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Mid-Term Outcomes of Veno-Venous Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation: Comparison with Non-Bridged Recipients

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Abstract

Objectives: Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is increasingly being used in acutely deteriorating patients with end-stage lung disease as a bridge to transplantation (BTT). It can allow critically ill recipients to remain eligible for lung transplant (LTx) while reducing pretransplant deconditioning. We analyzed early and mid-term postoperative outcomes of patients on VV-ECMO as a BTT and the impact of preoperative VV-ECMO on posttransplant survival outcomes.

Methods: All consecutive LTx performed at our institution between January 2012 and December 2018 were analyzed. After matching, BTT patients were compared with non-bridged LTx recipients.

Results: Out of 297 transplanted patients, 21 (7.1%) were placed on VV-ECMO as a BTT. After matching, we observed a similar 30-day mortality between BTT and non-BTT patients (4.6% vs. 6.6%, p=0.083) despite a higher incidence of early postoperative complications (need for ECMO, delayed chest closure, acute kidney injury). Furthermore, preoperative VV-ECMO did not appear associated with 30-day or 1-year mortality in both frequentist and Bayesian analysis (OR 0.35, 95%CI 0.03-3.49, p=0.369; OR 0.27, 95%CrI 0.01-3.82, P=84.7%, respectively). In sensitivity analysis, both subgroups were similar in respect to 30-day (7.8% vs. 6.5%, p=0.048) and 1-year mortality (12.5% vs. 18%, p=0.154).

Conclusions: Patients with acute refractory respiratory failure while waiting for LTx represent a high-risk cohort of patients. VV-ECMO as a BTT is a reasonable strategy in adult patients with acceptable operative mortality and 1-year survival comparable to non-BTT patients.

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INTRODUCTION

In patients with end-stage lung disease awaiting lung transplantation (LTx), waiting list mortality remains high due to the shortage of available donor organs and the risk of acute respiratory failure in many patients on the transplant list. Recent reports have demonstrated that mechanically ventilated lung recipients have significantly higher post-transplant mortality when compared to non-ventilated recipients.[1-3]

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is increasingly being used to bridge acutely deteriorating candidates to LTx as it can allow critically ill recipients to remain eligible for LTx while reducing pretransplant deconditioning.[4-8] In particular, VV-ECMO as a bridge to transplantation (BTT) can facilitate early ambulation, thus improving their condition, and may mitigate detrimental intensive care unit (ICU) complications including weakness, delirium, and ventilator-associated pneumonia or lung injury.[4] However, a decade ago few reports have raised skepticism for this strategy as they have suggested a negative effect of bridging with ECMO on post-transplant survival.[2,9] Since then, there is a growing evidence from high-volume and experienced lung transplant centers that BTT strategy using ECMO can provide satisfactory outcomes.[10-14]

In the present study, our aim was to analyze postoperative outcomes of patients on VV-ECMO as a BTT and the impact of preoperative VV-ECMO on posttransplant survival outcomes. Early and mid-term outcomes of BTT patients were evaluated and compared after matching with non-bridged LTx recipients. In order to achieve the best possible matching between both subgroups, we have performed optimal full matching based on Mahalanobis distance and sensitivity analysis.

METHODS

Study design

This study is a retrospective analysis of all consecutive LTx performed at Harefield Hospital (London, UK) between June 2012 and December 2018. Patients who underwent heart-lung transplantation were excluded from this study. Approval from the Institutional Ethics Committee was obtained, and all the patients provided their written informed consent for LTx as well as for donation after circulatory death (DCD). Data were extracted from the institutional electronic system. Primary endpoints were posttransplant 30-day and 1-year survival. Secondary endpoints were early and mid-term postoperative outcomes.

Patient selection

All patients were listed for transplant after being reviewed by a multidisciplinary team in accordance with the current guidelines. As recommended by our Institutional Ethics Committee, all patients on the LTx waiting list were additionally consented for LTx from DCD donors. Donors were selected based on the current standard ISHLT criteria including extended donor criteria.[15] Preoperative VV-ECMO was considered as a BTT in patients who were already listed for LTx, have suffered acute decompensation in their end-stage lung disease and continued to deteriorate despite standard medical treatment, non-invasive or invasive mechanical ventilation (MV). Further considerations for BTT included intact neurological status, the absence of active bacteremia or organ failure, and the potential to participate in pretransplant physical therapy. Donor lung assessment, procurement and preservation were described earlier by our group.[16-18]

VV-ECMO and surgical technique

Most patients on VV-ECMO as a BTT were awake throughout the period before the transplant and participated in regular physical therapy. At our institution, awake and ambulatory ECMO protocols have been implemented in order to provide rehabilitation, physical therapy, and minimization of sedation prior to LTx. Whenever feasible, VV-ECMO cannulation was performed with the patient awake in the presence of two experienced operators, using short-acting agents to provide anxiolysis and relying on local anesthetic to maintain patient comfort. The VV-ECMO circuit consisted of a conventional centrifugal pump (Levitronix CentriMag™, Thoratec, Pleasanton, CA, USA or Cardiohelp, Maquet, Rastatt, Germany) combined with an oxygenator. Our preferred cannulation strategies were a dual-site (femoro-femoral or femoro-jugular) or single-site dual-lumen cannula through the right internal jugular vein (Avalon Elite® bi-caval dual-lumen catheter, Maquet, Rastatt, Germany). In the case of femoro-femoral configuration, a 25Fr Bio-Medicus™ multi-stage cannula (Medtronic) for drainage and a 23Fr single-stage cannula were used. Our institutional anticoagulation protocol involves the administration of a loading dose of 100 units/kg before ECMO cannulation on the surgeon's request and then continuous intravenous infusion of unfractionated heparin. Continuous intravenous infusion of unfractionated heparin was administered and regularly monitored by measuring activated partial thromboplastin time (aPTT, target range 60-80 sec) and anti-Xa (target range 0.3-0.5 IU/ml for VV-ECMO or 0.2-0.5 IU/ml for VA-ECMO). Anti-Xa level is checked 4 hours after the initiation of heparin, 4 hours after each change in rate, and every 4-6 hours until levels are stable. If heparin anti-Xa level is stable and within range, heparin anti-Xa level and full blood count can be carried out once daily.

