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ORIGINAL ARTICLE

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Risk factors associated with 30-day mortality for out-of-center ECMO support: experience from the newly launched ECMO retrieval service

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Abstract

Out-of-hospital extracorporeal membrane oxygenation (ECMO) implantation and ECMO transport have become a growing field useful for emergent treatment of heart or lung failure with increasing number of centers launching such service. This study was designed to present risk factors predicting 30-day mortality for patients receiving ECMO support in a newly launched ECMO retrieval service. From 01/2015 till 01/2017 28 consecutive patients received ECMO support in peripheral hospitals using a miniaturized portable Cardiohelp System® (Maquet, Rastatt Germany) for heart, lung or heart/lung failure as a bridge-to-decision as a part of our newly launched ECMO retrieval service. Outcomes and predictors for 30-day mortality were presented. The mean age was 56 ± 15 (maximum 78) years. The mean ECMO support duration was 97 ± 100 h, whereas 11 patients (40%) were weaned off support and discharged from hospital. Presence of hemolysis ($p = 0.041$), renal failure ($p = 0.016$), lower platelet count before ECMO implantation ($p = 0.001$), and higher lactate 24 h after initiation of support ($p = 0.006$) were factors associated with 30-day mortality. Initial success of an ECMO retrieval service depends on logistic organization and clinical management. Taking into consideration highly deleterious effects of hemodynamic malperfusion of end organs, rapid initiation of ECMO support is a vital factor for survival. This is highlighted by predictive factors of early mortality that are associated with peripheral organ failure or complications.

Keywords ECMO · ECMO retrieval · Risk factors

Introduction

Extracorporeal membrane oxygenation (ECMO) therapy has become a widely used therapeutic approach for heart, lung or heart/lung failure with a broad spectrum of indications [1]. In recent years, a large number of ECMO programs have been established worldwide providing therapy opportunities for patients with refractory cardiac or pulmonary failure including implantations in peripheral hospitals with subsequent transport to specialized centers for further diagnostics and therapy, while maintaining body perfusion and oxygenation [2]. Such mobile or out-of-hospital ECMO programs are increasingly becoming the standard of care [3, 4]. However, compared to in-hospital ECMO implantations in experienced tertiary centers, distant implantations in local hospitals or even out-of-hospital implantations with subsequent patient transport on ECMO support are associated with further organizational aspects [5]. Due to these additional organizational, logistical and clinical efforts, optimal pre-, intra-, and postimplantational workflow is of enormous relevance [6]. Especially under ongoing cardiopulmonary resuscitation (CPR), these procedures must be well coordinated in order to give such critically ill patient's a real chance of survival. In fact, current survival rates in patients under ECMO therapy have been steadily improving

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over the last decade [7–11]. Nevertheless, optimization of already established procedures and therapeutic management must be further continued in patient's best interest.

To identify factors influencing outcomes before as well as at an early stage after ECMO implantation and to incorporate them in therapy related decisions, such parameters should be emphasized. Therefore, the presented study mainly focuses on mid-term results of a newly launched ECMO retrieval program in a surgical cardio-thoracic unit with special attention to potential factors associated with 30-day mortality.

Methods

This study is a retrospective observational analysis of prospectively collected data on patients included from January 2015 to January 2017. All patients received ECMO support at distant hospitals that do not have their own ECMO programs for refractory cardiac, pulmonary or combined cardiopulmonary failure and were transported for further treatment to our institution. Due to severe hemodynamic and/or respiratory instability patients were not considered transportable or were at a very high risk of not surviving transport without additional mechanical support. Veno-arterial (va) or veno-venous (vv) ECMO systems were implanted as a bridge-to-decision as a part of our newly launched ECMO retrieval service. ECMO implantation was performed peripherally using percutaneous Seldinger's technique bedside on intensive care units (ICU) using miniaturized portable Cardiohelp System® (Maquet, Rastatt Germany) in all patients. The entire cohort was anticoagulated with a single-shot unfractionated heparin (10,000 I.U.) before ECMO implantation. Due to limited measurement possibilities on retrieval effectiveness of anticoagulation was immediately measured at arrival in our institution by performing ACT (activated clotting time) analysis. However, patients were transported ground-based to our institution with the support of the local fire department. There were no complications or transportation problems during the transport supported by the ambulance staff. All patients completed a follow-up period of at least 30 days to be included in this analysis and were divided into two groups depending on 30-day survival. Demographics and periprocedural variables of 30-day survivors and non-survivors were compared to identify factors associated with 30-day mortality.

