NHS England

Evidence review: Extracorporeal Membrane Oxygenation (ECMO) for Bridge to Lung Transplant

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1. Introduction

Bridge to Lung Transplant

Lung transplantation is routinely performed for selected patients with respiratory failure. However, approximately 25% of patients on the waiting list die before a suitable donor becomes available or are removed from the waiting list due to deteriorating health rendering lung transplantation futile and inappropriate. There are therefore a substantial proportion of patients who would benefit from ventilatory support to bridge them to transplant. Traditionally, mechanical ventilation (MV) has formed the mainstay of this bridging support but it is not sufficient for all patients and has been associated with devastating complications and poor post-transplant outcomes (Todd et al 2017) which means that lung transplants are rarely performed in invasively ventilated patients any more. An alternative to MV is extracorporeal life support which comprises extracorporeal membrane oxygenation (ECMO) and interventional lung assist (iLA).

Extracorporeal life support (ECLS)

ECMO and iLA are techniques for providing respiratory support for those people whose lungs are no longer able to sustain life despite all other therapeutic and supportive interventions. Treatment is provided for critically ill people in a level 3 critical care area. Blood is removed from the patient's circulation and passes through a gas exchanged device before being returned to the circulation. ECMO removes blood from the venous circulation which is then pumped through a gas exchange device and is returned to either the arterial circulation (veno-arterial (VA) ECMO) or the venous circulation (veno-venous (VV) ECMO). VV ECMO provides respiratory support only whereas VA ECMO can provide full cardiorespiratory support. The iLA relies on patients own arterial blood pressure to drive blood flow from an artery through the iLA typically without a mechanical pump, blood is then returned to the venous circulation. The iLA can allow clearance or carbon dioxide but has limited capacity for oxygenation and no capacity for circulatory support.

These techniques have been used in respiratory failure for several decades but the poor outcomes traditionally experienced by patients who received ventilation support while on the waiting list have until recently made these a contraindication to transplant. However, this view has begun to change after the publication of the CESAR trial which clearly showed an improvement in the mortality and severe disability at 6-month follow up of patients with severe respiratory failure who had been randomised to treatment with ECMO in an expert high-case-volume centre compared with no specialised hospital care (Peek et al 2009). Popularity for using it as a method of bridging to transplant is now increasing as improved technology and clinical expertise, together with thoughtful, deliberate patient selection is resulting in the emergence of a strong body of evidence that outcomes on ECMO for bridge to transplant (BTT) are comparable to those of non-bridged patients (Hoetzenecker et al 2017; Hayanga et al 2018; Todd et al 2017).

Complications

ECMO is an invasive procedure and complications are common and it is therefore associated with significant increases in morbidity and mortality. Complications can be related to the underlying lung pathology that needed ECMO, or with the ECMO procedure itself (surgical insertion, circuit tubing or anticoagulation etc) (Majdisi and Wang 2015):

- The most common complication is bleeding which can occur at the insertion site or any other tissue site, pulmonary haemorrhage or intracerebral haemorrhage.
- Systemic thromboembolism due to thrombus formation within the extracorporeal circuit.
- Neurological complications are highly variable and include seizures, infarction and haemorrhage.
- Arrhythmias may occur as a result of hypoxia and electrolyte imbalance or an underlining cardiac pathology.
- Oliguria is a commonly observed renal complication during the early part of ECMO and acute tubular necrosis is observed in some patients and may require hemofiltration and dialysis.
- Septic complications may also result because the ECMO circuit represents a large intravascular foreign body, and frequent manipulation increases the risk of infection.
- Metabolic complications include electrolyte imbalances, and hypo or hyperglycaemia.

- GI tract complications include haemorrhage which may occur as a result of stress, ischemia, or bleeding tendencies.
- Direct hyperbilirubinemia and biliary calculi may occur secondary to prolonged fasting and total parenteral nutrition, haemolysis, and diuretics.

Technological developments

Significant advances in technology and clinical expertise have taken place over the past decade, which have led to improvements in outcomes using ECMO BTT. The new ECMO systems are simpler and safer and reduce the risk of many of the complications listed above. They include the use of heparin-coated circuits which are less thrombogenic and produce less activation of blood cells, polymethylpentene membranes which increases the durability and prevent plasma leak, magnetically levitated centrifugal pumps which are durable and less prone to wear, and better cannulas which are easy to insert percutaneously and allows less bleeding around them (Cypel and Keshavjee 2012). These developments combined with improvements in patient selection have made it possible to bridge successfully (to transplant) a set of selected extremely sick patients (Hoetzenecker et al 2018) and have resulted in 1-year survival post-transplant nearly equivalent to that seen in patients not receiving any bridging support, and a near doubling of the 5-year post-transplant survival over this time (Hayanga et al 2015).

Procedural developments

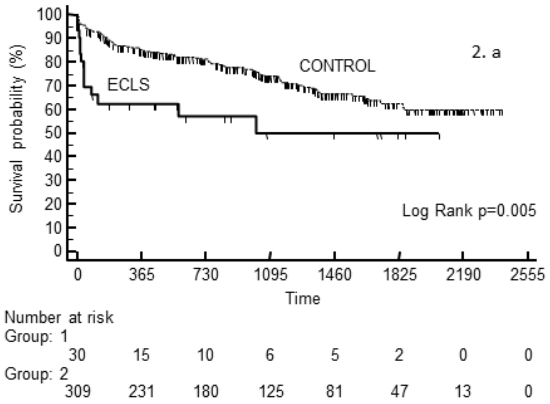
In addition to developments in ECMO technology there have been considerable advances in ECMO BTT practice and procedures. ECMO has traditionally been carried out in heavily sedated patients to prevent inadvertent cannula dislodgement, to avoid respiratory compromise and to deal with agitation and air hunger. However, there is now growing evidence for the beneficial outcomes of adopting an awake ECMO strategy either by commencing ECMO on awake patients or by awakening patients on ECMO once it has been initiated. The benefits of this are the avoidance of many of the complications associated with immobilisation, prolonged ventilation and enteral feeding. The patients can maintain their musculoskeletal strength, nutrition and airway clearance. Recent advances in the cannulation equipment can provide full respiratory support while permitting patients to be separated from mechanical ventilation and to ambulate and participate in physiotherapy while awaiting transplantation.

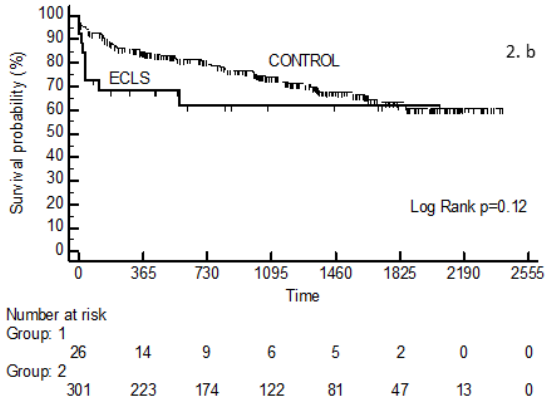
There is a substantial body of evidence for the survival and safety benefits of ECMO compared with MV as methods of ventilatory support. More generally this began with the CESAR trial (Hayes et al 2014) which revealed a superiority of ECMO over MV in potentially reversible respiratory failure patient but has now been extended to include the benefits in BTT. Fuehner et al (2012) compared post-transplant outcomes of patients BTT with either awake ECMO or conventional MV and found that survival at 6 months post-transplant was significantly better in the awake ECMO group (80% vs 50% respectively). Interestingly, the survival rate of the awake ECMO patients dropped to 43% when secondary intubation became necessary. Similarly, a study comparing patients with ECMO BTT with and without MV was conducted at a centre in Milan (Nosotti et al 2013) and found spontaneously breathing patients on ECMO BTT showed a tendency to require a shorter duration of invasive MV, ITU stay hospital stay after transplantation than patients on MV BTT. One-year survival rate was 85.7% in patients with spontaneous breathing vs 50% in patients with invasive MV.

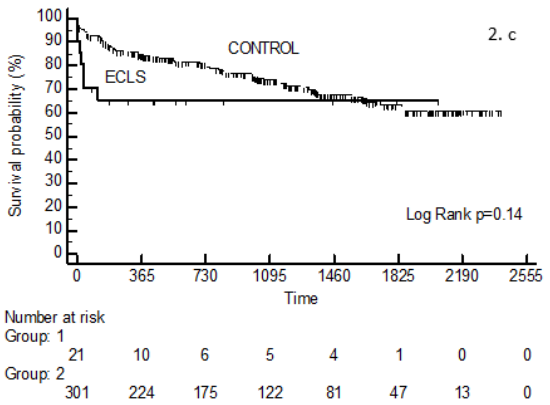
Further to this, there is now also emerging evidence that suggests that awake ECMO results in post-transplant outcomes in high risk patients comparable to those requiring no bridging support at all. For example, Mohite et al (2015) report post-transplant outcomes of a cohort of patients bridged to transplant with awake ECMO who achieved a 1-year survival not significantly different to patients receiving lung transplant without any bridging support (awake ECMO 85.7% vs. non-ECMO 86.3%). Admittedly, numbers in each of these studies has tended to be small because it is difficult to have many awake patients on ECMO at any single centre, but the favourable outcomes are becoming increasingly apparent.

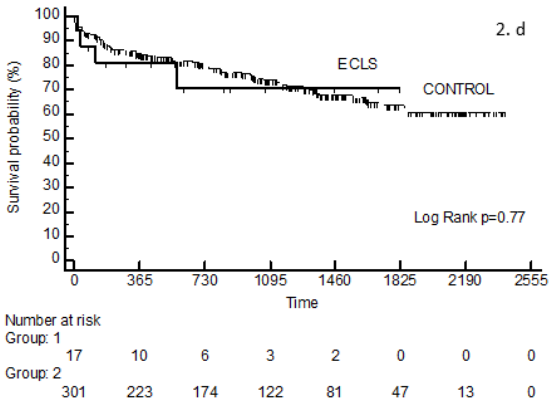
A review was performed of patients receiving lung transplants at Harefield Hospital between 2010 and 2016 (unpublished data). 339 transplantations were performed during this time with 34 patients receiving BTT with various types of ECLS. When survival of entire ECLS population was compared to the non-BTT patients it was found to be significantly lower (figure 2a). However, when patients having retransplants (known to be higher risk) were excluded no significant difference was observed (Figure 2 b). Similarly if the patients who underwent

semi-elective ECLS implantation was also excluded there was no significant difference (figure 2c). When first time ECLS bridged patients who stayed self-ventilated for at least half of the duration of support were considered, their survival even at long-term follow up was equivalent to those receiving standard non-bridged support (1 to 4 years): 81.7 vs. 84.6 %, 71.1 vs. 80.8 %, 71.1 vs. 73.9 % and 71.1 vs. 67.7 % (Log Rank p=0.77).









Taken together, these studies suggest that not only can ECMO BTT provide an effective method of bridging critically ill patients to potentially lifesaving transplant, it may also offer a significant post-transplant survival benefit over the traditional method of support with MV. Moreover, the benefits in safety and survival offered by ECMO might be further enhanced by the adoption of an awake ECMO strategy.

There may also be an economic advantage to the adoption of an awake and ambulatory approach to ECMO BTT. In the US, Bain et al (2016) conducted an economic evaluation of the costs of care associated with a cohort of patients who were ambulatory and could be rehabilitated while supported with ECMO BTT compared with a cohort who were not ambulatory. Ambulatory ECMO patients had a 22% ($60,204) reduction in total hospital cost, a 73% ($104,939) reduction in post-transplant ICU cost, and 11% ($32,133) reduction in total cost compared with non-ambulatory ECMO patients. Although this evaluation was based on a small cohort of patients (total sample of 9 patients) in a single centre, it provides some initial support that awake ECMO strategies offer a financial advantage over traditional sedated strategies.

The clinical problem

At Harefield hospital selected patients are currently bridged to lung transplantation with ECMO funded by non-NHS patient revenue. Following the implementation of the Super Urgent Lung Allocation Scheme in May 2017 the average waiting time to lung transplant for this group of patients is 10 days. The introduction of this change to the national waiting list gives this group of patients a realistic chance of a transplant within a short

time allowing for the use of ECMO for a short period to bridge these patients to lung transplant. Use of ECMO would improve post-transplant outcomes for this clearly defined group of patients, who otherwise have no chance of survival.

Indications for ECMO and expected survival without it

The approach to allocation of ECMO BTT has generally been to restrict it to patients who are refractory to maximal respiratory support but who otherwise remain viable candidates for transplantation (Shafii et al 2012). Without ECMO most of these patients would not survive to transplant and would die (Cypel and Keshavjee 2012, du Perrot et al 2011, Hoetzenecker et al 2018).

It is very difficult to quantify the risk of death in patients who need ECMO BTT but do not receive it as data on this is rarely collected and presented. However, one study looking at the waiting list mortality rate before and after the introduction of ECMO BTT noticed that the implementation of the Lung Allocation Score (LAS) scheme in the United States significantly reduced the waiting list mortality rate for patients with idiopathic pulmonary fibrosis and cystic fibrosis but did not affect the waiting list mortality rate for idiopathic pulmonary arterial hypertension (PAH) patients. However, a comparison of mortality on the waiting list of PAH patients between 1997 and 2005 before the use of ECLS and between 2006 and 2010 when this technology was more readily available demonstrated a reduction in the rate of death of PAH patients from 22% to 0% which was attributed to the use of this ECLS in these patients (Du Perrot et al 2011).

Although the mortality rates differ in other conditions commonly resulting in acute respiratory failure and the need for ECMO, it demonstrates that patients who are otherwise excellent candidates for transplant often die on the waiting list because they are too sick to survive until an organ becomes available. Without ECMO, the only alternative is to support them by maximal MV in the intensive care unit, but this can further aggravate the lung injury and often leads to remote organ dysfunction with subsequent high mortality before or after transplant. For many of these patients, refractory hypercapnia or hypoxemia will develop despite maximal ventilatory support and therefore extracorporeal life support (ECLS) is their only chance to survive until a compatible donor lung becomes available.

Assessing post-transplant outcomes of ECMO BTT

As ECMO is reserved for patients who are critically ill and in whom all other respiratory support is failing, they tend to sicker and at higher risk of poor outcomes and death than those in whom ECMO is not indicated. This has consistently been supported in the evidence: ECMO BTT patients tend to be younger, with cystic fibrosis and PAH over-represented (Ius et al 2018, Hayanga et al 2018, Todd et al 2017), and have higher LAS and lower functional status (Todd et al 2017). Patients on ECMO also tend to have more evidence of multiple organ system dysfunction, as evidenced by a higher incidence of dialysis, poorer kidney function, and elevated bilirubin before transplantation (Schechter et al 2016).

This critically ill state of ECMO BTT candidates has several implications when assessing the evidence for outcomes of bridging and transplant in these patients. Firstly, it means that in most cases ECMO BTT is their only chance of survival and death is an almost inevitable consequence of not receiving ECMO. Secondly, the near certain risk of death means that it is not possible to compare outcomes of transplant between patients in this critically ill state who did or did not receive ECMO, as those who do not receive it will not survive to transplant. Thirdly, it means that comparisons made with a surrogate 'next best' control group - those who did not require bridging support – will be skewed by differences in baseline levels of health and functionality. For the purposes of this evidence review, this will contribute to an overly conservative impression of the survival outcomes offered by ECMO BTT as the baseline risk of mortality is so much greater in these patients.

As mentioned above, the fact that ECMO is initiated in patients as a last resort treatment option means that it is extremely difficult to assess the impact of this treatment on survival. Evaluation of most therapeutic interventions relies on comparisons with the best available alternative, or with no treatment at all. In the case of ECMO there is no available alternative as by definition, ECMO will only be initiated when all alternatives have failed or are no longer sufficient to sustain life, and if ECMO is not initiated then death is nearly certain in 100% of patients. An ideal body of evidence would include studies where patients on the waiting list for lung transplant who were at the point of fulfilling the indication for ECMO (i.e. worsening respiratory function needing ECMO to stay alive) were randomised to receiving ECMO or not receiving ECMO, but not only would

this be unethical on clinical grounds, it would not yield any useful outcome data because those not receiving ECMO would quickly deteriorate and die before transplantation occurred. Well conducted cohort studies where the only difference in the patient groups being compared are the intervention they are given are also a good source of evidence of effectiveness and safety of interventions. However, in the case of ECMO these too suffer from the same problem that any patient on the transplant waiting list who needs ECMO for survival but does not receive it will die on the waiting list. Their inclusion as controls in cohort studies evaluating ECMO is therefore not sensible and not used in the published literature.

Given that the indications for ECMO preclude the use of patients who have a level of respiratory failure requiring ECMO but do not receive it as a control group, a rational alternative is to compare patients receiving ECMO BTT with patients who do not need ECMO BTT. As lung transplantation is a high-risk procedure with associated mortality and complications, this has the benefit of providing a comparative set of outcome data which contextualises the outcome data of ECMO BTT patients and gives some indication of magnitudes of effect and risk. This is therefore the approach taken in this evidence review.

2. Summary of results

Eight studies were used in this review: one systematic review and seven cohort studies containing between 12 and 68 patients on ECMO BTT. All the cohort studies included comparison of post-transplant outcomes in an ECMO BTT cohort and a non-bridged cohort of patients, and some contained additional comparison groups.

Survival

All studies reported 1-year survival, two reported 3-year survival and three reported 5-year survival (in all cases 'survival' means survival after transplant). Results suggest that 70-90% of patients who receive ECMO BTT are still alive at 1 year, around 60-80% are alive at 3 years, and around a 65% are alive at 5 years post-transplant. The rate of survival is no worse in critically ill patients requiring ECMO compared with less ill patients who survive to transplant without ECMO bridging support. There is also evidence that survival is better in patients receiving ECMO BTT than in those receiving MV (either with or without ECMO).