Surgical technique of LTx was described by our group in earlier reports.[16] Intraoperative mechanical circulatory support was considered in the case of severe pulmonary hypertension, inability to tolerate one-lung ventilation, and hemodynamic instability after pulmonary artery clamping. Most commonly, patients who were bridged to transplantation with VV-ECMO were transplanted on VV-ECMO; however, in some cases, intraoperative conversion to veno-arterial (VA) ECMO was required. While ECMO was our preferred method of intraoperative support, cardiopulmonary bypass (CPB) has been used depending on the surgeon's preference, and in the case of severe hemodynamic instability or uncontrolled intraoperative bleeding.

Intraoperative VA-ECMO was used to support patients who developed primary graft dysfunction, protamine sulphate-related right ventricular failure, or profound vasoplegia. In these cases, our preference was the use of central cannulation.

If CPB was required, full heparinization (300 IU/kg) was provided before initiation of CPB to maintain an activated clotting time (ACT) greater than 400 seconds during the period of CPB. After discontinuation of the CPB, protamine sulphate was administered to reverse the effect of heparin. On the other hand, when ECMO was used, an initial bolus of 5,000 IU intravenous heparin was given and ACT was maintained between 180 to 250 seconds. Protamine sulphate administration was considered after decannulation only in cases of significant bleeding. Postoperatively, VV-ECMO was used to facilitate the improvement of gas exchange when required. Main clinical indications for postoperative VV-ECMO were difficulties with MV leading to inadequate gas exchange (primary graft dysfunction, reperfusion pulmonary oedema secondary to vasoplegic syndrome or massive transfusion, and acute rejection). On the other hand, VA-ECMO was used in the case of severe pulmonary hypertension to protect the new lungs from hyperperfusion or for additional hemodynamic support. Among all patients requiring postoperative VV-ECMO, lung protective ventilation strategies were applied with the provision of MV and lower plateau pressures. Protective MV was maintained during the post-transplant ECMO support in order to avoid ventilator-induced lung injury.

Data collection and analysis

Data were collected retrospectively from the electronic and archived hospital medical records. We attempted to specifically identify the effects of VV-ECMO as a BTT on: posttransplant 30-day mortality and complications (need for postoperative ECMO, delayed chest closure, surgical re-exploration, tracheostomy, chest drainage within 24 hours, chest infection, sepsis, stroke, acute kidney injury [AKI] requiring renal replacement therapy [RRT]) and 1-year mortality.

Preoperative, intraoperative, and postoperative data are summarized for BTT and non-BTT patients. In the main analysis, both subgroups were submitted to optimal full matching based on Mahalanobis distance in respect to preoperative covariates. Based on their potential relevance to the observed outcomes and imbalance between the two subgroups, included covariates were age, gender, body mass index (BMI), serum creatinine and hemoglobin levels, platelet count $<150x10^9$/L and main diagnosis, with exact matching on the gender, low platelet count and underlying diagnosis (cystic fibrosis [CF] or "other").[19,20] We had no patients that required VV-ECMO as BTT among those with chronic obstructive pulmonary disease (COPD), emphysema, bronchiolitis, bronchiectasis, pulmonary hypertension and lymphangioleiomyomatosis. Therefore, in order to avoid aliasing between potential effects of VV-ECMO and diagnosis, a sensitivity analysis (using the same methodology) was performed including only diagnoses where at least one patient was bridged to LTx with VV-ECMO. To evaluate the effect of VV-ECMO as a BTT (vs. non-BTT), generalized mixed models (binary distribution, logit link; subclass as a random effect [cluster]) were fitted to each binary outcome with further adjustment for unbalanced covariates: frequentist (maximum likelihood estimation with Gauss-Hermite quadrature approximation; classical [sandwich] robust estimator) and Bayesian (4 chains, 4000 iterations, 8000 samples of the posterior, vaguely informative normal priors for ln[odds] and the intercept [0, 2.5; scaled], and priors on the terms of a decomposition of the covariance matrices [Gamma shape=1, scale=1; LKJ for correlation matrix, regularization=1; Dirichlet for the simplex vectors, concentration=1]). To evaluate the effect of VV-ECMO as a BTT on the chest drainage within the first 24 hours, data were ln-transformed (since right-skewed) and the same models, although with normal distribution and identity link, were fitted. We used package *MatchIt* in R for matching,[21] SAS 9.4 for Windows *proc glimmix* (SAS Inc., Cary, NC) for fitting frequentist and package *rstanarm* in R for Bayesian models.[22] We evaluated susceptibility of the observed effects to unmeasured confounding by determining the E-value (package *Evalue* in R).[23] Despite a large number of analyzed outcomes and related formal statistical tests, we considered more appropriate not to implement multiplicity adjustments as adjustments of comparison-wise alpha could have resulted in falsely overlooked adverse effects of VV-ECMO as a BTT.

