Evaluation of factors affecting prognosis in venoarterial extracorporeal membrane oxygenation

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Venoarterial extracorporeal membrane oxygenation prognostic factors

Abstract

Aim: The aim of this study is to identify the risk variables for mortality in patients undergoing venoarterial extracorporeal membrane oxygenation (VA ECMO) in order to better predict their prognosis.

Material and Methods: Following a retrospective analysis of VA ECMO patients treated between January 2013 and April 2021, they were classified into mortality and survival groups. Those over the age of 18 and on VA ECMO for more than 24 hours were included in the study.

Results: A total of 50 patients were included in the study, and the mortality rate was found to be 84%. VA ECMO support lasted an average of 5.8± 4.61 (1-18) days, while ICU stays averaged 17.8± 25.85 (1-124) days. (p < 0.05). The MELD-XI score (modeling end-stage liver disease without INR), the ECMO-ACCEPTS score (a VA ECMO scoring system for patients undergoing ECMO), the 18th and 24th lactate levels, the lactate peak value within the first 24 hours, following ECMO were all factors associated with mortality.

Discussion: The MELD-XI score, calculated during the early period, and the measurements of lactate levels at 12 hours, 18 hours, and 24 hours, and the peak lactate value, rather than lactate clearance, were identified as crucial prognostic factors for mortality. Furthermore, the ECMO-ACCEPTS score was also determined to be a significant predictor of mortality.

Keywords
ECMO-ACCEPTS Score, Lactate, MELD-XI Score, Venoarterial Extracorporeal Membrane Oxygenation

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This study was approved by the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (Date: 2021-06-24, No: 300)
Introduction
In cases of acute and reversible heart-lung injury unresponsive to standard treatment, venoarterial extracorporeal membrane oxygenation (VA ECMO) is a modality of hemodynamic support used to deliver adequate oxygenation. Although its use has increased over the past decade, concerns over its prognosis have arisen due to serious complications and high mortality rates (40-84%) [1]. Improving clinical outcomes in ECMO relies heavily on identifying risk factors. The prognostic value of lactate, lactate clearance, and scoring systems optimized for the early phases has been demonstrated in the most current literature on the subject [2-4]. A high-accuracy scoring system, which incorporates all mortality predictors and indications and meets worldwide standards has yet to be devised, despite the growing body of study in this area. Therefore, there is a greater emphasis in the literature on the significance of appropriate patient selection. The aim of this study is to identify the prognostic parameters for patients undergoing VA ECMO for common indications.

Material and Methods
Patients who had surgery at the Cardiovascular Surgery clinic of Izmir Katip Celebi University Hospital between January 2013 and April 2021 were retrospectively evaluated for VA ECMO after receiving ethical approval (decision No. 300, dated 24-06-2021) from Izmir Katip Celebi University Non-Interventional Clinical Research Ethics Committee. Only patients aged 18 or older who received VA ECMO for at least 24 hours were included in the study. Those on venovenous (VV) ECMO, those with respiratory failure requiring ECMO, and pregnant women were excluded from the study. A total of 56 patients on ECMO were considered for the study, with five of them excluded due to respiratory failure and one due to pregnancy. A total of fifty patients were included and categorized into two groups: a mortality group consisting of 42 patients (84%) and a survival group comprising 8 patients (16%). Hospital information management system records, archives, and file records were used for patient data. All patients were managed by a multidisciplinary team pursuing standard institutional protocols. Demographic information and comorbidities and VA ECMO indications were recorded. If the indication was postcardiotomy, type of operation, emergency or elective surgery status, cross-clamp duration, duration of cardiopulmonary bypass (CPB), and the time to initiate ECMO after cross-clamp removal were recorded in addition to such factors as renal replacement therapy need, inotrope scores (IS), intra-aortic balloon pump (IABP) support before the procedure, EuroSCORE II (European System for Cardiac Operative Risk Evaluation), transthoracic echocardiography findings, hemogram, biochemistry, coagulation values, blood gas parameters, blood product transfusion, length of stay on a mechanical ventilator, length of stay in the intensive care unit, complications together with 30-day survival. Several lactate readings were taken on admission to the intensive care unit (ICU) and at the 6th, 12th, 18th, and 24th hours to determine “lactate clearance” over the formula: Initial Lactate - Delayed Lactate / Initial Lactate x 100 [4]. The highest serum lactate value in the first 24 hours during ECMO was recorded as “lactate peak level.”