Variables of interest

The analysis was performed using a prospectively maintained institutional patient database. The variables evaluated included: patient's demographics (age, height, weight, sex), patients status prior to ECMO support [cardiopulmonary resuscitation (CPR), duration of CPR, use of intraaortic balloon pump (IABP), mechanical ventilation, need for dialysis, presence of multiorgan failure], the cause of ECMO indication, preoperative hemodynamics [heart rate, mid arterial pressure (MAD), central venous pressure (CVP), venous oxygen saturation (SVO_2)] and laboratory parameters [hemoglobin, hematocrit, pH, C-reactive protein (CRP), white blood cell count (WCC), creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, activated partial thromboplastin time (aPTT), lactate, sodium, potassium]; implantation data [status of alertness, way of implantation, cannula size (inflow/outflow), presence of distal perfusion cannula and size, initial flow, resolutions per minute (RPM); early outcome data (duration of ECMO support, hospital stay, transfusion of red blood cells (RBC), fresh frozen plasma (FFP) and platelets, the presence of infection, bleeding, limb ischemia (requiring surgery), hemolysis, stroke, hepatic failure, renal failure and sepsis, successful weaning, discharge from hospital)].

Definitions

Bleeding was defined as hemoglobin-relevant blood loss requiring transfusion of more than two RBC units over 24 h. Hepatic failure was defined as elevation of greater than or equal to two liver function parameters above twice the upper normal range. Renal failure was defined as any postoperative renal dysfunction that required dialysis/hemofiltration.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences, version 23.0 (SPSS Inc., Chicago, Illinois). All data were presented as continuous or categorical variables. Categorical data were expressed as total numbers and percentages. Continuous data were evaluated for normality using one sample Kolmogorov–Smirnov test and were expressed as the mean ± standard deviation (SD) in cases of normally distributed or median (interquartile range) in cases of non-normally distributed continuous variables. Univariate analysis was performed using either Student's t or Mann–Whitney U test for normally and non-normally distributed continuous variables, respectively. Pearson's χ^2 or Fisher exact tests were used for comparison of categorical data depending on the minimum expected count in each cross tab. p values < 0.05 were considered statistically significant.

Results

A total of 28 patients with cardiac, pulmonary or cardiac and pulmonary failure (mean age 56 ± 15 years) underwent implantation of ECMO at distant local hospitals. A total

of 15 patients (54%) were cannulated under CPR conditions, whereas the median duration of CPR was 30 (20; 110) min. All patients required mechanical ventilation and 36% ($n=10$) presented with multiorgan dysfunction prior to ECMO support. After implantation, the mean ECMO support duration for the entire patient cohort was 97 ± 100 h, whereas 11 patients (40%) were managed to be weaned off support and discharged from hospital. The mean hospital stay was 9 ± 8 days. A confirmed infection ($n=12$, 43%), bleeding ($n=12$, 43%) and renal failure ($n=15$, 54%) were the most common complications observed in the entire patient cohort.

Influence of cardio-pulmonary resuscitation on overall cumulative survival

In patients without the need for CPR the overall cumulative survival was 61.5% at 1 week and 38.5% at 1 month, 6 month and 1 year. Patients requiring CPR survived in 40% at 1 week and 33.3% at 1 month, 6 months and 1 year [log-rank (Mantel–Cox) $p=0.374$, Breslow (generalized Wilcoxon) $p=0.162$).

Analysis of 30-day survivors and non-survivors

A subgroup analysis of 30-day survivors and non-survivors is presented in Tables 1, 2, 3 and 4. There were no statistically significant differences in age (52 ± 17 vs. 58 ± 15 years, $p=0.349$). However, a trend towards lower frequency of female gender in the group of non-survivors (50% vs. 22%, $p=0.210$) could be identified. The CPR duration time [20 (7; 73) min vs. 60 (25; 120) min, $p=0.106$] was shorter in the survivor group, however not reaching statistical significance. The range of diagnoses requiring ECMO support did not differ significantly between the two groups. ACT values after arrival at our department were similar among all patients (232 ± 41 s in survivors vs. 230 ± 35 s in non-survivors, $p=0.451$).