RESULTS

Patients' perioperative characteristics, early and mid-term outcomes

Out of 297 transplanted patients in the study period, 21 (7.1%) were placed on VV-ECMO as BTT. Out of these 21, 13 (62%) patients were awake, non-invasively ventilated and participated in rehabilitation and ambulation. There were no mechanically ventilated patients in the non-BTT group (Table 1). As compared to non-BTT patients, BTT patients were younger with a slightly lower BMI and, in line with the VV-ECMO support, had considerably lower preoperative hemoglobin and platelet count, longer activated partial thromboplastin time and higher international normalized ratio (Table 1). The most common diagnosis in both groups was cystic fibrosis (90.5% in BTT patients vs. 39.1% in non-BTT patients; Table 1). Single LTx was performed only in 8 out of 276 non-BTT patients (Table 1). Intraoperative use of CPB was similar in both groups, while the use of intraoperative ECMO and perioperative blood transfusion were considerably higher in BTT patients (Table 1). Postoperative 30-day mortality and the incidence of early postoperative complications (need for ECMO, delayed chest closure, surgical re-exploration, tracheostomy, chest drainage, chest infection, sepsis and AKI requiring RRT) were higher in BTT patients compared with non-BTT patients (Table 2). In the BTT group, need for postoperative ECMO was observed in 10 (47.6%) patients (4 VA-ECMO and 6 VV-ECMO), while in the non-BTT group 21 (7.6%) patients required ECMO postoperatively (18 VA-ECMO and 3 VV-ECMO) (Table 2.). In the BTT group, 2 patients developed dehiscence of the bronchial anastomosis and only one required re-implantation of the left lung, while in the non-BTT group 3 patients had dehiscence of the bronchial anastomosis with 2 requiring surgical re-exploration. One-year mortality was also higher in BTT than in non-BTT patients (Figure S1.).

Effect of VV-ECMO as a BTT on postoperative 30-day outcomes and 1-year mortality - primary matched subgroups analysis

After matching, BTT and non-BTT patients were well-balanced with respect to the age, preoperative laboratory characteristics and main diagnosis (all standardized mean differences [d] <0.1; Table 3), but there was still imbalance (d >0.1) in the proportion of female patients, BMI and hemoglobin levels (lower in BTT patients) (Table 3). Intraoperatively, CPB was used less often, while the use of ECMO was considerably higher in BTT patients than in non-BTT patients after matching (Table 3). Regarding 30-day outcomes, need for postoperative

ECMO (73.0% vs. 8.6%), delayed chest closure (11.9% vs. 6.3%) and incidence of AKI requiring RRT (63.6% vs. 29.7%) were higher in BTT vs. non-BTT patients (Table 3). However, chest drainage within 24 hours, incidence of surgical re-exploration, tracheostomy, chest infection, and 30-day mortality appeared similar in the two matched subgroups, while 1-year mortality was lower in BTT patients (Table 3). With further adjustment for the unbalanced covariates (gender, BMI and hemoglobin level), preoperative VV-ECMO support was associated with around 20-fold higher odds of postoperative ECMO (frequentist and Bayesian estimates; Table 4). It was also associated with around 4-fold higher odds of AKI requiring RRT: the Bayesian estimate (95%CrI 1.31-14.2) appeared robust (a rather high E-value indicated a rather low susceptibility to unmeasured confounding) and was more precise than the frequentist estimate (95%CI 0.43-39.2), leaving some uncertainty about this effect (Table 4). There was also a tendency of higher odds of tracheostomy (OR 2.3), but both frequentist and Bayesian estimates were imprecise (Table 4). VV-ECMO as a BTT did not appear associated with other 30-day outcomes including mortality or with 1-year mortality (Table 4).

Sensitivity analysis

Patients with an underlying diagnosis of COPD, emphysema, bronchiectasis, lymphangioleiomyomatosis and pulmonary hypertension (n = 107) were excluded, since none of them was placed on VV-ECMO (to avoid aliasing between diagnosis and ECMO support), resulting in 21 BTT and 169 non-BTT patients in the sensitivity analysis (Table 5). Perioperative characteristics (Table 5) and postoperative outcomes (Table 6) in BTT and non-BTT patients were similar to those in the entire cohort. After matching, both subgroups were well-balanced with respect to the age, low platelet count, serum creatinine and prevalence of CF, while imbalance remained regarding the proportion of men, BMI, and preoperative hemoglobin levels (Table 7). Intraoperatively, CPB was used less often, while the use of ECMO was considerably higher in BTT compared with non-BTT patients (Table 7). Need for postoperative ECMO (62.0% vs. 8.7%), delayed chest closure (16.5% vs. 5.6%), tracheostomy (50.8% vs. 34.4%), chest infection (60.8% vs. 41.2%) and AKI requiring RRT (45.7% vs. 30.5%) were more common in BTT than in non-BTT patients, while the two subgroups were similar in respect to 30-day mortality, surgical re-exploration, chest drainage within 24 hours, sepsis, stroke and 1-year mortality (Table 7). With further adjustment for the unbalanced covariates (gender, BMI and hemoglobin level), VV-ECMO as a BTT was associated with 12.8-fold higher odds of need for postoperative ECMO and with 6-fold higher odds of tracheostomy, but it did not appear associated with any other early and mid-term outcome (Table 8).

DISCUSSION

The use of VV-ECMO as a BTT can allow patients with decompensated end-stage lung disease to remain eligible for LTx and offer a viable strategy for improving their post-transplant survival outcomes. In this study, we reported our single-center experience with 297 transplanted patients, 21 (7.1%) of whom were bridged to LTx with VV-ECMO. The most common diagnosis in both BTT and non-BTT recipients was CF. One of the reasons is that there is a well-established CF Unit in our institution which attracts tertiary referrals from the whole country. In the primary analysis, both 30-day and 1-year posttransplant mortality were considerably higher in patients requiring VV-ECMO as a BTT than in non-BTT patients. In addition, the incidence of the most important early postoperative complications, including need for ECMO, delayed chest closure, surgical re-exploration and AKI requiring RRT, was significantly increased in the bridged patients.