Quality of life and functional status

Health-related quality of life (HRQL) was reported by one study. Patients on ECMO BTT achieved similar improvements in HRQL and depressive symptoms as those who did not require ECMO bridging, these improvements were greatest in the first six months post-transplant and then remained stable at 12 months. Functional status was also assessed in only one study and showed that the 1-year post-transplant functional status of patients on ECMO BTT was equivalent to that of non-bridged patients and could be described as excellent.

Complications

General complications were reported in five studies, acute graft rejection in four studies, long-term graft survival in one study and post-operative ventilation in four studies. Acute graft rejection is not clearly worse in ECMO BTT than non-bridged patients and long-term follow up suggests that overall graft survival is equal. The impact of ECMO BTT on post-transplant ventilation requirements is also unclear but the higher rates seen in ECMO BTT patients in some studies may be explained by concurrent MV use. More convincingly though, ECMO BTT is associated with higher rates of some serious complications such as bleeding, delirium, myopathy and vascular and thrombotic events, although the exact magnitude of these risks is difficult to determine due

to heterogeneity in the post-transplant outcomes and indicators used in different studies. ECMO is associated with a risk of mortality in patients on this treatment, based on five studies around 20% - 30% of patients die on ECMO before transplantation.

Duration pre-transplant ECMO and length of stay

Duration of ECMO was reported by five studies and ranged from a mean of 3.2 to 15 days. There is little certainty about the exact duration to expect as the ranges are big within studies, but it seems to be the case that durations do not tend to exceed around 16 days in the majority of patients. There is a general trend towards the reporting of longer hospital and ITU stays in patients receiving ECMO BTT but big variability within studies and between studies makes it difficult to identify the exact magnitude of difference or indeed be clear about whether any differences are statistically significant.

Awake versus sedated ECMO

Although several studies included both awake and sedated patients in their ECMO BTT cohorts, only one study made a substantial comparison of post-transplant outcomes in these ECMO strategies. There is suggestion that an awake ECMO strategy offers a survival advantage over sedated strategies which use concurrent MV.

Cost effectiveness

None of the studies provided any data on cost or cost effectiveness of ECMO BTT.

Interventional Lung Assist (iLA)

None of the studies provided data on iLA.

Limitations

No studies provided data on cost effectiveness of ECMO BTT. As randomized control trials are neither practical nor ethical this review included observational studies and a systematic review. Some of the studies had small sample sizes, particularly in the ECMO BTT group, and included patients recruited over long periods of time when ECMO technology and practice may have changed.

3. Methodology

The report aimed to identify and assess the evidence comparing the effectiveness and safety of ECMO as bridge to lung transplant compared to best supportive care (no bridging).

The Medline databases were searched for any systematic reviews, clinical trials or observational studies that reported post-transplant outcomes for ECMO BTT and iLA BTT compared with patients not receiving bridging support prior to lung transplant. No restriction on study post-transplant outcomes was used in the search. Full details of the search strategy are available in section 9 (literature search terms). Exclusion criteria included:

- Only papers published in last ten years were included. There have been significant advances in ECMO technology, practice and safety over the last decade and studies published before this time may be presenting results that do not reflect outcomes of current practice which will limit applicability to the research questions.
- Only papers that report results of patient samples which include a proportion recruited in the last ten

years were included. This is for the same reasons outlined above. It was chosen not to restrict all recruitment to the last ten years as several studies used long patient recruitment periods which span beyond the last ten years to some extent.

- Only papers which reported results for 10 or more patients who underwent ECMO BTT or iLA were included. These procedures are highly technical and including single case reports or small case series might have included poorer outcomes obtained from patients with unusual circumstances (warranting case reports) or centres who have not completed a learning curve. The selection of a threshold of 10 patients is arbitrary but reflects the general distinction between small case series reports and more comprehensively deigned observational studies at larger centres or groups of centres. From a data analysis point of view the exclusion of very small studies also reduces the risk of type 1 and 2 errors (over or under estimating the causal inference).
- Only papers which included a defined control group who reached transplant without receiving bridging support were included. Lung transplantation is a high-risk procedure, even when no bridging is required, and has associated complications and mortality. It is therefore essential to review outcomes of ECMO BTT and iLA BTT in light of the outcomes expected from lung transplant alone.
- Conference abstracts were excluded due to difficulty in assessing methods and quality.
- Non-English language articles would have been excluded due to lack of translation facilities, unless they were thought to add substantially to the English language evidence base. The search and abstract review included non-English language articles, and no potentially eligible articles were identified for consideration.

Full details of the search are available in section 10 (search strategy). In brief, 402 abstracts were screened, and 31 selected for full text review. The reference lists of evidence reviews and eligible studies were screened and this identified no new eligible studies. 8 eligible studies were identified which fulfilled the search criteria and the exclusion criteria. These are described in section 11 (evidence selection).

4. Results

Overall results

Eight studies were used in this review; one systematic review and seven cohort studies. Of the cohort studies, six were retrospective and one was prospective, six were from a single centre and one used data obtained from an organ sharing database. No papers were found on iLA. Follow-up of ECMO BTT patients and controls ranged from 1-year to 5-years. Although each study included a control group of non-bridged patients, the ECMO strategy in the ECMO BTT group varied between studies (i.e. whether ECMO BTT alone was given or ECMO+MV), as did the inclusion of other comparison groups (MV alone). As bridging strategy appears to have potentially important impact on post-transplant outcomes data from all groups is included in this review. There was also variation in the post-transplant outcomes reported and the measures and indicators used to express these. This heterogeneity makes it difficult to combine the results of studies so instead a descriptive analysis of the results of most of the post-transplant outcomes has been undertaken for this evidence review.

Overall survival (including post-transplant) in patients receiving ECMO or iLA as bridge to transplant

Survival

All studies included post-transplant survival at 1-year as an outcome, two included survival at 3-years and three included it at 5-years.

1-year survival

The proportion of patients surviving to 1-year post-transplant can be seen in Table 1. Survival is broadly similar across all the groups, ranging from 75%-91% in non-bridged patients and 68%-100% in ECMO BTT groups (regardless of strategy). Although Todd et al 2017 report 100% survival of ECMO BTT patients at 1-year, they had a small sample size so this may not be a reliable and generalisable estimate of survival in this population. Kolaitis et al 2018 and Chiumello et al 2015 do not present data for the non-bridged patients, but the remaining studies all found there to be no statistically significant difference between the ECMO BTT and non-bridged patients 1-year survival.

There may, however, be some effect of ECMO bridging strategy adopted. Hayanga et al 2018 report no difference between the MV only group and the ECMO + MV and non-bridged group but Schechter et al 2016 found survival in ECMO + MV patients to be significantly lower than that of ECMO alone or non-bridged patients.

This suggests that 1-year survival in ECMO BTT is equivalent to that of non-bridged patients and is likely to be in the range of 60-80%.

Table 1: 1-year survival reported by bridging strategy, % of cohort

Study	No support	ECMO only/ ECMO+MV	ECMO + MV	ECMO only	MV only
Schechter et al 2016	84.2%		61%	70.4%	72%
Hayanga et al 2018	84%		77%		81%
Ius et al 2018	90%	79%			
Todd et al 2017	91%	100%			
Kolaitis et al 2018		97%			
Lehmann et al 2015	71%	68%			
Toyoda et al 2013	83%	74%			
Chiumello et al 2015		50-90%			

3-year survival

Two good-sized, recent studies also report survival at 3-years. Both include a control cohort who have not received bridging support but the ECMO bridging strategies and additional comparison groups differ in the two studies. Schechter et al 2016 report the difference in survival at 3 years between the 3 bridge strategies was significant (p=0.0097), but survival for patients on ECMO alone was not significantly different from those requiring no support (P = 0.16). Patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support (P < 0.0001 for both) (see Table 2). Hayanga et al 2018 reported very similar survival probabilities at 1-year and 3-years in the three groups they assessed and (not statistically different) but they did not include an ECMO only group for comparison.

Table 2: 3-year survival reported by bridging strategy, % of cohort

Study	No support	ECMO only/	ECMO + MV	ECMO only	MV only

		ECMO+MV			
Schechter et al 2016	67%		45%	65%	57%
Hayanga et al 2018	73%		77%		56%

5-year survival

The proportion of patients surviving to 5 years can be seen in table 3. Ius et al 2018 report a 5-year post-transplant survival rate of 65% in ECMO BTT (no statistically significant difference compared with those not bridged). Hayanga et al 2018 also report similar 5-year survival probabilities with no statistically significant difference between them, but their ECMO BTT group are all on MV (compared to the majority of the Ius et al 2018 ECMO BTT cohort who are awake and not on MV). Lehmann et al 2015 report slightly lower survival at 5 years but the study includes patients recruited a longer time ago when ECMO techniques may not have been so good. Again, no difference in survival at 5 years was found between the groups.

Table 3: 5-year survival reported by bridging strategy, % of cohort

Study	No support	ECMO only/ ECMO+MV	ECMO + MV	ECMO only	MV only
Ius et al 2018	71%	65%			
Hayanga et al 2018	59%		66%		43%
Lehmann et al 2015	52%	34%			

In summary, these results suggest that 70-90% of patients who receive ECMO BTT are still alive at 1 year post-transplant, around 60-80% are alive at 3 years post-transplant, and around a 65% are alive at 5-years post-transplant, and this rate of survival is no different to that of patients not receiving any bridging support. There is also some evidence that survival is better in patients receiving ECMO BTT than in those receiving MV (either with or without ECMO).

Quality of life on ECMO

Quality of Life and functional status

Health-related quality of life

Only one study looked at health-related quality of life (HRQL) as a post-transplant outcome. Kolaitis et al 2018 reported changes in scores on 5 different measures of HRQL from pre-transplant to 6 months post-transplant in patients on ECMO BTT, patients who were hospitalised (inpatients) but not on ECMO, and patients who were called in for a transplant as outpatients.

Before transplantation, HRQL and depressive symptoms were similar among the 3 groups, although outpatients reported better baseline HRQL on two of the surveys (SF12-MCS and EQ5D). After transplantation, HRQL and depressive symptoms generally improved across all 3 groups. Overall, peak improvement in HRQL and depressive symptoms was seen in the early period, within 6 months post-transplantation, and remained stable through to 12 months post-transplantation. The magnitude of these early improvements at 6 months varied by instrument. The greatest improvement was seen in respiratory-specific HRQL, but there were also substantial improvements in health utility and depressive symptoms, and some improvement in generic mental HRQL.

In summary, patients ill enough to require ECMO BTT achieve similar improvements in HRQL and depressive symptoms as those who are less ill and do not require ECMO bridging support. These improvements are greatest in the 6 months post-transplant and then remain stable to 12 months. There is a low to moderate uncertainly with these conclusions, the study was high quality and used several different measures of HRQL which make the results reliable and valid, but only one study with relatively small sample size included measures of HRQL as an outcome.

Functional Status

One study included assessment of post-transplant functional status. Todd et al 2017 used the Karnofsky scale index which is an assessment tool for functional impairment. A score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed.

Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year post-transplant functional status in ECMO BTT group was not different from the non-bridged group. It was concluded that 1-year functional status was excellent in both groups. However, they highlight that this is in a select group of patients (under 65 years old, ambulatory before deterioration, no other organ dysfunction and good rehabilitation potential).

These results suggest that there is no difference between the post-transplant functional status of critically ill patients requiring ECMO BTT and less ill patients who do not require ECMO bridging support, however there is some degree of uncertainty around this. Although the study is of high quality and used a recognised and validated measure of functional status, the findings were based on relatively few patients in the ECMO group who have been selected for ECMO on the basis of being of good functional status before deterioration, therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.

Clinical effectiveness and safety of ECMO or interventional lung assistance (iLA) in improving survival to transplant among patients listed to transplant

Complications

Death on ECMO pre-transplant

Five studies report rates of death of patients while on ECMO awaiting a lung transplant. Ius et al 2018 provide the most comprehensive data on this, they report that 19/87 (22%) patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation (cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1). Similar rates were found by Schechter et al 2016, 68.8% of patients on ECMO at time of listing were transplanted and 18.8% either died or their condition deteriorated such that they were removed from the list. For the patients listed on MV alone 53.4% were transplanted and 41.4% either died or becoming too sick for consideration. For the patients listed on ECMO and MV, 61.2% were transplanted and 33.9% either died or deteriorated. These differences in deaths by bridging strategy were not likely due to chance (P = 0.004). However, these data are limited by reporting only deaths for those on each method of support at the time of listing so unclear how they relate to each cohort across their whole time on the waiting list.

Three other studies report death on ECMO but are limited by small size or inclusion of older data. Todd et al 2017 reported that of a cohort of 12 patients receiving ECMO BTT none died before transplant, and Lehmann et al reported 2/15 deaths pre-transplant on ECMO. Chiumello et al 2015 reported that 10/14 studies included in the systematic review presented data on deaths while on ECMO and the proportion of the ECMO BTT cohorts that died ranged between 17% and 50% with multiple organ failure, septic shock,

cardiac failure and bleeding as the most common causes. However, this study is limited by the inclusion of several older studies which assessed post-transplant outcomes on ECMO a long time ago when the technology and safety was less advanced.

There is some uncertainty as to the exact rate of mortality to expect in patients on ECMO BT while awaiting transplant but this is likely to be between 20% and 30%. Varying rates have been reported in the studies due to small sample sizes in several studies and differences in the level of sickness and comorbidities of the patients put on ECMO, and advances in ECMO technology and safety which will affect survival. A lack of a control group for comparison also makes it difficult to interpret this data, however it should be noted that without ECMO 100% of the patients who need it would have died.

Acute rejection and graft survival

The short-term complication of acute rejection of the graft was reported by four studies. One of the largest and most recent studies (Ius et al 2018) report higher rates of acute rejection (PGD score Grade 2-3) of the graft in ECMO BTT patients than in non-bridged patients at 24 hr (37% vs 15% respectively), 48 hrs (46% vs 14%) and 72hrs (42% vs 11%), all differences significant at p=<0.001. However, other studies did not find any difference in rates of acute rejection immediately post-transplant. Schechter et al 2016 reported the proportion of patients experiencing an episode of acute rejection before discharge. This occurred in 8.7% of those receiving no bridging support, 10.8% in those receiving only ECMO, 12.9% of those on only MV, and 18.5% of those on ECMO + MV, however these differences were not statistically significant. Todd et al report primary graft dysfunction (grade 3) at 48-72 hours post-transplant of 26% in the control non-ECMO group and 33% in the ECMO group, with these proportions not being statistically different. Hayanga et al 2018 report median graft failure as 2,406 days for the control group and 1,696 for the MV group, but they report 'not reached' for the ECMO + MV group so this is of limited use as an outcome (although they do however state the difference in the graft survival between the groups is not statistically significant). They also reported rates of acute rejection at different grades (0-4) and found no statistical difference in the bridging strategies.

Graft survival at follow up was only reported by one study. Ius et al 2018 followed up graft survival at 1 and 5 years. They found that 90% of non-ECMO and 79% of ECMO BTT patients had grafts that survived at 1 year, and 68% of non-ECMO and 61% of ECMO BTT patients with grafts surviving at 5 years. These differences were not statistically significant (p=0.13) suggesting that graft survival is no worse in ECMO BTT patients.

Although all studies report a trend towards higher rates of acute rejection in ECMO BTT patients in the short-term immediately post-transplant, there is some disagreement over whether this difference is statistically significant. Long-term follow up of graft survival is only reported by one study but clearly shows that there is no difference between ECMO BTT and non-bridged patients at 1- and 5-years

Post-operative ventilation

Four studies report post-operative ECMO requirement in patients, and one also reports duration of MV (see Table 5). Hayanga et al 2018 found patients receiving pre-transplant MV + ECMO were significantly more likely than each of other two groups to require post-operative ECMO whereas Ius et al 2018 who reported secondary ECMO requirements in patients who were on ECMO BTT but without MV (awake strategy) found no difference in the rate of secondary ECMO in patients on ECMO BTT (p=0.18). The two smaller studies also lack consensus on whether differences in need for post-transplant ECMO in ECMO BTT and non-bridged patients was due to chance or not, with Toyoda et al 2013 finding it unlikely to be due to chance and Todd et al 2017 finding this was not the case.

Table 5: Proportion of patients requiring post-operative ECMO in each bridging strategy, % cohort

Study	No support	ECMO only/ ECMO+MV	ECMO + MV	ECMO only	MV only
Hayanga et al 2018	19%		28%		8%
Ius et al 2018	2%			4%	
Todd et al 2017	2.5%	0%			
Toyoda et al 2013	6%	54%			

Hayanga et al 2018 also report the duration of MV required post-transplant. Patients who had been on MV alone or MV + ECMO BTT were more likely to be on MV for longer compared with control patients who had not been bridged with support (>5 days MV in 22% non-bridged, 54% MV only and 67% in ECMO + MV).

Overall, there is some disagreement about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively but taken together the two recent large studies (Hayanga et al 2018 and Ius et al 2018) suggest that ECMO BTT is associated with greater need for post-operative ECMO if pre-transplant MV has been given but not if an ECMO alone (awake) strategy has been adopted. There is also some suggestion that patients who have received pre-transplant MV or MV and ECMO will experience a slower recovery in the days immediately post-transplant and will spend longer on MV.

