Prediction of 6-Month Mortality Using Pre-Extracorporeal Membrane Oxygenation Lactate in Patients with Acute Coronary Syndrome Undergoing Veno-Arterial-Extracorporeal Membrane Oxygenation

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Background: The effectiveness of extracorporeal membrane oxygenation (ECMO) for patients with refractory cardiogenic shock or cardiac arrest is being established, and serum lactate is well known as a biomarker of end-organ perfusion. We evaluated the efficacy of pre-ECMO lactate for predicting 6-month survival in patients with acute coronary syndrome (ACS) undergoing ECMO.
Methods: We reviewed the medical records of 148 patients who underwent veno-arterial (VA) ECMO for ACS between January 2015 and June 2020. These patients were divided into survivors and non-survivors based on 6-month survival. All clinical data before and during ECMO were compared between the 2 groups.
Results: Patients' mean age was 66.0±10.5 years, and 116 (78.4%) were men. The total survival rate was 45.9% (n=68). Cox regression analysis showed that the pre-ECMO lactate level was an independent predictor of 6-month mortality (hazard ratio, 1.210; 95% confidence interval [CI], 1.064–1.376; p=0.004). The area under the receiver operating characteristic curve of pre-ECMO lactate was 0.64 (95% CI, 0.56–0.72; p=0.002; cut-off value=9.8 mmol/L). Kaplan-Meier survival analysis showed that the cumulative survival rate at 6 months was significantly higher among patients with a pre-ECMO lactate level of 9.8 mmol/L or less than among those with a level exceeding 9.8 mmol/L (57.3% vs. 31.8%, p=0.0008).
Conclusion: A pre-ECMO lactate of 9.8 mmol/L or less may predict a favorable outcome at 6 months in ACS patients undergoing VA-ECMO. Further research aiming to improve the accuracy of predictions of reversibility in patients with high pre-ECMO lactate levels is essential.

Keywords: Cardiogenic shock, Acute coronary syndrome, Lactic acid, Extracorporeal membrane oxygenation

Introduction

Cardiogenic shock (CS) is a clinical condition involving inadequate tissue perfusion due to cardiac dysfunction. The definition includes the following hemodynamic parameters: persistent hypotension (systolic blood pressure <90 mm Hg or mean arterial blood pressure 30 mm Hg lower than baseline) with a severe reduction in the cardiac index (<1.8 L/min/m^2 without support or <2 to 2.2 L/min/m^2 with support) and adequate or elevated filling pressures [1]. Some patients with CS are resistant to medical treatment, and in that case, extracorporeal membrane oxygenation (ECMO) provides practical cardiopulmonary support for myocardial recovery [2]. In addition, ECMO can be used as

a "bridge to decision" in patients with acute and rapidly deteriorating heart failure or CS to stabilize hemodynamics, recover end-organ function, and enable an evaluation of the possibility of either heart transplantation or a more durable ventricular assist device [3].

ECMO is an important rescue therapy for severe CS, but mortality and morbidity remain high. The Survival After Veno-Arterial ECMO (SAVE) score may be the most popular tool to predict survival for patients receiving ECMO for refractory CS [4]. The SAVE score consists of several pre-ECMO parameters: age, weight, diagnosis, chronic renal failure, acute pre-ECMO organ failure, peak inspiratory pressure, duration of intubation, cardiac arrest (CA), pulse pressure, diastolic pressure, and HCO_3^- level [4]. This tool has been regarded as a complex model that includes many variables and numerous categories, necessitating an electronic calculation.

Lactate is formed from pyruvate in the cytosol as part of glycolysis [5]. Raised blood lactate concentrations in critically ill patients are frequently viewed as evidence of tissue hypoxia (type A hyperlactatemia). This tissue hypoxia has been widely believed to be a major cause of organ failure and mortality. Moreover, changes in lactate concentration over time during an intervention have been proposed as a treatment endpoint [6-8].

ECMO patients often die in a worsening condition after discharge from hospital or 1 month after ECMO initiation. However, most previous studies focused on predictive value of serum lactate levels for short-term outcomes, such as in-hospital or 1-month mortality, in ECMO patients. The purpose of our study was to evaluate the effect of pre-ECMO lactate levels on 6-month survival in patients with acute coronary syndrome (ACS) undergoing ECMO.

