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Veno-Venous Extracorporeal Membrane Oxygenation in COVID-19-Associated ARDS: Predictors of Mortality

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Summary

The aim of the study was to identify factors associated with hospital mortality in patients with COVID-19-associated acute respiratory distress syndrome (ARDS) receiving veno-venous extracorporeal membrane oxygenation (VV-ECMO).

Materials and methods. The retrospective study included data from the medical records of 123 patients treated in the intensive care unit (ICU) № 7 of the City Clinical Hospital № 52 of Moscow Department of Health. ECMO was initiated in all patients for respiratory indications according to current recommendations. A number of factors potentially associated with mortality were systematized and analyzed. Statistical processing to identify predictors of death included univariate analysis and calculation of odds ratio (OR), ROC analysis with calculation of area under the ROC curve (AUROC).

Results. The resulting mortality rate was 87% (107/123), 11% (14/107) of all deaths occurred after weaning from ECMO. High VV-ECMO flow, delayed initiation of mechanical ventilation and ECMO therapy, and low pH at the time of ECMO initiation were identified as independent predictors of death in the study group. Low median albumin concentration and prolonged use of vasopressors were identified as predictors of death within 28 days of initiation of VV-ECMO. Development of acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), septic shock and its recurrences, and the use of extracorporeal blood purification therapy for septic shock were found to be predictors of death during VV-ECMO therapy.

Conclusion. High-flow VV-ECMO regimen, delayed initiation of mechanical ventilation and ECMO support, hypoalbuminemia, prolonged need for norepinephrine infusion, development of AKI requiring CRRT, septic shock occurrence and the number of its recurrences requiring extracorporeal blood purification therapy during VV-ECMO support were identified as predictors of death in patients with COVID-19-associated ARDS after initiation of VV-ECMO therapy.

Keywords: veno-venous extracorporeal membrane oxygenation; COVID-19; acute respiratory distress syndrome; ARDS; predictors of mortality

Conflict of interest. The authors declare no conflict of interest.

Introduction

One of the most severe manifestations of COVID-19 is acute respiratory distress syndrome (ARDS), with a prevalence of 32.2% [1]. When protective lung ventilation fails to provide adequate blood gas parameters, veno-venous extracorporeal membrane oxygenation (VV ECMO) is the last option to maintain gas exchange, serving as a «bridge» to recovery and creating conditions for repair processes in the lung tissue. Despite the available expertise in the use of VV ECMO in respiratory failure of various etiologies, in-hospital mortality remains high, reaching 50% [2].

The respiratory support strategy in this group of patients involves «pulmonary rest» to maximize the reduction of secondary lung injury while achieving adequate gas exchange rates with VV ECMO.

The high economic cost, the need for human resources and the complexity of a multidisciplinary approach in the management of such patients require a thorough evaluation of indications and contraindications, as well as the identification of predictors of mortality for potential correction.

The aim of the study was to identify factors associated with in-hospital mortality in patients with COVID-19-associated ARDS undergoing VV ECMO.

Materials and Methods

Study design. We conducted a single-center retrospective cohort study of factors influencing mortality in ICU patients treated with VV ECMO for COVID-19 during the entire pandemic period in the ICU #7 of Moscow City Clinical Hospital #52 (March 2020-August 2022).

Inclusion criteria: age ⩾ 18 years, confirmed diagnosis of COVID-19 (U07.1; U07.2), initiation of VV ECMO for respiratory indications due to respiratory failure associated with ARDS.

Exclusion criteria: initiation of VV ECMO in other departments and medical institutions, death within 24 hours after vascular cannulation due to its complications, death due to septic shock within 48 hours after initiation of VV ECMO, baseline veno-arterial ECMO. The scheme of patient selection in the study is shown in Fig. 1.

