NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant

A donor lung for transplant is usually stored in a cold liquid after it has been removed to preserve lung function for a limited period of time, until the lung can be transplanted.

In this procedure, a machine is used to deliver oxygenated solution to the donor lung and keep it at normal body temperature. The aim is to reduce damage to the donor lung, increase the time the lung can be stored, and allow assessment of how well the lung works before it is transplanted. This procedure may also allow more donor lungs to be used for transplant.

Contents

Abbreviations

Word or phrase	Abbreviation
Confidence interval	CI
Donors after circulatory death	DCD
Donors after brain death	DBD
Extended criteria donors	ECD
Ex-vivo lung perfusion	EVLP
Weighted mean difference	WMD
Primary graft dysfunction	PGD
Risk ratio	RR
Odds ratio	OR
Hazard ratio	HR
Intensive care unit	ICU
Not reported	NR
Forced expiratory volume	FEV
Forced vital capacity	FVC
Extracorporeal membrane oxygenation	ECMO

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2020 and updated in January 2021.

Procedure name

- Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant

Professional societies

- The British Heart and Lung Transplant Association
- United Kingdom Transplant Coordinators Society
- Intensive Care Society
- NHS Blood and Transplant (NHSBT) Cardiothoracic Transplant Advisory Group
- British Transplantation Society
- Society of Clinical Perfusion Scientists (SCPS)
- British Thoracic Society
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- Royal College of Surgeons.

Description of the procedure

Indications and current treatment

Lung transplant is usually done in patients with non-malignant advanced or end-stage pulmonary diseases (such as severe pulmonary fibrosis, cystic fibrosis, pulmonary hypertension and obliterative bronchiolitis) that is minimally responsive or unresponsive to treatment and who have a life expectancy of less than a year. This improves patients' quality of life and prolongs survival.

On average, 20% of potential deceased donor lungs in the UK are used for transplant. The rest are considered unsuitable, usually because of complications associated with attempts to save the donor or injury which happens in association with death. Limited availability of deceased donor lungs that meet standard criteria for transplant results in up to 30% of patients clinically deteriorating and dying while waiting for a lung transplant.

Standard lung transplant protocol involves cold preservation to maintain the donor lungs. Various other strategies are used to increase the available pool of deceased donor lungs and these include brain death donor lungs from extended criteria donors (ECDs) and donors after circulatory death (DCDs). Living donor lobal/lung transplant (LLDs) is another option.

What the procedure involves

Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion, EVLP) is a technique of lung preservation that may allow donor lungs to be preserved for longer in better physiologic conditions, and may allow marginal donor lungs or pulmonary grafts which are working poorly to be improved and reconditioned so that they can be used in lung transplant. It therefore may allow more donor lungs to be used for transplant.

Ex-situ machine perfusion for extracorporeal preservation of lungs is done once the lungs have been removed from the donor after cold pulmonary flush using surgical techniques. An adequate donor left atrial cuff and pulmonary artery are preserved to allow anastomosis to the recipients' organs.

After being transferred in cold solution being ischemic for a period of time, the lungs are placed in a specially designed organ chamber and connected to a modified heart-lung bypass machine, a ventilator and filtration or EVLP system A specialised nutrient solution(perfusate) is pumped from the filtration or EVLP system through a perfusion circuit (gas exchange membrane, heat exchanger and leukocyte filter) under optimal colloid pressure through the pulmonary artery to the lungs. Pulmonary effluent from the pulmonary veins drains back to the EVLP system and is recirculated. Perfusion flow is then gradually increased, pulmonary artery pressure is carefully monitored, and protective controlled mechanical lung ventilation with low tidal volume and positive end expiratory pressure is started. The lungs are gradually rewarmed to body temperature while reaching a targeted flow. EVLP is possible for a number of hours after removal from the donor. During this period, the lungs can be assessed and if necessary, treated to remove unwanted fluid, and to re-expand areas of lung that have collapsed (atelectatic areas). If EVLP treated lungs recover well enough, they may be considered suitable for recipient transplant in the conventional way.

Ex-situ machine perfusion can be done using different devices or machines and protocols. The perfusate composition, perfusion and ventilation settings (target flow, temperature, pressure) may vary.

Efficacy summary

Overall survival

In a systematic review and meta-analysis of 13 studies comparing patients transplanted with ex-vivo lung perfusion (EVLP) treated lungs (n=407) compared with standard protocol or cold preservation lungs (n=1,765), pooled survival analysis of all included studies showed no statistically significant difference in mid to long-term survival between the groups (hazard ratio [HR] 1.00; 95% confidence interval [CI] 0.79 to 1.27, p=0.981). Pooled analysis of 12 cohort studies also showed no statistically significant difference in survival for EVLP compared with standard protocol lung transplant recipients (HR 1.16; 95% CI: 0.89 to 1.51; p=0.276). Survival at 12, 24, and 36 months for the EVLP group was 84%, 79%, and 74%, respectively. Survival at 12, 24, and 36 months for the standard protocol or cold preservation group was 85%, 79%, and 73%, respectively.[1]

In a meta-analysis of 20 studies comparing efficacy of EVLP of donor lungs (in 586 recipients) with standard cold preservation for lung transplant (in 1,985 recipients), pooled analysis showed that there was no statistically significant difference in survival rate at 30 days (15 studies, risk ratio [RR] 1.69, 95% CI 0.99 to 2.87; I^2=55%, p=0.008), 90 days (10 studies, RR 1.46, 95% CI 0.93 to 2.30; I^2=0%, p=0.541),1 year after lung transplant (15 studies, RR 0.98, 95% CI 0.77 to 1.24; I^2=0%, p=0.535), and accumulative survival after lung transplant (14 studies, RR 1.25, 95% CI 1.0 to 1.56; I^2=0%, p=0.912) between the groups.[2]

In a meta-analysis of 8 studies comparing efficacy of EVLP of donor lungs (in 186 recipients) with standard cold preservation for lung transplant (in 1,005 recipients), pooled analysis of 7 studies showed that there was no significant difference in survival rate at 30 days (odds ratio [OR] 0.77, 95% CI 0.32 to 1.82; I^2=55%, p=0.55), and 1 year after lung transplant (OR 0.89, 95% CI 0.57 to 1.40; I^2=0%, p=0.62), between the groups.[3]

In a retrospective cohort study of 936 patients who had lung transplant with EVLP treated donor lungs (n=230) or standard cold preservation lungs (n=706), there was no significant difference in allograft survival between the EVLP treated donor lung recipients and standard cold preservation lung recipients (73% compared with 72% at 3 years; 62% compared with 58% at 5 years; and 50% compared with 44% at 9 years; log-rank p=0.97). [4]

In a case series of 93 lung pairs from extended criteria donors (ECD) and donors after circulatory death (DCD) treated with EVLP and used for bilateral lung transplant, patient survival rate was 99% (78/79) in transplanted patients at

30 days. It was similar when stratified according to donor inclusion criteria (donors above 55 years, lungs from donors after DCD death, ischemic time longer than 6 hours and PaO_2: FiO_2 ratio is more than 300 mmHg) and when compared with those of the standard lung criteria control group (in the INSPIRE study). Survival rate was 94% (74/79) and 91% (72/79) at 6- and 12-months follow up.[5]

In a retrospective cohort study of 262 patients who had EVLP treated lung transplants, patient survival (by Kaplan–Meier curves) was similar among the 4 EVLP groups (group 1, high-risk brain death donors (HR-BDD); group 2, standard-risk donation after cardiac death (S-DCD); group 3, high-risk donation after cardiac death (HR-DCD); and group 4, transplant logistics; p=0.97). When compared, recipients who had EVLP treated lung transplants (n=262) or standard preservation lung transplants (n=844), short and long-term survival was similar between the groups (HR 0.97; 95% CI, 0.75 to 1.27; p=0.83).[6]

In a retrospective cohort study of 906 patients who had lung transplants, survival (on Kaplan–Meier curves) was not statistically significantly different between lungs treated with EVLP combined with more than 12 hours of preservation time (n=97) and those with standard protocol and less than 12 hours of preservation time (n=809), (p=0.61).[7]

Patient and graft survival 30 days after transplant and absence of primary graft dysfunction grade 3 within 72 hours post-transplant

In the case series of 93 lung pairs (from extended criteria donors after brain death and donors after circulatory death) treated with EVLP and used for bilateral lung transplant, patient and graft survival at 30 days after transplant and absence of primary graft dysfunction (PGD) grade 3 within 72 hours post-transplant was achieved in 54% (44/79) of patients but did not meet the prespecified objective performance goal of 65%.[5]

Chronic lung allograft dysfunction (CLAD)-free survival

In the retrospective cohort study of 936 patients who had lung transplant, with EVLP donor lungs (n=230) or standard cold preservation lungs (n=706), there was no statistically significant difference in time to chronic lung allograft dysfunction between the EVLP treated donor lung recipients and standard cold preservation recipients (70% compared with 72% at 3 years; 56% compared with 56% at 5 years; and 53% compared with 36% at 9 years; log-rank p=0.68).[4]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, chronic lung allograft disease-free survival was similar among the 4 EVLP groups (group 1, high-risk brain death donors (HR-BDD); group 2,

standard-risk donation after cardiac death (S-DCD); group 3, high-risk donation after cardiac death (HR-DCD); and group 4, transplant logistics; p=0.88).[6]

PaO_2/FiO_2 ratio after lung transplant

In the meta-analysis of 20 studies, pooled analysis of 4 studies showed that there was no significant difference in postoperative PaO_2/FiO_2 100% ratio (mmHg) after lung transplant between the EVLP and standard cold preservation lung transplant recipients (WMD 27.54 [95% CI -35.67 to 90.7], I^2=88%, p=0.000).[2]

In the meta-analysis of 20 studies, pooled analysis of 15 studies showed that lung function (PaO_2/FiO_2 100% ratio) significantly improved after EVLP in donor lungs compared with pre-EVLP (WMD 184.38, 95% CI 130.17 to 238.59 mmHg, I^2=96.6%, p<0.001) with the conversion rate ranging from 34% to 100%.[2]

Peak pulmonary function

In the meta-analysis of 20 studies, pooled analysis of 8 studies showed that there was no significant difference in peak pulmonary function after lung transplant between the EVLP and standard cold preservation lung transplant recipients (forced expiratory volume [FEV] 1% in 6 studies, WMD -0.30 [95% CI -3.23 to 2.63], I^2=14%, p=0.293; forced vital capacity [FVC] 1% in 2 studies, WMD -0.06 [95% CI -5,93 to 5.80], I^2=0%, p=0.981).[2]

Post-operative extracorporeal life support [ECLS] /extracorporeal membrane oxygenation [ECMO] use requirement/use

In the meta-analysis of 20 studies, pooled analysis of 12 studies showed that there was no significant difference in postoperative ECMO need after lung transplant between the EVLP and standard cold preservation lung transplant recipients (RR 0.70 [95% CI 0.52 to 0.94], I^2=9.2%, p=0.355). EVLP group showed more intraoperative ECMO needs (RR 1.34, 95% CI 1.01 to 1.78, p<0.05) compared with the traditional cold preservation group.[2]

In the meta-analysis of 8 studies, pooled analysis of 5 studies showed that the rate of postoperative ECMO/ECLS use in the EVLP group was 3.72 times higher (95% CI 0.83 to 16.66, p=0.09) that in the standard cold preservation lung transplant group. However, there was no significant difference between the 2 groups. The statistical heterogeneity was high (I^2=62%).[3]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, ECMO use after transplant was similar among the 4 groups (3.5% in group 1, high-risk brain death donors [HR BDD]; 5% in group 2, standard-risk

donation after cardiac death [S-DCD]; 10% in group 3, high-risk donation after cardiac death [HR-DCD]; and 7.6% in group 4, transplant logistics; p=0.28).[6]

