS, Kim SU, Ahn SH, Park YN, Kim DY, Park JY et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology. 2011; 53(3):885-894

383 Junge G, Schewior L, Neuhaus P. Hepatorenal syndrome in patients waiting for LTx - Efficacy of different plasma volume expansion/vasoconstriction regimens compared to TIPS. Liver Transplantation. 2010; 16(Suppl.1):S81-S82

384 Kage M, Shimamatu K, Nakashima E, Kojiro M, Inoue O, Yano M. Long-term evolution of fibrosis from chronic hepatitis to cirrhosis in patients with hepatitis C: morphometric analysis of repeated biopsies. Hepatology. 1997; 25(4):1028-1031

385 Kalman R, Nunes D. Screening for hepatocellular carcinoma associated with meeting milan criteria at diagnosis. American Journal of Gastroenterology. 2014; 109(Suppl.2):S135

386 Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001; 33(2):464-470

387 Kamper-Jorgensen M, Gronbaek M, Tolstrup J, Becker U. Alcohol and cirrhosis: dose--response or threshold effect? Journal of Hepatology. 2004; 41(1):25-30

388 Kamphues C, Lotz K, Rocken C, Berg T, Eurich D, Pratschke J et al. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clinical Transplantation. 2010; 24(5):652-659

389 Kaneda H, Hashimoto E, Yatsuji S, Tokushige K, Shiratori K. Hyaluronic acid levels can predict severe fibrosis and platelet counts can predict cirrhosis in patients with nonalcoholic fatty liver disease. Journal of Gastroenterology and Hepatology. 2006; 21(9):1459-1465

390 Kang W, Kim SU, Ahn SH. Non-invasive prediction of forthcoming cirrhosis-related complications. World Journal of Gastroenterology. 2014; 20(10):2613-2623

391 Kansagara D, Papak J, Pasha AS, O'Neil M, Freeman M, Relevo R et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. Annals of Internal Medicine. 2014; 161(4):261-269

392 Karagiannakis DS, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Diastolic cardiac dysfunction is a predictor of dismal prognosis in patients with liver cirrhosis. Hepatology International. 2014; 8(4):588-594

393 Karoui S, Romdhane SB, Serghini M, Mustapha NB, Boubaker J, Haouet S et al. Is apri score a suitable tool for prediction of fibrosis in tunisian patients with genotype 1 chronic viral hepatitis c? Tunisie Medicale. 2012; 90(4):282-285

394 Kemp W, Pianko S, Nguyen S, Bailey MJ, Roberts S. Survival in hepatocellular carcinoma: impact of screening and etiology of liver disease. Journal of Gastroenterology and Hepatology. 2005; 20(6):873-881

395 Kersh ES, Rifkin H. Lactulose enemas. Annals of Internal Medicine. 1973; 78(1):81-84

396 Khalili K, Menezes R, Kim TK, Kochak Yazdi L, Jang HJ, Sharma S et al. The effectiveness of ultrasound surveillance for hepatocellular carcinoma in a Canadian centre and determinants of its success. Canadian Journal of Gastroenterology and Hepatology. 2015; 29(5):267-273

397 Khambaty M, Nehra M, Singal A. Surveillance endoscopic variceal ligation is underutilized in patients with cirrhosis and bleeding esophageal varices. American Journal of Gastroenterology. 2014; 109(Suppl.2):S181

398 Khan DA, Fatima-Tuz-Zuhra, Khan FA, Mubarak A. Evaluation of diagnostic accuracy of APRI for prediction of fibrosis in hepatitis C patients. Journal of Ayub Medical College, Abbottabad. 2008; 20(4):122-126

399 Khokhar N, Qureshi MO, Ahmad S, Ahmad A, Khan HH, Shafqat F et al. Comparison of once a day rifaximin to twice a day dosage in the prevention of recurrence of hepatic encephalopathy in patients with chronic liver disease. Journal of Gastroenterology and Hepatology. 2015; 30(9):1420-1422

400 Khullar V, Firpi RJ. Hepatitis C cirrhosis: New perspectives for diagnosis and treatment. World Journal of Hepatology. 2015; 7(14):1843-1855

401 Khuroo MS, Khuroo NS, Farahat KLC, Khuroo YS, Sofi AA, Dahab ST. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. Alimentary Pharmacology and Therapeutics. 2005; 21(4):347-361

402 Kim BH, Lee JM, Lee Yj, Lee KB, Suh KS, Han JK et al. MR elastography for noninvasive assessment of hepatic fibrosis: experience from a tertiary center in Asia. Journal of Magnetic Resonance Imaging. 2011; 34(5):1110-1116

403 Kim JN, Sohn KM, Kim MY, Suk KT, Jeong SW, Jung HE et al. Relationship between the hepatic venous pressure gradient and first variceal hemorrhage in patients with cirrhosis: a multicenter retrospective study in Korea. Clinical and Molecular Hepatology. 2012; 18(4):391-396

404 Kim SG, Kim YS, Jung SW, Kim HK, Jang JY, Moon JH et al. [The usefulness of transient elastography to diagnose cirrhosis in patients with alcoholic liver disease]. Korean Journal of Hepatology. 2009; 15(1):42-51

405 Kim SU, Lee JH, Kim DY, Ahn SH, Jung KS, Choi EH et al. Prediction of liver-related events using fibroscan in chronic hepatitis B patients showing advanced liver fibrosis. PloS One. 2012; 7(5):e36676

406 Kim WR, Poterucha JJ, Wiesner RH, LaRusso NF, Lindor KD, Petz J et al. The relative role of the Child-Pugh classification and the Mayo natural history model in the assessment of survival in patients with primary sclerosing cholangitis. Hepatology. 1999; 29(6):1643-1648

407 Kim YS, Um SH, Ryu HS, Lee JB, Lee JW, Park DK et al. The prognosis of liver cirrhosis in recent years in Korea. Journal of Korean Medical Science. 2003; 18(6):833-841

408 Kimer N, Krag A, Moller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Alimentary Pharmacology and Therapeutics. 2014; 40(2):123-132

409 Kimer N, Krag A, Bendtsen F, Møller S, Gluud LL. Rifaximin for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2015;(3):CD011585. DOI:10.1002/14651858.CD011585

410 Kircheis G, Nilius R. Therapeutic effects of L-ornithine-L-aspartate infusion concentrate in hepatic encephalopathy. Results of a placebo-controlled clinical trial (abtracts-GASL). Zeitschrift Fur Gastroenterologie. 1992; 30(4):290

411 Kircheis G, Wettstein M, Dahl S, Haussinger D. Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. Metabolic Brain Disease. 2002; 17(4):453-462

412 Kirk GD, Astemborski J, Mehta SH, Spoler C, Fisher C, Allen D et al. Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. Clinical Infectious Diseases. 2009; 48(7):963-972

413 Klatsky AL, Friedman GD, Siegelaub AB. Alcohol and mortality. A ten-year Kaiser-Permanente experience. Annals of Internal Medicine. 1981; 95(2):139-145

414 Klotz U, Walker S. Flumazenil and hepatic encephalopathy. The Lancet. 1989; 1(8630):155-156

415 Kobayashi K, Nakao H, Nishiyama T, Lin Y, Kikuchi S, Kobayashi Y et al. Diagnostic accuracy of real-time tissue elastography for the staging of liver fibrosis: a meta-analysis. European Radiology. 2015; 25(1):230-238

416 Kohli A, Murphy AA, Agarwal C, Shivakumar B, Kottilil S, Polis MA et al. HCC surveillance results in earlier HCC detection: results from an Indian cohort. Springerplus. 2014; 3:610

417 Koizumi Y, Hirooka M, Kisaka Y, Konishi I, Abe M, Murakami H et al. Liver fibrosis in patients with chronic hepatitis C: noninvasive diagnosis by means of real-time tissue elastography--establishment of the method for measurement. Radiology. 2011; 258(2):610-617

418 Koo JK, Kim JH, Choi YJ, Lee CI, Yang JH, Yoon HY et al. Predictive value of Refit Model for End-Stage Liver Disease, Refit Model for End-Stage Liver Disease-Na, and pre-existing scoring system for 3-month mortality in Korean patients with cirrhosis. Journal of Gastroenterology and Hepatology. 2013; 28(7):1209-1216

419 Korula J. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology. 1991; 101(2):590-592

420 Kramer C, Jaspers N, Nierhoff D, Kuhr K, Bowe A, Goeser T et al. Acoustic structure quantification ultrasound software proves imprecise in assessing liver fibrosis or cirrhosis in parenchymal liver diseases. Ultrasound in Medicine and Biology. 2014; 40(12):2811-2818

421 Kramer JR, Giordano TP, Souchek J, Richardson P, Hwang LY, El-Serag HB. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. American Journal of Gastroenterology. 2005; 100(1):56-63

422 Krystallis C, Masterton GS, Hayes P, Plevris JN. Update of endoscopy in liver disease: more than just treating varices. World Journal of Gastroenterology. 2012; 18(5):401-411

423 Kumar R, Rastogi A, Sharma MK, Bhatia V, Tyagi P, Sharma P et al. Liver stiffness measurements in patients with different stages of nonalcoholic fatty liver disease: diagnostic performance and clinicopathological correlation. Digestive Diseases and Sciences. 2013; 58(1):265-274

424 Kuo YH, Lu SN, Chen CL, Cheng YF, Lin CY, Hung CH et al. Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis. European Journal of Cancer. 2010; 46(4):744-751

425 Kuroda H, Kakisaka K, Tatemichi Y, Sawara K, Miyamoto Y, Oikawa K et al. Non-invasive evaluation of liver fibrosis using acoustic radiation force impulse imaging in chronic hepatitis patients with hepatitis C virus infection. Hepato-Gastroenterology. 2010; 57(102-103):1203-1207

426 La Spada E, Soresi M, Giannitrapani L, La Spada M, Campagna E, Terranova A et al. Long-term follow-up of hepatitis C virus-positive patients with persistently normal serum transaminases. Annals of Hepatology. 2013; 12(1):36-43

427 Ladero JM, Delkader J, Ortega L, Fernandez C, Devesa MJ, Lopez-Alonso G et al. Non-invasive evaluation of the fibrosis stage in chronic hepatitis C: a comparative analysis of nine scoring methods. Scandinavian Journal of Gastroenterology. 2010; 45(1):51-59

428 Lagging M, Westin J, Svensson E, Aires N, Dhillon AP, Lindh M et al. Progression of fibrosis in untreated patients with hepatitis C virus infection. Liver. 2002; 22(2):136-144

429 Landoni G, Bove T, Szekely A, Comis M, Rodseth RN, Pasero D et al. Reducing mortality in acute kidney injury patients: systematic review and international web-based survey. Journal of Cardiothoracic and Vascular Anesthesia. 2013; 27(6):1384-1398

430 Lang I, Tompos G, Gogi A, Varga L, Varga L, Feher J. Effect of ornithin -aspartate therapy on serum ammonia level in patients with hepatic encephalopathy. Zeitschrift Fur Gastroenterologie. 1995; 33(5):298

431 Lannerstedt H, Konopski Z, Sandvik L, Haaland T, Loberg EM, Haukeland JW. Combining transient elastography with FIB4 enhances sensitivity in detecting advanced fibrosis of the liver. Scandinavian Journal of Gastroenterology. 2013; 48(1):93-100

432 Lata J, Jurankova J, Husova L, Senkyrik M, Dite P, Dastych M et al. Variceal bleeding in portal hypertension: bacterial infection and comparison of efficacy of intravenous and per-oral application of antibiotics--a randomized trial. European Journal of Gastroenterology and Hepatology. 2005; 17(10):1105-1110

433 Lebrec D. Pharmacologic prevention of variceal bleeding and rebleeding. Journal of Hepatology. 1993; 17(Suppl.2):S29-S33

434 Lebrec D. Long-term management of variceal bleeding: the place of pharmacotherapy. World Journal of Surgery. 1994; 18(2):229-232

435 Lebrec D, Giuily N, Hadengue A, Vilgrain V, Moreau R, Poynard T et al. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. French Group of Clinicians and a Group of Biologists. Journal of Hepatology. 1996; 25(2):135-144

436 Lebrec D, Poynard T, Capron JP, Hillon P, Geoffroy P, Roulot D et al. Nadolol for prophylaxis of gastrointestinal bleeding in patients with cirrhosis. A randomized trial. Journal of Hepatology. 1988; 7(1):118-125