General short-term post-operative complications

Short-term post-operative complications were reported by five studies. The large range of different complications and the various direct and indirect measures of each make a comparison of the rates of these in ECMO BTT across studies difficult, but there were several complications which were reported as more likely to occur in ECMO BTT patients than non-bridged controls. Ius et al 2018 present a comprehensive list of complications in their good-sized study and identify an increased risk of bleeding (indicated by need for blood products and rethoracotomy for bleeding: 21% vs 8% in ECMO BTT and non-bridged respectively), renal failure (indicated by need for dialysis: 27% vs 7%), vascular complications (10% vs 2%), need for pulsed steroid therapy (52% vs 26%), tracheostomy (34% vs 11%), longer ventilation times (median 3 days vs 1 day), and higher in hospital mortality (15% vs 5%).

Todd et al (2017) also present a comprehensive list of post-operative complications, but this study was based on only 12 patients in the ECMO BTT group and 9/12 of these patients were sedated. Some of these complications were more likely in patients receiving ECMO BTT than controls, including delirium (50% vs 13.5% respectively), myopathy (83.3% vs 12.3%) and thrombotic events (50% vs 18.5%), and the need for return to the operating theatre (67% vs 16%). Blood transfusions were borderline more likely in ECMO BTT (median of 2.5 vs 1).

Hayanga et al 2018 also provide a detailed account of the post-operative complications for patients who received ECMO + MV BTT compared with those receiving only MV and controls who received no bridging support. There was no difference in renal insufficiency requiring dialysis (9% of controls, 13% of those on MV alone, and 8% of those on ECMO + MV) and no difference in airway complications (15% of controls, 21% of those on MV alone, and 18% of those on ECMO + MV). However, bleeding requiring operation was higher in MV alone and EMO +MV groups compared with controls but no different in MV alone compared with ECMO+MV (9% in controls, 19% in MV alone, and 20% in ECMO + MV).

Schechter et al 2016 included two measures of post-operative complications, episode of acute rejection before discharge (outlined in outcome above) and new onset of dialysis. The incidence of new-onset dialysis was significantly different among the bridging strategies ($P < 0.0001$), with ECMO + MV patients having the highest incidence (23.5%) compared with both ECMO only patients (13.9%) and MV only

(10.3%).

Chiumello et al 2015 looked at all the post-operative complications reported in the 14 studies included in their systematic review. The proportions of ECMO BTT patients in each study experiencing these complications was presented but no control group data is provided which makes interpretation limited.

Overall, there is evidence that ECMO BTT is associated with some increased post-operative complications. There is relatively high certainly that the risk of bleeding is higher in ECMO BTT patients as this has been found in all the studies that report this outcome. Higher risk of renal failure is a little less consistently reported with one of the three studies including this outcome finding it to be more common in ECMO BTT (when ECMO alone given), one study finding no difference (ECMO + MV given), and another study finding it depends on the use of concurrent MV which increases risk of dialysis. There is therefore quite a high degree of uncertainty about this outcome.

It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g. blood transfusion vs rethoractotomy for bleeding).

Although there is some degree uncertainty due to small sample size in the single study that reports it (Todd et al 2017), there is suggestion that ECMO BTT is associated with higher risk of delirium and myopathy with around 50% and 80% of patients experiencing each of these respectively. There is slightly more certainty that thrombotic and vascular events may be an increased risk int his procedure as this was also found by a larger, more robust study (Ius et al), albeit at a far lower rate (10% compared with 50% of ECMO BTT patients in Todd et al 2017).

Duration of pre-transplant ECMO and post-transplant hospital stay

Duration of pre-transplant ECMO

Duration of pre-transplant ECMO was reported by five studies (Table 4). There is little certainty about the exact duration of pre-transplant ECMO in these patients but it certainly seems to be the case that durations do not tend to exceed around 16 days in the majority of patients.

Table 4: Average duration of ECMO received pre-transplant of patients in the ECMO BTT groups.

Study	Duration of ECMO
Ius et al 2018	Median 9 days (range 5-16)
Hayanga et al 2018	Mean 14.58 days (SD 15.10)
Todd et al 2017	Mean 103.6 hours (range 16 – 395 hours) (equivalent to 4.2 days, range 0.6 – 16.5)
Toyoda et al 2013	171±242 hours (range, 2-1104 hours) (equivalent to 7.1 days, range 0.08 – 46 days)
Chiumello et al 2015	12/14 studies: medians range 3.2 – 16 days

Length of ITU stay

Two studies report length of ITU stay. Ius et al 2018 found the median length of stay in their cohort study was 11 days (IQR 4-23 days) in ECMO BTT compared with 2 days (IQR 1-4 days) in those without bridging support, this difference is unlikely due to chance ($p<0.001$). The systematic review by Chiumello et al 2015 identified median length of stay ranging from 15 – 47 days in patients receiving ECMO but no control group

data was provided. The authors note that a study that compared length of ITU stay in different ventilation strategies found non-invasive ventilation during ECMO bridge was associated with significantly shorter ICU and hospital stays than invasive MV and similarly another study found shorter mean ITU stay after lung transplantation in the awake-ECMO group than the mechanically ventilated ECMO group, but the difference was not statistically significant. However, the systematic review by Chiumello et al 2015 is limited by the inclusion of studies which are generally quite old so may be using less advanced ECMO procedures so complications and therefore ITU stays may have been longer than they would be with more modern and safe techniques. Most studies included also have relatively small sample sizes.

There is reasonable certainty that the length of post-transplant ITU stays are longer in patients who receive ECMO BTT than those who do not require bridging support, and there is some suggestion, although with less certainty, that awake ECMO or ECMO without concurrent MV resulted in shorter length of ITU stay than MV. As only one recent study reports length of ITU stay the exact duration of ITU stay to be expected for an ECMO BTT patent remains unclear as it may vary centre to centre

Length of hospital stay

Length of hospital stay was reported by six studies and generally shows a trend of longer length of stay (LOS) in ECMO BTT compared to non-bridged patients. Three of these are good-sized studies: Schechter et al 2016 report median LOS of 15 days (IQR 10-24) for patients not receiving any support, 25 days (IQR 19-39.5) for those receiving ECMO alone, 27 days (IQR 18-46) for those receiving MV alone, and 32 days (IQR 19-58) for those receiving both ECMO and MV. The difference between the LOS for each of these bridging strategies was not statistically significant. Ius et al 2018 report median length of hospital stays of 23 days (IQR 21-28 days) for non-bridged patients and 42 days (IQR 26 – 67 days) for those on ECMO BTT. This difference was unlikely due to chance (P<0.001). Hayanga et al 2018 report a median LOS of 27 days in those not receiving support, 36 days in patients on ECMO + MV, and 39 days in patients on MV only. The difference between the control group and the ECMO+MV group was unlikely due to chance. However, this study does not report LOS in patients who are on ECMO without MV.

Three of the studies were smaller or more limited: The small study by Todd et al report LOS of 25 days after ECMO BTT, and 13 days in non-ECMO. This difference was unlikely due to chance. Toyoda et al 2015 report a median LOS of 46 days in ECMO BTT patients compared with 27 days in non-ECMO patients but this difference is not statistically significant. Chiumello et al 2015 report a range of median LOS of 22-47 days in ECMO patients in the studies included in their systematic review but no comparison group data is presented.

Overall therefore it seems that there are longer LOS in ECMO BTT than in non-ECMO patents, and slightly longer LOS in patients receiving MV with or without ECMO than in those receiving only ECMO, however the exact LOS stay is not consistently reported and there is no consensus on whether differences in LOS are statistically significant between bridging strategies.

Cost effectiveness of ECMO or interventional lung assistance (iLA) in improving survival to transplant among patients listed to transplant

Cost effectiveness of ECMO BTT

No studies addressed the cost of ECMO BTT or provided any data with which cost-effectiveness could be evaluated.

Does the evidence identify any subgroups of patients in whom clinical and cost effectiveness are different?

Awake versus sedated ECMO

Although several studies include both sedated and awake patients in their ECMO groups (Ius et al 2018; Lehmann et al; Chiumello et al 2015), only one study includes a full comparison in the study design between patients who are awake and those who are sedated and therefore on concurrent MV. Schechter et al 2016 compared post-transplant outcomes for patients on ECMO alone with those on MV alone, ECMO + MV, and those on no bridging support. Survival at 3 years post-transplant for patients on ECMO alone was not significantly different from those not requiring support (P = 0.16), however patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support (P < 0.0001 for both).

After adjustment with a multivariate Cox regression model, MV +/– ECMO was independently associated with worse survival compared with patients not requiring mechanical bridge (MV only: hazard ratio [HR] = 1.46; MV + ECMO = 2.26, P < 0.0001 for both), whereas ECMO alone was not (P = 0.39).

These results suggest that awake ECMO is associated with better survival than sedated ECMO which requires MV, and supports the survival outcome results (above) which demonstrates that post-transplant survival for ECMO BTT is comparable to non-bridged patients. This was supported by Chiumello et al 2015 who refer to one study in their systematic review which found one-year survival in ECMO BTT was significantly better in spontaneously breathing patients than mechanically ventilated ones (85% versus 50%) but no further details are given.

Ius et al 2018 present some analysis of the differences between the awake and sedated patients in their study and report that post-transplant outcomes did not differ between patients who underwent an awake ECMO strategy and those who did not with regards to graft survival (P=0.38), patient survival (P=0.25), freedom from biopsy-confirmed rejection (P=0.53), freedom from pulsed steroid therapy (P=0.98), freedom from chronic lung allograft rejection (P=0.58), and freedom from retransplant (P=0.46). However, the number of patients on the sedated strategy was small (only 11 of the 68 patients on ECMO) so results should be treated with some caution.

Although a single study does not allow a high degree of certainty about the survival benefits of awake ECMO strategies over sedated ones, the results of the high-quality study outlined above does go some way to supporting the suggestion that patients on this ECMO strategy may demonstrate additional effectiveness of bridging over sedated strategies.

Interventional Lung Assist (iLA)

No studies provided data on iLA.

5. Discussion

The results are discussed by post-transplant outcome, or groups of outcomes if they refer to similar aspects of care or explanation. A more in-depth description of outcomes can be found in section 8 Grade of evidence table.

Survival

All studies included in this review contained post-transplant survival as an outcome, all report this at 1-year post-transplant and two include survival at 3-years, and three report it at 5-years. Although there was some variation in the exact rates of survival at each of these time points, there was very high agreement

that survival is no worse in critically ill patients requiring ECMO BTT compared with less ill patients who survive to transplant without ECMO bridging support.

These results suggest that 70-90% of patients who receive ECMO BTT are still alive at 1 year, around 60-80% are alive at 3 years post-transplant, and around a 65% are alive at 5-years, and this rate of survival is no different to that of patients not receiving any bridging support. There is also evidence that survival is better in patients receiving ECMO BTT than in those receiving MV (either with or without ECMO).

Although the exact rates vary a little between studies, probably due to different criteria for ECMO, different case mix for transplants, procedural differences and differing use of MV, it is likely that with ever improving technologies and techniques for ECMO the survival rates increase further. The general finding that patients with ECMO BTT show comparable survival at 1-year and 5-years to patients not requiring bridging support is particularly striking in light of their degree of critical illness prior to transplantation and speaks to the overall effectiveness of ECMO BTT.

Quality of life and functional status

Quality of life was only assessed by one study included in the review. Overall it was found that ECMO BTT patients achieve similar improvements in health-related quality of life after transplant as patients who do not require ECMO. The improvements are greatest in the first 6 months after transplant and then remain stable at 12 months. The greatest improvement was seen in respiratory-specific HRQL, but there were also substantial improvements in health utility and depressive symptoms, and some improvement in generic mental HRQL.

These improvements are notable given that patients who received ECMO have survived critical illness which is itself associated with marked impairments in HRQL. There are some possible explanations of why patients on ECMO BTT experience this improvement in HRQL beyond what you would expect of other critically ill patients, including an expected progression of illness, fewer comorbidities and strong support networks in transplant patients. Although these results give some very promising indication that ECMO BTT can confer significant benefits to quality of life, this study was relatively small and the absence of a longer duration of follow up provides no indication of the long-term impacts in these patients. It also does not cover some mental health problems that may be expected to be more common in ECMO BTT such as post-traumatic stress disorder (PTSD).

Functional status was also only assessed by one study. At 1-year post-transplant Todd et al 2017 concluded that functional status was excellent in the 12 ECMO BTT patients reviewed. A mean score of 87.5 (range 70-100) was found on the Karnofsky scale index scale where a score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs, and a score of 80-100 signifies ability to carry out normal activity and work with no assistance needed. These results suggest that there is no difference between the post-transplant functional status of critically ill patients requiring ECMO BTT and less ill patients who do not require ECMO bridging support. As with quality of life, further evidence would be helpful before confidence in these results could be achieved, for example the findings were based on relatively few patients in the ECMO group who have been selected for ECMO on the basis of being of good functional status before deterioration, therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.

Complications

Death on ECMO pre-transplant

Results for deaths on ECMO are varied and somewhat difficult to interpret. They are not reported by all studies as some only include post-transplant outcomes on patients that were successfully transplanted and others give very limited detail about the outcome of those who do not get transplanted. Among the cohort studies that report death on ECMO, the rate ranges from 0% (Todd et al 2017) to 22% (Ius et al 2018), and the systematic review by Chiumello reports mortality ranging from 17% - 50% in the studies included within it but this review generally included older studies where ECMO technology and practice may not have been as good as in more recent years. The variation seen in the mortality rates reported are likely to be due to small sample sizes in studies, differences in the level of sickness and comorbidities of the patients put on

ECMO, and advances in ECMO technology and safety. The best study reporting deaths on ECMO is by Ius et al 2018 who reported that 19/87 (22%) of the patients requiring ECMO BTT died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding, acute haemodynamic decompensation, right heart failure, or massive haemolysis.

The exact rate of mortality on ECMO while awaiting transplant is difficult to determine from the studies reviewed but it is likely to be between 20% and 30%. It is apparent that ECMO BTT is not without risk of death as the procedure is inherently a risky one and the patients who receive it are by definition very sick. A lack of a control group for comparison also makes it difficult to interpret this data, however it should be noted that without ECMO 100% of the patients who need it would have died.

Acute rejection and graft survival

The short-term complication of acute rejection of the graft is consistently reported in the literature as more likely to occur in ECMO BTT patients than in those with no bridging support, however there is no agreement about whether this difference is significant or not. One good sized, recent study suggest that around 40% of ECMO BTT patients experience acute rejection at 24, 48 and 72 hours post-transplant compared with just over 10% of controls (Ius et al 2018), but other, equally high-quality studies have this rate to be much lower (13% on ECMO BTT vs 11% controls, Schechter et al 2016). It is unclear why these discrepancies exist as there are no obvious methodological or clinical differences that could be attributed (for example, both studies report patients receiving ECMO without MV). It is also not entirely clear why ECMO might be associated with graft dysfunction but it may in part be due to the ECMO circulation and anticoagulation for the ECMO which triggers a systemic inflammatory state (Toyoda et al 2013). Alternatively, it may be an artefact due to the current PGD definition used in some studies (International Society for Heart and Lung Transplantation [ISHLT] Grading System) which will automatically patients on ECMO to a PGD grade 3.

Long-term follow up of graft survival is only reported by one study but it shows that there is no difference between ECMO BTT and non-bridged patients at 1- and 5-years. Ius et al 2018 found that 90% of non-ECMO and 79% of ECMO patients had grafts that survived at 1 year, and 68% of non-ECMO and 61% of ECMO patients with grafts surviving at 5 years (these differences were not statistically significant). The robust nature if this study allows a good degree of confidence in the results, however some caution is needed in the absence of support from other studies and as the authors themselves note the results may be affected by a greater number of paediatric patients in the ECMO BTT group.

Post-operative ventilation

There is some disagreement in the studies reviewed about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively. Excluding a very small study which did not find any ECMO BTT patients required post-operative ventilation (Todd et al 207), the studies reviewed all found a trend towards these patients requiring more ventilation, both MV (Hayanga et al 2018) and ECMO (Ius et al 2018, Hayanga et al 2018, Toyoda et al 2013) but there is no agreement over whether these differences are significant or not. One possible explanation for this is the different ECMO bridging strategies that were used in the studies, ECMO alone (Ius et al 2018) or ECMO + MV (Hyanaga et al 2018, Toyoda et al 2013). This explanation would suggest that ECMO BTT is associated with greater need for post-operative ECMO if pre-transplant MV has been given but not if an ECMO alone strategy has been adopted.

This indicates that patients who have received pre-transplant MV or MV and ECMO will experience a slower recovery in the days immediately post-transplant and will spend longer on a ventilator in a high dependency or ITU bed, but patients who have received ECMO alone (awake ECMO) will have ventilation needs and recovery times comparable to non-bridged patients.

General short-term post-operative complications

The literature reports a number of post-operative complications seen in ECMO BTT, some of which seem to

be more common in patients receiving this bridging compared to non-bridged patients. Some of these are likely to be associated with the ECMO procedure itself, for example an increased risk of bleeding which could be explained by central cannulation and the administration of anticoagulants during ECMO. Others are likely to be associated with the type of ECMO strategy used, for example Todd et al 2017 identified a higher rate of delirium, myopathy and thrombotic events in ECMO BTT which may be due to the sedation and bedbound status of the majority of the patients (although it should also be noted that this study had only a small number of patients on ECMO BTT). It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g. blood transfusion vs rethoractotomy for bleeding).

Higher risk of renal failure is a little less consistently reported with some discrepancies between studies over whether indirect measures of this such as occurrence of dialysis are actually more likely in ECMO BTT compared to non-bridged controls or not. Other complications which affect both ECMO BTT and non-bridged patients equally include respiratory complications such as pneumonia, need for reintubation, need for tracheostomy, need for bronchoscopy (Todd et al 2017), and general airway complications (Hayanaga et al 2018), atrial fibrillation and cerebrovascular events (Ius et al 2018).

