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ECMO without anticoagulation in patients with disease-related severe thrombocytopenia: Feasible but futile?

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Abstract

Severe thrombocytopenia poses a high risk for bleeding thus representing a relative contraindication for anticoagulation and therefore ECMO. We herein report on a series of immunocompromised patients with severe thrombocytopenia undergoing long-term ECMO without systemic anticoagulation.

We retrospectively identified 7 adult patients with anticoagulation withdrawal for ≥ 3 days (range 5-317) during venovenous ECMO therapy due to thrombocytopenia < 50 G / L treated in a university-affiliated hospital from January 2013 until April 2017. All ECMO systems used were heparin coated. Overall, 530 ECMO-days were observed, 404 (76%) of them without systemic anticoagulation. Platelet count during ECMO treatment was 24 G/L (median, range 1-138), ECMO duration was 35 days (5-317), and ECMO was run without any anticoagulation for 20 days (5-317). Altogether, five clotting events were seen leading to oxygenator exchanges. Bleeding was common including one fatal intracerebral haemorrhage. Altogether, 29 platelet concentrates per patient (7-207) were administered, which corresponds to 0.8 per day (0.6 -

1.3). One patient survived ICU and hospital.

In patients with thrombocytopenia ECMO can be run without anticoagulation even for considerably long periods of time. Bleeding remains common, while clotting events seem to be rare. However, prognosis of this patient population undergoing ECMO support seems grim.

Keywords

venovenous, ECMO, ECLS, thrombocytopenia, anticoagulation withdrawal

Background

Veno-venous extracorporeal gas exchange is increasingly used as supportive therapy in severe respiratory failure. The technological progress during the last decades has resulted in more biocompatible and effective systems minimizing invasiveness and suppressing cellular activation. However, the physiologic hemostatic balance is shifted towards a hypercoagulative state due to the continuous contact between the artificial surfaces of the extracorporeal life support (ECLS) system and the blood. This results in activation of inflammatory and procoagulatory pathways leading to a prothrombotic state increasing the risk for thrombosis. [1, 2] Thus, administration of anticoagulatory therapy is still a therapeutic cornerstone to prevent system breakdown owing to clotting of the membrane, the centrifugal pump, the tubing or cannulae. [1, 3] Heparin coating has enabled lowering anticoagulation targets to the currently recommended activated partial thromboplastin time (aPTT) levels of 1.5-2.0 times baseline values, thus lowering the risk for bleeding complications. [3] However, hemorrhagic diathesis remains a commonly observed side effect in ECLS patients and has been associated with increased mortality. [4-6] Intracranial bleeding (ICB) has decreased over time but it is still

particularly dreaded as prognosis is unfavorable. [7, 8] The actual role of systemic anticoagulation as a risk factor for ICB remains unclear. [9]

Thrombocytopenia itself poses a high risk for bleeding thus representing a relative contraindication for anticoagulation and therefore for the use of ECLS itself. However, an increasing number of patients presenting with immunocompromised state or selected hematologic disorders leading to non-heparin-induced thrombocytopenia have undergone full-code ICU management, even under consideration of ECLS. [10, 11] Since to date no recommendations regarding accurate management of these patients exist, decision-making has been made on an individual basis. In this single center experience, we report on a series of patients with severe thrombocytopenia undergoing long-term ECMO without anticoagulation.

Methods

We retrospectively identified adult patients who were treated in an 8-bed medical intensive care unit of a tertiary care university hospital from January 2013 until April 2017. Inclusion criteria were age ≥ 18 years, thrombocytopenia and withheld anticoagulation for at least 3 days while ongoing venovenous ECMO therapy.

