MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2023; 29: e942119
DOI: 10.12659/MSM.942119

Received: 2023.08.10
Accepted: 2023.09.01
Available online: 2023.09.05
Published: 2023.09.14

Predicting Survival Outcomes in Post-Cardiac Arrest Syndrome: The Impact of Combined Sequential Organ Failure Assessment Score and Serum Lactate Measurement

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Financial support: None declared
Conflict of interest: None declared

Background: Post-cardiac arrest syndrome (PCAS) is a major concern and shares pathophysiology with sepsis. Sequential organ failure assessment (SOFA) scores and serum lactate levels, as suggested in the Survival Sepsis Guidelines, have shown significant predictive value for prognosis in patients with sepsis. This retrospective study aimed to evaluate combined use of the SOFA score and serum lactate measurement on survival prognosis in PCAS.

Material/Methods: Our study included patients with return of spontaneous circulation after cardiac arrest who were age >18 years and underwent targeted temperature management. The 438 patients were allocated to a surviving group and a deceased group at discharge. Multivariable regression models were used to evaluate any association with SOFA scores, serum lactate levels, and survival. To evaluate the predictive value of regression models, the area under the receiver operating characteristic curve (AUROC) was assessed.

Results: Lower SOFA score and serum lactate level were associated with better survival rates in the post-cardiac arrest patients (SOFA score: odds ratio (OR), 0.77; 95% confidence interval (CI), 0.67-0.88; *P*<0.001; lactate level: OR, 0.85; 95% CI, 0.81-0.94; *P*<0.001). The combined model of the SOFA score and serum lactate level was superior to models including either SOFA score or serum lactate level alone in predicting survival (AUROC, 0.86 vs 0.83, *P*=0.028, 0.86 vs 0.81, *P*=0.004).

Conclusions: Because of the superiority of the combined model of SOFA score and serum lactate level, combining these 2 factors could improve prediction of prognosis and survival outcomes in PCAS.

Keywords: Lactic Acid • Organ Dysfunction Scores • Post-Cardiac Arrest Syndrome • Prognosis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/942119

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Background

Cardiac arrest and management of survivors are major public health issues [1]. The estimated incidence of out-of-hospital cardiac arrest (OHCA) was 50-60 per 100 000 person-years in North America [2]. In South Korea, the number of patients with sudden cardiac arrests in 2020 was 61.6 per 100 000 individuals [3]. However, even when first resuscitated, the overall survival rate to hospital discharge after OHCA was 8.8% globally and 8.2% in South Korea [3,4]. In this context, research on the prognosis of cardiac arrest is important for determining the direction and scope of future treatment for critical patients who survive cardiac arrest and informing caregivers of their prognosis; therefore, there have been many studies on factors predicting survival in patients with cardiac arrest [5-7].

Post-cardiac arrest syndrome (PCAS), which is defined as the clinical status that involves global ischemic-reperfusion injury, aggressive inflammation, myocardial dysfunction, coagulopathy, and adrenal dysfunction after cardiac arrest event, and sepsis are 2 distinct medical conditions that share some similarities, even though cardiac arrest may not be caused by a serious infection [8]. During cardiac arrest, blood flow to organs is reduced or stopped, leading to ischemia and tissue damage [9]. When blood flow is restored after resuscitation, a burst of reactive oxygen species is produced, which can cause further tissue damage and inflammation, known as reperfusion injury [10]. As a result of ischemic/reperfusion injury, a systemic inflammatory response occurs throughout the body, and this aggressive and dysregulated inflammatory response has a deleterious effect on patients [11]. Similar to PCAS, sepsis is characterized by a dysregulated host response to infection, resulting in tissue hypoxia and shock, followed by multiorgan damage [12].

The sequential organ failure assessment (SOFA) score is a scoring system commonly used to evaluate the severity of multiorgan failure in intensive care unit (ICU) patients and is useful for assessing the clinical outcomes of critically ill patients with various conditions, including sepsis [13]. Likewise, the serum level of lactate, which is a normal byproduct of glucose metabolism and can be elevated by increased anaerobic glycolysis in the hypoperfusion state, may also have prognostic value in patients with septic shock [14]. The Surviving Sepsis Campaign recommends the SOFA score and lactate measurement as risk stratification methods and important components in the management of patients with sepsis [12]. Elevation of the SOFA score and serum lactate levels after ICU admission predicted higher mortality in critically ill patients [15-17].

Because patients with PCAS have similar characteristics to patients with sepsis, both SOFA score and serum lactate level could be predictive factors in patients with PCAS, as they are in patients with sepsis. Nevertheless, these factors have not been studied together; therefore, this retrospective study of 438 patients who had cardiac arrest and post-cardiac arrest syndrome (PCAS) after return of spontaneous circulation (ROSC) evaluated the effect of combined use of the sequential organ failure assessment (SOFA) score and serum lactate measurements on patient prognosis and survival.

Material and Methods

Ethics Considerations

Our study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Ajou University Medical Center (AJOUIRB-DB-2023-0113). Owing to the retrospective nature of this study, the requirement for informed consent was waived.

