Outcomes of patients with initial acute respiratory failure on veno-venous extracorporeal membrane oxygenation (ECMO) requiring additional circulatory support by VVA ECMO

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Abstract

Background: Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is increasingly used to support patients with severe acute respiratory distress syndrome (ARDS). In case of additional cardio-circulatory failure, some experienced centers upgrade the VV-ECMO with an additional arterial backflow cannula (termed VVA-ECMO). Here we analyzed short- and long-term outcome together with potential predictors of mortality.

Methods: Retrospective analysis of outcome in VV ECMO patients with ARDS that received VVA upgrade due to acute cardio-circulatory deterioration from 2008-2021 at three ECMO referral centers.

Results: We identified 73 VVA ECMO patients that either required an upgrade from VV to VVA (n=53) or were directly triple cannulated (n=20), most commonly for concomitant right-sided heart failure. Median (Interquartile Range) age was 49 (28-57) years and SOFA score was 14 (12-17) at VVA ECMO upgrade. ECMO support was required over 12 (6-22) days and ICU length of stay was 32 (16-46) days. Overall ICU mortality was 48% and hospital mortality 51%. Two additional patients died after hospital discharge while the remaining patients survived up to two years (with six patients being lost to follow-up). A SOFA score > 14 at the day of VVA upgrade and higher lactate level were independent predictors of mortality in the multivariate regression analysis.

Conclusions: In this analysis, the use of VVA ECMO in patients with initial ARDS and concomitant cardiocirculatory failure was associated with a hospital survival of about 50%, and most of these patients survived up to 2 years. A SOFA score >14 and elevated lactate levels at the day of VVA upgrade predict unfavorable outcome.

Background

Extracorporeal membrane oxygenation (ECMO) has become an integral part in supporting patients with severe acute respiratory distress syndrome (ARDS) at specialized referral centers, despite equivocal results from the randomized EOLIA trial (1–3). A veno-venous (VV) cannulation technique is primarily employed to correct life-threatening hypoxemia and/or hypercapnia and to enable lung protective ventilation strategies (4). In cases of additive refractory cardio-circulatory deterioration, an upgrade of the VV-system using an additional arterial backflow cannula (termed VVA ECMO) to retain sufficient organ perfusion has been used by experienced centers (5). In such a triple cannulation set-up, VVA ECMO provides both respiratory and hemodynamic support potentially representing a therapeutic option for patients with ARDS who develop secondary severe hemodynamic impairment (or heart failure). However, the literature of ARDS patients with secondary shock supported by VVA ECMO is scarce and confined to case reports (6–9) and small series (10–12). Moreover, patient populations were heterogeneous, including both primary cardiogenic shock patients (starting with VA ECMO) who were later upgraded with an additional venous cannula for treatment of respiratory failure (7,11), as well as patients with primary ARDS (starting on VV ECMO) who were later upgraded to VVA for treatment of secondary cardio-

circulatory failure (9,12). Heterogeneity in cannulation sequences makes conclusions about the outcomes of patients with ARDS that subsequently require an arterial cannulation upgrade difficult. Additionally, no data exist concerning long-term survival of these patients beyond the period of critical care or hospital stay and the extent of chronic organ failure in survivors is unknown.

This retrospective study from three ECMO referral centers aimed at describing the short and long-term outcomes of a homogenous cohort of patients with ARDS receiving VV ECMO support who required an upgrade to VVA ECMO because of secondary cardiocirculatory failure. Additionally, factors associated with poor outcome of VVA ECMO support strategy were analyzed.

Methods

Design and study population

In this retrospective observational cohort study, we aimed to describe characteristics and outcome of patients with ARDS and additional acute cardio-circulatory failure under VVA-ECMO support. Data were collected from the clinical information system by the local study team of two centers in Germany (Hannover Medical School, University Hospital Bonn) and one center in Switzerland (University Hospital Zurich). Inclusion criteria were ARDS with VV-ECMO support and upgrade to VVA ECMO or direct VVA ECMO implantation to treat combined cardiorespiratory failure during the period from January 2008 to September 2021. Patients with primary cardiac failure requiring VA ECMO therapy that later developed respiratory failure and required additional venous cannulation (e.g. upgrade from VA ECMO to VVA ECMO) were excluded from this analyses. Written informed consent for analysis of clinical data was given either by patients or proxy. The study was approved by the institutional review boards at all sites.

Variables and Definitions

We collected demographic data, current illness leading to ECMO support and relevant comorbidities. Respiratory and hemodynamic parameters and the extent of organ support were analyzed at two time points – before VV ECMO implantation and before VVA ECMO upgrade. ECMO configuration and initial settings for VV-ECMO and VVA ECMO were collected. The following outcome parameters were included: ECMO runtime, ICU and hospital length of stay, organ-specific outcomes (lung transplantation, long-term oxygen therapy, chronic kidney disease, congestive heart failure), mortality during ICU- and hospital stay and after one and two years.

ARDS was defined according to the Berlin definition (13). ARDS was further classified as primary, when a direct lung insult was the most likely cause, or as secondary in case of an extra-pulmonary origin of ARDS. Primary ARDS was further divided into identified lung insults according to the RESP-score (14).

The PRESERVE mortality risk score comprises pre-ECMO parameters that were shown to be correlated with mortality as a lower PRESERVE score is associated with a lower risk of death 6 months after ICU discharge (15).