Transport data showed no significant differences in distance and arrival time at the peripheral hospital. Neither the implantation time nor the transport time to our center differed significantly between both groups.

Despite a trend towards lower initial flow in the group of 30-day survivors [3.6 L/min (3; 4.2) vs. 4.5 (3.374; 5) L/min, $p=0.191$] both patient groups were provided with similar sizes of ECMO cannulas.

Table 1 Demographics and baseline clinical characteristics prior to ECMO implantation for 30-day survivors and non-survivors

Parameter	30-day survivors	30-day non-survivors	*p* value
Age (years)	52 ± 17	58 ± 15	0.349
Height (cm)	174 ± 12	176 ± 7	0.479
Weight (kg)	72 (57; 86)	80 (75; 93)	0.051
Female	5 (50%)	4 (22%)	0.210
CPR	5 (50%)	10 (56%)	1.000
CPR duration (min)	20 (7; 73) (max 90)	60 (25; 120) (max 180)	0.106
IABP	0 (0%)	1 (6%)	1.000
Mechanical ventilation	10 (100%)	18 (100%)	1.000
CVVH	2 (20%)	2 (11%)	0.601
MOF	2 (20%)	8 (44%)	0.247
Diagnosis			0.374
ARDS	1 (10%)	2 (11%)	–
DCM	1 (10%)	0 (0%)	–
ICM	5 (50%)	12 (67%)	–
PAE	2 (20%)	3 (17%)	–
Myocarditis	1 (10%)	0 (0%)	–
Postcardiotomy cardiogenic shock	0 (0%)	1 (6%)	–
Presence of cardiac failure			0.556
No cardiac failure	1 (10%)	2 (11%)	–
BV failure	2 (20%)	8 (44%)	–
LV failure	5 (50%)	5 (28%)	–
RV failure	2 (20%)	3 (17%)	–

CPR, cardio-pulmonary resuscitation; IABP, intraaortic balloon pump; GFR, glomerular filtration rate; CVVH, continuous veno-venous hemofiltration; MOF, multiorgan failure; ARDS, acute respiratory distress syndrome; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; PAE, pulmonary artery embolism; BV, biventricular; LV, left ventricular; RV, right ventricular

Table 2 Hemodynamics and laboratory parameters prior to ECMO implantation

Parameter	30-day survivors	30-day non-survivors	*p* value
Hemodynamics			
Heart rate (bpm)	96 ± 37	85 ± 21	0.386
MAP (mmHg)	50 (48.75; 75)	50 (37.50; 63.75)	0.562
CVP (mmHg)	14 (14; 14) (max 14)	10 (6.50; 22) (max 30)	0.667
SvO_2 (%)	41 ± 22 (min 20)	46 ± 13 (min 20)	0.708
Laboratory parameters			
Hemoglobin (mg/dL)	12.4 ± 2.2	10.0 ± 3.3	0.063
Hematocrit (%)	35 ± 8	29 ± 9	0.167
pH	7.2 (7.1; 7.27) (min 6.9)	7.3 (7.17; 7.35) (min 6.9)	0.519
CRP	14 (12; 43) (max 305)	39 (5; 139) (max 230)	0.695
WCC ($\times 10^9$/L)	17.9 ± 5.5	16.9 ± 10.1	0.759
Creatinine (mg/dL)	1.6 (1.1; 2.7)	1.7 (1.4; 2.4)	0.877
Urea (mg/dL)	53 (35.50; 80) (max 109)	53 (36.50; 87) (max 194)	0.794
AST (U/L)	583 (40;1603)	456 (114;1505)	0.681
ALT (U/L)	82 (34.25; 553.25)	406 (42; 877)	0.482
Platelet count ($\times 10^9$/L)	320 (218; 359) (min 118)	117 (65; 166) (min 34)	0.001
aPTT (s)	115 (30.75; 120)	59 (40; 120)	0.682
Lactate (mmol/L)	6 (3.3; 11) (max 25)	15 (7.5; 19.5) (max 33)	0.058
Sodium (mmol/L)	140 ± 6	143 ± 6	0.270
Potassium (mmol/L)	4.4 ± 0.6	4.7 ± 0.8	0.394

MAP, mean arterial pressure; CVP, central venous pressure; CRP, C-reactive protein; WCC, white cell count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time

The preprocedural hemodynamic and laboratory parameters were in general comparable between both groups. Only the platelet count prior to ECMO implantation significantly differed between the two groups [320 (218; 359) $\times 10^9$/L vs. 117 (65; 166) $\times 10^9$/L, $p = 0.001$].

