Procalcitonin dynamics, lactates, and haemoglobin serum levels might be a useful predictive tool of mortality in patients undergoing veno-venous extracorporeal oxygenation membrane support. Single centre experience

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Abstract

Background: Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a well-established therapeutic option in respiratory failure refractory to mechanical ventilation. Due to the growing popularity of VV-ECMO, new methods to improve patient outcome are desired. This study aimed to evaluate the impact of patient age, sequential organ failure assessment score, respiratory ECMO survival prediction score, and early laboratory results on mortality of patients undergoing VV-ECMO.

Methods: The study population included 39 patients who underwent VV-ECMO between 2016 and 2019. The study compared the laboratory results during the first three days of therapy. The parameters included procalcitonin, C-reactive protein, haemoglobin, lactates, arterial blood partial pressure of carbon dioxide and oxygen.

Results: The decrease of procalcitonin by 10% between the 1st and the 3rd day was more often observed in the positive outcome group (71.4% vs. 38.9%, $P = 0.041$). Serum lactate concentrations at the 1st day corresponded with the negative outcome (AUC = 0.70, $P = 0.026$). The negative outcome group had a higher occurrence of serum lactates of 2 mmol L^{-1} at the 1st day ($P = 0.039$). The haemoglobin levels at the 1st and 3rd day corresponded with patients' outcome (AUC = 0.69, $P = 0.023$ and AUC = 0.074, $P = 0.006$, respectively).

Conclusions: The study showed significant differences in early laboratory results between patients with a positive and negative outcome. In our opinion, serum lactate, haemoglobin and procalcitonin concentrations should be monitored daily to ensure an optimal therapeutic strategy and improve patient outcome. Our study provides valuable observations on predictive tools in VV-ECMO and possible directions for future research.

Key words: procalcitonin, haemoglobin, extracorporeal membrane oxygenation, ECMO, predictive tools.

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Veno-venous extracorporeal membrane oxygenation (VV-ECMO) support is a well-established therapeutic option in respiratory failure refractory to mechanical ventilation [1]. The number of veno-venous therapies in the international registry is over 19,000 procedures; however, approximately 3,000 VV-ECMO supports were performed between June 2018 and January 2019. This shows the growing popularity of VV-ECMO, although guidelines based on well-established evidence are missing.

The qualification of patients who could benefit from ECMO therapy remains elusive. The survival rate in respiratory failure among adult patients is reported to be approximately 59% [2]. Patient inclusion criteria are based on Murray's score, which includes consolidations presented in chest X-ray, PaO_2/FiO_2 ratio, positive end-expiratory pressure value and patient lung compliance [3]. Multiple predictive models of mortality in VV-ECMO patients have been proposed [4]. The authors of these predictive models evaluated the patient's age, pre-ECMO treatment and laboratory results and patient condition severity measured by the sequential organ failure assessment score (SOFA). However, each of these predictive models concerns variables obtained prior to the therapy only. Most ECMO studies did not assess the impact of parameters collected during the early period of ECMO support on patient outcome. Thus, the predictors of adequate therapeutic approaches should be constantly researched in order

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to help clinicians determine the optimal therapy direction.

The aim of this study was to evaluate the impact of the patient's age, SOFA score, respiratory ECMO survival prediction (RESP) score and early laboratory results on mortality of patients undergoing VV-ECMO support in our centre.

METHODS

This was a retrospective study approved by the Ethical Committee of the Medical University of Lublin. Focusing on the nature of the study, the requirement for obtaining informed consent from each patient was waived.

The study population included 39 consecutive patients who underwent VV-ECMO support between 2016 and 2019. The patients were qualified for VV-ECMO using the standard department inclusion criteria of potentially reversible severe respiratory failure with pulmonary infiltrates in chest X-ray and insufficient mechanical ventilation defined as $PaO_2/FiO_2 < 100$ despite PEEP > 15 cm H_2O (1 kPa). Each patient had SOFA and the respiratory ECMO survival prediction (RESP) score calculated before implanting the device.