The Sequential Organ Failure Assessment (SOFA) score was used to assess the severity of organ dysfunction and to determine the predicted mortality risk (16). The Vasoactive-inotropic score (VIS) was used to quantify pharmacologic hemodynamic support by different inotropes and vasopressors and to compare it between groups (17).

We used a clinical definition of acute cardio-circulatory deterioration based on evidence of cardiac impairment on echocardiography or extended hemodynamic monitoring including cardiac output measurements, the degree of hemodynamic support, signs of impaired organ perfusion on clinical examination and laboratory parameters such as lactate levels and urine output. Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) were semi quantitatively categorized as good/sustained and reduced, respectively.

Comorbidities were extracted from the clinical information system. For immunosuppression we used the definition of the APACHE II Score (18,19) and defined high-dose steroid therapy as prednisone-equivalent doses of ≥ 7.5 mg / day. Obesity was defined as body-mass index (BMI) of ≥ 30 kg/m^2.

Intracranial hemorrhages were classified as minor when occasionally identified on routine cerebral imaging or as major when requiring neurosurgical intervention or resulting in any neurological deficit. Anemia requiring four or more red blood cell concentrates within 24 hours after VVA-ECMO upgrade was chosen as a clinically relevant cut-off for bleeding complications.

Statistical Analysis

Comparison of variables between the two time-points was performed using the Wilcoxon Signed Rank and Chi-Squared Test, as appropriate. A two-sided p-value < 0.05 was considered statistically significant. Clinically relevant population characteristics and characteristics before VVA ECMO implantation were stratified according to ICU-mortality and compared using Cox proportional-hazards model for 60-day ICU-mortality. Variables with a signification association in the univariate Cox-model were entered into the multivariate Cox-model. Proportional-hazards assumptions were checked visually and with Schoenfeld Individual Test. Ordinal variables were categorized into two groups with the cut-off chosen according to the receiver operating characteristic (ROC) curve and Youden Index. After model reduction method and input of interaction terms, variables were only retained if they were found to contribute to the model. Survival plots were generated for overall survival and 60-day survival stratified by variables in the multivariate Cox-model using the best cut-off chosen with ROC curve and Youden Index. Missing data are indicated in Supplementary file **Tables S1** to **S4**.

Results

Population characteristics

In the three study centers, 73 patients met the inclusion criteria and were analyzed. In 53 (73%) patients VV ECMO was upgraded to VVA ECMO after a median of 12 (Interquartile Range, 0–96) hours. In 20

(27%) patients, primary VVA ECMO support was applied due to simultaneous presence of respiratory and cardio-circulatory failure. Most common reason for respiratory failure was primary ARDS (n = 65, 89%), particularly bacterial pneumonia (n = 33, 47%). **Table 1** summarizes the patient characteristics.

The most common reason for upgrading to VVA ECMO was right-sided heart failure. Reduced right ventricular systolic function was observed in 64% of patients before VVA-ECMO upgrade (25 out of 39 patients with available data). A trend towards higher vasopressor and inotropic doses was observed before VVA ECMO upgrade, represented by a numerically higher median vasoactive-inotropic score (VIS) of 27 (0–77) at VV-ECMO implantation and 53 (12–123) at VVA ECMO upgrade (p = 0.054). Epinephrine was used significantly more frequently before VVA ECMO (n = 18, 25%) than before VV ECMO (n = 3, 6%) (p = 0.014). Eleven (15%) patients had undergone cardiopulmonary resuscitation before VVA ECMO implantation. Clinical condition and organ support before VV and VVA ECMO are summarized in **Table 2.**

ECMO configurations and complications

The femoral site for venous drainage (n = 66, 90%) and the jugular site for venous return (n = 63, 86%) was the most frequent configuration of VV ECMO. Cannulation of both the femoral artery (n = 41, 56%) and the subclavian artery (n = 32, 44%) where used in VVA ECMO upgrade. The most frequent complication following ECMO insertion was anemia requiring four or more red blood cell concentrates in 24 hours (n = 38, 52%). ECMO configurations and complications are summarized in **Table 3**.

Outcome

Thirty-five (48%) VVA ECMO patients died during their ICU stay. Two patients (3%) died during the later hospital course. Of those patients, one died of pericardial tamponade and another patient died of recurrent respiratory failure due to progressive lung allograft dysfunction. After hospital discharge another two patients (3%) died during a two-year follow-up. Given that in six (8%) patients follow-up time was less than two years, an overall two year-mortality of 58% (39 of 67) was observed. Follow-up data and organ-specific outcomes are summarized in **Table 4**.

Predictors of ICU mortality

Stratification of predictive variables at the time of VV ECMO upgrade to VVA ECMO and results from Cox regression for 60-day ICU-mortality are shown in Fig. 1. Of the variables that showed a significant association with 60-day ICU-mortality, five variables (SOFA score, lactate, VIS, renal replacement therapy and pH) were entered into the multivariate analysis. The PaO_2/FiO_2 ratio was excluded because it is not a reliable parameter for oxygen requirements under ECMO support. In the final multivariable model, SOFA score > 14 (Hazard ratio 4.28; 95% CI, 1.55–11.80, p = 0.005) and lactate level (Hazard ratio 1.004; 95% CI, 1.000-1.008), p = 0.049) were significantly associated with 60-day ICU-mortality. The results of the of the Cox proportional-hazards model are provided in **Table 5**. Survival plots stratified for these predictors are shown in Fig. 2 and **Figure S1**.