Overall it seems that ECMO BTT is associated with an increased likelihood of some very serious post-operative complications, most clearly bleeding but also very likely delirium, myopathy and thrombotic events. As mentioned above, bleeding is likely to be secondary to anticoagulation required for ECMO. Delirium tends to be associated with critically ill patients and is exacerbated by sedation. Although air hunger and agitation experienced on ECMO can be an indication for sedation, the use of shorter acting sedatives or even awake ECMO strategies may reduce this complication. Likewise, myopathy and thrombosis are caused by sedation and bedbound status among other things so if ambulation can be achieved while on ECMO this complication may also decrease.

Post-operative complications associated with ECMO BTT are not easy to assess. Nearly half of the studies did not report them at all, one only reported very limited complications as it used data from a national organ sharing database (Schechter et al 2016) so is likely to have been limited by the data recorded on the database, one was comprehensive in its reporting of complications but was based on a small sample of patients on ECMO BTT (Todd et al 2017), and the systematic review (Chiumello et al 2015) listed all the complications reported within the studies included, but provided no control group data for comparison of expected rates and the majority of studies recruited patients over ten years ago when ECMO safety was less advanced. Additionally, the results can be difficult to interpret considering the different ECMO strategies used i.e. awake or sedated with concurrent MV, the different indirect measures of the complications used, and the different time periods of follow up included.

In summary, Approximately 20 – 30% of patients will die on ECMO prior to lung transplant. Post-transplant there is no clear evidence that acute rejection is higher in ECMO BTT than non-bridged patients, and long-term follow up suggests that overall graft survival is equal. The impact of ECMO BTT on post-transplant ventilation requirements is also uncertain but the higher rates seen in ECMO BTT patients in some studies may be explained by concurrent MV use. More convincingly though, ECMO BTT is associated with higher rates of some serious complications such as bleeding, delirium, myopathy and vascular and thrombotic events. The exact magnitude of these risks is difficult to determine, but ECMO BTT is performed on very sick patients who would not survive without the bridging and subsequent lung transplant.

Duration of pre-transplant ECMO and post-transplant hospital stay

Duration of pre-transplant ECMO

The average number of days on ECMO prior to lung transplant across the studies ranged from 3.2 days to 13.7 days in the systematic review (Chiumello et al 2015) and from 4.2 days (Todd et al 2017) to nearly 15 days (Hayanga et al 2018) in the cohort studies. This is also reflective of the range of time reported for patients within each study. Although there is little certainty about the exact duration of ECMO BTT, probably due to the different indications for ECMO at different centres and the slightly different management of transplant waiting lists, the duration does not seem to exceed around 16 days in most of

the studies. This is likely to be because once a patient is on ECMO they become a high priority on the waiting list for available donor lungs.

Length of ITU and hospital stay

The length of hospital stay for patients receiving ECMO BTT is consistently reported to be longer than that of non-bridged patients, however there is considerable variation in the exact length of stay reported both within and between centres, and there is little consensus on whether differences in length of stay are between bridging strategies are likely due to chance or not. For example, Ius et al 2018 report median length of hospital stays of 23 days for non-bridged patients and 42 days for those on ECMO BTT, with this difference being unlikely due to chance, and Schechter et al 2016 report median length of stays of 15 days for non-bridged patients, 25 days for those on ECMO alone, 27 days for those receiving MV alone, and 32 days for those receiving both ECMO and MV (difference between the length of stay for each of these bridging strategies was due to chance). Other studies length of stay range from 13 to 27 days for non-bridged patients and 25 to 47 days for ECMO BTT patients.

The Schechter et al 2016 study also highlights a trend (although not statistically significant) towards slightly longer length of stays in patients receiving MV with or without ECMO than in those receiving ECMO alone.

The length of ITU stay was less frequently reported and only one study compared length of stay in ECMO BTT and non-bridged patients. Ius et al 2018 found that ECMO BTT is clearly associated with longer ITU stays post-transplant than no-bridging (median of 11 days compared with 2 days). A systematic review by Chiumello et al 2015 reported medians ranging from 15 – 47 days in ITU in six of 14 studies it reviewed, but no comparison with a control group was made. This systematic review included mostly older studies that may have involved less developed ECMO technology and strategies which may have affected recovery speed. There was also some suggestion from the systematic review (Chiumello et al 2015) that the use of non-invasive ventilation strategies or awake ECMO during was associated with shorter ITU stays than invasive methods, but these were due to chance.

Overall, there is a general trend towards the reporting of longer hospital and ITU stays in patients receiving ECMO BTT but big variability within studies and between studies makes it difficult to identify the exact magnitude of difference or indeed be clear about whether any differences are significant or not. Nonetheless, It is unlikely to be surprising that patients on EMCO BTT have a longer hospital and ITU stay given that they tend to be critically ill patients with higher care needs to start with. Many of them will also have been bedbound at the time of ECMO initiation (e.g. Todd et al 2017) so prolonged recovery was anticipated. Recovery time and rehabilitation potential will be affected by many factors, including acuity of illness, ECMO duration, immobility and sedation. Although patients requiring ECMO will always be critically sick, it may be the case that a move towards awake ECMO strategies results in a reduction in the recovery period and length of stay.

Awake versus sedated ECMO

Several studies included a mix of awake and sedated ECMO patients but only one study included a comprehensive comparison of patients on these two strategies (Schechter et al 2016). This study found post-transplant survival at 3-years for patients on ECMO alone was no different from those not requiring any bridging support, but patients requiring either MV alone or ECMO plus MV had significantly worse survival compared with patients not requiring support. In further support of this, regression analysis identified MV (with or without ECMO) to be independently associated with worse survival compared with patients not requiring MV.

These results suggest that survival is better with ECMO alone (awake ECMO) than with ECMO and MV. This may be explained by the fact that awake ECMO offers the patients the potential to participate in ambulation and physiotherapy which prevents musculoskeletal deconditioning, ear and drink normally which maintains their nutritional status and actively clear their own airway. They are therefore able to optimise their condition prior to transplant which improves recovery and outcomes post-transplant. In addition to the potential survival advantages of using awake ECMO, it also brings the avoidance of some of the risks and complications of MV such as general muscle atrophy and diaphragm abnormalities and weakness which can all prolong recovery and need for ITU and hospital stays. This may explain why the

requirement for post-operative ECMO is greater in patients who received pre-operative MV, either with or without ECMO, than those who received ECMO alone (discussed above).

In summary, there is evidence that awake ECMO offers a survival advantage over sedated strategies with concurrent MV and may also be associated with lower ventilation requirements post-operatively. However, this evidence is limited to only one study in this review, albeit a high quality one, and would benefit from further research.

Strengths and limitations

This review includes eight studies, seven of which are cohort studies (seven retrospective and one prospective (Kolaitis et al 2018)) and one systematic review (Chiumello et al 2015. The studies are all highly relevant and directly applicable to the research questions posed. They all include direct outcomes that are mainly defined by objective measures which mean they are not subject to measurement or reporting bias.

However, there are several limitations of the studies included. Most are single centre studies which may limit generalisability to other centres as case mix, clinical procedures and algorithms of care may be different. Nonetheless, some of the trends in post-transplant outcomes, such as survival, have been reported so consistently across studies that it would be unreasonable to discount them on these grounds.

One of the most notable sources of heterogeneity in the studies is the ECMO strategy used, i.e. ECMO alone (awake ECMO), or ECMO with MV (sedated ECMO) or a mixture of the two in the cohort. Given that there is some evidence that outcomes such as survival and complications may be affected by ECMO strategy used, some caution when trying to combine or interpret results is needed.

Some of the studies had small numbers of participants, particularly in the ECMO BTT group, which makes interpretation of the results difficult as it increases the risk of type 1 and type 2 errors (over or under estimating the causal inference). Although this could have potentially serious consequences, it is unlikely to be a major problem in this review as there are sufficient studies included with larger sample sizes to support the results and conclusions. Some studies include patients who received ECMO over ten years ago when technology and expertise was not so good, but again, sufficient high-quality recent studies are included to ensure this is not a source of confounding.

Due to small numbers of patients undergoing ECMO BTT many of the studies recruited patient data over long periods of time which may subject the results to a learning curve bias as the centre becomes more proficient and expert at the clinical and surgical procedures. The studies have not adjusted for effects of contemporaneous improvements in anaesthesia, pharmaceutical, or intensive care practice. This has not been accounted for in any of the studies and the magnitude of this limitation is therefore not known.

Observational studies have a number of disadvantages over randomised studies. The fact that the majority of the studies were retrospective could have introduced an element of selection bias at enrolment (with the choice to include only those patients with certain characteristics or outcomes), but all state that consecutive cases of lung transplant were included which should minimise this bias. The retrospective review of hospital records to obtain data can also provide limitations as records may be incomplete, difficult to interpret and not include information on potential confounders. In the majority of studies the outcome data only includes patients who survive to transplant (only a couple report brief intention to treat results), and this may introduce a selection bias.

One of the fundamental limitations of this review is the absence of randomised control studies. As outlined in the introduction, studies of this type are not ethical or practical in this situation. However, there is good confidence that the controlled cohort studies included in this review (with the addition of one systematic review) have provided a reasonably robust comparison of post-transplant outcomes of ECMO BTT with an adequate control group to allow inference about the level of clinical effectiveness and safety of this procedure.

Summary of main findings

Post-transplant survival is shown with good certainty to be equal to non-bridged patients and is likely to be around 70-90% at 1-year and 65% at 5-years. Although less certainty, long-term graft survival has also been

shown to be equal. Patients on ECMO BTT appear to achieve the same level of quality of life and functional status as those not undergoing this support, although the level of evidence for this is not as strong as they have been less frequently reported as outcomes.

However, the evidence convincingly indicates that ECMO BTT is associated with a higher incidence of some serious complications including bleeding, delirium, myopathy and vascular and thrombotic events. Other complications such as acute graft rejection and post-operative ventilation requirements may also be at an increased risk in these patients but the evidence is less certain. Similarly, ECMO BTT is associated with longer ITU stays and possibly also longer hospital stays overall, although there is less certainty about the exact duration of these and whether they are truly different from non-bridged patients. Being on ECMO is associated with a risk of death pre-transplant, 20–30% of patients put on ECMO will die before transplant.

There is evidence, albeit from a single study, that an adoption of an awake ECMO strategy offers a survival advantage over sedated strategies which use concurrent MV. This finding potentially has significant impact on the choice of patient and ECMO strategy selected for ECMO BTT to optimise post-transplant outcomes and therefore warrants further research.

Overall, this evidence review has indicated that post-transplant outcomes (including survival) are no worse in critically ill patients requiring ECMO compared with less ill patients who survive to transplant without ECMO bridging support. Short-term complications after transplant are greater in ECMO BTT and around 20 – 30% of those on ECMO will die before transplant.

Recommendations for further research

This evidence review has revealed some gaps or paucities in the evidence where further research would be beneficial to the international body of evidence around ECMO BTT and to decision making around care. The most notable of these is the absence of evidence of cost-effectiveness of ECMO BTT. Although it is acknowledged that this wold not be a simple and straightforward evaluation to complete, it would provide invaluable information when presenting a comprehensive and balanced appraisal of the procedure.

Further research on the post-transplant outcomes of awake and ambulatory ECMO strategies is also indicated. Given that a key aim of health care is to maximise health benefits and outcomes it would greatly facilitate decisions about local ECMO BTT protocols and procedures if there was a little more certainty about the actual survival and safety benefit from awake versus sedated ECMO, ideally from large and generalisable studies.

A final research need identified by this review is around the psychological impact of ECMO BTT and the most appropriate and effective psychological support that can be offered to these patients before and after ECMO and transplant to help them achieve optimal mental health and quality of life post-transplant.

6. Conclusion

Lung transplantation is routinely performed for selected patients with respiratory failure. However approximately 25% of patients on the waiting list die before a suitable donor becomes available or are removed from the waiting list due to deteriorating health rendering lung transplantation futile and inappropriate. MV has traditionally been used to support these patients with the aim of bridging them to transplant but ECMO may provide a superior alternative.

This evidence review has indicated that post-transplant outcomes (including survival) are no worse in critically ill patients requiring ECMO compared with less ill patients who survive to transplant without ECMO bridging support. Short-term complications after transplant are greater in ECMO BTT and 20 – 30% of those put on ECMO will die before transplant.

In light of the fact that patients who need ECMO are critically ill and have very little chance of survival without ECMO BTT, the finding of equivalent post-transplant outcomes to patients who receive no bridging support provides evidence for the use for ECMO BTT, despite the potential increased risk of complications and pre-transplant mortality. Furthermore, the suggestion that use of an awake ECMO strategy offers a post-transplant survival advantage over sedated strategies which use concurrent MV warrants consideration of adopting this approach in clinical practice.

7. Evidence Summary Table (to be completed in line with the evidence review guidance document)

Use of Intervention X Vs. Comparator Y to treat Indication Z

(Create separate table for studies with different comparators)

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome measure type</th><th>Outcome measures and Results
(Columns combined from report template)</th><th>Applicability and Quality of Evidence Score
(Columns combined from report template)</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td>Hayanga et al 2018</td>
<td>P1 - Retrospective cohort study</td>
<td>Total population of patients who underwent primary lung transplantation between 2008 and 2015 (N=826) Split into three cohorts: Control with no bridging support (n =29), MV only BTT (n = 48), MV+ECMO BTT (n = 49)

Single centre: Pittsburgh Medical Center, USA</td>
<td>To analyse outcomes, 194/729 patients in the control group were propensity matched by age and diagnostic category to those in the ECMO+MV or MV alone groups (2:1)</td>
<td>Primary CE</td>
<td>Overall survival

Median survival (days)
<table>
<tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr>
<tr><td>2437</td><td>1696</td><td>Not reached</td></tr>
</table>
P values: Control Vs MV p=0.0869, Control Vs MV & ECMO p=0.4693, MV Vs MV & ECMO p=0.0691, overall p-value=0.1328

Survival Probability
<table>
<tr><td></td><td>Control</td><td>MV</td><td>MV & ECMO</td></tr>
<tr><td>30-day</td><td>0.974 (0.939-0.989)</td><td>0.958 (0.844-0.989)</td><td>0.939 (0.822-0.980)</td></tr>
<tr><td>90-day</td><td>0.949 (0.906-0.972)</td><td>0.938 (0.819-0.979)</td><td>0.898 (0.772-0.956)</td></tr>
<tr><td>1 year</td><td>0.839 (0.779-0.884)</td><td>0.807 (0.661-0.895)</td><td>0.815 (0.675-0.899)</td></tr>
<tr><td>3 years</td><td>0.731 (0.659-0.789)</td><td>0.559 (0.397-0.693)</td><td>0.769 (0.621-0.865)</td></tr>
<tr><td>5 years</td><td>0.588 (0.502-</td><td>0.427 (0.266-</td><td>0.656 (0.477-</td></tr>
</table>
</td>
<td>Applicability: Direct. Looks at outcomes of patients bridged to lung transplant with ECMO and MV.

Quality: 7/10 total

Aims and design clearly stated 2/2: purpose of study clearly stated as being to evaluate pre-transplantation MV with and without ECMO. Primary and secondary outcomes pre-determined.

Design appropriate: 2/2: retrospective cohort study appropriate.

Methods clearly described: 1/2: Not described fully in this paper but references full methods described elsewhere.

Data adequate for authors' interpretation: 1/2: Clear objective outcomes used but</td>
<td>Positives:

All consecutive patients undergoing lung transplant during the defined period included so selection bias minimal.

Relatively large numbers in MV+ECMO group provide power for statistical analysis.

Propensity matching of controls used to make groups more similar for comparison.

Outcomes are objective.

Survival data for 5 years included.

Negatives:

Not clear if MV and ECMO were used concurrently or sequentially and no detail about level of sedation.

Patients in MV and MV+ECMO group were more likely to have bilateral lung transplants compared with the control unbridged group which may have impacted survival and complications data.</td>
</tr>
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<table>
<tr><td></td><td>0.664)</td><td>0.579)</td><td>0.787)</td></tr>
</table>
Survival conditioned on surviving to 1 year, median
<table>
<tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr>
<tr><td>2858</td><td>1811</td><td>Not reached</td></tr>
</table>
P values: Control Vs MV p=0.0651, Control Vs MV & ECMO p=0.1559, MV Vs MV & ECMO p=0.0127, overall p-value=0.0361
</td>
<td rowspan="3">unclear what ‘not reached’ means in results presented and how this contributes to conclusions

Results generalizable:1/2: generalisable to population receiving ECMO with concurrent MV only, no inclusion of patients on ECMO alone for comparison.</td>
<td rowspan="3">Does not include ECMO only group for comparison so although authors conclude that MV+ECMO is associated with better outcomes than MV alone, no conclusions about ECMO as BTT alone can be made.

Unclear if time on ventilator includes time on ECMO or just time on MV, and whether it is pre-op or pre- and post-op.