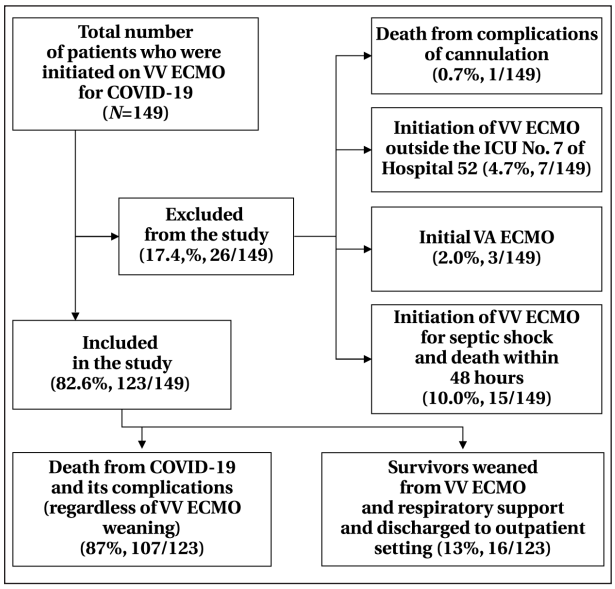

Fig. 1. Scheme of patient selection in the study.

The study was approved by the Ethical Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (No. 1/23/6, April 5, 2023). Informed consent was not obtained for this study.

Information was collected from paper and electronic versions of the ORBITA KIS and EMIAS KIS case histories using Microsoft Excel spreadsheet software (Microsoft Corp., USA). A number of parameters potentially associated with mortality were analyzed: age, body mass index, time points of decision (from onset of illness to transfer to mechanical ventilation and initiation of VV ECMO), duration of VV ECMO and its maximum flow rate, blood gas and acid-base status ($PaCO_2$, pH), P/F, norepinephrine dose and SOFA (Sequential Organ Failure Assessment) score at the time of VV ECMO initiation, and static lung compliance value after transition to protective ventilation parameters.

During the first 28 days of VV ECMO, the duration of norepinephrine use, mean albumin concentration, and number of blood component transfusions (fresh frozen plasma, erythrocyte suspension, platelet concentrate, and cryoprecipitate) were evaluated. During the entire period of VV ECMO, we evaluated recurrences of septic shock and their number, frequency of thrombotic events related to the ECMO machine circuit and to the patient, bleeding, use of renal replacement therapy (RRT) for renal indications, and methods of extracorporeal blood purification for septic shock.

Indications and contraindications for VV ECMO initiation and weaning were based on the current ELSO guidelines [3]. The adapted algorithm is shown in Fig. 2.

All patients underwent peripheral VV ECMO, primarily in a femoro-jugular configuration, with ultrasound guidance during vascular cannulation. All patients received protective ventilation in a prone position, recruitment maneuvers, and therapeutic bronchoscopy (if necessary). A puncture dilatation tracheostomy was performed within the first three days of starting lung ventilation. The anticoagulant used during VV ECMO was unfractionated heparin, which was monitored using measurement of APTT. In the event of hemorrhagic complications, anticoagulant therapy was de-escalated or discontinued. Thrombotic complications were categorized as either circuit-related (impeller or oxygenator thrombosis requiring circuit replacement) or patient-related (new thrombosis developing during VV ECMO).

Hemorrhagic complications were classified as major (any bleeding that necessitated the discontinuation of anticoagulation therapy or surgical hemostasis, such as intracranial/intracerebral, gastrointestinal, pulmonary, or bladder bleeding, or severe nosebleeds) or minor (bleeding from ECMO catheter and cannula sites, bleeding from pleural drainage sites, erosive gastritis, nasal bleeding), depending on severity.Patients were started on renal replacement therapy (RRT) for acute kidney injury (AKI) based on common indications like hyperkalemia, the need for rehydration, uremia, and uncorrected metabolic acidosis.

Statistical analysis. The data were analyzed using IBM SPSS Statistics 27. The data were checked for normality using the Shapiro–Wilk test. The results showed that parametric criteria were not applicable for all parameters due to the small number of outcomes. Mann–Whitney *U*-test was used to compare groups of quantitative data, Fisher's exact test was used for qualitative binary outcomes, and a Pearson's χ^2 test of agreement was used for ordinal outcomes. The null hypothesis was rejected at the significance level of 0.05. One-factor regression analysis (binary logistic regression) was used to search for predictors