437 Lebrec L. Beta-blockers in the prevention of gastrointestinal bleeding. Revista De Investigacion Clinica. 1990; 42(Suppl.):159-164

438 Lee HS, Kim JK, Cheong JY, Han EJ, An SY, Song JH et al. Prediction of compensated liver cirrhosis by ultrasonography and routine blood tests in patients with chronic viral hepatitis. Korean Journal of Hepatology. 2010; 16(4):369-375

439 Lee HW, Yoo EJ, Kim BK, Kim SU, Park JY, Kim DY et al. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. American Journal of Gastroenterology. 2014; 109(8):1241-1249

440 Lee HJ, Yeon JE, Yoon EL, Suh SJ, Kang K, Kim HR et al. Long-term follow-up of chronic hepatitis C patients treated with interferon-alpha: risk of cirrhosis and hepatocellular carcinoma in a single center over 10 years. Intervirology. 2015; 58(1):14-21

441 Lee I, Agarwal R, and Williams K. Albumin use in hepatorenal syndrome and large volume paracentesis. Philadelphia. Center for Evidence-based Practice (CEP), 2009

442 Lee JS. Albumin for end-stage liver disease. Korean Journal of Internal Medicine. 2012; 27(1):13-19

443 Lee MH, Yang HI, Liu J, Batrla-Utermann R, Jen CL, Iloeje UH et al. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. Hepatology. 2013; 58(2):546-554

444 Lee MH, Cheong JY, Um SH, Seo YS, Kim DJ, Hwang SG et al. Comparison of surrogate serum markers and transient elastography (Fibroscan) for assessing cirrhosis in patients with chronic viral hepatitis. Digestive Diseases and Sciences. 2010; 55(12):3552-3560

445 Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-Carrie N, Kazemi F et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Alimentary Pharmacology and Therapeutics. 2008; 28(9):1102-1110

446 Leroy V, Sturm N, Faure P, Trocme C, Marlu A, Hilleret MN et al. Prospective evaluation of FibroTest, FibroMeter, and HepaScore for staging liver fibrosis in chronic hepatitis B: comparison with hepatitis C. Journal of Hepatology. 2014; 61(1):28-34

447 Levy RE, Catana AM, Durbin-Johnson B, Halsted CH, Medici V. Ethnic differences in presentation and severity of alcoholic liver disease. Alcoholism: Clinical and Experimental Research. 2015; 39(3):566-574

448 Leykum LK, El-Serag HB, Cornell J, Papadopoulos KP. Screening for hepatocellular carcinoma among veterans with hepatitis C on disease stage, treatment received, and survival. Clinical Gastroenterology and Hepatology. 2007; 5(4):508-512

449 Li L, Yu C, Li Y. Endoscopic band ligation versus pharmacological therapy for variceal bleeding in cirrhosis: a meta-analysis. Canadian Journal of Gastroenterology. 2011; 25(3):147-155

450 Li SM, Li GX, Fu DM, Wang Y, Dang LQ. Liver fibrosis evaluation by ARFI and APRI in chronic hepatitis C. World Journal of Gastroenterology. 2014; 20(28):9528-9533

451 Lichtinghagen R, Pietsch D, Bantel H, Manns M, Brand K, Bahr M. The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values. Journal of Hepatology. 2013; 59(2):236-242

452 Lim AKP, Patel N, Eckersley RJ, Fitzpatrick J, Crossey MME, Hamilton G et al. A comparison of 31P magnetic resonance spectroscopy and microbubble-enhanced ultrasound for characterizing hepatitis c-related liver disease. Journal of Viral Hepatitis. 2011; 18(10):e530-e534

453 Lim AKP, Taylor-Robinson SD, Patel N, Eckersley RJ, Goldin RD, Hamilton G et al. Hepatic vein transit times using a microbubble agent can predict disease severity non-invasively in patients with hepatitis C. Gut. 2005; 54(1):128-133

454 Liu CH, Hsu SJ, Lin JW, Hwang JJ, Liu CJ, Yang PM et al. Noninvasive diagnosis of hepatic fibrosis in patients with chronic hepatitis C by splenic Doppler impedance index. Clinical Gastroenterology and Hepatology. 2007; 5(10):1199-1206

455 Liu CH, Liang CC, Huang KW, Liu CJ, Chen SI, Lin JW et al. Transient elastography to assess hepatic fibrosis in hemodialysis chronic hepatitis C patients. Clinical Journal of the American Society of Nephrology. 2011; 6(5):1057-1065

456 Liu D, Fong DYT, Chan ACY, Poon RTP, Khong PL. Hepatocellular carcinoma: surveillance CT schedule after hepatectomy based on risk stratification. Radiology. 2015; 274(1):133-140

457 Liu J, Jing Z-F, Yan J-H, Luo M, Hu R. Therapeutic effects of octreotide combined with alprostadil on cirrhosis with hepatorenal syndrome. World Chinese Journal of Digestology. 2014; 22(14):2034-2038

458 Lo GH, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI et al. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. Gastrointestinal Endoscopy. 2004; 59(3):333-338

459 Lombard M, Abraldes JG, Altamirano J, Decaens T, Forns X. Clinical trial watch: reports from the AASLD Liver Meeting, Boston, November 2014. Journal of Hepatology. 2015; 62(5):1196-1203

460 Longheval G, Vereerstraeten P, Thiry P, Delhaye M, Le Moine O, Deviere J et al. Predictive models of short- and long-term survival in patients with nonbiliary cirrhosis. Liver Transplantation. 2003; 9(3):260-267

461 Lontos S, Gow P, Roberts S, Vaughan RB, Angus P. Spontaneous bacterial peritonitis (SBP) prophylaxis: a randomised controlled trial comparing trimethoprim-sulfamethoxazole and norfloxacin. Journal of Hepatology. 2008; 48(Suppl.2):S119

462 Lontos S, Shelton E, Angus P, Vaughan R, Roberts S, Gordon A et al. A randomized controlled study of trimethoprim-sulfamethoxazole versus norfloxacin for the prevention of infection in cirrhotic patients. Journal of Digestive Diseases. 2014; 15(5):260-267

463 Loomba R, Wesley R, Bain A, Csako G, Pucino F. Role of fluoroquinolones in the primary prophylaxis of spontaneous bacterial peritonitis: meta-analysis. Clinical Gastroenterology and Hepatology. 2009; 7(4):487-493

464 Lopez-Acosta ME, Mora-Levy J-G, Blancas-Valencia J-M, Paz-Flores V-M. Primary prophylaxis of variceal bleeding comparing propranolol versus recharging a multiple band ligator: up to 4 years follow-up. Gastrointestinal Endoscopy. 2002; 55(5):AB195

465 Lu M, Jia Y, Lu H, Peng Y. The effects of the combined administration of GTW and Zinc on posthepatic hepatorenal syndrome and its mechanism. Journal of Gastroenterology and Hepatology. 1999; 14(Suppl.):A405

466 Lucidarme D, Foucher J, Le Bail B, Vergniol J, Castera L, Duburque C et al. Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C. Hepatology. 2009; 49(4):1083-1089

467 Luo JC, Hwang SJ, Chang FY, Chu CW, Lai CR, Wang YJ et al. Simple blood tests can predict compensated liver cirrhosis in patients with chronic hepatitis C. Hepato-Gastroenterology. 2002; 49(44):478-481

468 Luo X, Wang Z, Tsauo J, Zhou B, Zhang H, Li X. Advanced cirrhosis combined with portal vein thrombosis: a randomized trial of TIPS versus endoscopic band ligation plus propranolol for the prevention of recurrent esophageal variceal bleeding. Radiology. 2015; 276(1):286-293

469 Lupsor M, Badea R, Stefanescu H, Grigorescu M, Serban A, Radu C et al. Performance of unidimensional transient elastography in staging non-alcoholic steatohepatitis. Journal of Gastrointestinal and Liver Diseases. 2010; 19(1):53-60

470 Lupsor M, Badea R, Stefanescu H, Grigorescu M, Sparchez Z, Serban A et al. Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients. Journal of Gastrointestinal and Liver Diseases. 2008; 17(2):155-163

471 Lutz HH, Gassler N, Tischendorf FW, Trautwein C, Tischendorf JJW. Doppler ultrasound of hepatic blood flow for noninvasive evaluation of liver fibrosis compared with liver biopsy and transient elastography. Digestive Diseases and Sciences. 2012; 57(8):2222-2230

472 Lv X-H, Liu H-B, Wang Y, Wang B-Y, Song M, Sun M-J. Validation of model for end-stage liver disease score to serum sodium ratio index as a prognostic predictor in patients with cirrhosis. Journal of Gastroenterology and Hepatology. 2009; 24(9):1547-1553

473 Macias J, Camacho A, Von Wichmann MA, Lopez-Cortes LF, Ortega E, Tural C et al. Liver stiffness measurement versus liver biopsy to predict survival and decompensations of cirrhosis among HIV/hepatitis C virus-coinfected patients. AIDS. 2013; 27(16):2541-2549

474 Macias-Rodriguez MA, Rendon-Unceta P, Ramos-Clemente-Romero MT, Troiteiro-Carrasco LM, Serrano-Leon MD. Prospective validation of two models for ultrasonographic diagnosis of cirrhosis. Revista Espanola De Enfermedades Digestivas. 2011; 103(5):232-237

475 Mahadeva S, Mahfudz AS, Vijayanathan A, Goh KL, Kulenthran A, Cheah PL. Performance of transient elastography (TE) and factors associated with discordance in non-alcoholic fatty liver disease. Journal of Digestive Diseases. 2013; 14(11):604-610

476 Maharshi S, Sharma BC, Srivastava S, Jindal A. Randomised controlled trial of lactulose versus rifaximin for prophylaxis of hepatic encephalopathy in patients with acute variceal bleed. Gut. 2015; 64(8):1341-1342

477 Malaguarnera M, Pistone G, Astuto M, Dell'Arte S, Finocchiaro G, Lo Giudice E et al. L-Carnitine in the treatment of mild or moderate hepatic encephalopathy. Digestive Diseases. 2003; 21(3):271-275

478 Malaguarnera M, Pistone G, Astuto M, Vecchio I, Raffaele R, Lo Giudice E et al. Effects of L-acetylcarnitine on cirrhotic patients with hepatic coma: randomized double-blind, placebo-controlled trial. Digestive Diseases and Sciences. 2006; 51(12):2242-2247

479 Malaguarnera M, Pistone G, Elvira R, Leotta C, Scarpello L, Liborio R. Effects of L-carnitine in patients with hepatic encephalopathy. World Journal of Gastroenterology. 2005; 11(45):7197-7202

480 Malaguarnera M, Risino C, Cammalleri L, Malaguarnera L, Astuto M, Vecchio I et al. Branched chain amino acids supplemented with L-acetylcarnitine versus BCAA treatment in hepatic coma: a randomized and controlled double blind study. European Journal of Gastroenterology and Hepatology. 2009; 21(7):762-770

481 Malik R, Lai M, Sadiq A, Farnan R, Mehta SH, Nasser I et al. Comparison of transient elastography, serum markers and clinical signs for the diagnosis of compensated cirrhosis. Journal of Gastroenterology and Hepatology. 2010; 25(9):1562-1568

482 Mallaiyappan M, Sawalakhe NR, Sasidharan M, Shah DK, Rathi PM, Bhatia SJ. Retrospective and prospective validation of model for end-stage liver disease (MELD) score in predicting mortality in patients of alcoholic liver disease. Tropical Gastroenterology. 2013; 34(4):252-258

483 Manera J, Mappala HT. A meta-analysis of propranolol versus rubber band ligation as primary prophylaxis for variceal bleeding in patients with cirrhosis. Journal of Gastroenterology and Hepatology. 2012; 27(Suppl.5):223

484 Manini MA, Sangiovanni A, Fornari F, Piscaglia F, Biolato M, Fanigliulo L et al. Clinical and economical impact of 2010 AASLD guidelines for the diagnosis of hepatocellular carcinoma. Journal of Hepatology. 2014; 60(5):995-1001

485 Marbet UA, Bianchi L, Meury U, Stalder GA. Long-term histological evaluation of the natural history and prognostic factors of alcoholic liver disease. Journal of Hepatology. 1987; 4(3):364-372

