Review paper

Complications associated with bridging to lung transplantation – systematic review and meta-analysis

Powikłania związane z pomostowaniem do przeszczepienia płuc – systematyczny przegląd i metaanaliza

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Key words: extracorporeal membrane oxygenation, lung transplantation, extracorporeal life support, bridging to transplantation.

Słowa kluczowe: pozaustrojowe utlenowanie błonowe, transplantacja płuc, pozaustrojowe podtrzymywanie życia, pomostowanie do przeszczepienia.

Abstract

Introduction: Lung transplantation (LuTx) is a treatment method of end-stage pulmonary diseases when conventional therapy does not provide further improvement. Preoperative use of extracorporeal life support is known as bridging to LuTx and is associated with several complications.
Aim of the research: To investigate the frequencies of complications that may develop during bridging to lung transplantation with extracorporeal life support.
Material and methods: A thorough, systematic review in the Medline and Google Scholar databases was performed. Inclusion criteria consisted of studies with or without a control group reporting experience with bridging to lung transplantation. Preferred reporting items for systematic reviews and meta-analysis protocols were used. Forest plots were generated with Open Meta Analyst software. Heterogeneity was assessed using I2 statistics.
Results: Thirteen studies met the inclusion criteria. The articles were published between 2011 and 2020. A total of 461 patients bridged to transplantation were included. Bleeding and thrombotic complications occurred in 24.6% of patients; cerebrovascular events were observed in 4.5%; while renal replacement therapy was implemented in 13.2% of the included patients.
Conclusions: Frequencies of possible complications occurring during a bridging procedure cannot be overlooked and may lead to death instead of lifesaving surgery.

Streszczenie

Wprowadzenie: Przeszczepienie płuc (LuTx) to metoda leczenia schyłkowych chorób płuc, gdy konwencjonalna terapia nie zapewnia dalszej poprawy. Przedoperacyjne zastosowanie pozaustrojowego wspomagania funkcji życiowych jest znane jako pomostowanie do LuTx i wiąże się z wystąpieniem różnych powikłań.
Cel pracy: Zbadanie częstości występowania powikłań, jakie mogą pojawić się podczas pomostowania do przeszczepienia płuc z pozaustrojowym podtrzymywaniem życia.
Materiał i metody: Przeprowadzono dokładny przegląd systematyczny w bazach danych Medline i Google Scholar. Kryteria włączenia obejmowały badania z grupą kontrolną lub bez niej, w których autorzy przedstawiali swoje doświadczenie z pomostowaniem do transplantacji płuc. Wykorzystano protokół: *Preferred reporting items for systematic reviews and meta-analyses*. Wykresy wygenerowano za pomocą oprogramowania Open Meta Analyst. Niejednorodność oceniano za pomocą statystyki I^2.
Wyniki: Kryteria włączenia spełniło 13 badań. Artykuły zostały opublikowane w latach 2011–2020. Uwzględniono łącznie 461 pacjentów pomostowanych do przeszczepienia. Krwawienia i powikłania zakrzepowe wystąpiły u 24,6% chorych, incydenty mózgowo-naczyniowe u 4,5%, a terapię nerkozastępczą wdrożono u 13,2% pacjentów.
Wnioski: Częstość możliwych powikłań występujących podczas zabiegu pomostowego nie może zostać pominięta; mogą one prowadzić do śmierci zamiast operacji ratującej życie.

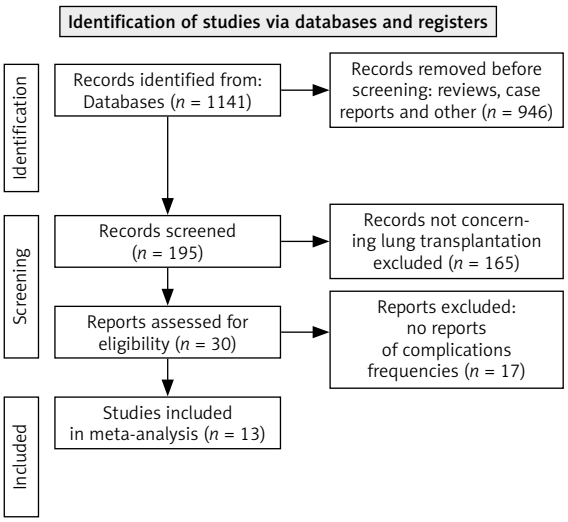

Figure 1. Flow diagram illustrating selection of the articles included in the meta-analysis