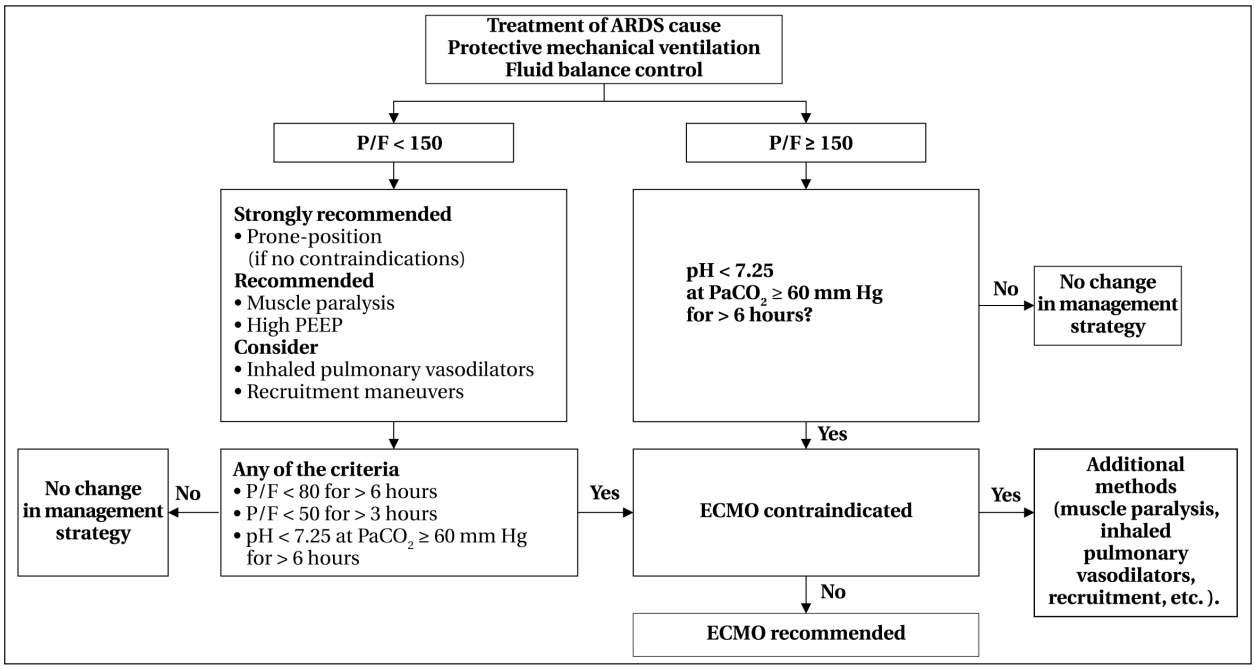

Fig. 2. Decision-making algorithm and indications for initiation of VV ECMO (ELSO) [2].

of mortality. The risk of poor outcome was estimated using the odds ratio and its 95% confidence interval.

Results

The hospital mortality rate was 87% (107/123); 11% of patients (14/123) died after weaning from VV ECMO, while 13% (16/123) were weaned from VV ECMO and respiratory support and discharged. Infectious complications resulting in septic shock and multiorgan failure were the leading causes of mortality.

Patients in both groups (non-survivors and survivors) were comparable in the main parameters (Table 1) and were predominantly male: the male-to-female ratio in the groups was similar (79/28 (73.8%/26.2%) in the non-survivor group and 12/4 (75%/25%) in the survivor group).

The comparative analysis revealed statistically and clinically significant differences between the groups in a number of parameters (Tables 1, 2).

The mean age of the non-survivors was higher than that of the survivors.

Table 1. Characteristics of patients.