The therapy was performed using ILA Novalung and Maquet consoles, standard ECMO circuits (X Lung Kit, Xenios, Heilbronn, Germany) and oxygenators (Maquet Cardiopulmonary GmbH, Rastatt, Germany) with blood flow set between 4.5 and 6 L min^{-1} and sweep gas of 3–5 L min^{-1}. A protective ventilation protocol was used in all patients with $FiO_2 \leq 60\%$, a tidal volume of 4–5 mL kg^{-1}, PEEP of 12–20 cm H_2O (1–2 kPa) and driving pressure under 15 cm H_2O (1 kPa). Muscle-relaxation drugs were used in all patients for the first 48 hours of the support. None of the patients underwent a prone position manoeuvre due to an increased risk of decannulation.

The patients were divided into two groups based on therapy outcome: positive (group P) and negative (group N). A positive outcome was defined as surviving until discharge from the department. A negative outcome was defined as death during or after ECMO support while the patient stayed in the department. The patient demographics are presented in Table 1.

The study evaluated the patients' age, SOFA score and RESP score prior to implementing the ECMO support. The study compared the laboratory results of the first three days of VV-ECMO therapy. The parameters included procalcitonin, C-reactive protein (CRP), haemoglobin, lactates, arterial blood partial pressure of carbon dioxide (pCO_2) and oxygen. In cases where more than one measurement was performed per day, the highest value of the day was used in the study for lactates and pCO_2, and the lowest value of the day was used for haemoglobin and arterial blood partial pressure of oxygen.

Additionally, the dynamics of inflammatory markers were evaluated. We observed a noticeable reduction of procalcitonin and CRP, defined as a decrease of at least 10% of the value between the first and the third day of the therapy. We also analysed and compared the frequency of patients reaching a serum lactate level of 2 mmol L^{-1} or above in both groups.

Statistical analysis

Statistical data were collected in Microsoft Excel sheets (Microsoft, Redmond, USA). Categorical variables are presented as numbers and frequencies and are analysed using the χ^2 test (χ). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test in the Lilliefors modification. Continuous variables with normal distribution are presented as means and 95% confidence intervals (95% CI) and are analysed using Student's *t*-test (*t*). Non-normally distributed variables are presented as medians and interquartile range (IQR) and analysed using the Mann-Whitney *U* test (*U*). Impact of the parameter on the mortality was established using the receiver operating characteristics (ROC) curves and the area under the curve (AUC). All statistical calculations were performed using Statistica 13.3 (StatSoft Inc., Tulsa, USA). *P*-values are presented with letters in brackets (χ, *t* or *U*) indicating which statistical test was used to calculate the value.

Missing data

Due to the retrospective nature of the study, some of the laboratory results were unavailable. The patients were excluded from some comparisons

TABLE 1. Patient characteristics

Demographics	Positive outcome group	Negative outcome group	*P*
Patients (male)	21 (17)	18 (11)	0.17 (χ^2)
Age, years	47 (33–70)	52 (30–71)	0.37 (*U*)
SOFA score	11 (6–18)	11 (6–16)	0.70 (*U*)
RESP score	4 ([–9]–7)	1 ([–3]–6)	0.13 (*U*)
Diagnosis			
Bacterial pneumonia	10 (47.6%)	11 (61.1%)	0.52 (χ^2)
Viral pneumonia	8 (38.1%)	4 (22.2%)	0.32 (χ^2)
Pancreatitis	2 (9.5%)	1 (5.6%)	0.64 (χ^2)
Mediastinitis	1 (4.8%)	2 (11.1%)	0.45 (χ^2)

The table presents patient characteristics of positive and negative outcome groups. Values are presented as medians, minima, maxima for age, SOFA and RESP, and as the number of patients and frequencies for gender and diagnosis.
SOFA – sequential organ failure assessment, RESP – respiratory ECMO survival prediction
P-value was calculated using the Mann-Whitney *U* test or the χ^2 test

in cases where particular results were unobtainable. Therefore, the actual number of a patient compared for each day and laboratory result are given in the second column of the tables.

RESULTS

Demographics and clinical status of patients

Our population was mostly constituted by males (71.8%) with median SOFA admission score 11, and median RESP score 3. The main cause of respiratory failure in our patients was viral and bacterial pneumonia (84.6%).

