Prognostic factors in lung transplantation after extracorporeal membrane oxygenation bridging therapy: a systematic review and meta-analysis

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Background: Extracorporeal membrane oxygenation (ECMO) has recently emerged as a critical support system for lung function in patients awaiting lung transplantation. This meta-analysis investigates the prognostic factors of lung transplantation following ECMO bridging therapy.
Methods: A comprehensive search was conducted in PubMed, Cochrane Library, Embase, CINAHL, Web of Science, Scopus, and ProQuest databases from inception to August 11, 2023. Included were cohort or case-control studies focusing on prognostic factors of lung transplantation with ECMO bridging therapy. Data extraction was performed independently, and study quality was assessed. A meta-analysis was carried out using RevMan 5.4 and Stata17.0 software to aggregate mortality rates and pertinent prognostic factors of ECMO as a bridge to lung transplantation.
Results: The search identified eight trials encompassing 1,086 participants. The prognosis of patients undergoing lung transplantation with ECMO bridging was significantly associated with several factors: prolonged ECMO support [odds ratio 1.07, 95% confidence interval (CI): 1.02–1.12, I^2=77%], deterioration in liver and kidney function (odds ratio 3.62, 95% CI: 2.37–5.54, I^2=0%), and complications during ECMO (odds ratio 2.24, 95% CI: 1.45–3.44, I^2=5%).
Conclusions: Prolonged ECMO support, declining liver and kidney functions, and complications during ECMO are vital prognostic factors in lung transplantation following ECMO bridging therapy.

Keywords: Lung transplantation; extracorporeal membrane oxygenation (ECMO); prognostic factors; meta-analysis

Introduction

In recent decades, lung transplantation has emerged as the definitive treatment for end-stage lung disease. However, a critical limitation to its rapid advancement is the scarcity of donors (1,2). Currently, there is a notable disparity between the limited availability of donors and the excess of patients awaiting transplantation, leading to prolonged waiting times and a consequent high mortality rate during this period (3-5).

A 2023 analysis from the United Network for Organ Sharing database reveals that, although the case fatality rate during the waiting period at lung transplant centers in the United States has declined compared to previous years, it remains alarmingly high at 23% (6).

Confronted with this challenge, medical professionals worldwide are focused on enhancing the survival rates of patients with end-stage lung disease during the

transplant waiting period. In the past several decades, extracorporeal membrane oxygenation (ECMO) systems have experienced significant advancements (7,8). The primary goal of employing ECMO as a bridging therapy before lung transplantation is to prevent the deterioration of the patients' physical condition and to improve their overall health and resilience, thereby creating optimal conditions for successful post-transplant outcomes (9). These improvements have led to the growing use of ECMO as a preferred bridging therapy over tracheal intubation for patients with cardiopulmonary failure, primarily to avoid hospital-acquired pneumonia, ventilator-refractory hypoxia and to maintain walking ability and participation in preoperative rehabilitation (10-12). However, despite these advancements, ECMO usage carries inherent risks, with the duration of use correlating to an increased likelihood of complications (13,14).

Despite existing research exploring the prognostic factors associated with ECMO as a bridging therapy before lung transplantation, these studies often lack consistency, and their findings vary (15-17). In response to this gap, our research reviews prognostic factors related to lung transplantation following ECMO bridging therapy. This analysis aims to provide robust evidence supporting the efficacy of ECMO bridging in enhancing the prognosis of lung transplant patients. We present this article in

accordance with the MOOSE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1709/rc) (18).

Methods

Protocol and guidelines

The protocol for this review is registered with PROSPERO (CRD42023453709).

Inclusion criteria

Eligible trials include those that enroll adult patients (age ≥18 years) undergoing lung transplantation bridging ECMO, focus on risk factors affecting prognosis, provide information on all-cause (non-accidental) mortality, or report specific causes separately, and are case-control or cohort studies.

Exclusion criteria

This study excludes case reports or case series, studies where only abstracts are available or the full text is inaccessible, and studies with data that cannot be converted or applied.