486 Marcolongo M, Young B, Dal Pero F, Fattovich G, Peraro L, Guido M et al. A seven-gene signature (cirrhosis risk score) predicts liver fibrosis progression in patients with initially mild chronic hepatitis C. Hepatology. 2009; 50(4):1038-1044

487 Marks RM, Ryan A, Heba ER, Tang A, Wolfson TJ, Gamst AC et al. Diagnostic per-patient accuracy of an abbreviated hepatobiliary phase gadoxetic acid-enhanced MRI for hepatocellular carcinoma surveillance. American Journal of Roentgenology. 2015; 204(3):527-535

488 Marmo R, Romano M, de Sio I, Peduto A, Caporaso N, Persico M et al. Decision-making model for a non-invasive diagnosis of compensated liver cirrhosis. Italian Journal of Gastroenterology. 1993; 25(1):1-8

489 Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology. 2002; 36(6):1349-1354

490 Martí-Carvajal AJ, Gluud C, Arevalo-Rodriguez I. Acetyl-L-carnitine for patients with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2014;(12):CD011451. DOI:10.1002/14651858.CD011451

491 Martin J, Khatri G, Gopal P, Singal AG. Accuracy of ultrasound and noninvasive markers of fibrosis to identify patients with cirrhosis. Digestive Diseases and Sciences. 2015; 60(6):1841-1847

492 Maruyama H, Okugawa H, Kobayashi S, Yoshizumi H, Takahashi M, Ishibashi H et al. Non-invasive portography: a microbubble-induced three-dimensional sonogram for discriminating idiopathic portal hypertension from cirrhosis. British Journal of Radiology. 2012; 85(1013):587-595

493 Maruyama H, Ishibashi H, Takahashi M, Imazeki F, Yokosuka O. Effect of signal intensity from the accumulated microbubbles in the liver for differentiation of idiopathic portal hypertension from liver cirrhosis. Radiology. 2009; 252(2):587-594

494 Massa P, Vallerino E, Dodero M. Treatment of hepatic encephalopathy with rifaximin: Double blind, double dummy study versus lactulose. European Journal of Clinical Research. 1993; 4:7-18

495 Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T et al. Comparison of liver biopsy and transient elastography based on clinical relevance. Canadian Journal of Gastroenterology. 2008; 22(9):753-757

496 Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology. 2009; 49(6):1954-1961

497 Mathiesen UL, Franzen LE, Aselius H, Resjo M, Jacobsson L, Foberg U et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. Digestive and Liver Disease. 2002; 34(7):516-522

498 Mathurin P, Beuzin F, Louvet A, Carrie-Ganne N, Balian A, Trinchet JC et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Alimentary Pharmacology and Therapeutics. 2007; 25(9):1047-1054

499 Mayo MJ, Parkes J, Adams-Huet B, Combes B, Mills AS, Markin RS et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. Hepatology. 2008; 48(5):1549-1557

500 Mazariegos GV, Kramer DJ, Linden P, Pinna A, Fung JJ, Ash SR et al. Treatment of hepatic failure with advanced encephalopathy using the biologic-DT: preliminary clinical results. Critical Care Medicine. 1998; 26(1 Suppl.):A78

501 McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2011;(11):CD008716. DOI:10.1002/14651858.CD008716.pub2

502 McGowan CE, Edwards TP, Luong MUT, Hayashi PH. Suboptimal surveillance for and knowledge of hepatocellular carcinoma among primary care providers. Clinical Gastroenterology and Hepatology. 2015; 13(4):799-804

503 McMahon BJ, Alberts SR, Wainwright RB, Bulkow L, Lanier AP. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. Archives of Internal Medicine. 1990; 150(5):1051-1054

504 McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology. 2009; 49(5 Suppl.):S45-S55

505 McPherson S, Anstee QM, Henderson E, Day CP, Burt AD. Are simple noninvasive scoring systems for fibrosis reliable in patients with NAFLD and normal ALT levels? European Journal of Gastroenterology and Hepatology. 2013; 25(6):652-658

506 McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010; 59(9):1265-1269

507 Meek DR, Mills PR, Gray HW, Duncan JG, Russell RI, McKillop JH. A comparison of computed tomography, ultrasound and scintigraphy in the diagnosis of alcoholic liver disease. British Journal of Radiology. 1984; 57(673):23-27

508 Meier R, Gyr K. Treatment of hepatic encephalopathy (HE) with the benzodiazepine antagonist flumazenil: a pilot study. European Journal of Anaesthesiology Supplement. 1988; 2:139-146

509 Meikle PJ, Mundra PA, Wong G, Rahman K, Huynh K, Barlow CK et al. Circulating lipids are associated with alcoholic liver cirrhosis and represent potential biomarkers for risk assessment. PloS One. 2015; 10(6):e0130346

510 Melin P, Schoeny M, Dacon A, Gauchet A, Diebold MD. Dépistage non invasif de la fibrose hépatique. Intérêt du FibroScan(R) en consultation d'alcoologie. Alcoologie Et Addictologie. 2005; 27:191-196

511 Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E et al. Beta-blockers in the prevention of aggravation of esophageal varices in patients with cirhosis and small varices: a placebo-controlled clinical trial. Hepatology. 2003; 38(4 Suppl.1):217A

512 Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterology. 2004; 127(2):476-484

513 Michel H, Bories P, Aubin JP, Pomier-Layrargues G, Bauret P, Bellet-Hermann H. Treatment of acute hepatic encephalopathy in cirrhotics with a branched-chain amino acids enriched versus a conventional amino acids mixture. A controlled study of 70 patients. Liver. 1985; 5(5):282-289

514 Michel H, Pomier-Layrargues G, Aubin JP, Bories P, Mirouze D, Bellet-Hermann H. Treatment of hepatic encephalopathy by infusion of a modified amino acid solution: results of a controlled study in 47 cirrhotic patients. In: Capocaccia L, Fischer JE, Rossi-Fanelli F (eds), Hepatic encephalopathy in chronic liver failure, New York: Plenum Press, 1984: 301-310

515 Miglio F, Valpiani D, Rossellini SR, Ferrieri A. Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial. Current Medical Research and Opinion. 1997; 13(10):593-601

516 Mishra P, Desai N, Alexander J, Singh DP, Sawant P. Applicability of MELD as a short-term prognostic indicator in patients with chronic liver disease: An Indian experience. Journal of Gastroenterology and Hepatology. 2007; 22(8):1232-1235

517 Mishra SR, Kumar A, Gupta LB, Kishore R, Sharma BC, Sarin S. Early primary prophylaxis with beta-blockers and role of hepatic venous pressure gradient assessment in prevention of growth of small esophageal varices in cirrhosis. Hepatology. 2007; 46(4 Suppl.1):574A

518 Mittal R, Wu BU. Risk factors for liver cirrhosis among chronic hepatitis B patients in a regional Unites States population. Gastroenterology. 2015; 148(4 Suppl.1):S1067

519 Mohammad RA, Regal RE, Alaniz C. Combination therapy for the treatment and prevention of hepatic encephalopathy. Annals of Pharmacotherapy. 2012; 46(11):1559-1563

520 Montagnese S, De Rui M, Schiff S, Ceranto E, Valenti P, Angeli P et al. Prognostic benefit of the addition of a quantitative index of hepatic encephalopathy to the MELD score: the MELD-EEG. Liver International. 2015; 35(1):58-64

521 Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. World Journal of Gastroenterology. 2014; 20(25):8061-8071

522 Moodley J, Lopez R, Carey W. Compliance with practice guidelines and risk of a first esophageal variceal hemorrhage in patients with cirrhosis. Clinical Gastroenterology and Hepatology. 2010; 8(8):703-708

523 Moon KM, Kim G, Baik SK, Choi EH, Kim MY, Kim HA et al. Ultrasonographic scoring system score versus liver stiffness measurement in prediction of cirrhosis. Clinical and Molecular Hepatology. 2013; 19(4):389-398

524 Moreau R, Valla DC, Durand-Zaleski I, Bronowicki JP, Durand F, Chaput JC et al. Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trail. Liver International. 2006; 26(1):46-54

525 Moreno J-P, Grandclement E, Monnet E, Clerc B, Agin A, Cervoni J-P et al. Plasma copeptin, a possible prognostic marker in cirrhosis. Liver International. 2013; 33(6):843-851

526 Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut. 1982; 23(1):1-7

527 Morikawa H, Fukuda K, Kobayashi S, Fujii H, Iwai S, Enomoto M et al. Real-time tissue elastography as a tool for the noninvasive assessment of liver stiffness in patients with chronic hepatitis C. Journal of Gastroenterology. 2011; 46(3):350-358

528 Morosan E, Mihailovici MS. Fibrosis assessment in chronic hepatitis C--is the liver biopsy still necessary? The pathologist point of view. Revista Medico-Chirurgicala a Societatii De Medici Si Naturalisti Din Iasi. 2014; 118(4):992-999

529 Mostafa TM, Ibrahim OM, Badra GAE-K, Abdallah MS. Role of pentoxifylline and sparfloxacin in prophylaxis of spontaneous bacterial peritonitis in cirrhotic patients. ISRN Gastroenterology. 2014; 2014:595213

530 Mudireddy PR, Agarwal R, Williams K. The role of albumin in the management of hepatorenal syndrome: A systematic review. Journal of Clinical Outcomes Management. 2013; 20(6):264-270

531 Murakami C, Hino K, Korenaga M, Okazaki M, Okuda M, Nukui K et al. Factors predicting progression to cirrhosis and hepatocellular carcinoma in patients with transfusion-associated hepatitis C virus infection. Journal of Clinical Gastroenterology. 1999; 28(2):148-152

532 Myers RP, Elkashab M, Ma M, Crotty P, Pomier-Layrargues G. Transient elastography for the noninvasive assessment of liver fibrosis: a multicentre Canadian study. Canadian Journal of Gastroenterology. 2010; 24(11):661-670

533 Naaleini F, Farshchian N, Sayad B, Rezaie M, Rahbar M, Mehrbakhsh M. Diagnostic values of fibrosis index in ultrasonography for differentiation of chronic viral hepatitis from liver cirrhosis. Scientific Journal of Kurdistan University of Medical Sciences. 2013; 18(1):59-66

534 Nadim MK, Kellum JA, Davenport A, Wong F, Davis C, Pannu N et al. Hepatorenal syndrome: the 8th International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care. 2012; 16(1):R23

535 Nagata N, Miyachi H, Nakano A, Nanri K, Kobayashi H, Matsuzaki S. Sonographic evaluation of the anterior liver surface in chronic liver diseases using a 7.5-MHz annular-array transducer: correlation with laparoscopic and histopathologic findings. Journal of Clinical Ultrasound. 2003; 31(8):393-400

536 Nahon P, Kettaneh A, Tengher-Barna I, Ziol M, de Ledinghen V, Douvin C et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. Journal of Hepatology. 2008; 49(6):1062-1068

537 Nahon P, Thabut G, Ziol M, Htar MT-T, Cesaro F, Barget N et al. Liver stiffness measurement versus clinicians' prediction or both for the assessment of liver fibrosis in patients with chronic hepatitis C. American Journal of Gastroenterology. 2006; 101(12):2744-2751

538 National Institute for Health and Care Excellence. Virtual Touch Quantification to diagnose and monitor liver fibrosis in chronic hepatitis B and C: NICE medical technology guidance 24. London. National Institute for Health and Clinical Excellence (NICE), 2015. Available from: http://guidance.nice.org.uk/MTG27

539 National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance. 2nd edition. London: National Institute for Health and Clinical Excellence; 2008. Available from: http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf

540 Navasa M, Fernandez J, Montoliu S, Planas R, Monfort D, Soriano G. Randomized, double-blind, placebo-controlled trial evaluating norfloxacin in the primary prophylaxis of spontaneous bacterial peritonitis in cirrhotics with renal impairment, hyponatremia or severe liver failure. Journal of Hepatology. 2005; 44(2 Suppl.):S51

541 Navasa M, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. Gastroenterology. 1996; 111(4):1011-1017

542 Naveau S. Body mass index and risk of liver cirrhosis in middle aged UK women: Prospective study. Gastroenterologie Clinique Et Biologique. 2010; 34(8-9):429-430

543 Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. Hepatology. 1997; 25(1):108-111