Methods

Patient selection

We retrospectively collected information on CS or CA patients who underwent veno-arterial (VA) ECMO from January 2015 to June 2020 at Chonnam National University Hospital. CS was diagnosed based on the 2016 European Society of Cardiology guideline (systolic blood pressure <90 mm Hg with appropriate fluid resuscitation with clinical and laboratory evidence of end-organ damage, such as cold extremities, oliguria, narrow pulse pressure, metabolic acidosis, elevated serum lactate, and elevated serum creatinine) [2]. VA ECMO was indicated for CA or refractory CS patients with tissue hypoperfusion, reduced left ventricular ejection fraction, and hypotension resistant to high-dose vasopressors or inotropic agents. In this period, 293 patients underwent VA-ECMO. Moreover, 148 adult patients were diagnosed with CA or refractory CS following ACS. Patients meeting the following criteria were excluded from the study: other causes of VA-ECMO support (such as post-cardiotomy shock, septic shock, and other undifferentiated origins of shock), age ≤18 years, total ECMO duration <12 hours, and the availability of insufficient laboratory data. We divided all patients into survivors and non-survivors at 6 months, regardless of ECMO weaning. Clinical data were compared between the 2 groups.

Extracorporeal membrane oxygenation protocol

The cannulation technique and management strategy have been described in detail in previous studies [9]. In short, all ECMO-related procedures were performed under sterilized conditions with chlorhexidine. A polymethyl pentene fiber oxygenator (Maquet Inc., Hirrlingen, Germany) was applied for gas exchange in the extracorporeal circulation machines. Unfractionated heparin was infused during ECMO circulation. A multidisciplinary ECMO team determined the initiation of ECMO support based on the patient's characteristics, disease progression, and organ failure. We applied a peripheral cannulation strategy to all patients. Antibiotics were not routinely used unless there was distinct evidence of infection during ECMO support.

Revascularization strategy

The revascularization strategy in patients with ACS complicated by CA or CA who have single-vessel disease is an emergent percutaneous coronary intervention for the culprit artery. In cases of multivessel disease, we performed culprit-only revascularization in nearly all cases based on the results of the CULPRIT-SHOCK trial [10,11]. In ACS patients undergoing VA-ECMO for profound CS or CA, we usually revascularized only the culprit artery in patients dependent on VA-ECMO in the index procedure. Even though the decision and timing for revascularization of the non-culprit artery is at the operators' discretion, it was recommended to perform revascularization of a non-culprit artery with large myocardial blood supply territory, such as the left main or proximal left anterior descending artery, in the index procedure. If patients had left main or multivessel disease with good antegrade flow, coronary artery bypass graft was also performed as emergent or urgent surgery according to the operators' discretion.

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Data collection

All clinical variables of patients, including clinical and laboratory data before and during the ECMO period, were retrospectively collected. Pre-ECMO laboratory data were collected within 2 hours before ECMO onset. In-hospital mortality was assessed according to whether the death occurred during hospitalization, and 6-month mortality was calculated after 6 months of ECMO initiation. Serum lactate levels were measured from arterial blood gas analysis (GEM Premier 3000 system; Werfen Company, Bedford, MA, USA).

Statistical analyses

The results are expressed as mean values±standard devi-

ation for continuous variables and as frequency and percentages (%) for categorical variables. We used the independent t-test or chi-square test to compare continuous variables or categorical variables, respectively, according to 6-month survival. Cox proportional-hazards models were used to evaluate the univariable and multivariable hazard ratios (HRs) for 6-month mortality with a linear combination of pre-ECMO covariates that were confirmed to be statistically significant through the independent t-test and chi-square test. A candidate variable with a univariate p-value ≤0.05 was retained in the multivariable model. Receiver operating characteristic (ROC) curve analysis was done to identify the cut-off value of pre-ECMO lactate levels related to 6-month mortality with the DeLong test. The area under the ROC curve (AUC) was compared between pre-ECMO lactate levels and SAVE scores with and with-

Table 1. Patients' characteristics before ECMO support and a comparison between survivors and non-survivors defined in terms of 6-month mortality

