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ORIGINAL ARTICLE

The absolute lactate levels versus clearance for prognostication of post-cardiotomy patients on veno-arterial ECMO

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Abstract

Aims Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a life-saving procedure for supporting patients with cardiogenic shock after cardiac surgery. This work aimed to analyse the impact of changes in blood lactate levels on the survival of patients on post-cardiotomy ECMO (PC-ECMO) and whether lactate clearance (LC) performs better than absolute lactate levels.

Methods and Results We retrospectively analysed the data of adult patients who received PC-ECMO at our centre between 2016 and 2022. The primary outcome was the in-hospital mortality rate. Arterial lactate levels were measured at ECMO initiation, peak and 12 and 24 h after VA-ECMO support. LC was calculated at 12 and 24 h. Out of 2368 patients who received cardiac surgeries, 152 (median age, 48 years; 57.9% of them were men) received PC-ECMO. Of them, 48 (31.6%) survived and were discharged, while 104 (68.4%) died during the index hospitalization. Non-survivors had higher frequencies of atrial fibrillation (41.35% vs. 12.5%, $P < 0.001$), chronic kidney disease (26.9% vs. 6.3%, $P = 0.004$), prolonged cardiopulmonary bypass (237 vs. 192 min, $P = 0.016$) and aortic cross-clamping times (160 vs. 124 min, $P = 0.04$) than survivors. Non-survivors had a significantly higher median Sequential Organ Failure Assessment (SOFA) score at ECMO initiation (13.5 vs. 9, $P < 0.001$) and a lower median Survival After Veno-arterial ECMO (SAVE) score (−3 vs. 3, $P < 0.001$) with higher SAVE classes ($P < 0.001$) than survivors. After 12 h of VA-ECMO support, the blood lactate level was negatively correlated with LC in survivors ($r = -0.755$, $P < 0.001$) and non-survivors ($r = -0.601$, $P < 0.001$). After 24 h, the same negative correlation was identified between survivors ($r = -0.764$, $P < 0.001$) and non-survivors ($r = -0.847$, $P < 0.001$). Blood lactate levels measured at 12 h to determine hospital mortality [>8.2 mmol/L, area under the receiver operating characteristic curve (AUROC): 0.868] and 24 h (>2.6 mmol/L, AUROC: 0.896) had the best performance, followed by LC-T12 (<21.94%, AUROC: 0.807), LC-T24 (<40.3%, AUROC: 0.839) and peak blood lactate (>14.35 mmol/L, AUROC: 0.828). The initial pre-ECMO blood lactate (>6.25 mmol/L, AUROC: 0.731) had an acceptable ability to discriminate mortality but was less than the following measurements and clearance. Kaplan–Meier curves demonstrated that LC of <21.94% at T12 h and <40.3% at T24 h was associated with decreased survival (log-rank $P < 0.001$). Cox proportional hazards regression analysis for mortality revealed that LC of <21.94% at T12 h had an adjusted hazard ratio (HR) of 2.73 [95% confidence interval (CI): 1.64–5.762, $P < 0.001$] and LC of <40.3% at T24 h had an adjusted HR of 1.98 (95% CI: 1.46–4.173, $P < 0.001$). The predictors of hospital mortality after PC-ECMO were the lactate level at 12 h [odds ratio (OR): 1.67, 95% CI: 1.121–2.181, $P = 0.001$], initial SOFA score (OR: 1.593, 95% CI: 1.15–2.73, $P < 0.001$), initial blood lactate (OR: 1.21, 95% CI: 1.016–1.721, $P = 0.032$) and atrial fibrillation (OR: 6.17, 95% CI: 2.37–57.214, $P = 0.003$). Bivariate models using lactate levels and clearance at the same points revealed that blood lactate levels performed better than the clearance percentage.

Conclusions Serial measurements of arterial blood lactate and LC help in obtaining early prognostic guidance in adult patients supported by VA-ECMO after cardiac surgery. Absolute lactate levels, compared with LC at the same time points, demonstrated better performance in differentiating mortality.

Keywords atrial fibrillation; cardiotomy; extracorporeal membrane oxygenation (ECMO); lactate; lactate clearance; mortality; SAVE score; SOFA score

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Background

Cardiogenic shock (CS) is a life-threatening state that occurs after cardiac surgery and is associated with systemic hypoperfusion and increased hospital mortality.[1,2] Post-cardiotomy CS (PCS) occurs because of impaired myocardial function after cardiopulmonary bypass (CPB) circulation, inadequate cardioplegia, surgical disruption and ischaemic reperfusion damage.[3] Approximately 0.5%–3.6% of patients receiving cardiac surgery develop PCS requiring mechanical circulatory support.[4,5] Post-cardiotomy veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a salvage procedure for cardiopulmonary support until recovery or further planning. The use of post-cardiotomy ECMO (PC-ECMO) has significantly increased in recent years, with variable worldwide reports of mortality and morbidities owing to different study designs, populations, timing of ECMO initiation and centre experiences.[6–10]

Blood lactate is a widely used point-of-care parameter for inadequate tissue perfusion and an imbalance between oxygen delivery and oxygen consumption.[11] Many studies have investigated the correlation between blood lactate levels and poor outcomes in patients with CS; however, data on the validity of lactate clearance (LC) as a surrogate for survival in PCS and PC-ECMO are limited.[12–15] This study aimed to investigate the impact of changes in blood lactate levels on the survival of patients receiving PC-ECMO. We believe that LC may differentiate mortality after PC-ECMO with a better performance than absolute lactate levels and can be a surrogate point to achieve better outcomes.

Methods

Study design and population

Data of all patients aged ≥18 years who received cardiac surgeries and PC-ECMO in our tertiary care centre between 2016 and 2022 were retrospectively analysed. This study was approved by the institutional review board (reference: 2191042). Patients who received VA-ECMO for non-cardiotomy causes and those referred from other hospitals on ECMO were excluded from the study.

ECMO implementation and lactate measurements

The studied patients had PCS despite inotropic support and standard care measures, and the cardiac surgeons initiated VA-ECMO either during the surgical operation or in the intensive care unit (ICU) in case of deterioration after surgery. According to the local hospital policy, blood lactate levels were measured every 2 h post-operatively until clearance and haemodynamic stabilization. For this study, we collected four measurements of arterial blood lactate levels: lactate level before ECMO insertion (L0), peak lactate level and lactate level at 12 h (L12) and 24 h (L24) after ECMO insertion. LC was calculated at two points[14,16]:

$$\text{Lactateclearance (T12)} = [(\text{L12} - \text{initiallactate}) \div \text{initiallactate}] \times 100.$$

$$\text{Lactateclearance (T24)} = [(\text{L24} - \text{initiallactate}) \div \text{initiallactate}] \times 100.$$

Studied variables and outcomes

Pre-operative variables included age, sex, diabetes mellitus (DM), underlying heart disease, chronic kidney disease (CKD), body mass index, atrial fibrillation (AF) and previous cardiotomy or cerebrovascular disease. The operative variables included intra-aortic balloon pump (IABP) use, the type of surgery, ECMO cannulation strategy, aortic cross-clamping (ACC) and CPB times. Laboratory data included arterial blood base excess, arterial lactate, haemoglobin, platelet count, liver enzymes, serum creatinine and bilirubin levels. To assess the risk profiles of the patients, two scores were used: Survival After Veno-arterial ECMO (SAVE) and Sequential Organ Failure Assessment (SOFA). The SAVE score was calculated once before VA-ECMO initiation with five risk classes and a range (−35 to 17).[17] The SOFA score was tested in many groups of patients with critical illnesses, including ECMO-supported patients.[18,19] The SOFA score was calculated three times in this study: before the initiation of ECMO and on the third and fifth days after ECMO support. The SOFA score difference was calculated as a positive or negative change from the third or fifth day to the initial score. The primary study outcome was the in-hospital mortality rate. The CHA_2DS_2–VASc score was calculated for the patients who

Table 1 Baseline characteristics of the study patients.