Introduction

Lung transplantation (LuTx) is a life-saving surgery performed in patients with end-stage respiratory diseases, such as chronic obstructive pulmonary disease, cystic fibrosis, or pulmonary fibrosis. It is considered as a last-chance treatment when there are no benefits from conventional therapy [1]. Being on the waiting list is associated with deconditioning, which in some cases may require mechanical ventilation (MV). However, MV may provide insufficient gas exchange and it increases the risks of ICU-related complications [2]. Deconditioning may lead to death or worse outcomes after transplantation, due to chest muscle weakening, infections, or other complications. The introduction of extracorporeal membrane oxygenation (ECMO) may prevent deconditioning and ensure better outcomes after transplantation (possible physical therapy and enteral nutrition). ECMO supports cardiac or lung function, depending on the cannulation strategy, and may be applied in veno-venous or veno-arterial modes. Despite the difficulties of conducting ECMO support and its costs, the use of this support device is associated with several complications, such as bleeding, clotting or air bubbles in the cannulas, or acute kidney injury [3].

Aim of the research

The aim of this meta-analysis is to determine the frequencies of ECMO-related complications during bridging to lung transplantation.

Material and methods

This analysis was conducted using the PRISMA protocol (preferred reporting items for systematic reviews and meta-analyses) [4]. A thorough literature search was performed in the Medline and Google Scholar databases. The following terms were used in the search: "Bridging to lung transplantation" and "Bridging to lung transplantation – complications". Inclusion criteria were composed of retrospective or prospective articles in English presenting experience with extracorporeal life support as a bridge to lung transplantation. Studies with or without a control group were included, while complications occurring during the bridging procedure had to be reported. Two independent reviewers screened the titles and abstracts, and the data were extracted manually. Forest plots were generated using Open Meta Analyst software, and heterogeneity was assessed with I^2 statistics.

Results

After a primary search, we identified 1141 results. Ultimately, 13 studies met the inclusion criteria. The search strategy is presented in Figure 1. The characteristics of the included studies together with bridging and short-term LuTx outcomes are presented in Table 1. The included studies were published between 2011 and 2020. Out of 601 patients enrolled to a bridging procedure, 461 underwent lung transplantation. The mean time of extracorporeal life support was 12.4 days. Bleeding and thrombotic complications occurred in 24.6% of the included patients. Cerebrovascular events happened in 4.5% of patients, and acute kidney injury occurred in 13.2% of the included patients (Figures 2, 3).

Discussion

Veno-venous ECMO (VV ECMO) supports respiratory function only while veno-arterial EMCO (VA ECMO) cannulation supports both cardiac and lung function. It can be used as a rescue therapy, for instance, in severe COVID-19 [18]. Another use of this device is to bridge patients to lung transplantation. Deterioration while on a waiting list may cause death before matching with an appropriate organ. The first case of ECMO used as a bridge to lung transplantation was performed in 1977. However, after initial trials it was considered that ECMO is associated with worse outcomes and increased risk of infections and bronchial ischaemia. The first successful reports of bridging to LuTx were performed in the early 1990s [19]. Pulmonary deterioration with hypoxia or hypercapnia despite medical treatment, haemodynamic failure, or pulmonary hypertension are indications to place a patient on ECMO support. On the other hand, not qualifying for LuTx, bacteriemia, or failure of other major organs, among others, are considered as absolute contraindications [20] (Table 2).