Characteristic	Total patients (N=148)	Survivors (N=68)	Non-survivors (N=80)	p-value
Age (yr)	66.0±10.5	65.0±10.8	66.8±10.3	0.323
Age >80 yr	10 (6.8)	4 (5.9)	6 (7.5)	0.950
Body mass index (kg/m^2)	23.5±2.8	23.8±3.0	23.3±2.6	0.282
Underlying disease				
Hypertension	84 (56.8)	40 (58.8)	44 (55.0)	0.763
Previous AMI	25 (16.9)	15 (22.1)	10 (12.5)	0.185
Dyslipidemia	16 (10.8)	9 (13.2)	7 (8.8)	0.542
Heart failure	6 (4.1)	2 (2.9)	4 (5.0)	0.830
Diabetes mellitus	68 (45.9)	33 (48.5)	35 (43.8)	0.677
Chronic kidney disease	6 (4.1)	1 (1.5)	5 (6.2)	0.293
Cerebrovascular accident	14 (9.5)	5 (7.4)	9 (11.2)	0.599
Smoking	70 (47.3)	28 (41.2)	42 (52.5)	0.226
Laboratory data				
White blood count (10^3/mm^3)	13.8±5.5	14.7±6.2	13.2±5.0	0.130
Hemoglobin (g/dL)	12.0±2.5	12.4±2.4	11.8±2.6	0.171
Platelets (10^3/mm^3)	214.2±86.3	226.4±89.2	203.3±82.9	0.126
Lactate (mmol/L)	8.6±5.0	7.2±4.3	9.8±5.3	0.002
Troponin (ng/mL)	75.0±92.9	59.9±79.4	89.3±102.5	0.065
HCO$_3^-$ (mmol/L)	15.4±6.0	16.8±5.2	14.2±6.3	0.008
CPR information				
ED ECMO	60 (40.5)	26 (38.2)	34 (42.5)	0.720
ECPR	64 (43.2)	17 (25.0)	47 (58.8)	<0.001
CPR to ECMO time (min)	36.9±23.5	35.1±24.7	37.6±23.2	0.708
Bystander CPR	16 (10.8)	4 (5.9)	12 (15.0)	0.130
Witness arrest	19 (12.8)	5 (7.4)	14 (17.5)	0.111
SAVE score	-7.6±5.1	-5.7±5.1	-9.3±4.6	<0.001
Shock to ECMO time (hr)	4.9±7.5	3.9±5.3	5.3±8.8	0.24
MV before ECMO (hr)	9.5±13.9	28 (41.2)	18 (22.5)	0.023
2DE EF (%)	32.0±14.8	31.0±14.6	33.6±15.3	0.438

Values are presented as mean±standard deviation or number (%).
ECMO, extracorporeal membrane oxygenation; AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation; ED, emergency department; ECPR, extracorporeal cardiopulmonary resuscitation; SAVE, Survival After Veno-Arterial Extracorporeal Membrane Oxygenation; MV, mechanical ventilation; 2DE EF, 2-dimensional echocardiography ejection fraction.

out a history of extracorporeal cardiopulmonary resuscitation (ECPR). Kaplan-Meier curves and the log-rank test were used to assess time to death from the date of ECMO initiation to 180-day survival for groups stratified according to the cut-off value of pre-ECMO lactate for 6-month mortality. We used MedCalc statistical software ver. 17.9.7 (MedCalc Software bvba, Ostend, Belgium) for the statistical analysis. A generalized additive model was used to evaluate the nonlinear regression between the biomarkers and mortality using Stata ver. 17.0 (StataCorp., College Station, TX, USA). In all analyses, p-values <0.05 were considered to indicate statistical significance.

Ethics statement

The Institutional Review Board validated the research. All data from this study were obtained without the consent of patients due to the retrospective nature of this work (IRB no., CNUH-2020-023).

Results

Patient demographics and outcomes of extracorporeal membrane oxygenation support

We evaluated 148 patients with CA or refractory CS following ACS who were treated with VA-ECMO. The mean

Table 2. Analysis of clinical information related to coronary revascularization during ECMO support

Variable	Total (N=148)	Survivors (N=68)	Non-survivors (N=80)	p-value
Diagnosis				
ST-segment elevation myocardial infarction	80 (54.1)	36 (52.9)	44 (55.0)	0.932
Left main coronary artery lesion	49 (33.1)	22 (32.4)	27 (33.8)	0.996
Initial revascularization				0.099
Percutaneous coronary intervention	127 (85.8)	54 (42.5)	73 (57.5)	
Coronary artery bypass graft[a]	14 (9.5)	10 (71.4)	4 (28.6)	
No revascularization[b]	7 (4.7)	4 (57.1)	3 (42.9)	
Definite stent thrombosis	10 (6.8)	5 (7.4)	5 (6.2)	1.000

Values are presented as or number (%).
ECMO, extracorporeal membrane oxygenation.
[a]Patients who underwent veno-arterial-ECMO in the preoperative period. not related to post-cardiotomy shock. [b]Clinically relevant with acute coronary syndrome, but spasm on coronary artery angiogram findings.