Outcomes

The primary outcome is the mortality rate, with the secondary outcome being risk factors.

Search strategy

One author (Y.Z.) searched databases such as PubMed, Cochrane Library, Embase, CINAHL, Web of Science, Scopus, and ProQuest from their inception until August 11, 2023 (Tables S1-S6). Searches were also performed on ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform to identify ongoing and unpublished trials meeting our inclusion criteria. We also reviewed the reference lists of identified trials and systematic reviews to ensure thoroughness. There were no language restrictions imposed.

Study selection

Duplicate records were removed, after which two independent researchers (Y.Z. and J.S.Y.L.) screened all titles and abstracts.

Highlight box

Key findings
- Prolonged extracorporeal membrane oxygenation (ECMO) support, declining liver and kidney functions, and complications during ECMO are vital prognostic factors in lung transplantation following ECMO bridging therapy.

What is known and what is new?
- Prior cohort and case-control studies indicate significant improvements in the prognosis of lung transplant patients undergoing ECMO bridging therapy. Clinical data on the prognostic factors of ECMO as a bridging therapy for lung transplantation have shown inconsistency.
- This manuscript contributes a systematic review of prognostic factors in lung transplant recipients following ECMO bridging therapy.

What is the implication, and what should change now?
- This systematic review and meta-analysis can inform the establishment of standardized nursing protocols and the development of an evaluation index system for ECMO patient care.

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Studies meeting the initial eligibility criteria had their full texts obtained for further scrutiny. Discrepancies between researchers were resolved by consensus.

Data collection process

Two independent researchers (Y.Z. and J.S.Y.L.) employed a standardized data extraction form to gather data from the included trials. Extracted details encompassed author, publication year, study location, study design, sample size, and risk factors. A third researcher settled any disagreements.

Assessment of risk of bias and quality of evidence

The quality of the included trials was independently evaluated by two researchers (Y.Z. and J.S.Y.L.) using the Newcastle-Ottawa Scale (19). This scale assesses study population selection, group comparability, and exposure factors. A total score of six or more was deemed indicative of high-quality literature.

Statistical analysis

Statistical analyses were conducted using RevMan (version 5.4) and STATA (version 17.0). Odds ratio and their 95% confidence intervals (CIs) were used to assess outcomes, considering a P value of less than 0.05 as statistically significant. Heterogeneity was evaluated using the I^2 test ($I^2 < 50\%$), fixed (20). Fixed effects models were used to combine the outcomes. However, random effects models were utilized if significant heterogeneity was present ($I^2 \geq 50\%$). The presence of small study effects was assessed both qualitatively, through funnel plot inspection, and quantitatively, using Egger's test (21).

Sensitivity analyses

Sensitivity analyses were executed using the following methodology: each paper was individually removed from the dataset, and the resultant impact on the combined effect size (ES) was assessed to determine the influence of each study on the overall meta-analysis.

Results

Eligible studies and study characteristics

The initial search yielded 12,886 records, culminating in the

inclusion of eight eligible trials (22-29) in the final meta-analysis (*Figure 1*). The methodological quality evaluation scores of these eight studies were six points or higher, indicating high quality. The characteristics of the included trials are summarized in *Table 1*.

First outcome: mortality rate

Seven of the studies reported the mortality rate associated with ECMO support as a bridge to lung transplantation. Due to heterogeneity among these studies, a random effect model was employed for analysis. The pooled was 37% (ES 0.37, 95% CI: 0.28–0.46, I^2=83.57%, *Figure 2*). The mortality rate for ECMO support as a bridge to lung transplantation was found. This high rate underscores the need for further investigation into prognostic factors. Sensitivity analysis indicated minimal impact on the combined ES when any single study was excluded. The funnel plot analysis suggested symmetry, and Egger's tests revealed no significant minor study effects (Figure S1).