Relatively long period of recruitment of participants could mean there is learning curve bias or confounding effect of changing ECMO technology or practice, this is not considered by the authors.</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary CE</td>
<td>Duration of ECMO

Time on ventilator (days) mean (SD)
<table>
<tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr>
<tr><td>N/A</td><td>7.68 (11.40)</td><td>14.58 (15.10)</td></tr>
</table>
P values: MV Vs MV & ECMO p=0.6309</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>Secondary CE</td>
<td>Post-operative ventilation

Ventilation postoperative, n (%)
<table>
<tr><td></td><td>Control</td><td>MV</td><td>MV & ECMO</td></tr>
<tr><td>MV <48h</td><td>119 (61.66)</td><td>3 (6.25)</td><td>2 (4.08)</td></tr>
<tr><td>MV 48h – 5days</td><td>31 (67.35)</td><td>19 (39.58)</td><td>14 (28.57)</td></tr>
<tr><td>MV >5 days</td><td>43 (22.28)</td><td>26 (54.17)</td><td>33 (67.35)</td></tr>
<tr><td>MV ECMO</td><td>19 (9.79)</td><td>8 (16.67)</td><td>28 (57.14)</td></tr>
</table>
<48h P values: Control Vs MV p=<0.001, Control Vs MV & ECMO p=<0.001, MV Vs MV & ECMO p=0.678

48h – 5 days P values: Control Vs MV p=<0.001, Control Vs</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>MV & ECMO p=0.044, MV Vs MV & ECMO p=0.289
>5 days P values: Control Vs MV p=<0.001, Control Vs MV & ECMO p=0.184, MV Vs MV & ECMO p=0.215
ECMO P values: Control Vs MV p=0.176, Control Vs MV & ECMO p=<0.001, MV Vs MV & ECMO p=<0.001</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary CE</td><td>Length of hospital stay
Hospital stay (days), median (IQR)<table><tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr><tr><td>27 (21)</td><td>39 (23)</td><td>36 (21)</td></tr></table>P values: Control Vs MV p=0.0008, Control Vs MV & ECMO p=0.0012, MV Vs MV & ECMO p=0.8055</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary safety</td><td>Incidence of complications
Graft survival (days), median<table><tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr><tr><td>2406</td><td>1696</td><td>Not reached</td></tr></table>P values: Control Vs MV p=0.1280, Control Vs MV & ECMO p=5358, MV Vs MV & ECMO p=0.1226, overall p-value=0.2090
Retransplant, n (%)<table><tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr><tr><td>7 (3.61)</td><td>1 (2.08)</td><td>1 (2.04)</td></tr></table>P values: Control Vs MV p=1.00, Control Vs MV & ECMO p=1.00, MV Vs MV & ECMO p=1.00
Time to retransplantation (days), median (IQR)<table><tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr><tr><td>129 (572)</td><td>1998</td><td>1490</td></tr></table>P values: Control Vs MV p=0.285, Control Vs MV & ECMO p=0.285, MV Vs MV & ECMO p=1.57
Acute rejection grade, n (%)</td><td></td><td></td></tr>
</table>

	Control	MV	MV & ECMO
[0,1]	108 (57.75)	26 (59.09)	31 (68.89)
[1,2]	31 (16.58)	6 (13.64)	7 (15.56)
[2,3]	29 (15.51)	7 (8.89)	4 (8.89)
[3,4]	19 (10.16)	5 (11.36)	3 (6.67)

Acute rejection overall P values: Control Vs MV p=0.972, Control Vs MV & ECMO p=0.555, MV Vs MV & ECMO p=0.628

[0,1] P values: Control Vs MV p=1.00, Control Vs MV & ECMO p=0.181, MV Vs MV & ECMO p=0.382

[1,2] P values: Control Vs MV p=0.820, Control Vs MV & ECMO p=1.00, MV Vs MV & ECMO p=1.00

[2,3] P values: Control Vs MV p=1.00, Control Vs MV & ECMO p=0.344, MV Vs MV & ECMO p=0.353

[3,4] P values: Control Vs MV p=0.786, Control Vs MV & ECMO p=0.582, MV Vs MV & ECMO p=0.485

Renal insufficiency on dialysis, n (%)

Control	MV	MV & ECMO
18 (9.28)	6 (12.50)	4 (8.16)

P values: Control Vs MV p=0.589, Control Vs MV & ECMO p=1.00, MV Vs MV & ECMO p=0.524

Bleeding requiring operation, n (%)

Control	MV	MV & ECMO
16 (8.25)	9 (18.75)	10 (20.41)

P values: Control Vs MV p=0.032, Control Vs MV & ECMO p=0.014, MV Vs MV & ECMO p=0.837

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<td>Airway complication, n (%)
<table>
<tr><td>Control</td><td>MV</td><td>MV & ECMO</td></tr>
<tr><td>29 (14.95)</td><td>10 (20.83)</td><td>9 (18.37)</td></tr>
</table>
P values: Control Vs MV p=0.321, Control Vs MV & ECMO p=0.556, MV Vs MV & ECMO p=0.760</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Todd et al 2017</td>
<td>P1 – retrospective cohort study</td>
<td>Total patients undergoing lung transplant during 2015 (N=93) split into 2 cohorts:
ECMO BTT (n=12), Control with no bridging support (n=81)

Single centre: Norton Thoractic Institute, Arizona, USA</td>
<td>3/12 patients on ECMO were awake and 9/12 were sedated</td>
<td>Primary CE</td>
<td>Length of stay
Length of hospital stay, median (IQR)
<table>
<tr><td>variable</td><td>Non-BTT</td><td>ECMO BTT</td><td>P value</td></tr>
<tr><td>Total LOS, median (IQR)</td><td>15 (11-26)</td><td>39 (32.5-50.5)</td><td><.001</td></tr>
<tr><td>Post-transplant LOS, median (IQR)</td><td>13 (10-17)</td><td>25 (18-31)</td><td><.001</td></tr>
</table>
</td>
<td rowspan="3">Applicability: Direct. Compares patients bridged to transplant with ECMO and those not requiring bridging.

Quality: 8/10
Aims and design clearly stated 1/2: Aims clearly stated as comparing the outcomes of all patients who received ECMO BTT with those of patients who were not bridged during the same period. Outcomes predetermined but no reference to whether primary or secondary.
Design appropriate 2/2: Retrospective cohort study appropriate.
Methods clearly described 2/2: Methods of study and procedure clearly described.
Data adequate for authors' interpretation 1/2: Generally yes, but unable to find 90 day survival results and the functional status data of ECMO BTT patients have comparison data from control group.
Results generalizable 2/2: Patient and procedure characteristics are</td>
<td rowspan="3">Positives:
All consecutive patients undergoing lung transplant during study period included so selection bias minimal.
Outcomes are objective and therefore prone to minimal measurement bias and test for functional status is a validated tool.
Patients recruited from a single year so learning curve bias or confounding effects of changing ECMO technology and practice is minimal.

Negatives:
Small sample size, particularly in ECMO BTT group (n=12) may increase risk of type 2 error and make interpretation of results difficult.
Although study states that 3/12 patients were awake on ECMO, outcomes are not presented in relation to this so no inferences or conclusions about the impact of the ECMO strategy can be drawn.
Functional status scores reported for ECMO BTT patients but not for non-BTT patients so no comparison possible which therefore limits the interpretation of the magnitude of scores in ECMO BTT group difficult.</td>
</tr>
<tr>
<td></td><td></td><td></td><td>Primary CE</td>
<td>Duration of pre-transplant ECMO
Mean duration 103.6 hours (range 16 – 395 hours)</td>
</tr>
<tr>
<td></td><td></td><td></td><td>Primary CE</td>
<td>Survival
Pre-transplant survival:
All patients on ECMO BTT survived to transplant

Post-transplant survival:
<table>
<tr><td>variable</td><td>Non-BTT</td><td>ECMO BTT</td><td>P value</td></tr>
<tr><td>30-d mortality, n (%)</td><td>1 (1.2)</td><td>0 (0)</td><td>>.99</td></tr>
<tr><td>Survival at 1 y, n (%)</td><td>73/80 (91.3)</td><td>12/12 (100)</td><td>1.0</td></tr>
</table>
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</table>

<table>
<tr>
<td></td><td></td><td></td><td></td><td></td><td></td><td>generalisable to most ECMO BTT.</td><td></td>
</tr>
<tr>
<td></td><td></td><td></td><td></td><td>Primary CE</td><td>Functional status at one year

Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year functional status in ECMO BTT group was not significantly different from the non-ECMO group (p=0.74)

Score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed.</td><td></td><td></td>
</tr>
<tr>
<td></td><td></td><td></td><td></td><td>Secondary

Safety</td><td>postoperative complications
<table>
<tr><th>variable</th><th>Non-BTT (n=81)</th><th>ECMO BTT (n=12)</th><th>P value</th></tr>
<tr><td>Primary Graft Dysfunction grade 3 at 48-72 h</td><td>21 (25.9)</td><td>4 (33.3)</td><td>0.72</td></tr>
<tr><td>ECMO for PGD</td><td>2 (2.5)</td><td>0 (0)</td><td>>.99</td></tr>
<tr><td>Postoperative PRBC transfusion, median (IQR)</td><td>1 (0-2)</td><td>2.5 (0.5-8)</td><td>.05</td></tr>
<tr><td>Return to OR, n (%)</td><td>13 (16.1)</td><td>8 (66.7)</td><td>.001</td></tr>
<tr><td>Reintubation post-transplant, n (%)</td><td>5 (6.2)</td><td>1 (9.3)</td><td>.57</td></tr>
<tr><td>Tracheostomy post-transplant, n (%)</td><td>6 (7.4)</td><td>2 (16.7)</td><td>.27</td></tr>
<tr><td>Pneumonia, n (%)</td><td>9 (11.1)</td><td>2 (16.7)</td><td>.63</td></tr>
<tr><td>Post-transplant bronchoscopies during hospital</td><td>3 (2-4)</td><td>3.5 (3-6)</td><td>.04</td></tr>
</table></td><td></td><td></td>
</tr>
</table>

<table>
<tr>
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<td></td>
<td>
<table>
<tr><td>stay, median (IQR)</td><td></td><td></td><td></td></tr>
<tr><td>Delirium, n (%)</td><td>11 (13.5)</td><td>6 (50)</td><td>.01</td></tr>
<tr><td>Myopathy, n (%)</td><td>10 (12.3)</td><td>10 (83.3)</td><td><.001</td></tr>
<tr><td>Thrombotic event, n (%)</td><td>15 (18.5)</td><td>6 (50)</td><td>.03</td></tr>
</table>
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolaitis et al 2018</td>
<td>P1 – Prospective cohort study</td>
<td>Three cohorts recruited 2010 - 2017: ECMO BTT (N=17), patients hospitalised but not on ECMO (N=48), patients called in for transplant as outpatients (N=124)

Single centre: San Francisco, USA</td>
<td>Patients over 65 years old excluded</td>
<td>Primary CE</td>
<td>Health-related Quality of Life

Measured with:

SF12-PCS (Short Form 12–Physical Component Score), range 0 to 100

SF12-MCS (Short Form 12–Mental Component Score), range 0 to 100

AQ20R (Airways Questionnaire 20–Revised), range 0 to 20, reverse-coded for analysis

EQ5D (EuroQoL 5D), range -1.11 to 1

GDS (Geriatric Depression Scale), range 0 to 15

Effect estimates for change in HRQL over time from before to 6 months after transplant, mean effect estimates with 95% CI
<table>
<tr><td></td><td>ECMO</td><td>Inpatient</td><td>Outpatient</td><td>P value</td></tr>
<tr><td>SF12-PCS</td><td>16.78 (10.65-21.91)</td><td>19.56 (15.62-23.50)</td><td>20.78 (18.50-23.07)</td><td>.27</td></tr>
<tr><td>SF12-MCS</td><td>8.78 (3.31-14.26)</td><td>7.48 (3.97-10.99)</td><td>4.48 (2.47-6.49)</td><td>.01</td></tr>
<tr><td>AQ20R</td><td>10.76 (8.57-12.96)</td><td>9.84 (8.45-11.23)</td><td>9.76 (8.96-10.56)</td><td>.59</td></tr>
<tr><td>EQ5D</td><td>0.31 (0.20-</td><td>0.29 (0.22-</td><td>0.17 (0.13-</td><td>.001</td></tr>
</table>
</td>
<td>Applicability: Direct. Looks at outcomes of patients bridged to lung transplant with ECMO.

Quality: 9/10

Aims and design clearly stated 2/2: Aims clearly stated as seeking to evaluate whether the impact of lung transplantation on HRQL within first postoperative year was different in patients with ECMO BTT compared with those who were not.

Design appropriate 2/2: prospective cohort study completely appropriate.

Methods clearly described 2/2: Study methods and clinical details clearly described, good detail on loss to follow up.

Data adequate for authors' interpretation 2/2: Clear and comprehensive data on HRQL supports interpretation and conclusions.

Results generalizable 1/2: Generalisable in so far as likely to represent a population of</td>
<td>Positives:

Included all patients in centre receiving ECMO during study period with participants prospectively identified so selection bias minimised.

Several measures of health-related quality of life used to get comprehensive picture.

Sensitivity analysis with imputed data performed to assess impact of missing data.

Negatives:

Some loss to follow up with survey completion which led to missing data - overall the number of missing surveys was 104 of 742 potential timepoints (14%). As authors acknowledge, informative missingness could therefore have impacted results. This was minimised by imputing missing data and performing sensitivity analysis.

Relatively small number in ECMO BTT (n=17) may increase risk of type 2 error and make interpretation of statistical analyses difficult.

Only followed up for 1 year so no detail on long term effects on HRQL are</td>
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<table>
<tr><td></td><td>0.42)</td><td>0.36)</td><td>0.21)</td><td></td></tr>
<tr><td>GDS</td><td>4.81 (3.15-6.48)</td><td>3.43 (2.38-4.49)</td><td>3.54 (2.94-4.14)</td><td>.09</td></tr>
</table>
</td>
<td>patients undergoing ECMO BTT, but no mention of what psychiatric or psychological support these patients are given at the centre.</td>
<td>provided by this study.

Very few details of ECMO procedure given so generalisability to other populations is limited, e.g. no details of level of sedation of patients on ECMO so no inferences can be made about impact of this, and no details of duration of ECMO given so impact of this cannot be inferred.

Only includes those who underwent transplant. As no data on patients who died on ECMO while awaiting transplant are included which may skew results.</td>
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<td>Secondary CE</td>
<td>Overall Survival at 1 year

Overall survival at 1 year was 97% and was similar in all three groups (p=.44). One patient in the ECMO group (1/17; 6%), 2 patients in the inpatient but not on ECMO group (2/48; 4%), and 2 patients in the outpatient group (2/124; 2%) died within the first year.</td>
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<tr>
<td>Schechter et al 2016</td>
<td>P1 – retrospective cohort study</td>
<td>Total population of all adults with lung transplantation 2005 – 2013 (N=12,403) in four cohorts: ECMO only BTT (n=65), MV only BTT (n=612), ECMO + MV BTT (n=119), no bridging support (n=11,607).

Data obtained from the United Network of Organ Sharing database</td>
<td></td>
<td>Primary CE</td>
<td>Survival

Cumulative survival, %:
<table>
<tr><td></td><td>6 months</td><td>1 year</td><td>3 years</td></tr>
<tr><td>ECMO only</td><td>75.2%</td><td>70.4%</td><td>64.5%</td></tr>
<tr><td>MV only</td><td>79.9%</td><td>72%</td><td>57%</td></tr>
<tr><td>MV+ECMO</td><td>68.1%</td><td>61%</td><td>45.1%</td></tr>
<tr><td>No Support</td><td>89.4%</td><td>84.2%</td><td>67%</td></tr>
</table>
Difference in long-term survival between the 3 bridge strategies was significant (p=0.0097).

Mid-term survival for patients on ECMO alone was not significantly different from those with not requiring support (P = 0.16).

patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support (P < 0.0001 for both).

After adjustment with a multivariate Cox regression model, MV +/− ECMO was independently associated with worse</td>
<td>Applicability: Direct. Compares outcomes of lung transplants using different bridging strategies including ECMO.

Quality: 10/10

Aims and design clearly stated 2/2: Aims clearly stated as evaluating the effect of non-intubated ECMO on survival after lung transplantation. Primary and Secondary outcomes predetermined and clearly detailed.

Design appropriate 2/2: retrospective cohort study completely appropriate

Methods clearly described 2/2: Yes, study methods clearly described.

Data adequate for authors' interpretation 2/2: Authors make appropriate conclusions about the survival benefits of ECMO</td>
<td>Positives:

All isolated lung transplants on register included so selection bias is minimal.

Relatively large sample size means that statistical analyses can be interpreted with some confidence and risk of type 2 errors is small.

Provides data for ECMO alone compared with ECMO + MV which therefore gives evidence relative impacts of each of these bridging strategies (in comparison with several of the other studies which include these as one cohort).

Negatives:

Only outcomes available on the registry could be included so limited results of effectiveness and safety presented.

Lack of detail on the level of mobility or ambulation of the patients receiving only ECMO (beyond stating that they are awake) limit the clinical</td>
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<td>survival compared with patients not requiring mechanical bridge (MV only: hazard ratio [HR] = 1.46; MV + ECMO = 2.26, P < 0.0001 for both), whereas ECMO alone was not (P = 0.39)</td>
<td rowspan="3">alone versus other bridging strategies.

Results generalizable 2/2: Use of data from large organ sharing database and comparison of several bridging strategies make results highly generalisable.</td>
<td rowspan="3">interpretation of the outcomes of this strategy.

Data on deaths on waiting list appears to include only those on that method of support at time of listing so it is unclear how this relates to the whole cohort (e.g. are some patients changing strategy after time of listing?).