Intensive care unit stay (days)

In the meta-analysis of 20 studies, pooled analysis of 17 studies showed that the length of intensive care unit (ICU) stay of the EVLP transplant recipients was longer than the standard cold preservation lung transplant recipients (weighted mean difference [WMD] 3.30 [95% CI 0.54 to 6.0], I^2=77.1%, p=0.000).[2]

In the meta-analysis of 8 studies, pooled analysis of 7 studies showed that length of ICU stay was 2.56 days longer (95% CI -2.29 to 7.42, p=0.30) in the EVLP transplant group than in the standard cold preservation lung transplant group but the difference was not statistically significant. The statistical heterogeneity was high.[3]

In the retrospective cohort study of 936 patients who had lung transplant, with EVLP donor lungs (n=230) or standard cold preservation lungs (n=706), there was no difference in ICU stay between the 2 groups.[4]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, length of ICU stay was similar among the 4 groups (median 4 days in group 1, high-risk brain death donors [HR BDD], 3 days in group 2, standard-risk donation after cardiac death [S-DCD]; 5 days in group 3, high-risk donation after cardiac death [HR-DCD]; and 4 days in group 4, transplant logistics; p=0.17).[6]

In the retrospective cohort study of 906 patients who had lung transplants, the median intensive care unit length of stay was similar between lungs treated with EVLP and more than 12 hours of preservation time (n=97), and those with standard protocol and less than 12 hours of preservation time (n=809), (4 days compared with 4 days, p=0.53).[7]

Length of hospital stay (days)

In the meta-analysis of 20 studies, pooled analysis of 15 studies showed that there was no significant difference in length of hospital stay after lung transplant between the EVLP and standard cold preservation lung transplant recipients (WMD 3.72 [95% CI -0.49 to 7.93], I^2=73.8%, p=0.000).[2]

In the meta-analysis of 8 studies, pooled analysis of 6 studies showed that hospital stay was 3.15 days longer (95% CI -0.99 to 7.29, p=0.14) in the EVLP group than in the standard cold preservation lung transplant group but the difference was not statistically significant between the groups.[3]

In the retrospective cohort study of 936 patients who had lung transplant, with EVLP donor lungs (n=230) or standard cold preservation lungs (n=706), patients in the EVLP group stayed fewer days in the hospital compared with those in the standard lung preservation group. The overall length of stay was similar in patients receiving a single-lung transplant but shorter in recipients of a bilateral-lung transplant treated with EVLP.[4]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, hospital stay was longer in group 3, high risk donation after cardiac death [HR-DCD] compared with other groups (median 28 days compared with 21 days, 21 days, and 17 days in groups 2, 3, and 4, p=0.09).[6]

In the retrospective cohort study of 906 patients who had lung transplants, the median length of hospital stay was similar between lungs treated with EVLP and more than 12 hours of preservation time (n=97), and those with standard protocol and less than 12 hours of preservation time (n=809), (23 days compared with 25.5 days, p=0.53).[7]

Length of postoperative intubation/ventilation/ time to extubation

In the meta-analysis of 20 studies, pooled analysis of 15 studies showed that there was no significant difference in time to extubation after lung transplant between the EVLP and standard cold preservation lung transplant recipients (WMD 5.47 [95% CI -25.42 to 36.37], I^2=63.3%, p=0.001).[2]

In the meta-analysis of 8 studies, pooled analysis of 7 studies showed that the length of ventilation was 2.17 days longer (95% CI -0.63 to 4.96, p=0.13) than in the standard cold preservation lung transplant group. This difference was not statistically significant, and the statistical heterogeneity was high (I^2=64%).[3]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, time on mechanical ventilation was similar among the 4 groups (median 2 days in group 1, high-risk brain death donors and group 2, standard-risk donation after cardiac death [S-DCD]; 3 days in group 3, high-risk donation after cardiac death [HR-DCD]; and 2.5 days in group 4, transplant logistics; p=0.29).[6]

Preservation time of donor lungs

In the meta-analysis of 20 studies, pooled analysis of 11 studies showed that EVLP group had longer lung preservation time (WMD 379.54, 95% CI 271.16 to 487.91 minutes, p<0.001) compared with the traditional cold preservation group[2].

Organ utilisation rates

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, organ utilisation rates were 70% (140/198) for group 1, high-risk brain death donors; 82% (40/49) for group 2, standard-risk donation after cardiac death [S-DCD]; 63% (69/109) for group 3, high-risk donation after cardiac death [HR-DCD]; and 81% (13.16) group 4, transplant logistics; p=0.42).[6]

Safety summary

30-day mortality

In the systematic review and meta-analysis of 13 studies comparing patients transplanted with EVLP treated lungs (n=407) compared with standard /cold preservation protocol lungs (n=1,765), pooled analysis of 9 cohort studies showed no significant difference in risk of 30-day mortality between the groups (EVLP 5.7% [11/253], 95% CI 3.4 to 9.5 compared with standard/ cold preservation lungs 3.5% [19/1005], 95% CI 2.5 to 4.9; RR 2.04, 95% CI: 0.88 to 4.72, I^2=0%, p=0.095).[1]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, 30-day mortality was 2.1% in group 1, high-risk brain death donors; 5% in group 2, standard-risk donation after cardiac death [S-DCD]; 2.9% in group 3, high-risk donation after cardiac death [HR-DCD]; and 0% in group 4, transplant logistics; p=0.87).[6]

In the retrospective cohort study of 906 patients who had lung transplants, mortality at 30 days and 1 year was not significantly different between lungs treated with EVLP and more than 12 hours of preservation time (n=97) and those with standard protocol and less than 12 hours of preservation time (n=809), (30 days, 2% [2/97] versus 4% [34/809], p=0.42; 1 year, 13% [13/97] compared with 14% [116/809], p=0.88).[7]

Primary graft dysfunction (PGD)

In the systematic review and meta-analysis of 13 studies comparing patients transplanted with EVLP treated lungs (n=407) compared with standard protocol /cold preservation lungs (n=1,765), pooled analysis of 7 studies showed no significant difference in primary graft dysfunction grade 3 at 72 hours post-transplant between the groups (EVLP 9.7% [15/247], 95% CI 4.5 to 19.8 compared with standard 10.5% [82/829]), 95% CI 5.9 to 18.0; RR 1.15; 95% CI: 0.69 to 1.89, I^2=0%, p=0.592).[1]

In the meta-analysis of 20 studies, pooled analysis of 11 studies showed that EVLP recipients showed lower incidence of primary graft dysfunction grade 3

within 72 hours after lung transplant than the standard cold preservation lung transplant recipients (RR 1.70, 95% CI 0.64 to 4.53, I^2=62.7%, p=0.003).[2]

In the meta-analysis of 8 studies, pooled analysis of 7 studies did not show a significant difference in primary graft dysfunction grade 3 at 72 hours post-transplant between the EVLP group and standard cold preservation lung transplant group (OR 0.79, 95% CI 0.42 to 1.50, p=0.47).[3]

In the retrospective cohort study of 936 patients who had lung transplant, with EVLP donor lungs (n=230) or standard cold preservation lungs (n=706), fewer patients in the EVLP group had PGD grades 2 and 3 at 72 hours compared with the standard lung preservation group but this was not statistically significant.[4]

In the case series of 93 lung pairs (from extended criteria brain death donors and donors after circulatory death) treated with EVLP and used for bilateral lung transplant, 44% (35/79) of patients had PGD grade 3 within 72 hours post transplant and 6% (5/79) at 72 hours after transplant. The results are similar to those seen in a control group with standard criteria donor lungs (in the INSPIRE study). When stratified by time and donor inclusion criteria, PGD 3 was high at transplant (44% within 72 hours) and in lungs from donors after circulatory death (64%).[5]

In the retrospective cohort study of 262 patients who had EVLP treated lung transplants, the incidence of primary graft dysfunction grade 3 at 72 hours was similar across the 4 groups (group 1, 6.5%; group 2, 12.5%; group 3 10.1% and group 4, 0%; p=0.37).[6]

In the retrospective cohort study of 906 patients who had lung transplants, primary grade dysfunction grade 3 at 72 hours after transplant was not significantly different between lungs treated with EVLP and more than 12 hours of preservation time (n=97) and those with standard protocol and less than 12 hours of preservation time (n=809), (10% [10/97] compared with 10% [83/809], p=0.85).[7]

Lung graft related serious adverse events

In the case series of 93 lung pairs (from extended criteria brain death donors and donors after circulatory death) treated with EVLP and used for bilateral lung transplant, the mean number of lung graft related serious adverse events (respiratory failure and major pulmonary related infection) was 0.3 events per patient.[5]

Respiratory failure

In the case series of 93 lung pairs (from extended criteria brain death donors and donors after circulatory death) treated with EVLP and used for bilateral lung transplant, respiratory failure (needing reintubation or prolonged ventilation up to 4 days after transplant/ tracheostomy) was reported in 15% (12/79) of eligible lungs transplanted.[5]

Major pulmonary related infections

In the case series of 93 lung pairs from extended criteria donors and donors after circulatory death treated with EVLP and used for bilateral lung transplant, major pulmonary related infection was reported in 9% (7/79) of eligible lungs transplanted.[5]

Bronchiolitis obliterans syndrome

In the case series of 93 lung pairs (from extended criteria brain death donors and donors after circulatory death) treated with EVLP and used for bilateral lung transplant, bronchiolitis obliterans syndrome was diagnosed in 1 patient at 12 months after transplant.[5]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse event: ischemia reperfusion injury (IRI) after transplant. They considered that the following were theoretical adverse events: damage to left atrial cuff .

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant. The following databases were searched, covering the period from their start to 22.07.2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria shown in the following table were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients needing lung transplant.
Intervention/test	Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion).
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1,857 patients from 3 systematic reviews and meta-analysis[1-3], 3 retrospective cohort studies[4,6,7] and 1 case series[5].

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant

Study 1 Chakos A (2020)

Study details

Study type	Systematic review and meta-analysis
Country	Australia (studies were mainly from European countries)
Search details	Search period: inception to August 2019, 10 databases were searched: Medline, Embase, PubMed, Ovid reviews including Cochrane databases as well as national and government repositories. Reference lists of included studies were also assessed for further studies.
Study population and number	N=13 studies (with 2,172 transplant recipients receiving donor lungs treated with ex-vivo lung perfusion [EVLP, n=407] or standard protocol/cold preservation [n=1,765]). 1 randomised controlled trial [RCT] and 12 cohort studies (4 prospective, 6 retrospective and 2 unknown study designs).
Age and sex	Mean age: 51.3 years in EVLP lung transplant recipients; 48.6 years in standard protocol lung transplant recipients Sex: 51% male in EVLP lung transplant recipients; 54% male in standard protocol lung transplant recipients.
Study selection criteria	Inclusion criteria: studies with at least 5 transplant recipients per arm, reporting primary mid to long-term outcome data for recipients after lung transplant using standard protocol [cold storage] or EVLP. Exclusion criteria: non-comparative studies, animal studies, case reports, conference abstracts, reviews, editorials and duplicate studies were excluded.
Technique	EVLP was done using static and portable EVLP systems (XVIVO system used in 5 studies, Vivoline LS-1 in 3 studies, Organ Care System in 2 studies, and not-fully described or administered with custom circuits in 4 studies). EVLP protocols and methodologies varied across studies. Mean EVLP time was 234 minutes. Most patients had double-lung transplants. Intraoperative parameters were similar between EVLP and standard protocol groups.
Follow up	mean follow up ranged from 0.7 to 10 years; (median 1-year follow up)

Conflict of interest/source of funding	None

Analysis

Follow-up issues: varied follow up in studies.