Secondary outcome: risk factors

All eight trials investigated various risk factors. The prognosis for patients undergoing lung transplantation with ECMO bridging was found to be significantly influenced by several key factors. Prolonged ECMO support in lung transplantation bridging was associated with increased mortality (odds ratio 1.07, 95% CI: 1.02–1.12, I^2=77%, *Figure 3*). Additionally, deterioration in liver and kidney function was linked to a higher risk of mortality (odds ratio 3.62, 95% CI: 2.37–5.54, I^2=0%, *Figure 4*), as were complications occurring during ECMO (odds ratio 2.24, 95% CI: 1.45–3.44, I^2=5%, *Figure 5*). Notable heterogeneity was observed among the studies. Sensitivity analysis indicated that excluding any individual study had minimal impact on the overall ES. The funnel plot analysis demonstrated symmetry, and Egger's tests found no significant minor study effects (Figures S2-S4).

Discussion

In this meta-analysis involving 1,086 participants across eight trials, the mortality rate for ECMO support as a bridge to lung transplantation was 37% (ES 0.37, 95% CI: 0.28–0.46). The prognosis for patients undergoing lung transplantation with ECMO bridging was notably influenced by factors like extended ECMO support duration
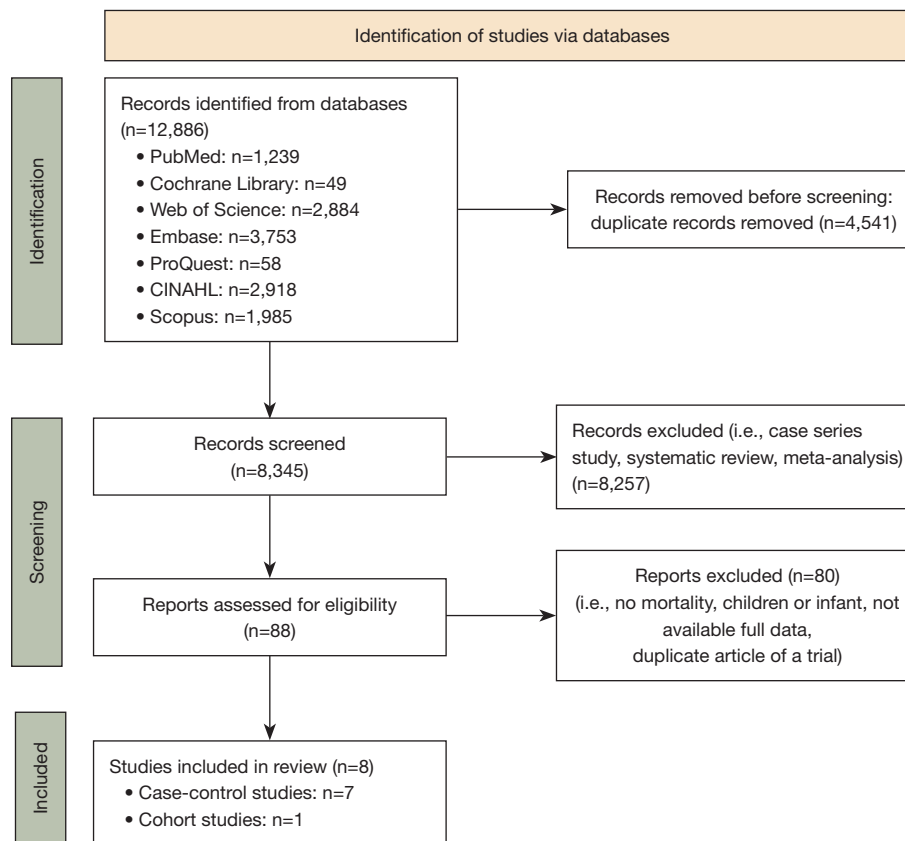
Figure 1 Search strategy and the shortlisting of studies to be reviewed.

(odds ratio 1.07, 95% CI: 1.02–1.12, I^2=77%), worsening of liver and kidney functions (odds ratio 3.62, 95% CI: 2.37–5.54, I^2=0%), and complications during ECMO (odds ratio 2.24, 95% CI: 1.45–3.44, I^2=5%). The findings suggest that longer ECMO support, deteriorating liver and kidney function, and complications during ECMO in lung transplant patients are indicative of a poorer prognosis.