Table 3. Comparison of ECMO outcomes between survivors and non-survivors defined in terms of 6-month mortality

Variable	Total (N=148)	Survivors (N=68)	Non-survivors (N=80)	p-value
Microbiology data				
Blood culture (bacteria)	36 (24.3)	21 (30.9)	15 (18.8)	0.128
Blood culture (fungus)	3 (2.0)	2 (2.9)	1 (1.2)	0.887
Respiratory culture	58 (39.2)	32 (47.1)	26 (32.5)	0.101
Complications				
Targeted temperature management	8 (5.4)	0	8 (10.0)	0.021
Cerebral infarction	6 (4.1)	2 (3.0)	4 (5.0)	0.844
Cerebral hemorrhage	3 (2.0)	1 (1.5)	2 (2.5)	1.000
Acute brain injury	4 (2.7)	0	4 (5.0)	0.178
Acute kidney injury	59 (40.1)	42 (62.7)	46 (57.5)	0.638
Continuous renal replacement therapy	68 (46.3)	23 (34.3)	45 (56.2)	0.638
ECMO outcome				
ECMO duration (day)	5.8±6.5	5.7±5.5	5.9±7.2	0.804
ECMO weaning success	79 (53.4)	66 (97.1)	13 (16.2)	<0.001
Hospital stays (day)	37.4±101.1	49.3±65.0	27.3±123.3	0.169
1-Month death	72 (48.6)			
6-Month death	80 (54.1)			

Values are presented as number (%) or mean±standard deviation.
ECMO, extracorporeal membrane oxygenation.

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patient age at the time of ECMO support was 66.0±10.5 years, and 116 patients (78.4%) were men. Among them, 25 patients (16.9%) had a history of previous acute myocardial infarction. The duration of shock before ECMO initiation was 4.9±7.5 hours. There were significant differences in 6-month mortality between the 2 groups in pre-ECMO lactate and HCO_3^- levels, the duration of mechanical ventilation (MV) before ECMO, and ECPR. Patient characteristics before ECMO support and the results of the risk factor analysis for 6-month mortality are summarized in Table 1. Clinical information on coronary revascularization before and after ECMO support is presented in Table 2.

In the analysis of clinical outcomes, the mean duration of ECMO support was 5.8±6.5 days, and the rate of successful ECMO weaning was 53.4%. There were no statistically differences in these variables between survivors and non-survivors. Sixty-eight patients (45.9%) were discharged from the hospital alive and reached a 180-day follow-up after ECMO initiation. Renal replacement therapy was applied during ECMO support in 68 patients (46.3%). Eight patients (5.4%) underwent target temperature management (TTM), but all of these patients died after TTM. All causes of acute brain injury (cerebral infarction, hemorrhage, hypoxic ischemic brain injury) were diagnosed in fewer than 5% of patients. The outcomes of ECMO support are summarized in Table 3.

Cox proportional-hazards regression for covariates associated with 6-month mortality

The Cox proportional-hazards regression estimated the hazard for 6-month death according to pre-ECMO covariates that were confirmed to be statistically significant through the independent t-test and chi-square test: pre-ECMO lactate, pre-ECMO HCO_3^-, MV duration before ECMO initiation, and ECPR history. The Cox model showed that pre-ECMO lactate level and MV duration before ECMO

application were significantly associated with 6-month mortality (HR, 1.19; 95% CI, 1.06–1.34; p=0.003 and HR, 1.04; 95% CI, 1.02–1.07; p=0.002, respectively) (Table 4).