Patients were eligible for venovenous extracorporeal life support when either being severely hypoxemic or when developing hypercapnic respiratory acidosis despite adequate respiratory support by mechanical or non-invasive ventilation, or if invasive ventilation with inspiratory plateau pressures of more than 35 mbar were necessary to maintain decarboxylation. We used the iLA Activve© (Xenios, Heilbronn, Germany) or the Cardiohelp© system (Maquet, Rastatt, Germany) for ECMO therapy. Both systems have been well described for venovenous extracorporeal gas exchange. [12-16] Cannulation was performed either using a bicaval double-lumen cannula (Avalon ELITE©, Maquet, Rastatt, Germany), a unicaval double-lumen cannula (Novaport twin©, Xenios, Heilbronn, Germany), or a two-cannula setting

with separate drainage and a reperfusion cannulas (HLS, Maquet, Rastatt, Germany). We used Seldinger's technique [17] for percutaneous cannula insertion controlled by ultrasound guidance. During the therapy normothermia was maintained by using heating blankets and the integrated ECMO heater units.

According to our center's standards, unfractionated heparin is administered continuously for anticoagulation monitored by aPTT. Interruption of systemic anticoagulation is thoroughly considered in cases with thrombocytopenia (≤ 50 G / L) plus bleeding diathesis or severe thrombocytopenia (≤ 30 G / L) regardless of haemorrhagic tendency. When bleeding occurs in patients with less severe thrombocytopenia, anticoagulation is usually reduced or suspended upon individual decision. During extracorporeal gas exchange therapy, platelet and red blood cell transfusions are administered aiming for a platelet count of ≥ 50 G / L and a hemoglobin level ≥ 8 g / dL. We use fresh frozen plasma (FFP) transfusions upon independent clinical decision. In patients with ongoing haemorrhage we consider the administration of 15ml/kg FFP when a specific therapy such as factor concentrate or vitamin k seems not appropriate.

Patient identification and data were gathered from both the patient data management system (ICCA©, Philips, Amsterdam, Netherlands) and the local ECMO database. The routine documentation includes demographic data of patients, underlying disease, reason for admission, severity of illness expressed by admission SAPS II score [18], blood product consumption, vital parameters, daily routine blood chemistry including coagulation testing and blood cell counts, as well as blood gas analysis at least every four hours together with documentation of ventilator settings and machine-related parameters (pump speed, blood flow and sweep gas flow), indication for ECMO, duration of extracorporeal therapy, reason for end of ECMO therapy, changes of components, type of cannula, complications during the course of therapy, survival, cause of death, body temperature, information about anticoagulation including the drug used, its administration route and dosage. We retrospectively assessed the RESP-Score [19] immediately

before starting the extracorporeal system and the duration of mechanical ventilation prior to inclusion.

Descriptive statistics were used by calculating median as a location parameter and range (min-max). Calculations were performed by a statistics software package (GraphPad Prism®; GraphPad Software, San Diego, California, U.S.A.). The datasets generated during and/or analysed during the current study are available on reasonable request.

The study protocol was approved by the local ethical review board according to Austrian law regulations (EK No. 1270/2017).

Results

Between January 2013 and April 2017, seven patients (3 males, 4 females) with severe thrombocytopenia were treated with venovenous ECMO for ≥ 3 days. Demographics and clinical data are shown in Table 1. Median age was 46 years. Underlying illness was acute myelogenous leukaemia (AML) in 3 cases, acute lymphatic leukaemia (ALL) following peripheral blood stem cell transplantation (PBSCT) in 2 cases, multiple myeloma in one case and pneumocystis pneumonia after lung transplantation due to fibrosis in another case. All patients were immunocompromised due to myelosuppressive chemotherapy or immunosuppressants. Thrombocytopenia was a disease- or therapy-related pre-existing condition in all cases and developed prior to ECMO start. Indications for venovenous ECMO was ARDS caused by hyperleukocytosis and pneumonia in 2 cases, pneumocystis jirovecii pneumonia (PJP) in 2 cases, pulmonary graft versus host disease (GVHD) in one case and influenza A in one case, respectively.

Five patients were treated with the Cardiohelp® system, two patients with iLA Activve®.