Principal findings and their comparison with other studies

The observed mortality rate in this study aligns with findings from two prior systematic reviews (30,31). An earlier meta-analysis revealed that patients receiving long-term ECMO-supported lung transplantation as bridging therapy had a worse prognosis compared to those not receiving ECMO. However, this gap has narrowed significantly between 2009 and 2011 (31). Over the last decade, there have been remarkable improvements in the prognosis of patients undergoing ECMO bridging therapy. Hayanga *et al*. (32) noted that the 1-year survival rate for

patients who underwent lung transplantation after ECMO bridging between 2000 and 2002 was 25%, increasing to as high as 74% between 2009 and 2011. This significant enhancement is attributed to advanced ECMO system design, improved patient care during bridging, and more effective patient selection (5,33,34).

The mortality rate was significantly higher in trials with prolonged ECMO support. With advancements in extracorporeal life support, ECMO as a bridge for lung transplantation has become crucial for intraoperative and postoperative circulatory support, sustaining recipients during the lung transplantation window period (35). Patients requiring extended ECMO support exhibited a 1.07-fold increase in post-transplant mortality. Such patients are typically critically ill, often requiring combined mechanical ventilation, which may exacerbate organ damage during acute recovery (35,36). Recipients needing longer ECMO support tend to have more extended hospital stays and poorer physical conditions, suggesting that prolonged ECMO may be a key predictor of outcomes in these

Table 1 Summary characteristics and the outcome measures of the included studies

Studies	Country	Study design	Year	Sample size	Mortality rate (%)	Risk factors
Neumann (22)	Switzerland	Case-control	2023	221	29.40	Age, newly detected liver failure, red blood cell transfusion, platelet concentrate transfusion
Kim (23)	South Korea	Case-control	2022	100	27.50	Intracranial hemorrhages, RRT use, bloodstream infection occurrence
Minqiang (24)	China	Case-control	2021	267	NR	Delayed withdrawal ECMO
Kim (25)	South Korea	Cohort	2021	64	53.80	Sedated BTT ECMO
Weig (26)	German	Case-control	2013	26	46.20	SOFA score lower, maximal bilirubin, bilirubin prior to transplantation
Crotti (27)	Italian	Case-control	2013	25	24	Waiting time on ECMO (up to 14 days or longer), invasive mechanical ventilation
Oh (28)	Korean	Case-control	2021	41	55	Long-term ECMO support (14 days)
Hayanga (29)	American	Case-control	2016	342	26.90	Low-volume centers

RRT, renal replacement therapy; NR, not reported; ECMO, extracorporeal membrane oxygenation; BTT, bridge to transplant; SOFA, sequential organ failure assessment.
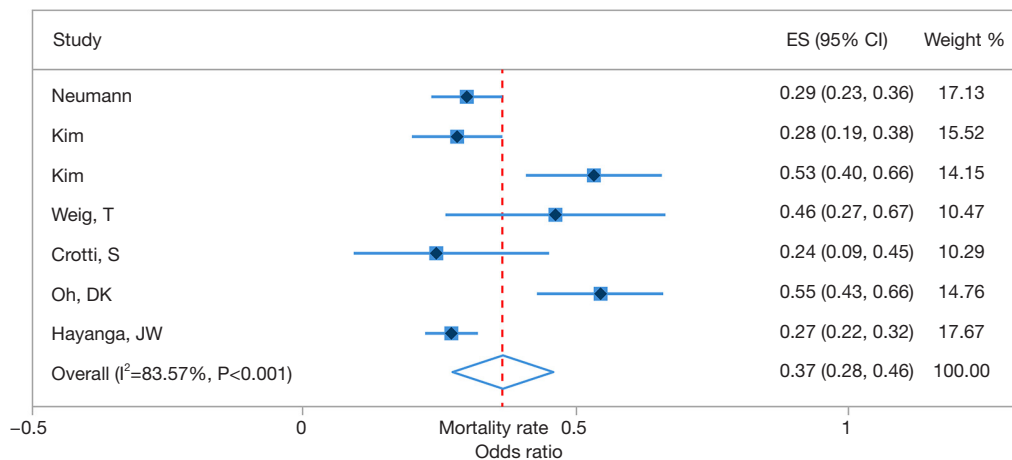