Discussion

In the present retrospective study, patients with initial ARDS on VV ECMO support who required additional VVA ECMO support secondary to acute cardio-circulatory failure had an encouraging ICU survival rate of 52%. Two patients died during the later hospital course thereafter and only an additional two died in the two-years follow-up. Besides this unexpected high long-term survival only a minority of survivors suffered from relevant persistent organ dysfunction. A SOFA-score of more than 14 at the day of VVA-ECMO upgrade independently predicted an unfavorable outcome in these critically ill patients.

Previous studies and case series have found survival rates of patients with VVA ECMO support ranging from 39–75% (10–12,20–25). This wide range might be attributable to heterogeneity of the patient cohorts, including those with cardiogenic shock requiring initial VA ECMO and later venous ECMO upgrade grouped together with ARDS patients on initial VV ECMO support with a later arterial upgrade. Furthermore, the number of investigated patients in these studies (10,12,22–24) was small (1–21 patients), with high risk of bias, which might contribute to the wide range of survival outcomes. The registry of the Extracorporeal Life Support Organization (ELSO) showed a survival rate of 42% in patients requiring VVA ECMO support (26). The reason for the more favorable outcome of patients in the current study might be explained by a more stringent selection of patients and by a homogenization focusing on a group with primary severe acute respiratory failure and a subsequent or concomitant cardio-circulatory deficit.

After hospital discharge, only 2 patients died during the 2-year follow-up, and survivors possessed a surprisingly good organ function. Consistently, previous studies demonstrated good long-term outcomes after classical ECMO support (i.e VV- or VA-cannulation) with most patients' health almost restored to their previous level (3,27,28). VA ECMO patients seem to have a worse long-term health status, what might be explained by a more serious initial clinical condition (e.g., acute (on chronic) heart failure, eCPR) (27). The fact that long-term outcome presented in this study is comparable with outcome of individuals after classical VA or VV EMCO support (3,27,28) shows that VVA ECMO upgrading is feasible and should be considered for appropriate patients.

Identifying patients who will benefit from VVA ECMO upgrade remains a challenge. We showed that the outcome of VVA patients significantly worsened when their SOFA score exceeded 14 at the time of VVA consideration. While the SOFA score was initially developed to describe the degree of organ function (16), it is increasingly used to predict mortality for patients with various conditions in the ICU (29,30). While reliable data for triple cannulated VVA ECMO patients are missing, a recent study found a higher SOFA score in non-survivors compared to survivors before classical VV ECMO implantation, but with only moderate prognostic performance (31). In contrast, there was no difference in VA ECMO patients in terms of survival reported in the same study (31). Besides the prognostic value of the SOFA-score as a global marker of organ dysfunction, we found that parameters of hemodynamic compromise, e.g., high serum levels and an increased need for vasopressors, were associated with ICU-mortality. While the significance of elevated serum lactate on outcome of patients who are commenced on either VA- or VV ECMO support is widely appreciated (32–34), this is to our knowledge the first study that extents the value of these clinical parameters to prognosis prediction before VVA-cannulation. We found that elevated lactate levels

independently predicted ICU-mortality. Therefore, the clinical decision for VVA ECMO implementation should not rely solely on a risk score such as SOFA but be incorporated in the complex interaction of clinical status including lactate levels, need for vasopressor support and assessment of renal function in addition to clinical experience.

When patients develop cardio-circulatory failure while under VV ECMO support, an alternative to VVA upgrade might be converting from VV to VA cannulation. Falk et al. have shown that patients who required a conversion from VV to VA ECMO had a higher mortality than patients with initial VA cannulation (35). Similarly, another study showed that initial VA cannulation in ARDS patients is an independent predictor for increased mortality (36). In the current work, patients were approximately half of their overall ECMO runtime on VVA configuration, suggesting that the need for respiratory support outlives the requirement for cardio-circulatory support. Since VA ECMO support increases the risk for bleeding (37), renal failure, vascular complications and the Harlequin syndrome (38), downgrading VVA to VV cannulation, when hemodynamic stability has reached, might improve outcome compared to continued VA-ECMO support. In line with this approach, Stöhr et al. showed a lower 30-day-mortality for ARDS patients with VVA cannulation when compared to VA or VV ECMO support (10).

Limitations of the present study are the retrospective design including missing data on follow-up and hemodynamic monitoring. On the other hand, in only six patients the follow-up time was less than two years. The analysis of three high-volume centers data might provide generalized recommendations to ECMO providers. The design also limits the possibility of objectifying the individual clinical decisions that led to VVA ECMO upgrade/cannulation. Furthermore, patients were recruited over a period of 13 years in which the therapy of ARDS and handling of ECMO support has evolved (39), which might have influenced the outcome. Regarding the organ specific outcomes, patients with worse outcomes might have been more likely to drop out of the follow up.

Conclusions

In summary, this work demonstrated in the currently largest cohort of VVA ECMO patients coming from VV ECMO due to initial ARDS that approximately every second patient survived until hospital discharge. This encouraging survival rate was preserved over a two-year period where only a minority suffered from relevant organ dysfunction. Thus, an arterial upgrade of VV ECMO patients suffering from ARDS to VVA ECMO should not be rendered as futile *per se*. In our cohort, a SOFA score > 14 and elevated lactate levels at the time of VVA upgrade evaluation predicted unfavorable outcome.

