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Complications related to extracorporeal membrane oxygenation support as a bridge to lung transplantation and their clinical significance

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ABSTRACT

Background: Incidence of complications related extracorporeal membrane oxygenation (ECMO) support as a bridge to lung transplantation (BTT) and its association with the patient outcome in lung transplantation (LT) has not been well documented in previous studies.
Objectives: We evaluated the incidence of complications related to the use of ECMO support as a BTT, and the association between the occurrence of the complications and patient outcomes in LTs.
Methods: This retrospective cohort study investigated 100 consecutive patients who started ECMO support as a BTT between April 2013 and March 2020. Data for the analyses were retrieved from electronic medical records.
Results: Fifty-six percent of the patients experienced at least one complication during the BTT with ECMO. Major bleeding was the most common complication. In multivariate logistic regression analysis, occurrence of oxygenator thromboses (OR 16.438, $P = 0.008$) and the use of renal replacement therapy (RRT) (OR 32.288, $P < 0.001$) were associated with a failed BTT. In the subgroup analysis of the LT recipients, intracranial hemorrhages, (OR 13.825, $P = 0.021$), RRT use, (OR 11.395, $P = 0.038$), and bloodstream infection occurrence (OR 6.210; $P = 0.034$) were identified as risk factors for in-hospital mortality.
Conclusions: The occurrence of complications during the use of ECMO support as a BTT was associated with unfavorable outcomes in LTs. Close monitoring and the proper management of these complications may be important to achieve better outcomes in patients using ECMO support as a BTT.

Introduction

Lung transplantation (LT) is a viable treatment option for patients with a variety of end-stage lung diseases.[1] Unfortunately, the number of donated lungs is limited; therefore, a bridging strategy may be required for the survival of patients with severe respiratory failure. Although mechanical ventilation (MV) as a bridge to lung transplantation (BTT), has been the mainstay of respiratory support, it has poor short-term survival with a 2-fold increase in mortality compared to non-ventilated patients.[2] An alternate strategy is to use extracorporeal membrane oxygenation (ECMO) support as a BTT.[3,4] With advances in technology and the accumulation of experience in ECMO support, there has been an increase in the use of ECMO support as a BTT.[5]

However, ECMO support is invasive, requires anticoagulation for the duration of the therapy, and can be associated with serious complications.[6] Although there have been studies regarding general outcomes of patients in whom ECMO support has been used as a BTT,[7,8] the incidence of complications related to ECMO support as a BTT and its association with the patient outcomes in LTs has not been well documented in previous studies.

Therefore, we performed the current study to evaluate the incidence of complications related to the use of ECMO support as a BTT, and to identify the association between the complications and the outcomes of the BTT.

Methods

Study design and data collection

This retrospective study investigated 100 consecutive patients who commenced with ECMO support as a bridge to lung transplantation between April 2013 and March 2020 in Severance Hospital, a university-affiliated tertiary referral hospital in South Korea.

The candidates for ECMO bridging were decided by an institutional multidisciplinary team comprising a thoracic surgeon and pulmonary physicians. Most of the patients underwent a right

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jugular-femoral venous configuration. Some patients who developed a right heart failure underwent a femoro-femoral veno-arterial cannulation. The standard ECLS circuit at our institution includes the use of a Rotaflow centrifugal pump (Maquet, Wayne, NJ) and Quadrox oxygenator (Maquet). The standard anticoagulant that was used was unfractionated heparin and the activated clotting time (ACT) was used for to monitor the heparin, with goal ACT being between 180 and 200 s for veno-arterial (VA) ECMO and between 160 and 180 s for veno-venous (VV) ECMO. Regarding the transfusion decisions, the hemoglobin targets were typically greater than 10 g/dL and the platelet counts were greater than 100,000/μL. Transfusions were performed to maintain the target levels. The blood flow and sweep gasses were adjusted to maintain a partial pressure of oxygen >60 mmHg, partial pressure of carbon dioxide ≤45 mmHg, and a pH of >7.35 in the arterial blood.

The data for the analyses were retrieved from the electronic medical records. The study was approved by the Ethics Review Committee of Severance Hospital (IRB No. 4–2021–0854), and the need for informed consent was waived by the Committee due to the retrospective nature of this study.