Parameter	Values in groups		*P*-value
	Non-survivors, *N*=107	Survivors, *N*=16	
Demographic and anthropometric parameters			
Age, years	52.0 [42.0–59.0]	38.0 [35.25–50.75]	0.036*
BMI, kg/m²	30.86 [26.34–34.7]	32,76 [26.5–34.6]	0.913
Time points for management decisions			
Time from disease onset to ventilation, days	16.0 [12.0–21.0]	8.0 [7.0–11.75]	<0.001*
Time from disease onset to initiation of VV ECMO, days	18.0 [14.0–22.0]	11.0 [8.25–14.0]	<0.001*
Time from ventilation transfer to initiation of VV ECMO, days	1.0 [1.0–2.0]	1,5 [0.0–3.75]	0.692
Values at the time of initiation of VV ECMO			
$PaCO_2$ at the time of VV ECMO initiation, mmHg	78.5 [54.75–90.0]	52.5 [45.0–72.5]	0.035*
P/F at the time of VV ECMO initiation, mmHg	71.0 [59.0–87.53]	80.0 [71.25–92.5]	0.056
pH at the time of VV ECMO initiation	7.2 [7.1–7.3]	7.32 [7.17–7.4]	0.076
Norepinephrine dose at the time of VV ECMO initiation, μg/kg/min	0.1 [0.0–0.25]	0.1 [0.0–0.3]	0.451
SOFA at the time of VV ECMO initiation	8.0 [6.0–10.0]	6,5 [5.0–9.0]	0.230
VV ECMO characteristics			
Duration of ECMO, days	17.0 [9.0–30.0]	11.5 [7.0–25.5]	0.196
C_{stat} immediately after initiation of VV ECMO	21.3 [16.6–29.0]	28.5 [23.75–38.75]	0.035*
Maximum flow rate of VV ECMO, L/min	4.6 [4.2–5.2]	3.8 [3.5–4.0]	<0.001*
Duration of norepinephrine use in the first 28 days of VV ECMO, days	11.0 [5.0–19.0]	3.0 [1.0–10.0]	0.002*
Median albumin concentration in the first 28 days of VV ECMO, g/L	28.6 [25.7–33.0]	34.08 [29.18–37.68]	0.002*
Transfusions of fresh frozen plasma in the first 28 days of VV ECMO, doses	2.0 [0.0–6.0]	4.0 [0.0–9.5]	0.420
Cryoprecipitate transfusions in the first 28 days of VV ECMO, doses	6.0 [0.0–25.0]	18.0 [0.0–49.0]	0.149
Platelet concentrate transfusions in the first 28 days of VV ECMO, doses	5.0 [1.0–12.0]	3.0 [0.0–4.75]	0.049*
Red cell suspension transfusions in the first 28 days of VV ECMO, doses	5.0 [2.0–10.0]	5.0 [0.25–7.75]	0.317
Mean incidence of septic shock during VV ECMO	1.0 [1.0–2.0]	0.0 [0.0–1.0]	<0.001*

Notes. Shown are *Me [Q1; Q3]*. C_{stat} — static pulmonary compliance. * — significant differences ($P<0.05$).

Table 2. Complications in survivors and non-survivors (categorical parameters).

Parameter, *N*	Values in groups				*P*-value
	Non-survivors, *N*=107		Survivors, *N*=16		
	Present	Absent	Present	Absent	
Thrombotic complications					
ECMO circuit thrombotic events requiring circuit replacement	28	79	6	10	0.374
Thrombotic events in patients on VV ECMO	43	64	5	11	0.589
AKI, septic shock					
RRT for renal indications during the VV ECMO procedure	87	20	5	11	<0.001*
Septic shock during the VV ECMO procedure	95	12	6	10	<0.001*
Use of extracorporeal blood purification techniques during VV ECMO	65	42	5	11	0.032*
Hemorrhagic complications					
Bleeding during ECMO	Absent	Minor	Major	Absent	Minor	Major	0.256
	32	31	44	8	4	4	

Note. * — significant differences ($P<0.05$).

When blood gases were analyzed at the time of VV ECMO initiation, the P/F value was less than 100 mmHg in all patients, and significant differences between the groups were seen only in $PaCO_2$: more severe hypercapnia at the time of VV ECMO initiation was observed in the non-survivors.

The non-survivors had longer vasopressor support than the survivors, which was not due to drug sedation. In addition, the non-survivor group was characterized by a higher incidence of septic shock and AKI requiring initiation of RRT and a higher rate of extracorporeal blood purification.

Patients in the survivor group were placed on mechanical ventilation and subsequently on VV ECMO earlier. The median albumin concentration was higher in the survivors group.

In the survivor group, higher C_{stat} values on protective ventilation and lower maximum required flow rate of VV ECMO throughout the treatment period were observed.

Survivors received platelet concentrate transfusions less frequently than non-survivors.

There were no significant differences in other parameters between the groups.

Candidate predictors influencing outcome using single factor regression analysis and ROC analysis are shown in Table 3.