The MELD-XI score was calculated over ‘MELD-XI = 11.76 x log (creatinine) + 5.112 x log (total bilirubin) + 9.44’ based on the laboratory results measured within the first 6-12 hours [5], while the ECMO-ACCEPTS score was calculated over the parameters in the figure [6].

Statistical Analysis
Data analysis was performed using the SPSS 25 software package (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The frequencies, rates, mean and standard deviations of the patients in terms of different variables were presented as descriptive statistics. Since the survival group consisted of eight individuals, the Mann-Whitney-U Test was used in the comparisons between the groups. In addition to the mean and standard deviation values, the mean rank and median values were also included. Fisher’s exact analysis was carried out and cross tables were added to examine whether there was a significant difference between the distribution ratios of the groups into categories in the categorical data. In addition, logistic regression was used in which mortality and survival groups were considered as dependent variables, also sensitivity and specificity values were examined for potential variables to differentiate these groups, the cut-off values were calculated, and ROC (Receiver Operating Characteristics) curves were drawn. The significance level for all analysis results was determined as p < 0.05.

Ethical Approval
Ethics Committee approval for the study was obtained.

Results
We evaluated 50 patients (11 females, 39 males, mean age: 56.24±14.57 years, range 18-77 years) who underwent VA ECMO. The mortality group consisted of 42 (84%) cases, the survival group consisted of 8 (16%) cases. Demographic characteristics, comorbidities, and data of postcardiotomy patients are shown in Table 1. The ECMO - ACCEPT score and the MELD- XI score were significantly higher in the mortality group (Table 2).

Figure 1. ROC curve for MELD-XI score
ROC: Receiver operating characteristic curves of scoring systems; MELD-XI: Model for end-stage liver disease excluding INR.
There was no statistically significant difference found among the indications for VA ECMO (cardiogenic shock after acute myocardial infarction, arrhythmia, extracorporeal cardiopulmonary resuscitation, congestive heart failure, left ventricular assist device bridging, postcardiotomy cardiogenic shock) between the groups ($p > 0.05$).

Lactate peak levels and lactate levels at 12, 18, and 24 hours were significantly higher in the mortality group (respectively $p = 0.036, p = 0.009, p = 0.028$). Both groups had similar lactate clearances at 6, 12, 18, and 24 hours. No statistically significant

### Table 1. Demographic data, comorbidities and operational data on postcardiotomy patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mortality Group (n=42)</th>
<th>Survival Group (n=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>55.67±15.53</td>
<td>59.25±8.69</td>
<td>0.751</td>
</tr>
<tr>
<td>BMI (mean±SD)</td>
<td>26.83±4.07</td>
<td>27.51±2.72</td>
<td>0.653</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>8(19)</td>
<td>3(37)</td>
<td>0.351</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>32(11.8)</td>
<td>40(19.64)</td>
<td>0.471</td>
</tr>
<tr>
<td>Diabetes Mellitus (n, %)</td>
<td>12(28)</td>
<td>2(25)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>16(37.5)</td>
<td>3(37.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peripheral artery disease (n, %)</td>
<td>12(4)</td>
<td>0(0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cerebrovascular disease (n, %)</td>
<td>3(7.1)</td>
<td>0(0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