Evaluation of the pre-extracorporeal membrane oxygenation lactate level as a survival predictor at 6 months

The AUC of pre-ECMO lactate was 0.64 (standard error [SE]=0.05; 95% CI, 0.56–0.72; p=0.002; cut-off value=9.8) (Fig. 1). We compared the AUC between the pre-ECMO lactate level and SAVE score for predicting 6-month mortality. A subgroup analysis was also performed based on ECPR history, which was one of the 6-month survival predictors, and the following results were obtained. In the analysis of all included patients, although the AUC of the SAVE score (0.69) was slightly higher than that of the
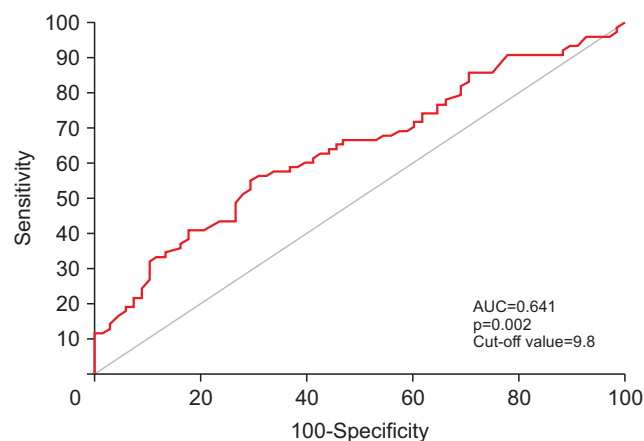

Fig. 1. Receiver operating characteristic (ROC) curve of pre-extracorporeal membrane oxygenation (ECMO) lactate levels for the prediction of 6-month mortality. The area under the ROC curve of pre-ECMO lactate levels was 0.64 (standard error=0.05; 95% confidence interval, 0.56–0.72; p=0.002, cut-off value=9.8 mmol/L). AUC, area under ROC curve.

Table 4. Cox proportional-hazards regression with pre-ECMO covariates based on 6-month mortality

Variable	Univariable analyses[a]		Multivariable analyses[b]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Lactate (pre-ECMO)	1.096 (1.045–1.149)	<0.001	1.210 (1.064–1.376)	0.004
ECPR history	2.968 (1.725–4.221)	<0.001	0.408 (0.105–1.584)	0.195
HCO_3^-	0.940 (0.904–0.978)	0.002	1.040 (0.923–1.172)	0.519
MV before ECMO	1.034 (1.007–1.061)	0.012	1.046 (1.017–1.076)	0.002

ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; CI, confidence interval; ECPR, extracorporeal cardiopulmonary resuscitation; MV, mechanical ventilation.
[a]Combination of pre-ECMO covariates, which were confirmed to be statistically significant through the independent t-test and chi-square test, were included in the univariable analysis. [b]Candidate variables with a univariate p-value ≤0.05 were retained in the multivariable model.

pre-ECMO lactate (0.65) in predicting the 6-month survival probability, the AUCs did not show a statistically significant difference (difference between areas=0.06; SE=0.06; 95% CI, 0.06–0.17; p=0.342) (Fig. 2A). In the subgroup analysis of non-ECPR patients, there was no statistically significant difference in the AUC (difference between areas=0.04; SE=0.08; 95% CI, 0.13–0.20; p=0.643) (Fig. 2B). However, in the subgroup analysis of ECPR patients, the AUC did show a statistically significant difference (difference between areas=0.2; SE=0.09, 95% CI, 0.02–0.38; p=0.031) (Fig. 2C). These results confirmed that the pre-ECMO lactate level was not inferior to the SAVE score in predicting 6-month survival, and that the pre-ECMO lactate level had low efficacy in predicting survival in patients who underwent ECPR. Additional nonlinear regression testing showed no significant relationships between pre-ECMO lactate or the SAVE score and mortality risk (p=0.450 for pre-ECMO lactate, p=0.160 for the SAVE score) (Supplementary Fig. 1). The impact of the pre-ECMO lactate level on 6-month mortality was estimated by Kaplan-Meier survival analysis in patients who had pre-EC-

MO lactate levels of more than 9.8 mmol/L and less than 9.8 mmol/L. The patients with pre-ECMO lactate levels of more than 9.8 mmol/L had a lower survival probability (p<0.0008) (Fig. 3).

Discussion

According to a recent Extracorporeal Life Support Organization report, approximately 45% of patients treated with VA-ECMO are discharged alive, but some are known to die after discharge [12]. The mortality rate after VA-ECMO remains high due to the underlying disease that has not been cured and the worsening of ECMO-related complications. As the clinical outcomes of ECMO support (especially VA-ECMO) are still unsatisfactory, even after the intensive use of large-scale medical resources, so accurate evaluation is essential from the first initiation of ECMO.