Discussion

Epidemiologic and anthropometric characteristics. The findings regarding the effect of patient age on COVID-19 outcome are consistent with previously published results. According to a large meta-analysis of the characteristics of patients undergoing VV ECMO for COVID-19-associated ARDS, age was an independent predictor of mortality and was lower in surviving patients [4, 5]. Other publications and data from large meta-analyses also demonstrated a significant decrease in survival and difficulty weaning from ECMO in patients older than 60 years [6–8].

In contrast, body mass index did not differ between groups. No differences in BMI between non-surviving and surviving patients have been previously reported [4,9–18], which is also true for patients with other etiologies of ARDS [19]. Excessive body weight in the context of VV ECMO may present difficulties in obtaining vascular access for cannulation, as well as requiring the implantation of larger diameter cannulae due to the potential need for a higher ECMO machine flow rate.

The results of large meta-analyses regarding the effect of patient sex on survival are mixed. There is evidence of both significant differences in mortality between the sexes and increased mortality in male patients [4, 7, 8]. In addition, mortality has been re-

Table 3. Predictors of outcome in COVID-19-associated ARDS.

Parameter	OR	95% CI	*P*-value	AUROC	Asymptotic significance
Maximum flow rate of VV ECMO, L/min	21.808	4.647–102.345	<0.001*	0.852	<0.001*
Time from disease onset to ventilation, days	12.840	3.399–48.500	<0.001*	0.849	<0.001*
Time from disease onset to initiation of VV ECMO, days	16.406	3.523–76.401	<0.001*	0.840	<0.001*
P/F at the time of VV ECMO initiation, mmHg	3.150	1.023–9.704	0.103	0.357	0.065
pH at the time of VV ECMO initiation	8.727	2.731–27.888	0.026*	0.315	0.018*
Median albumin concentration in the first 28 days of VV ECMO, g/L	14.182	1.808–111.212	0.003*	0.263	0.002*
Duration of norepinephrine use in the first 28 days of VV ECMO, days	25.750	6.354–104.350	0.010*	0.743	0.002*
Cryoprecipitate transfusions in the first 28 days of VV ECMO, doses	2.906	0.981–8.609	0.017*	0.392	0.163
RRT for renal indications during the VV ECMO procedure	9.570	2.990–30.635	<0.001*	0.750	0.001*
Use of extracorporeal blood purification techniques for septic shock during VV ECMO, cases	3.405	1.104–10.499	0.033*	0.647	0.058
Frequency of septic shock during the VV ECMO procedure	13.194	4.067–42.805	<0.001*	0.756	0.001*
Cases of septic shock during the VV ECMO procedure	13.194	4.067–42.805	0.001*	0.754	0.001*

Note. * — significant differences.

ported to be higher in patients with two or more comorbidities than in those with fewer than two comorbidities [7, 9, 20].

Time frame from disease onset to mechanical ventilation and initiation of VV ECMO. In a single-factor analysis, later time from disease onset to mechanical ventilation (OR: 12.840 [95% CI: 3.399–48.500], $P<0.001$; AUC=0.849 [95% CI: 0.759–0.939], $P<0.001$) and to initiation of VV ECMO (OR: 16.406 [95% CI: 3.523–76.401], $P<0.001$; AUC=0.840 [95% CI: 0.757–0.923], $P<0.001$) were found to be predictors of mortality. The time from onset of symptoms to initiation of VV ECMO was also an independent factor associated with mortality in previous studies. In particular, an increased risk of death has been shown on the 12th day or more after the onset of clinical symptoms [6, 8]. At the same time, no significant association was found between the time from initiation of mechanical ventilation and the start of VV ECMO, which is inconsistent with data available in the literature and may be due to insufficient sample size.

There is evidence of increased mortality as the time from placement on mechanical ventilation to initiation of VV ECMO increases [8, 21]. According to data from German ECMO centers, the survival rate of patients significantly decreased when VV ECMO was initiated on day 5 and later from the time of mechanical ventilation placement [22]. Data from a large multicenter study show a significantly shorter duration of mechanical ventilation before VV ECMO initiation in survivors compared to non-survivors (3 and 6 days, respectively) [22]. In another sample, this was the only parameter independently associated with mortality, with values of 1 and 6 days in the survivor and non-survivor groups, respectively [24].