The use of ECMO itself is associated with several complications. Exposure of the blood to the non-bio-

Table 1. Characteristics of included studies

Author	Publication year	Country	Study design	Number of patients undergoing bridging procedure	Patients successfully bridged	LuTx outcomes
Hämmäinen P *et al.* [5]	2011	Finland, Sweden	Retrospective	13	12	1-year survival rate: 92 ±7%
Fuehner T *et al.* [6]	2012	Germany	Retrospective	26	20	6-months survival rate: 80%
Lafarge M *et al.* [7]	2013	France	Retrospective	36	30	2-year survival rate: 50.4%
Dellgren G *et al.* [8]	2015	Sweden	Retrospective	20	16	1-year survival rate: 75%
Inci I *et al.* [9]	2015	Switzerland	Prospective	30	26	1-year survival rate: 68%
Biscotti M *et al.* [10]	2017	USA	Retrospective	72	40	1-year survival rate: 90%
Yeo HJ *et al.* [11]	2017	South Korea	Retrospective	19	14	1-year survival rate: 64.3%
Hoetzenecker K *et al.* [12]	2018	Austria	Retrospective	71	63	1-year survival rate: 76%
Hakim AH *et al.* [13]	2018	USA	Retrospective	30	26	1-year survival rate: 74%
Ius F *et al.* [14]	2018	Germany	Retrospective	87	68	1-year survival rate: 79%
Hayanga AJ *et al.* [15]	2018	USA	Retrospective	49	49	1-year survival rate: 82%
Tipograf Y *et al.* [16]	2019	USA	Retrospective	121	70	1-year survival rate: 88%
Ko RE *et al.* [17]	2020	South Korea	Prospective	27	27	6-months survival rate: 66.6%

logic surfaces of the cannulas may lead to adherence of blood cells to the surfaces, platelet activation, and fibrinogen deposition. These outcomes may lead to thrombotic complications, in turn leading to a cerebrovascular event. Therefore, the surfaces of the cannulas are covered in heparin, together with significant intravenous amounts of heparin introduced in anticoagulation protocol. An adequate anticoagulation strategy allows for the balance between thromboembolic and bleeding risks. However, use of heparin may result in heparin-induced thrombocytopaenia (HIT), which develops in approximately 0.5% to 5% of patients. The diagnosis of HIT while on ECMO support is challenging due to platelet consumption and various factors that may contribute to a platelet drop while on a circulatory support device, which might mimic HIT [21]. Alternatively, direct thrombin inhibitors may be introduced (bivalirudin) to prevent HIT. Anticoagulation is monitored using the actual clotting time (ACT), aPPT, PT, or anti-Xa. ACT is available at the bedside and is the most frequently used option with a target range of between 150 and 170 s. However, the results of ACT may be influenced by heparin-independent factors such as hypothermia, thrombocytopaenia, or anaemia [22]. ACT was designed to monitor heparin anticoagulation during cardiopulmonary bypass support, and aPTT has been used to monitor heparin in prophylactic ranges. aPTT is considered as more reliable, but studies comparing ACT and aPTT during ECMO support are inconclusive [23]. According to a recent meta-analysis conducted by Willems *et al.*, anti-Xa-factor versus ACT and aPTT during ECMO is associated with fewer incidents of bleeding, while no increase in thrombotic events was observed [24]. Use of ECMO may also contribute to the development of renal injury and the need for renal replacement therapy. Constant inflammatory processes that take place while on ECMO or due to underlying dis-