Abbreviations

ARDS Acute respiratory distress syndrome

BMI body-mass index

ECMO Extracorporeal membrane oxygenation

ELSO Extracorporeal Life Support Organization

ICU Intensive care unit

ROC receiver operating characteristic

SOFA Sequential Organ Failure Assessment

VA veno-arterial

VIS Vasoactive-inotropic score

VV veno-venous

VVA veno-venous arterial

Declarations

Ethics approval and consent to participate

All analyses performed involving human data were in accordance with the ethical standards of the institutional and national research committee of Switzerland and Germany, with the 1964 Helsinki Declaration and its latest amendments and with the guidelines on Good Clinical Practice issued by the European Medicines Agency. The study was approved from all three ethics committees responsible for the trial centers (ZH 2021-01804, MHH #9720 BO K 2021, Bonn 488/21).

Consent for publication

Not applicable.

Availability of data and materials

Authors can confirm that all relevant data are included in the article and/or its supplementary information files. The corresponding author may provide specified analyses or fully de-identified parts of the dataset upon reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

RE, LW, BS, AR, PW, SD; CB and KS conceived and designed the research project. RE, LW, AR, RA and PW handled the data acquisition. RE, BS, DH, PDWG, SD, CB and KS analysed the data. All authors substantially contributed to the interpretation of the data. RE, LW, AR, BS, CB, SD and KS wrote the first draft of the manuscript. MMH, RE, LW, BS, RA, DAH, JCS, CCG, CP, JB, TW, PW, SD, CB and KS critically revised the draft. All authors read and approved the final manuscript. Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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References

1. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018 May 24;378(21):1965–75.
2. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. Lancet. 2021 Oct 2;398(10307):1230–8.
3. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351–63.
4. Serpa Neto A, Schmidt M, Azevedo LCP, Bein T, Brochard L, Beutel G, et al. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis : Mechanical ventilation during ECMO. Intensive Care Med. 2016 Nov;42(11):1672–84.
5. Napp LC, Kühn C, Hoeper MM, Vogel-Claussen J, Haverich A, Schäfer A, et al. Cannulation strategies for percutaneous extracorporeal membrane oxygenation in adults. Clin Res Cardiol. 2016;105:283–96.
6. Madershahian N, Wittwer T, Strauch J, Franke UFW, Wippermann J, Kaluza M, et al. Application of ECMO in multitrauma patients with ARDS as rescue therapy. J Card Surg. 2007 Jun;22(3):180–4.
7. Choi JH, Kim SW, Kim YU, Kim S-Y, Kim K-S, Joo S-J, et al. Application of veno-arterial-venous extracorporeal membrane oxygenation in differential hypoxia. Multidiscip Respir Med. 2014;9(1):55.

8. Lee JH, Park JH, Min HK, Seo G-W, Song P-S, Her C, et al. Veno-veno-arterial ECMO support for acute myocarditis combined with ARDS: a case report. Int J Artif Organs. 2015 Dec;38(12):667–70.
9. Jeon YJ, Byun JH, Hwang SW, Park JH, Lee JH. Successful Application of Veno-Venoarterial Extracorporeal Membrane Oxygenation for Acute Exacerbation of Asthma Followed by Stress Cardiomyopathy. Yonsei Med J. 2016 Mar;57(2):536–7.
10. Stöhr F, Emmert MY, Lachat ML, Stocker R, Maggiorini M, Falk V, et al. Extracorporeal membrane oxygenation for acute respiratory distress syndrome: is the configuration mode an important predictor for the outcome? Interact Cardiovasc Thorac Surg. 2011 May;12(5):676–80.
11. Biscotti M, Lee A, Basner RC, Agerstrand C, Abrams D, Brodie D, et al. Hybrid configurations via percutaneous access for extracorporeal membrane oxygenation: a single-center experience. ASAIO J. 2014 Dec;60(6):635–42.
12. Ius F, Sommer W, Tudorache I, Avsar M, Siemeni T, Salman J, et al. Veno-veno-arterial extracorporeal membrane oxygenation for respiratory failure with severe haemodynamic impairment: technique and early outcomes. Interact Cardiovasc Thorac Surg. 2015 Jun;20(6):761–7.
13. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526–33.
14. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med. 2014 Jun 1;189(11):1374–82.
15. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt C-E, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med. 2013 Oct;39(10):1704–13.
16. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996 Jul;22(7):707–10.
17. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive–inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass*: Pediatric Critical Care Medicine. 2010 Mar;11(2):234–8.
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818–29.
19. Headley J, Theriault R, Smith TL. Independent validation of APACHE II severity of illness score for predicting mortality in patients with breast cancer admitted to the intensive care unit. Cancer. 1992 Jul 15;70(2):497–503.
20. Werner NL, Coughlin M, Cooley E, Haft JW, Hirschl RB, Bartlett RH, et al. The University of Michigan Experience with Veno-Venoarterial Hybrid Mode of Extracorporeal Membrane Oxygenation. ASAIO J. 2016 Oct;62(5):578–83.

21. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg. 2014 Feb;97(2):610–6.
22. Vogel DJ, Murray J, Czapran AZ, Camporota L, Ioannou N, Meadows CIS, et al. Veno-arterio-venous ECMO for septic cardiomyopathy: a single-centre experience. Perfusion. 2018 May;33(1_suppl):57–64.
23. Yeo HJ, Jeon D, Kim YS, Cho WH, Kim D. Veno–veno–arterial extracorporeal membrane oxygenation treatment in patients with severe acute respiratory distress syndrome and septic shock. Crit Care. 2015 Dec;20(1):28.
24. Cakici M, Gumus F, Ozcinar E, Baran C, Bermede O, Inan MB, et al. Controlled flow diversion in hybrid venoarterial–venous extracorporeal membrane oxygenation. Interactive CardioVascular and Thoracic Surgery. 2018 Jan 1;26(1):112–8.
25. Blandino Ortiz A, Belliato M, Broman LM, Lheureux O, Malfertheiner MV, Xini A, et al. Early Findings after Implementation of Veno-Arteriovenous ECMO: A Multicenter European Experience. Membranes (Basel). 2021 Jan 22;11(2):81.
26. Extracorporeal Life Support Organization. ECLS Registry Report: International Summary July, 2019 [Internet]. 2019 Jul [cited 2021 Oct 22]. Available from: http://www.elso.org/Portals/0/Files/Reports/2019/International%20Summary%20July%202019.pdf
27. Combes A, Leprince P, Luyt C-E, Bonnet N, Trouillet J-L, Léger P, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock*: Critical Care Medicine. 2008 May;36(5):1404–11.
28. Lindén VB, Lidegran MK, Frisén G, Dahlgren P, Frenckner BP, Larsen F. ECMO in ARDS: a long-term follow-up study regarding pulmonary morphology and function and health-related quality of life. Acta Anaesthesiologica Scandinavica. 2009 Apr;53(4):489–95.
29. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001 Oct 10;286(14):1754–8.
30. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: A systematic review. Crit Care. 2008;12(6):R161.
31. Fisser C, Rincon-Gutierrez LA, Enger TB, Taccone FS, Broman LM, Belliato M, et al. Validation of Prognostic Scores in Extracorporeal Life Support: A Multi-Centric Retrospective Study. Membranes (Basel). 2021 Jan 24;11(2):84.
32. Chen W-C, Huang K-Y, Yao C-W, Wu C-F, Liang S-J, Li C-H, et al. The modified SAVE score: predicting survival using urgent veno-arterial extracorporeal membrane oxygenation within 24 hours of arrival at the emergency department. Crit Care. 2016 Oct 22;20(1):336.
33. Bonizzoli M, Lazzeri C, Cianchi G, Boddi M, Cozzolino M, Di Valvasone S, et al. Serial Lactate Measurements as a Prognostic Tool in Venovenous Extracorporeal Membrane Oxygenation Support. Ann Thorac Surg. 2017 Mar;103(3):812–8.

34. Shah N, Said AS. Extracorporeal Support Prognostication-Time to Move the Goal Posts? Membranes (Basel). 2021 Jul 15;11(7):537.
35. Falk L, Fletcher-Sandersjöö A, Hultman J, Broman LM. Conversion from Venovenous to Venoarterial Extracorporeal Membrane Oxygenation in Adults. Membranes. 2021 Mar;11(3):188.
36. Kon ZN, Bittle GJ, Pasrija C, Pham SM, Mazzeffi MA, Herr DL, et al. Venovenous Versus Venoarterial Extracorporeal Membrane Oxygenation for Adult Patients With Acute Respiratory Distress Syndrome Requiring Precannulation Hemodynamic Support: A Review of the ELSO Registry. Ann Thorac Surg. 2017 Aug;104(2):645–9.
37. Delius R, Anderson H, Schumacher R, Shapiro M, Otsu T, Toft K, et al. Venovenous compares favorably with venoarterial access for extracorporeal membrane oxygenation in neonatal respiratory failure. J Thorac Cardiovasc Surg. 1993 Aug;106(2):329–38.
38. Rupprecht L, Lunz D, Philipp A, Lubnow M, Schmid C. Pitfalls in percutaneous ECMO cannulation. Heart Lung Vessel. 2015;7(4):320–6.
39. Griffiths MJD, McAuley DF, Perkins GD, Barrett N, Blackwood B, Boyle A, et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Respir Res. 2019;6(1):e000420.

Tables

Table 1: Patient characteristics

Values are expressed as n (%) or median (interquartile range). ARDS: acute respiratory distress syndrome, COPD: chronic obstructive pulmonary disease.

Variable	Overall (n=73)
Age, years	49 (28-57)
Sex, female	24 (33)
Body-mass index, kg/m^2	25 (22-30)
ARDS, primary	65 (89)
Resp-Score diagnosis	
Bacterial pneumonia	33 (47)
Viral pneumonia	11 (16)
Aspiration pneumonitis	7 (10)
Other acute respiratory diagnosis	10 (14)
Non-respiratory and chronic respiratory diagnoses	8 (11)
Trauma / burn	1 (1)
PRESERVE Score	4 (3-6)
Sepsis	58 (79)
Comorbidities	
Adipositas	19 (26)
COPD	10 (14)
Arterial hypertension	25 (34)
Coronary artery disease	5 (7)
Congestive heart failure	4 (5)
Diabetes mellitus	6 (8)
Chronic kidney disease	6 (8)
Immunosuppression	21 (29)
Solid organ transplantation	8 (11)

Table 2: Clinical condition and organ support before VV ECMO implantation and VVA ECMO upgrade

Values are expressed as n (%) or median (interquartile range). Doses of norepinephrine, epinephrine and dobutamine refer to the median dose of patients that received the drug.