Variables		All patients (n = 152)	Survivors (n = 48, 31.6%)	Non-survivors (n = 104, 68.4%)	P value
Age (years)		48 (31, 56)	43 (31, 56)	48 (32, 57)	0.18
Body mass index (kg/m^2)		26.5 (22.6, 32.1)	24.9 (22.3, 29.9)	27.2 (22.75, 33.1)	0.19
Sex (n, %)	Male	88 (57.9)	29 (60.42%)	59 (56.7)	0.44
	Female	64 (42.1)	19 (39.6%)	45 (43.3)	
Diabetes mellitus (n, %)		50 (32.9)	19 (39.6)	31 (35.6)	0.26
CKD (n, %)		31 (20.4)	3 (6.3)	28 (26.9)	0.004
ESRD on dialysis (n, %)		7 (4.6)	1 (2.08)	6 (5.77)	0.43
Previous cardiac surgery (n, %)		78 (51.3)	18 (37.5)	60 (57.7)	0.014
Systemic hypertension (n, %)		52 (34.2)	15 (31.3)	37 (35.6)	0.55
Atrial fibrillation (n, %)		49 (32.2)	6 (12.5)	43 (41.35)	<0.001
CHA_2DS_2–VASc score		4 (3, 5)	3 (2, 4)	4 (3, 5)	0.08
Old cerebrovascular stroke (n, %)		11 (7.2)	4 (8.3)	7 (6.73)	0.522
Admission SOFA score (SOFA-1)		12 (10, 14.5)	9 (8, 11)	13.5 (12, 16)	<0.001
SAVE score		−1 (−5, 3)	3 (1, 5)	−3 (−6, 0.5)	<0.001
SAVE risk class (n, %)	I	16 (10.5)	11 (23.4)	5 (5)	<0.001
	II	48 (31.6)	27 (56.3)	21 (20.2)	
	III	44 (28.9)	9 (18.8)	34 (32.7)	
	IV	38 (25)	2 (4.2)	36 (34.6)	
	V	6 (3.9)	0	6 (5.8)	
Heart disease (n, %)	Rheumatic heart disease	57 (37.5)	15 (31.3)	42 (40.4)	0.057
	Idiopathic cardiomyopathy	31 (20.4)	10 (20.8)	21 (20.2)	
	Ischaemic cardiomyopathy	27 (17.8)	8 (16.7)	19 (18.3)	
	ACHD	17 (11.2)	5 (10.4)	12 (11.54)	
	Others	20 (13.2)	12 (25)	8 (7.69)	
ECPR (n, %)		3 (2)	1 (2.1)	2 (1.9)	1
Cardiac surgery (n, %)	CABG	8 (5.3)	3 (6.25)	5 (4.81)	0.005
	Valve surgery	71 (46.7)	19 (39.6)	52 (50)	
	Valve + CABG surgery	18 (11.8)	4 (8.3)	14 (13.5)	
	Heart transplantation	24 (15.8)	8 (16.7)	16 (15.4)	
	Aortic surgery	9 (5.9)	1 (2.1)	8 (7.69)	
	LVAD insertion	6 (3.9)	0	6 (5.8)	
	Pulmonary endarterectomy	1 (0.7)	0	1 (0.9)	
	Lung transplantation	15 (9.9)	11 (22.9)	4 (3.8)	
CPB time (min)		218 (167, 317)	192 (149, 250)	237 (169, 319)	0.016
ACC time (min)		145 (105, 174)	124 (93, 163)	160 (108, 179)	0.04
IABP use (n, %)		27 (17.8)	8 (16.7)	19 (18.3)	0.77
ECMO cannulation (n, %)	Peripheral	55 (36.2)	22 (45.8)	33 (31.7)	0.362
	Central	87 (57.2)	25 (52.1)	62 (59.6)	
	Peripheral then central	4 (2.6)	1 (2.1)	3 (2.9)	
	Central then peripheral	6 (3.9)	1 (2.1)	5 (4.8)	

Abbreviations: ACC, aortic cross-clamping; ACHD, adult congenital heart disease; CABG, coronary artery bypass graft; CHA_2DS_2–VASc score, congestive heart failure, hypertension, age of ≥75 years, diabetes mellitus, stroke, vascular disease, age of 65–74 years and sex (female) score; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ESRD, end-stage renal disease; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; SAVE score, Survival After Veno-arterial ECMO; SOFA, Sequential Organ Failure Assessment.

had AF. It stands for heart failure, hypertension, age of ≥75 years, DM, stroke, vascular disease, age of 65–74 years and female sex.[20]

Statistical analysis

Data were analysed and summarized as counts (with percentages) for categorical variables and medians (with interquartile ranges P25–P75) for quantitative variables. Normally distributed continuous variables were analysed using the unpaired Student's t-test. Categorical variables were analysed using the Fisher exact test or χ^2 test. The Mann–Whitney U test was used to compare quantitative variables. The data were considered significant if the two-sided P value was <0.05. The Hosmer–Lemeshow test was used to detect the goodness of fit of the logistic regression models to determine the predictors of mortality.[21] Variance inflation testing was performed to check for multicollinearity. Bivariate models were used to compare the performance of lactate levels and clearance at the same time points in predicting mortality. The Kaplan–Meier method was used to obtain survival curves according to LC, and comparison was done by the log-rank test. A Cox proportional hazards regression analysis was performed to determine the hazard ratio (HR) of LC for in-hospital mortality. The ability to predict mortality was determined using the area under the receiver operating characteristic curve (AUROC). Youden's index analysis was performed to obtain the best cut-off values with the highest index.[22]

Results

Characteristics of pre-ECMO patients

Of the 2368 adult patients who received cardiac surgeries between 2016 and 2022, 152 developed PCS and required VA-ECMO support. In the PC-ECMO group, 48 (31.6%) patients survived and were discharged, whereas 104 (68.4%) died during the index hospitalization. Non-survivors had higher frequencies of AF ($P < 0.001$) and CKD ($P = 0.004$) than survivors. Non-survivors had prolonged ACC time ($P = 0.04$), CPB time ($P = 0.016$) and a higher frequency of valve surgeries ($P = 0.005$) than survivors. Non-survivors had a significantly higher median SOFA score at ECMO initiation ($P < 0.001$) and a lower median SAVE score ($P < 0.001$) with higher SAVE risk classes ($P < 0.001$) than survivors. There were no significant differences in the underlying heart disease, IABP use or cannulation approaches between the two groups (*Table* 1).