We did not notice a predictable value of RESP (AUC = 0.65; P = 0.10) and SOFA (AUC = 0.53; P = 0.69) scores or a patient's age (AUC = 0.59; P = 0.37) to anticipate patient mortality in our study group.

Laboratory data

Neither oxygen nor carbon dioxide arterial pressures obtained during the first three days of the therapy predicted the patient outcome. pCO_2 (1st day AUC = 0.56; P = 0.57; 2nd day AUC = 0.55; P = 0.63; 3rd day AUC = 0.55; P = 0.66); pO_2 (1st day AUC = 0.54; P = 0.67; 2nd day AUC = 0.5; P = 1.0; 3rd day AUC = 0.57; P = 0.49).

Serum concentrations of inflammatory markers did not correspond with the patient outcome (Figure 1).

The decrease of procalcitonin by at least 10% between the first and the third day was significantly more often observed in the positive outcome group (71.4%, 15/21) than in the negative outcome group (38.9%, 7/18) (P = 0.041). A similar correlation pertained to CRP dynamics (P = 0.051).

Serum lactate concentrations on the first day had a significant predictive value for the negative outcome, AUC = 0.70 (95% CI: 0.52–0.88; P = 0.026). No difference was observed on the second and the third day (Figure 2, Table 2). The negative outcome group had significantly higher occurrence of serum lactate concentrations of 2 mmol L^{-1} or above on the first day, 64.7% (11/17) vs. 29.4% (5/17) in the positive outcome group (P = 0.039). The prevalence of 2 mmol L^{-1} or above of lactates on the second or third day was not associated with greater mortality (P = 0.086 and 0.059 respectively).

The haemoglobin levels on the first and the third day corresponded with the patients outcome with AUC = 0.69 (95% CI: 0.52–0.86; P = 0.023) and AUC = 0.74 (95% CI: 0.57–0.90; P = 0.006) respectively. Mean values of haemoglobin are presented in Table 2.

DISCUSSION

The study showed statistically significant differences in early laboratory results between patients with positive and negative outcome of VV-ECMO support.

In the current study, patient's age, SOFA and RESP score did not have a predictive value. In our opinion, the course of the therapy might have a huge impact on patients' outcome that potentially cannot be predicted by pre-ECMO scales. It