CPR: cardiopulmonary resuscitation, FiO_2: fraction of inspired oxygen, HFOT: high-flow oxygen therapy, ICU: intensive care unit, iMV: invasive mechanical ventilation, LVEF: left ventricular ejection fraction (as

estimated by echocardiography), NIV: non-invasive ventilation, $PaCO_2$: partial pressure of carbon dioxide, PaO_2: partial pressure of oxygen, PEEP: positive end-expiratory pressure, RVEF: right ventricular ejection fraction (as estimated by echocardiography), SaO_2: arterial oxygen saturation, SOFA: Sequential Organ Failure Assessment.

Variables	Time of VV ECMO implantation (N=53)	Time of VVA ECMO upgrade (N=73)	p-value
Primary VVA ECMO		20 (27)	
VV to VVA ECMO cannulation, hours		12 (0-96)	
CPR before VVA ECMO		11 (15)	
Hospital admission to cannulation, days	6 (3-12)	11 (4-20)	0.027
ICU admission to cannulation, days	3 (1-8)	6 (2-13)	0.027
iMV to cannulation, days	1 (0-6)	3 (1-11)	0.011
SOFA score	13 (11-16)	14 (12-17)	0.179
Respiratory support			0.394
iMV	48 (92)	71 (97)	
NIV / HFOT	4 (8)	2 (3)	
PEEP, cmH_2O	14 (11-16)	13 (10-16)	0.579
Minute ventilation, L/min	9.0 (7.0-11.0)	4.6 (2.7-8.1)	<0.001
Plateau pressure, cmH_2O	30 (28-34)	28 (25-30)	0.046
SaO_2, %	89 (82-92)	89 (79-93)	0.949
PaO_2/FiO2, mmHg	71 (54-92)	67 (57-98)	0.876
$PaCO_2$, mmHg	60 (51-68)	47 (41-55)	<0.001
pH	7.23 (7.16-7.34)	7.31 (7.19-7.38)	0.054
Lactate, mmol/L	2.1 (1.3-3.7)	2.5 (1.6-5.9)	0.104
Inhalative nitric oxide	16 (32)	25 (36)	0.776
Norepinephrine	38 (76)	64 (89)	0.1
Norepinephrine dose, mg/kg/min	0.50 (0.23-0.89)	0.53 (0.19-1.08)	0.912
Epinephrine	3 (6)	18 (25)	0.014
Epinephrine dose, mg/kg/min	0.56 (0.30-0.78)	0.25 (0.08-0.64)	0.695
Dobutamine	7 (14)	22 (31)	0.066

Dobutamine dose, mg/kg/min	2.05 (1.77-4.69)	3.33 (2.04-4.15)	0.878
Vasoactive-inotropic score	27 (0-77)	53 (12-123)	0.054
LVEF			0.380
good/sustained	22 (88)	28 (76)	
reduced	3 (12)	9 (24)	
RVEF			0.001
good/sustained	20 (80)	14 (36)	
reduced	5 (20)	25 (64)	
Renal replacement therapy (n)	19 (37)	32 (44)	0.526

Table 3: ECMO configuration, setting and complications

Values are expressed as n (%) or median (interquartile range). FsO2: Sweep gas inlet oxygen fraction, major intracranial hemorrhage: requiring neurosurgical intervention or resulting in any neurological deficit, minor intracranial hemorrhage: occasionally identified on cerebral imaging, rpm: revolutions per minute.

Variable	Overall
ECMO cannulation (N = 73)	
Venous drainage site	
Femoral	66 (90)
Jugular	7 (10)
Venous return site	
Femoral	10 (14)
Jugular	63 (86)
Arterial return site	
Femoral	41 (56)
Subclavian	32 (44)
Antegrade leg perfusion cannula (% of patients with femoral cannulation)	28 (70)
VV ECMO settings (N = 53)	
Pump speed, rpm	3000 (2885-3345)
Blood flow, L/min	4.0 (3.1-4.6)
Sweep gas flow, L/min	3 (2-4)
FsO2	1 (1-1)
VVA ECMO settings (N = 73)	
Pump speed, rpm	3580 (3222-3938)
Total blood flow, L/min	5.0 (4.4-5.9)
Arterial blood flow, L/min	2 (2-3)
Sweep gas flow, L/min	6 (4-8)
Complications of VVA ECMO therapy (N = 73)	
Complications during insertion	19 (26)
Complications during insertion requiring surgery	17 (23)
≥4 red blood cell concentrates / 24 hours	38 (52)
Major intracranial hemorrhage	5 (7)
Minor intracranial hemorrhage	5 (7)
Thromboembolic events	14 (19)

Leg ischemia	7 (10)
Other complications	13 (18)

Table 4: Outcome and Follow-up

Values are expressed as n (%) or median (interquartile range).

ICU: intensive care unit, KDIGO: Kidney Disease: Improving Global Outcomes, NYHA: New York Heart Association.