Laboratory data of the patients

Non-survivors had significant lactic acidosis with less base excess ($P < 0.001$), higher initial blood lactate ($P < 0.001$), higher peak blood lactate ($P < 0.001$) and higher lactate levels at 12 h ($P < 0.001$) and 24 h, respectively ($P < 0.001$), with delayed LC at 12 h ($P < 0.001$) and at 24 h ($P < 0.001$), respectively, compared with survivors. Non-survivors had significantly higher preoperative thrombocytopenia ($P < 0.001$), anaemia ($P < 0.001$), renal impairment ($P = 0.006$) and hyperbilirubinaemia ($P < 0.001$) than survivors. The percentage of LC was lower in non-survivors than in survivors at 12 and 24 h after ECMO support. After 24 h, non-survivors had significant thrombocytopenia ($P < 0.001$), anaemia ($P = 0.038$), renal impairment ($P = 0.023$) and hyperbilirubinaemia ($P < 0.001$) compared with survivors. The non-survivors exhibited increasing trends in SOFA scores on the third and fifth days ($P < 0.001$) compared with the survivors (*Table* 2).

After 12 h of VA-ECMO support, the blood lactate level was negatively correlated with LC in survivors ($r = -0.755$, $P < 0.001$) and non-survivors ($r = -0.601$, $P < 0.001$). After 24 h, the same negative correlation was identified between survivors ($r = -0.764$, $P < 0.001$) and non-survivors ($r = -0.847$, $P < 0.001$) (Figure 1).

Clinical outcomes

In the cohort analysis, 74 (48.7%) patients died on ECMO, 30 (19.7%) died after ECMO decannulation and 48 (31.6%)

Table 2 Laboratory variables and risk scores of the patients studied.

Variables	Survivors	Non-survivors	*P* value
Before ECMO initiation			
Haemoglobin (g/L)	107 (96, 121)	94 (84, 105)	<0.001
Platelet count (10^9/L)	137 (82, 185)	66 (43, 126.5)	<0.001
Serum creatinine (μmol/L)	88 (58, 121)	115 (72, 156)	0.006
Serum bilirubin (μmol/L)	17.7 (13.4, 32)	43.5 (23.65, 90.65)	<0.001
Base excess (mmol/L)	−4.6 (−6.9 to −3.4)	−8.15 (−11.65 to −5.9)	<0.001
Blood HCO_3 (mmol/L)	20.1 (18.1, 21.3)	18.05 (14.35, 19.6)	<0.001
INR	1.9 (1.45, 2.4)	1.6 (1.4, 2.1)	0.048
ALT (units/L)	28 (20.7, 80)	45.85 (23.4, 171.85)	0.079
AST (units/L)	82.4 (47.9, 194)	129.35 (61.1, 293.65)	0.027
Initial blood lactate (mmol/L)	5.8 (4.8, 8.3)	9.75 (6.55, 13.4)	<0.001
After ECMO support			
Peak blood lactate (mmol/L)	10.8 (9.2, 14.3)	19.05 (14.7, 30)	<0.001
Blood lactate at T12 (mmol/L)	4.1 (2.8, 6.4)	11.25 (7.3, 18.9)	<0.001
Blood lactate at T24 (mmol/L)	1.9 (1.4, 3.1)	6.55 (4.05, 20)	<0.001
Lactate clearance % (LC-T12)	39.29 (7.25, 52.17)	−24.15 (−59.22, 15.3)	<0.001
Lactate clearance % (LC-T24)	66.04 (53.1, 77.78)	20.71 (−72.64, 53.15)	<0.001
Haemoglobin at 24 h (g/L)	92 (84, 115)	79 (74, 93)	0.038
Platelet count at 24 h (10^9/L)	119 (89.3, 137)	52 (39, 92.4)	<0.001
Serum creatinine at 24 h (μmol/L)	117 (87.4, 186.3)	198 (102, 231.2)	0.023
Serum bilirubin at 24 h (μmol/L)	65.4 (23.7, 83)	113.6 (73.4, 189.27)	<0.001
ALT at 24 h (units/L)	79 (51.3, 173)	121.6 (93.2, 232.7)	0.046
AST at 24 h (units/L)	127 (82.3, 316)	231.4 (162.7, 438.2)	0.032
Third day SOFA (SOFA-3)	9 (8, 11)	16 (14, 18)	<0.001
SOFA difference (D3-1)	1.5 (0.5, 2)	3 (2, 3)	<0.001
Fifth day SOFA (SOFA-5)	8 (6, 9)	17 (15, 19)	<0.001
SOFA difference (D5-3)	−1 (−2, −1)	2 (1, 2)	<0.001
SOFA difference (D5-1)	−2 (−3, 0)	4 (3, 5)	<0.001

Note: Data are presented as medians with the 25th and 75th interquartile ranges.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; LC, lactate clearance; SOFA, Sequential Organ Failure Assessment score.

Figure 1 Scatter plots demonstrating the negative correlations between blood lactate levels and lactate clearance (LC) in survivors and non-survivors.