### Table 2. Scoring of patients and sub-parameters of scoring

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mortality Group (n=38)</th>
<th>Survival Group (n=32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARG (n, %)</td>
<td>16(50)</td>
<td>3(50)</td>
<td>1.000</td>
</tr>
<tr>
<td>MVR (n, %)</td>
<td>5(15.6)</td>
<td>2(33)</td>
<td>0.302</td>
</tr>
<tr>
<td>AVR (n, %)</td>
<td>6(18.7)</td>
<td>0(0)</td>
<td>0.562</td>
</tr>
<tr>
<td>Other surgery (n, %)</td>
<td>5(15.6)</td>
<td>2(33)</td>
<td>0.302</td>
</tr>
<tr>
<td>Cross clamp time (minutes) (mean±SD)</td>
<td>76.55±46.46</td>
<td>92.17±57.48</td>
<td>0.327</td>
</tr>
<tr>
<td>CPB duration (minutes) (mean±SD)</td>
<td>159.2±88.56</td>
<td>159±75.08</td>
<td>0.546</td>
</tr>
</tbody>
</table>

### Table 3. Areas under the curve (AUC), specificity and sensitivity of significant variables and cut off value

<table>
<thead>
<tr>
<th>Time to initiate ECMO (hour)</th>
<th>AUC*</th>
<th>95% Confidence Interval (CI)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Standard Error (SE)</th>
<th>Cut off value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to initiate ECMO (hour)</td>
<td>0.690</td>
<td>0.517–0.864</td>
<td>62.5</td>
<td>67</td>
<td>0.069</td>
<td>0.75</td>
<td>0.028</td>
</tr>
<tr>
<td>ECMO-ACCEPTS score</td>
<td>0.737</td>
<td>0.545–0.928</td>
<td>62.5</td>
<td>83</td>
<td>0.098</td>
<td>20.5</td>
<td>0.035</td>
</tr>
<tr>
<td>MELD-XI score</td>
<td>0.786</td>
<td>0.645–0.927</td>
<td>75</td>
<td>73.8</td>
<td>0.072</td>
<td>16.89</td>
<td>0.011</td>
</tr>
<tr>
<td>12-hour lactate</td>
<td>0.735</td>
<td>0.558–0.912</td>
<td>75</td>
<td>73.8</td>
<td>0.090</td>
<td>4.45</td>
<td>0.037</td>
</tr>
<tr>
<td>18-hour lactate</td>
<td>0.792</td>
<td>0.623–0.961</td>
<td>75</td>
<td>76.2</td>
<td>0.086</td>
<td>2.90</td>
<td>0.010</td>
</tr>
<tr>
<td>24-hour lactate</td>
<td>0.777</td>
<td>0.605–0.949</td>
<td>75</td>
<td>78.6</td>
<td>0.088</td>
<td>2.45</td>
<td>0.014</td>
</tr>
<tr>
<td>Lactate peak level</td>
<td>0.747</td>
<td>0.588–0.906</td>
<td>62.5</td>
<td>71.4</td>
<td>0.081</td>
<td>8.75</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*Time to initiate ECMO: time to initiate ECMO after cross-clamp removal; AUC: area under the receiver operating characteristic curve; ECMO: extracorporeal membrane oxygenation; ECMO-ACCEPTS score: mortality prediction score for patients undergoing ECMO; ROC: Receiver operating characteristic curves of scoring systems.
difference was observed in baseline lactate, 1-hour, and 6-hour lactate values (p > 0.05). Figure 1 shows the MELD-XI score ROC curve graph, Figure 2 shows the ECMO-ACCEPTS score, and Figure 3 shows the lactate level at 18 hours.

Discussion

This single-center study examines the predictive prognostic factors indicative of mortality in VA ECMO application. It was found that MELD-XI and ECMO-ACCEPTS scores, lactate values at the 12th, 18th, and 24th hours, and lactate peak values could be predictive of mortality. In our study, the 30-day mortality rate was 84%, which was quite high, but was consistent with the range reported in studies with small sample sizes (55-84%) [1,2,3,7]. The current ELSO registry shows the results of ECMO applied after postcardiotomy in more than 430 centers (n=4,520) worldwide, reporting a mortality rate of 58.3% [8]. Risk factor classification for VA ECMO is extremely important to identify high mortality risk group patients and to reasonably allocate the resources for patients with a chance of recovery.