Variables	Overall (N=73)
ECMO runtime, days	12 (6-22)
VVA ECMO runtime, days	6 (3-9)
ICU length of stay, days	32 (16-46)
Hospital length of stay, days	44 (24-78)
ICU mortality	35 (48)
Hospital mortality	37 (51)
Lung Transplantation	12 (16)
Mortality at 1 year	39 (57)
Mortality at 2 years	39 (58)
Organ specific outcome at 2 years (N = 28)	
Long-term oxygen therapy	1 (4)
Chronic kidney disease	
KDIGO grade ≤3	25 (89)
KDIGO grade 4-5	1 (4)
unknown	2 (7)
Congestive heart failure	
NYHA stage ≤2	21 (75)
NYHA stage 3-4	0 (0)
unknown	7 (25)

Table 5: Cox proportional-hazards model for 60-day ICU-mortality

Values are expressed as Hazard ratio (HR) with 95% confidence interval (CI) and p-value. Variable were taken from time of VVA-cannulation. SOFA: Sequential Organ Failure Assessment, VIS: Vasoactive-inotropic score

	Univariate			Multivariate		
Variable	HR	CI 95%	p-value	HR	CI 95%	p-value
SOFA score > 14	4.139	1.997-8.576	<0.001	4.275	1.548-11.805	0.005
Lactate, mmol/L	1.006	1.003-1.009	<0.001	1.004	1.000-1.008	0.049
VIS	1.004	1.000-1.007	0.034	1.001	0.997-1.006	0.632
Renal replacement therapy	2.107	1.069-4.153	0.031	0.830	0.328-2.101	0.694
pH	0.100	0.010-0.962	0.046	-	-	-

Figures

Variables	Survivors (N=39)	Non−survivors (N=34)	HR (95% CI)	P−value
Age, years	46 (29−55)	49 (26−58)	1.01 (0.99−1.03)	0.379
Sex, female	15 (38)	9 (26)	0.68 (0.32−1.45)	0.314
Body mass index, kg/m^2	26 (22−30)	24 (22−29)	0.99 (0.94−1.03)	0.529
Primary ARDS	35 (90)	30 (88)	0.89 (0.31−2.52)	0.823
Resp−Score Diagnosis, bacterial pneumonia*	15 (39)	18 (56)		
viral pneumonia vs. *	6 (16)	5 (16)	0.90 (0.33−2.43)	0.838
aspiration pneumonitis vs. *	3 (8)	4 (12)	0.93 (0.31−2.74)	0.893
other acute respiratory diagnosis vs. *	8 (21)	2 (6)	0.30 (0.07−1.28)	0.103
non/chronic respiratory diagnosis vs. *	5 (13)	3 (9)	0.59 (0.17−2.01)	0.402
Hosp. admission to VVA cannulation, days	9 (4−18)	12 (5−20)	1.00 (1.00−1.01)	0.597
ICU admission to VVA cannulation, days	6 (2−12)	6 (2−13)	1.00 (0.97−1.03)	0.840
iMV to VVA cannulation, days	3 (1−10)	4 (1−11)	1.01 (0.97−1.05)	0.671
VV cannulation to VVA cannulation, hours	7 (0−72)	42 (2−96)	1.00 (1.00−1.00)	0.891
SOFA Score	13 (12−14)	16 (12−18)	1.15 (1.05−1.26)	0.002
CPR before VVA cannulation	4 (10)	7 (21)	1.72 (0.75−3.96)	0.202
PEEP, cmH_2O	12 (8−15)	13 (10−16)	1.01 (0.95−1.08)	0.715
Minute ventilation, L/min	4.3 (2.6−9.4)	4.7 (2.8−5.3)	0.91 (0.82−1.01)	0.082
Plateau pressure, cmH_2O	30 (23−32)	27 (25−29)	0.96 (0.89−1.04)	0.284
SaO_2, %	89 (80−92)	90 (76−94)	1.00 (0.98−1.01)	0.391
PaO_2/FiO_2, mmHg	60 (56−75)	81 (61−124)	1.01 (1.00−1.01)	0.001
$PaCO_2$, mmHg	48 (41−57)	45 (41−51)	0.99 (0.96−1.02)	0.559
pH	7.35 (7.25−7.4)	7.28 (7.16−7.36)	0.10 (0.01−0.96)	0.046
Lactate, mmol/L	2.1 (1.4−3.8)	4.4 (1.9−7.2)	1.14 (1.07−1.22)	<0.001
Norepinephrine	32 (82)	32 (97)	5.16 (0.70−37.78)	0.106
Norepinephrine dose, mcg/kg/min	0.35 (0.16−0.83)	0.57 (0.25−1.31)	1.54 (1.03−2.31)	0.034
Epinephrine	6 (15)	12 (36)	2.17 (1.06−4.42)	0.033
Epinephrine dose, mcg/kg/min	1 (0.28−1.85)	0.12 (0.08−0.46)	0.30 (0.07−1.28)	0.105
Dobutamine	6 (15)	16 (48)	3.20 (1.61−6.35)	0.001
Dobutamine dose, mcg/kg/min	2.15 (1.18−4.37)	3.52 (2.29−3.88)	1.03 (0.77−1.38)	0.853
Vasoactive inotropic score	31 (8−103)	69 (28−166)	1.00 (1.00−1.01)	0.034
Nitric oxide	15 (42)	10 (30)	0.64 (0.30−1.35)	0.241
Renal replacement therapy	13 (33)	19 (56)	2.11 (1.07−4.15)	0.031
LVEF − good/sustained*	14 (82)	14 (70)		
reduced vs. *	3 (18)	6 (30)	1.46 (0.56−3.79)	0.442
RVEF − good/sustained*	9 (53)	5 (23)		
reduced vs. *	8 (47)	17 (77)	2.37 (0.87−6.43)	0.091

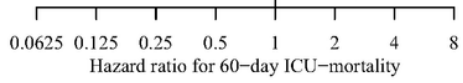

Figure 1

Stratification of predictive variables at VVA ECMO cannulation

Left: Predictive variables at the time of VVA ECMO cannulation stratified in survivors and non-survivors according to 60-day ICU mortality. Values are expressed as n (%) or median (interquartile range).