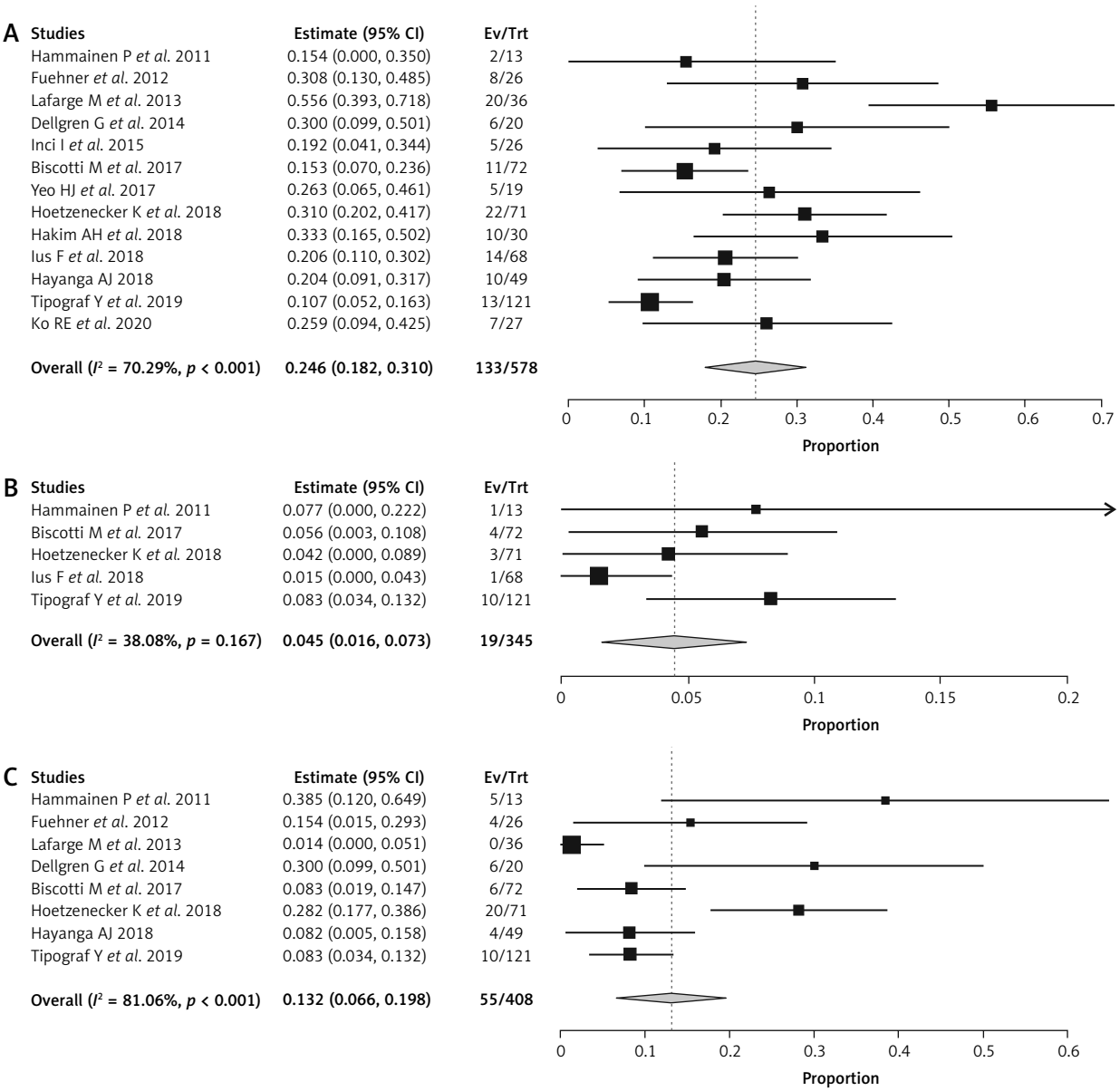

Figure 2. Forest plots of frequencies of complications associated with bridging to lung transplantation. **A** – bleeding and thrombotic complications, **B** – cerebrovascular complications, **C** – renal replacement therapy