No details of duration of ECMO or other support in patients while awaiting transplant is provided and this could be a confounding factor in the outcome results.</td>
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<td></td>
<td>Secondary CE</td>
<td>length of post-transplant hospital stay

length of stay, median (IQR)

<table>
<tr><th>No support (n=11607)</th><th>ECMO only (n=65)</th><th>MV only (n=612)</th><th>MV+ECMO (n=119)</th></tr>
<tr><td>15 (10-24)</td><td>25 (19-39.5)</td><td>27 (18-46)</td><td>32 (19-58)</td></tr>
</table>
p-value for difference in length of stay by between bridging strategy p=0.076</td>
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<td></td>
<td>SecondarySafety</td>
<td>Post-transplant complications

Episode of acute rejection before discharge, n (%):

<table>
<tr><th>No support (n=11607)</th><th>ECMO only (n=65)</th><th>MV only (n=612)</th><th>MV+ECMO (n=119)</th></tr>
<tr><td>997 (8.7%)</td><td>7 (10.8%)</td><td>79 (12.9%)</td><td>22 (18.5%)</td></tr>
</table>
P (bridging strategy)=0.21

New onset of dialysis, n (%):

<table>
<tr><th>No support (n=11607)</th><th>ECMO only (n=65)</th><th>MV only (n=612)</th><th>MV+ECMO (n=119)</th></tr>
<tr><td>552 (4.8%)</td><td>9 (13.9%)</td><td>63 (10.3%)</td><td>28 (23.5%)</td></tr>
</table>
P (bridging strategy)=<0.0001</td>
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<table>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Deaths on waiting list pre-transplant
Of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either died or their condition deteriorated such that they were removed from the list.
For the patients listed on MV alone, 231 (53.4%) were transplanted, with 109 (41.4%) either dying or becoming too sick for consideration.
For the patients listed on ECMO + MV, 38 (61.2%) were transplanted, whereas 21 (33.9%) either died or deteriorated.
P value for differences in outcomes after listing: P = 0.004</td><td></td><td></td></tr>
<tr><td>Lehmann et al 2015</td><td>P1 – Retrospective cohort study</td><td>Total population of all patients undergoing lung transplantation 2002-2011 (N=143) in two cohorts: Mechanical lung assist (ECMO or extracorporeal lung assist (ECLA)) (n=13), not on ECMO (n=130)
Single centre: Leipzig, Germany</td><td>Of the total population: 74/143 patients had a single lung transplant and 69/143 underwent bilateral lung transplants
Of those receiving MLA: 12/13 received ECMO and 1/13 received ECLA.
5/13 patients on ECMO BTT were awake and extubated.</td><td>Primary CE</td><td>Survival
<table><tr><td></td><td>30 day</td><td>90 day</td><td>1 year</td><td>5 year</td></tr><tr><td>Non-ECMO</td><td>95±1.8%</td><td>90±2.6%</td><td>71±4%</td><td>52±5.7%</td></tr><tr><td>ECMO</td><td>85±1%</td><td>77±1.2%</td><td>68±1.3%</td><td>34±1.8%</td></tr></table>P value for difference between non-ECMO and ECMO p-=0.281</td><td rowspan="3">Applicability: Direct. Compares patients bridged to transplant with ECMO with those not receiving ECMO.
Quality: 6/10
Aims and design clearly stated 1/2: Aims clearly stated as conducting a study to compare survival in lung transplant patients with and without preoperative MLA support. Design clearly outlined but outcomes of interest not specified.
Design appropriate 2/2: A retrospective cohort design is appropriate.
Methods clearly described 1/2: generally described adequately but very little detail about the outcome variables is provided.</td><td rowspan="3">Positives:
Study includes all consecutive lung transplant patients during study time so selection bias is minimal.
Follow up was 100% complete and ranged from 0.5 to 11.4 years.
5-year survival presented which provides good data on long-term effectiveness of ECMO BTT.
Negatives:
Small sample size, particularly in ECMO group (n=13) make interpretation of statistical analyses difficult and increase risk of type 2 error.
heterogeneity in lung transplant procedure and MLA procedure make interpretation and generalising of results difficult. For example, 6 patients from the non-ECMO group and 8 from the ECMO BTT group were preoperatively on MV which may</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Duration of pre-transplant ECMO
Mean duration on ECMO = 146 ±404 hours (range = 6 hours – 30 days)</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Deaths while on ECMO pre-transplant
2/15 patients died on ECMO while on the waiting list due to multiorgan failure or brain haemorrhage.</td></tr>
</table>

						Data adequate for authors' interpretation 1/2: Data presented support conclusion that MLA has no impact on long term survival but sample is small and variable characteristics of lung transplant and MLA may be affecting results. Results generalizable 1/2: Results include single and bilateral lung transplants and some concomitant heart surgery, and ECMO procedure is variable (e.g. some patients sedated and some awake) so some difficulty generalising results occurs from this.	confound the results but data presented do not account for this, and no details given about effect of single vs bilateral transplant. Very few outcome measures presented as comparison between the ECMO BTT and the non-ECMO group so interpretation of the magnitude of outcomes in ECMO BTT patients is limited. No data presented to indicate if there were any deaths on ECMO while awaiting transplant or not
Chiumello et al 2015	S1 – systematic review	14 studies included, all retrospective case series studies with total N=441 enrolled patients.	Due to substantial heterogeneity across studies a meta-analysis was not attempted	Primary CE	Survival 14/14 studies reported 1-year survival. In five studies it ranged from 50% to 70%, in four 70% to 90% and in two up to 90% one-year survival was significantly better in spontaneously breathing patients than mechanically ventilated ones (85% versus 50%) or when the ECMO bridge duration was shorter than 14 days (82% versus 29%).	**Applicability:** Direct. Included studies with at least 10 patients on ECMO bridging. **Quality**: 8/10 Aims and design clearly stated 2/2: clearly stated as a systematic review to assess the current evidence on the use of ECMO in patients with advanced respiratory failure awaiting lung transplant. Design appropriate 2/2: Systematic review completely appropriate. Methods clearly described 1/2: systematic review methods and quality assessment clearly described, but outcomes not specified or described in advance.	**Positives:** Search included all major databases with broad search strategy so should include all relevant studies therefore inclusion bias likely to be minimal. References and abstracts reviewed by 3 independent reviewers, methodology and quality assessed by 2 independent reviewers. Review of several studies together make the conclusions more reliable than if only a single study was used. **Negatives:** Studies included were case series with no control groups so confounding factors are not controlled for within each study. It is also difficult to make inference about the magnitude of outcomes observed or discern whether or not survival/risk actually from differs
				Primary CE	Mortality on ECMO pre-transplant Reported in 10/14 studies and ranged between 17% and 50% with multiple organ failure, septic shock, cardiac failure, and bleeding as most common causes		
				Secondary CE	Length of stay ICU stay: reported in 6/14 studies and medians ranged from 15 – 47 days. Hospital length stays: reported in 9/14 studies and medians ranged from 22 – 47 days		
				Secondary safety	Post-operative complications Respiratory complications:		

					Post-op graft dysfunction requiring Post-Ltx ECMO: 4/14 studies (20% - 54%) Post-op graft dysfunction 72 hours 3rd grade: 3/14 studies (15%-36%) Tracheostomy: 4/14 studies (27% - 77%) Bronchopleural fistula: 2/14 studies (8%- 14%) Open chest management: 2/14 studies (8%-50%) Acute rejection: 2/14 studies (15%- 28%) Acute kidney injury: 2/14 studies (12% - 35%) Renal replacement therapy: 7/14 studies (12% - 54%) Infective complications: Pneumonia: 1/14 studies (52%) Sepsis: 3/14 studies (14% - 23%) Haemorrhagic complications: GI bleeding: 1/14 studies (5%) Bleeding from femoral artery: 1/14 studies (5%) Re-op. for bleeding: 5/14 studies (15%-36%) Haemorrhage: 2/14 studies (31%- 35%) Massive haemoptysis: 1/14 studies (15%) Neurological complications: Cerebral haemorrhage: 1/14 studies (5%)	Data adequate for authors' interpretation 2/2: Authors are appropriately cautious about the conclusions that can be drawn from a heterogeneous set of case series studies. Results generalizable 1/2: results do refer to patients on ECMO as BTT, but due to old studies and heterogeneity of them some caution is needed when generalising.	from patients not on ECMO BTT. Studies included are all relatively old (published 2010 – 2013) and may therefore reflect survival and risks associated with older, less developed ECMO technology and practice. Sample sizes in studies were relatively small (11 – 122 patients) which may have resulted in imprecision in the data and a lack of adequate statistical power within studies. There were substantial differences in the inclusion criteria for patients, ECMO program times, and ECMO support technologies therefore it is not possible to exclude a possible confounding role of some important procedural aspects. As the authors acknowledge, there was substantial heterogeneity across studies a meta-analysis was not attempted because it would not have yielded clinically meaningful results.

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Stroke: 1/14 studies (8%)
Ischemia thoracic spinal cord: 1/14 studies (3%)
Digital ischemia: 2/14 studies (14%-17%)</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Duration on ECMO pre-transplant
Time on ECMO pre-transplant ranged in the studies from a median of 3.2 days to 16 days.</td><td></td><td></td></tr>
<tr><td>Toyoda et al 2013</td><td>P1 – Retrospective cohort study</td><td>Total population of patients transplanted 2005 - 2011 (N=715) in two cohorts: ECMO BTT (n=31 on ECMO, n= 24 transplanted), non-bridged patients (n=691)

Single centre: university of Pittsburgh Medical Centre</td><td>3/24 patient in ECMO BTT group had a retransplant</td><td>Primary CE</td><td>Survival
Actuarial survival, %
<table><tr><td></td><td>ECMO BTT</td><td>Non-ECMO</td></tr><tr><td>1 month</td><td>96%</td><td>97%</td></tr><tr><td>3 months</td><td>88%</td><td>94%</td></tr><tr><td>6 months</td><td>83%</td><td>90%</td></tr><tr><td>12 months</td><td>74%</td><td>83%</td></tr><tr><td>24 months</td><td>74%</td><td>74%</td></tr></table>Difference in survival between ECMO BTT and non-ECMO group p=0.787</td><td rowspan="4">Applicability: Direct. Includes outcomes of patients undergoing ECMO BTT and non-bridged controls.

Quality: 7/10
Aims and design clearly stated 1/2: Aims clearly stated as reviewing the efficacy of ECMO BTT, not including heart-lung transplantation. Outcomes not detailed.
Design appropriate 2/2: Retrospective cohort study completely appropriate.
Methods clearly described 1/2: methods of clinical procedure detailed well but no detail about gathering of outcome data.
Data adequate for authors' interpretation 2/2: data clearly support the conclusions
Results generalizable 1/2: Although results relate to patients on ECMO BTT, period of recruitment began over 10 years ago and changes in procedure may affect generalisability to survival and safety in current</td><td rowspan="4">Positives:
All consecutive patients who underwent ECMO BTT at the institution included so selection bias is minimised.

Negatives:
Relatively small sample size, particularly in ECMO BTT group may have affected precision of results (although no measure of error provided so it is not possible to discern if this is an issue).
ECMO BTT group contained patients undergoing retransplants as well as first transplants which may confound the survival and safety outcomes but this has not been considered in the analysis.
The long recruitment period may have introduced a learning curve bias and the inclusion of some patients who underwent ECMO over 10 years ago could be resulting in confounding from changes in ECMO technology and practice seen over this time.
No details are given of the 7 patients who were on ECMO with intention to transplant but did not receive transplant. It is unclear if they died as a result of ECMO complications or failed to have a suitable donor identified.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary CE</td><td>Length of stay
Median length of hospital stay was 46 days in ECMO BTT group compared with 27 in non-ECMO control group (p=0.16)</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Post-transplant complications
ECMO support was used postoperatively for primary graft dysfunction in 54% of patients in the pre-transplant ECMO group and 6% of patients in the control group (P <.01)</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Secondary Safety</td><td>Duration of ECMO pre-transplantation
The duration of pre-transplant ECMO support in the ECMO BTT group was 171±242 hours (range, 2-1104 hours)</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>practice.</td><td>6 of the 24 patients on ECMO BTT received cadaveric lobar transplants because a suitable donor could not be found. It is unclear how this might affect the results with regards to outcomes of these patients but as this is potentially a risky procedure it may decrease survival and increase complication estimates in this group.</td></tr>
<tr><td>Ius et al 2018</td><td>P1 – Retrospective cohort study</td><td>Total population of all patients undergoing transplant 2010 – 2017 (N=917) in two cohorts: patients with ECMO BTT (N=68), patients with no bridging support (N=849).

Single centre: Hannover, Germany</td><td>Awake ECMO strategy used in 57/68 of the ECMO BTT patients.

9/68 ECMO BTT patients and 52/849 non-ECMO BTT patients had retransplant.

11/68 patients in ECMO BTT and 53/849 patients in non-ECMO BTT were <18 years old</td><td>Primary CE</td><td>Survival

Patient survival overall, % (n)
<table><tr><td></td><td>ECMO BTT (n=68)</td><td>Non-ECMO BTT (n=849)</td><td>P-value</td></tr><tr><td>1 year</td><td>79 (5)</td><td>90 (1)</td><td rowspan="2">0.095</td></tr><tr><td>5 years</td><td>65 (9)</td><td>71 (2)</td></tr></table>
Patient survival conditioned to hospital discharge, % (n)
<table><tr><td></td><td>ECMO BTT (n=68)</td><td>Non-ECMO BTT (n=849)</td><td>P-value</td></tr><tr><td>1 year</td><td>93 (3)</td><td>95 (1)</td><td rowspan="2">0.97</td></tr><tr><td>5 years</td><td>77 (6)</td><td>75 (2)</td></tr></table></td><td rowspan="2">Applicability: Direct. Includes outcomes of patients undergoing ECMO BTT compared with those not receiving ECMO BTT.

Quality: 9/10

Aims and design clearly stated 2/2: Aim stated as investigating impact of ECMO BTT on graft survival at follow up. Primary and Secondary end points clearly pre-determined.

Design appropriate 2/2: Retrospective cohort study completely appropriate

Methods clearly described 2/2: study methods and clinical procedures clearly outlined.

Data adequate for authors' interpretation 1/2: mostly the data do support the conclusions, but the authors state that an awake ECMO strategy should be used when their data suggest there is no difference in outcomes between those awake and those not (although numbers in not-awake group were very</td><td rowspan="2">Positives:

Includes all consecutive cases of lung transplant at the centre therefore selection bias is unlikely

Relatively large sample size and number of patients receiving ECMO BTT so results are more generalisable and risk of type 2 error is not too great.

Compares awake and sedated ECMO (with MV) in results which accounts for a potentially important confounding factor in analysis of survival and safety of ECMO and provides useful data on optimal ECMO strategy.

Negatives:

As authors acknowledge, the greater number of paediatric patients in the ECMO BTT group than the non-ECMO group may have positively influenced transplant survival in the former group.

Patients who died on ECMO while awaiting transplantation were excluded form analysis. The authors explain this as being due to a desired focus on the impact of ECMO BTT. However, this could inflate survival data post-transplant and reduce the apparent</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Primary CE</td><td>Graft survival

Graft Survival, % (n)
<table><tr><td></td><td>ECMO BTT (n=68)</td><td>Non-ECMO BTT (n=849)</td><td>P-value</td></tr><tr><td>1 year</td><td>79 (5)</td><td>90 (1)</td><td rowspan="2">0.13</td></tr><tr><td>5 years</td><td>61 (6)</td><td>68 (2)</td></tr></table></td></tr>
</table>

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<td></td><td></td><td></td><td></td><td></td><td></td><td>small).
Results generalizable 2/2: Good confidence in generalisability due to large sample size and relatively recent recruitment of patients.</td><td>complications of ECMO BTT as the sickest patients won't be considered in the analysis.</td>
</tr>
<tr>
<td></td><td></td><td></td><td></td><td>Secondary
CE</td><td>ICU and hospital stay
Duration of ICU and hospital stay, days (IQR)
<table>
<tr><th></th><th>ECMO BTT (n=68)</th><th>Non-ECMO BTT (n=849)</th><th>P-value</th></tr>
<tr><td>ICU stay</td><td>11 (4-23)</td><td>2 (1-4)</td><td><0.001</td></tr>
<tr><td>Hospital stay</td><td>42 (26-67)</td><td>23 (21-28)</td><td><0.001</td></tr>
</table></td><td></td><td></td>
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<tr>
<td></td><td></td><td></td><td></td><td>Secondary
Safety</td><td>Post-operative complications
Median (IQR) or n (%)
<table>
<tr><th></th><th>ECMO BTT (n=68)</th><th>Non-ECMO BTT (n=849)</th><th>P-value</th></tr>
<tr><td>PGD 2 or 3 at 24h</td><td>25 (37)</td><td>125 (15)</td><td><0.001</td></tr>
<tr><td>PGD 2 or 3 at 48hr</td><td>30 (46)</td><td>122 (14)</td><td><0.001</td></tr>
<tr><td>PGD 2 or 3 at 72h</td><td>28 (42)</td><td>93 (11)</td><td><0.001</td></tr>
<tr><td>Rethoracotomy for bleeding</td><td>14 (21)</td><td>64 (8)</td><td><0.001</td></tr>
<tr><td>Dialysis</td><td>18 (27)</td><td>63 (7)</td><td><0.001</td></tr>
<tr><td>Atrial Fibrillation</td><td>9 (13)</td><td>91 (11)</td><td>0.52</td></tr>
<tr><td>Cerebrovascular event</td><td>1 (2)</td><td>12 (1)</td><td>0.63</td></tr>
<tr><td>Vascular</td><td>7 (10)</td><td>16 (2)</td><td>0.001</td></tr>
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					complication			
					Posy-op pulsed steroid therapy	34 (52)	223 (26)	<0.001
					Blood products (PRBCs)	23 (15-43)	6 (4-10)	<0.001
					Secondary ECMO	3 (4)	17 (2)	0.18
					Tracheostomy	23 (34)	90 (11)	<0.001
					Ventilation time (days)	3 (1 – 17)	1 (1-1)	<0.001
					In-hospital mortality	10 (15)	42 (5)	0.003
				Secondary CE	Outcomes at Follow up Freedom from biopsy-confirmed rejection, % (n)			
						ECMO BTT (n=68)	Non-ECMO BTT (n=849)	P-value
					1 year	70 (7)	64 (2)	0.42
					5 years	59 (8)	52 (2)	
					Freedom from pulsed steroid therapy, % (n)			
						ECMO BTT (n=68)	Non-ECMO BTT (n=849)	P-value
					1 year	60 (6)	52 (2)	0.17
					5 years	40 (7)	35 (2)	
					Freedom from chronic lung allograft dysfunction, % (n)			
						ECMO BTT (n=68)	Non-ECMO BTT (n=849)	P-value

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<table>
<tr><td>1 year</td><td>95 (3)</td><td>96 (1)</td><td rowspan="2">0.46</td></tr>
<tr><td>5 years</td><td>61 (8)</td><td>66 (2)</td></tr>
</table>

Freedom from retransplant, % (n)
<table>
<tr><td></td><td>ECMO BTT (n=68)</td><td>Non-ECMO BTT (n=849)</td><td>P-value</td></tr>
<tr><td>1 year</td><td>98 (2)</td><td>99 (1)</td><td rowspan="2">0.82</td></tr>
<tr><td>5 years</td><td>92 (4)</td><td>94 (1)</td></tr>
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<td></td>
<td>Secondary safety</td>
<td>Duration of ECMO and deaths of patients on ECMO before transplantation

19 patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation (cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1).