Definitions and outcome measurement

The complications related to ECMO BTT were defined as the following six categories: major bleeding, thrombotic events, bloodstream infections, renal replacement therapy, machine failure, and lower limb ischemia. The complications were defined based on a complication code list suggested by Extracorporeal Life Support Organization (ELSO)[9] and a systematic review of previous literature.[10]

Major bleeding was defined according to the criteria of the ELSO as bleeding responsible for death,[11] which is consisted of intracranial bleeding, bleeding requiring hemostatic procedures (surgery, embolization, or endoscopy), or bleeding associated with transfusions ≥2 red blood cell (RBC) units in 24 h. Pulmonary hemorrhages which resulted in airway compromise were also defined as major bleeding.

Thrombotic events were defined as transient ischemic attacks, ischemic strokes, systemic emboli, deep venous thromboses, pulmonary emboli, and membrane oxygenator changes due to the formation of thrombi.

Bloodstream infection (BSIs) were defined as the presence of one or more positive blood cultures from peripheral blood samples, associated with systemic signs of infections. Use of renal replacement therapy, incident of machine failure, and lower limb ischemia were also investigated.

Patient outcomes were evaluated using three indicators: (1) failed BTTs among the LT candidates, (2) in-hospital mortality among the LT recipients and (3) mean survival time after the LT among the recipients.

Statistical analysis

The descriptive variables were summarized using means, standard deviations, and proportions. The continuous variables were compared using the t-tests and categorical variables were compared using the Fisher's exact test. Firth's bias reduced logistic regression analysis was performed for identifying the risk factors related to failed-BTT and in-hospital mortality among the recipients. We also used Kaplan–Meier survival analysis to examine the effect of complications during the use of ECMO support as a BTT on the survival after the LT.

A *P*-value of <0.05 was considered to be significant for all the analyses. Data analysis was performed using SPSS version 26 (IBM, Armonk, NY, USA).

Results

Clinical characteristics of the study population

Of the 100 patients, 33 (33.0%) were women and the mean age ± SD was 53.9 ± 12.3 years. Idiopathic pulmonary fibrosis (IPF) was the cause of end-stage lung disease that required the BTT with ECMO support in 49 (49.0%) patients. Eighty-seven (87.0%) patients started VV ECMO support as a BTT. The mean ± SD duration of the ECMO support was 15.9 ± 11.5 days (Table 1).

Incidence of ECMO related complications during BTT

Fifty-six percent of the patients experienced at least one complication during the BTT with ECMO support. Major bleeding (38.0%) was the most common complications experienced by the participants, followed by thrombotic events (20.0%), renal replacement therapy (RRT) (20.0%), bloodstream infections (BSIs) (11.0%), machine related complications (4.0%), and lower limb ischemia (3.0%). A detailed description of the incidence of complications is presented in Table 2.

Patient outcomes

Among the 100 participants, 80 (80.0%) patients proceeded to LT surgeries with BTTs, while 20 (20.0%) patients failed to proceed and died. The causes of the failed BTTs were patient deterioration or recipient inadequacy (Table S1). The major causes of failed BTTs were septic shock (*n* = 7, 35.0%) followed by major bleeding (*n* = 6, 30.0%).

Among the 80 LT recipients, 58 (72.5%) were discharged and 22 (27.5%) died during their hospital stay (Fig. 1). The Kaplan–Meier survival analysis showed that an occurrence of any complication during the use of the ECMO support as a BTT was associated with shorter survival among the LT recipients (mean survival time 4.8 vs 2.3 years; log rank test: $P < 0.05$) (Fig. 2A). Furthermore, the analysis also showed that the greater the complications that the patients

Table 1
Clinical characteristics of the participants.

Variables	n (%)	
Sex, female	33	(33.0)
Age, years	53.9	±12.3
Indication of lung transplantation		
Idiopathic pulmonary fibrosis	49	(49.0)
Connective tissue disease-associated ILD	13	(13.0)
Other ILDs*	21	(21.0)
Bronchiolitis obliterans after HSCT	6	(6.0)
COPD	6	(6.0)
Primary pulmonary hypertension	4	(4.0)
ARDS	1	(1.0)
ECMO type		
Veno-venous	87	(87.0)
Veno-arterial	13	(13.0)
Duration of ECMO support, days	15.9	±11.5
LT recipients, total	80	(80.0)
BTT with veno-venous ECMO	75	(75.0)
BTT with veno-arterial ECMO	5	(5.0)

Categorical data are presented as n (%) or mean ± SD.