It has been reported that Euroscore can be used to predict the need for perioperative prophylactic VA ECMO in high-risk patients [9]. However, EuroSCORE II only evaluates CABG, heart valve, and thoracic aorta surgery patients, not heart transplantation or left ventricular assist device (LVAD) patients [10]. A total of 240 cardiovascular surgery patients received VA ECMO in an observational single-center study and EuroSCORE II did not predict short-term or long-term results in this patient population [11].

This study examined EuroSCORE II in mortality and survival groups, but the results were not found statistically significant (p =0.354). Our heterogeneous patient sample was mostly post-cardiotomy. It is believed that EuroSCORE II should be tested in a varied VA ECMO patient population to evaluate whether EuroSCORE II would be adequate.

The MELD XI score, which clinically analyzes liver and kidney functions, has become increasingly important in predicting the prognosis of ECMO patients in the past ten years. The MELD XI score, obtained by subtracting the INR from the MELD score used to assess end-stage liver disease, was first devised to better categorize cirrhotic patients on anticoagulation awaiting transplantation [5].

It has been cited in the literature as a predictive factor for decompensated heart failure (HF), heart transplantation, LVAD implantation, and other cardiac surgery operations [5,12,13]. In a retrospective study of 194 VA ECMO patients, the MELD score was found to be related with 90-day mortality, while MELD IX was not [14].

Ayers et al [2] examined the effect of the MELD-XI score on mortality in 187 patients undergoing VA ECMO. Their creatinine, total bilirubin values and MELD-XI scores in the first 48 hours on ECMO were calculated, which were classified as high-risk indicator if the score was >14, and low risk if the score was <14. The In-hospital mortality rate was higher in the high-risk group (74% vs. 39%; p <0.001). The high-risk group had a significantly greater in-hospital mortality rate than the low-risk group (74% vs 39%; p 0.001). MELD-XI was found to have high prognostic value (AUC 0.690, 95% CI 0.62-0.77) in a ROC analysis conducted within the same study. Different from findings by Ayers et al [2] we found that the MELD-XI score, calculated in the first 6-12 hours instead of the first 48 hours, was similarly significantly higher in the mortality group (27.79±7.92; p=0.011) (AUC 0.786; 95% CI 0.545-0.928). The calculated threshold value in our study was 16.89, suggesting a higher discrimination result (AUC 0.690 vs AUC 0.786).

Becher et al [6] developed the ECMO-ACCEPTS score to identify VA ECMO risk predictors. While doing so, patients were selected from 3 groups: acute HF, acute coronary syndrome and post-transplantation HF groups. The presence of atrial fibrillation (AF) or pulmonary hypertension (PH) were included in a low-mortality risk category. The thorough remark that the researchers penned [15] did not explain how preexisting comorbidity lowers the chances of mortality. We believe that this circumstance may also lead to confusion in evaluations of prognosis because patients with a worse clinical status will also present with these comorbidities. In our study, there was significantly higher ECMO-ACCEPTS in the mortality group (p =0.035). Moreover, while an AUC of 0.64 was obtained in the study by Becher et al [6] it was seen in our study that the acceptable level of discrimination could be obtained with an AUC of 0.73. However, the heterogeneity of VA ECMO indications in our study should not be ignored.

To assess prognosis in VA ECMO, various scoring systems, including ENCORE (prediction of cardiogenic shock outcome for AMI patients salvaged by VA-ECMO) and REMEMBER (Extracorporeal membrane oxygenation after coronary artery bypass grafting), derived from selecting populations, are also mentioned in the literature [16,17]. However, the aforementioned scoring systems’ application is constrained by their small sample sizes and origins in specific communities. Similar to prior research, our study’s small and heterogeneous sample size could have an effect on the findings. Multicenter studies using a bigger sample size are necessary for this particular patient population.