The non-survivor group had lower static lung compliance values after the initiation of VV ECMO and placement on protective lung ventilation, which could be attributed to increased lung tissue damage. Lung compliance is not typically listed as an indication for VV ECMO. Previous studies have found no association between this parameter at the time of VV ECMO initiation and mortality [25].

Blood gases at initiation of VV ECMO. At the time of initiation of VV ECMO, hypercapnia, respiratory acidosis, and a severe (<100 mm Hg) decrease in P/F were observed, which was an indication for ECMO. The P/F value at the time of VV ECMO initiation did not predict a poor outcome which could be due to insufficient sample volume.

At the time of VV ECMO initiation, pH was slightly lower in the non-survivor group than in the survivor group (Table 1). However, lower pH at the time of VV ECMO initiation was a predictor of mortality (OR: 8.727 [95% DI: 2.731–27.888], $P=0.026$; AUC=0.315 [95% DI: 0.159–0.471], $P=0.018$). According to the literature, acidosis, hypercapnia and elevated blood lactate levels are associated with mortality. In particular, a pH below 7.23 significantly increased the risk of death in patients over 60 years of age, suggesting that VV ECMO should be initiated early, i. e. before the development of severe metabolic disturbances [9, 26].

At the time of VV ECMO initiation, the survivor group had a higher P/F and lower $PaCO_2$ than the non-survivors (Table 1), which is consistent with previous studies [7, 8, 25].

Performance of VV ECMO. Single factor analysis showed that a high flow rate of VV ECMO required to achieve target gas exchange values was a predictor of mortality (OR: 21.808 [95% CI: 4.647–102.345], $P<0.001$; AUC=0.852 [95% CI: 0.766-0.937], $P<0.001$). There were no significant differences in the duration of ECMO between the groups. The results of a previous study with a small sample showed a similar duration of VV ECMO in survivors and non-survivors of COVID-19 (11 days) [18]. In another study, the duration of VV ECMO in patients with COVID-19 was longer than in patients with other etiologies of respiratory failure [27].

Sepsis and multiorgan failure. Identification of septic shock during VV ECMO (OR: 13.194 [95% CI: 4.067–42.805], $P<0.001$; AUC=0.756 [95% CI: 0.609–0.904], $P=0.001$) and the number of its reported cases during this period (OR: 13.194 [95% CI: 4.067–42.805], $P=0.001$; AUC=0.754 [95% CI: 0.607–0.901], $P=0.001$) were predictors of adverse outcome. Septic shock during VV ECMO developed in 101/123 patients (82.1%) and was the leading cause of death regardless of ECMO weaning. The use of extracorporeal purification techniques for septic shock was also a predictor of mortality (OR: 3.405 [95% CI: 1.104–10.499], $P=0.033$; AUC=0.647 [95% CI: 0.505–0.790], $P=0.058$). Nosocomial infections increase the length of stay in the ICU for patients of any profile, and their negative impact can be fairly extrapolated to a cohort of patients with COVID-19 [28–30]. According to the literature, bacterial pneumonia was one of the most common (34.7%) complications after VV-ECMO initiation [19], and positive bacterial culture of ascitic or pleural fluid was associated with increased mortality [31].

In our study, sepsis and septic shock were the main causes of hemodynamic instability requiring vasopressor support. The duration of norepinephrine administration during the first 28 days of VV ECMO was a predictor of poor outcome (OR: 25.750 [95% CI: 6.354–104.350], $P=0.010$; AUC=0.743 [95% CI: 0.592–0.893], $P=0.002$). Norepinephrine was used longer in the non-survivor group than in the survivor group (Table 1).

Meanwhile, no significant differences were found between the groups regarding the dose of norepinephrine at the time of VV ECMO initiation.

The use of vasopressors in intensive care patients is often considered as one of the parameters indicating the severity of organ dysfunction (e. g., SOFA score). However, the need for vasopressor support may be due to the effects of drug sedation as well as respiratory acidosis due to hypercapnia, which in turn is an indication for VV ECMO. According to a systematic review, no differences in survival were found in relation to the use of vasopressors prior to VV ECMO initiation: of 13 studies, only 3 (in hematological patients) showed an association between the need for vasopressor support and decreased survival [19, 32, 33].