Patients had a median total ECMO treatment time of 33 days (min-max range 5-317 days) with an overall median platelet count of 24 G/L (overall min-max range 1-138 G/L), an aPTT of 45.6 s (29-172.8 s) and a prothrombin time (PT) of 17.6 % (11.4-79.5 %). The longest continuous extracorporeal therapy duration was 317 days in patient 6, during which time no systemic anticoagulation was applied. In five patients, systemic anticoagulation was withheld from the beginning of ECMO initiation, in two patients it was stopped during ECMO operation after 7 and 56 days on ECMO, respectively. Median continuous anticoagulation-free time was 20 days (min-max range 5-317 days). The reason for heparin withdrawal was thrombocytopenia ≤ 50 G/L with bleeding diathesis in one patient and severe thrombocytopenia ≤ 30 G/L in six patients, respectively. All patients had negative laboratory testing for heparin induced thrombocytopenia by means of ELISA and serotonin release assay. Overall, 530 ECMO-days were observed, 404 (76%) of them without any anticoagulation. Table 2 summarizes laboratory findings and coagulation associated events during ECMO therapy. Table 3 reflects the clinical picture leading to withdrawal of anticoagulation.

Clotting events

We performed a total of 10 uncomplicated system exchanges, eight of them during withdrawn heparin therapy. Five system exchanges were performed due to suspected oxygenator clotting, 3 of them during withdrawn heparin therapy, resembling an oxygenator exchange rate of 0.007 per treatment day due to clotting during anticoagulation free ECMO therapy. In patient 6, while receiving uninterrupted heparin-free ECMO for 317 days, the extracorporeal system had to be changed 6 times: Twice due to suspected membrane clotting after a running time of 34 days and again 18 days later following a perioperative low-flow incidence. A system exchange had to be

performed three times due to air bubble aspiration, presumably from a blood sampling port, and once it was done electively following an uncomplicated 130 days operation period. Patient 4 underwent elective system exchange on day 3 to exclude mechanical hemolysis as a reason for anemia and another one on day 18 because of membrane efficiency loss, presumably caused by gradual clotting. Patient 7 developed membrane clotting following massive transfusion due to severe lower gastrointestinal (GI) bleeding on ECMO day 23. In patient 1, two exchanges were necessary due to air bubble aspiration and one for configuration change. In patient 5, configuration was changed once. Median ECMO operation time per system was 17.5 days (min-max range 5-130 days).

Bleeding events

Two patients (2 and 4) developed neither major nor minor bleeding during a runtime of 5 and 25 days, respectively. Patient 1 had suffered from diffuse bleeding of lung parenchyma and hematothorax before and throughout ECMO therapy and died from fatal intracranial hemorrhage. Patient 3 developed recurrent macrohematuria and major upper GI bleeding. In patient 5, a small subarachnoideal hemorrhage and lower GI bleeding occurred simultaneously. Patient 6 had chronic hematuria and urinary bladder hematoma prior to ECMO start as well as intermittent bleeding from central venous and peripheral arterial catheter entry sites continuing during ECMO therapy. Patient 7 suffered from pulmonary and lower GI bleeding with the need of recurrent colonoscopy and multiple surgical ligation attempts, both unsuccessful. In all patients, red packed blood cell (RBC) as well as platelet transfusions were administered to prevent or stop bleeding diathesis as well as to maintain hemoglobin levels > 8 g/dL and platelet levels ≥ 50 G / L. Patients received a median total number of 29 platelet transfusions (7-207) resulting in a median of 0.8 platelet transfusions per day (0.6-1.3) and a medial total number of 34 red packed blood cells (4-280) resulting in a median of 0.7 red packed blood cell transfusions per day

(0.6-1.3), respectively. FFP was used in 3 of 7 patients (43%). Altogether, 3.1 units of FFP per patient (0-8) were administered, which corresponds to 0.05 per ECMO day (0-0.24). Although repeatedly considered during uncontrollable haemorrhage, no recombinant factor VII was given to any of the included patients.

Outcome

Six patients died during ECMO therapy, one of them due to intracranial haemorrhage and three due to multi organ failure (MOF). Therapy was discontinued in two patients. Reasons were relapse of acute myelogenous leukaemia in patient 4 and inability to be weaned from ECMO after prolonged extracorporeal therapy time in patient 6, respectively. In both cases a desired physiologic outcome seemed highly unlikely. One patient survived ECMO and hospital. These results constitute an ICU and hospital mortality of 86 %. The median RESP score at initiation of ECMO was 0 (-3 to 4). Overall, no fatal clotting occurred.