544 Naveau S, Essoh BM, Ghinoiu M, Marthey L, Njike-Nakseu M, Balian A et al. Comparison of Fibrotest and PGAA for the diagnosis of fibrosis stage in patients with alcoholic liver disease. European Journal of Gastroenterology and Hepatology. 2014; 26(4):404-411

545 Naveau S, Gaude G, Asnacios A, Agostini H, Abella A, Barri-Ova N et al. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. Hepatology. 2009; 49(1):97-105

546 Naveau S, Lamouri K, Pourcher G, Njike-Nakseu M, Ferretti S, Courie R et al. The diagnostic accuracy of transient elastography for the diagnosis of liver fibrosis in bariatric surgery candidates with suspected NAFLD. Obesity Surgery. 2014; 24(10):1693-1701

547 Naveau S, Raynard B, Ratziu V, Abella A, Imbert-Bismut F, Messous D et al. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. Clinical Gastroenterology and Hepatology. 2005; 3(2):167-174

548 Neff GW, Kemmer N, Zaccharias VC, Kaiser T, Duncan C, McHenry R et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. Transplantation Proceedings. 2006; 38(10):3552-3555

549 Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP et al. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests. Alimentary Pharmacology and Therapeutics. 2008; 28(10):1188-1198

550 Nishiura T, Watanabe H, Ito M, Matsuoka Y, Yano K, Daikoku M et al. Ultrasound evaluation of the fibrosis stage in chronic liver disease by the simultaneous use of low and high frequency probes. British Journal of Radiology. 2005; 78(927):189-197

551 Nitta Y, Kawabe N, Hashimoto S, Harata M, Komura N, Kobayashi K et al. Liver stiffness measured by transient elastography correlates with fibrosis area in liver biopsy in patients with chronic hepatitis C. Hepatology Research. 2009; 39(7):675-684

552 Noda I, Kitamoto M, Nakahara H, Hayashi R, Okimoto T, Monzen Y et al. Regular surveillance by imaging for early detection and better prognosis of hepatocellular carcinoma in patients infected with hepatitis C virus. Journal of Gastroenterology. 2010; 45(1):105-112

553 Norberto L, Polese L, Cillo U, Grigoletto F, Burroughs A, Neri D et al. A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation. Liver Transplantation. 2007; 13(9):1272-1278

554 Novella M, Sola R, Soriano G, Andreu M, Gana J, Ortiz J et al. Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. Hepatology. 1997; 25(3):532-536

555 Nudo CG, Jeffers LJ, Bejarano PA, Servin-Abad LA, Leibovici Z, De Medina M et al. Correlation of Laparoscopic Liver Biopsy to Elasticity Measurements (FibroScan) in Patients With Chronic Liver Disease. Gastroenterology and Hepatology. 2008; 4(12):862-870

556 Nunes D, Fleming C, Offner G, O'Brien M, Tumilty S, Fix O et al. HIV infection does not affect the performance of noninvasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease. Journal of Acquired Immune Deficiency Syndromes. 2005; 40(5):538-544

557 Nunes D, Fleming C, Offner G, Craven D, Fix O, Heeren T et al. Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. American Journal of Gastroenterology. 2010; 105(6):1346-1353

558 Nyberg LM, Li X, Chiang K, Cheetham TC, Nyberg AH, Younossi ZM et al. The natural history of chronic Hepatitis C. An updated look at the rate of progression to cirrhosis and the incidence of decompensation in a large U.S. Health maintenance organization. Gastroenterology. 2015; 148(4 Suppl.1):S998

559 Ochi H, Hirooka M, Koizumi Y, Miyake T, Tokumoto Y, Soga Y et al. Real-time tissue elastography for evaluation of hepatic fibrosis and portal hypertension in nonalcoholic fatty liver diseases. Hepatology. 2012; 56(4):1271-1278

560 Office for National Statistics. Death tables 2013: table 5.11. 2014. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Causes+of+Death#tab-data-tables [Last accessed: 22 October 2014]

561 Office for National Statistics. Interim Life Tables 2011-13. 2014. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables#tab-data-tables [Last accessed: 22 November 2014]

562 Ogawa E, Furusyo N, Toyoda K, Takeoka H, Otaguro S, Hamada M et al. Transient elastography for patients with chronic hepatitis B and C virus infection: Non-invasive, quantitative assessment of liver fibrosis. Hepatology Research. 2007; 37(12):1002-1010

563 Omar MM, Mustafa I. Endoscopic band ligation for prophylaxis of first esophageal variceal bleeding. Digestion. 1998; 59(Suppl.3):333

564 Ong TZ, Tan HJ. Ultrasonography is not reliable in diagnosing liver cirrhosis in clinical practice. Singapore Medical Journal. 2003; 44(6):293-295

565 Onodera H, Ukai K, Nakano N, Takeda T, Suzuki H, Okata T et al. Outcomes of 116 patients with hepatocellular carcinoma. Cancer Chemotherapy and Pharmacology. 1994; 33(Suppl.):S103-S108

566 Ooi M, Shadbolt B, Farrell GC, Teoh NC. The effectiveness of oesophageal variceal surveillance of cirrhotic patients in a hospital-based practice. Journal of Gastroenterology and Hepatology. 2013; 28(Suppl.2):65

567 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2014. Available from: http://www.oecd.org/std/ppp [Last accessed: 15 January 2014]

568 Orlandi F, Freddara U, Candelaresi MT, Morettini A, Corazza GR, Di Simone A et al. Comparison between neomycin and lactulose in 173 patients with hepatic encephalopathy: a randomized clinical study. Digestive Diseases and Sciences. 1981; 26(6):498-506

569 Osaki A, Kubota T, Suda T, Igarashi M, Nagasaki K, Tsuchiya A et al. Shear wave velocity is a useful marker for managing nonalcoholic steatohepatitis. World Journal of Gastroenterology. 2010; 16(23):2918-2925

570 Pagliaro L, D'Amico G, Sorensen TI, Lebrec D, Burroughs A, Morabito A et al. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. Annals of Internal Medicine. 1992; 117(1):59-70

571 Pagliaro L, Pasta L, D'Amico G. A randomized clinical trial of propranolol for the prevention of initial bleeding in cirrhosis with portal hypertension. New England Journal of Medicine. 1986; 314(4):244-245

572 Panda D. Role of surveillance in prevention of hepatocellular carcinoma. Journal of Clinical and Experimental Hepatology. 2014; 4(Suppl 3):S43-S49

573 Panella C, Guglielmi FW, Mastronuzzi T, Contento F, Siciliano N, Francavilla A. Oral Na-benzoate in the treatment of chronic hepatic encephalopathy. Italian Journal of Gastroenterology. 1993; 25:228

574 Pang JXQ, Zimmer S, Niu S, Crotty P, Tracey J, Pradhan F et al. Liver stiffness by transient elastography predicts liver-related complications and mortality in patients with chronic liver disease. PloS One. 2014; 9(4):e95776

575 Papageorgiou MV, Papatheodoridis GV, Manolakopoulos S, Tsochatzis E, Kranidioti H, Kafiri G et al. Elastography for hepatic fibrosis severity in chronic hepatitis B or C. Case Reports in Gastroenterology. 2011; 5(1):63-72

576 Parini P, Cipolla A, Ronchi M, Salzetta A, Mazzella G, Roda E. Effect of rifaximin and paromomycin in the treatment of portal-systemic encephalopathy. Current Therapeutic Research - Clinical and Experimental. 1992; 52(1):34-39

577 Parise ER, Oliveira AC, Figueiredo-Mendes C, Lanzoni V, Martins J, Nader H et al. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. Liver International. 2006; 26(9):1095-1099

578 Park GJ, Lin BP, Ngu MC, Jones DB, Katelaris PH. Aspartate aminotransferase: alanine aminotransferase ratio in chronic hepatitis C infection: is it a useful predictor of cirrhosis? Journal of Gastroenterology and Hepatology. 2000; 15(4):386-390

579 Park MS, Kim SU, Kim BK, Park JY, Kim DY, Ahn SH et al. Prognostic value of the combined use of transient elastography and fibrotest in patients with chronic hepatitis B. Liver International. 2015; 35(2):455-462

580 Park YH, Kim BK, Kim JK, Kim HC, Kim DY, Park JY et al. Long-term outcomes of chronic hepatitis B virus infection in the era of antiviral therapy in Korea. Journal of Gastroenterology and Hepatology. 2014; 29(5):1005-1011

581 Parker MJ, Guha N, Stedman B, Hacking N, Wright M. Trans-jugular intrahepatic porto-systemic shunt placement for refractory ascites: a 'real-world' UK health economic evaluation. Frontline Gastroenterology. 2013; 4(3):182-186

582 Parrish KM, Higuchi S, Dufour MC. Alcohol consumption and the risk of developing liver cirrhosis: implications for future research. Journal of Substance Abuse. 1991; 3(3):325-335

583 Pasqualetti P, Di Lauro G, Festuccia V, Giandomenico G, Casale R. Prognostic value of Pugh's modification of Child-Turcotte classification in patients with cirrhosis of the liver. Panminerva Medica. 1992; 34(2):65-68

584 Patel VC, Shawcross DL. A placebo controlled single centre double blind randomised trial to investigate the efficacy of rifaximin in improving systemic inflammation and neutrophil malfunction in patients with cirrhosis and chronic hepatic encephalopathy ('rifsys'). Journal of Hepatology. 2015; 62(Suppl.2):S854

585 Pavlov CS, Casazza G, Nikolova D, Tsochatzis E, Burroughs A, Ivashkin VT et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. Cochrane Database of Systematic Reviews. 2015;(1):CD010542. DOI:10.1002/14651858.CD010542.pub2

586 Pavlov CS, Casazza G, Pavlova M, Nikolova D, Tsochatzis E, Liusina E et al. Ultrasonography for diagnosis of cirrhosis in people with alcoholic liver disease. Cochrane Database of Systematic Reviews. 2015;(3):CD011602. DOI:10.1002/14651858.CD011602

587 Pedersen JF, Madsen LG, Larsen VA, Hamberg O, Horn T, Federspiel B et al. A Doppler waveform index to characterize hepatic vein velocity pattern and evaluate hepatic fibrosis. Journal of Clinical Ultrasound. 2008; 36(4):208-211

588 Pedretti G, Calzetti C, Missale G, Fiaccadori F. Rifaximin versus neomycin on hyperammoniemia in chronic portal systemic encephalopathy of cirrhotics. A double-blind, randomized trial. Italian Journal of Gastroenterology. 1991; 23(4):175-178

589 Pedrosa M, Cook D. Prevention of first bleeding from varices: A meta-analysis. Annals of Internal Medicine. 1992; 117(Suppl.3):66

590 Pequignot G, Tuyns AJ, Berta JL. Ascitic cirrhosis in relation to alcohol consumption. International Journal of Epidemiology. 1978; 7(2):113-120

591 Petta S, Di Marco V, Camma C, Butera G, Cabibi D, Craxi A. Reliability of liver stiffness measurement in non-alcoholic fatty liver disease: the effects of body mass index. Alimentary Pharmacology and Therapeutics. 2011; 33(12):1350-1360

592 Petta S, Grimaudo S, Tripodo C, Cabibi D, Calvaruso M, Di Cristina A et al. The hepatic expression of vitamin D receptor is inversely associated with the severity of liver damage in genotype 1 chronic hepatitis C patients. Journal of Clinical Endocrinology and Metabolism. 2015; 100(1):193-200

593 Pfeifer L, Goertz RS, Sturm J, Wachter D, Riener MO, Schwitulla J et al. Acoustic radiation force impulse (ARFI) and high-frequency ultrasound of the liver surface for the diagnosis of compensated liver cirrhosis. Ultraschall in Der Medizin. 2014; 35(1):44-50

594 Phillips KT, Ohsfeldt R, Voigt M. Albumin versus crystalloid therapy in the management of hepatorenal syndrome: a model for using meta analysis in cost effectiveness studies and the design of clinical trials. AMIA Annual Symposium Proceedings. 2003;970

595 Piano S, Salinas F, Morando F, Cavallin M, Romano A, Rosi S et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis: Results of a randomized controlled clinical trial. Hepatology. 2014; 60(Suppl.1):479A

596 Planas R, Gines P, Arroyo V, Llach J, Panes J, Vargas V et al. Dextran-70 versus albumin as plasma expanders in cirrhotic patients with tense ascites treated with total paracentesis. Results of a randomized study. Gastroenterology. 1990; 99(6):1736-1744