Right: Forest-plot and results Cox regression for 60-day ICU-mortality. Values are expressed as Hazard ratio (HR) with 95% confidence interval (CI) and p-value.

ARDS: acute respiratory distress syndrome, CPR: cardiopulmonary resuscitation, FiO_2: fraction of inspired oxygen, Hosp.: Hospital, ICU: intensive care unit, iMV: invasive mechanical ventilation, LVEF: left ventricular ejection fraction, $PaCO_2$: partial pressure of carbon dioxide, PaO_2: partial pressure of oxygen, PEEP: positive end-expiratory pressure, RVEF: right ventricular ejection fraction, SaO_2: arterial oxygen saturation, SOFA: Sequential Organ Failure Assessment

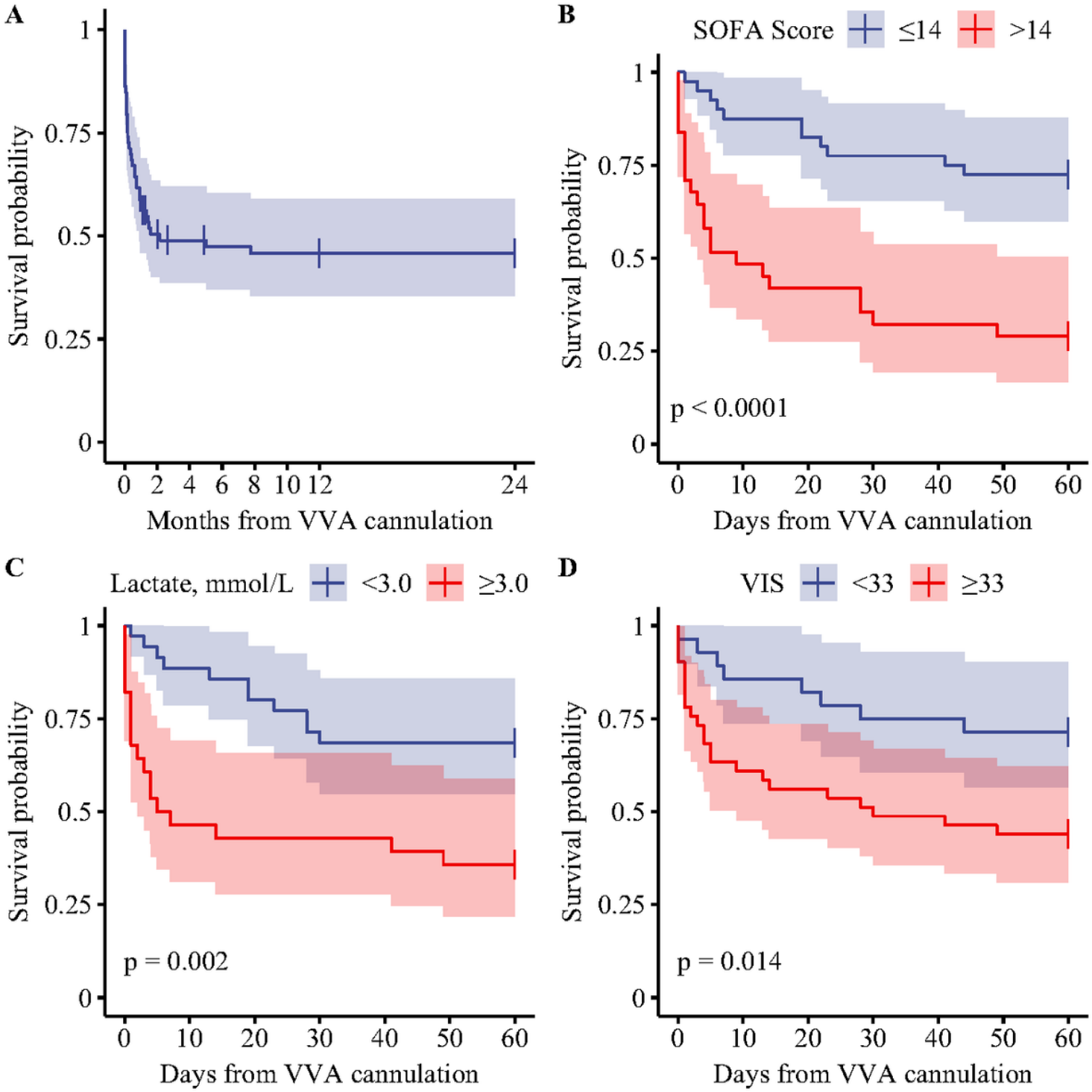

Figure 2

Survival function from VVA ECMO cannulation

A) Overall survival, B-D) stratified survival function for 60-day ICU mortality. SOFA: Sequential Organ Failure Assessment, VIS: Vasoactive inotropic score

Supplementary Files

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