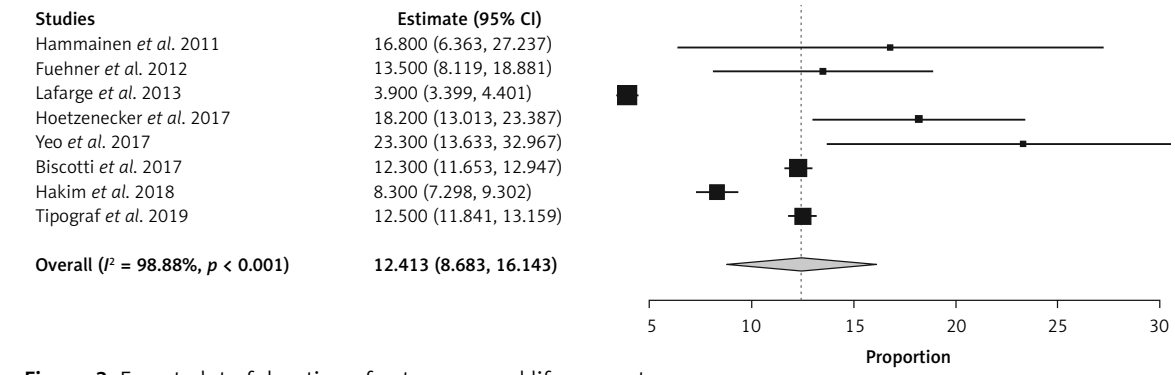

Figure 3. Forest plot of duration of extracorporeal life support

Table 2. Information about ECMO cannulation strategies

ECMO Mode	Drainage	Return	Common indication
VA ECMO (Central)	Inferior vena cava via right atrium	Ascending aorta	Cardiogenic shock
VA ECMO (Peripheral)	Femoral vein	Femoral artery	
VV ECMO	Femoral vein	Internal jugular vein	ARDS

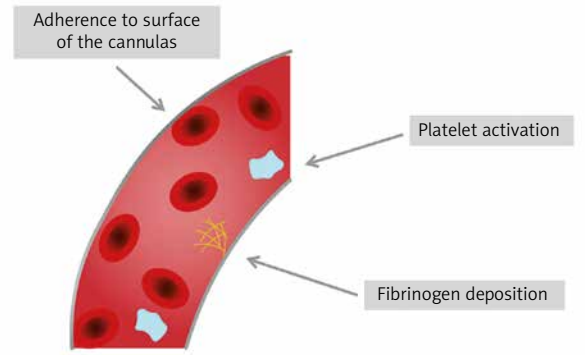

Figure 4. Scheme presenting possible mechanisms of thrombotic complications due to blood exposure to non-biologic surfaces

ease, together with coagulation abnormalities, use of nephrotoxic substances, and ischaemia reperfusion injury may lead to acute kidney injury. Additionally, other complications that occur during ECMO, such as bleeding or thrombosis, might also increase the risk of kidney failure [25]. Renal replacement therapy is thought to prevent metabolic acidosis and hypervolaemia [26]. The occurrence of some complications depends on the cannulation strategy. The harlequin effect is a rare complication that might appear in peripheral VA ECMO support when blood from the native pulmonary circuit returns to the aorta together with oxygenated blood reinfused by the centrifugal pump of ECMO. Consequently, saturation in the lower parts of the body would be normal, while in the right hand it can be as low as 40%. Therefore, hypoperfusion of the upper body together with cerebral and coronary hypoperfusion may develop [27]. Limb ischaemia is another complication that may develop in femoral cannulation. The potential mechanisms include catheter thrombosis, emboli, or obstruction of flow by cannula [28]. Despite such complications, use of extracorporeal support devices is beneficial for some patients. As a rescue therapy, withholding ECMO would cause further deterioration, delisting from lifesaving LuTx and death. As seen in Table 1, most bridging procedures were successful and allowed for subsequent transplantation. This study cannot be considered without several limitations. Firstly, 11 out of 13 of the included studies were retrospective, which introduces the risk that some of the complications could have been underreported. Secondly, patients were not divided into separate groups based on underlying diseases. In addition, in some patients VV ECMO had to be changed to VA ECMO, which includes full anticoagulation (Figure 4).

Conclusions

Bridging to lung transplantation is a procedure that allows critically ill patients to undergo a lifesaving procedure. Our analysis proves that the frequencies of complications that may develop during bridging are non-negligible and may lead to death instead of surgery. Further studies should be focused on improving anticoagulation guidelines.