* Includes 7 acute interstitial pneumonia, 1 chronic hypersensitivity pneumonitis, 3 organizing pneumonia, 1 Hermansky-pudlak syndrome, 1 lymphangioleiomyomatosis, 2 nonspecific interstitial pneumonia, 1 combined pulmonary fibrosis and emphysema, 2 pleuroparenchymal fibroelastosis, 1 humidifier disinfectant-associated lung injury, and 2 unspecified ILD, interstitial lung disease; HSCT, hematopoietic stem cell transplantation; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; LT, lung transplantation; BTT, bridge to lung transplantation.

Table 2
Incidence and number of complications that occurred during the use of extracorporeal membrane oxygenation support as a bridge to lung transplantation.

	n (%)	
Incidence of complications		
Complication, any	56	(56.0)
Major bleeding	38	(38.0)
Cannulation site bleeding	11	(11.0)
Pulmonary hemorrhage	10	(10.0)
Internal bleeding*	9	(9.0)
Gastrointestinal bleeding	8	(8.0)
Intracranial hemorrhage	4	(4.0)
Thrombotic event	20	(20.0)
Oxygenator thrombosis	8	(8.0)
Deep vein thrombosis	8	(8.0)
Pulmonary artery thromboembolism	4	(4.0)
Cerebral infarction	3	(3.0)
Renal replacement therapy	20	(20.0)
Blood stream infection	11	(11.0)
Bacteremia	10	(10.0)
Fungemia	3	(3.0)
Bacteremia and fungemia	2	(2.0)
Machine failure†	4	(4.0)
Lower limb ischemia	3	(3.0)
Number of complications		
None	44	(44.0)
1	20	(20.0)
2	26	(26.0)
3	9	(9.0)
4	1	(1.0)

* Bleeding into thorax, peritoneum, retroperitoneum, or soft tissue.
† Includes 2 oxygenator leakage, 1 catheter malposition, and 1 oxygenator malfunction.

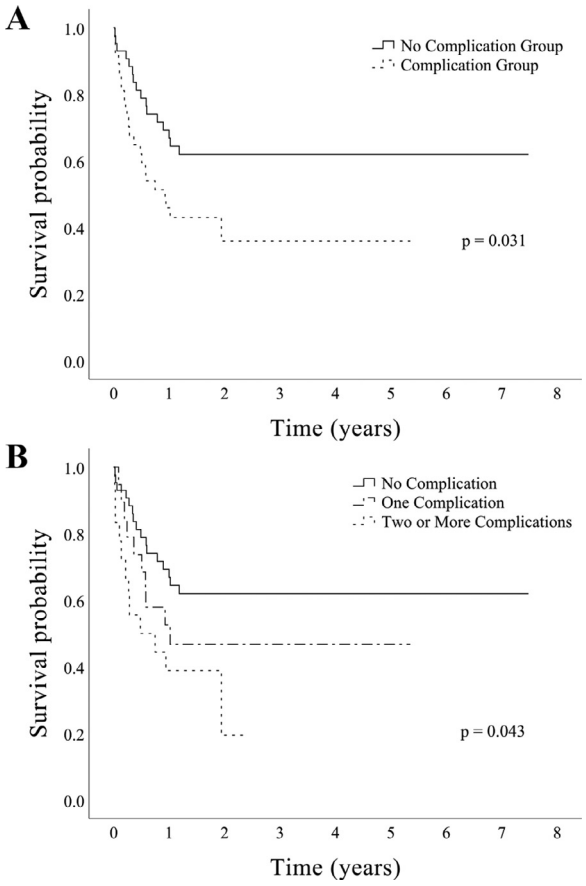

Fig. 2. Kaplan–Meier curves displaying the estimated probability of the survival for the different groups of patients according to the occurrence of complications.

experienced during the use of ECMO support as a BTT, the greater the impact on mortality (log rank test: $P < 0.05$) (Fig. 2B).