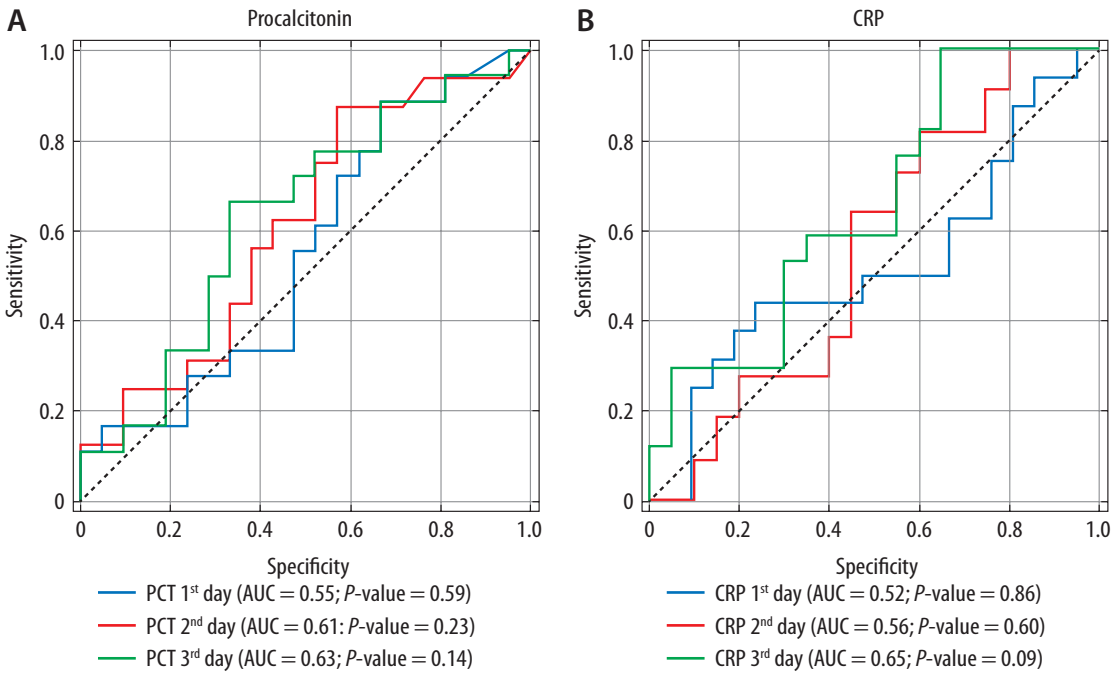

FIGURE 1. ROC curves for procalcitonin (**A**) and C-reactive protein (**B**) with calculated AUC and P-value
ROC – receiver operating characteristics, AUC – area under curve, CRP – C-reactive protein

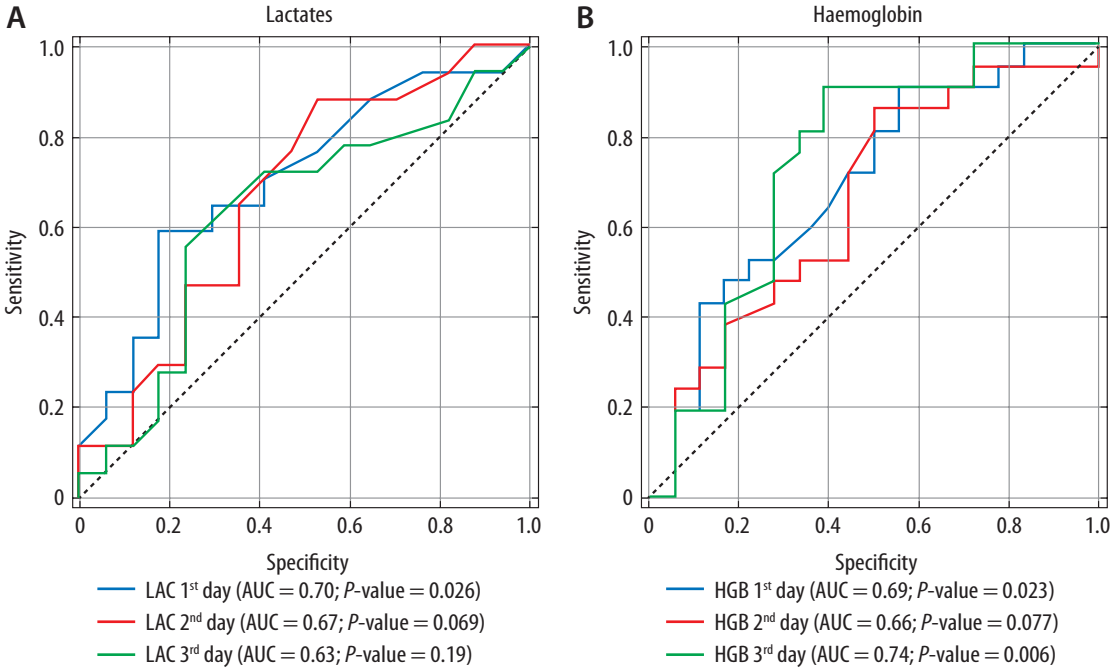

FIGURE 2. ROC curves for lactates (**A**) and haemoglobin (**B**) with calculated AUC and *P*-value
ROC – receiver operating characteristics, AUC – area under curve, LAC – lactates, HGB – haemoglobin

includes occurrence of complications, different protocols across the ECMO centres, and heterogeneous population of intensive care patients. Even the RESP score, which is postulated as the most accurate prediction model for VV-ECMO, had different external validation results in various cohorts which were presented in a recent meta-analysis [5].