Median support time of ECMO BTT in patients surviving to transplant was 9 (5-16 days)</td>
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<td></td>
<td></td>
<td>Secondary CE</td>
<td>Outcomes of patients on awake ECMO strategy Vs not awake

Outcomes did not differ between patients who underwent an awake ECMO strategy and those who did not (graft survival, P=0.38; patient survival, P=0.25; freedom from biopsy-confirmed rejection, P=0.53; freedom from pulsed steroid therapy, P=0.98; freedom from chronic lung allograft rejection, P=0.58; freedom from retransplant, P=0.46)</td>
<td></td>
<td></td>
</tr>
</table>

8. Grade of evidence table (to be completed in line with the evidence review guidance document)

<table>
<tr><td colspan="6">Use of Intervention X Vs. Comparator Y to treat Indication Z
(Create separate table for studies with different comparators)</td></tr>
<tr><td>Outcome Measure</td><td>Reference</td><td>Quality of Evidence Score</td><td>Applicability</td><td>Grade of Evidence</td><td>Interpretation of Evidence</td></tr>
<tr><td rowspan="11">Survival at 1 year (& 3 years if reported)</td><td>Ius et al 2018</td><td>9/10</td><td>Direct</td><td rowspan="11">Grade A</td><td rowspan="11">This outcome reports the likelihood of a patient being alive at various time points post-transplant and is generally reported at the proportion (percentage) of patients alive at that time.

The best study of survival post-transplant is Schechter et al 2016 who reported cumulative survival at 6 months, 1 year and 3 years in ECMO only, VM+ECMO, MV only and no support patients:

<table><tr><td></td><td>ECMO only</td><td>MV only</td><td>MV+ECMO</td><td>No support</td></tr><tr><td>1-year</td><td>70.4%</td><td>72%</td><td>611%</td><td>84.2%</td></tr><tr><td>3-years</td><td>64.5%</td><td>57%</td><td>45.1%</td><td>67%</td></tr></table>
The difference in survival at 3 years between the 3 bridge strategies was significant (p=0.0097), but survival for patients on ECMO alone was not significantly different from those requiring no support (P = 0.16). Patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support (P < 0.0001 for both).

Two other recent, relatively large studies have found slightly higher 1-year (and 3-year) survival rates in both ECMO BTT patients and non-bridged patients:

• Ius et al 2018 report survival at 1 year of 79% in ECMO BTT patients compared with 90% in non-ECMO patients. This difference was not statistically significant. They also report survival</td></tr>
<tr><td>Hayanga et al 2018</td><td>7/10</td><td>Direct</td></tr>
<tr><td>Todd et al 2017</td><td>8/10</td><td>Direct</td></tr>
<tr><td>Kolaitis et al 2018</td><td>9/10</td><td>Direct</td></tr>
<tr><td>Schechter et al 2016</td><td>10/10</td><td>Direct</td></tr>
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<tr><td>Chiumello et al 2015</td><td>8/10</td><td>Direct</td></tr>
<tr><td>Toyoda et al 2013</td><td>7/10</td><td>Direct</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
</table>

at 1-year conditioned to hospital discharge and this shows an even smaller difference between the groups with ECMO BTT patients at 93% and non-ECMO patients at 95%. This suggests that if patients bridged with ECMO remain alive in the early days post-transplant until discharge they have virtually the same rate of survival at 1 year. This was a recent, high quality study with a relatively large number of patients.

- Hayanga et al 2018 reported very similar survival probabilities at 1-year and 3-years in the three groups they assessed. These were not statistically different. This is a large, recent study but unfortunately does not include patients who were only on ECMO for comparison:

	Control	MV	MV & ECMO
1 year	0.839 (0.779-0.884)	0.807 (0.661-0.895)	0.815 (0.675-0.899)
3 years	0.731 (0.659-0.789)	0.559 (0.397-0.693)	0.769 (0.621-0.865)

Several other, smaller or more limited studies have also found similar patterns of survival:

- Todd et al found 2017 100% survival in ECMO BTT patients at 1 year, compared with 91.3% non-bridged patients, this difference was not statistically significant. The sample of patients on ECMO was small (n=12).
- Kolaitis et al 2018 report that survival was 97% at 1 year and was similar in the other two comparison groups (hospitalised patients not on ECMO and outpatient transplant patients) but do not give figures for survival in these.
- Lehmann et al 2015 found no difference between survival at 1-year between ECMO BTT and non-EMO patients (68% and 71% respectively), but sample size was small in the ECMO group.
- Toyoda et al 2018 also found no difference in survival at 1 year between ECMO BTT and non-bridged patients with 74% and 83% alive at 1 year. The ECMO BTT group included some retransplanted patients so survival may actually be higher in this group if only first transplants were considered.
- All 14 studies in the systematic review by Chiumello et al 2015 included data on survival at 1 year, and this ranged from 50% - 90% in patients receiving ECMO BTT. No comparison with a control group not receiving ECMO is provided.

These results suggest that 70-90% of patients who receive ECMO BTT are still alive at 1 year, and

					around 60-80% are alive at 3 years post-transplant, and this rate of survival is no different to that of patients not receiving any bridging support. There is also evidence that survival is better in patients receiving ECMO BTT than in those receiving MV (either with or without ECMO). Given the large body of evidence supporting this outcome, including several good-sizes, high quality studies, there is a high degree of certainty that survival for ECMO BTT is no different from patients not requiring bridging. Although the exact rates vary a little between studies, probably due to different criteria for ECMO, different case mix for transplants, procedural differences and differing use of MV, it is likely that with ever improving technologies and techniques for ECMO the survival rates increase further.
Survival at 5 years	Ius et al 2018 Hayanga et al 2018 Lehmann et al 2015	9/10 7/10 6/10	Direct Direct Direct	Grade A	This outcome reports the likelihood of a patient being alive at 5 years post-transplant and is generally reported at the proportion (percentage) of patients alive at this time. The best study including data on survival at 5 years is Ius et al 2018 who report the percentage of patients who are still alive at 5 years post-transplant in the group receiving ECMO BTT versus no support. At 5 years 65% of patients who had ECMO and 71% of those who did not were still alive. This difference in survival was not statistically significant suggesting that there is no difference in-5 year survival of patients on ECMO BTT and those not. • Hayanga et al 2018 also report similar 5-year survival probabilities (ECMO + MV 66%; MV only 43%; control 59%) with no statistically significant difference between them, but their ECMO BTT group are all on MV (compared to the majority of the Ius et al 2018 ECMO BTT cohort who are awake and not on MV). • Lehmann et al 2015 report slightly lower survival at 5 years (ECMO BTT 34%, non-ECMO BTT 52%) but the study includes patients recruited a longer time ago when ECMO techniques may not have been so good. Again, no difference in survival at 5 years was found between the groups. This outcome has a relatively high degree of certainty as the outcome is very objective and it is reported by several studies with a good level of consistency. The evidence therefore suggests that two thirds of patients who receive ECMO BTT survive until at least 5 years and that this survival is no different to those not receiving ECMO BTT.
Death on ECMO	Ius et al 2018	9/10	Direct	Grade A	This outcome refers to the deaths that occur in patients who are on ECMO while they are on the

while awaiting transplant	Schechter et al	10/10	Direct	waiting list for a suitable donor for lung transplant. It is usually reported as a number or proportion of the patients who are in the ECMO BTT group who die before transplant. The best study providing data on deaths on ECMO while awaiting transplant is Ius et al 2018. They reported that 19/87 (22%) patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation (cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1). Other studies have also reported this outcome, but with more limitations: • Schechter et al 2016 reported that of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either died or their condition deteriorated such that they were removed from the list. For the patients listed on MV alone, 231 (53.4%) were transplanted, with 109 (41.4%) either dying or becoming too sick for consideration. For the patients listed on ECMO and MV, 38 (61.2%) were transplanted, whereas 21 (33.9%) either died or deteriorated. These differences in deaths by bridging strategy were significant (P = 0.004). However, these data are limited by reporting only deaths for those on each method of support at the time of listing so unclear how they relate to each cohort as a whole. • Todd et al 2017 reported that of a cohort of 12 patients receiving ECMO BTT none died before transplant, but the sample size is small so caution is needed when interpreting this result. • Chiumello et al 2015 reported that 10/14 studies included in the systematic review presented data on deaths while on ECMO and the proportion of the ECMO BTT cohorts that died ranged between 17% and 50% with multiple organ failure, septic shock, cardiac failure and bleeding as the most common causes. However, this study is limited by the inclusion of several older studies which assessed outcomes on ECMO a long time ago when the technology and safety was less advanced. • Lehmann et al reported 2/15 deaths pre-transplant on ECMO, from brain haemorrhage and multi organ failure. This study is limited by small sample size. There is a high degree of uncertainty as to the exact rate of mortality to expect in patients on ECMO BT while awaiting transplant as varying rates have been reported in the studies. This is likely to be due to small sample sizes in several studies and differences in the level of sickness and comorbidities of the patients put on ECMO, and advances in ECMO technology and safety which will affect survival. A
	Todd et al 2017	8/10	Direct	
	Lehmann et al 2015	6/10	Direct	
	Chiumello et al 2015	8/10	Direct	

					lack of a control group for comparison also makes it difficult to interpret this data, however it should be noted that without ECMO 100% of the patients who need it would have died.
Length of hospital stay	Ius et al 2018	9/10	Direct	Grade A	This outcome measure refers to the length of time that patients stay in hospital post-transplant. A shorter length of stay indicates a quicker recovery after the operation. Two studies could be considered the best for providing length of stay data: • Schechter et al 2016 report median length of stays of 15 days (IQR 10-24) for patients not receiving any support, 25 days (IQR 19-39.5) for those receiving ECMO alone, 27 days (IQR 18-46) for those receiving MV alone, and 32 days (IQR 19-58) for those receiving both ECMO and MV. The difference between the length of stay for each of these bridging strategies was not statistically significant. • Ius et al 2018 report median length of hospital stays of 23 days (IQR 21-28 days) for non-bridged patients and 42 days (IQR 26 – 67 days) for those on ECMO BTT. This difference was statistically significant (P<0.001). Other studies also present similar data on length of stay but have limitations: • Hayanga et al 2018 report a median LOS of 27 days in those not receiving support, 36 days in patients on ECMO + MV, and 39 days in patients on MV only. The difference between the control group and the ECMO+MV group was statistically significant. However, this study does not report LOS in patients who are on ECMO without MV. • Todd et al report LOS of 13 days after transplant in patients receiving no support, and 25 days in those receiving ECMO BTT. This difference was statistically significant. The study is limited by having a sample of only 12 patients on ECMO. • Chiumello et al 2015 report a range of median LOS of 22-47 days in ECMO patients in the studies included in their systematic review. No comparison group data is presented. • Toyoda et al 2015 report a median LOS of 46 days in ECMO BTT patients compared with 27 days in non-ECMO patients but this difference is not statistically significant. This study has a relatively small sample size and recruitment of patients began a long time ago when ECMO techniques may not have been as good as more recently. This outcome has a moderate level of uncertainty. It is objectively measured and has been reported in
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		
	Schechter et al 2016	10/10	Direct		
	Chiumello et al 2015	8/10	Direct		
	Toyoda et al 2013	7/10	Direct		

					several studies with a similar pattern of outcome (longer LOS in ECMO BTT than in non-ECMO patents, and slightly longer LOS in patients receiving MV with or without ECMO than in those receiving only ECMO), however the exact LOS stay is not consistently reported and there is no consensus on whether differences in LOS are statistically significant between bridging strategies.
Length of ITU stay	Ius et al 2018	9/10	Direct	Grade A	This outcome measure refers to the length of time that patients stay in ITU post-transplant. A shorter length of ITU stay indicates a quicker recovery after the operation. Two high quality studies report data on ITU stay post-transplant. The best study providing data on the length of ITU stay is by Ius et al 2018 who found that the length of ITU stay in patients on ECMO BTT was a median of 11 days (IQR 4-23) compared with 2 days (IQR 1-4) in those without bridging support. This difference was statistically significant (p=<0.001) One other study also reports length of ITU stay data: Chiumello et al 2015 found that 6/14 studies included in their systematic review reported length of ITU stay data with medians ranging from 15 – 47 days in patients receiving ECMO. The authors note that a study that compared length of ITU stay in different ventilation strategies found non-invasive ventilation during ECMO bridge was associated with significantly shorter ICU and hospital stays than invasive mechanical ventilation and similarly another study found shorter mean ITU stay after lung transplantation in the awake-ECMO group than the mechanically ventilated ECMO group, but the difference was not statistically significant. The systematic review by Chiumello et al 2015 is limited by the inclusion of studies which are generally quite old so may be using less advanced ECMO procedures so complications and therefore ITU stays may have been longer than they would be with more modern and safe techniques. Most studies included also have relatively small sample sizes. There is reasonable certainty that the length of post-transplant ITU stays are longer in patients who receive ECMO BTT than those who do not require bridging support, and there is some suggestion, although with less certainty, that awake ECMO or ECMO without concurrent MV resulted in shorter length of ITU stay than MV. As only one recent study reports length of ITU stay the exact duration of ITU stay to be expected for an ECMO BTT patent remains unclear as it may vary centre to centre.
	Chiumello et al 2015	8/10	Direct		

Duration of ECMO/MV	Ius et al 2018	9/10	Direct	Grade A	This outcome refers to the duration of time patients spend on ECMO before having a lung transplant. Five studies report this outcome, the best of which is Ius et al 2018 who found that the median support time of ECMO BTT in patients surviving to transplant was 9 (range 5-16 days). The majority (57/68) of these patients were awake on ECMO therefore had no MV. Several other studies report very similar results: • Chiumello et al 2015 found that 12 of the 14 studies included in their systematic review reported duration of ECMO and it ranged from a median of 3.2 days to 16 days. This systematic review includes mostly older studies with small sample sizes. • Hayanga et al 2018 reported a mean duration of ECMO + MV of 14.58 days (SD, 15.10) compared with a mean duration of MV alone of 7.68 (SD, 11.40). This difference in duration was not statistically significant (p=0.63) This study is limited by not including patients on ECMO without MV. • Todd et al 2017 report a mean duration on ECMO of 103.6 hours (range 16 – 395 hours), which is equivalent to 4.2 days (range 0.6 – 16.5), however the sample size of patients on ECMO is small. • Toyoda et al 2013 report the duration of pre-transplant ECMO support in the ECMO group as 171±242 hours (range, 2-1104 hours) which is equivalent to 7.1 days (range 0.08 – 46 days). Again, this study has a small sample size. There is little certainty about the exact duration of pre-transplant ECMO in these patients, probably due to the different indications for ECMO at different centres and slightly different management of transplant waiting lists. However, it certainly seems to be the case that durations do not tend to exceed around 16 days. This is likely to be due to the fact that once on ECMO, a patient becomes a high priority for available donor lungs.
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		
	Chiumello et al 2015	8/10	Direct		
	Toyoda et al 2013	7/10	Direct		
Health-related Quality of life (HRQL)	Kolaitis et al 2018	9/10	Direct		This outcome refers to an individual's perceived physical and mental health over time. Patients who undergo lung transplantation and ECMO are critically ill and both procedures are high-risk and associated with complications and potentially long hospital stays, and can therefore impact on an individuals perceived physical and mental health. Only one study looked at HRQL as an outcome. Kolaitis et al 2018 reported changes in scores on 5 different measures of HRQL from pre-transplant to 6 months post-transplant in patients on ECMO

Grade B

BTT, patients who were hospitalised (inpatients) but not on ECMO, and patients who were called in for a transplant as outpatients.