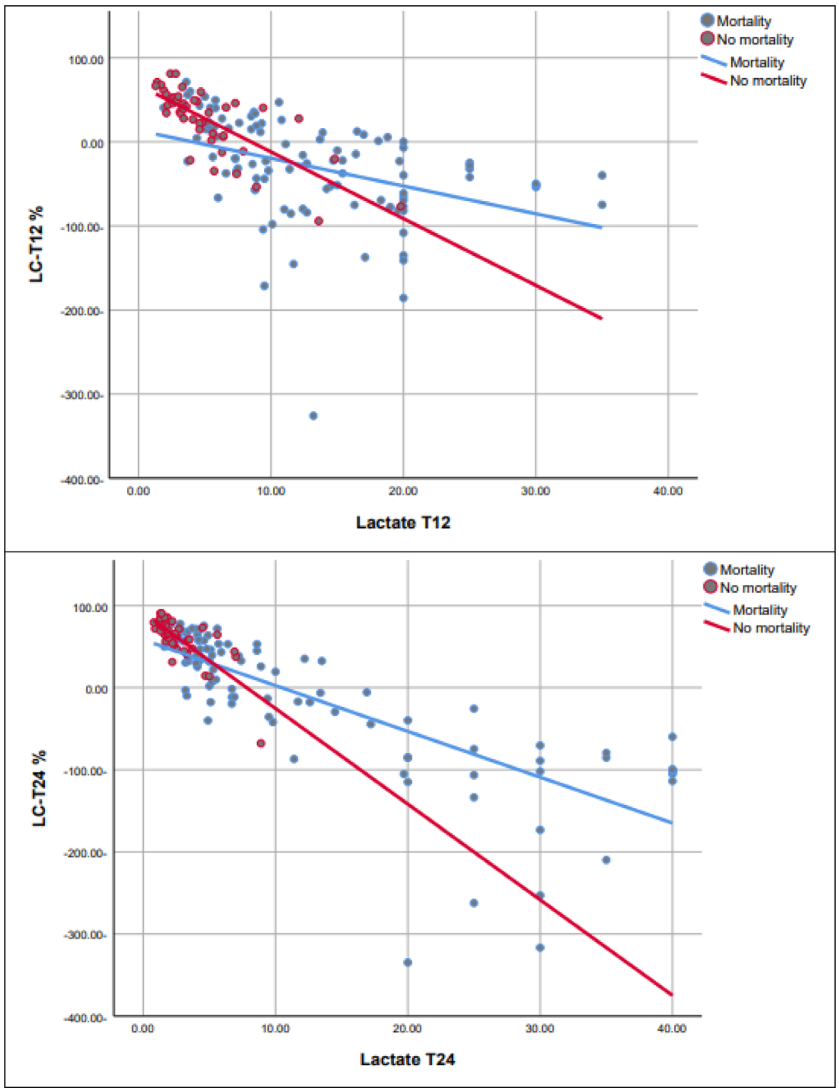
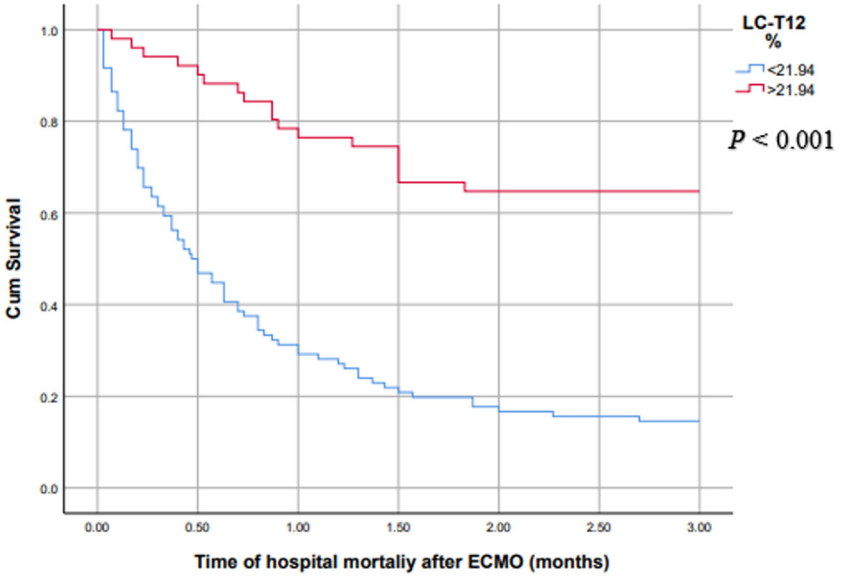


Table 3 Clinical outcomes of the patients studied.

Variables	Survivors	Non-survivors	*P* value
ECMO days	5 (3, 8)	6 (2, 11.5)	0.61
ICU days	21 (14, 41)	14 (5, 28)	0.002
New need for CRRT (*n*, %)	7 (14.6)	65 (62.5)	<0.001
Acute ischaemic stroke (*n*, %)	6 (12.5)	12 (11.54)	0.94
Cerebral bleeding (*n*, %)	2 (4.2)	7 (6.7)	0.71
Limb ischaemia (*n*, %)	3 (6.25)	14 (14)	0.07
Bowel ischaemia (*n*, %)	0	6 (5.8)	0.18
Bowel surgery (*n*, %)	0	1 (0.9)	0.17
Post-ECMO durable LVAD (*n*, %)	1 (2.1)	1 (0.9)	1
Post-ECMO heart transplantation (*n*, %)	2 (4.2)	2 (1.9)	0.54

Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LVAD, left ventricular assist device.

Figure 2 Kaplan–Meier curves for the patients studied according to LC-T12 (log-rank $P < 0.001$). ECMO, extracorporeal membrane oxygenation; LC, lactate clearance.



survived and were discharged. The need for continuous renal replacement therapy was more frequent in non-survivors ($P < 0.001$), whereas no significant differences in cerebrovascular stroke, limb ischaemia or bowel ischaemia were observed ($P > 0.05$). Survivors had a longer ICU stay than non-survivors (*Table* 3).

The Kaplan–Meier curves demonstrated that LC of <21.94% at T12 h and <40.3% at T24 h was associated with decreased survival (log-rank $P < 0.001$) (Figures 2 and 3, respectively).

The Cox proportional hazards regression analysis revealed that LC of <21.94% at T12 h had an increased risk of mortality with a crude HR of 4.56 [95% confidence interval (CI): 2.718–7.636, $P < 0.001$] and adjusted HR of 2.73 (95% CI: 1.64–5.762, $P < 0.001$) and that LC of <40.3% at T24 h had an increased risk of mortality with a crude HR of 4.68 (95% CI: 3.058–7.171, $P < 0.001$) and adjusted HR of 1.98 (95% CI: 1.46–4.173, $P < 0.001$). Adjusting was done for SAVE and SOFA scores, CKD, AF and CPB time.

Figure 3 Kaplan–Meier curves for the patients studied according to LC-T24 (log-rank $P < 0.001$). ECMO, extracorporeal membrane oxygenation; LC, lactate clearance.

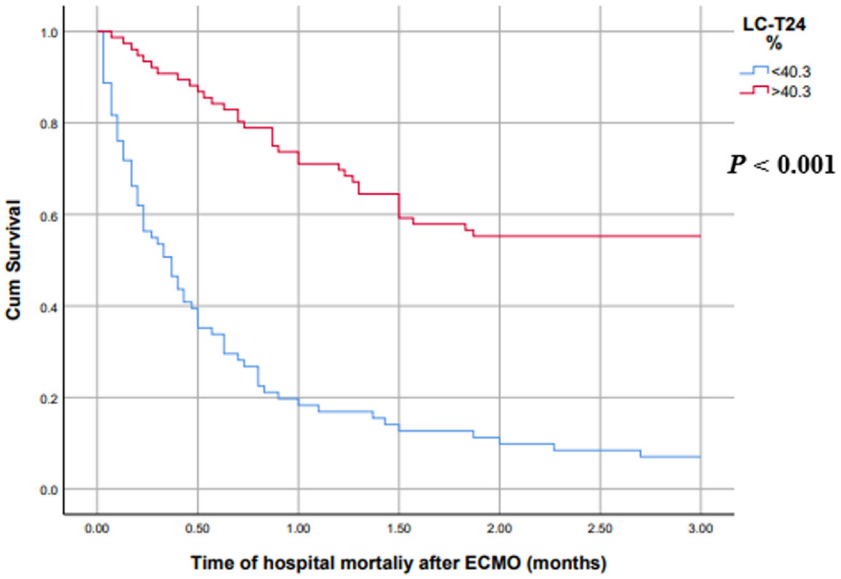


Table 4 Details of ROC curves in differentiating mortality.