Discussion

Portraying the immunocompromised critically ill with coexisting thrombocytopenia and ECMO indication is challenging. Typically, this exclusive patient population undergoes reluctant consideration for ECMO initiation as prognosis is unfavourable. [20] This reservation notwithstanding, highly selected cases such as the small population reported herein receive ECMO as a rescue strategy when recovery potential is conceivable at the time of decision. Therefore, in our hematology-affiliated intensive care unit number of patients fulfilling our entry criteria was as low as 7 during an observational period of just below four years. This rather small sample size represents the major limitation of our study. To our knowledge, however, this report contains not only the first description of selective ECMO use without systemic anticoagulation in immunosuppressed patients but also the first mention of a continuous anticoagulation-free use of extracorporeal gas exchange therapy for >300 days. Thus, novelty and

hypothesis-generating potential are major strengths of the present study.

In patients receiving extracorporeal gas exchange therapy, systemic anticoagulation is recommended from the very beginning in order to prevent possibly evolving system clotting as well as systemic thromboembolic complications. [3] On the other hand, bleeding remains the leading complication of ECMO therapy and occurs in up to 60% of patients. [6] A high risk for systemic bleeding during anticoagulation is therefore commonly regarded as a (relative) contraindication for ECMO. [21] With recent improvements in extracorporeal gas exchange therapy there has been an increasing demand for treating hematologic malignancies and its concomitant diseases in intensive care, also applying extracorporeal life support in selected patients. [10, 11] This aggravates the challenge of walking the narrow line between bleeding and clotting.

In most cases, anticoagulation is achieved by continuous administration of unfractioned heparin (UFH) and monitored with the aPTT, Activated Clotting Time (ACT) or Anti-Factor Xa Activity Levels (anti-Xa). [3] More prolonged aPTT as well as high APACHE-II score and need for ECMO following surgery are considered risk factors for bleeding, which suggests that lowering anticoagulation target values could improve bleeding occurrence and outcome. [6]

Up to the present, reports of ECLS operation under subtherapeutic anticoagulation are scarce. An observational study of 61 patients treated with venovenous extracorporeal membrane oxygenation (ECMO) and subcutaneous prophylactic anticoagulation only reported no fatal thrombotic events, while incidence of clinically relevant bleeding and consumption of blood transfusions were lower in comparison to current data. [22] Similar results were found in a patient population on unfractionated heparin with lower target ACT of 140-160 seconds instead of the recommended 180-220 seconds. [23] Only few case descriptions report on the use of venovenous ECLS without anticoagulation. In highly selected patients such as trauma victims with hemorrhagic tendency or ongoing bleeding, heparin-free extracorporeal therapy seems to be a considerable option for initial [24, 25] or long-term [26]

extracorporeal respiratory or circulatory support. In two patients with diffuse alveolar hemorrhage, venovenous ECMO was used without anticoagulation for 6 and 9 days, respectively. In the first case continuing refractory bleeding led to death while in the other patient bleeding ceased but clotting occurred prior to weaning from ECMO [27]. One single case experience reports on the use of venovenous ECMO for pulmonary hemorrhage due to Goodpasture's syndrome. Systemic anticoagulation was withheld during 25 days without thrombotic events. [28] Another case report renders obvious heparin-free ECMO operation during bleeding associated with antecedent pulmonary endarterectomy. [29]

Our report describes a series of 7 patients with severe thrombocytopenia receiving venovenous ECMO with a total of 530 observed ECMO days. It shows that anticoagulation withdrawal in patients with haemorrhagic tendency due to thrombocytopenia is feasible even during long periods of time. Despite the absence of systemic anticoagulation, bleeding was more common than extracorporeal circuit clotting, underlining the fundamental role of sufficient platelet count and functioning for thrombus formation.