Before transplantation, HRQL and depressive symptoms were similar among the 3 groups, although outpatients reported better baseline HRQL on two of the surveys (SF12-MCS and EQ5D). After transplantation, HRQL and depressive symptoms generally improved across all 3 groups. Overall, peak improvement in HRQL and depressive symptoms was seen in the early period, within 6 months post-transplantation, and remained stable through to 12 months post-transplantation. The magnitude of these early improvements at 6 months varied by instrument:

Estimates for change in the 5 HRQL measures over time from before transplant through to 6 months post-transplant

	ECMO	Inpatient	Outpatient	P value
SF12-PCS (Short Form 12–Physical Component Score)	16.78 (10.65-21.91)	19.56 (15.62-23.50)	20.78 (18.50-23.07)	.27
SF12-MCS (Short Form 12–Mental Component Score)	8.78 (3.31-14.26)	7.48 (3.97-10.99)	4.48 (2.47-6.49)	.01
AQ20R (Airways Questionnaire 20–Revised)	10.76 (8.57-12.96)	9.84 (8.45-11.23)	9.76 (8.96-10.56)	.59
EQ5D (EuroQoL5D)	0.31 (0.20-0.42)	0.29 (0.22-0.36)	0.17 (0.13-0.21)	.001
GDS (Geriatric Depression Scale)	4.81 (3.15-6.48)	3.43 (2.38-4.49)	3.54 (2.94-4.14)	.09

					The greatest improvement was seen in respiratory-specific HRQL, but there were also substantial improvements in health utility and depressive symptoms, and some improvement in generic mental HRQL. In summary, patients ill enough to require ECMO BTT achieve similar improvements in HRQL and depressive symptoms as those who do not require ECMO. These improvements are greatest in the 6 months post-transplant and then remain stable to 12 months. There is a low to moderate uncertainly with these conclusions, the study was high quality and used several different measures of HRQL which make the results reliable and valid, but only one study with relatively small sample size included measures of HRQL as an outcome. It is also not clear what duration of ECMO or level of sedation was experienced by patients which may affect generalisability.
Graft Survival	Ius et al 2018	9/10	Direct	Grade A	This outcome measure refers to the duration of time that the lung transplant remains functional, or the time from transplantation to the time when the lung transplant has irreversible failure and is no longer functioning. At this point, respiratory support is needed and a retransplant may be required. This outcome is reported in the studies in the short term as rates of acute rejection (proportion of transplants that have been rejected), or in the longer-term as graft survival (the proportion of patients who have a surviving graft at various time points) or graft dysfunction (the proportion of patients with transplants that are no longer functioning at various time points). The best study of graft survival is provided by Ius et al 2018 who report higher rates of acute rejection (PGD score Grade 2-3) of the graft in ECMO BTT patients than in non-bridged patients at 24 hr (37% vs 15% respectively), 48 hrs (46% vs 14%) and 72hrs (42% vs 11%), all differences significant at p=<0.001. They also followed up graft survival at 1 and 5 years. They found that 90% of non-ECMO and 79% of ECMO BTT patients had grafts that survived at 1 year, and 68% of non-ECMO and 61% of ECMO BTT patients with grafts surviving at 5 years. These differences were not statistically significant (p=0.13) suggesting that graft survival is no worse in ECMO BTT patients. This relatively large and high-quality study suggests that acute rejection of the graft in the days immediately after transplantation is far more likely in ECMO BTT, but that in the long-term graft survival does not differ from non-bridged patients.
	Hayanga et al 2018	7/10	Direct		
	Todd et al 2017	8/10	Direct		
	Schechter et al 2016	10/10	Direct		

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other studies have not found any difference in rates of acute rejection immediately post-transplant and have not included a long-term follow up f graft survival:
Schechter et al reported the proportion of patients experiencing an episode of acute rejection before discharge. This occurred in 8.7% of those receiving no bridging support, 10.8% in those receiving only ECMO, 12.9% of those on only MV, and 18.5% of those on ECMO + MV, however these differences were not statistically significant. This is also a relatively large, high-quality study.
Todd et al report primary graft dysfunction (grade 3) at 48-72 hours post-transplant of 26% in the control non-ECMO group and 33% in the ECMO group, with these proportions not being statistically different. However, the number of patients on ECMO in this study was small.
Hayanga et al report median graft failure as 2,406 days for the control group and 1,696 for the MV group, but they report 'not reached' for the ECMO + MV group so this is of limited use as an outcome (although they do however state the difference in the graft survival between the groups is not statistically significant). They also reported rates of acute rejection at different grades (0-4) and found no statistical difference in the bridging strategies.
Although all studies report a trend towards higher rates of acute rejection in ECMO BTT patients in the short-term immediately post-transplant, there is some disagreement over whether this difference is statistically significant. There are no clear methodological or clinical reasons why this might be the case. Long-term follow up of graft survival is only reported by one study but clearly shows that there is no difference between ECMO BTT and non-bridged patients at 1- and 5-years.</td></tr>
<tr><td rowspan="5">Post-operative complications</td><td>Ius et al 2018</td><td>9/10</td><td>Direct</td><td rowspan="5">Grade A</td><td rowspan="5">Post-operative complications refer to any adverse consequences of having the lung transplant operation.

The best study providing a comprehensive list of the post-operative complications seen in ECMO BTT patients compared with non-bridged patients is Ius et al 2018. The majority (57/68) of the patients in the ECMO BTT group were on an awake ECMO strategy and so did not receive concurrent MV.<table><tr><td></td><td>ECMO BTT (n=68)</td><td>Non-ECMO BTT</td><td>P-value</td></tr></table></td></tr>
<tr><td>Hayanga et al 2018</td><td>7/10</td><td>Direct</td></tr>
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<tr><td>Chiumello et al 2015</td><td>8/10</td><td>Direct</td></tr>
</table>

		(n=849)	
PGD 2 or 3 at 24h	25 (37)	125 (15)	<0.001
PGD 2 or 3 at 48hr	30 (46)	122 (14)	<0.001
PGD 2 or 3 at 72h	28 (42)	93 (11)	<0.001
Rethoracotomy for bleeding	14 (21)	64 (8)	<0.001
Dialysis	18 (27)	63 (7)	<0.001
Atrial Fibrillation	9 (13)	91 (11)	0.52
Cerebrovascular event	1 (2)	12 (1)	0.63
Vascular complication	7 (10)	16 (2)	0.001
Post-op pulsed steroid therapy	34 (52)	223 (26)	<0.001
Blood products (PRBCs)	23 (15-43)	6 (4-10)	<0.001
Secondary ECMO	3 (4)	17 (2)	0.18
Tracheostomy	23 (34)	90 (11)	<0.001
Ventilation time (days)	3 (1 – 17)	1 (1-1)	<0.001
In-hospital mortality	10 (15)	42 (5)	0.003

Several post-operative complications were more likely in ECMO BTT patients including bleeding (indicated by need for blood products and rethoracotomy for bleeding), renal failure (indicated by need for dialysis), vascular complications, need pulsed steroid therapy, tracheostomy, longer ventilation times, and higher in hospital mortality.

Four other studies report post-operative complications:

- Todd et al (2017) also present a comprehensive list of post-operative complications, but this study was based on only 12 patients in the ECMO BTT group and 9/12 of these patients were sedated. Some of these complications were more likely in patients receiving ECMO BTT than controls, including delirium (50% vs 13.5% respectively), myopathy (83.3% vs 12.3%) and

					thrombotic events (50% vs 18.5%), and the need for return to the operating theatre (67% vs 16%). Blood transfusions were borderline more likely in ECMO BTT (median of 2.5 vs 1). • Hayanga et al 2018 also provide a detailed account of the post-operative complications for patients who received ECMO + MV BTT compared with those receiving only MV and controls who received no bridging support. There was no difference in renal insufficiency requiring dialysis (9% of controls, 13% of those on MV alone, and 8% of those on ECMO + MV) and no difference in airway complications (15% of controls, 21% of those on MV alone, and 18% of those on ECMO + MV). However, bleeding requiring operation was higher in MV alone and EMO +MV groups compared with controls but no different in MV alone compared with ECMO+MV (9% in controls, 19% in MV alone, and 20% in ECMO + MV). • Chiumello et al 2015 looked at all the post-operative complications reported in the 14 studies included in their systematic review. The proportions of ECMO BTT patients in each study experiencing these complications was presented. Although this provides a very comprehensive list of post-operative complications that were associated with ECMO BTT, it is limited by not including comparison with rates of complications seen in lung transplant patients not bridged with ECMO. The systematic review also includes mostly older studies in which ECMO technology and safety may not have been so good. In summary therefore, this study gives a good indication of the possible complications that can occur with ECMO BTT, but no indication of high likely they are with current procedures or in comparison with a non-bridged transplant. • Schechter et al 2016 included two measures of post-operative complications, episode of acute rejection before discharge (outlined in outcome above) and new onset of dialysis. The incidence of new-onset dialysis was significantly different among the bridging strategies ($P < 0.0001$), with ECMO + MV patients having the highest incidence (23.5%) compared with both ECMO only patients (13.9%) and MV only (10.3%). This is a high-quality study with a relatively large cohort of patients on ECMO, however it obtained data from a national organ sharing database so is likely to have been limited in the complications it reports due to only being able to include information recorded on the database. Overall, there is evidence that ECMO BTT is associated with some increased post-operative complications. There is relatively high certainly that the risk of bleeding is higher in ECMO BTT patients as this has been found in all the studies that report this outcome. Higher risk of renal failure is a little less consistently reported with one of the three studies including this outcome finding it to be more common in ECMO BTT (when ECMO alone given), one study finding	

					no difference (ECMO + MV given), and another study finding it depends on the use of concurrent MV which increases risk of dialysis. There is therefore quite a high degree of uncertainty about this outcome. It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g. blood transfusion vs rethoractotomy for bleeding). Although there is some degree uncertainty due to small sample size in the single study that reports it (Todd et al 2017), there is clear suggestion that ECMO BTT is associated with far higher risk of delirium and myopathy with around 50% and 80% of patients experiencing each of these respectively. There is slightly more certainty that thrombotic and vascular events may be an increased risk in this procedure as this was also found by a larger, more robust study (Ius et al), albeit at a far lower rate (10% compared with 50% of ECMO BTT patients in Todd et al 2017).
Functional status	Todd et al 2017	8/10	Direct	Grade B	This outcome refers to an individual's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being. One study included assessment of functional status with the Karnofsky scale index which is an assessment tool for functional impairment. A score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed. Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year functional status in ECMO BTT group was not significantly different from the non-ECMO group (p=0.74) It was concluded that 1-year functional status was excellent in both groups. However, they highlight that this is in a select group of patients (under 65 years old, ambulatory before deterioration, no other organ dysfunction and good rehabilitation potential). These results suggest that there is no difference between the functional status of patients on ECMO BTT as those who do not receive bridging support, however there is a moderate degree of uncertainty around this. Although the study is of high quality and used a recognised and validated measure of functional status, the findings were based on relatively few patients in the ECMO group who have been selected for ECMO on the basis of being of good functional status before deterioration,

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<tr><td></td><td></td><td></td><td></td><td></td><td>therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.</td></tr>
<tr><td rowspan="5">Post-operative ventilation</td><td>Hayanga et al 2018</td><td>7/10</td><td>Direct</td><td rowspan="5">Grade B</td><td rowspan="5">This outcome refers to whether or not patients required either MV or ECMO post-operatively, and in the case of MV the duration of time they needed it for before they could be taken off the ventilator to breath for themselves. A shorter time on MV, or not requiring MV or ECMO at all indicates a faster recovery after the lung transplant.

Four studies present data on the need for ECMO post-transplant and one of these also includes data on MV. Hayanga et al 2018 report the number and proportion of patients who required MV for <48 hours, 48hrs-5days and >5 days, and the number and proportion who required ECMO at all, in each of their groups (patients

<table><tr><td></td><td>Control</td><td>MV</td><td>MV + ECMO</td></tr><tr><td>MV <48h</td><td>119 (61.66)</td><td>3 (6.25)</td><td>2 (4.08)</td></tr><tr><td>MV 48h – 5days</td><td>31 (67.35)</td><td>19 (39.58)</td><td>14 (28.57)</td></tr><tr><td>MV >5 days</td><td>43 (22.28)</td><td>26 (54.17)</td><td>33 (67.35)</td></tr><tr><td>ECMO</td><td>19 (9.79)</td><td>8 (16.67)</td><td>28 (57.14)</td></tr></table>

Patients who had been on MV alone or MV + ECMO BTT were more likely to be on MV for longer compared with control patients who had not been bridged with support. Patients receiving pre-transplant MV + ECMO were also more likely than each of other two groups to require post-operative ECMO (these differences were statistically significant).

This indicates that patients who have received pre-transplant MV or MV and ECMO will experience a slower recovery in the days immediately post-transplant and will spend longer on a ventilator in a high dependency or ITU bed. However, it does not give any indication of the duration of MV required beyond 5 days so the full recovery duration is unclear. It also does not indicate whether patients who receive ECMO without MV (i.e. awake or ambulatory ECMO) would require this post-operative support as the study did not include these patients.

Ius et al 2018 did look at secondary ECMO requirements in patients who were on ECMO BTT but without MV (awake strategy) and report no difference in the rate of secondary ECMO in patients on</td></tr>
<tr><td>Ius et al 2018</td><td></td><td></td></tr>
<tr><td>Todd et al 2017</td><td></td><td></td></tr>
<tr><td>Toyoda et al 2013</td><td></td><td></td></tr>
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					ECMO BTT (4% vs 2%, p=0.18). Two smaller studies also report rates of ECMO post-transplant: • Todd et al 2017 report the proportion of patients who required ECMO for primary graft dysfunction as 0% In ECMO BTT and 2.5% (2 patients) non-bridged patients, with no statistical difference between these rates. However, this study had a small sample size with only 12 patients on ECMO and the majority of these (9/12) were sedated on ECMO. • Toyoda et al 2013 report significantly higher rates of use of post-transplant ECMO in 54% of patients undergoing ECMO BTT compared with in those not bridged (54% vs 6%, p=<0.01), however this study includes patients who received ECMO over ten years ago when outcomes may not have been so good. Overall, there is some disagreement about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively but taken together the two recent large studies (Hayanga et al 2018 and Ius et al 2018) suggest that ECMO BTT is associated with greater need for post-operative ECMO if pre-transplant MV has been given but not if an ECMO alone strategy has been adopted.
Awake Vs sedated ECMO	Schechter et al 2016	10/10	Direct	Grade A	Although several studies include both sedated and awake patients in their ECMO groups (Ius et al 2018; Lehmann et al; Chiumello et al 2015), only one study includes a full comparison in the study design between patients who are awake and those who are sedated and therefore on concurrent MV. Schechter et al 2016 compared outcomes for patients on ECMO alone with those on MV alone, ECMO + MV, and those on no bridging support. Survival at 3 years for patients on ECMO alone was not significantly different from those not requiring support (P = 0.16), however patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support (P < 0.0001 for both). After adjustment with a multivariate Cox regression model, MV +/− ECMO was independently associated with worse survival compared with patients not requiring mechanical bridge (MV only: hazard ratio [HR] = 1.46; MV + ECMO = 2.26, P < 0.0001 for both), whereas ECMO alone was not (P = 0.39). These results suggest that awake ECMO is associated with better survival than sedated ECMO which requires MV and supports the survival outcome data (above) which demonstrates that survival for
	Ius et al 2018	9/10	Direct		
	Lehmann et al 2015	6/10	Direct		
	Chiumello et al 2015	8/10	Direct		

					ECMO BTT is comparable to non-bridged patients. Other studies that provide a less comprehensive comparison of awake versus sedated ECMO: • Ius et al 2018 present some analysis of the differences between the awake and sedated patients in their study and report that outcomes did not differ between patients who underwent an awake ECMO strategy and those who did not with regards to graft survival (P=0.38), patient survival (P=0.25), freedom from biopsy-confirmed rejection (P=0.53), freedom from pulsed steroid therapy (P=0.98), freedom from chronic lung allograft rejection (P=0.58), and freedom from retransplant (P=0.46). However, the number of patients on the sedated strategy was small – only 11 of the 68 patients on ECMO – so results should be treated with some caution. • Chiumello et al 2015 refer to one study in their systematic review which found one-year survival in ECMO BTT was significantly better in spontaneously breathing patients than mechanically ventilated ones (85% versus 50%) but no further details are given. Although it has not been extensively reported in the literature, probably because it is a relatively new and emerging strategy for ECMO and the benefits are only recently being recognised, there is moderate to high level of certainty from the large, recent, high quality study by Schechter et al 2016 that awake ECMO confers a survival advantage over sedated ECMO that requires MV.

9. Literature Search Terms

Search strategy Indicate all terms to be used in the search	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be	Patients listed for lung transplant per NHS BT policy: NHSBT Policy 231/2 (http://odt.nhs.uk/pdf/lung_selection_policy.pdf)

considered?	
I – Intervention Which intervention, treatment or approach should be used?	ECMO or interventional lung assist
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Supportive care
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	Critical to decision-making: Survival to transplant Overall survival at 1 and 5 years Quality of life during the period of bridge to transplant and after transplant Important to decision-making: Adverse events including thrombosis, haemorrhage and infection Duration of ECMO (or ILA) Length of stay post transplant, both in intensive care and overall Cost effectiveness
Assumptions / limits applied to search	
Inclusion Criteria	Peer reviewed publications English language
Exclusion Criteria	Abstracts Letters

	Commentaries Conference papers Studies without comparators (including before and after studies) Papers published greater than 10 years ago

10. Search Strategy

	Search terms	Search details	Results
MEDLINE	1. (((extracorporeal membrane oxygenation) OR ECMO) OR interventional lung assist) OR iLA) 2. lung transplant 3. bridg* 4. (((#1) AND #2) AND #3)	Searched on Pubmed on 18th July 2018 Filters: published in last 10 years, English	402 articles

11. Evidence selection

Total number of publications reviewed: 402 titles and abstracts screened, 31 full text reviewed

Total number of publications considered relevant: 21

Total number of publications selected for inclusion in this briefing: 8

12. References

Included Studies:

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Fuehner T, Kuehn C, Hadem J, Wiesner O, Gottlieb J, Tudorache I et al. (2012) Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med, 185(7):763-8.

Hayanga AJ, Aboagye J, Esper S, Shigemura N, Bermudez CA,D'Cunha J, Bhama JK. (2015) Extracorporeal membrane oxygenation as a bridge to lung transplantation in the United States: An evolving strategy in the management of rapidly advancing pulmonary dis- ease. J Thorac Cardiovasc Surg, 149: 291–296.

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