Outcome data also showed significantly longer total hospital stay in the survivor group (15 ± 9 days vs. 5 ± 4 days, $p = 0.001$), however this variable was not considered a predictive factor, but rather a consequence of potential complication leading to earlier death in non-survivors. The incidence of bleeding [$n = 2$ (20%) vs. $n = 10$ (56%), $p = 0.114$) and the need for red blood cell transfusions (8 ± 6 units vs. 16 ± 15 units, $p = 0.131$) were higher in the group of non-survivors without statistical significance. The presence of hemolysis [$n = 1$ (10%) vs. $n = 10$ (56%), $p = 0.041$] and renal failure [$n = 2$ (20%) vs. $n = 13$ (72%), $p = 0.016$] were shown to be statistically significant in terms of prediction of 30-day mortality.

Whereas there were no statistically significant differences observed in lactate levels measured prior to ECMO support [6 (3.3; 11) mmol/L vs. 15 (7.5; 19.5) mmol/L, $p = 0.058$], lactate 24 h after initiation of ECMO support [1.4 (0.8; 2.0) mmol/L vs. 3.7 (1.9; 8.6) mmol/L, $p = 0.006$] indicated significantly higher levels in the non-survivor group as a potential risk factor for 30-day mortality (Fig. 1).

Discussion

The current report represents a single-center experience with particular attention to the first period of launching a new ECMO retrieval service in a high-volume tertiary center and the medical conditions of the supported patients. This special focus of the present manuscript may therefore help clinicians working in the field and institutions considering launching ECMO transport service in terms of initial steps during the first phase of treating transported patients under ECMO support.

Previous results dealing with ECMO retrieval services are increasingly focusing on potential factors associated with the outcome after this life-saving therapy in order to further improve early and long-term outcomes of this highly demanding patient cohort with severe heart, lung or combined heart–lung failure [12]. Comparing 30-day survivors with 30-day non-survivors and taking into account clinical and demographic variables before ECMO support as well as clinical characteristics in the early postinterventional phase, in our retrospective study the presence of hemolysis, renal failure, lower platelet count before ECMO implantation and higher lactate 24 h after initiation of support were revealed factors associated with 30-day mortality in our patient collective.

Table 3 Transport, implantation and early outcome data for 30-day survivors and non-survivors

Parameter	30-day survivors	30-day non-survivors	*p* value
Transport data			
Time of first contact to arrival (min)	39 ± 19	40 ± 19	0.407
Transport time under ECMO (min)	33 ± 15	30 ± 14	0.454
Distance to peripheral hospital (km)	19 ± 19	17 ± 17	0.433
Implantation data			
Time of implantation (min)	36 ± 19	41 ± 22	0.232
Asleep	10 (100%)	18 (100%)	1.000
Peripheral	10 (100%)	18 (100%)	1.000
vaECMO switch to vv ECMO	1 (10%)	1 (6%)	1.000
Inflow cannula size (Fr)	22 (21; 23)	23 (21; 23)	0.382
Outflow cannula size (Fr)	17 (17; 19)	18 (17; 19)	0.408
Distal perfusion cannula	7 (70%)	12 (67%)	1.000
Distal perfusion cannula size (Fr)	6.5 (6.5; 8)	6.5 (6.5; 8)	1.000
Initial flow (L/min)	3.6 (3; 4.2)	4.5 (3.375; 5)	0.191
RPM	3500 (3000; 3850)	3500 (3200; 3600)	1.000
Early outcome			
Support duration (h)	105 ± 106	91 ± 99	0.737
Hospital stay (day)	15 ± 9	5 ± 4	0.001
RBC (U)	8 ± 6	16 ± 15	0.131
FFP (U)	2 (0; 4)	4 (0; 14.25)	0.298
Platelets (U)	0 (0; 1)	0 (0;2)	0.403
Infection	4 (40%)	8 (45%)	1.000
Bleeding	2 (20%)	10 (56%)	0.114
Limb ischemia (surgery)	1 (10%)	2 (11%)	1.000
Hemolysis	1 (10%)	10 (56%)	0.041
Stroke	0 (0%)	5 (28%)	0.128
Hepatic failure	2 (20%)	8 (44%)	0.247
Renal failure	2 (20%)	13 (72%)	0.016
Sepsis	2 (20%)	6 (33%)	0.669
Successful weaning	10 (100%)	1 (6%)	< 0.001
Discharged from hospital	10 (100%)	1 (6%)	< 0.001