To minimize potential effects of selection bias and decrease variability of both groups, we performed further analysis comparing matched groups which were well-balanced in terms of preoperative recipients' baseline characteristics. Importantly, after matching, we observed a similar 30-day mortality between the BTT and non-BTT patients (4.6% vs. 6.6%, p=0.083) despite a higher incidence of early postoperative complications (need for ECMO, delayed chest closure, AKI requiring RRT), while the 1-year mortality was even lower in the BTT patients (8.0% vs. 15.6%, p=0.238). Furthermore, when evaluating the effect of preoperative VV-ECMO on postoperative outcomes, it did not appear associated with 30-day or 1-year mortality. Moreover, in the sensitivity analysis, the two subgroups were similar in respect to 30-day (BTT 7.8% vs. 6.5%, p=0.048) and 1-year mortality (12.5% vs. 18%, p=0.154). The clinical condition of patients who were bridged to LTx with VV-ECMO is usually more critical than that among the rest of the patients who were not bridged, and this may negatively influence their outcomes. However, in our experience, post-transplant survival in bridged patients was comparable to that in patients who did not have pre-transplant VV-ECMO. Therefore, VV-ECMO has been demonstrated to be a valuable supportive strategy to prolong life in these critically ill patients while increasing the waiting period for suitable organs. Our early and mid-term results are in general consistent with previous reports that have shown no significant difference in post-transplant survival among BTT and non-BTT patients, especially in high-volume centers.[4,10-12,24-29] Surprisingly, we have found that 1-year mortality was even lower in the BTT group but this might be related to several other factors. One of the reasons could be that the average duration of pre-transplant support with VV-ECMO in our cohort was relatively short (8 days) and this could positively affect the outcomes. As recently reported by *Crotti et al.*, patients who underwent LTx after a waiting period longer than 14 days had significantly higher rates of post-transplant mortality and morbidity.[30] Furthermore, shorter waiting times after urgent listing have likely contributed to these favorable outcomes. In addition, we have observed more commonly intraoperative ECMO than CPB among BTT patients when compared to the non-BTT group, and it is well known that the intraoperative use of ECMO might have several advantages.[31,32] Obviously, among BTT patients our preferred approach was to use VV- or VA-ECMO as intraoperative support. However, the choice of intraoperative mechanical circulatory support was at the surgeon's discretion and related to the patient's characteristics and specific indications as described previously. Similarly, Hoetzenecker and colleagues reported recently that use of intraoperative ECMO resulted in excellent mid-term outcomes among LTx recipients.[32] Intraoperative use of ECMO can provide controlled reperfusion without increased risk of systemic inflammatory response and early postoperative bleeding related to the use of CPB.[32] In addition, several high-volume LTx centers demonstrated that intraoperative use of ECMO outperforms CPB. The use of ECMO has several advantages, including partial heparinization, possibility of extending the support into the postoperative period and lower rates of primary graft dysfunction.[33-35] We believe that the improved survival among BTT patients can be also related to an increased experience with this strategy, early ambulation of these patients, advancement in the perioperative care, and development of an experienced ECMO and multidisciplinary team.

On the other hand, *Schechter et al.* have reported a decreased 1-year post-transplant survival among patients requiring preoperative support including ECMO with MV.[3] However, they have demonstrated in a multivariable analysis that ECMO alone was not associated with decreased 1-year survival.[3] In our study, 38.1% of patients were supported using both VV-ECMO and MV before LTx, but the sample size was too small to perform a further analysis whether MV could have had any effect on postoperative outcomes. Furthermore, *Mason et al.* have reported that survival after LTx is markedly worse (1-month and 1-year post-transplantation survival were 72% and 50%, respectively) when preoperative mechanical support is necessary, although they suggested that additional risk factors for mortality should be considered when selecting patients for LTx in order to improve survival.[2] In addition, *Fischer et al.* have reported that the perioperative mortality of LTx after preoperative ECMO can be even up to 60%.[9]

As expected, need for postoperative ECMO, delayed chest closure, tracheostomy, chest infection, and AKI requiring RRT were more common among BTT patients. This can be related to the common and well-known risks related to the use of ECMO such as bleeding complications, systemic inflammatory response, acute kidney injury and thromboembolic complications.[36-43] However, the rate of these complications was lower than in some of the previous reports that demonstrated an incidence of tracheostomy in up to 77%[39], delayed chest closure in 50%[40] and stroke in 8%[39] of recipients. Furthermore, nearly half of BTT patients required ECMO postoperatively and we have used VV-ECMO in 6 (60%) of these patients. One of the potential reasons could be that VV-ECMO was already used preoperatively and continued intraoperatively. Therefore, it was easier to decide for the same modality postoperatively in the cases of difficult MV and impaired gas exchange. Still, in our study it seems that both 30-day and 1-year survival have not been negatively affected by the increased incidence of early postoperative complications.

The strength of this study is the comparison of two cohorts of patients (BTT and non-BTT) that were matched. However, we acknowledge several study limitations. First, the analysis was performed retrospectively and designed as a single-center study, although the study period was up to 7 years and included moderate sample size with 1-year follow-up. The present study also lacks donor data as we were not able to collect these data for the majority of the study period. For the same reason, it was not possible to obtain or compare data regarding DCD donation for the majority of recipients, including warm ischemic time. However, recent analysis from the ISHLT DCD Lung Transplant Registry reported that current experience with DCD category III LTx did not show a relationship between the duration of donor warm ischemic time up to 60 minutes and early survival.[44] Further studies with analysis of donor data and type of organ donation would be needed. Regarding the need for postoperative ECMO, due to the fact that the subgroups (postoperative VA- and VV-ECMO) were too small, it was not possible to include them in our matching analysis. In addition, it would be interesting to expand the research and study primary graft dysfunction and rejection rate as we did not have this data. Further studies with long-term follow-up would be useful in order to analyze occurrence of late complications. Lastly, we were not able to extend our analysis including patients bridged with other devices (VA-ECMO, Novalung) due to a small sample size and different clinical characteristics some of these patients.