The oxygenator exchange rate per ECMO day in our patients was as low as 0.007. In a series of 265 patients undergoing 3411 days of VV-ECMO therapy, Lubnow et al. observed 71 system exchanges due to acute or progressive clotting, resulting in an oxygenator exchange rate of 0.02/ECMO day. [30] In all our patients, despite high demands for platelet and packed red blood cell transfusions, the number of clotting-associated system exchanges turned out to be lower. Besides, while one of the clotting events in our study could have been due to an antecedent accidental low-flow incidence during surgery, another was caused by a massive transfusion episode.

The bleeding complications in five of our patients (71 %) must be considered as major bleeding according to current definitions. [3] One patient died from fatal intracranial haemorrhage. Two patients developed no bleeding events despite severe thrombocytopenia during a total ECMO runtime of 5 and 25 days, respectively.

A considerable change with respect to ICU admission of critically ill immunocompromised patients has evolved during the last two decades: Since treatment options and supportive therapies have impressingly enhanced the chances of cure or sustained remission, a general reluctance concerning ICU treatment is no longer justified. [31, 32] Severe respiratory failure, however, is still associated with mortality rates of up to 80%. [33] Patients with newly diagnosed and potentially curable disease or under treatment with the goal of long-term survival are regarded as candidates for full-code intensive care treatment in case of acute critical illness. [31, 34] There exists, however, an increased risk for bleeding in hematological or immunocompromised patients, who are prone to thrombocytopenia due to chemotherapy or their underlying disease. ECMO might be an option in selected patients and could be shown to lead to acceptable outcome by our own group. [11] In this case series of 14 patients undergoing rescue ECMO therapy, median platelet count at ECMO start was 38 G/L, major bleeding occurred in 5 patients, including a non-fatal intracranial haemorrhage. Fifty percent of these patients were long-term survivors. All patients received full or at least low dose anticoagulation with heparin or low molecular weight heparin. In a retrospective multicentric analysis of patients undergoing ECMO therapy after allogeneic stem cell transplantation, the outcome data were considerably worse. In the group of patients in need for ECMO during the first 240 days after transplantation, survival was as low as 4%. [10] One of the reasons for the poor outcome in our group of patients reported herein could have been due to the fact that two of them were treated after allogeneic stem cell transplantation. Based on the latest data, ECMO as a therapeutic option should be regarded with extreme caution at least in the peri-transplant period.

In order to better estimate chances of survival we calculate the RESP-score at the time of ECMO initiation. RESP-Score was designed as a predictive hospital survival score model on adults undergoing venovenous ECMO therapy. It is composed of 12 different pre-ECMO items with the aim to assist clinicians in an adequate selection process for ECMO candidates. [19] The only survivor in our population had a calculated RESP score of 0 at the time of ECMO initiation reflecting a predicted hospital survival of around 57 %. All other subjects' scores varied considerably ranging from -3 to 4, which challenges the use of RESP score for this particular patient population. Not incorporating platelet count may be an accountable explanation, since thrombocytopenia is regarded as a risk factor for intracranial haemorrhage and thus death. [7] Moreover, in immunocompromised populations including patients with hematologic malignancies, low platelet count was shown to be an independent predictor of 6-month mortality. [20]

Our report does not yield precise estimates and needs to be interpreted carefully. It should not be misinterpreted as advocating for the general use of ECMO in patients suffering from severe thrombocytopenia due to hematological malignancies or other conditions. The present study rather shows that in patients with thrombocytopenia, continuous ECMO support without the use of systemic anticoagulation is feasible. Thorough selection of patients and experience in treating critically ill patients suffering from malignancies are prerequisites for any individual decision concerning ECMO therapy. Further research is needed to meet the challenges of hemostatic management in these patients receiving ECLS.

Conclusion

In immunocompromised patients with hemorrhagic tendency due to thrombocytopenia, indication for extracorporeal respiratory support should be critically discussed, as prognosis seems grim. However, in

case of ECMO implementation, withdrawal of systemic anticoagulation seems an appropriate and safe strategy in these selected patients, since clotting events rarely occur.

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Disclosure

Two of the authors (Thomas Staudinger, Peter Schellongowski) received speaker fees from Maquet and Novalung.