In our study inflammatory marker values were similar in both groups. However, a procalcitonin decrease had a negative correlation with patient mortality. At least 10% decrease of the value between the first and the third day of the therapy was significantly more often observed in patients with a positive outcome. In contrast, statistical significance was not obtained for CRP in the current study. It might be caused by higher sensitivity of procalcitonin due to shorter half-time in comparison to CRP [6]. The result of this observation suggests that procalcitonin measurements and monitoring of its dynamics should be performed daily in VV-ECMO patients to establish the most adequate treatment of the primary disease.

The results of arterial blood gases were undifferentiated between both groups. Hypercapnia was reported as an independent factor of mortality in ICU patients [7]. In the current study, median values of pCO_2 were over 50 mm Hg in both groups in the whole observation period. However, this parameter did not correlate with patient outcome.

In our study the haemoglobin levels differed between both groups during the first and the third day, indicating the importance of monitoring and maintaining optimal haemoglobin levels. The goal of optimal haemoglobin levels remains elusive. The mean haemoglobin levels in our patient were over 10 g dL^{-1} in both groups as recommended in the Polish VV-ECMO guidelines [8]. In the current study a significant correlation was observed be-

TABLE 2. Lactates and haemoglobin

Parameter	P vs. N	Group P	Group N	*P*
Lactates 1st day	17 vs. 17	1.7 (IQR 1.3–2.1)	2.2 (IQR 1.7–3.3)	0.045 (*U*)
Lactates 2nd day	17 vs. 17	1.7 (IQR 1.4–2.4)	2.1 (IQR 1.8–2.9)	0.091 (*U*)
Lactates 3rd day	17 vs. 18	1.7 (IQR 1.4–2.0)	2.2 (IQR 1.6–2.8)	0.19 (*U*)
Haemoglobin 1st day	21 vs. 18	11.68 (95% CI: 10.97–12.38)	10.54 (95% CI: 9.54–11.54)	0.055 (*t*)
Haemoglobin 2nd day	21 vs. 18	11.76 (95% CI: 11.12–12.39)	10.94 (95% CI: 10.20–11.69)	0.089 (*t*)
Haemoglobin 3rd day	21 vs. 18	11.42 (95% CI: 10.97–11.88)	10.47 (95% CI: 9.68–11.26)	0.028 (*t*)

The table presents the daily median values with interquartile range for lactates (mmol L^{-1}), and mean and 95% confidence intervals for haemoglobin (g dL^{-1}). Numbers in the second column indicate number of patients from each group in analysis.
P-value was calculated using the Mann-Whitney test (*U*) or Student's *t*-test (*t*)
P – positive outcome, N – negative outcome

tween haemoglobin concentration and patient mortality. This observation might lead to the conclusion that even a higher goal of haemoglobin level could be beneficial for this group of patients. Although the results of some studies suggested that 7–9 g dL^{-1} of haemoglobin levels should be sufficient to maintain adequate oxygen delivery in an ECMO patient [9, 10], some experts postulate higher haemoglobin concentrations (12–14 g dL^{-1}) [11].

In our patients, the first day lactate levels corresponded with the mortality. Reaching the level of ≥ 2 mmol L^{-1} during the first 24 hours of the therapy was significantly more often observed in patients in the negative outcome group. The predictive value of lactate peak during the first 24 hours was previously observed in veno-arterial ECMO therapy [12]. The potential benefits of preventing lactate elevation during the first day require further studies.

Limitations

The study has some limitations. It was a small-population retrospective study. We only compared the lowest daily values of haemoglobin levels, and we did not take into account whether the patient required a red blood cell transfusion to maintain the haemoglobin levels and whether transfusions reduced the mortality. We did not evaluate the impact of ECMO-related complications such as major bleeding; therefore the patient could have had a negative outcome despite improving during the therapy. We did not correlate the decrease of inflammatory markers with the use of continuous renal replacement therapy (CRRT), which could have affected the results, as CRRT is reported to reduce the procalcitonin values but not CRP [13].

CONCLUSIONS

Serum lactate, haemoglobin and procalcitonin concentrations should be monitored daily to ensure an optimal therapeutic strategy and improve patient outcome. It seems that the decrease of serum procalcitonin in an early phase of VV-ECMO support is associated with reduced mortality. However, there is a need for further studies to confirm our findings.

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