Variables	AUROC	95% CI	Cut-off	*P* value	Sensitivity	Specificity	PPV	NPV	Accuracy (%)
SAVE score	0.831	0.766–0.896	<0.5	<0.001	75	78.7	88.24	59.68	76.19
Initial SOFA	0.875	0.82–0.93	>11.5	<0.001	76	87.2	92.68	63.08	79.59
Initial blood lactate	0.731	0.644–0.818	>6.25	<0.001	79	61.7	81.44	58	73.47
Peak lactate	0.828	0.76–0.896	>14.35	<0.001	78	76.6	87.64	62.07	77.55
Lactate T12	0.868	0.805–0.93	>8.2	<0.001	71	87.2	92.21	58.57	76.19
Lactate T24	0.896	0.843–0.95	>2.6	<0.001	92	72.3	87.62	80.95	85.71
LC-T12	0.807	0.73–0.883	<21.94	<0.001	82	70.2	85.42	64.71	78.23
LC-T24	0.839	0.775–0.903	<40.3	<0.001	66	89.4	92.96	55.26	73.47

Abbreviations: AUROC, area under the ROC curve; CI, confidence interval; LC, lactate clearance; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SAVE, Survival After Veno-arterial Extracorporeal Membrane Oxygenation; SOFA, Sequential Organ Failure Assessment score.

Discrimination of hospital mortality

The admission SOFA score (>11.5, AUROC: 0.875) can better discriminate hospital mortality than the SAVE score (<0.5, AUROC: 0.831) (*Table* 4 and Figure 4).

To discriminate hospital mortality, the absolute blood lactate levels at 12 h (>8.2 mmol/L, AUROC: 0.868) and 24 h (>2.6 mmol/L, AUROC: 0.896) had the best performance, followed by LC-T12 (<21.94%, AUROC: 0.807), LC-T24 (<40.3%, AUROC: 0.839) and peak blood lactate (>14.35 mmol/L, AUROC: 0.828). The initial pre-ECMO blood lactate (>6.25 mmol/L, AUROC: 0.731) had an acceptable ability to discriminate mortality, although this was less than the following measurements and clearance (*Table* 4 and Figures 4–6).

Predictors of mortality

Multivariable logistic regression analyses were performed using four models because of the multicollinearity between blood lactate variables. Model A had the best performance as per the Hosmer–Lemeshow test with goodness of fit (Pearson's χ^2 = 17.59, *P* = 0.82), and the mean variance infla-

Figure 4 Receiver operating characteristic curve of initial blood lactate [area under the receiver operating characteristic curve (AUROC): 0.731, $P < 0.001$], Survival After Veno-arterial Extracorporeal Membrane Oxygenation (SAVE) score (AUROC: 0.831, $P < 0.001$) and Sequential Organ Failure Assessment (SOFA) score (AUROC: 0.875, $P < 0.001$) in differentiating mortality with post-cardiotomy extracorporeal membrane oxygenation.

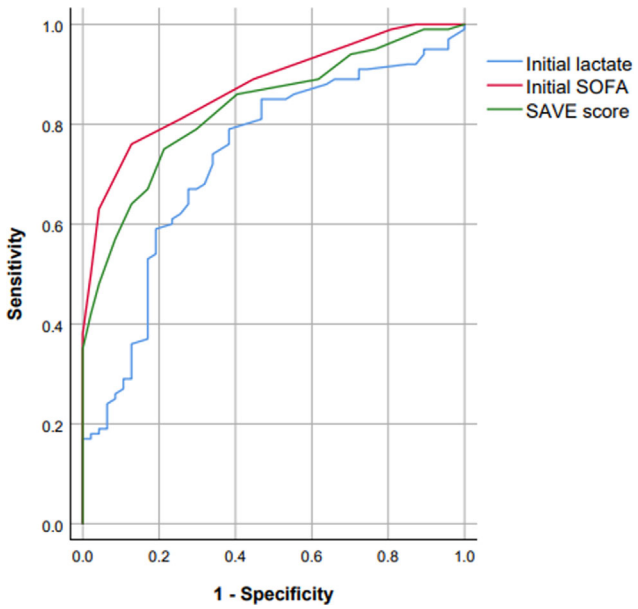
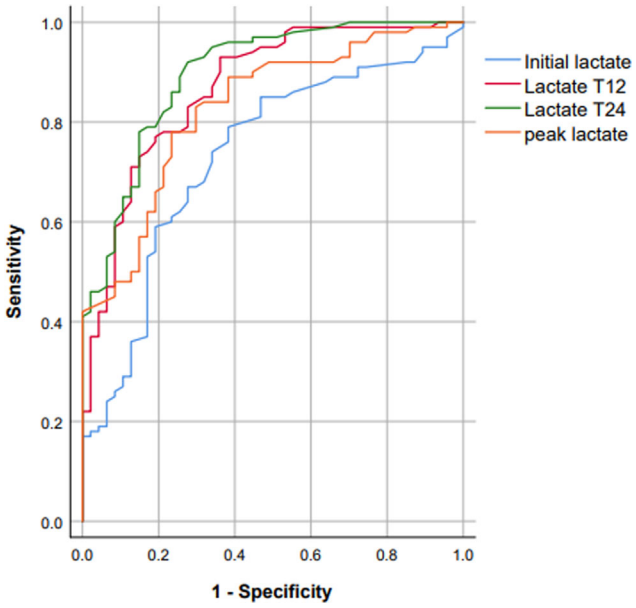


Figure 5 Receiver operating characteristic curve of initial blood lactate [area under the receiver operating characteristic curve (AUROC): 0.731, $P < 0.001$], peak lactate (AUROC: 0.828, $P < 0.001$), lactate T12 h (AUROC: 0.868, $P < 0.001$) and lactate T24 h (AUROC: 0.896, $P < 0.001$) in differentiating mortality with post-cardiotomy extracorporeal membrane oxygenation.



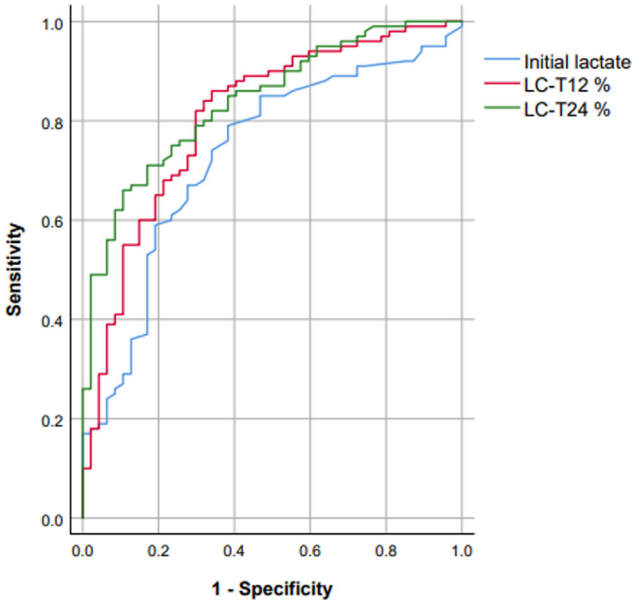
tion was 1.13. The independent predictors of hospital mortality after PC-ECMO were the lactate level at 12 h [odds ratio (OR): 1.67, 95% CI: 1.121–2.181, $P = 0.001$], initial blood lactate (OR: 1.21, 95% CI: 1.016–1.721, $P = 0.032$), initial SOFA score (OR: 1.593, 95% CI: 1.15–2.73, $P < 0.001$) and AF (OR: 6.17, 95% CI: 2.37–57.214, $P = 0.003$). The other three models demonstrated that increased LC was associated with decreased odds of death (*Table* 5). Because of multicollinearity, we used additional bivariate models using lactate levels and clearance at the same points, and the absolute lactate levels maintained statistical significance compared with the clearance percentage (*Table* 6).