Risk factors for failed BTT

From the univariate logistic analysis using Firth's method, VA ECMO use, occurrence of oxygenator thrombosis, and RRT use were the risk factors related to failed BTTs ($P < 0.001$). The multivariate analysis, which included the statistically significant variables (age, VA-ECMO use, oxygenator thrombosis and RRT use), showed that oxygenator thrombosis (OR 16.438; 95% CI 2.100–151.593, $P = 0.008$) and RRT use (OR 32.288; 95% CI 8.282–159.433, $P < 0.001$) were the risk factors for failed BTTs in our cohort (Table 3).

Risk factors for in-hospital mortality of recipients after BTT

We performed a subgroup analysis in 80 (80.0%) of the participants who proceeded to LTs after BTTs, to investigate risk factors for mortality.

The univariate analysis indicated that intracranial hemorrhages, RRT use, and BSIs during ECMO BTTs were the risk factors for in-hospital mortality among the LT recipients ($P < 0.05$). The multivariate analysis which included age, intracranial hemorrhages, RRT use, and BSIs showed that intracranial hemorrhages (OR 13.825; 95% CI 1.403–1848.206, $P = 0.021$), RRT use (OR 11.395; 95% CI 1.126–1531.115, $P = 0.038$), and occurrence of BSIs (OR 6.210; 95% CI 1.139–63.647, $P = 0.034$) during ECMO BTT were the risk factors for in-hospital mortality after LTs (Table 4).

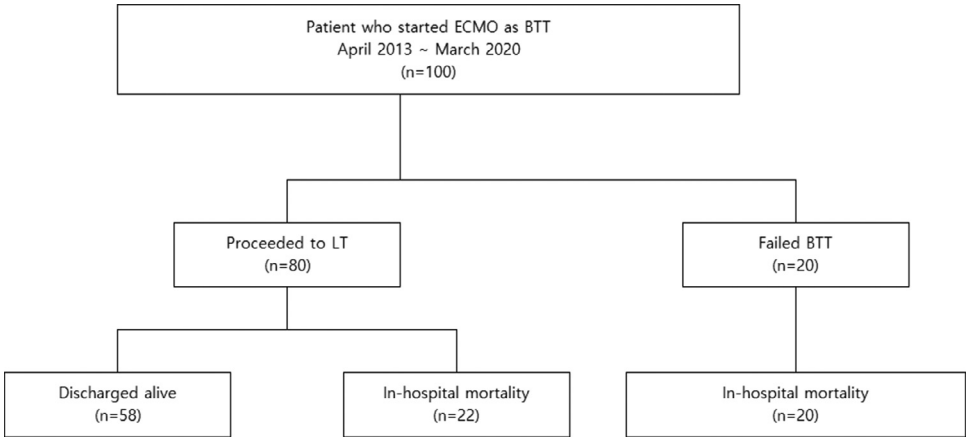

Fig. 1. Flowchart of the study participants.

Table 3
Firth's bias-reduced logistic regression evaluating the risk factors for a failed bridge to lung transplantation.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	0.970 (0.936–1.005)	0.091	0.995 (0.942–1.051)	0.860
Female	0.872 (0.293–2.381)	0.794		
Veno-arterial ECMO	9.335 (2.799–33.869)	<0.001	4.222 (0.648–29.707)	0.132
Duration of ECMO support, days	1.030 (0.989–1.071)	0.149		
Cannulation site bleeding	1.706 (0.388–6.227)	0.451		
Pulmonary hemorrhage	1.153 (0.205–4.642)	0.854		
Internal bleeding*	3.744 (0.917–14.717)	0.065		
Gastrointestinal bleeding	1.549 (0.268–6.677)	0.589		
Intracranial hemorrhage	0.415 (0.003–4.138)	0.516		
Oxygenator thrombosis	14.076 (3.231–82.946)	<0.001	16.438 (2.100–151.593)	0.008
Deep vein thrombosis	0.208 (0.002–1.796)	0.185		
Pulmonary artery thromboembolism	0.415 (0.003–4.138)	0.516		
Cerebral infarction	2.415 (0.212–19.233)	0.427		
Renal replacement therapy	38.686 (11.355–157.907)	<0.001	32.288 (8.282–159.433)	<0.001
Blood stream infection	1.706 (0.388–6.227)	0.451		
Machine related complications†	1.703 (0.158–11.086)	0.610		

* Bleeding into thorax, peritoneum, retroperitoneum, or soft tissue ECMO, extracorporeal membrane oxygenation.