ECMO, extracorporeal membrane oxygenation; va, veno-arterial; vv, veno-venous; RPM, resolutions per minute; RBC, red blood cells; FFP, fresh frozen plasma

Table 4 Summarize of factors associated with 30-day mortality

Parameter	30-day survivors	30-day non-survivors	*p* value
Hemolysis	1 (10%)	10 (55.6%)	0.041
Renal failure	2 (20%)	13 (72%)	0.016
Platelet count before implantation ($\times 10^9$/L)	320 (218; 359)	117 (65; 166)	0.001
Lactate 24 h after implantation (mmol/L)	1.4 (0.8; 2.0)	3.7 (1.9; 8.6)	0.006

According to previous extensive research on the topic of CPR timing was shown to be one of the most critical aspects that may influence outcomes [11, 12]. Our data also show a shorter CPR time in the group of 30-day survivors [20 (7; 73) (max 90) min vs. 60 (25; 120) (max 180) min; $p = 0.106$], however it remained not statistically significant probably due to our small patient cohort. Indeed timing may be directly associated with significant pathophysiological changes, as the time of inadequate tissue perfusion and oxygenation particularly in cases of ongoing CPR is always related to the rise of lactate levels as a product of anaerobic metabolism [13]. Also, as shown in the present study, higher lactate 24 h after initiation of ECMO support may strongly predict 30-day mortality. In this context, this easily available parameter seems to be of paramount interest for therapy related decisions regarding ECMO initiation, monitoring

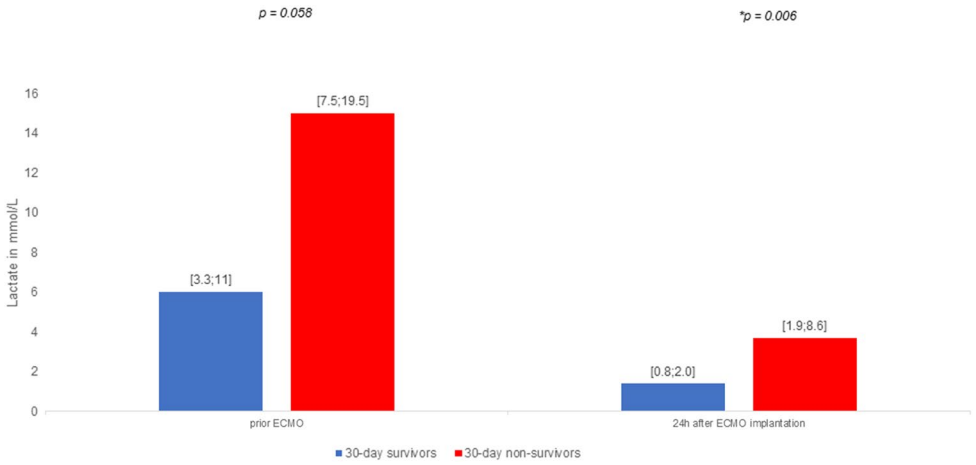

Fig. 1 Lactate improvement after 24 h of ECMO-support (*statistically significant; $p < 0.05$)

and withdrawal of support in cases of unfavorable prognosis. In this regard Rückert et al. emphasized higher lactate at the time of ECMO implantation as a significant factor associated with poor outcome for ECMO support [14]. Debaty et al. also showed that lower serum lactate concentration was significantly associated with better outcomes in patients requiring ECMO support following out-of-hospital cardiac arrest [15]. In contrast, Slottosch et al. described for 139 patients with the need for ECMO therapy with postcardiotomy cardiogenic shock that lactate prior to ECMO support and peak lactate level during ECMO support showed no significant relationship to mortality, while lactate and lactate clearance at 24 h after initiation of support were predictive of 30-day mortality [16]. This finding also corroborates our result concerning the impact of 24-h lactate levels on early outcome. Our study also showed a decrease in lactate levels 24 h after initiation of support compared to lactate levels before ECMO implantation both in 30-day survivors and 30-day non-survivors accounting for a decrease from 6 to 1.4 mmol/L in survivors and from 15 to 3.7 mmol/L in non-survivors. These data revealed in the present study can be supported by Arlt et al. who also reported on a decrease in lactate serum concentration for the same time points, however with obviously higher initial values (from 70 to 40 mmol/L after 24 h of ECMO initiation) [17]. However, Pabst et al. reported for patients receiving vaECMO under CPR that lactate serum concentration higher than 8 mmol/L may be a potential negative predictor for survival [18].