CONCLUSIONS

End-stage lung disease patients with acute refractory respiratory failure while waiting for LTx represent a challenging and high-risk cohort of patients. However, VV-ECMO is our favored bridging strategy and we have observed that these patients can be successfully bridged to LTx and can have post-transplant mortality comparable to non-BTT patients. The results of this study provide further insight into early and mid-term outcomes and evidence for the clinical use of VV-ECMO as a bridging strategy for patients with refractory respiratory failure, especially in carefully selected recipients and high-volume ECMO and lung transplant centers. VV-ECMO as a BTT is a reasonable strategy in adult patients with acceptable operative mortality and 1-year survival comparable to non-BTT patients.

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Data Availability Statement

Data available on request due to privacy/ethical restrictions.

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Table 1. Patients' preoperative and intraoperative characteristics.

	BTT with VV-ECMO	Non-BTT	*p*[1]
N	21	276	---
Preoperative characteristics			
Age, years	30.5 (23-34.8; 19-56)	49 (30.2-57.8; 19-71)	<0.001
Male gender	13 (61.9)	152 (55.1)	0.544
Body mass index, kg/m^2	20.2 (19-23; 17.7-27.9)	22.1 (19.5-25.5; 14.7-58.1)	0.062
Hemoglobin, g/L	84 (78-91; 71-103)	137 (121-149; 59-196)	<0.001
Hemoglobin <90 g/L	16 (76.2)	11 (4.0)	<0.001
Platelet count, $x10^9$/L	153 (84-257; 37-550)	273 (221-357; 52-659)	<0.001
Platelet count <150 $x10^9$/L	11 (52.4)	19 (6.9)	<0.001
aPTT, seconds	49.5 (43.8-66.2; 34.5-97.1)	32 (29-34.5; 17.7-108.5)	<0.001
INR	1.2 (1.1-1.4; 0.9-1.7)	1.0 (0.9-1.1; 0.8-2.5)	<0.001
Creatinine, μmol/L	58 (33-70; 19-94)	59 (50-72.5; 24-142)	0.237
FVC, L	1.62 (1.36-2.18; 0.73-3.23)	1.88 (1.43-2.37; 0.39-4.98)	0.316
FEV1, L	0.97 (0.62-1.36; 0.41-2.30)	0.73 (0.55-0.92; 0.20-3.61)	0.037
Renal replacement therapy	1 (4.8)	1 (0.4)	0.100
Mechanical ventilation	8 (38.1)	0	---
Diagnosis			
Cystic fibrosis	19 (90.5)	108 (39.1)	<0.001
COPD/emphysema/bronchiectasis	0	99 (35.9)	---
α1-antitrypsin deficiency	1 (4.8)	34 (12.3)	0.300
Pulmonary fibrosis/ILD	1 (4.8)	27 (9.8)	0.448
Lymphangioleiomyomatosis	0	5 (1,8)	---
Pulmonary hypertension	0	3 (1.1)	---
Preoperative VV-ECMO duration, d	8 (6.5-16; 1-53)	---	---
Intraoperative characteristics			
Bilateral lung transplant	21 (100)	268 (97.1)	---
Cardiopulmonary bypass	6 (28.6)	94 (34.1)	0.608
ECMO	15(71.4)	15 (5.4)	<0.001
Transfusion (24h)			
Red blood cells, units	13.5 (8.2-41.8; 5-53)	3 (1-3, 0-71)	<0.001
Platelets, pools	3.5 (1.2-8.5; 0-21)	1 (0-2; 0-18)	<0.001
Fresh frozen plasma, units	6 (2.5-11; 0-37)	2 (0-4; 0-32)	<0.001
Cryoprecipitate, units	8 (38.1) (median 3.5 units)	45 (16.3) (median 2 units)	0.022

Data are median (quartiles; minimum-maximum) or count (percent)
aPTT, activated partial thromboplastin time; BTT, bridge to transplantation; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal mechanical oxygenation; FEV1, forced expiratory volume (1st second); FVC, forced vital capacity; ILD, interstitial lung disease; INR, international normalized ratio; VV, veno-venous.
[1] Mann-Whitney U-test or likelihood ratio test

Table 2. Early and mid-term postoperative outcomes.

Outcomes	BTT with VV-ECMO	Non-BTT	*p*[1]
N	21	276	---
30-day outcomes			
30-day mortality	5 (23.8)	15 (5.4)	<0.001
Postoperative ECMO	10 (47.6)	21 (7.6)	<0.001
VV-ECMO/VA-ECMO	6/4 (60.0/40.0)	3/18 (14.3/85.7)	---
ECMO duration, days	9 (1-15; 1-19)	7 (2.2-26; 2-49)	---
Delayed chest closure	9 (42.8)	18 (6.5)	<0.001
Chest drainage within 24h, mL	2225 (975-3450)	1125 (825-1725)	0.006
Surgical re-exploration	8 (38.1)	35 (12.7)	<0.001
AKI requiring RRT	12 (57.1)	81 (29.4)	0.001
Tracheostomy	12 (57.1)	94 (34.1)	0.037
Chest infection	12 (57.1)	108 (39.1)	0.109
Sepsis	12 (57.1)	84 (30.4)	0.015
Stroke	0	12 (4.3)	---
ICU length of stay, d	19 (12-22.5; 1-52)	7 (4-21; 1-98)	0.011
1-year all-cause mortality	7 (33.3)	40 (14.5)	0.023
Cause of death			
Multiorgan failure	5/7 (71.4)	19/40 (47.5)	---
Primary graft dysfunction	1/7 (14.3)	0	---
Acute rejection	0	1/40 (2.5)	---
Chronic rejection	1/7 (14.3)	6/40 (15.0)	---
Infectious complications	0	6/40 (15.0)	---
Pulmonary embolism	0	1/40 (2.5)	---
Malignancy	0	2 (5.0)	---
Cardiac arrest	0	1 (2.5)	---
Other causes	0	4 (10.0)	---