Discussion

The main findings of this study were the significant association between hyperlactataemia and PC-ECMO mortality, the ability of LC to predict and discriminate hospital mortality after PC-ECMO support and the superior performance of absolute lactate levels to that of LC in differentiating mortality. The use of PC-ECMO to allow for circulatory support for cardiac recovery after PCS is increasing. Our mortality analysis revealed that 48.7% of patients had on-ECMO mortality and 68.4% had hospital mortality, which is similar to other large PC-ECMO studies.[7,8,10,23] Biancari *et al*. studied patients with post-cardiotomy VA-ECMO and reported death rates between 64.4% and 76.1% in patients aged >70 years.[7] A recent meta-analysis that enrolled 1269 post-cardiotomy patients on VA-ECMO has reported a hospital mortality rate of 66.7%.[8] Mariani *et al*. have reported a 60% mortality rate in a retrospective analysis of 2003 patients with PC-ECMO.[23]

Blood lactate is a widely used point-of-care variable that can be measured from the arterial blood gas of patients with critical illnesses to obtain data on tissue oxygenation and organ perfusion. Different studies have reported a link between poor outcomes and hyperlactataemia, using different measurement protocols. Our study reveals that initial blood lactate levels and subsequent behaviour following PC-ECMO can predict survival after cardiac surgery. Serial measurements of arterial blood lactate are beneficial for detecting the imbalance between lactate production, as a marker of inadequate tissue perfusion, and LC, as a marker of improved organ perfusion. The pre-ECMO initial lactate level of >6.25 mmol/L was able to differentiate mortality (AUROC: 0.731, $P < 0.001$), whereas the blood lactate level of >8.2 mmol/L at 12 h (AUROC: 0.868, $P < 0.001$) and >2.6 mmol/L at 24 h (AUROC: 0.896, $P < 0.001$) demonstrated better differentiation of mortality with a larger AUROC. This may be explained by continued inadequate tissue hypoperfusion despite achieving good haemodynamic profiles after mechanical circulatory support. Li *et al*.[15] have reported that despite achieving good haemodynamics and organ perfusion, lactate levels continued to increase in many patients and that a negative correlation was identified be-

Figure 6 Receiver operating characteristic curve of initial blood lactate [area under the receiver operating characteristic curve (AUROC): 0.731, $P < 0.001$], lactate clearance (LC)-T12 (AUROC: 0.807, $P < 0.001$) and LC-T24 (AUROC: 0.839, $P < 0.001$) in differentiating mortality with post-cardiotomy extracorporeal membrane oxygenation.



tween mean blood lactate level and mean arterial blood pressure during the first 12 h of ECMO support. Biancari *et al*.[8] conducted a large meta-analysis involving 1269 post-cardiotomy patients with VA-ECMO and reported a mortality rate of 55.7% if the lactate level was <6.8 mmol/L and 76.7% if the lactate level was ≥6.8 mmol/L at ECMO initiation. The association between initial and 12 h blood lactate levels and hospital mortality was reported in other VA-ECMO studies.[12,24]

In our cohort analysis, LC-T12 < 21.94% (adjusted HR: 2.73, 95% CI: 1.64–5.762, $P < 0.001$) and LC-T24 h < 40.3% (adjusted HR: 1.98, 95% CI: 1.46–4.173, $P < 0.001$) were associated with an increased risk of death after PC-ECMO. Owing to multicollinearity, we performed four logistic regression analyses and used two bivariate models and observed that despite LC having the ability to predict and discriminate mortality, absolute lactate levels performed better. The best logistic model demonstrated that the blood lactate level at 12 h after PC-ECMO (OR: 1.67, 95% CI: 1.121–2.181, $P = 0.001$) was a predictor of mortality and that the level > 8.2 mmol/L had excellent discrimination (AUROC: 0.868, $P < 0.001$).

Li *et al*.[15] studied PC-ECMO LC at 6 and 12 h and concluded that LC-T12 h had a better discrimination of mortality and a negative correlation with mean arterial blood pressure compared with LC-T6 h. Mungan *et al*.[25] conducted a small study including 48 patients on VA-ECMO, followed the trend of blood lactate over 48 h and reported that the time to achieve 10% LC had a strong discrimination of 30 day mortality. Mizutani *et al*.[26] retrospectively analysed the data of 64 adult patients who underwent extracorporeal cardiopulmonary resuscitation and reported LC at 6 h as an independent predictor of mortality (OR: 7.1, $P < 0.01$, 95% CI: 1.7–29.5). Marbach *et al*.[14] analysed blood lactate levels at 36 h in 192 adult patients with CS without ECMO support and reported that complete LC (lactate level < 2 mmol/L) was the strongest predictor of survival at 8 h (OR: 2.46, $P = 0.03$) and 24 h (OR: 5.44, $P < 0.01$).

Survivors in our cohort had higher SAVE scores and fewer risk classes than non-survivors. The SAVE score had a better discrimination of hospital mortality than the initial blood lactate level but a comparable discrimination to the lactate level at 12 and 24 h after ECMO support. Logistic multivariate regression analysis demonstrated a trend for the SAVE score to predict survival, although this was not significant. Schrutka *et al*. studied 240 patients on PC-ECMO and reported the ability of the SAVE score to differentiate between short- and long-term mortality.[27] Lactate modification of the SAVE score has been demonstrated to improve the predictive ability for survival after VA-ECMO.[28,29] The SOFA score was calculated during the first few days of mechanical circulatory support to determine the clinical severity and trend of organ function after haemodynamic stabilization and LC. Non-survivors initially had higher SOFA scores and trends than survivors. The initial SOFA score had a better discrimination of hospital mortality than

Table 5 Logistic multivariate regression for predicting PC-ECMO mortality.

Variables	OR	95% CI	*P* value
Model A			
Initial SOFA	1.593	1.15–2.73	<0.001
Initial blood lactate	1.21	1.016–1.721	0.032
Blood lactate at 12 h (L12)	1.67	1.121–2.181	0.001
SAVE score	0.817	0.614–1.026	0.07
Atrial fibrillation	6.17	2.37–57.214	0.003
Prior cardiotomy	0.782	0.46–3.621	0.56
CPB time	1.131	0.995–1.93	0.43
Model B			
SAVE score	0.802	0.736–1.161	0.09
Initial SOFA	1.761	1.241–2.67	<0.001
Initial blood lactate	1.18	1.024–1.671	0.042
Atrial fibrillation	7.14	2.19–58.482	0.004
Prior cardiotomy	0.86	0.317–3.713	0.62
CPB time	1.086	0.926–1.217	0.64
Lactate clearance (LC-T12)	0.921	0.901–0.983	0.036
Model C			
Initial SOFA	1.565	1.211–2.023	0.003
SAVE score	0.818	0.708–1.001	0.092
Initial blood lactate	1.13	1.003–1.426	0.037
Atrial fibrillation	6.43	2.69–58.72	0.002
Prior cardiotomy	0.813	0.472–3.95	0.71
CPB time	1.034	0.946–2.237	0.63
Blood lactate at 24 h (L24)	1.521	1.042–2.219	0.031
Model D			
Initial SOFA	1.523	1.156–2.006	0.003
SAVE score	0.809	0.762–1.003	0.062
Initial blood lactate	1.104	1.012–1.274	0.021
Atrial fibrillation	6.28	2.57–56.286	0.003
Prior cardiotomy	0.79	0.477–4.194	0.48
CPB time	1.016	0.926–1.421	0.58
Lactate clearance (LC-T24)	0.974	0.962–0.987	0.027

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; LC, lactate clearance; OR, odds ratio; PC-ECMO, post-cardiotomy extracorporeal membrane oxygenation; SAVE, Survival After Veno-arterial Extracorporeal Membrane Oxygenation; SOFA, Sequential Organ Failure Assessment score.