Figure 2 Forest plot of mortality in lung transplantation bridging ECMO. ES, effect size; ECMO, extracorporeal membrane oxygenation; CI, confidence interval.

patients.

A key observation from our analysis is the significantly higher mortality in trials involving patients with deteriorated liver and kidney function. Complications such as acute kidney injury and new liver damage frequently occur during ECMO treatment (37). Fluid overload, a common issue in ECMO patients, often necessitates renal replacement therapy (RRT) to maintain fluid balance and metabolic control, a practice widely implemented across different centers (38). The association of liver and kidney function deterioration with increased mortality

(odds ratio 3.62, 95% CI: 2.37–5.54) underscores the importance of comprehensive care. Management of patients undergoing ECMO for lung transplantation should involve a multidisciplinary team, including the establishment of an anticoagulation nursing team and integrated medical care for dynamic management. Such a collaborative approach allows for timely adjustments in diagnosis and treatment, ensuring patient safety.

ECMO's broad application brings with it a range of complications during patient care, including infections, bleeding, thrombosis, hemolysis, renal injury, and hepatic
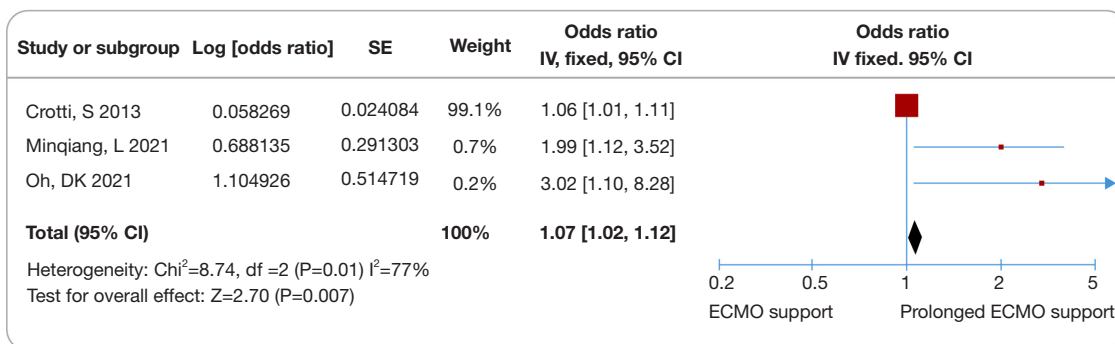
Study or subgroup	Log [odds ratio]	SE	Weight	Odds ratio IV, fixed, 95% CI	Odds ratio IV fixed. 95% CI
Crotti, S 2013	0.058269	0.024084	99.1%	1.06 [1.01, 1.11]	
Minqiang, L 2021	0.688135	0.291303	0.7%	1.99 [1.12, 3.52]	
Oh, DK 2021	1.104926	0.514719	0.2%	3.02 [1.10, 8.28]	
Total (95% CI)			100%	**1.07 [1.02, 1.12]**	

Heterogeneity: Chi^2=8.74, df =2 (P=0.01) I^2=77%
Test for overall effect: Z=2.70 (P=0.007)