Discussion

This study investigated the incidence of complications related to ECMO and the association of the complications with clinical outcomes in patients who were using ECMO support as a BTT. In this study, the incidence of ECMO-related complications with ECMO support as a BTT were comparable to previous reports based on general populations (i.e., non-LT candidates),[12–14] and in addition, also similar to a previous systematic review of patients on ECMO support as a BTT.[15]

In contrast, we identified an association between the occurrence of complications during the use of ECMO support as a BTT and unfavorable outcomes of LTs, defined using three separate indicators: (1) failed BTT among LT candidates, (2) in-hospital mortality among LT recipients, and (3) mean survival time after LTs among the recipients. To our knowledge, these associations between the clinical outcomes of BTTs and the occurrence of ECMO-related complications have not been investigated previously.

In our study, an episode of oxygenator thrombosis requiring change-out was identified as a risk factor for a failed BTT. Despite adequate anticoagulation, oxygenator thrombosis may develop. The fibrin deposition varies in severity and manifests itself as an abnormal increase in the oxygenator inlet pressure.[16] Subsequently, this obstruction causes alterations in blood flow through the device and, if excessive, may impair gas transfer to the extent where a change-out of the oxygenator is necessary.[16] Such a thrombosis poses a risk to patients in two ways, first, is that the effects of hypoxemia itself that can result from oxygenator failure (e.g., tissue hypoxia,[17] decreased cardiac output,[18] and exacerbation of pulmonary hypertension[19]). Second, is the risk related to the oxygenator change-out procedure (e.g., interruption of ECMO support, possible blood loss, and contamination[20]). It has been reported that, in the US, one patient dies each month as a result of the emergency oxygenator change-out procedure with the permanent injuries of some patients being the result of the oxygenator change-out procedures or oxygenator failures.[20] The aforementioned data may explain the association between oxygenator thrombosis and the failed BTT in our cohort, and optimal anticoagulation strategies should be adopted to avoid the poor outcomes in the BTT.

On the other hand, the incidence of bleeding events did not affect the outcome measures in our study. In terms of this observation, a previous study[12] conducted a detailed investigation of the incidence of serious bleeding events, red blood cell transfusions, and their impact on mortality during the use of ECMO support. In that study,

Table 4
Firth's bias-reduced logistic regression evaluating the risk factors for in-hospital mortality of lung transplant recipients with a BTT.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	0.991 (0.952–1.030)	0.646	0.994 (0.948–1.042)	0.806
Female	2.009 (0.802–5.177)	0.137		
Veno-arterial ECMO	1.597 (0.294–10.066)	0.583		
Duration of ECMO support, days	1.024 (0.985–1.068)	0.225		
Cannulation site bleeding	0.672 (0.146–2.722)	0.579		
Pulmonary hemorrhage	0.672 (0.146–2.722)	0.579		
Internal bleeding*	3.609 (0.629–37.251)	0.155		
Gastrointestinal bleeding	2.113 (0.439–12.742)	0.352		
Intracranial hemorrhage	11.087 (1.123–1488.423)	0.038	13.825 (1.403–1848.206)	0.021
Oxygenator thrombosis	0.210 (0.002–2.694)	0.252		
Deep vein thrombosis	0.672 (0.146–2.722)	0.579		
Pulmonary artery thromboembolism	1.110 (0.164–7.527)	0.910		
Cerebral infarction	5.822 (0.455–813.173)	0.190		
Renal replacement therapy	13.955 (1.496–1856.378)	0.016	11.395 (1.126–1531.115)	0.038
Blood stream infection	6.587 (1.338–64.781)	0.019	6.210 (1.139–63.647)	0.034
Machine related complications†	1.895 (0.241–21.407)	0.539		

BTT, bridge to lung transplantation; ECMO, extracorporeal membrane oxygenation.

the volume of red blood cells transfused was associated with in-hospital mortality after controlling for confounding variables, while the occurrence of the bleeding itself did not affect mortality.[12] This suggested that it was the volume of blood loss and transfusion, rather than the occurrence of a bleeding event, that affected the clinical outcome. Therefore, vigilance and the timely management of bleeding events is important to achieve better outcome in patients using ECMO support as a BTT.