No significant differences in the severity of illness according to the SOFA scale at the time of VV ECMO initiation were found between the groups, which casts doubt on the reliability and representativeness of the scale in the assessment of such patients. Several recommendations include a SOFA score greater than 12 as a contraindication to ECMO [19]. Despite the very high accuracy of this scale in predicting mortality [33–35], there are currently only a few studies evaluating its use in patients with VV ECMO and COVID-19, where a score of more than 10 points is associated with increased mortality [37].

Single factor analysis showed that the development of AKI during VV ECMO requiring RRT was a predictor of mortality (OR: 9.570 [95% CI: 2.990–30.635], $P<0.001$; AUC=0.750 [95% CI: 0.611–0.890], $P=0.001$). Renal dysfunction can be associated with life-threatening electrolyte abnormalities, promote the progression of secondary lung injury, lead to coagulopathy, and impair dehydration, which is critical in patients with ARDS. According to the literature, patients with COVID-19 and renal failure, including new-onset renal failure during hospitalization, had a significantly higher risk of death [38], and the use of RRT was associated with mortality [22], as was the fact of developing ARDS itself [38, 39].

Dehydration and normal pharmacokinetics and pharmacodynamics of drugs can be further exacerbated by hypoalbuminemia, which is more common in patients undergoing VV ECMO. The median albumin concentration values during the first 28 days of VV ECMO were lower in the non-survivor group compared to the survivor group (Table 1), which was a predictor of mortality (OR: 14.182 [95% CI: 1.808–111.212], $P=0.003$; AUC=0.263 [95% CI: 0.131–0.394], $P=0.002$), consistent with the results of sparse previous publications [40, 41].

Thrombotic and hemorrhagic complications. Among all blood component transfusions during the first 28 days of VV ECMO, only the number of cryoprecipitate doses was a predictor of mortality: survivors had more transfusions than non-survivors (OR: 2.906 [95% CI: 0.981–8.609], $P=0.017$; AUC=0.392 [95% CI: 0.234–0.549], $P=0.163$). Statistical data on the number of blood component transfusions and the impact of this parameter on outcome have been reported in a very limited number of studies. According to observational studies, an increased number of transfusions of red cell mass and fresh frozen plasma was associated with an unfavorable outcome, which may be explained by the need for massive blood transfusions in more critically ill patients, while a high number of platelet concentrate transfusions was associated with thrombotic complications of the ECMO circuit [42].

No significant association was found between mortality and the development of hemorrhagic complications or any thrombotic complications. Similarly, among patients with bleeding complications, no differences were found in the effect of different categories of bleeding (major or minor) on mortality. In a study with a similar number of patients surviving and a lower number of patients dying, the incidence of «major» bleeding complications was 42.5% of the total number of patients [43]. The results of other studies show a high incidence of both thrombotic and hemorrhagic complications in COVID-19 and VV ECMO patients [44–46]: an increased incidence of hemorrhagic complications and the need for blood transfusion in non-survivors has been demonstrated [16]. The results of an analysis of 620 patients with COVID-19 showed an association of hemorrhagic complications (mainly intracranial) with mortality, which was not true for thrombotic complications [47]. Furthermore, according to a large meta-analysis including 6878 patients, the incidence of intracranial complications in patients with COVID-19 was significantly higher than in patients with other etiologies of respiratory failure [48].

Study limitations. This is a retrospective, single-center cohort study with all the limitations associated with this type of design. The patient groups varied considerably in size, which may have influenced the statistical results. Given the multifactorial nature of the causes of death in this patient cohort, the list of parameters studied could be expanded to include several other characteristics potentially associated with mortality (echocardiographic features, development of right ventricular failure, sepsis, etc.) if adequate data collection were possible.

Conclusion

We identified a number of predictors of mortality during VV ECMO in COVID-19 patients. In selected patient groups, reducing the duration of non-protective respiratory support and initiating VV ECMO as early as possible, when indicated, before major gas exchange disturbances develop, may reduce secondary lung injury and promote lung repair. The development of AKI and septic shock, as well as hypoalbuminemia and duration of vasopressor support, are all associated with mortality in this patient population.

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