Summary of Author contributions

All co-authors contributed substantially to this work. PS and TS made fundamental contribution to patient care, study design, interpretation of data and correcting the manuscript. OR contributed substantially in study design, patient care and interpretation of data as well as with a critical revision of the paper before final approval. AB and NB equally made essential contributions to patient care, data interpretation and reviewing the manuscript.

References

1. Marasco SF, Lukas G, McDonald M, McMillan J, Ihle B. Review of ECMO (extra corporeal membrane oxygenation) support in critically ill adult patients. Heart Lung Circ. 2008;17 Suppl 4:S41-7.

2. Oliver WC. Anticoagulation and coagulation management for ECMO. Semin Cardiothorac Vasc Anesth. 2009;13:154-75.

3. The Extracorporeal Life Support Organization (ELSO). ELSO Anticoagulation Guidelines. Ann Arbor, MI, USA. 2014.

4. Kumar TK, Zurakowski D, Dalton H, Talwar S, Allard-Picou A, Duebener LF, et al. Extracorporeal membrane oxygenation in postcardiotomy patients: factors influencing outcome. J Thorac Cardiovasc Surg. 2010;140:330-6 e2.

5. Smith A, Hardison D, Bridges B, Pietsch J. Red blood cell transfusion volume and mortality among patients receiving extracorporeal membrane oxygenation. Perfusion. 2013;28:54-60.

6. Aubron C, DePuydt J, Belon F, Bailey M, Schmidt M, Sheldrake J, et al. Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation. Ann Intensive Care. 2016;6:97.

7. Kasirajan V, Smedira NG, McCarthy JF, Casselman F, Boparai N, McCarthy PM. Risk factors for intracranial hemorrhage in adults on extracorporeal membrane oxygenation. Eur J Cardiothorac Surg. 1999;15:508-14.

8. Luyt CE, Brechot N, Demondion P, Jovanovic T, Hekimian G, Lebreton G, et al. Brain injury during venovenous extracorporeal membrane oxygenation. Intensive Care Med. 2016;42:897-907.

9. Sklar MC, Sy E, Lequier L, Fan E, Kanji HD. Anticoagulation Practices during Venovenous Extracorporeal Membrane Oxygenation for Respiratory Failure. A Systematic Review. Ann Am Thorac Soc. 2016;13:2242-50.

10. Wohlfarth P, Beutel G, Lebiedz P, Stemmler HJ, Staudinger T, Schmidt M, et al. Characteristics and Outcome of Patients After Allogeneic Hematopoietic Stem Cell Transplantation Treated With Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. Crit Care Med. 2017;45:e500-e7.

11. Wohlfarth P, Ullrich R, Staudinger T, Bojic A, Robak O, Hermann A, et al. Extracorporeal membrane oxygenation in adult patients with hematologic malignancies and severe acute respiratory failure. Crit Care. 2014;18:R20.

12. Haneya A, Philipp A, Foltan M, Camboni D, Mueller T, Bein T, et al. First experience with the new portable extracorporeal membrane oxygenation system Cardiohelp for severe respiratory failure in adults. Perfusion. 2012;27:150-5.

13. Hermann A, Riss K, Schellongowski P, Bojic A, Wohlfarth P, Robak O, et al. A novel pump-driven veno-venous gas exchange system during extracorporeal CO-removal. Intensive Care Med. 2015.

14. Hermann A, Staudinger T, Bojic A, Riss K, Wohlfarth P, Robak O, et al. First experience with a new miniaturized pump-driven venovenous extracorporeal CO2 removal system (iLA Activve): a retrospective data analysis. ASAIO J. 2014;60:342-7.

15. Muller T, Philipp A, Lubnow M, Weingart C, Pfeifer M, Riegger GA, et al. First application of a new portable, miniaturized system for extracorporeal membrane oxygenation. Perfusion. 2011;26:284-8.

16. Malfertheiner MV, Philipp A, Lubnow M, Zeman F, Enger TB, Bein T, et al. Hemostatic Changes During Extracorporeal Membrane Oxygenation: A Prospective Randomized Clinical Trial Comparing Three Different Extracorporeal Membrane Oxygenation Systems. Crit Care Med. 2016;44:747-54.

17. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta radiol. 1953;39:368-76.

18. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270:2957-63.

19. 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;189:1374-82.

20. Schmidt M, Schellongowski P, Patroniti N, Taccone FS, Reis Miranda D, Reuter J, et al. Six-month Outcome of Immunocompromised Severe ARDS Patients Rescued by ECMO. An International Multicenter Retrospective Study. Am J Respir Crit Care Med. 2018.

21. The Extracorporeal Life Support Organization (ELSO). Guidelines for Adult Respiratory Failure. Ann Arbor, MI, USA. 2017.

22. Krueger K, Schmutz A, Zieger B, Kalbhenn J. Venovenous Extracorporeal Membrane Oxygenation With Prophylactic Subcutaneous Anticoagulation Only: An Observational Study in More Than 60 Patients. Artif Organs. 2016.

23. Yeo HJ, Kim DH, Jeon D, Kim YS, Cho WH. Low-dose heparin during extracorporeal membrane oxygenation treatment in adults. Intensive Care Med. 2015;41:2020-1.

24. Arlt M, Philipp A, Voelkel S, Rupprecht L, Mueller T, Hilker M, et al. Extracorporeal membrane oxygenation in severe trauma patients with bleeding shock. Resuscitation. 2010;81:804-9.

25. Wen PH, Chan WH, Chen YC, Chen YL, Chan CP, Lin PY. Non-heparinized ECMO serves a rescue method in a multitrauma patient combining pulmonary contusion and nonoperative internal bleeding: a case report and literature review. World J Emerg Surg. 2015;10:15.

26. Muellenbach RM, Kredel M, Kunze E, Kranke P, Kuestermann J, Brack A, et al. Prolonged heparin-free extracorporeal membrane oxygenation in multiple injured acute respiratory distress syndrome patients with traumatic brain injury. J Trauma Acute Care Surg. 2012;72:1444-7.

27. Pacheco Claudio C, Charbonney E, Durand M, Kolan C, Laskine M. Extracorporeal membrane oxygenation in diffuse alveolar hemorrhage secondary to systemic lupus erythematosus. J Clin Med Res. 2014;6:145-8.

28. Herbert DG, Buscher H, Nair P. Prolonged venovenous extracorporeal membrane oxygenation without anticoagulation: a case of Goodpasture syndrome-related pulmonary haemorrhage. Crit Care Resusc. 2014;16:69-72.

29. Cronin B, Maus T, Pretorius V, Nguyen L, Johnson D, Ovando J, et al. Case 13--2014: Management of pulmonary hemorrhage after pulmonary endarterectomy with venovenous extracorporeal membrane

oxygenation without systemic anticoagulation. J Cardiothorac Vasc Anesth. 2014;28:1667-76.

30. Lubnow M, Philipp A, Foltan M, Bull Enger T, Lunz D, Bein T, et al. Technical complications during veno-venous extracorporeal membrane oxygenation and their relevance predicting a system-exchange--retrospective analysis of 265 cases. PLoS One. 2014;9:e112316.

31. Kiehl MG, Beutel G, Boll B, Buchheidt D, Forkert R, Fuhrmann V, et al. Consensus statement for cancer patients requiring intensive care support. Ann Hematol. 2018.

32. Azoulay E, Mokart D, Pene F, Lambert J, Kouatchet A, Mayaux J, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol. 2013;31:2810-8.

33. Azoulay E, Lemiale V, Mokart D, Pene F, Kouatchet A, Perez P, et al. Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med. 2014;40:1106-14.

34. Azoulay E, Afessa B. The intensive care support of patients with malignancy: do everything that can be done. Intensive Care Med. 2006;32:3-5.