Data are median (quartiles; minimum-maximum) or count (percent)
AKI, acute kidney injury; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; ICU, intensive care unit; RRT, renal replacement therapy; VV, veno-arterial; VV, veno-venous.
[1] Mann-Whitney U-test or likelihood ratio test

Table 3. Patients' preoperative and intraoperative characteristics, 30-day outcomes and 1-year mortality before and after matching – primary analysis. Variables used for matching are shaded. Standardized mean differences (d) <0.1 indicate irrelevant differences between BTT and non-BTT lung transplant recipients.

	Before matching			After matching		
Characteristics	BTT with VV-ECMO	Non-BTT	d	BTT with VV-ECMO	Non-BTT	d
N	21	276	---	21	276	---
Preoperative						
Age, years	30.5 (23-34.8)	49 (30.2-57.8)	-1.064	44.0±14.0	44.4±14.7	-0.035
Male gender	13 (61.9)	152 (55.1)	0.139	16.3 (77.8)	152.5 (55.3)	0.458
BMI, kg/m^2	20.2 (19-23)	22.1 (19.5-25.5)	-0.495	21.6 (20.2-21.6)	21.9 (19.5-25.2)	-0.517
Hemoglobin, g/L	84 (78-91)	137 (121-149)	-2.910	82 (82-87)	136 (119-148)	-2.804
Platelets <150 x10^9/L	11 (52.4)	19 (6.9)	1.149	2.1 (10.1)	27.9 (10.1)	0.000
Creatinine, μmol/L	58 (33-70)	59 (50-72.5)	-0.434	70 (57-70)	58 (50-71)	0.071
Cystic fibrosis	19 (90.5)	108 (39.1)	1.275	9.0 (42.8)	118 (42.8)	0.000
Intraoperative						
CPB	6 (28.6)	94 (34.1)	-0.118	2.6 (12.5)	94.9 (34.4)	-0.533
ECMO	15 (71.4)	15 (5.4)	1.846	18.4 (87.5)	15.6 (5.6)	2.866
30-day outcomes						
30-day mortality	5 (23.8)	15 (5.4)	0.539	0.97 (4.63)	18.1 (6.55)	-0.083
Postop ECMO	10 (47.6)	21 (7.6)	1.120	15.3 (73.0)	23.7 (8.6)	1.735
Delayed chest closure	9 (42.8)	18 (6.5)	0.929	2.5 (11.9)	17.3 (6.3)	0.196
Chest drainage 24h, mL	2225 (975-3450)	1125 (825-1725)	0.745	975 (975-1100)	1150 (825-1750)	0.045
Re-exploration	8 (38.1)	35 (12.7)	0.611	2.3 (11.2)	39.2 (14.2)	-0.090
AKI requiring RRT	12 (57.1)	81 (29.4)	0.584	13.3 (63.6)	81.9 (29.7)	0.722
Tracheostomy	12 (57.1)	94 (34.1)	0.476	7.03 (33.5)	92.2 (33.4)	0.002
Chest infection	12 (57.1)	108 (39.1)	0.366	8.45 (40.2)	111.1 (40.2)	-0.000
Sepsis	12 (57.1)	84 (30.4)	0.559	4.48 (21.4)	88.2 (32.0)	-0.241
Stroke	0	12 (4.3)	-1.395	0	11.4 (4.2)	-0.535
1-year mortality	7 (33.3)	40 (14.5)	0.453	1.68 (8.0)	43.1 (15.6)	-0.238

Data are count (percent), median (quartiles) or mean±SD.
AKI, acute kidney injury; BMI, body mass index; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement therapy; VV, veno-venous

Table 4. Adjusted (for gender, body mass index and hemoglobin level) odds ratios and geometric means ratios (GMR)[1] (for chest drainage within the first 24 hours): BTT with VV-ECMO vs. non-BTT recipients in the matched subgroups – primary analysis.

	Frequentist		Bayesian		
	OR (95%CI)	*p*	OR (95%CrI)	P(OR≠1)	E-value[2]
30-day outcomes					
30-day mortality	0.35 (0.03-3.49)	0.369	0.27 (0.01-3.82)	84.7%	---
Postoperative ECMO	19.3 (1.38-270)	0.028	22.3 (4.35-113)	100%	8.91; 3.59
Delayed chest closure	2.31 (0.63-8.52)	0.209	2.35 (0.31-14.4)	81.2%	---
Chest drainage 24h, mL	1.38 (0.86-2.23)	0.177	1.16 (0.56-2.25)	67.2%	---
Re-exploration	1.18 (0.26-5.41)	0.834	1.10 (0.14-6.17)	54.2%	---
AKI requiring RRT	4.09 (0.43-39.2)	0.220	4.18 (1.31-14.2)	99.2%	3.51; 1.55
Tracheostomy	2.28 (0.41-12.6)	0.343	2.34 (0.71-8.00)	91.4%	---
Chest infection	0.92 (0.16-5.43)	0.926	1.16 (0.36-3.90)	60.6%	---
Sepsis	0.60 (0.11-3.19)	0.546	0.83 (0.19-3.10)	59.9%	---
Stroke	---	---	---	---	---
1-year mortality	0.48 (0.10-2.30)	0.360	0.41 (0.04-3.13)	81.2%	---