Study design issues: studies included were mainly small retrospective observational studies. Only 1 RCT with a large proportion of patients and donor lungs with high arterial oxygen tension/inspired oxygen fraction [PaO_2/FiO_2 ratio] was included in this meta-analysis. Studies were screened and assessed by two independent researchers and any disagreements were resolved by consensus. Quality of studies was assessed using a 19-point metric tool adopted from the Canadian Institute of Health Economics. 8 studies were rated of high quality, 1 was of standard quality and 4 were of moderate quality. Meta-analyses of reported outcomes were conducted using a random-effects model. Survival data from Kaplan–Meier curves digitized, and individual patient data imputed to conduct aggregated survival analysis. Hazard ratio (HR) between EVLP and standard treatment protocol is calculated from Kaplan–Meier data using a Cox proportional hazard model. Pooling of other secondary outcomes was not possible because of heterogeneity in reporting across studies.

Study population issues: donor/recipient baseline criteria and operative protocols and parameters varied across studies. Most of the donor lungs were from brain death donors (88%). Chronic obstructive pulmonary disease was more common in the EVLP recipients than standard lung preservation recipients (40.4% compared with 32.8%, p=0.046). EVLP lungs in case series had significantly worse PaO_2/FiO_2 ratio (287 mmHg versus 439 mmHg, p<0.001) and significantly greater rate of abnormal chest X-ray (62% versus 37%, p=0.01). Indications for lung transplant varied across studies in both groups.

Other issues: there is an overlap of studies between the 3 meta-analyses[1-3] included in the overview.

Key efficacy findings

Number of patients analysed: 2,172 patients (with 407 EVLP-treated lung transplants versus 1,765 standard protocol /cold-preservation lung transplants).

Hospital length of stay ranged from 23 to 54 days across studies.

Length of stay in intensive care unit (ICU) ranged from 3 to 19 days.

Extubation time ranged from 7 to 221 hours.

Kaplan Meier survival post-transplant

Overall survival	EVLP treated lungs % (n=397)	Standard protocol lungs % (n=1761)	HR (95% CI)
12 months	84	85	
24 months	79	79	
36 months	74	73	
All studies			1.00 (0.79 to 1.27, p=0.981)
Non-randomised studies			1.16 (0.89 to 1.51, p=0.276)

Key safety findings

Outcome	EVLP treated lungs % (n=397)	Standard protocol lungs (n=1,761)	RR (95% CI)	I^2, p value
30-day mortality (in non-randomised studies) ^	5.7 (11/253) (95% CI 3.4 to 9.5)	3.5 (19/1005) (95% CI 2.5 to 4.9)	2.04 (0.88 to 4.72)	0% 0.095
30-day mortality (including all studies)	NR	NR	2.39 (1.07 to 5.35)	0% 0.034
Grade 3 primary graft dysfunction (at 72 hours post-transplant) *	9.7 (15/247) (95% CI 4.5 to 19.8)	10.5 (82/829) (95% CI 5.9 to 18.0)	1.15 (0.69 to 1.89)	0% 0.592
In-hospital mortality	3 (12/397)	1.3 (24/1761)	NR	NR
Pneumonia (reported in 2 studies)	4.2% (17/397)	1.9 (34/1761)	NR	NR
Post-operative ECMO use	n=5 (4 studies)	n=8 (2 studies)	NR	NR

^excluded RCT data as higher 30-day mortality rate was not related to EVLP (but due to surgical complications, cardiac risk factors and non-compliance with medications).

* PGD was graded based on the International Society for Heart and Lung Transplantation (ISHLT) criteria, with grade 3 representing P/F ratio <200 within 72 hours and radiographic infiltrates.

Study 2 Lou 2020

Study details

Study type	Meta-analysis
Country	China (included studies were mainly from Europe, USA, Canada, and Australia)
Search details	Databases searched: PubMed, PMC, EMBASE, and Ovid. search period: inception to March 2019. References in included studies were also scanned.
Study population and number	N=20 studies (including 2,574 donors and 2,567 recipients) comparing EVLP treated donor lungs (n=582) with standard cold preservation lungs (n=1,985) used for lung transplant. 3 RCTs (including one abstract), 3 prospective cohort studies, and 14 retrospective cohort studies
Age and sex	Mean age: recipients with EVLP lungs (range 41 to 59 years); recipients with standard cold storage lungs (range 39 to 52 years) Sex: EVLP group had more female patients.
Study selection criteria	Inclusion criteria: RCTs or cohort studies assessing lung transplant; comparing EVLP technique and traditional cold storage techniques. Exclusion criteria: animal studies, duplicate articles, single-arm analysis about EVLP technique and review articles without original data.
Technique	Marginal donor lungs were treated with EVLP and used for lung transplant. Different EVLP techniques were used (Toronto in 11 studies, Lund in 6 studies, OCS in 2 studies and combined Toronto and Lund technique in 1 study) and protocols also varied in terms of perfusion duration and EVLP solutions used. Standard criteria donor lungs were treated with standard protocol/cold preservation technique and were used for lung transplant. Most of the lung transplants were bilateral lung transplants.
Follow up	Varied in studies (range 90 days to 7 years)
Conflict of interest/source of funding	Study was supported and funded by different research and development programs of China.

Analysis

Follow-up issues: varied follow up in studies.

Study design issues: Studies included in the meta-analysis were mainly retrospective studies with small sample size; meta-analysis was performed according to the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Comprehensive search was done, studies were screened and assessed by 2 independent reviewers and any disagreements were resolved by discussion. Quality of studies was assessed using the Jadad scale for RCTs and Newcastle-Ottawa Scale for cohort studies. Studies were rated as high to moderate quality. The hazard ratio (HR), relative risk (RR), and weighted mean difference (WMD) were used as the effect size to evaluate the survival outcomes, categorical and continuous variables, respectively. Effect sizes and its 95% CI were calculated by extracting the data from Kaplan–Meier curves.

Significant heterogeneity was noted for donor/recipient characteristics, EVLP processes, and follow up.

Study population issues: there was no significant difference in donor age, gender, type of donor lungs (donation after circulatory death [DCD] or donation after brain death [DBD]), and mechanical ventilation between the 2 donor groups. There was also no significant difference for recipients' age, lung allocation score, mechanical ventilation use, ECMO support after lung transplant, type of lung transplant, or total cold ischemia time between the 2 recipient groups.

Indications for lung transplant varied across studies in both groups.

Other issues: there is an overlap of studies between the 3 meta-analyses[1-3] included in the overview.

Key efficacy findings

- Number of patients analysed: 2,567 patients (582 recipients with EVLP lung transplants versus 1,985 recipients with standard cold preservation lung transplants).

- Pooled analysis of 8 studies showed that EVLP donor lung group had more chest x-ray abnormalities (RR 1.39, 95% CI 1.03–1.87, p<0.05); and analysis of 14 studies showed more inferior PaO_2/FiO_2 ratio (WMD -106.06, 95% CI -150.78 mmHg to 61.33 mmHg, p<0.001) than standard cold storage donor group.
- Pooled analysis of 13 studies showed that EVLP recipient group needed more intraoperative extracorporeal circulation/ECMO (RR 1.34, 95% CI 1.01 to 1.78, p<0.05), and had extended preservation time (11 studies, WMD 379.54, 95% CI 271.16 to 487.91 minute, p<0.001), compared with the traditional cold storage recipient group.

Peri-operative clinical outcomes of recipients after lung transplant (pooled analysis)

Clinical outcome	No of studies	WMD/RR, 95% CI, p value
Postoperative PaO_2/FiO_2 100% ratio (mmHg)	4 studies	WMD 27.54 (95% CI -35.67 to 90.75), I^2=88%, p=0.000
Time to extubation of recipients (hours)	13 studies	WMD 5.47 (95% CI -25.42 to 36.37), I^2=63.3%, p=0.001
Need for postoperative ECMO	12 studies	RR 0.70 (95% CI 0.52 to 0.94), I^2=9.2%, p=0.355
ICU stays (days)	17 studies	WMD 3.30 (95% CI 0.54 to 6.07), I^2=77.1%, p=0.000
Hospital stays (days)	15 studies	WMD 3.72 (95% CI -0.49 to 7.93), I^2=73.8%, p=0.000
Peak pulmonary function		
FEV1% after lung transplant	6 studies	WMD -0.30 (95% CI -3.23 to 2.63), I^2=14%, p=0.293
FVC% after lung transplant	2 studies	WMD -0.06 (95% CI -5,93 to 5.80), I^2=0%, p=0.981

Function of EVLP treated donor lungs (pooled analysis)

	No of studies	WMD (95% CI), p value
PaO_2/FiO_2 100% ratio pre-EVLP versus post-EVLP, mmHg	15 studies	WMD 184.38, 95% CI 130.17 to 238.59 mmHg, I^2=96.6%, p<0.001

Survival outcomes of recipients after lung transplant

Follow up	No of studies	RR (95% CI), P value
30 days	15 studies	RR 1.69, 95% CI 0.99 to 2.87; I^2=55%, p=0.008
90 days	10 studies	RR 1.46, 95% CI 0.93 to 2.30; I^2=0%, p=0.541
1 year	15 studies	RR 0.98, 95% CI 0.77 to 1.24; I^2=0%, p=0.535
Accumulated survival rate	14 studies	RR 1.25, 95% CI 1.0 to 1.56; I^2=0%, p=0.912

Key safety findings

Adverse events

	No of studies	RR, 95% CI, p value
Primary graft dysfunction (PGD) grade 3 within 72 h after lung transplant*	11 studies	RR 1.70, 95% CI 0.64 to 4.53), I^2=62.7%, p=0.003

*PGD was graded based on the International Society for Heart and Lung Transplantation (ISHLT) criteria, with grade 3 representing P/F ratio <200 within 72 hours and radiographic infiltrates.

Study 3 Tian D 2019

Study details

Study type	Systematic review and meta-analysis
Country	Japan (included studies were mainly from Europe and Canada)
Search details	Databases searched: PubMed, the Cochrane Library, and Embase; search period: inception to December 2018. References in included studies were also scanned.
Study population and number	N=8 studies (with 1,191 patients comparing EVLP treated donor lungs [n=186] with standard cold preservation lungs [n=1,005] used for lung transplant. 6 prospective cohort studies, and 2 retrospective cohort studies
Age and sex	Mean age: EVLP group (range 45 to 54 years); standard cold storage group (range 40 to 54 years)
Study selection criteria	Inclusion criteria: English articles with more than 5 patients, describing lung transplant following EVLP for marginal donor lungs compared with standard lung transplant without EVLP. Exclusion criteria: animal studies, duplicate articles, several publications from same data source, non-English studies, not original/full articles, studies with less than 5 patients, unmatched outcomes, EVLP for non-marginal donors (PaO_2/FiO_2 >300 mmHg), and review articles without original data.
Technique	Marginal donor lungs were treated with EVLP and used for lung transplant in 186 recipients. Different technologies were used for EVLP (Toronto in 5 studies, Lund in 2 studies, and combined Toronto and Lund technique in 1 study) and protocols also varied in terms of perfusion duration and EVLP solutions used. Donor lungs treated with standard protocol/cold preservation technique were used for lung transplant in 1,005 recipients. The majority of the lung transplants were bilateral lung transplants.
Follow up	Varied in studies (ranged from days to years)
Conflict of interest/source of funding	None, study was supported by Japan-China Saskawa medical foundation.