ECMO support — Prolonged ECMO support

Figure 3 Forest plot of the effects of prolonged ECMO support on mortality. SE, standard error; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.
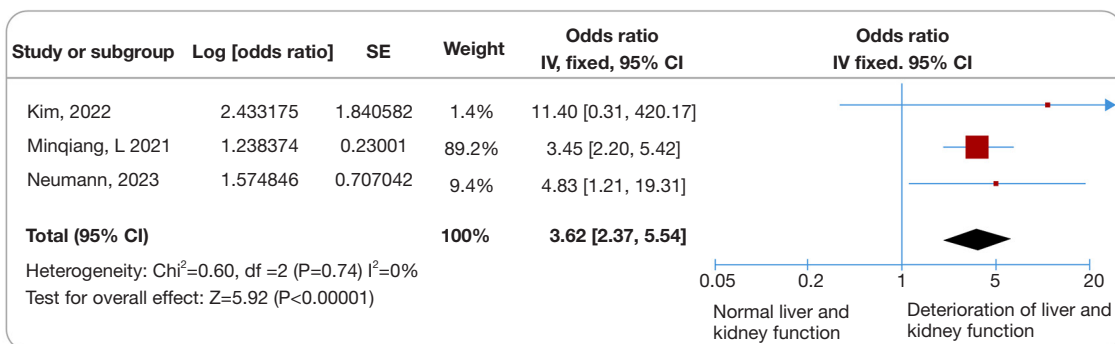
Study or subgroup	Log [odds ratio]	SE	Weight	Odds ratio IV, fixed, 95% CI	Odds ratio IV fixed. 95% CI
Kim, 2022	2.433175	1.840582	1.4%	11.40 [0.31, 420.17]	
Minqiang, L 2021	1.238374	0.23001	89.2%	3.45 [2.20, 5.42]	
Neumann, 2023	1.574846	0.707042	9.4%	4.83 [1.21, 19.31]	
Total (95% CI)			100%	**3.62 [2.37, 5.54]**	

Heterogeneity: Chi^2=0.60, df =2 (P=0.74) I^2=0%
Test for overall effect: Z=5.92 (P<0.00001)

Normal liver and kidney function — Deterioration of liver and kidney function

Figure 4 Forest plot of the effects of deterioration of the liver and kidney functions on mortality. SE, standard error; CI, confidence interval.

Study or subgroup	Log [odds ratio]	SE	Weight	Odds ratio IV, fixed, 95% CI	Odds ratio IV fixed. 95% CI
Kim, 2022 (1)	2.626479	1.832489	1.4%	13.83 [0.38, 501.74]	
Kim, 2022 (2)	1.826161	1.026327	4.6%	6.21 [0.83, 46.42]	
Minqiang, L 2021	0.727549	0.226353	94.0%	2.07 [1.33, 3.23]	
Total (95% CI)			100%	**2.24 [1.45, 3.44]**	

Heterogeneity: Chi^2=2.10, df =2 (P=0.35) I^2=5%
Test for overall effect: Z=3.67 (P=0.0002)

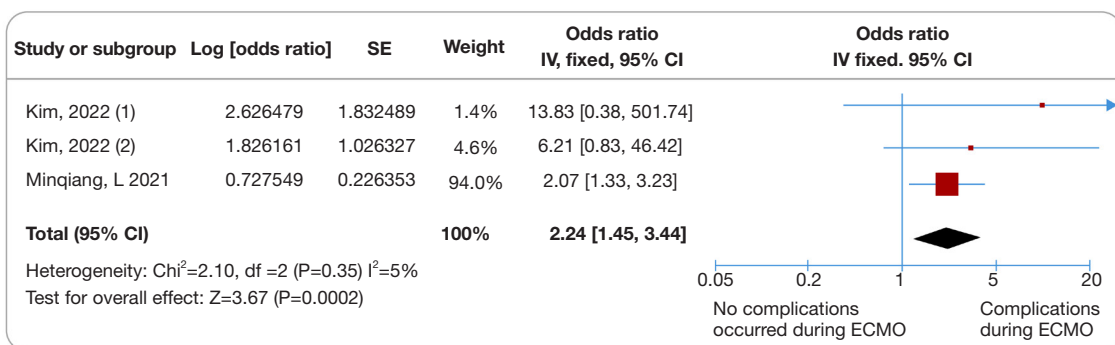No complications occurred during ECMO — Complications during ECMO