Lactate is another prognostic factor for patients receiving VA ECMO. A complicated process called perioperative lactate metabolism occurs in cardiac surgery. In addition to suggesting tissue hypoxia, hyperlactatemia can also be affected by clinical situations such as low cardiac output syndrome, septic shock, cardiac tamponade, mesenteric ischemia, and renal failure [18]. When the mortality and survival groups were compared in our study, no difference was observed in terms of peripheral artery disease, septic shock, and renal failure.

In a study by Park SJ et al [19], conducted on 115 patients, 12-hour lactate value during ECMO was the highest prognostic value in terms of mortality prediction in the analysis (AUC 0.79, 95% CI 0.69-0.89, p<0.001). The 18th-hour lactate value was more significant than the 12th-hour value in our study. The cut-off value was 2.9 (Youden index 0.51) (95% CI 0.62-0.96%, sensitivity 76.2%, specificity 75%, p=0.01). The 18-hour lactate measurement demonstrated stronger discrimination with 0.792 AUC. However, studies have not generally evaluated the 18-hour lactate value to date. We found that 12-hour and 24-hour lactate readings could possibly be a predictive factor.

Laimoud et al [20] examined lactate levels in 106 patients undergoing VA ECMO for cardiogenic shock. In addition to static
lactate values, the highest lactate value in the first 24 hours was determined as a lactate peak level and was an important prognostic indicator (AUC 0.889, 95% CI 0.825-0.953, p<0.001). Our mortality group had greater lactate peak levels (p=0.028) at which the threshold level was 8.75 (Youden index 0.33). Its distinctive feature was lower than other static lactate levels (AUC 0.747, 95% CI 0.588-0.906, sensitivity 71%, specificity 62.5%). Several studies have examined lactate dynamics, suggesting that serial lactate variations and clearance may be better circulatory support and prognostic markers than single lactate measurements [4,20,21].

In our study, we did not find a significant difference in terms of lactate clearance between the mortality and survival groups (p>0.05).

Delaying ECMO-onset can cause tissue hypoxia and permanent organ failure, whereas early treatment reduces comorbidities and improves overall survival [22]. Yet, another study found that initiating ECMO earlier did not improve 30-day patient outcomes, particularly in low-volume hospitals [23].

In our study, the mortality group had a mean of 56.2 hours on ECMO starting from the initiation, while the survival group had 5.7 hours (sensitivity 67%, specificity 62.5%; AUC 0.690; 95% CI 0.517-0.864). Early VA ECMO application for the inability to wean from postcardiomyopathy CPB can boost cardiac output (CO) and prevent multi-organ failure, but it is invasive and risky [24].

**Limitations**

Our study was planned as a single-center retrospective study, in this respect, we think that it should be supported by multicenter and prospective studies. Our patient sample population was made up of a small group. In our patient group, the indication for ECMO was predominantly postcardiomyopathy shock. The number of patients has been limited with extra-corporeal cardiopulmonary resuscitation, bridging to heart transplantation, LVAD bridging, and other indications. Therefore, our patient group does not have a homogeneous distribution.

**Conclusion**

There is currently no standardized scoring method for VA ECMO patients that is both highly accurate and comprehensive, including all indications and the vast majority of mortality factors. Despite the controversy surrounding the MELD-XI score, which is generated shortly after, we aim to draw attention to the prognostic value of the recently defined ECMO-ACCEPTS score in this patient group, proposing that static lactate levels and peak lactate values are useful criteria for assessing the risk associated with impaired lactate clearance. However, we believe these findings need to be confirmed by larger randomized controlled studies.

**Scientific Responsibility Statement**

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

**Animal and Human Rights Statement**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Conflict of Interest**

The authors declare that there is no conflict of interest.

**References**

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