The SAVE score is the most popular tool to predict successful ECMO weaning based on the pre-ECMO situation, and its usefulness has been reported in several studies [4,13,14]. Chen et al. [14] reported that serum lactate levels
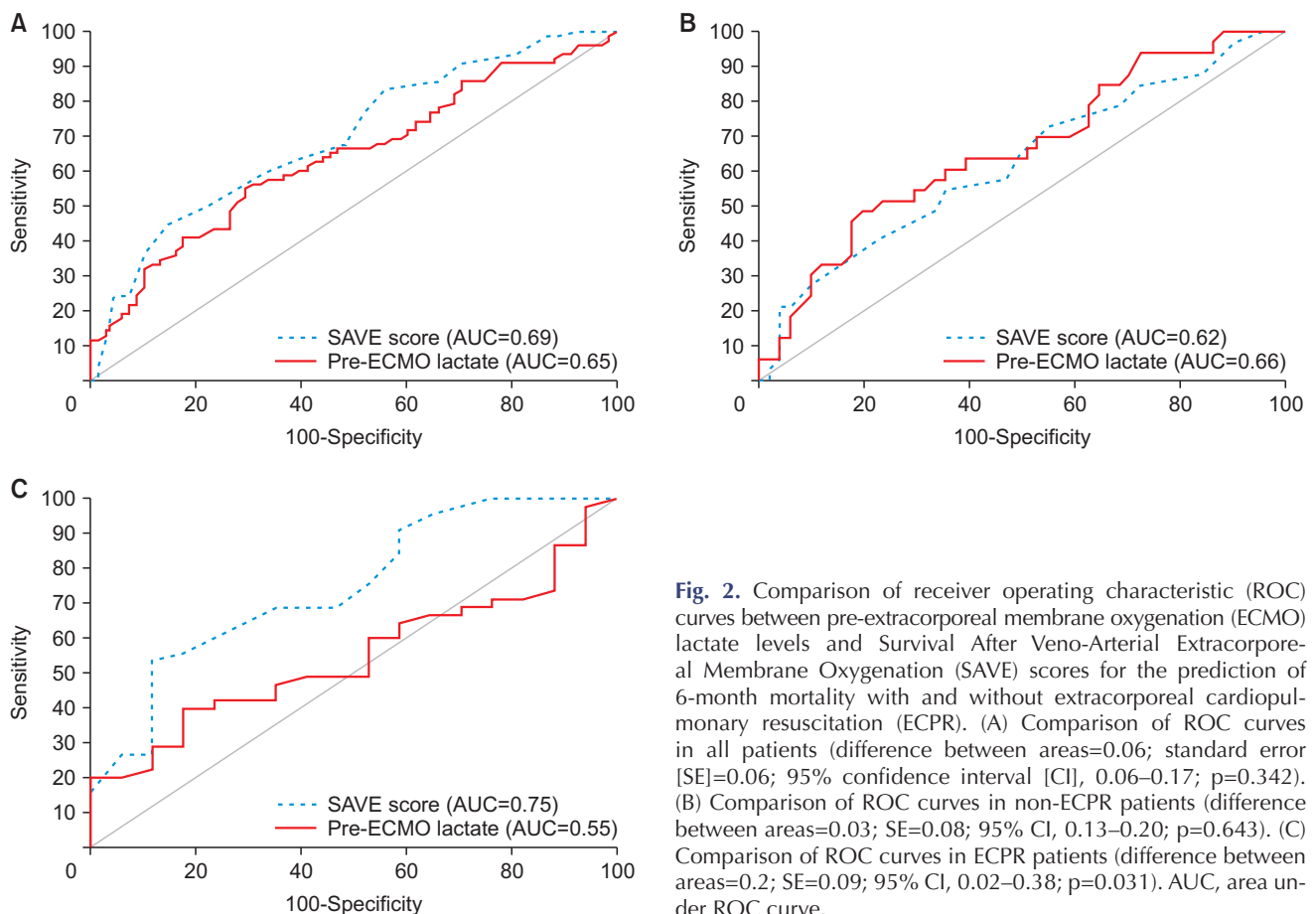
Fig. 2. Comparison of receiver operating characteristic (ROC) curves between pre-extracorporeal membrane oxygenation (ECMO) lactate levels and Survival After Veno-Arterial Extracorporeal Membrane Oxygenation (SAVE) scores for the prediction of 6-month mortality with and without extracorporeal cardiopulmonary resuscitation (ECPR). (A) Comparison of ROC curves in all patients (difference between areas=0.06; standard error [SE]=0.06; 95% confidence interval [CI], 0.06–0.17; p=0.342). (B) Comparison of ROC curves in non-ECPR patients (difference between areas=0.03; SE=0.08; 95% CI, 0.13–0.20; p=0.643). (C) Comparison of ROC curves in ECPR patients (difference between areas=0.2; SE=0.09; 95% CI, 0.02–0.38; p=0.031). AUC, area under ROC curve.
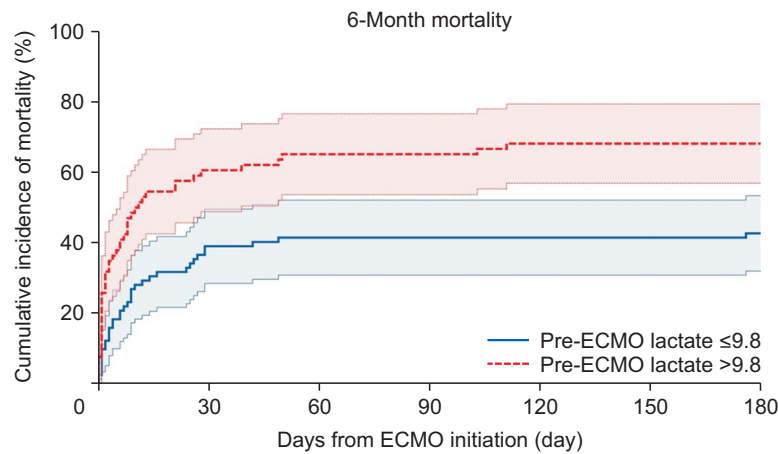
Fig. 3. Survival analysis with cumulative mortality incidence from the time of extracorporeal membrane oxygenation (ECMO) initiation. Patients with pre-ECMO lactate levels of more than 9.8 mmol/L had a lower survival probability (p<0.0008) than patients with pre-ECMO lactate levels of less than 9.8 mmol/L.