The endeavor to achieve myocardial recovery avoiding end organ failure is one of the most important goals in clinical practice dealing with ECMO therapy. This is also clearly shown for specific circumstances of our study in terms of challenges related to the newly established program. In this way, it was not surprising that one of the examples of end organ dysfunction, such as renal failure, had a significant impact on survival of patients requiring ECMO therapy (20% renal failure in the group of 30-day survivors vs. 72% in the group of 30-day non-survivors, $p = 0.016$). Similarly, a French study with 87 patients who were treated with ECMO due to a refractory cardiogenic shock identified oligo- and anuria as factors associated with in-hospital mortality [7]. Moreover, data by Aubin et al. provide additional evidence to these findings, showing that renal failure may also be a significant risk factor associated with mortality after ECMO weaning [5]. This evidence can also be strengthened by the retrospective study by Combes et al. who analyzed 81 patients with ECMO support for cardiogenic shock and showed urine output under 500 mL within the first 24 h after initiation of ECMO support was to be an independent predictor for death on intensive care unit [19].

In addition to a number of various risk factors revealed in previous studies and the present work, hemolysis induced by surface contact of the hardware with blood as well as flow characteristics of extracorporeal circulation also seems to play an important role in prediction of outcomes. For patients supported with left ventricular assist device (LVAD) systems, hemolysis was also described as a crucial complication [20]. Importantly, shear stress generated by flow through the pump in LVAD and circuit and oxygenator in ECMO was shown to be a factor responsible for this pathophysiological condition in mechanical circulatory support [21, 22]. Again, for our specific population of patients treated under conditions of establishing the program with pertinent learning curve, hemolysis was shown to be a factor predictive of early mortality. Importantly, Williams et al. shed some more light on this issue investigating the impact of oxygenator size on the severity of hemolysis. In their study presented using an ex vivo ECMO model with different dimensions of the oxygenator surface area, the use of smaller dimensions was associated with increased hemolysis compared to larger dimensions [23]. In addition to these experimental findings, a large retrospective study that included 318 adult patients with acute respiratory failure requiring vvECMO therapy

demonstrated that hemolysis was predictive of increased risk of overall mortality. The authors claimed increased extracorporeal blood flow to be main cause of hemolysis [24].

Another prejudicial complication leading to poor outcome described in our study is bleeding which has already been reported as a severe state for patients under ECMO support even in experienced centers with established programs [25]. However, bleeding in our study did not reach statistical significance to be a factor associated with 30-day mortality, the difference between survivors and non-survivors (56% vs. 20%; $p = 0.114$) was of obvious value. We strongly believe that statistical significance would be reached after inclusion of further patients in this study, as we found out that the platelet count prior to ECMO implantation was associated with 30-day mortality. In addition to this, the extracorporeal circulation induces a well-known prothrombotic state, requiring obligatory monitoring of anticoagulation to prevent clotting in the extracorporeal circuit. This conflict between the need for anticoagulation on the one hand and preventing of bleeding on the other hand has been challenging clinicians dealing with ECMO therapy [26].

Limitations

This study is a retrospective analysis of a single institution with a relatively low number of patients representing initial results of a newly launched ECMO retrieval service. Also factors influencing survival might be triggered by survival itself.

Conclusion

Initial success of an ECMO retrieval service depends on logistic organization and clinical management. Factors influencing survival are of high clinical importance and therefore should be taken into account while indicating, monitoring and withdrawal of ECMO support.

Taking into consideration highly deleterious effects of end organ malperfusion, rapid initiation of ECMO support is a vital factor for survival. This is highlighted by predictive factors of early mortality that are associated with peripheral organ failure or complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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