597 Plevris JN, Elliot R, Mills PR, Hislop WS, Davies JM, Bouchier IA et al. Effect of propranolol on prevention of first variceal bleed and survival in patients with chronic liver disease. Alimentary Pharmacology and Therapeutics. 1994; 8(1):63-70

598 Poh Z, Goh BBG, Chang PE, Tan CK. Rates of cirrhosis and hepatocellular carcinoma in chronic hepatitis B and the role of surveillance: a 10-year follow-up of 673 patients. European Journal of Gastroenterology and Hepatology. 2015; 27(6):638-643

599 Pomier-Layrargues G, Giguere JF, Lavoie J, Perney P, Gagnon S, D'Amour M et al. Flumazenil in cirrhotic patients in hepatic coma: a randomized double-blind placebo-controlled crossover trial. Hepatology. 1994; 19(1):32-37

600 Poo JL, Gongora J, Sanchez-Avila JF, Aguilar-Castillo S, Garcia-Ramos G, Fernandez-Zertuche M. Efficacy and safety of L-ornithine-L-aspartate (LOLA) administration. Open label randomized

controlled trial versus lactulose in cirrhotic patients with hyperammonemic hepatic encephalopathy. Journal of Hepatology. 2007; 46(4 Suppl.1):S36

601 Poo JL, Gongora J, Sanchez-Avila F, Aguilar-Castillo S, Garcia-Ramos G, Fernandez-Zertuche M et al. Efficacy of oral L-ornithine-L-aspartate in cirrhotic patients with hyperammonemic hepatic encephalopathy. Results of a randomized, lactulose-controlled study. Annals of Hepatology. 2006; 5(4):281-288

602 Poustchi H, Eslami M, Ostovaneh MR, Modabbernia A, Saeedian FS, Taslimi S et al. Transient elastography in hepatitis C virus-infected patients with beta-thalassemia for assessment of fibrosis. Hepatology Research. 2013; 43(12):1276-1283

603 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. The Lancet. 1997; 349(9055):825-832

604 Poynard T, Cales P, Pasta L, Ideo G, Pascal JP, Pagliaro L et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. New England Journal of Medicine. 1991; 324(22):1532-1538

605 Poynard T, Halfon P, Castera L, Charlotte F, Le Bail B, Munteanu M et al. Variability of the area under the receiver operating characteristic curves in the diagnostic evaluation of liver fibrosis markers: impact of biopsy length and fragmentation. Alimentary Pharmacology and Therapeutics. 2007; 25(6):733-739

606 Poynard T, Munteanu M, Deckmyn O, Ngo Y, Drane F, Castille JM et al. Validation of liver fibrosis biomarker (FibroTest) for assessing liver fibrosis progression: Proof of concept and first application in a large population. Journal of Hepatology. 2012; 57(3):541-548

607 Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. Journal of Hepatology. 2001; 34(5):730-739

608 Poynard T, de Ledinghen V, Zarski JP, Stanciu C, Munteanu M, Vergniol J et al. Performances of Elasto-FibroTest(), a combination between FibroTest() and liver stiffness measurements for assessing the stage of liver fibrosis in patients with chronic hepatitis C. Clinics and Research in Hepatology and Gastroenterology. 2012; 36(5):455-463

609 Poynard T, de Ledinghen V, Zarski JP, Stanciu C, Munteanu M, Vergniol J et al. FibroTest and Fibroscan performances revisited in patients with chronic hepatitis C. Impact of the spectrum effect and the applicability rate. Clinics and Research in Hepatology and Gastroenterology. 2011; 35(11):720-730

610 Poynard T, Ngo Y, Perazzo H, Munteanu M, Lebray P, Moussalli J et al. Prognostic value of liver fibrosis biomarkers: a meta-analysis. Gastroenterology and Hepatology. 2011; 7(7):445-454

611 Poynard T, Vergniol J, Ngo Y, Foucher J, Munteanu M, Merrouche W et al. Staging chronic hepatitis C in seven categories using fibrosis biomarker (FibroTest) and transient elastography (FibroScan). Journal of Hepatology. 2014; 60(4):706-714

612 Pradat P, Trepo E, Potthoff A, Bakshi R, Young B, Trepo C et al. The cirrhosis risk score predicts liver fibrosis progression in patients with initially mild chronic hepatitis C. Hepatology. 2010; 51(1):356-357

613 Prapruttam D, Suksai J, Kitiyakara T, Phongkitkarun S. Ultrasound surveillance for hepatocellular carcinoma of at-risk patients in Ramathibodi Hospital. Journal of the Medical Association of Thailand. 2014; 97(11):1199-1208

614 Procopet B, Cristea VM, Robic MA, Grigorescu M, Agachi PS, Metivier S et al. Serum tests, liver stiffness and artificial neural networks for diagnosing cirrhosis and portal hypertension. Digestive and Liver Disease. 2015; 47(5):411-416

615 Psilopoulos D, Mavrogiannis C, Vafiadis I, Dourakis S, Papanikolaou IS, Alexopoulo A et al. A randomized controlled trial comparing endoscopic variceal ligation (EVL) with propranolol for primary prevention of variceal bleeding (preliminary report). Gastrointestinal Endoscopy. 2002; 55(5):AB196

616 Qi X, Jia J, Bai M, Guo X, Su C, Garcia-Pagan JC et al. Transjugular intrahepatic portosystemic shunt for acute variceal bleeding. Journal of Clinical Gastroenterology. 2015; 49(6):495-505

617 Qian HG, Hao CY. Hepatitis B virus infection is an independent factor influencing the occurrence of liver metastasis in colorectal cancer: a retrospective analysis of 1413 cases. Hepato-Gastroenterology. 2014; 61(135):1908-1914

618 Rao BH, Siyad I, Rajesh G, Venu RP, Geetha M, Bhanu VP et al. Antibiotic prophylaxis for SBP in cirrhosis-A validated preventive measure or an exercise in futility? Indian Journal of Gastroenterology. 2014; 33(1 Suppl.1):A78-A79

619 Ratnaike RN, Hicks EP, Hislop IG. The rectal administration of lactulose. Australian and New Zealand Journal of Medicine. 1975; 5(2):137-140

620 Ratziu V, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L et al. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. BMC Gastroenterology. 2006; 6:6

621 Raza MA, Bhatti RS, Akram J. Effect of rectal lactulose administration with oral therapy on time to recovery from hepatic encephalopathy: a randomized study. Annals of Saudi Medicine. 2004; 24(5):374-377

622 Reddy KR. Ascites-causes and management-western perspective. Hepatology International. 2012; 6(1):23

623 Reiberger T, Ferlitsch A, Payer BA, Pinter M, Schwabl P, Stift J et al. Noninvasive screening for liver fibrosis and portal hypertension by transient elastography--a large single center experience. Wiener Klinische Wochenschrift. 2012; 124(11-12):395-402

624 Reichel C, Sudhop T, Braun B, Kreuzer K-A, Hahn C, Look MP et al. Elevated soluble tumour necrosis factor receptor serum concentrations and short-term mortality in liver cirrhosis without acute infections. Digestion. 2000; 62(1):44-51

625 Rena NMR, Wibawa IDN. Albumin infusion in liver cirrhotic patients. Acta Medica Indonesiana. 2010; 42(3):162-168

626 Resino S, Bellon JM, Asensio C, Micheloud D, Miralles P, Vargas A et al. Can serum hyaluronic acid replace simple non-invasive indexes to predict liver fibrosis in HIV/Hepatitis C coinfected patients? BMC Infectious Diseases. 2009; 10:244

627 Ricca Rosellini S, Miglio F. Beta-blockers for the prevention of variceal haemorrhage in patients with cirrhosis: an updated meta-analysis of randomized controlled trials. Italian Journal of Gastroenterology. 1991; 23(7):408-415

628 Ricci P, Marigliano C, Cantisani V, Porfiri A, Marcantonio A, Lodise P et al. Ultrasound evaluation of liver fibrosis: preliminary experience with acoustic structure quantification (ASQ) software. La Radiologia Medica. 2013; 118(6):995-1010

629 Rigali VT. Rifaximin: an alternative for the treatment of hepatic encephalopathy. Connecticut Medicine. 2006; 70(8):499-501

630 Riley TR, Smith JP. Preventive care in chronic liver disease. Journal of General Internal Medicine. 1999; 14(11):699-704

631 Ripoll C, Banares R, Rincon D, Catalina MV, Lo Iacono O, Salcedo M et al. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD era. Hepatology. 2005; 42(4):793-801

632 Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R et al. Hepatic Venous Pressure Gradient Predicts Clinical Decompensation in Patients With Compensated Cirrhosis. Gastroenterology. 2007; 133(2):481-488

633 Ripoll C, Lastra P, Rincon D, Catalina V, Baaares R. Comparison of MELD, HVPG, and their changes to predict clinically relevant endpoints in cirrhosis. Scandinavian Journal of Gastroenterology. 2012; 47(2):204-211

634 Ripoll C, Zipprich A, Garcia-Tsao G. Prognostic factors in compensated and decompensated cirrhosis. Current Hepatitis Reports. 2014; 13(3):171-179

635 Ripoll C, Bari K, Garcia-Tsao G. Serum Albumin Can Identify Patients With Compensated Cirrhosis With a Good Prognosis. Journal of Clinical Gastroenterology. 2015; 49(7):613-619

636 Rodriguez-Torres M, Rios-Bedoya CF, Rodriguez-Orengo J, Fernandez-Carbia A, Marxuach-Cuetara AM, Lopez-Torres A et al. Progression to cirrhosis in Latinos with chronic hepatitis C: differences in Puerto Ricans with and without human immunodeficiency virus coinfection and along gender. Journal of Clinical Gastroenterology. 2006; 40(4):358-366

637 Romeiro FG, da Silva Yamashiro F, Americo MF, Cora LA, Silva GF, Miranda JRdA et al. Erythromycin versus neomycin in the treatment of hepatic encephalopathy in cirrhosis: a randomized double-blind study. BMC Gastroenterology. 2013; 13:13

638 Romero R, Nomorosa KM, Birjandi EC, Torres PM, Uy M, Zano F. Meta analysis: Propranolol versus rubber band ligation in primary prophylaxis of esophageal variceal bleeding. Journal of Gastroenterology and Hepatology. 2011; 26(Suppl.5):160

639 Ruelas-Villavicencio AL, Vargas-Vorackova F. In whom, how and how often is surveillance for hepatocellular carcinoma cost-effective? Annals of Hepatology. 2004; 3(4):152-159

640 Ruiz del Arbol L, Achecar L, Serradilla R, Rodriguez-Gandia MA, Rivero M, Garrido E et al. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. Hepatology. 2013; 58(5):1732-1741

641 Runge JH, Bohte A, Verheij J, Terpstra V, Nederveen AJ, Van Nieuwkerk KMJ et al. Comparison of interobserver agreement of magnetic resonance elastography with histopathological staging of liver fibrosis. Abdominal Imaging. 2014; 39(2):283-290

642 Saab S, DeRosa V, Nieto J, Durazo F, Han S, Roth B. Costs and clinical outcomes of primary prophylaxis of variceal bleeding in patients with hepatic cirrhosis: a decision analytic model. American Journal of Gastroenterology. 2003; 98(4):763-770

643 Saab S, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. American Journal of Gastroenterology. 2009; 104(4):993-1002

644 Sacher-Huvelin S, Cales P, Bureau C, Valla D, Vinel JP, Duburque C et al. Screening of esophageal varices by esophageal capsule endoscopy: results of a French multicenter prospective study. Endoscopy. 2015; 47(6):486-492

645 Safdar K, Schiff ER. Alcohol and hepatitis C. Seminars in Liver Disease. 2004; 24(3):305-315

646 Said Y, Salem M, Mouelhi L, Mekki H, Houissa F, Ben Rejeb M et al. Correlation between liver biopsy and fibrotest in the evaluation of hepatic fibrosis in patients with chronic hepatitis C. La Tunisie Medicale. 2010; 88(8):573-578

647 Salami A, Ditah IC, El-Khider FA, Huang MAY. Variceal band ligation versus beta blockers in the primary prophylaxis of variceal bleeding: Has recent evidence shifted our opinion? A meta-analysis of randomized controlled trials. Gastroenterology. 2011; 140(5 Suppl.1):S208-S209