Conflict of interest

The authors declare no conflict of interest.

References

1. Lesińska A, Piotrowska M, Dec P, Wasilewski P, Kubisa A, Pieróg J, Wójcik N, Czarnecka M, Kubisa B, Grodzki T. Single lung transplantation in a patient with retrospective positive cross-match. Kardiochir Torakochir Pol 2015; 12: 351-354.
2. Javidfar J, Bacchetta M. Bridge to lung transplantation with extracorporeal membrane oxygenation support. Curr Opin Organ Transplant 2012; 17: 496-502.
3. Kubisa B, Dec PŁ, Lesińska AJ, Bocheńska A, Wasilewski P, Feldyk G, Kubisa A, Pieróg J, Bielewicz M, Grodzki T. Veno-venous extracorporeal membrane oxygenation in a patient with severe acute respiratory failure – case report. Kardiochir Torakochir Pol 2015; 12: 65-68.
4. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: 1000097.
5. Hämmäinen P, Schersten H, Lemström K, Riise GC, Kukkonen S, Swärd K, Sipponen J, Silverborn M, Dellgren G. Usefulness of extracorporeal membrane oxygenation as a bridge to lung transplantation: a descriptive study. J Heart Lung Transplant 2011; 30: 103-107.
6. Fuehner T, Kuehn C, Hadem J, Wiesner O, Gottlieb J, Tudorache I, Olsson KM, Greer M, Sommer W, Welte T, Haverich A, Hoeper MM, Warnecke G. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012; 185: 763-768.
7. Lafarge M, Mordant P, Thabut G, Brouchet L, Falcoz PE, Haloun A, Le Pimpec-Barthes F, Maury JM, Reynaud-Gaubert M, Saint-Raymond C, Sage E, Stern M, Thomas P, Castier Y, Dorent R, Mal H. Experience of extracorporeal