AKI, acute kidney injury; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement therapy

[1]Chest drainage volume data were right-skewed and were ln-transformed. The BTT vs. non-BTT difference is geometric means ratio (GMR)= exp[mean ln(BTT) – mean ln(non-BTT)]

[2]Lowest unmeasured confounder effect (on the relative risk scale) needed to shift the (Bayesian) point estimate (first value) or the lower limit of the 95% CrI to 1.0 (second value).

Table 5. Patients' preoperative and intraoperative characteristics – subgroups included in the sensitivity analysis.

	BTT with VV-ECMO	non-BTT	*p*[1]
N	21	169	---
Preoperative characteristics			
Age, years	30.5 (23-34.8; 19-56)	38 (26-53; 19-70)	0.048
Male gender	13 (61.9)	99 (58.6)	0.770
Body mass index, kg/m^2	20.2 (19-23; 17.7-27.9)	20.6 (18.9-24.2; 15.8-58.1)	0.586
Hemoglobin, g/L	84 (78-91; 71-103)	132 (115-146; 70-196)	<0.001
Hemoglobin <90 g/L	16 (76.2)	9 (5.3)	<0.001
Platelet count, $x10^9/L$	153 (84-257; 37-550)	293 (217-376; 52-659)	<0.001
Platelet count <150 $x10^9/L$	11 (52.4)	14 (8.3)	<0.001
aPTT, seconds	49.5 (43.8-66.2; 34.5-97.1)	31.9 (29.5-34.6; 21.4-108)	<0.001
INR	1.2 (1.1-1.4; 0.9-1.7)	1.0 (1.0-1.1; 0.8-2.5)	<0.001
Creatinine, μmol/L	58 (33-70; 19-94)	57 (46-69.5; 27-142)	0.333
FVC, L	1.62 (1.36-2.18; 0.73-3.23)	1.83 (1.35-2.33; 0.39-4.98)	0.561
FEV1, L	0.97 (0.62-1.36; 0.41-2.30)	0.78 (0.63-0.99; 0.28-3.21)	0.217
Renal replacement therapy	1 (4.8)	1 (0.6)	0.168
Mechanical ventilation	8 (38.1)	0	---
Diagnosis			
Cystic fibrosis	19 (90.5)	108 (63.9)	0.015
α1-antitrypsin deficiency	1 (4.8)	34 (20.1)	0.087
Pulmonary fibrosis/ILD	1 (4.8)	27 (16.0)	0.171
Preoperative ECMO duration (days)	8 (6.5-16; 1-52)	---	---
Intraoperative characteristics			
Bilateral lung transplant	21 (100)	162 (95.9)	---
Cardiopulmonary bypass	6 (28.6)	60 (35.5)	0.529
ECMO	15 (71.4)	12 (7.1)	<0.001
Transfusion (24h)			
Red blood cells, units	13.5 (8.2-41.8; 5-53)	4.0 (2.0-8.0; 0-71)	<0.001
Platelets, pools	3.5 (1.2-8.5; 0-21)	1.0 (0-2.0; 0-18)	<0.001
Fresh frozen plasma, units	6 (2.5-11; 0-37)	2.0 (0-4.5; 0-32)	<0.001
Cryoprecipitate, units	8 (38.1) (median 3.5 units)	27 (16.0) (median 2 units)	0.023

Data are median (quartiles; minimum-maximum) or count (percent)
aPTT, activated partial thromboplastin time; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; FEV1, forced expiratory volume (1st second); FVC, forced vital capacity; ILD, interstitial lung disease; INR, international normalized ratio; VV, veno-venous.
[1] Mann-Whitney U-test or likelihood ratio test

Table 6. Early and mid-term postoperative outcomes – subgroups included in the sensitivity analysis.

Outcomes	BTT with VV-ECMO	non-BTT	*p*[1]
N	21	169	---
30-day outcomes			
30-day mortality	5 (23.8)	8 (4.7)	0.001
Postoperative ECMO	10 (47.6)	12 (7.1)	<0.001
ECMO duration, days	9 (1-15; 1-19)	3 (2-27.5; 2-49)	
Delayed chest closure	9 (42.8)	10 (5.9)	<0.001
Chest drainage 24h, mL	2225 (975-3450)	1125 (719-1750)	0.005
Surgical re-exploration	8 (38.1)	24 (14.2)	0.006
AKI requiring RRT	12 (57.1)	50 (29.6)	0.011
Tracheostomy	12 (57.1)	60 (35.5)	0.058
Chest infection	12 (57.1)	66 (39.1)	0.112
Sepsis	12 (57.1)	52 (30.8)	0.019
Stroke	0	7 (4.1)	---
ICU length of stay, days	19 (12-22.5; 1-52)	7 (3.5-21.5; 1-97)	0.013
1-year all-cause mortality	7 (33.3)	27 (16.0)	0.050
Cause of death			
Multiorgan failure	5/7 (71.4%)	13/27 (48.2%)	---
Primary graft dysfunction	1/7 (14.3%)	0	---
Acute rejection	0	1/27 (3.7%)	---
Chronic rejection	1/7 (14.3%)	5/27 (18.5%)	---
Infectious complication	0	5/27 (18.5%)	---
Other causes	0	3 (11.1%)	---

Data are median (quartiles; minimum-maximum) or count (percent)
AKI, acute kidney injury; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; ICU, intensive care unit; RRT, renal replacement therapy; VV, veno-venous
[1]Mann-Whitney U-test or likelihood ratio test

Table 7. Patients' preoperative and intraoperative characteristics, 30-day outcomes and 1-year mortality before and after matching – sensitivity analysis. Variables used for matching are shaded. Standardized mean differences <0.1 indicate irrelevant differences between BTT and non-BTT lung transplant recipients.