Figure 5 Forest plot of the effects of complications during ECMO on mortality. SE, standard error; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.

impairment. The balance between the risks and benefits of ECMO should be carefully considered in clinical practice. Our review found a significant increase in mortality in trials involving patients who experienced complications during ECMO (odds ratio 2.24, 95% CI: 1.45–3.44). Notably, complications such as intracranial hemorrhages and bloodstream infections were strongly linked to mortality. ECMO assistance elevates the risk of bleeding, thrombosis, and infections, all of which can adversely affect patient prognosis (13,23). Patients may experience blood pressure fluctuations and excessive bleeding during surgery. Post-transplantation, pulmonary artery pressure often remains

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elevated compared to normal levels (39,40). Inadequate removal of ECMO support can lead to hemodynamic instability (41). Therefore, this study emphasizes the criticality of patient selection, particularly in evaluating perioperative tolerance to ECMO and its associated complications. The optimal utilization of ECMO, coupled with continuous assessment of patients during bridge therapy, is vital to determining their lung transplantation eligibility.

Strengths and limitations

This systematic review and meta-analysis boasts several methodological strengths. We strictly adhered to the Cochrane Collaboration guidelines and the MOOSE statement, including the implementation of a pre-defined protocol. Additionally, the Newcastle-Ottawa Scale was employed to rigorously assess the quality of evidence, which was found to be high for the primary outcome. Our study provides a comprehensive review of the current data on this subject. Nonetheless, our study is not without limitations. One significant issue is the variability in the definitions of certain risk factors. Different interpretations of specific risks and/or the duration of ECMO support could lead to heterogeneity in risk estimates. Consequently, our analysis could not fully explore the interplay between various risks.

At present, there are a limited number of studies focusing on the risk factors affecting the prognosis of patients undergoing lung transplantation with ECMO bridging. The relatively small number of studies in this analysis restricts our ability to evaluate related risk factors comprehensively. Therefore, future research should involve large-scale, high-quality prospective studies to better understand and identify these risk factors.

Implications

The current lack of a standardized approach for the appropriate withdrawal of ECMO represents a significant gap in clinical practice. Additionally, there is a scarcity of studies exploring patient prognosis post-successful ECMO withdrawal, as well as a deficiency in long-term clinical follow-up data. Enhancing the withdrawal process and developing a predictive scoring system for successful withdrawal outcomes are crucial for maximizing the potential of ECMO technology in future clinical applications. The management of patients receiving both ECMO and RRT is notably complex and demands highly skilled nursing

staff. Standardization in nursing practices for this combined therapy is lacking, as are unified nursing evaluation criteria. The clinical application of ECMO and RRT combined is still exploratory, with most existing studies deriving from empirical observations. Future research should evaluate various nursing interventions during ECMO via employing diverse nursing models and multidisciplinary approaches to generate substantial-high-quality data.

Advancing ECMO nursing scientifically necessitates the establishment of standardized nursing protocols and the development of an evaluation index system specific to ECMO nursing. Such initiatives will play a pivotal role in minimizing ECMO-related complications, enhancing the quality of nursing care, and improving the survival rates of critically ill patients. Consequently, this will lead to improved prognoses and outcomes for these patients.

Conclusions

Overall, this meta-analysis found the mortality rate associated with ECMO bridging in lung transplantation to be 37%, influenced by factors such as prolonged ECMO support, declining liver and kidney function, and complications during ECMO. The prognosis for lung transplant recipients is adversely impacted by longer ECMO support durations, deteriorating liver and kidney functions, and ECMO-related complications. Nevertheless, there is a significant opportunity for caregivers to improve outcomes. By proactively identifying and managing these risk factors through early intervention, the mortality rate among lung transplant recipients can potentially be reduced. This approach emphasizes the importance of vigilant monitoring and timely response to changes in patient conditions during the ECMO bridging process.

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Footnote

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article/view/10.21037/jtd-23-1709/prf

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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