Analysis

Follow-up issues: varied follow up in studies, most studies had short median follow up.

Study design issues: studies included in the meta-analysis were mainly cohort studies with small sample size; meta-analysis was performed according to the recommendations

of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Comprehensive search was done, studies were screened and assessed by 2 independent reviewers and any disagreements were resolved by discussion with a third reviewer. Quality of studies was assessed using the Newcastle-Ottawa Scale for cohort studies. Studies were rated as moderate quality. The odds ratio (OR), and weighted mean difference (WMD) were used as the effect size to evaluate the survival outcomes, categorical and continuous variables, respectively. Data from the survival curves was extrapolated.

Significant heterogeneity was noted for donor/recipient characteristics, EVLP protocols/processes, and follow up.

Study population issues: donation was mainly after brain death. Compared with the standard lung transplant without EVLP, the EVLP group had similar donor age and sex but had more abnormalities on donor lung chest x-rays (OR, 5.69, 95% CI 2.28 to 14.19, p = 0.0002), a higher smoking history rate (OR 3.36, 95% CI 1.15 to 9.84, p = 0.03), and worse or inferior donor arterial oxygen tension/inspired oxygen fraction (PaO_2/FiO_2 ratio WMD -182.78, 95% CI -238.55 to -127.00, p < 0.00001). There was no significant difference for recipients' age, sex, BMI, bridge by ventilator/extracorporeal life support/extracorporeal membrane oxygenation (OR 2.96, 95% CI 0.74 to 11.81, p=0.12) and rate of double lung transplants (OR 1.03, 95% CI 0.28 to 3.73, p=0.97) between the 2 recipient groups.

Indications for lung transplant varied across studies in both groups.

Other issues: there is an overlap of studies between the 3 meta-analyses[1-3] included in the overview.

Key efficacy findings

- Number of patients analysed: 1,191 patients (with 186 EVLP lung transplants versus 1,005 standard cold preservation lung transplants)

Peri-operative clinical outcomes of recipients after lung transplant (pooled analysis)

Clinical outcome	No of studies	WMD/OR, 95% CI, p value
Length of postoperative ventilation	7 studies	WMD 2.17 (95% CI -0.63 to 4.96), I^2=64%, 0.13
Postoperative ECMO/extracorporeal life support	5 studies	OR 3.72 (95% CI 0.83 to 16.66), I^2=62%, p=0.09
Length of ICU stay (days)	7 studies	WMD 2.56 (95% CI -2.29 to 7.42), I^2=84%, p=0.30
Length of hospital stay (days)	6 studies	WMD 3.15 (95% CI -0.99 to 7.29), I^2=0%, p=0.14

Survival outcomes of recipients after lung transplant

Follow up	No of studies	EVLP group % (n)	Standard protocol lungs % (n)	OR (95% CI), P value
30 days	7 studies	95 (126/132)	96 (706/734)	OR 0.77, 95% CI 0.32 to 1.82; I^2=0%, p=0.55
1 year	7 studies	84 (150/178)	84 (825/977)	OR 0.89, 95% CI 0.57 to 1.40; I^2=1%, p=0.62

Key safety findings

	No of studies	Total events in EVLP group % (n)	Total events in standard protocol lungs % (n)	OR, 95% CI, p value
Primary graft dysfunction grade 3 within 72 h after lung transplant*	6 studies	11 (14/123)	14 (86/616)	OR 0.79, 95% CI 0.42 to 1.50), I^2=0%, p=0.47

*PGD was graded based on the International Society for Heart and Lung Transplantation (ISHLT) criteria, with grade 3 representing P/F ratio <200 within 72 hours and radiographic infiltrates.

Study 4 Divithotawela C 2019

Study details

Study type	Retrospective cohort study
Country	Canada (single centre)
Recruitment period	2008-2017
Study population and number	N= 936 patients with single or bilateral lung transplants (donor lungs treated with EVLP (n=230) versus standard cold preservation of lungs (n=706).
Age and sex	Median age: Donors: EVLP group 46 years; standard preservation group 50 years Recipients: EVLP group 58 years; standard preservation group 57 years Sex: Recipients: EVLP group 63% (145/230) male, standard preservation group 56% (395/706) male
Study selection criteria	Inclusion criteria: retransplant recipients and patients bridged to transplant with invasive mechanical ventilation or extracorporeal life support, who received high-risk extended criteria donor lungs that were treated with EVLP and compared with standard preservation lung recipients. Exclusion criteria: donor lungs with established pneumonia, severe mechanical lung injury, and evidence of aspiration of gastric contents were excluded.
Technique	Portable normothermic EVLP -Toronto lung transplant EVLP protocol was used.
Follow up	Median follow up: EVLP group: 898 days (range, 1 to 3,364 days) and standard preservation group: 1,182 days (range, 1 to 3411 days)
Conflict of interest/source of funding	Authors received fees and grants from various companies and institutes. 4 authors are also founders of a company dedicated to the development of EVLP systems.

Analysis

Follow-up issues: longer follow-up period in standard preservation group.

Study design issues: large sample size; all patients received standardised protocol and post-transplant care; data was collected prospectively; study followed the strengthening the reporting of observational studies in epidemiology (STROBE) reporting guideline. There might be some heterogeneity in donor lung management.

Study population issues: majority of donations were after brain death. Selection of recipients for lung transplant and post-transplant care was similar in both groups.

Compared with the standard preservation lung transplant without EVLP, the EVLP group had similar donor age but had more DCD donors (41% [95/230] versus 6.5% [46/706]); significantly lower donor arterial oxygen tension/inspired oxygen fraction (PaO_2:FiO_2 ratio 348 ±108 mmHg versus 422± 88 mmHg; p< .001), had more abnormalities on donor chest x-rays (59% [135/230] versus 49% [349/706] p=0.02), and higher smoking history rate (61% [125/204 versus 49% [322/650]; p=0.007). The total median preservation time was long in the EVLP group (914 minutes versus 481 minutes, p< 0.001) compared with standard preservation group.

There was no significant difference for recipients' baseline demographic characteristics but more recipients in the EVLP group received single lung transplant (27% [62/230] versus 14% [100/706], p<0.01).

Indications for lung transplant were mainly interstitial lung disease and chronic obstructive pulmonary disease. Around 6.5% patients in EVLP group and 6% patients in the standard preservation group were bridged to transplant. 20% of patients in both groups had a positive donor specific virtual cross match.

Key efficacy findings

- Number of patients analysed: 986 (230 EVLP lung transplants versus 706 standard cold preservation lung transplants).

Allograft survival (freedom from death from all causes or retransplant)

Follow up	EVLP group % (n)	Standard protocol group (% (n)
Overall cohort		
3 years	73%	72%
5 years	62%	58%
9 years	50%	44% (log rank p=0.97)
Single-lung transplants		
2.7 years	64 (40/62)	62 (62/100)
5.4 years	24 (15/62)	37 (37/100)
8.2 years	8 (5/62)	16 (16/100)
11 years	1 (1/62)	6 (6/100)
DCD recipients		
2 years	61 (58/95)	57 (26/46)
4 years	19 (18/95)	35 (16/46)
6 years	11 (11/95)	17 (8/46)
8 years	1 (1/95)	4 (2/46)
BDD lung recipients		
2 years	57 (77/135)	66 (436/660)
4 years	27 (37/135)	43 (284/660)
6 years	10 (14/135)	18 (121/660)
8 years	4 (5/135)	6 (41/660)

Chronic lung allograft dysfunction (CLAD)–free survival (defined according to the International Society of Heart and Lung Transplantation criteria for the diagnosis of

bronchiolitis obliterans syndrome on the basis of a 20% or more decrease in forced expiratory volume in 1 second from the posttransplant baseline).

Follow up	EVLP group % (n)	Standard protocol group (% (n)
Overall cohort		
3 years	70	72
5 years	56	56
9 years	53	36 (log rank p=0.68)
Single-lung transplants		
2.7 years	35 (22/62)	50 (50/100)
5.4 years	14 (9/62)	26 (26/100)
8.2 years	1 (2/62)	12 (12/100)
11 years	0	1 (1/100)
DCD recipients		
2 years	34 (32/95)	41 (19/46)
4 years	13 (12/95)	24 (11/46)
6 years	3 (3/95)	2 (1/46)
8 years	0	0
BDD lung recipients		
2 years	41 (56/135)	50 (333/660)
4 years	16 (22/135)	26 (172/660)
6 years	5 (7/135)	9 (61/660)
8 years	2 (3/135)	2 (11/660)

There was no difference in CLAD or survival rates in bilateral-lung transplant recipients between the EVLP and standard lung preservation groups.

Length of intensive care unit (ICU) and hospital stay (days)

Patients in the EVLP group stayed fewer days in the hospital compared with those in the standard lung preservation group, but there was no difference in intensive care unit stay.

The overall length of stay was similar in patients receiving a single-lung transplant but shorter in recipients of a bilateral-lung transplant treated with EVLP.

Highest percentage of predicted forced expiratory volume in 1 second- there was no significant difference between the EVLP group and standard cold storage group.

Development of de novo donor-specific antibodies (DSAs)- DSAs happened in both groups in similar proportions, and there was no difference between the groups according to their virtual cross match status.

Key safety findings

Primary graft dysfunction [PGD] grade 3 within 72 h after lung transplant (graded based on the International Society for Heart and Lung Transplantation (ISHLT) criteria, with grade 3 representing P/F ratio <200 within 72 hours and radiographic infiltrates)

In the EVLP group, fewer patients had PGD grade 3 at 72 hours compared with the standard lung preservation group but there was no significant difference between the groups.

Study 5 Loor 2019

Study details

Study type	Prospective case series (EXPAND 1 trial-NCT01963780)
Country	International -USA, Germany and Belgium (8 centres)
Recruitment period	2014-2016
Study population and number	N= 93 adult bilateral lung transplant recipients who received EVLP treated extended criteria donor lung pairs from brain death donors and donation after circulatory death.
Age and sex	Mean age: donors 47 years; recipients 55 years Sex: donors 58% (46/79) male; recipients 58% (46/79) male
Patient selection criteria	Inclusion criteria: Donors: non ideal or extended criteria donors (ECD) lungs from brain death donors (BDD) that do not meet common donor lung acceptance criteria for transplant, but meet one or more of the following criteria– donor PaO_2/FiO_2 300 mmHg or less, expected ischemic time longer than 6 hours, donor age 55 years or older; or lungs from donors after circulatory death -(DCD) donors. Transplant recipients: 18 years or older and undergoing a bilateral lung transplant. Exclusion criteria: Donors: moderate to severe traumatic lung injury with air or blood leak, active pulmonary disease, active pneumonia, persistent pooling of purulent secretions on bronchoscopic evaluations, transfusions exceeding 10 units of red blood cells, ABO incompatibility with the recipient and smoking history. Transplant recipients: previous organ or bone marrow transplant, single lung transplant, chronic kidney disease or on renal replacement therapy.
Technique	Portable normothermic EVLP - OCS lung system was used to perfuse, ventilate and assess. Donor lungs were flushed with cold buffered OCS lung solution plus 50mg nitro-glycerine. Then lungs are connected to the OCS system, warmed, ventilated and perfused. Lungs were transplanted if they showed stability of OCS lung variables, PaO_2/FiO_2 was more than 300 mmHg, and confirmation by the transplanting surgeon of clinical suitability for transplant. Standard bilateral lung transplant done using centre specific protocols. The transplant procedure was done on cardiopulmonary bypass in 48% (38/79) recipients.
Follow up	12 months

Conflict of interest/source of funding	The device company (Transmedics) funded and assisted the study design/protocol, data collection, analyses and final report. 5 authors received grants, fees and support from Transmedics and other companies.