648 Salerno F, Badalamenti S, Lorenzano E, Moser P, Incerti P. Randomized comparative study of hemaccel vs. albumin infusion after total paracentesis in cirrhotic patients with refractory ascites. Hepatology. 1991; 13(4):707-713

649 Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007; 56(9):1310-1318

650 Salerno F, Camma C, Enea M, Rossle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology. 2007; 133(3):825-834

651 Samir AE, Dhyani M, Vij A, Bhan AK, Halpern EF, Mendez-Navarro J et al. Shear-wave elastography for the estimation of liver fibrosis in chronic liver disease: determining accuracy and ideal site for measurement. Radiology. 2015; 274(3):888-896

652 Sandhu BS, Gupta R, Sharma J, Singh J, Murthy NS, Sarin SK. Norfloxacin and cisapride combination decreases the incidence of spontaneous bacterial peritonitis in cirrhotic ascites. Journal of Gastroenterology and Hepatology. 2005; 20(4):599-605

653 Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound in Medicine and Biology. 2003; 29(12):1705-1713

654 Sanford NL, Walsh P, Matis C, Baddeley H, Powell LW. Is ultrasonography useful in the assessment of diffuse parenchymal liver disease? Gastroenterology. 1985; 89(1):186-191

655 Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, Romeo R et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Gastroenterology. 2004; 126(4):1005-1014

656 Santagostino E, Colombo M, Rivi M, Rumi MG, Rocino A, Linari S et al. A 6-month versus a 12-month surveillance for hepatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus. Blood. 2003; 102(1):78-82

657 Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology. 2008; 134(5):1360-1368

658 Saquib N, Saquib J, Ioannidis JPA. Does screening for disease save lives in asymptomatic adults? Systematic review of meta-analyses and randomized trials. International Journal of Epidemiology. 2015; 44(1):264-277

659 Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Variceal bleeding prophylaxis: Variceal banding or propranolol. HPB Surgery. 2000; 11(6):425-428

660 Sasso M, Tengher-Barna I, Ziol M, Miette V, Fournier C, Sandrin L et al. Novel controlled attenuation parameter for noninvasive assessment of steatosis using Fibroscan(): validation in chronic hepatitis C. Journal of Viral Hepatitis. 2012; 19(4):244-253

661 Schepke M. Hepatorenal syndrome: current diagnostic and therapeutic concepts. Nephrology Dialysis Transplantation. 2007; 22(Suppl.8):viii2-viii4

662 Schewior L, Frei U, Neuhaus P, Junge G. Treatment and impact of hepatorenal syndrome for patients on waiting list for liver transplantation. Liver Transplantation. 2008; 14(7 Suppl.1):S219

663 Schmidt LE, Ring-Larsen H. Vasoconstrictor therapy for hepatorenal syndrome in liver cirrhosis. Current Pharmaceutical Design. 2006; 12(35):4637-4647

664 Schneider ARJ, Teuber G, Kriener S, Caspary WF. Noninvasive assessment of liver steatosis, fibrosis and inflammation in chronic hepatitis C virus infection. Liver International. 2005; 25(6):1150-1155

665 Schubert ML, Sanyal AJ, Wong ES. Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis? Gastroenterology. 1991; 101(2):550-552

666 Schwabl P, Bota S, Salzl P, Mandorfer M, Payer BA, Ferlitsch A et al. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. Liver International. 2015; 35(2):381-390

667 Sebastiani G, Castera L, Halfon P, Pol S, Mangia A, Di Marco V et al. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. Alimentary Pharmacology and Therapeutics. 2011; 34(10):1202-1216

668 Sebastiani G, Halfon P, Castera L, Mangia A, Di Marco V, Pirisi M et al. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. Alimentary Pharmacology and Therapeutics. 2012; 35(1):92-104

669 Sebastiani G, Vario A, Guido M, Noventa F, Plebani M, Pistis R et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. Journal of Hepatology. 2006; 44(4):686-693

670 Segarra-Newnham M, Henneman A. Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis in patients without gastrointestinal bleeding. Annals of Pharmacotherapy. 2010; 44(12):1946-1954

671 Sen S, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R et al. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transplantation. 2004; 10(9):1109-1119

672 Shah HA, Rauf J, Azam Z, Abid S, Hamid S, Jafri SM et al. Randomized controlled trial of carvedilol vs variceal band ligation in the primary prophylaxis of variceal haemorrhage. Hepatology. 2012; 56(Suppl.1):272A

673 Sharma BC. Adding rifaximin to lactulose increased reversal and decreased mortality in hepatic encephalopathy. Annals of Internal Medicine. 2013; 159(8):JC8

674 Sharma P, Dhawan S, Bansal R, Tyagi P, Bansal N, Singla V et al. The usefulness of transient elastography by FibroScan for the evaluation of liver fibrosis. Indian Journal of Gastroenterology. 2014; 33(5):445-451

675 Sheen I-S, Liaw YF, Lin DY, Chu CM. Acute exacerbations in chronic hepatitis C: A clinicopathological and prognostic study. Journal of Hepatology. 1996; 24(5):525-531

676 Shehab H, Elattar I, Elbaz T, Mohey M, Esmat G. CUFA algorithm: assessment of liver fibrosis using routine laboratory data. Journal of Viral Hepatitis. 2014; 21(12):956-964

677 Shen JH, Li YL, Li D, Wang NN, Jing L, Huang YH. The rs738409 (I148M) variant of the PNPLA3 gene and cirrhosis: a meta-analysis. Journal of Lipid Research. 2015; 56(1):167-175

678 Shen L, Li JQ, Zeng MD, Lu LG, Fan ST, Bao H. Correlation between ultrasonographic and pathologic diagnosis of liver fibrosis due to chronic virus hepatitis. World Journal of Gastroenterology. 2006; 12(8):1292-1295

679 Sherman M. Surveillance for hepatocellular carcinoma. Best Practice and Research Clinical Gastroenterology. 2014; 28(5):783-793

680 Sherman M, Lee C, Flowers M. A screening program to detect hepatocellular carcinoma. Hepatology. 1991; 14(4 Pt.2):180A

681 Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. American Journal of Gastroenterology. 1998; 93(1):44-48

682 Shoreibah MG, Bloomer JR, McGuire B, Massoud OI. Surveillance for hepatocellular carcinoma: Evidence, guidelines and utilization. American Journal of the Medical Sciences. 2014; 347(5):415-419

683 Sigal SH, Stanca CM, Fernandez J, Arroyo V, Navasa M. Restricted use of albumin for spontaneous bacterial peritonitis. Gut. 2007; 56(4):597-599

684 Silveira MG, Suzuki A, Lindor KD. Surveillance for hepatocellular carcinoma in patients with primary biliary cirrhosis. Hepatology. 2008; 48(4):1149-1156

685 Simmons F, Goldstein H, Boyle JD. A controlled clinical trial of lactulose in hepatic encephalopathy. Gastroenterology. 1970; 59(6):827-832

686 Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Medicine. 2014; 11(4):e1001624

687 Singal AG, Li X, Tiro J, Kandunoori P, Adams-Huet B, Nehra MS et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. American Journal of Medicine. 2015; 128(1):90-97

688 Singh N, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Annals of Internal Medicine. 1995; 122(8):595-598

689 Singh S, Fujii LL, Murad MH, Wang Z, Asrani SK, Ehman RL et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2013; 11(12):1573-1579

690 Singh S, Venkatesh SK, Wang Z, Miller FH, Motosugi U, Low RN et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. Clinical Gastroenterology and Hepatology. 2015; 13(3):440-451

691 Singh V, Singh A, Singh B, Vijayvergiya R, Sharma N, Ghai A et al. Midodrine and clonidine in patients with cirrhosis and refractory or recurrent ascites: A randomized pilot Study. American Journal of Gastroenterology. 2013; 108(4):560-567

692 Singla A, Hart JL, Li Y, Tseng JF, Shah SA. Hospitalization for complications of cirrhosis: does volume matter? Journal of Gastrointestinal Surgery. 2011; 15(2):330-335

693 Skagen CL, Said A. Vasoconstrictor use in liver transplantation: is there evidence for rational use? Minerva Gastroenterologica e Dietologica. 2010; 56(3):279-296

694 Skog OJ. The risk function for liver cirrhosis from lifetime alcohol consumption. Journal of Studies on Alcohol. 1984; 45(3):199-208

695 Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. Cochrane Database of Systematic Reviews. 2002;(2):CD002907. DOI:10.1002/14651858.CD002907

696 Soares-Weiser K, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. Scandinavian Journal of Gastroenterology. 2003; 38(2):193-200

697 Sola-Vera J, Minana J, Ricart E, Planella M, Gonzalez B, Torras X et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. Hepatology. 2003; 37(5):1147-1153

698 Solmi L, Primerano AM, Gandolfi L. Ultrasound follow-up of patients at risk for hepatocellular carcinoma: results of a prospective study on 360 cases. American Journal of Gastroenterology. 1996; 91(6):1189-1194

699 Somsouk M, Guy J, Biggins SW, Vittinghoff E, Kohn MA, Inadomi JM. Ascites improves upon plus serum sodium model for end-stage liver disease (MELD) for predicting mortality in patients with advanced liver disease. Alimentary Pharmacology and Therapeutics. 2009; 30(7):741-748

700 Sorensen TI. Alcohol and liver injury: dose-related or permissive effect? Liver. 1989; 9(4):189-197

701 Sorensen TI, Orholm M, Bentsen KD, Hoybye G, Eghoje K, Christoffersen P. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. The Lancet. 1984; 2(8397):241-244

702 Sorensen TIA. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: A randomized multicenter trial. Hepatology. 1991; 14(6):1016-1024

703 Soriano G, Guarner C, Tomas A, Villanueva C, Torras X, Gonzalez D et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology. 1992; 103(4):1267-1272

704 Sort P, Muelas M, Isava A, Llao J, Porta F, Puig I et al. Diagnostic accuracy of abdominal ultrasound in the screening of esophageal varices in patients with cirrhosis. European Journal of Gastroenterology and Hepatology. 2014; 26(12):1335-1341

705 Spiegel B, Targownik L, Dulai GS, Karsan HA, Gralnek IM, Kowdley K et al. Endoscopic screening for esophageal varices in cirrhosis: Is it ever cost effective? Hepatology. 2003; 37(2):366-377

706 Sporea I, Sirli R, Popescu A, Danila M. Acoustic Radiation Force Impulse (ARFI)--a new modality for the evaluation of liver fibrosis. Medical Ultrasonography. 2010; 12(1):26-31

707 Stauber RE, Spindelboeck W, Haas J, Putz-Bankuti C, Stadlbauer V, Lackner C et al. Human nonmercaptalbumin-2: A novel prognostic marker in chronic liver failure. Therapeutic Apheresis and Dialysis. 2014; 18(1):74-78

708 Stauch S, Rosch W. Effects of L-ornithine-L-aspartate granulate on hyperammonemia in cirrhotic patients with hepatic encephalopathy (HE). A placebo-controlled double-blind study. Zeitschrift Fur Gastroenterologie. 1992; 30(4):300-301

709 Steadman R, Myers RP, Leggett L, Lorenzetti D, Noseworthy T, Rose S et al. A health technology assessment of transient elastography in adult liver disease. Canadian Journal of Gastroenterology. 2013; 27(3):149-158

710 Sterling R-K, Shiffman M-L, Schubert M-L. Flumazenil for hepatic coma: the elusive wake-up call? Gastroenterology. 1994; 107(4):1204-1205

711 Stevenson M, Lloyd-Jones M, Morgan MY, Wong R. Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation. Health Technology Assessment. 2012; 16(4):1-174

712 Stokes CS, Krawczyk M, Reichel C, Lammert F, Grunhage F. Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. European Journal of Clinical Investigation. 2014; 44(2):176-183

713 Stravitz RT, Heuman DM, Chand N, Sterling RK, Shiffman ML, Luketic V et al. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. American Journal of Medicine. 2008; 121(2):119-126

714 Su LN, Guo SL, Li BX, Yang P. Diagnostic value of magnetic resonance elastography for detecting and staging of hepatic fibrosis: a meta-analysis. Clinical Radiology. 2014; 69(12):e545-e552

715 Sugimoto K, Shiraishi J, Moriyasu F, Ichimura S, Metoki R, Doi K. Analysis of intrahepatic vascular morphological changes of chronic liver disease for assessment of liver fibrosis stages by micro-flow imaging with contrast-enhanced ultrasound: preliminary experience. European Radiology. 2010; 20(11):2749-2757