Tables

Table 1: Demographic data, severity of illness and outcome.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Median**
Sex	F	M	F	M	F	F	M	
Age	43	46	44	63	50	28	60	46
Underlying Disease	ALL, PBSCT	Myeloma	AML	AML	AML	ALL, PBSCT	Fibrosis, LuTX	
Cause for ARDS	PJP	Sepsis	Influenza A	Hyperleukocytosis, Pneumonia	Hyperleukocytosis, Pneumonia	Pulmonary GvHD	PJP	
SAPS-2	29	44	41	54	64	35	50	44
RESP Score at ECMO initiation	0	0	4	2	0	2	-3	0
ICU survival	N	Y	N	N	N	N	N	
Hospital survival	N	Y	N	N	N	N	N	
Cause of death	ICB	-	MOF	Relapse, therapy withdrawal	MOF	MOF, therapy withdrawal	MOF	
ECMO System	iLA Activve	Cardiohelp	Cardiohelp	Cardiohelp	Cardiohelp	iLA Activve	Cardiohelp	

ALL…acute lymphatic leukaemia, PBSCT…peripheral blood stem cell transplantation, AML…acute myelogenous leukaemia, LuTX…lung transplantation, ARDS…acute respiratory distress syndrome, GvHD…graft versus host disease, PJP…pneumocystis jirovecii pneumonia, ICB…intracranial bleeding, MOF… multi organ failure.

Table 2: Laboratory findings and coagulation associated events during ECMO (min-max).

Patient	1	2	3	4	5	6	7	Median
Median aPTT (s)	43.1 (35.6-80.0)	39.9 (34.8-42.4)	39.9 (32.6-47.7)	51.4 (39.5-94.0)	40.3 (29.0-75.0)	45.8 (30.0-172.8)	48.4 (39.0-63.9)	45.6*
Median PLT count (G/L)	46 (35-79)	10 (4-19)	31 (9-54)	31 (6-110)	28 (1-138)	19 (3-75)	47 (19-122)	24*
Lowest PLT count (G/L)	35	4	9	6	1	3	19	6
Median Thrombin Time (s)	12.2 (11.4-79.5)	13.6 (11.6-16.2)	12.7 (11.6-15.6)	16.2 (13.7-25.8)	22.1 (15.1-53.7)	17.7 (14.8-35.0)	19.1 (13.6-54.2)	17.6*
Median PT (%)	56 (19-86)	52 (39-72)	76.5 (52-104)	65 (63-80)	69 (29-111)	92 (36-125)	59 (33-89)	77*
Total No. of PLT transfusions	9	6	29	24	31	207	46	29
Mean PLT transfusions per day	0.3	1.0	0.8	1.0	0.6	0.7	0.5	0,7
Days on ECMO	27	5	35	25	51	317	90	35
w/o AC	20	5	16	17	32	317	32	20
Median ECMO Blood Flow	2.7 (1.6-3.0)	2.0 (1.9-2.4)	3.7 (2.0-4.2)	4.2 (2.7-4.8)	3.0 (2.1-3.8)	1.2 (0.8-2.1)	1.5 (1.0-2.4)	1.4*
System exchanges	0	0	0	2	1	6	1	
Clotting Events	0	0	0	2	0	2	1	
Major Bleeding Events	2	0	1	0	1	2	3	

*…Overall median

aPTT…activated partial thromboplastin time, PLT…platelet, PT…prothrombin time, AC…anticoagulation.

Table 3: Day of anticoagulation withdrawal or ECMO start.

Patient	1	2	3	4	5	6	7	Median
aPTT (s)	40.0	37.3	32.6	47.1	39.0	36.0	40.0	39
PLT Count (G/L)	50	4	9	16	2	20	27	16
Thrombin Time (s)	12.3	11.6	11.8	13.7	15.4	15.5	14.7	13.7
PT (%)	49	40	64	74	34	62	68	62
PLT Transfusions	0	1	3	1	1	0	0	1
Packed Red Blood Cells	8	0	2	4	2	0	0	2
Previous Heparin dosage (I.U./h)	400	0	0	0	0	0	200	
Previous Days on ECMO	7	0	0	0	0	0	56	
Blood Flow (L/min)	2.6	2.0	2.0	4.7	2.5	1.4	1.5	2

aPTT…Activated Partial Thromboplastin Time, PLT…Platelet, PT…Prothrombin Time,