Analysis

Follow-up issues: Short term follow up. Recipients were followed-up at regular planned intervals (30 days, 6 and 12 months).

Study design issues: multicentre single arm study. A prespecified objective performance goal of 65% was set for the composite efficacy outcome (patient and graft survival at 30-day and no primary graft dysfunction [PGD] grade 3 within 72 hours post-transplant) and was based on published data available for standard criteria donor lungs. Primary graft dysfunction grading data was judged by an independent medical monitoring committee. The OCS INSPIRE control group and US national UNOS data were used as comparators for benchmarking the results for survival and safety outcomes. All transplanted recipients were analysed.

Study population issues: 61 brain death donor lungs with multiple extended criteria and 32 from donors after circulatory death were assessed. Study recipients represented a real-world mix of lung transplant recipients with high risk factors and characteristics. 20% recipients had pulmonary fibrosis and 28% had secondary pulmonary hypertension.

Key efficacy findings

- Number of patients analysed: 93 lung pairs treated with EVLP followed by bilateral lung transplant.

OCS lung assessment outcomes	**N**
Lungs that met transplant criteria after EVLP	81
Lungs that did not meet transplant criteria	12*
Donor lung use	
Number of lungs transplanted	79
Lungs not used for transplant	2^
Cold ischemic time of donor lungs	2.6 to 3.9 hours
Total cross clamp (out of body) time	8.5 to 10.2 hours
Perfusion and ventilation parameters	
Vascular resistance (dyn)	Initial lung assessment 354 Final lung assessment 320
Peak airway pressure (cm H_2O)	Initial lung assessment 12 Final lung assessment 11
Donor lung PaO2/FiO2 (mmHg) assessment	Initial 378 Final 409

*6 had contusions or open lung injury resulting in visible air perfusate leakage into the bronchoalveolar space, 4 had unstable perfusion variables, 1 had oedema, and 1 had persistent purulent secretions.

^1 was diagnosed with lung cancer on transplant day and 1 because no surgeons were available.

Clinical outcomes

Efficacy -composite end point	**EXPAND I % (n)**		
Patient and graft survival at 30-day post-transplant and absence of PGD grade 3 within 72 hours post-transplant	54 (43/79)		
Composite end point according to donor inclusion criteria			
PaO_2/FiO_2 <300 mmHg	60		
>55 years	58		
Cross clamp time > 6 hours	48		
Donor after circulatory death (DCD)	39		
Survival rate	**EXPAND I % (n)**	**INSPIRE control group (standard criteria donor lungs) %**	**US national NUOS data %**
30 days	99 (78/79) *	100	96
6 months	94 (76/79)	91	90
12 months	91 (71/79)	90	85
Overall freedom from PGD grade 3	56		
Survival rate according to donor inclusion criteria			
PaO_2/FiO_2 <300 mmHg	60		
>55 years	58		
Cross clamp time > 6 hours	52		
Donor after circulatory death (DCD)	39		

*was similar for all donor inclusion criteria.

Key safety findings

IP overview: Ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant

Primary graft dysfunction (PGD)

	EXPAND I %(n)	**INSPIRE control group (standard criteria donor lungs)**
PGD grade 3 at 0/ within 72 hours after transplant*	44 (35/79)	
PGD according to donor inclusion criteria		
PaO_2/FiO_2 <300 mmHg	40	
>55 years	42	
Cross clamp time > 6 hours	48	
Donor after circulatory death (DCD)	64	
PGD grade 3 at 72 hours post-transplant*	6 (5/79)	5.5
PGD grade 3 or 2 at 72 hours*	16 (13/79)	10.9

* PGD was graded based on the International Society for Heart and Lung Transplantation (ISHLT) criteria, with grade 3 representing P/F ratio <200 within 72 hours and radiographic infiltrates.

Adverse events

	EXPAND I % (n)	**INSPIRE control group (standard criteria donor lungs) % (n)**
Lung graft related serious adverse events at 30 days^	Mean 0.3±0.5 (range 0 to 2.0)	Mean 0.3±0.5 (range 0 to2.0)
Bronchiolitis obliterans syndrome (diagnosed at 12 months)	1 (1/79)	4 (7)
Respiratory failure (needed reintubation or prolonged ventilation up to 4 days after transplant/ tracheostomy)	15 (12/79)	9 (16)
Major pulmonary related infection	9 (7/79)	16 (29)
Acute rejection	0	2 (4)
Bronchial anastomotic complication	0	2 (4)

^multiple occurrences of same event were counted once.

Study 6 Cypel M 2020

Study details

Study type	Retrospective cohort study
Country	Canada (single centre)
Recruitment period	2008-2017
Study population and number	N=262 recipients who had lung transplant after normothermic EVLP (divided into 4 groups - Group 1, high-risk brain death donors (HR-BDD) n=140. Group 2, standard-risk donation after cardiac death (S-DCD) n=40. Group 3, high-risk donation after cardiac death (HR-DCD) n=69; and Group 4, transplant logistics (the need for prolongation of preservation time or organ retrieval by a different transplant team) n=13.
Age and sex	Median age: donors 39 to 49 years; recipients 56 to 61 years Sex: not reported
Patient selection criteria	Inclusion criteria: donor lungs with a partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO^2) (P/F ratio) of >400 mmHg and stable or improving pulmonary artery pressure, airway pressures, or dynamic compliance were considered transplantable. Transplant recipients: selected based on blood type, size of the organ (that is, total lung capacity) and wait list status. Exclusion criteria: lungs with P/F ratio <400 mmHg or >15% deterioration in the other functional parameters, reflecting significant pulmonary deterioration. Transplant recipients: no exclusion criteria, but first 20 cases-retransplants and ECMO bridge-to-transplant recipients were excluded.
Technique	Toronto EVLP technique used - Donor lungs transported under standard conditions of cold storage in a low-potassium dextran solution (Perfadex; XVIVO Perfusion) and placed in the system and perfused. Care after transplant was provided according to standard practice.
Follow up	9 years
Conflict of interest/source of funding	3 authors are founders, received research support from XVIVO perfusion and served as consultants for a company.

Analysis

Follow-up issues: long term follow up.

Study design issues: a large retrospective cohort study that used prospectively collected data. Categorisation of lungs to 4 subgroups was based on subjective donor lung assessment. Kaplan–Meier curves were used for survival plots, and the log-rank test was used to compare proportional hazards of survival.

Study population issues: donors in group 1 (HR-BDD) were younger (p=0.002) and had a lower P/F ratio (p=0.001), and groups 1 (HR-BDD) and 3 (HR-DCD) had more chest X-ray abnormalities than the other groups (p=0.0007). Donor lungs from group 2 (S-DCD) had significantly shorter total preservation times compared with the other groups (p=0.008).

There were no significant differences among the 4 groups in recipient age, medical diagnosis, and urgency for transplant. Recipients in group 1 (HR-BDD) were less likely than those in the other 3 groups to receive double lung transplants (64.2% versus 82.5% in group 2, 82.6% in group 3, and 84.6% in group 4; p=0.01).

Key efficacy findings

- Number of patients analysed: 262 lung transplants with EVLP treated lungs.

Survival outcomes for EVLP versus standard preservation lungs

Short- and long-term survival from recipients receiving standard preservation lungs (n=844) and EVLP lungs (n=262) were similar, with a hazard ratio of 0.97 (95% CI, 0.75-1.27; p= 0.83) for EVLP versus standard preservation.

Patient survival and chronic lung allograft disease-free survival (comparison of recipients receiving EVLP lungs stratified by EVLP indication group)

Kaplan–Meier survival by EVLP indication group demonstrated no significant differences for patient survival (p=0.97) and chronic lung allograft disease-free survival (p=0.88) among the 4 EVLP groups.

Utilization rates

	Overall N=372	Group 1 (HR-BDD) N=140	Group 2 (S-DCD) N=40	Group 3 (HR-DCD) N=69	Group 4 (logistics) N=13	P value
Utilization rates	69% (255/372, 95% CI 64% to 73%)	70% (140/198, 95% CI, 64% to 77%)	82% (40/49, 95% CI, 69% to 90%)	63% (69/109, 95% CI, 54% to 72%)	81% (13/16, 95% CI, 57% to 93%)	0.09

Clinical outcomes of EVLP recipients by group

	Group 1 (HR-BDD) N=140	Group 2 (S-DCD) N=40	Group 3 (HR-DCD) N=69	Group 4 (logistics) N=13	P value

ICU stay, days, median (IQR)	4 (2-9)	3 (2-12)	5 (3-18)	4 (2-12)	0.17
Hospital stay, days, median (IQR)	21 (16-40)	21.5 (17-41)	28 (18-62)	17 (13-31)	0.09
Ventilation, days, median (IQR)	2 (1.5-5)	2 (1-6)	3 (2-7)	2.5 (1-8)	0.29
ECMO post-transplant %	3.5	5	10	7.6	0.28

Key safety findings

Adverse events

	Group 1 (HR-BDD) N=140	**Group 2 (S-DCD) N=40**	**Group 3 (HR-DCD) N=69**	**Group 4 (logistics) N=13**	**P value**
30-day mortality %	2.1	5	2.9	0	0.71
Primary graft dysfunction grade 2-3 at 72 hours, %	18.5	20	17.3	15	0.97
Primary graft dysfunction grade 3 at 72 hours %	6.5	12.5	10.1	0	.037
Primary graft dysfunction grade 3 at 24 hours %	11.5	10	15.1	15.4	0.88

Study 7 Yeung 2017

Study details

Study type	Retrospective cohort study
Country	Canada (single centre)
Recruitment period	2006-2015
Study population and number	N=906 recipients who had lung transplant after normothermic EVLP or standard cold preservation (recipients with preservation time of more than 12 hours, n=97 versus preservation time of less than 12 hours, n=809) % of EVLP recipients: > 12-hour preservation group 95%, [92/97] < 12-hour preservation group 5%, [43/809].
Age and sex	Mean recipient age: 51 years in recipients with preservation time > 12 hours; 52 years in recipients with preservation time < 12 hours Sex: 63% male recipients with preservation time > 12 hours 56% male recipients with preservation time < 12 hours
Patient selection criteria	Inclusion criteria: patients who received at-least one lung transplant and with sufficient data for analysis were included. Exclusion criteria: younger than 18 years, who received a heart and lung transplant.
Technique	Toronto EVLP technique used - Donor lungs transported under standard conditions of cold storage in a low-potassium dextran solution (Perfadex; XVIVO Perfusion) and placed in the system and perfused. Lung preservation done according to current standard of care. Indication for EVLP: <300mmHg or decreasing PaO2/FiO2 ratio, bronchoscopy with aspiration concerns, pulmonary oedema, substantial infiltrates in chest radiographs, donor after cardiac death with > 30 minutes withdrawal of life sustaining treatments and pulmonary embolism.
Follow up	Median follow up 991 days in group 1 with >12 hours preservation (range 667 to 1,396 days) 1,774 days in group 2 with <12 hours preservation (range 1,114-2,695 days)
Conflict of interest/source of funding	No source of funding, 2 authors are founders and served as consultants for a company.

Analysis

Follow-up issues: long term follow up.

Study design issues: a large retrospective cohort study with patients from the Toronto lung transplant program database. For bilateral transplants, a longer preservation time was used for the analysis. Kaplan–Meier curves were used for survival plots, and the log-rank test was used to compare proportional hazards of survival.

Study population issues: more than 12-hour preservation group had a higher proportion of lungs that had undergone EVLP and lungs donated after cardiac death (30 versus 7%, p<0.0001) than the less than 12-hour preservation group. There were no significant differences in donor and recipient age, sex and other characteristics between the 2 groups.