Table 6 Bivariate models for hospital mortality using lactate absolute levels and clearance.

Lactate variables		OR	95% CI	*P* value
At 12 h	Lactate level	1.599	1.116–1.912	0.001
	Lactate clearance	0.992	0.980–1.005	0.225
At 24 h	Lactate level	1.923	1.334–2.772	<0.001
	Lactate clearance	0.996	0.975–1.019	0.748

Abbreviations: CI, confidence interval; OR, odds ratio.

the initial blood lactate level, with a comparable discrimination of blood lactate level and LC at 12 and 24 h. Moreover, a high SOFA score at ECMO initiation was an independent predictor of in-hospital mortality in the logistic regression model. A high SOFA score and an increasing trend during follow-up represent the deterioration of multi-organ function and have been linked to mortality in different studies.[18,19,30,31]

AF was significantly more frequent in non-survivors in our univariate analysis and was a predictor in the logistic multivariate regression analysis. The studied patients had paroxysmal or persistent AF with high CHA_2DS_2–VASc scores and multiple cardiovascular and non-cardiovascular comorbidities. They were considered high-risk phenotypes of AF according to the cluster analysis of the clinical characteristics of patients with AF.[32,33] Vigneshwar *et al*.[34] analysed 789 patients on VA-ECMO and reported that pre-ECMO sinus rhythm was associated with a survival benefit. Wang *et al*.[35] conducted a small retrospective study of 87 patients on PC-ECMO and reported that the frequency of AF was 13% and 38% ($P < 0.001$) in survivors and non-survivors, respectively; however, it was not included in the logistic regression model. Another small study on PC-ECMO has reported that preoperative AF was a predictor of hospital mortality.[36] A recent large multicentre study has reported that AF was a predictor of mortality after PC-ECMO during follow-up rather than during hospitalization.[37]

Conclusions

Serial measurements of arterial blood lactate levels and LC help in obtaining early prognostic guidance in adult patients

supported by VA-ECMO after cardiac surgery. Absolute lactate levels demonstrated better performance in differentiating mortality than LC at the same time points.

Limitations

Owing to the retrospective, single-centre study design, collecting serial measurements of arterial blood lactate was feasible. However, infrequent central venous blood gases did not allow us to obtain mixed central venous oxygen saturation to combine with blood lactate in mortality discrimination.

Conflict of interest

There is no conflict of interest.

Data availability statement

The study data are available from the corresponding author upon request.

References

1. Vela JP, Jorge CL, Álvarez JD, Rivera JJ. Clinical management of postcardiotomy shock in adults. *Medicina Intensiva (English Edition)* 2022;**46**:312-325. doi:10.1016/j.medine.2022.04.014
2. Lorusso R, Whitman G, Milojevic M, Raffa G, McMullan DM, Boeken U, *et al*. 2020 EACTS/ELSO/STS/AATS expert consensus on post-cardiotomy extracorporeal life support in adult patients. *Eur J Cardiothorac Surg* 2021;**59**:12-53. doi:10.1093/ejcts/ezaa283
3. Weman SM, Karhunen PJ, Penttilä A, Järvinen AA, Salminen US. Reperfusion injury associated with one-fourth of deaths after coronary artery bypass grafting. *Ann Thorac Surg* 2000;**70**:807-812. doi:10.1016/s0003-4975(00)01638-6
4. Lorusso R, Raffa GM, Alenizy K, Sluijpers N, Makhoul M, Brodie D, *et al*. Structured review of post-cardiotomy extracorporeal membrane oxygenation: Part 1—Adult patients. *J Heart Lung Transplant* 2019;**38**:1125-1143. doi:10.1016/j.healun.2019.08.014
5. Whitman GJ. Extracorporeal membrane oxygenation for the treatment of postcardiotomy shock. *J Thorac Cardiovasc Surg* 2017;**153**:95-101. doi:10.1016/j.jtcvs.2016.08.024
6. Kowalewski M, Zielinski K, Brodie D, MacLaren G, Whitman G, Raffa GM, *et al*. Venoarterial extracorporeal membrane oxygenation for postcardiotomy shock-analysis of the extracorporeal life support organization registry. *Crit Care Med* 2021;**49**:1107-1117. doi:10.1097/CCM.0000000000004922
7. Biancari F, Dalén M, Fiore A, Ruggieri VG, Saeed D, Jónsson K, *et al*. Multicenter study on postcardiotomy venoarterial extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg* 2020;**159**:1844-1854. doi:10.1016/j.jtcvs.2019.06.039
8. Biancari F, Kaserer A, Perrotti A, Ruggieri VG, Cho SM, Kang JK, *et al*. Hyperlactatemia and poor outcome after postcardiotomy veno-arterial extracorporeal membrane oxygenation: An individual patient data meta-analysis. *Perfusion* 2023;026765912311709. doi:10.1177/02676591231170978
9. Kowalewski M, Raffa GM, Zielinski K, Alanazi M, Gilbers M, Heuts S, *et al*. The impact of centre's heart transplant status and volume on in-hospital outcomes following extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock: A meta-analysis. *BMC Cardiovasc Disord* 2020;**20**:10. doi:10.1186/s12872-019-01317-y
10. Biancari F, Kaserer A, Perrotti A, Ruggieri VG, Cho SM, Kang JK, *et al*. Central versus peripheral postcardiotomy veno-arterial extracorporeal membrane oxygenation: Systematic review and individual patient data meta-analysis. *J Clin Med* 2022;**11**:7406. doi:10.3390/jcm11247406
11. Fall PJ, Szerlip HM. Lactic acidosis: From sour milk to septic shock. *J Intesive Care Med* 2005;**20**:255-271. doi:10.1177/0885066605278644
12. Laimoud M, Alanazi M. The clinical significance of blood lactate levels in evaluation of adult patients with veno-arterial extracorporeal membrane oxygenation. *Egypt Heart J* 2020;**72**:1-8. doi:10.1186/s43044-020-00108-7
13. Marbach JA, Stone S, Schwartz B, Pahuja M, Thayer KL, Faugno AJ, *et al*. Lactate clearance is associated with improved survival in cardiogenic shock: A systematic review and meta-analysis of prognostic factor studies. *J Card Fail* 2021;**27**:1082-1089. doi:10.1016/j.cardfail.2021.08.012
14. Marbach JA, Di Santo P, Kapur NK, Thayer KL, Simard T, Jung RG, *et al*. Lactate clearance as a surrogate for mortality in cardiogenic shock: Insights from the DOREMI trial. *JAHA* 2022;**11**:e023322. doi:10.1161/JAHA.121.023322
15. Li CL, Wang H, Jia M, Ma N, Meng X, Hou XT. The early dynamic behavior of lactate is linked to mortality in postcardiotomy patients with extracorporeal membrane oxygenation support: A retrospective observational study. *J Thorac Cardiovasc Surg* 2015;**149**:1445-1450. doi:10.1016/j.jtcvs.2014.11.052 Epub 2014 Nov 24. PMID: 25534305
16. Fuernau G, Desch S, de Waha-Thiele S, Eitel I, Neumann FJ, Hennersdorf M, *et al*. Arterial lactate in cardiogenic shock: Prognostic value of clearance versus single values. *Cardiovasc Interv* 2020;**13**:2208-2216. doi:10.1016/j.jcin.2020.06.037
17. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, *et al*. Predicting survival after ECMO for refractory cardiogenic shock: The survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J* 2015;**36**:2246-2256. doi:10.1093/eurheartj/ehv194
18. Laimoud M, Alanazi M. The validity of SOFA score to predict mortality in adult patients with cardiogenic shock on venoarterial extracorporeal membrane oxygenation. *Crit Care Res Prac* 2020;**2020**:3129864. doi:10.1155/2020/3129864 PMID: 32963830; PMCID: PMC7495164
19. Laimoud M, Alanazi M, Qureshi R. Hospital outcomes after emergent peripheral veno-arterial extracorporeal membrane oxygenation in adult patients presenting with cardiogenic shock. *Signa Vitae* 2021;103-109. doi:10.22514/sv.2021.118
20. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibril-