membrane oxygenation as a bridge to lung transplantation in France. J Heart Lung Transplant 2013; 32: 905-913.
8. Dellgren G, Riise GC, Swärd K, Gilljam M, Rexius H, Liden H, Silverborn M. Extracorporeal membrane oxygenation as a bridge to lung transplantation: a long-term study. Eur J Cardiothorac Surg 2015; 47: 95-100.
9. Inci I, Klinzing S, Schneiter D, Schuepbach RA, Kestenholz P, Hillinger S, Benden C, Maggiorini M, Weder W. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation: an institutional experience and literature review. Transplantation 2015; 99: 1667-1671.
10. Biscotti M, Gannon WD, Agerstrand C, Abrams D, Sonett J, Brodie D, Bacchetta M. Awake extracorporeal membrane oxygenation as bridge to lung transplantation: a 9-year experience. Ann Thorac Surg 2017; 104: 412-419.
11. Yeo HJ, Lee S, Yoon SH, Lee SE, Cho WH, Jeon D, Kim YS, Kim D. Extracorporeal life support as a bridge to lung transplantation in patients with acute respiratory failure. Transplant Proc 2017; 49: 1430-1435.
12. Hoetzenecker K, Donahoe L, Yeung JC, Azad S, Fan E, Ferguson ND, Del Sorbo L, de Perrot M, Pierre A, Yasufuku K, Singer L, Waddell TK, Keshavjee S, Cypel M. Extracorporeal life support as a bridge to lung transplantation--experience of a high-volume transplant center. J Thorac Cardiovasc Surg 2018; 155: 1316-1328.e1.
13. Hakim AH, Ahmad U, McCurry KR, Johnston DR, Pettersson GB, Budev M, Murthy S, Blackstone EH, Tong MZ. Contemporary outcomes of extracorporeal membrane oxygenation used as bridge to lung transplantation. Ann Thorac Surg 2018; 106: 192-198.
14. Ius F, Natanov R, Salman J, Kuehn C, Sommer W, Avsar M, Siemeni T, Bobylev D, Poyanmehr R, Boethig D, Optenhoefel J, Schwerk N, Haverich A, Warnecke G, Tudorache I. Extracorporeal membrane oxygenation as a bridge to lung transplantation may not impact overall mortality risk after transplantation: results from a 7-year single-centre experience. Eur J Cardiothorac Surg 2018; 54: 334-340.
15. Hayanga AJ, Du AL, Joubert K, Tuft M, Baird R, Pilewski J, Morrell M, D'Cunha J, Shigemura N. Mechanical ventilation and extracorporeal membrane oxygenation as a bridging strategy to lung transplantation: significant gains in survival. Am J Transplant 2018; 18: 125-135.
16. Tipograf Y, Salna M, Minko E, Grogan EL, Agerstrand C, Sonett J, Brodie D, Bacchetta M. Outcomes of extracorporeal membrane oxygenation as a bridge to lung transplantation. Ann Thorac Surg 2019; 107: 1456-1463.
17. Ko RE, Lee JG, Kim SY, Kim YT, Choi SM, Kim DH, Cho WH, Park SI, Jo KW, Kim HK, Paik HC, Jeon K; Korean Organ Transplantation Registry Study Group. Extracorporeal membrane oxygenation as a bridge to lung transplantation: analysis of Korean organ transplantation registry (KOTRY) data. Respir Res 2020; 21: 20.
18. Kiełbowski K, Kubisa B. SARS-CoV-2 and lung transplantation. What do we know? Med Res J 2021; 6: 131-139.
19. Diaz-Guzman E, Hoopes CW, Zwischenberger JB. The evolution of extracorporeal life support as a bridge to lung transplantation. ASAIO J 2013; 59: 3-10.
20. Mattar A, Chatterjee S, Loor G. Bridging to lung transplantation. Crit Care Clin 2019; 35: 11-25.
21. Pollak U. Heparin-induced thrombocytopenia complicating extracorporeal membrane oxygenation support: review of the literature and alternative anticoagulants. J Thromb Haemost 2019; 17: 1608-1622.
22. Nguyen TP, Phan XT, Huynh DQ, Truong HTV, Le YNH, Nguyen TM, Du QQM, Le TP, Truong HN, Ho TT, Pham TTN. Monitoring unfractionated heparin in adult patients undergoing extracorporeal membrane oxygenation (ECMO): ACT, APTT, or ANTI-XA? Crit Care Res Pract 2021; 2021: 5579936.
23. Koster A, Ljajikj E, Faraoni D. Traditional and non-traditional anticoagulation management during extracorporeal membrane oxygenation. Ann Cardiothorac Surg 2019; 8: 129-136.
24. Willems A, Roeleveld PP, Labarinas S, Cyrus JW, Muszynski JA, Nellis ME, Karam O. Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis. Perfusion 2021; 36: 501-512.
25. Ostermann M, Connor M Jr, Kashani K. Continuous renal replacement therapy during extracorporeal membrane oxygenation: why, when and how? Curr Opin Crit Care 2018; 24: 493-503.
26. Worku B, Khin S, Gaudino M, Gambardella I, Iannacone E, Ebrahimi H, Savy S, Voevidko L, Oribabor C, Hadjiangelis N, Desiraju B, Gulkarov I. Renal replacement therapy in patients on extracorporeal membrane oxygenation support: who and how. Int J Artif Organs 2021; 44: 531-538.
27. Contento C, Battisti A, Agrò B, De Marco M, Iaiza A, Pietraforte L, Pisani P, Proietti A, Vitalini E, Montalto A, Musumeci F. A novel veno-arteriovenous extracorporeal membrane oxygenation with double pump for the treatment of Harlequin syndrome. Perfusion 2020; 35: 65-72.
28. Yau P, Xia Y, Shariff S, Jakobleff WA, Forest S, Lipsitz EC, Scher LA, Garg K. Factors associated with ipsilateral limb ischemia in patients undergoing femoral cannulation extracorporeal membrane oxygenation. Ann Vasc Surg 2019; 54: 60-65.

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