Key efficacy findings

- Number of patients analysed: 906 lung transplants (lungs with preservation time of more than 12 hours, n=97 versus preservation time of less than 12 hours, n=809)

Clinical outcomes of recipients by group

	Group 1 >12 hours preservation time (n=97)	**Group 2 <12 hours preservation time (n=809)**	**P value**
Mean lung preservation time^ (minutes)	400.8±121.8	875.7±109	<0.0001
ICU stay, days, (mean±SD)	10.2 ±13.2	11.8±24.9	0.53
Hospital stay, days, (mean±SD)	36.0±26.1	38.4±45.6	0.60
Survival (Kaplan-Meier analysis)			**0.61**
1 year % (n)	87 (84/97)	86 (693/809)	
2 years % (n)	58 (56/97)	73 (595/809)	
3 years % (n)	32 (31/97)	59 (479/809)	
4 years % (n)	18 (17/97)	45 (367/809)	

^defined as sum of first cold ischemic time, EVLP time and second cold ischemic time.
Multivariate analysis (using Cox model) shows that increasing recipient age to be a significant variable associated with reduced survival (HR 1.011, 95% CI 1.0005 to 1.0215, p=0.04). The different components of preservation time (first cold ischemic time, EVLP time, and second ischemic time) did not have an effect on survival.

Key safety findings

Adverse events

	Group 1 >12 hours preservation time % (n=97)	Group 2 <12 hours preservation time % (n=809)	P value
Mortality			
30-days	2 (2/97)	4 (34/809)	0.42
90 days	3 (3/97)	7 (58/809)	0.19
1-year	13 (13/97)	14 (116/809)	0.88
ISHLT primary graft dysfunction grade 72 hours^			0.85*
Grade 0	63 (61/97)	60 (487/809)	
Grade 1	13 (13/97)	13 (103/809)	
Grade 2	13 (13/97)	17 (137/809)	
Grade 3	10 (10/97)	10 (83/809)	

*difference between all groups

^ PGD was graded based on the International Society for Heart and Lung Transplantation (ISHLT) criteria, with grade 3 representing P/F ratio <200 within 72 hours and radiographic infiltrates.

Validity and generalisability of the studies

- Most of the studies included in systematic reviews were either retrospective or prospective cohort studies. Only one study included in the systematic reviews was from the UK.
- Three different ex-vivo lung perfusion (EVLP) devices and protocols have been reported in studies included in the overview (1) Toronto protocol; (2) Lund protocol and (3) Organ Care SystemTM (OCS) protocol. There are differences between these devices in terms of technology, design, and concept. All these vary in composition of the perfusate, perfusion and ventilation settings, and equipment used.
- There are limited randomised controlled trials, but no comparative studies between different EVLP systems to identify the optimal technique and solution for EVLP.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation. NICE interventional procedures guidance 636 (2019). Available from http://www.nice.org.uk/guidance/IPG636
- Living-donor lung transplantation for end-stage lung disease. NICE interventional procedures guidance 170 (2006). Available from http://www.nice.org.uk/guidance/IPG170

NICE guidelines

- Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation. NICE clinical guideline 135 (2011, updated 2016). Available from http://www.nice.org.uk/guidance/CG135

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One professional expert questionnaires for ex-situ machine perfusion for extracorporeal preservation of lungs (ex-vivo lung perfusion) for transplant was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sought patient commentary for this procedure but none was received.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials

1. NCT01365429 Novel Lung Trial: Normothermic Ex Vivo Lung Perfusion (Evlp) As An Assessment Of Extended/Marginal Donor Lungs (device: XPS with Steen solution), non-randomised study, n=252, prospective,

nonrandomised, controlled, clinical study in 84 recipients in eight US centres comparing 30 days post-transplant mortality as primary endpoint between standard donor lungs (42 cases) versus extended-criteria donor lungs (42 cases) after EVLP reconditioning according to the Toronto protocol using the XPSTM device, location USA, completion date: December 2020.

2. NCT02235610: Use of Ex Vivo Lung Perfusion (EVLP) in Reconditioning Marginal Donor Lungs for Transplantation (EVLP-CHUM) n=50, non-randomised study, primary outcome, survival 12 months after transplantation, completion date: December 2022, Canada, status: recruiting.

3. NCT03293043: The University of Alberta Negative Pressure Ventilation Ex-Vivo Lung Perfusion (NPV-EVLP) Trial. device (NPV-EVLP) feasibility study; n=12, single group assignment; primary outcome- survival at 30 days, primary graft dysfunction grade 3 at 72 hours, completion date December 2020, Canada, status: active.

4. NCT03053349: Ex Vivo Lung Perfusion in Bergamo Lung Transplant Program n=10, cohort study, primary outcome- primary graft dysfunction at 72 hours, completion date March 2020; Italy, status: recruiting

5. NCT02234128: Extending Preservation and Assessment Time of Donor Lungs Using the Toronto EVLP System™ at a Dedicated EVLP Facility (device Toronto EVLP system), non-randomised study, n=117, USA, completion date: April 2020.

6. NCT03641677: Increasing Lung Transplant Availability Using Normothermic Ex Vivo Lung Perfusion (EVLP) at a Dedicated EVLP

Facility n=186, non-randomised study, primary outcome-6 months survival, completion date: June 2021, USA, status: recruiting.

7. NCT03343535: Trial to Evaluate the Safety and Effectiveness of the Portable Organ Care System (OCS™) Lung System for Recruiting, Preserving and Assessing Non-Ideal Donor Lungs for Transplantation, [EXPAND LUNG II], single group assignment, n=90, primary outcome-patient survival at 30 days, donor lung utilisation rate, location-USA, completion date 2022.

8. NCT04017338: Transplantation Using Hepatitis C Positive Donors, A Safety Trial recipients on the wait-list for lung, heart, kidney, and/or pancreas transplants will all receive antiviral treatment. Lung recipients will also receive donor lungs that are treated with normothermic EVLP, n=40, single group assignment, primary outcome-survival at 6 months, incidence of adverse events at 30 days, Canada, completion date December 2024.

9. ChiCTR1800017807: Application and promotion of normothermic ex-vivo lung perfusion (EVLP) for extended criteria lungs in lung transplantation. Non-randomised observational study, n= 20, primary outcome- survival, quality of life, transplant complications; location -China, status: ongoing.

References

1. Chakos A, Ferret P, Muston B et al. (2020) Ex-vivo lung perfusion versus standard protocol lung transplantation—mid-term survival and meta-analysis. Annals of Cardiothoracic Surgery. 9 (1):1-9.
2. Luo Q, Zhu L, Wang Y et al. (2019) The conversional efficacy of ex vivo lung perfusion and clinical outcomes in patients undergoing transplantation of donor lungs by ex vivo lung perfusion: a meta-analysis. Annals of Transplantation; 24: 647-660.
3. Tian D, Wang Y, Shiiya H et al. (2019) Outcomes of marginal donors for lung transplantation after ex vivo lung perfusion: a systematic review and

meta-analysis. The Journal of Thoracic Cardiovascular Surgery, 159 (2), 720-730e6.

4. Divithotawela C, Cypel M, Martinu T et al. (2019) Long-term outcomes of lung transplant with ex vivo lung perfusion. *JAMA Surg*;154(12):1143-1150.
5. Loor G, Warnecke G, Villavicencio M et al. (2019). Portable Normothermic ex-vivo Lung Perfusion, ventilation, and functional assessment with the Organ Care System (OCS) on donor lung use for transplantation from extended criteria donors (EXPAND): a single arm, pivotal trial. The Lancet Respiratory medicine 7(11): 975-984.
6. Cypel M, Yeung JC, Donahoe L et al. (2020) Normothermic ex vivo lung perfusion: Does the indication impact organ utilization and patient outcomes after transplantation? Thoracic Cardiovascular Surgery; 159:346-55.
7. Yeung JC, Krueger T, Yasufuku K et al. (2017) Outcomes after transplantation of lungs preserved for more than 12 hours: a retrospective study. Lancet Respiratory Medicine, 5 (2), 119-124.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	13/01/2021	Issue 1 of 12, January 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	13/01/2021	Issue 1 of 12, January 2021
MEDLINE (Ovid)	12/01/2021	1946 to January 08, 2021
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	12/01/2021	1946 to January 08, 2021
EMBASE (Ovid)	13/01/2021	1974 to 2021 January 12

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Lung/ (220978)
2 Perfusion/ (49040)
3 Organ preservation/ (8879)
4 1 and (2 or 3) (2864)
5 ((Normothermi* or Ex-Vivo or "ex vivo" or warm* or ex-situ or "ex situ" or machin* or extracorporeal*) adj4 lung* adj4 (perfus* or evaluat* or apprais* or assess* or ventilat*)).tw. (605)
6 Warm Ischemia/ (1159)
7 Organ Preservation Solutions/ (3426)
8 EVLP.tw. (204)
9 ((Lung* or pulmonar*) adj4 (recondition* or re-condition* or regenerat* or refurbish* or renovat* or restor* or wash* or solution* or stimulat* or revital* or reviv* or resuscit* or revamp* or preserv* or sustenat*)).tw. (9982)
10 or/4-9 (16779)
11 Lung transplantation/ (15101)
12 ((Lung* or pulmonar*) adj4 (transplant* or graft*)).tw. (18970)
13 Primary graft dysfunction/ (771)
14 ((Primary* or chronic*) adj4 graft* adj4 dysfunct*).tw. (1054)
15 PGD.tw. (3482)

16 ((donor* or donat* or remov*) adj4 (lung* or pulmonar* or high risk*)).tw. (6215)
17 or/11-16 (30113)
18 Vivoline.tw. (1)
19 TransMedics.tw. (17)
20 Vitrolife.tw. (78)
21 Portable Organ Care System.tw. (3)
22 (lung assist or organ assist).tw. (284)
23 xps ex-vivo perfusion system.tw. (0)
24 XVIVO Perfusion System.tw. (2)
25 or/18-23 (380)
26 (10 or 25) and 17 (1968)
27 animals/ not humans/ (4686361)
28 26 not 27 (921)
29 limit 28 to english language (852)
30 limit 29 to ed=20191101-20210131

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Aigner C, Slama A, Hötzenecker K, et al. (2012) Clinical ex vivo lung perfusion--pushing the limits. Am J Transplant; 12:1839-47.	Prospective cohort study n=EVLP 9 lungs Standard n=119 lungs Follow up mean 0.77 years	Median total ischemic time of 577 min. No patients developed primary graft dysfunction grades 2/3 within 72h after transplant. One patient had prolonged ECMO postoperatively. 30-day mortality was 0%, in-hospital mortality was 1.	Study included in systematic review added to table 2.
Bennett DT, Reece TB, Smith PD et al. (2014) Ex Vivo Lung Perfusion Allows Successful Transplantation of Donor Lungs from Hanging Victims. Ann Thorac Surg; 98:1051–6	Case series N=5 BDD lungs (from victims of asphyxia) treated with EVLP and followed by transplant.	Donor organs rejected for transplant showed either signs of worsening PaO2 or deterioration of physiologic metrics. There were no intraoperative complications in the patients who underwent transplant, and	Larger studies included in table 2.