In addition, the use of RRT during the use of ECMO support as a BTT was a risk factor for failed BTT, as well as a predictor of in-hospital mortality after LTs. A previous study that investigated the effects of RRT in patients receiving ECMO[21] reported that the RRT mortality rates in patients receiving ECMO were high regardless of age or the indication for the use of ECMO itself. However, the higher the mortality in the control population, the greater the overall decrease in mortality, suggesting that this was more likely to have been caused by the disease severity than the RRT itself. This may indicate that poor outcomes in patients with RRT was associated with the overall severity of disease, rather than RRT itself.

Intracranial hemorrhages were also shown to have a significant association with in-hospital mortality after LTs. A previous study that investigated the neurologic complications of LT recipients, showed that neurological complications of any level of severity were associated with an increased risk of death.[22]

In our study, all the patients with intracranial hemorrhages ($n = 4$) proceeded to LTs without knowing that bleeding had occurred. The hemorrhages were all confirmed by brain images in the 1 month period after the LTs. Brain imaging was performed due to delayed recoveries of their mental statuses or observed neurologic abnormalities. None of them had been suspected of having the complications before proceeding to the LTs despite regular interruptions of intravenous sedatives with checking of the mental statuses or neurologic deficits being adopted as surveillance strategies during the ECMO support. In consideration of the scarcity of donor lungs and the poor outcome after LTs, further screening strategies (i.e., electroencephalogram monitoring, computed tomography scans) to properly screen or prevent intracranial hemorrhages during the use of ECMO support as a BTT, may be warranted.

The occurrence of BSIs during the use of ECMO support as a BTT also predicted mortality after LTs in our cohort. Maintenance immunosuppressive therapy is administered to all LT recipients to help prevent acute and chronic rejection. In that sense, precedent BSIs may pose a greater risk to the LT recipients compared to other populations using ECMO support. Some precautions and novel approaches have been suggested regarding infection control in ECMO,[23,24] and those approaches may be considered for improving outcomes especially in patients using ECMO support as a BTT.

To our knowledge, this is the first study that investigated the association between the complications related to the use of ECMO support as a BTT and LT outcomes. A strength of our study is that, for the first time, it provides a list of certain complications associated with the outcomes of LT with ECMO support as a BTT, and our results can contribute to develop more targeted strategies to prevent and manage the critical complications so as to improve the clinical outcomes. For example, developing an improved strategy to achieve optimal anticoagulation and prevent oxygenator thrombosis during ECMO support as a BTT may be a good target for a future research (e.g., routine use of anti-factor Xa assay to monitor anticoagulation with heparin,[25] use of direct thrombin inhibitor for anticoagulation,[26] combined use of thromboelastography for anticoagulation monitoring[27]). On the other hand, efficacy of previously suggested preventive measures for BSI during ECMO (e.g., chlorhexidine bathing of the exposed circuits in ECMO[23]) on the transplantation outcome may also be a promising subject to investigate.

This study has some limitations. First, this was a single-center study and the possibility of selection bias cannot be excluded. However, since our center performed over 50% cases of LTs in the Republic of Korea as in 2017,[28] the representativeness of our study population may suffice. Second, the retrospective nature of this study may under/overestimate the incidence of complications, although our study's results were comparable to previous study that investigated the use of ECMO support as a BTT.[15] Third, the relatively small sample size may have affected the power of the statistical analysis investigating the association between the complications of ECMO support and LT outcomes. To reduce the small-sample bias, we used Firth's bias-reduced penalized-likelihood logistic regression.[29]

Conclusions

The incidence of ECMO-related complications during the use of ECMO support as a BTT is similar to that of ECMO support with other general indications. The occurrence of complications during the use of ECMO as a BTT was associated with unfavorable outcomes in LTs. Among the complications, oxygenator thrombosis, intracranial hemorrhages, the use of RRT, and BSIs were associated with poor outcomes in patients using ECMO support as a BTT. Development and validation of more targeted strategies to prevent, screen, and manage those complications may be needed to improve clinical outcomes of LT with ECMO support as BTT.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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