and SAVE scores were both statistically significant predictors of mortality in Cox proportional-hazards regression. The AUC of lactate levels was superior to that of SAVE scores to predict 90-day mortality (serum lactate level= 0.79, SAVE score=0.73) [14]. They proposed a combination of the blood lactate levels and the SAVE score, referred to as the modified SAVE score, although the lactate level alone showed sufficient clinical significance for differentiating the survival prognosis. As discussed earlier, the SAVE score has been regarded as a complex model that includes many variables and numerous categories.

From a historical viewpoint, many researchers have reported that increased lactic acid levels are a risk factor for death in critically ill patients with diverse diseases, including CS [8,15-17]. Several recent studies have investigated the use of lactate levels as a surrogate marker to evaluate end-organ hypoperfusion and survival after ECMO weaning [14,18,19]. In previous studies, pre-ECMO lactate levels and/or lactate metabolism after ECMO initiation had a strong effect on viability, and specific cut-off values of serum lactate have been suggested as thresholds for predicting short-term mortality, such as in-hospital or 1-month mortality. However, previous research contained little information on the association between pre-ECMO lactate levels and mid- to long-term outcomes after hospital discharge. For this reason, we set 6-month mortality as the primary outcome of our study, rather than a short-term outcome. As with the results of previous studies, serum lactate levels were a reliable predictor of 1-month and 6-month mortality in patients who underwent V-A ECMO in our study. The best threshold value of pre-ECMO lactate levels was more than 9.8 mmol/L in the ROC curve analy-

sis for 6-month survival in our results. Moreover, the Cox proportional-hazards ratio showed that pre-ECMO lactate levels were a robust predictor.

This study has some limitations. First, this single-center study enrolled a relatively small number of patients. Second, as a retrospective cohort study, a few patients were lost to follow-up, resulting in selection bias. Finally, we followed the general design of a clinical study performing a survival analysis. However, categorizing the study group into survivors and non-survivors was an intentional division, and this method may have also induced selection bias.

In conclusion, ACS patients who underwent VA-ECMO with lactate levels >9.8 mmol/L prior to ECMO had significantly lower 6-month survival rates. However, the serum lactate level before ECMO alone is still limited as a predictor of survival, and its efficacy is further reduced when it is accompanied by serious risk factors such as ECPR. In the next study, a more accurate analysis of pre-ECMO lactate levels will be performed to predict survival after VA-ECMO for CS patients with high lactate levels.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.5090/jcs.21.127. **Supplementary Fig 1**. Nonlinear regression test of mortality.

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