		all were alive at 30 days.	
Boffini M, Ricci D, Bonato R et al. (2014) Incidence and severity of primary graft dysfunction after lung transplantation using rejected grafts reconditioned with ex vivo lung perfusion. Eur J Cardiothorac Surg; 46(5): 789–93.	Cohort study EVLP n=8 (marginal donor) Standard n=28 All DBD lungs, mainly bilateral lung transplant. Follow up mean 30 days.	Incidence rate of primary graft dysfunction grade 3 at 0 days is 50 versus 37% (p=not significant) and at 72 hours was 25 versus 0%. ECMO was needed in 5 and 2 patients in each group.	Study included in systematic review added to table 2.
Bozso S, Vasanthan V, Luc JGY et al. (2015) Lung transplantation from donors after circulatory death using portable ex vivo lung perfusion. Canadian Respiratory Journal; 22(1):47-51.	Case series N= 3 bilateral lung transplants from donors after circulatory death were treated with EVLP Follow up 6-month period.	Lung function remained stable with improvement in partial pressure of oxygen/fraction of inspired oxygen ratios. Mechanical ventilation was discontinued within 48 h and no patient stayed in the intensive care unit longer than 8 days. There was no post-graft dysfunction at 72 h in 2 of 3 recipients. 90-day mortality for all recipients was 0%.	Larger studies included in table 2.
Buchko MT, Boroumand N, Cheng JC et al. (2020) Clinical transplantation using negative pressure ventilation ex situ lung perfusion with extended criteria	Case series N=12 extended criteria donor human lungs had negative	No patients demonstrated primary graft dysfunction scores grade 3	Larger studies included in table 2.

donor lungs. Nature communications; 11 (1); 5765 https://doi.org/10.1038/s41467-020-19581-4	pressure ventilation ex situ lung perfusion	at 72 h or requiring post-operative extracorporeal membrane oxygenation. Patients survived to 30 days and recovered to discharge from hospital.	
Cypel M, Yeung JC, Machuca T et al. (2012) Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg; 144(5): 1200–6	Cohort study EVLP n=50 (marginal donor) Standard n=253 DBD and DCD lungs; mainly bilateral lung transplant. Follow up up to 3.5 years.	Primary graft dysfunction grade 3 at 72 hours was 2% in EVLP group and 8.5% in the control group (p=0.14). One patient in EVLP group and 7 patients in control group required ECMO (p= 1.00). The median time to extubation, intensive care unit stay, and hospital length of stay were 2, 4, and 20 days, in the EVLP group and 2, 4, and 23 days, in the control group (p>.05). 30-day mortality (4%in the EVLP group and 3.5%in the control group, p=1.00) and 1-year survival	Study included in systematic review added to table 2.

		(87% in the EVLP group and 86% in the control group, p=1.00) were similar in both groups.	
Cypel M, Yeung JC, Liu M et al (2011) Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation. New England Journal of Medicine; 364:1431-1440.	Cohort study N=23 EVLP treated lungs. Standard 116 lungs Follow up 30 days	The incidence of primary graft dysfunction 72 hours after transplant was 15% in the EVLP group and 30% in the control group (P=0.11). No significant differences were observed for any secondary end points, and no severe adverse events were directly attributable to EVLP.	Larger studies included in table 2.
Fildes JE, Archer LD, Blaikley J, et al. (2015) Clinical Outcome of Patients Transplanted with Marginal Donor Lungs via Ex Vivo Lung Perfusion Compared to Standard Lung Transplantation. Transplantation; 99:1078-83.	Cohort study N=EVLP 9 double lung transplants Standard n=46 lungs Follow up not reported.	Length of stay in ICU EVLP 19 versus standard 10 days. Length of hospital stay EVLP 54 versus standard 39 days. 30-day mortality EVLP 0 versus 1 in standard group. Pneumonia EVLP 2 versus standard 8.	Study included in systematic review added to table 2.
Fisher A, Andreasson A, Chrysos A, et al. (2016) An observational study of Donor Ex vivo lung perfusion in UK lung transplantation: DEVELOP-UK.	Prospective cohort study EVLP n=18 (double lungs	30-day morality EVLP 1 versus standard 6. Primary graft dysfunction	Study included in systematic review

Health Technology Assessment; 20:1-276.	16, single lung 2) Standard n=184 (double lungs 152, single lungs 24) Follow up mean 1 year	EVLP 5 versus 32. ICU length of stay 14.5 versus 4.3 days. Hospital length of stay 28 days across both groups.	added to table 2.
Fumagalli J, Ross L, Gori F et al. (2020) Early pulmonary function and mid-term outcome in lung transplantation after ex-vivo lung perfusion – a single-center, retrospective, observational, cohort study. Transplant International; 33: 773–785	Retrospective case series EVLP 31 (marginal donor lungs) Standard n=160 DBD/ECD lungs Follow up median 2.5 years.	EVLP patients had worse PaO2/FiO2 [276 versus. 204 mmHg, $p < 0.05$], more frequent ECMO support (18% vs. 32%, $p = 0.053$) and longer mechanical ventilation duration [28 versus. 26 days, $p < 0.05$]. ICU length of stay [4 versus 6 days, $p = 0.208$], 28-day survival (99% vs. 97%, $p = 0.735$), and 1-year respiratory function were similar between groups. Survival was similar at 2.5 years.	Larger studies included in table 2.
Ghaidan H, Fakhro M, Andreasson J, et al. (2019) Ten year follow up of lung transplantations using initially rejected donor lungs after reconditioning using ex vivo lung perfusion. J Cardiothorac Surg; 14:125.	Retrospective cohort study EVLP 6 Standard 15 All double lung transplants	In-hospital mortality 0, 30-day mortality EVLP 0 versus standard 1.	Study included in systematic review added to table 2.

	Follow up mean 10 years		
Gu C, Pan X, Shi J. (2020) Progress of clinical ppplication for ex vivo lung perfusion (EVLP) in lung transplantation. Precision Medicine. Methods in Molecular Biology, vol 2204, 217-224.	Review	EVLP increases the number of lungs that meet the transplant criteria and, to some extent, alleviates the current situation of shortage of donor lungs. This chapter reviews the clinical application and research progress of EVLP in the field of lung transplant.	Review
Hauck J, Osho A, Castleberry A et al. (2014) Acute kidney injury after exvivo lung perfusion (EVLP).	Cohort study (retrospective) EVLP lungs 13 Standard lungs 52.	Acute kidney injury rates between EVLP and standard lung transplant procedures were similar (54% [8/13] versus 62% [32/52], p=0.61). One non-EVLP patient needed dialysis.	Larger studies included in table 2.
Ingemasson R, Ejyolfsson A, Mared L et al. (2009) Clinical Transplantation of Initially Rejected Donor Lungs After Reconditioning Ex Vivo. Annals of Thoracic Surgery; 87:255–60	Case series N=6 EVLP treated lungs used for transplant	Three-month survival was 100%. One patient died due to sepsis after 95 days, and one due to rejection after 9 months. Four recipients are alive and well without any sign	Larger studies included in table 2.

		of bronchiolitis obliterans syndrome at 24 months.	
Jawitz OK, Raman V, Becerra, D et al. (2020) Lung transplantation after ex vivo lung perfusion,. Annals of Surgery: July 24, Published Ahead of Print doi: 10.1097/SLA.0000000000004233	National transplant registry analysis 3334 lung transplant recipients (155 EVLP recipients and 3179 non-EVLP recipients).	Early recipient outcomes comparable to that of non-EVLP recipients. On unadjusted descriptive analysis, EVLP and non-EVLP cohorts had similar 180-day survival (92% vs 92%, P = 0.9). EVLP use was associated with a similar rate of acute rejection (13% vs 9%, P = 0.08) but increased rate of early extracorporeal membrane oxygenation use (12% vs 7%, P = 0.04). After adjustment, EVLP use was not associated with significantly increased mortality (adjusted hazard ratio 0.99, 95% confidence interval 0.62–1.58) or acute rejection (adjusted odds ratio 0.89, 95% confidence interval 0.40–1.97) compared	Larger studies included in table 2.

		to non-EVLP use.	
Koch A, Pizanis N, Olbertz C, et al. (2018) One-year experience with ex vivo lung perfusion: Preliminary results from a single center. International Journal of Artificial Organs; 41:460-6.	Retrospective cohort study EVLP n=11 Standard 41 All DBD lungs, all double lung transplants Follow up mean 1 year	Extubation time EVLP 221 versus 124 hours. In-hospital mortality 0, 30-day mortality 1 in each group. ICU stay EVLP 12.5 versus 19 days, hospital stay 26 days in both groups.	Study included in systematic review added to table 2.
Koch A, Pizanis N, Bessa V et al. Impact of normothermic ex vivo lung perfusion on early post-transplantation cytomegalovirus infection. J Thorac Dis 2020;12(4):1350-1356.	Retrospective study N=57 (16 EVLP treated lung transplants versus 41 lungs after cold storage preservation)	Donors were CMV IgG+ in EVLP 69% and CSP 61% (n.s.). Recipients were CMV IgG+ in EVLP 38% and CSP 63% (p<0.07). The seroconversion rate in the EVLP group (12%) showed a trend to be lower compared to the CSP (20%) group (p<0.05), Procalcitonin (PCT) levels from day 1 to day 5 were significantly lower for CSP group (p<0.05). 30-day mortality was 12% for EVLP recipients. 1 year survival rates were not significantly different (95% in	Larger studies included in table 2.

		CSP group and 78% in EVLP group). EVLP treatment did not negatively affect the post-transplant CMV seroconversion rate.	
Lindstedt S, Eyjolfsson A, Koul B et al. (2011) How to Recondition Ex Vivo Initially Rejected Donor Lungs for Clinical Transplantation: Clinical Experience from Lund University Hospital. Journal of Transplantation.	Review of 6 double lung transplants performed with donor lungs reconditioned EVLP for transplant	3 months survival was 100%. One patient died due to sepsis after 95 days, and one due to rejection after 9 months. 4 recipients are alive and well 24 months after transplant.	Larger studies included in table 2.
Lindstedt S, Hlebowicz J, Koul B et al. (2011) Comparative outcome of double lung transplantation using conventional donor lungs and non-acceptable donor lungs reconditioned ex vivo. Interact Cardiovasc Thorac Surg; 12(2): 162–65	Cohort study EVLP n=6 (marginal donors) Standard n=15 All DBD donors; bilateral lung transplants Follow up not reported	Time in intensive care unit between EVLP lungs 13 days, and recipients of conventional donor lungs 7 days, p=0.44. Total hospital stay for EVLP was 52 days and standard lungs 44 days, p=0.9. Given the small number of patients, there might be a failure to detect a difference between the 2 groups.	Study included in systematic review added to table 2.
Lightle W, Daoud Dm Loor G (2009) Breathing lung	Review	Review discusses the	Review

transplantation with the Organ Care System (OCS) Lung: lessons learned and future implications. J Thorac Dis; 11(Suppl 14): S1755-S1760		available literature on the clinical outcomes of OCS Lung as well as translational data.	
Loor G (2019) EVLP: ready for prime time. Semin Thoracic Surg 31:1-6	Review	Review focuses on the needs met by ex vivo lung perfusion, and the clinical literature on both devices.	Review
Luc JGY, Jackson K, Weinkauf JG et al (2017) Feasibility of lung transplantation from donation after circulatory death donors following portable ex vivo lung perfusion: A pilot study. Transplant Proc; 49(8): 1885–92	Cohort study EVLP 7 (marginal donor) Standard 4 All DCD lungs Follow up 1 year	EVLP has shorter cold ischemic time, lower grade of primary graft dysfunction at 72 hours, similar mechanical ventilation time, and hospital length of stay. All were alive at 1 year with improved functional outcomes and acceptable quality of life.	Study included in systematic review added to table 2.
Machuca TN; Cypel M. (2014) Ex vivo lung perfusion. Journal of Thoracic Disease. 6, (8); 1054-62.	Review	This article reviews the technical details of EVLP; the rationale behind the method; report the worldwide clinical experience with the EVLP, including the	Review