716 Sussman D, Barkin JS. Band ligation versus propanolol and isosorbide mononitrate for primary prophylaxis of variceal bleeding. American Journal of Gastroenterology. 2003; 98(8):1887-1889

717 Takahashi H, Ono N, Eguchi Y, Eguchi T, Kitajima Y, Kawaguchi Y et al. Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: a pilot study. Liver International. 2010; 30(4):538-545

718 Takase S, Tsutsumi M, Kawahara H, Takada N, Takada A. The alcohol-altered liver membrane antibody and hepatitis C virus infection in the progression of alcoholic liver disease. Hepatology. 1993; 17(1):9-13

719 Tanaka H, Nouso K, Kobashi H, Kobayashi Y, Nakamura S, Miyake Y et al. Surveillance of hepatocellular carcinoma in patients with hepatitis C virus infection may improve patient survival. Liver International. 2006; 26(5):543-551

720 Tandon P, Bain VG, Tsuyuki RT, Klarenbach S. Systematic review: renal and other clinically relevant outcomes in hepatorenal syndrome trials. Alimentary Pharmacology and Therapeutics. 2007; 25(9):1017-1028

721 Tatsumi C, Kudo M, Ueshima K, Kitai S, Takahashi S, Inoue T et al. Noninvasive evaluation of hepatic fibrosis using serum fibrotic markers, transient elastography (FibroScan) and real-time tissue elastography. Intervirology. 2008; 51(Suppl.1):27-33

722 Taura N, Hamasaki K, Nakao K, Ichikawa T, Nishimura D, Goto T et al. Clinical benefits of hepatocellular carcinoma surveillance: a single-center, hospital-based study. Oncology Reports. 2005; 14(4):999-1003

723 Tawada A, Maruyama H, Kamezaki H, Shimada T, Ishibashi H, Takahashi M et al. Magnitude of contrast-enhanced ultrasonography as a noninvasive predictor for hepatic fibrosis: Comparison with liver stiffness measurement and serum-based models. Hepatology International. 2013; 7(2):749-757

724 Tellez-Avila F, Sifuentes-Osornio J, Barbero-Becerra V, Franco-Guzman A, Ruiz-Cordero R, Alfaro-Lara R et al. Primary prophylaxis with ciprofloxacin in cirrhotic patients with ascites: a randomized, double blind study. Annals of Hepatology. 2013; 13(1):65-74

725 Teran JC, Imperiale TF, Mullen K, Tavill AS, McCullough AJ. Primary prophylaxis of variceal bleeding in cirrhosis:a cost effectiveness analysis. Gastroenterology. 1997; 112(2):473-482

726 Terg R, Cobas S, Fassio E, Landeira G, Rios B, Vasen W et al. Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis: results of a multicenter, randomized study. Journal of Hepatology. 2000; 33(4):564-569

727 Testa R, Eftimiadi C, Sukkar GS, de Leo C, Rovida S, Schito GC et al. A non-absorbable rifamycin for treatment of hepatic encephalopathy. Drugs Under Experimental and Clinical Research. 1985; 11(6):387-392

728 Testa R, Valente U, Risso D, Caglieris S, Giannini E, Fasoli A et al. Can the MEGX test and serum bile acids improve the prognostic ability of Child - Pugh's score in liver cirrhosis? European Journal of Gastroenterology and Hepatology. 1999; 11(5):559-563

729 Thein HH, Yi Q, Dore GJ, Krahn M. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008; 48(2):418-431

730 Thein HH, Yi Q, Dore GJ, Krahn M. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008; 22(15):1979-1991

731 Thevenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. Journal of Hepatology. 2015; 62(4):822-830

732 Thompson-Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. Health Technology Assessment. 2007; 11(34):1-206

733 Thompson-Coon J, Rogers G, Hewson P, Wright D, Anderson R, Jackson S et al. Surveillance of cirrhosis for hepatocellular carcinoma: a cost utility analysis. British Journal of Cancer. 2008; 98(7):1166-1175

734 Tomiyama Y, Takenaka K, Kodama T, Kawanaka M, Sasaki K, Nishina S et al. Risk factors for survival and the development of hepatocellular carcinoma in patients with primary biliary cirrhosis. Internal Medicine. 2013; 52(14):1553-1559

735 Toshima T, Shirabe K, Ikegami T, Yoshizumi T, Kuno A, Togayachi A et al. A novel serum marker, glycosylated Wisteria floribunda agglutinin-positive Mac-2 binding protein (WFA(+)-M2BP), for assessing liver fibrosis. Journal of Gastroenterology. 2015; 50(1):76-84

736 Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y et al. Impact of surveillance on survival of patients with initial hepatocellular carcinoma: a study from Japan. Clinical Gastroenterology and Hepatology. 2006; 4(9):1170-1176

737 Trepo E, Potthoff A, Pradat P, Bakshi R, Young B, Lagier R et al. Role of a cirrhosis risk score for the early prediction of fibrosis progression in hepatitis C patients with minimal liver disease. Journal of Hepatology. 2011; 55(1):38-44

738 Trevisani F, De Notariis S, Rapaccini G, Farinati F, Benvegnu L, Zoli M et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). American Journal of Gastroenterology. 2002; 97(3):734-744

739 Trevisani F, Magini G, Santi V, Morselli-Labate AM, Cantarini MC, Di Nolfo MA et al. Impact of etiology of cirrhosis on the survival of patients diagnosed with hepatocellular carcinoma during surveillance. American Journal of Gastroenterology. 2007; 102(5):1022-1031

740 Trey C, Brown H, Goransky L, McDermott WVJ. Lactulose treatment of hepatic encephalopathy: effects on carbohydrate metabolism and colonic hydrogen ion concentration. Surgical Forum. 1970; 21:355-356

741 Trinchet JC. Screening for hepatocellular carcinoma (HCC) in patients with cirrhosis. a multicenter randomized trial comparing two periodicities of ultrasonoraphic (US) screening, 3 months vs 6 months. Journal of Hepatology. 2007; 46(4 Suppl.1):S56

742 Tripathi D, Graham C, Hayes P. Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: a meta-analysis. European Journal of Gastroenterology and Hepatology. 2007; 19(10):835-845

743 Trivedi PJ, Lammers WJ, van Buuren HR, Pares A, Floreani A, Janssen HL et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut. 2015; [E publication]. DOI:doi:10.1136/gutjnl-2014-308351

744 Tsochatzis E, Bruno S, Isgro G, Hall A, Theocharidou E, Manousou P et al. Collagen proportionate area is superior to other histological methods for sub-classifying cirrhosis and determining prognosis. Journal of Hepatology. 2014; 60(5):948-954

745 Tsochatzis E, Crossan C, Longworth L, Gurusamy K, Rodriguez-Peralvarez M, Mantzoukis K et al. Cost-effectiveness of non-invasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis c: Systematic review and economic evaluation. Journal of Hepatology. 2014; 60(1 Suppl.1):S33

746 Tuma P, Jarrin I, Del Amo J, Vispo E, Medrano J, Martin-Carbonero L et al. Survival of HIV-infected patients with compensated liver cirrhosis. AIDS. 2010; 24(5):745-753

747 Tuncer I, Topcu N, Durmus A, Turkdogan MK. Oral ciprofloxacin versus intravenous cefotaxime and ceftriaxone in the treatment of spontaneous bacterial peritonitis. Hepato-Gastroenterology. Turkey 2003; 50(53):1426-1430

748 Turban S, Thuluvath PJ, Atta MG. Hepatorenal syndrome. World Journal of Gastroenterology. 2007; 13(30):4046-4055

749 Tuyns AJ, Pequignot G. Greater risk of ascitic cirrhosis in females in relation to alcohol consumption. International Journal of Epidemiology. 1984; 13(1):53-57

750 Urbain D, Botembe N, Muls V, Makhoul E, Ham HR. Thallium-201 per rectal scintigraphy improves prognostic evaluation in alcoholic liver cirrhosis of low and mid severity. American Journal of Gastroenterology. 1995; 90(9):1461-1464

751 Uribe M, Lewis H, Moreno J. Successful use of lactose enemas in acute portal systemic encephalopathy (PSE). A double blind controlled trial. Gastroenterology. 1980; 79(5 II):1061

752 Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007; 46(1):32-36

753 Van Dam GM, Gips CH, Reisman Y, Maas KW, Purmer IM, Huizenga JR et al. Major clinical events, signs and severity assessment scores related to actual survival in patients who died from primary biliary cirrhosis. A long-term historical cohort study. Hepato-Gastroenterology. 1999; 46(25):108-115

754 Van der Rijt CC, Schalm SW, Meulstee J, Stijnen T. Flumazenil therapy for hepatic encephalopathy. A double-blind cross over study. Gastroenterologie Clinique Et Biologique. 1995; 19(6-7):572-580

755 Van Vlierberghe H, Colle I, Henrion J, Michielsen P, Delwaide J, Reynaert H et al. The HepCar registry: report on a one-year registration program of hepatocellular carcinoma (HCC) in Belgium. What is daily practice in HCC? Acta Gastroenterologica Belgica. 2005; 68(4):403-411

756 Venkatesh SK, Yin M, Takahashi N, Glockner JF, Talwalkar JA, Ehman RL. Non-invasive detection of liver fibrosis: MR imaging features vs. MR elastography. Abdominal Imaging. 2015; 40(4):766-775

757 Venturini I, Ferrieri A, Farina F, Cosenza F, Avallone R, Corsi L et al. Evaluation of rifaximin, placebo and lactulose in reducing the levels of benzodiazepine-like compounds in patients with liver cirrhosis: a pilot study. Drugs Under Experimental and Clinical Research. 2005; 31(4):161-168

758 Verbaan H, Widell A, Bondeson L, Andersson K, Eriksson S. Factors associated with cirrhosis development in chronic hepatitis C patients from an area of low prevalence. Journal of Viral Hepatitis. 1998; 5(1):43-51

759 Vergniol J, Boursier J, Coutzac C, Bertrais S, Foucher J, Angel C et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology. 2014; 60(1):65-76

760 Vergniol J, Foucher J, Terrebonne E, Bernard PH, Le Bail B, Merrouche W et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology. 2011; 140(7):1970-1973

761 Verma S, Ajudia K, Mendler M, Redeker A. Prevalence of septic events, type 1 hepatorenal syndrome, and mortality in severe alcoholic hepatitis and utility of discriminant function and MELD score in predicting these adverse events. Digestive Diseases and Sciences. 2006; 51(9):1637-1643

762 Verveer C, Zondervan PE, ten Kate FJW, Hansen BE, Janssen HL, de Knegt R. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. Liver International. 2012; 32(4):622-628

763 Villalvazo YR, McDanel J, Sanchez AJ, Vaughn-Sarrazin M, Rahman H, David K. Effect of rural residence on surveillance for hepatocellular carcinoma in VA primary care patients with cirrhosis. Gastroenterology. 2015; 148(4 Suppl.1):S1068-S1069

764 Vlachogiannakos J, Montalto P, Burroughs A. Prevention of first upper gastrointestinal bleeding in cirrhosis. Minerva Gastroenterologica e Dietologica. 2000; 46(2):87-98

765 Wahib AA, El-Deen Salem MN, Ahmed MA, El-Dessouky YMM, El-Tiby DM, El-Mola K et al. Evaluation of rifaximin in management of hepatic encephalopathy. Journal of the Egyptian Society of Parasitology. 2014; 44(3):677-685

766 Wahl K, Rosenberg W, Vaske B, Manns M, Schulze-Osthoff K, Bahr M et al. Biopsy-controlled liver fibrosis staging using the enhanced liver fibrosis (ELF) score compared to transient elastography. PloS One. 2012; 7(12):e51906

767 Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003; 38(2):518-526

768 Wang C, Zhao C, Le AK, Nguyen L, Trinh HN, Li J et al. Poor adherence and poor persistency of consistent adherence to AASLD guidelines for hepatocellular carcinoma (HCC) screening and surveillance in chronic hepatitis B (CHB) patients at both university and community clinics: A multicenter U.S. cohort study. Gastroenterology. 2015; 148(4 Suppl.1):S992-S993

769 Wang HM, Hung CH, Lu SN, Chen CH, Lee CM, Hu TH et al. Liver stiffness measurement as an alternative to fibrotic stage in risk assessment of hepatocellular carcinoma incidence for chronic hepatitis C patients. Liver International. 2013; 33(5):756-761