lation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373-498. doi:10.1093/eurheartj/ehaa612 Erratum in: Eur Heart J. 2021 Feb 1;42(5):507. Erratum in: Eur Heart J. 2021 Feb 1;42(5):546–547. Erratum in: Eur Heart J. 2021 Oct 21;42(40):4194. PMID: 32860505

21. Hosmer DW, Hjort NL. Goodness-of-fit processes for logistic regression: Simulation results. *Stat Med* 2002;**21**:2723-2738. doi:10.1002/sim.1200 PMID: 12228887
22. Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF. Youden index and optimal cut-point estimated from observations affected by a lower limit of detection. *Biom J* 2008;**50**:419-430. doi:10.1002/bimj.200710415 PMID: 18435502; PMCID: PMC2515362
23. Mariani S, Wang IW, van Bussel BC, Heuts S, Wiedemann D, Saeed D, *et al*. The importance of timing in postcardiotomy venoarterial extracorporeal membrane oxygenation: A descriptive multicenter observational study. *J Thorac Cardiovasc Surg* 2023;**166**:1670-1682.e33. doi:10.1016/j.jtcvs.2023.04.042
24. Melvin A, Ayers BC, Wood K, Prasad S, Barrus B, Gosev I. Lactate predicts mortality 12 hours after VA ECMO initiation. *J Heart Lung Transplant* 2019;**38**:S174-S175. doi:10.1016/j.healun.2019.01.419
25. Mungan İ, Kazancı D, Bektaş Ş, Ademoglu D, Turan S. Does lactate clearance prognosticates outcomes in ECMO therapy: A retrospective observational study. *BMC Anesthesiol* 2018;**18**:1-8. doi:10.1186/s12871-018-0618-1
26. Mizutani T, Umemoto N, Taniguchi T, Ishii H, Hiramatsu Y, Arata K, *et al*. The lactate clearance calculated using serum lactate level 6 h after is an important prognostic predictor after extracorporeal cardiopulmonary resuscitation: A single-center retrospective observational study. *J Intensive Care* 2018;**6**:1-7. doi:10.1186/s40560-018-0302-z
27. Schrutka L, Rohmann F, Binder C, Haberl T, Dreyfuss B, Heinz G, *et al*. Discriminatory power of scoring systems for outcome prediction in patients with extracorporeal membrane oxygenation following cardiovascular surgery†. *Eur J Cardiothorac Surg* 2019;**56**:534-540. doi:10.1093/ejcts/ezz040 PMID: 30789227
28. Chen WC, Huang KY, Yao CW, Wu CF, Liang SJ, Li CH, *et al*. The modified SAVE score: Predicting survival using urgent veno-arterial extracorporeal membrane oxygenation within 24 hours of arrival at the emergency department. *Crit Care* 2016;**20**:336. doi:10.1186/s13054-016-1520-1 PMID: 27769308; PMCID: PMC5075192
29. Santore LA, Schurr JW, Noubani M, Rabenstein A, Dhundale K, Bilfinger TV, *et al*. SAVE score with lactate modification predicts in-hospital mortality in patients with ongoing cardiac arrest during VA-ECMO cannulation. *IJAO* 2021;**44**:787-790. doi:10.1177/03913988211021878
30. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;**286**:1754-1758.
31. Ahmed W, Laimoud M. The value of combining carbon dioxide gap and oxygen-derived variables with lactate clearance in predicting mortality after resuscitation of septic shock patients. *Crit Care Res Prac* 2021;**2021**:1-10. doi:10.1155/2021/6918940
32. Proietti M, Vitolo M, Harrison SL, Lane DA, Fauchier L, Marin F, *et al*. Impact of clinical phenotypes on management and outcomes in European atrial fibrillation patients: A report from the ESC-EHRA EURObservational Research Programme in AF (EORP-AF) General Long-Term Registry. *BMC Med* 2021;**19**:256. doi:10.1186/s12916-021-02120-3. PMID: 34666757; PMCID: PMC8527730
33. Vitolo M, Proietti M, Shantsila A, Boriani G, Lip GYH. Clinical phenotype classification of atrial fibrillation patients using cluster analysis and associations with trial-adjudicated outcomes. *Biomedicine* 2021;**9**:843. doi:10.3390/biomedicines9070843 PMID: 34356907; PMCID: PMC8301818
34. Vigneshwar NG, Kohtz PD, Lucas MT, Bronsert M, Weyant MJ, Masood MF, *et al*. Clinical predictors of in-hospital mortality in venoarterial extracorporeal membrane oxygenation. *J Card Surg* 2020;**35**:2512-2521. doi:10.1111/jocs.14758
35. Wang JG, Han J, Jia YX, Zeng W, Hou XT, Meng X. Outcome of veno-arterial extracorporeal membrane oxygenation for patients undergoing valvular surgery. *PLoS ONE* 2013;**8**:e63924. doi:10.1371/journal.pone.0063924
36. Saxena P, Neal J, Joyce LD, Greason KL, Schaff HV, Guru P, *et al*. Extracorporeal membrane oxygenation support in postcardiotomy elderly patients: The Mayo Clinic experience. *Ann Thorac Surg* 2015;**99**:2053-2060. doi:10.1016/j.athoracsur.2014.11.075 Epub 2015 Apr 10. PMID: 25865760
37. Mariani S, Heuts S, van Bussel BC, Di Mauro M, Wiedemann D, Saeed D, *et al*. Patient and management variables associated with survival after postcardiotomy extracorporeal membrane oxygenation in adults: The PELS-1 Multicenter Cohort Study. *J Am Heart Assoc* 2023;**12**:e029609. doi:10.1161/JAHA.123.029609