		Toronto technique and others; (IV) finally, discuss the growing literature on EVLP application for donation after cardiac death (DCD) lungs.	
Machuca TN, Mercier O, Collaud S et al. (2015) Lung transplantation with donation after circulatory determination of death donors and the impact of ex vivo lung perfusion. Am J Transplant; 15(4): 993–1002	Cohort study EVLP n= 28 (marginal donor) Standard n=27 All DCD lungs; mainly bilateral lung transplant Follow up up to 7 years	1-year and 5-year survival were 85 and 54% for EVLP group versus 86 and 62% for standard group (p=0.43). EVLP Group had shorter hospital stay (median 18 versus 23 days, p=0.047) and a trend toward shorter length of mechanical ventilation (2 versus 3 days, p=0.059).	Study included in systematic review added to table 2.
Mohite PN, Sabashnikov A, Gracia Saez D et al. (2015) Utilization of the Organ Care System Lung for the assessment of lungs from a donor after cardiac death (DCD) before bilateral transplantation. Perfusion, Vol. 30(5) 427–430	Case report N=1 EVLP and subsequent transplant - donation circulatory death (DCD) lungs, normothermic preservation Organ Care System (OCS) used	The OCS could potentially be a standard of care in the evaluation of marginal lungs from DCD.	Larger studies included in table 2.
Nilsson T, Wallinder A, Henriksen I, et al. (2019) Lung	Prospective cohort study	In-hospital mortality EVLP 1	Study included in

transplantation from initially rejected donors after ex vivo lung reconditioning: The French experience. Eur J Cardiothorac Surg; 55:766-72.	EVLP n=61 Standard n=271 All DBD lungs, mainly double lung transplants. Follow-up mean 1 year	versus standard 4. Extubation time EVLP 18 versus 7 hours. Length of stay in ICU EVLP 4 versus 3. Hospital stay EVLP 30 versus 28 days.	systematic review added to table 2.
Niikawa H, Okamoto T, Ayyat KS et al. (2020) Successful lung transplantation after acellular ex vivo lung perfusion with prone positioning. The Annals of Thoracic Surgery; 110 (4); e285-e287.	Case report N=2	This report describes 2 cases in which prone positioning during EVLP significantly reduced lung weight. One of the 2 cases resulted in successful double-lung transplant.	Larger studies included in table 2.
Prasad NK, Pasrija C, Talaie T et al. (2020) Ex vivo lung perfusion: current achievements and future directions. Transplantation; Volume Online First - Issue -doi: 10.1097/TP.0000000000003483	Review	In this review we discuss the history of EVLP, current evidence on its use for standard and extended criteria donors and consider the exciting future opportunities that this technology provides for lung transplant.	Review
Raemdonck, DV, Neyrinck A, Cypel M et al. (2015) Ex-vivo lung perfusion. Transplant International 28 643–656	Review on EVLP	The rationale, the experimental background, the technique and protocols, and available devices for	Review

		EVLP are discussed. The current clinical experience worldwide and ongoing clinical trials are reviewed.	
Sage E, Mussot S, Trebbia G, et al. (2014) Lung transplantation from initially rejected donors after ex vivo lung reconditioning: The French experience. Eur J Cardiothorac Surg; 46:794-9.	Prospective cohort study EVLP n=31 Standard n=81 All DBD lungs, and double lung transplants Follow-up mean 1 year	30-day mortality EVLP n=1 versus standard n=3. Extubation time 24 hours in both groups. Primary graft dysfunction EVLP 3 versus standard 7. ICU length of stay 9 versus 6; hospital length of stay 37 versus 28 hours.	Study included in systematic review added to table 2.
Sanchez PG, Davis RD, D'Ovidio F et al. (2014) The NOVEL lung trial one-year outcomes. J Heart Lung Transplant; 33(4): S71–72	Randomised controlled trial EVLP 42 (marginal donor) versus standard 42 Mainly DBD lungs Follow-up up to 1 year		Abstract only - included in systematic review added to table 2.
Schiavon M, Faggi G, Rebusso A et al. (2019) Extended criteria donor lung reconditioning with the Organ Care System Lung. A single institutional experience. Transplant Int 32: 131-40.	Case series N=8 EVLP treated lungs used for transplant. Follow-up 1 year.	All donor lungs improved in PaO2/FiO2 ratio. Primary grade dysfunction grade 3 at 72 hours was seen in 1 patient. 1 hospital death reported and 2 patients died at 1-year follow-up.	Larger studies included in table 2.

		Survival was 62.5%	
Shafaghi S, Najafizadeh K. (2016) The First Experience of Ex-Vivo Lung Perfusion (EVLP) in Iran: An Effective Method to Increase Suitable Lung for Transplantation. International Journal of Organ Transplantation Medicine. Vol 7 (4), 220-227	Case series N=4 EVLP lungs All DBD lungs	The initial experience of EVLP in Iran was successful in terms of important/critical parameters.	Larger studies included in table 2.
Slama A, Schillab L, Barta M et al. (2017) Standard donor lung procurement with normothermic ex vivo lung perfusion: A prospective randomized clinical trial. J Heart Lung Transplant; 36 (7): 744–53	Randomised controlled trial EVLP n=35 versus standard n=41 Mainly DBD donors, all double lung transplants Follow-up 90 days	Incidence of primary graft dysfunction was lower in the EVLP group compared to standard group at all time points. Need for ECMO was also lower in the EVLP group. Patients remained intubated for 1.6 days in both groups, ICU stay was 6 days, and hospital stay was comparable p=0.42. 30-day survival was 97.1% vs100% (p= 0.46).	Study included in systematic review added to table 2.
Tikkanen JM, Cypel M, Machuca TN, et al. (2015) Functional outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation. J Heart Lung Transplant; 34:547-56.	Retrospective cohort study EVLP n=63 Standard n=340 All DBD lungs, mainly double lung transplants Follow-up not reported	Graft survival EVLP 79 versus standard 85% at 1 year, 71 versus 73% at 3 years, 58 versus 57% at 5 years. Acute rejection episodes 1.5 versus 1.3%, p=0.36. Improved quality	Study included in systematic review added to table 2.

		of life but no significant difference between groups.	
Valenza F, Rosso L, Gatti S et al. (2012) Extracorporeal lung perfusion and ventilation to improve donor lung function and increase the number of organs available for transplantation. Transplantation proceedings, 44 1826-1829.	Case series N=2 EVLP and 4 standard lung transplants Follow-up 6 months	Functional outcomes were similar between groups. ICU and hospital stay were similar and mortality at 6 months.	Larger studies included in table 2.
Valenza F, Rosso L, Coppola S, et al. (2014) Ex vivo lung perfusion to improve donor lung function and increase the number of organs available for transplantation. Transplantation International; 27:553-61.	Cohort study EVLP n=7 Standard n=28 All DBD lungs, mainly double lung transplants. Follow-up mean 0.71 years	30-day mortality 0% in both groups. Extubation time EVLP 72 versus 36 hours. Primary graft dysfunction EVLP 2 versus 9. ICU length of stay EVLP 10 versus 5.5 days.	Study included in systematic review added to table 2.
Wallinder A, Ricksten SE, Hansson C (2012) Transplantation of initially rejected donor lungs after ex vivo lung perfusion. The Journal of Thoracic and Cardiovascular Surgery; 144:1222-8	Case series N=6 pairs of lungs had EVLP (marginal donors).	One patient had primary graft dysfunction grade 2 at 72 hours. Median time to extubation was 7 hours. All patients survived 30 days and were discharged in good condition from the hospital.	Larger studies included in table 2.
Wallinder A, Ricksten SE, Silverborn M et al. (2014) Early results in transplantation of initially rejected donor lungs after ex vivo lung perfusion: A case-control study. Eur J Cardiothorac	Cohort study EVLP n=11 (marginal donors) Standard n=47	The median time to extubation (12 versus 6 and median ICU stay (152 versus 48 hours) were longer in the EVLP group (p =	Study included in systematic review added to table 2.

Surg; 45 (1): 40–44; discussion 44–45	All DBD donors; mainly bilateral transplants Follow-up 3 months	0.05 and p = 0.01). There were no differences in length of hospital stay (median 28 versus 28, p = 0.21). 2 in the EVLP group and 6 in the control group had primary graft dysfunction grade 1 at 72 h. 3 patients in the control group died before discharge.	
Wallinder A, Riise GC, Ricksten SE, et al. (2016) Transplantation after ex vivo lung perfusion: A midterm follow-up. J Heart Lung Transplant; 35:1303-10.	Retrospective cohort study EVLP n=27 Standard n=145 Double or single lung transplants done. Follow-up EVLP mean 1.6 years, standard mean 1.3 years.	In-hospital mortality EVLP n=1 versus standard 8. 30-mortality 0 in both groups. ICU length of stay mean 8 days in both groups. Primary graft dysfunction EVLP n=3 versus standard n=17. ECMO use 2 versus 6.	Study included in systematic review added to table 2.
Warnecke G, Moradiellos J, Tudorache I et al. (2012) Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: A pilot study of 12 patients. Lancet; 380 (9856): 1851–58	Cohort study N=12 EVLP (marginal donor lungs). Follow-up not reported	The final ratio of PaO2 to FIO2 measured with the OCS Lung was 471·58. The difference between these ratios was not significant (p=0·72). All grafts and patients survived	Study included in systematic review added to table 2.

		to 30 days; all recipients recovered and were discharged from hospital.	
Warnecke G, Van Raemdonck D, Smith MA, et al. (2018) Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. Lancet Respir Med; 6:357-67.	Randomised controlled trial EVLP (OCS device) n=151 versus standard 169 All double lung transplants. Mean follow-up 2 years.	In-hospital mortality EVLP n=9 versus standard n=11; 30-day mortality 6 versus 0. Primary graft dysfunction EVLP n=3 versus n=7. Pneumonia n=15 versus 26.	Study included in systematic review added to table 2.
Zhang ZL, van Suylen V, van Zanden JE, et al. (2019) First experience with ex vivo lung perfusion for initially discarded donor lungs in the Netherlands: a single-centre study. Eur J Cardiothorac Surg; 55:920-6.	Retrospective cohort study EVLP 9 versus standard 18 Follow-up mean 3 years	30-day mortality 0% in both groups. Primary graft dysfunction EVLP 0 versus 2. ICU length of stay EVLP 11 days versus 5,2 days. Hospital length of stay EVLP 31 versus standard 42 days.	Study included in systematic review added to table 2.
Zeriouh M, Sabashnikov A, Mohite PN, et al. (2016) Utilization of the organ care system for bilateral lung transplantation: Preliminary results of a comparative study. Interact Cardiovasc Thorac Surg; 23:351-7.	Retrospective case series EVLP n=14 Standard n=308 Mainly DBD lungs, all double lung transplants. Follow-up EVLP mean 0.5 years, standard mean 2 years.	30-day mortality EVLP n=2 versus standard n=12. Primary graft dysfunction EVLP n=2 versus 25. ICU length of stay 5 versus 6 days, hospital stay 23 versus 32 days.	Study included in systematic review added to table 2.
Zych B, Popov AF, Stavri G et al. (2012) Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung	Cohort study	100% survival at 3 months.	Study included in systematic review

evaluation and reconditioning. J Heart Lung Transplant; 31(3): 274–81	EVLP n=6 (marginal donors) Standard n=86 Mainly DBD lungs Follow-up median 297.5 days	EVLP may facilitate reconditioning of borderline lungs with a conversion rate of 46% and good short-term survival.	added to table 2.