770 Wang JH, Chang KC, Hung CH, Chen CH, Lu SN. Hepatocellular carcinoma surveillance with 4 versus 12 months interval for patients with chronic viral hepatitis - a randomized community study. Hepatology. 2011; 54(4 Suppl.):1378A

771 Wang JH, Chang KC, Kee KM, Chen PF, Yen YH, Tseng PL et al. Hepatocellular carcinoma surveillance at 4- vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. American Journal of Gastroenterology. 2013; 108(3):416-424

772 Wang JH, Changchien CS, Hung CH, Eng HL, Tung WC, Kee KM et al. FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis. Journal of Gastroenterology. 2009; 44(5):439-446

773 Wang MH, Palmeri ML, Rotemberg VM, Rouze NC, Nightingale KR. Improving the robustness of time-of-flight based shear wave speed reconstruction methods using RANSAC in human liver in vivo. Ultrasound in Medicine and Biology. 2010; 36(5):802-813

774 Wang SB, Wang JH, Chen J, Giri RK, Chen MH. Natural history of liver cirrhosis in south China based on a large cohort study in one center: a follow-up study for up to 5 years in 920 patients. Chinese Medical Journal. 2012; 125(12):2157-2162

775 Wang Y-W, Huo T, Yang Y-Y, Hou MC, Lee PC, Lin HC et al. Correlation and comparison of the model for end-stage liver disease, portal pressure, and serum sodium for outcome prediction in patients with liver cirrhosis. Journal of Clinical Gastroenterology. 2007; 41(7):706-712

776 Wang Y, Ganger DR, Levitsky J, Sternick LA, McCarthy RJ, Chen ZE et al. Assessment of chronic hepatitis and fibrosis: comparison of MR elastography and diffusion-weighted imaging. American Journal of Roentgenology. 2011; 196(3):553-561

777 Weinmann A, Sattler T, Unold HP, Grambihler A, Teufel A, Koch S et al. Predictive scores in primary biliary cirrhosis: a retrospective single center analysis of 204 patients. Journal of Clinical Gastroenterology. 2015; 49(5):438-447

778 Whitfield JB, Rahman K, Haber PS, Day CP, Masson S, Daly AK et al. Brief report: genetics of alcoholic cirrhosis-GenomALC multinational study. Alcoholism: Clinical and Experimental Research. 2015; 39(5):836-842

779 Whittman D, Boyer T, Sanyal A. Terlipressin and albumin significantly improved renal function in patients with type I hepatorenal syndrome (HRS) enrolled in a randomized , double-blind, placebo controlled trial. Journal of the American Society of Nephrology. 2007; 18(Abstracts Issue):818A

780 Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A et al. Addressing liver disease in the UK: A blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. The Lancet. 2014; 384(9958):1953-1997

781 Williams R, James OF, Warnes TW, Morgan MY. Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: a double-blind, randomized, dose-finding multi-centre study. European Journal of Gastroenterology and Hepatology. 2000; 12(2):203-208

782 Wong F, Blendis L. New challenge of hepatorenal syndrome: Prevention and treatment. Hepatology. 2001; 34(6):1242-1251

783 Wong F, Pappas SC, Boyer T, Sanyal AJ, Jamil K. Systemic inflammatory response syndrome (SIRS) is a major determinant of treatment response to terlipressin for hepatorenal syndrome type 1 (HRS-1). Journal of Hepatology. 2015; 62(Suppl.2):S235-S236

784 Wong F. Drug insight: the role of albumin in the management of chronic liver disease. Nature Clinical Practice Gastroenterology and Hepatology. 2007; 4(1):43-51

785 Wong GL-H, Chan HLY, Wong CK-Y, Leung C, Chan CY, Ho PP-L et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. Journal of Hepatology. 2014; 60(2):339-345

786 Wong GL-H, Vergniol J, Lo P, Wai-Sun Wong V, Foucher J, Le Bail B et al. Non-invasive assessment of liver fibrosis with transient elastography (FibroScan): applying the cut-offs of M probe to XL probe. Annals of Hepatology. 2013; 12(4):570-580

787 Wong GL-H, Wong VW-S, Choi PC, Chan AWH, Chum RH-L, Chan HK-W et al. Assessment of fibrosis by transient elastography compared with liver biopsy and morphometry in chronic liver diseases. Clinical Gastroenterology and Hepatology. 2008; 6(9):1027-1035

788 Wong N, Haydon A, Kemp W, Wijeratne P, Roberts S. Improved survival trend of patients with hepatocellular carcinoma at an Australian tertiary hospital between 1995-2009. Internal Medicine Journal. 2013; 43(2):197-203

789 Wu GC, Zhou WP, Zhao YR, Guo SH, Wang ZY, Zou SB et al. The natural history of chronic hepatitis B: a retrospective study. Hepatobiliary and Pancreatic Diseases International. 2003; 2(4):566-570

790 Xie Y-D, Feng B, Gao Y, Wei L. Characteristics of alcoholic liver disease and predictive factors for mortality of patients with alcoholic cirrhosis. Hepatobiliary and Pancreatic Diseases International. 2013; 12(6):594-601

791 Xiong J, Wang J, Huang J, Sun W, Wang J, Chen D. Non-alcoholic steatohepatitis-related liver cirrhosis is increasing in China: A ten-year retrospective study. Clinics. 2015; 70(8):563-568

792 Xue T, Qiu J-H, Qiao L. Rifaximin treatment in hepatic encephalopathy [3]. New England Journal of Medicine. 2010; 362(25):2424

793 Yakoob R, Al Bozom I, Thandassery RB, Rahman MOA, Derbala MF, Al Mohannadi MJ et al. Noninvasive biomarkers fibrotest and actitest versus liver biopsy in chronic hepatitis C patients: The middle east experience. Annals of Gastroenterology. 2015; 28(2):265-270

794 Yang B, Zhang B, Xu Y, Wang W, Shen Y, Zhang A et al. Prospective study of early detection for primary liver cancer. Journal of Cancer Research and Clinical Oncology. 1997; 123(6):357-360

795 Yang JD, Harmsen WS, Slettedahl SW, Chaiteerakij R, Enders FT, Therneau TM et al. Factors that affect risk for hepatocellular carcinoma and effects of surveillance. Clinical Gastroenterology and Hepatology. 2011; 9(7):617-623

796 Yang K, Yang Q. Octreotide combined with alprostadil for treatment of cirrhosis with hepatorenal syndrome. World Chinese Journal of Digestology. 2014;(20):2942-2945

797 Yang W-B, Chen E-Q, Bi H-X, Bai L, Chen X-B, Feng P et al. Different models in predicting the short-term prognosis of patients with Hepatitis B virus-related acute-on-chronic liver failure. Annals of Hepatology. 2012; 11(3):311-319

798 Yang YZ, Dan ZL, Lin NZ, Lin M, Liang KH. Efficacy of terlipressin in treatment of liver cirrhosis with hepatorenal syndrome. Journal of Internal Intensive Medicine. 2001; 7(3):123-125

799 Yeh YP, Hu TH, Cho PY, Chen HH, Yen AM, Chen SL et al. Evaluation of abdominal ultrasonography mass screening for hepatocellular carcinoma in Taiwan. Hepatology. 2014; 59(5):1840-1849

800 Yilmaz Y, Senates E, Yesil A, Ergelen R, Colak Y. Not only type 2 diabetes but also prediabetes is associated with portal inflammation and fibrosis in patients with non-alcoholic fatty liver disease. Journal of Diabetes and Its Complications. 2014; 28(3):328-331

801 Yoneda M, Thomas E, Sclair SN, Grant TT, Schiff ER. Supersonic shear imaging and transient elastography with the XL probe accurately detect fibrosis in overweight or obese patients with chronic liver disease. Clinical Gastroenterology and Hepatology. 2015; 13(8):1502-1509

802 Yoon KT, Lim SM, Park JY, Kim DY, Ahn SH, Han KH et al. Liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography and effect of necroinflammation. Digestive Diseases and Sciences. 2012; 57(6):1682-1691

803 Younsi ME, Cadranel JF, Pidoux B, Zylberberg P, Valla D, Opolon P. Immediate effects of flumazenil in the clinical and encephalographic stage of hepatic encephalopathy in cirrhotic patients. Results of a controlled double blind trial. Gastroenterologie Clinique Et Biologique. 1991; 15(2):A216

804 Yu C, Wang L, Gong Z. Efficacy and safety of terlipressin on hepatorenal syndrome: A meta-analysis. Hepatology International. 2013; 7(Suppl.1):S504

805 Yu MW, Hsu FC, Sheen IS, Chu CM, Lin DY, Chen CJ et al. Prospective study of hepatocellular carcinoma and liver cirrhosis in asymptomatic chronic hepatitis B virus carriers. American Journal of Epidemiology. 1997; 145(11):1039-1047

806 Yu M-W, Shih W-L, Lin C-L, Liu C-J, Jian J-W, Tsai K-S et al. Body-mass index and progression of hepatitis B: A population-based cohort study in men. Journal of Clinical Oncology. 2008; 26(34):5576-5582

807 Yuan W, Li J, Xu L, Zhang M, Lu Z, Feng S et al. L-ornithine-L-aspartate for hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2008;(3):CD007344. DOI:10.1002/14651858.CD007344

808 Yuen MF, Lai CL. Screening for hepatocellular carcinoma: survival benefit and cost-effectiveness. Annals of Oncology. 2003; 14(10):1463-1467

809 Zapata E, Zubiaurre L, Castiella A, Salvador P, Garcia-Bengoechea M, Esandi P et al. Are hepatocellular carcinoma surveillance programs effective at improving the therapeutic options. Revista Espanola De Enfermedades Digestivas. 2010; 102(8):484-488

810 Zhang B, Yang B. Preliminary results of a randomized controlled trial to assess the effectiveness of screening for primary liver cancer (PLC). Journal of Clinical Epidemiology. 1997; 50(Suppl.1):12S

811 Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. Journal of Cancer Research and Clinical Oncology. 2004; 130(7):417-422

812 Zhang DK, Chen M, Liu Y, Wang RF, Liu LP, Li M. Acoustic radiation force impulse elastography for non-invasive assessment of disease stage in patients with primary biliary cirrhosis: A preliminary study. Clinical Radiology. 2014; 69(8):836-840

813 Zhang Q-B, Chen Y-T, Lian G-D, Qian C-C, Chen S-J, Huang K-H. A combination of models for end-stage liver disease and cirrhosis-related complications to predict the prognosis of liver cirrhosis. Clinics and Research in Hepatology and Gastroenterology. 2012; 36(6):583-591

814 Zhang ZF, Yang N, Zhao G, Liu LN, Wang YD, Duan Z. Meta-analysis of terlipressin in treatment of hepatorenal syndrome: an update. National Medical Journal of China. 2009; 89(28):1970-1974

815 Zheng M, Shi K, Fan Y, Li H, Ye C, Chen Q et al. A Model to Determine 3-Month Mortality Risk in Patients With Acute-on-Chronic Hepatitis B Liver Failure. Clinical Gastroenterology and Hepatology. 2011; 9(4):351

816 Zheng RQ, Wang QH, Lu MD, Xie SB, Ren J, Su ZZ et al. Liver fibrosis in chronic viral hepatitis: an ultrasonographic study. World Journal of Gastroenterology. 2003; 9(11):2484-2489

817 Zhu CW, Wang JY, Liu TS. Flumazenil in the treatment of cirrhotic patients with hepatic encephalopathy: A randomized doubled-blind clinical trial. Chinese Journal of Digestion. 1998; 18(6):355-358

818 Zhu GQ, Shi KQ, Huang S, Wang LR, Lin YQ, Huang GQ et al. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. Alimentary Pharmacology and Therapeutics. 2015; 41(7):624-635

819 Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology. 2005; 41(1):48-54

820 Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger M. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver International. 2012; 32(9):1407-1414

821 Zipprich A, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T et al. Incorporating indocyanin green clearance into the Model for End Stage Liver Disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. Gut. 2010; 59(7):963-968

822 Zoli M, Cordiani MR, Marchesini G, Abbati S, Bianchi G, Pisi E. Ultrasonographic follow-up of liver cirrhosis. Journal of Clinical Ultrasound. 1990; 18(2):91-96