Characteristics	Before matching			After matching		
	BTT with VV-ECMO	Non-BTT	d	BTT with VV-ECMO	Non-BTT	d
N	21	169	---	21	169	---
Preoperative						
Age, years	30.5 (23-34.8)	38 (26-53)	-0.599	37.9±13.3	38.8±14.5	-0.079
Male gender	13 (61.9)	99 (58.6)	0.068	14 (66.8)	98.8 (58.5)	0.172
BMI, kg/m^2	20.2 (19-23)	20.6 (18.9-24.2)	-0.212	20.2 (18.6-21.6)	20.6 (18.8-24.1)	-0.365
Hemoglobin, g/L	84 (78-91)	132 (115-146)	-2.555	85 (82-92)	131 (111-144)	-2.354
Platelets <150 x10^9/L	11 (52.4)	9 (5.3)	1.093	2.8 (13.2)	22.2 (13.2)	0.000
Creatinine, μmol/L	58 (33-70)	57 (46-69.5)	-0.306	66 (53-70)	57 (46-68)	0.016
Cystic fibrosis	19 (90.5)	108 (63.9)	0.668	14 (66.8)	113 (66.8)	0.000
Intraoperative						
CPB	6 (28.6)	60 (35.5)	-0.149	3.9 (18.5)	60.4 (35.7)	-0.394
ECMO	15 (71.4)	12 (7.1)	1.751	17.1 (81.5)	12.3 (7.3)	2.245
30-day outcomes						
30-day mortality	5 (23.8)	8 (4.7)	0.567	1.6 (7.8)	11 (6.5)	0.048
Postoperative ECMO	10 (47.6)	12 (7.1)	1.140	13.0 (62.0)	14.7 (8.7)	1.342
Delayed chest closure	9 (42.8)	10 (5.9)	0.953	3.4 (16.5)	9.4 (5.6)	0.352
Chest drainage 24h, mL	2225 (975-3450)	1125 (719-1750)	0.727	975 (975-3450)	1150 (750-1925)	0.382
Re-exploration	8 (38.1)	24 (14.2)	0.565	3.2 (15.4)	27.9 (16.5)	-0.030
AKI requiring RRT	12 (57.1)	50 (29.6)	0.579	9.6 (45.7)	51.5 (30.5)	0.316
Tracheostomy	12 (57.1)	60 (35.5)	0.445	10.6 (50.8)	58.1 (34.4)	0.336
Chest infection	12 (57.1)	66 (39.1)	0.368	12.8 (60.8)	69.6 (41.2)	0.340
Sepsis	12 (57.1)	52 (30.8)	0.551	6.7 (31.8)	55.9 (33.1)	-0.026
Stroke	0	7 (4.1)	-1.405	0	6.6 (3.9)	-0.783
1-year mortality	7 (33.3)	27 (16.0)	0.411	2.6 (12.5)	30.5 (18.0)	-0.154

Data are count (percent), median (quartiles) or mean±SD.
AKI, acute kidney injury; BMI, body mass index; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement therapy, VV, veno-venous

Table 8. Adjusted (for gender, body mass index and hemoglobin level) odds ratios and geometric means ratios (GMR)[1] (for chest drainage within the first 24 hours): BTT with VV-ECMO vs. non-BTT recipients in the matched subgroups – sensitivity analysis.

	Frequentist		Bayesian		
Outcomes	OR (95%CI)	*p*	OR (95%CrI)	P(OR≠1)	E-value[2]
30-day outcomes					
30-day mortality	0.96 (0.06-14.3)	0.977	0.85 (0.06-9.68)	55.4%	---
Postoperative ECMO	10.3 (1.37-77.0)	0.023	12.8 (2.86-77.5)	99.99%	6.61; 2.27
Delayed chest closure	3.08 (0.85-11.2)	0.087	3.59 (0.52-21.7)	91.2%	---
Chest drainage 24h, mL	1.58 (0.80-3.10)	0.183	1.33 (0.64-2.94)	77.8%	---
Re-exploration	0.94 (0.17-5.04)	0.939	0.48 (0.17-5.10)	53.5%	---
AKI requiring RRT	2.11 (0.32-13.6)	0.432	2.15 (0.66-7.32)	89.9%	---
Tracheostomy	5.66 (1.19-26.9)	0.029	6.06 (1.79-20.9)	99.9%	4.36; 2.01
Chest infection	2.16 (0.42-11.3)	0.357	2.48 (0.75-8.00)	94.3%	---
Sepsis	1.44 (0.24-8.72)	0.690	1.53 (0.44-6.62)	73.4%	---
Stroke	---	---	---	---	---
1-year mortality	0.90 (0.17-4.91)	0.905	0.84 (0.11-5.53)	57.7%	---

AKI, acute kidney injury; ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement therapy; VV, veno-venous
[1]Chest drainage volume data were right-skewed and were ln-transformed. The BTT vs. non-BTT difference is geometric means ratio (GMR)= exp[mean ln(BTT) – mean ln(non-BTT)]
[2]Lowest unmeasured confounder effect (on the relative risk scale) needed to shift the (Bayesian) point estimate (first value) or the lower limit of the 95% CrI to 1.0 (second value).