Study Setting and Enrolled Patients

At our institute, where this study was conducted, almost 90 000 patients visit the Emergency Department (ED) each year, and approximately 500 patients with return of spontaneous circulation (ROSC) after cardiac arrest were admitted and cared for in the ICU from January 2016 to December 2020. From our hospital's database of cardiopulmonary resuscitation (CPR) events, we collected data on all cardiac arrest cases with ROSC who were >18 years old and who were admitted and underwent targeted temperature management (TTM) in the ICU, regardless of the site of the cardiac arrest. The target temperature for our TTM protocol is 32-37°C [18]. TTM is performed with temperature-adjustable devices with a feedback loop system (Arctic Sun® Energy Transfer Pads™; Medivance Corp., Louisville, KY, USA, or Cool Guard Alsius Icy Heat Exchange Catheter; Alsius Corporation, Irvine, CA, USA) or water-circulating blankets as temperature management methods. Patients undergoing TTM receive sufficient sedative and analgesic treatments with immediate control of shivering and seizures. We excluded patients who could obey commands or had a traumatic cause of arrest, brain hemorrhage, or hemodynamic instability. We also excluded patients with end-stage cancer with a life expectancy of <6 months and those with a do-not-resuscitate order with consent from their families because they had not undergone TTM. Finally, the enrolled patients were grouped based on survival status at discharge, and their data were analyzed to compare the predictive values of SOFA score and lactate level in the survival status at discharge of patients with PCAS.

Study Variables and Data Collection

We retrospectively and comprehensively collected data from the electronic medical records and a data registry of patients

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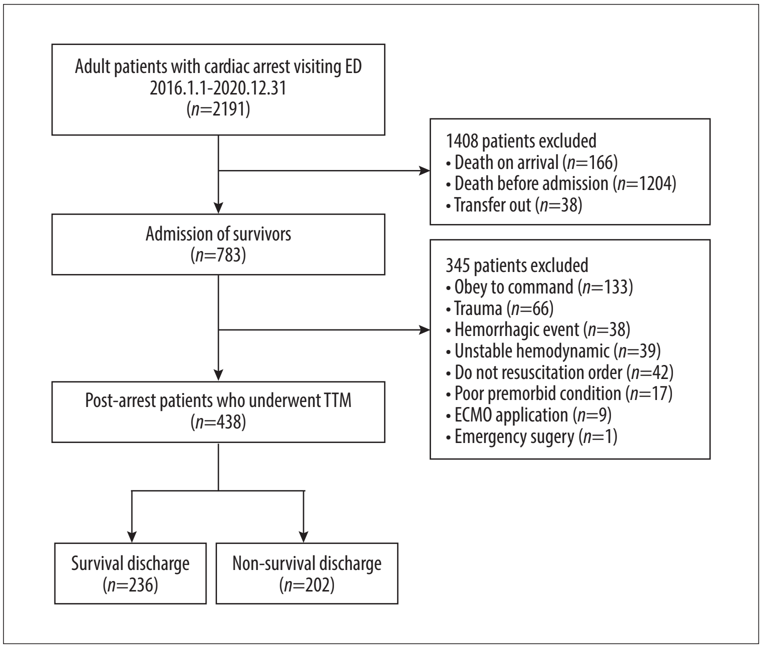

Figure 1. Study enrollment flowchart.

with PCAS who underwent TTM after ROSC. We collected demographic data, including age, sex, underlying disease (diabetes mellitus and hypertension), and variables related to cardiac arrests, such as witnessed arrest, bystander CPR, automatic external defibrillator (AED) application, prehospital/in-hospital initial rhythm, cause of arrest, no-flow time (time from collapse to the application of life support), total CPR time (time from the application of life support until ROSC), initial SOFA score, initial serum lactate level, serum C-reactive protein level, and TTM method. The SOFA score is used to assess organ dysfunction or failure for critical illness severity evaluation based on the degree of dysfunction of 6 organ systems and plays a crucial role as the main tool for sepsis diagnosis [17]. The SOFA score ranges from 0 to 24, with higher scores indicating a higher mortality risk. Laboratory findings, such as lactate levels, were retrieved from electronic medical records. Variables related to outcomes, including survival status at hospital discharge, were collected from the data registry of patients with PCAS.

Statistical Analysis

Continuous variables are presented as means (±standard deviations) or medians (interquartile ranges), depending on the data distribution, and categorical data are presented as numbers with percentages (%). We used a *t* test for continuous variables of normal distribution. Non-normally distributed continuous variables were analyzed using the Mann-Whitney U test. Categorical variables are reported as numbers and proportions and were tested using the chi-square test. Multivariable logistic regression models were performed using backward elimination to assess the association between survival events and the SOFA score or serum lactate level while adjusting for confounding variables. Receiver operating characteristic (ROC) curves were constructed to evaluate and compare the predictive values of the multivariable models, which included the SOFA score, serum lactate level, or both. Statistical analyses were performed using R software for Mac version 4.2.2 (The R Project, Vienna, Austria). *P* values <0.05 were considered statistically significant.

Results

Baseline Characteristics of Enrolled Patients

Of the 2191 adult patients presenting with cardiac arrest to the ED, 1408 were declared dead on arrival or dead before admission, or were transferred to another hospital and excluded. Of the 783 patients admitted alive, 345 were excluded from the TTM, including those who obeyed a command, had hemorrhagic events, or had unstable vital signs. Finally, 438 patients who underwent TTM were included in the study and divided into 2 groups: those who were discharged alive (n=236) and those who died in the hospital before discharge (n=202) (**Figure 1**). The baseline characteristics of the enrolled patients are presented in **Table 1**. Age differed significantly between the 2 groups (*P*<0.001). Other general demographics, including sex and underlying disease, did not differ significantly between the 2 outcome groups. AED application, first monitored rhythm, no-flow time, total CPR time, and presumed cause of arrest significantly differed between the 2 groups. The total SOFA score and lactic acid levels were also significantly different between the 2 groups (*P*<0.001) (**Table 1**).

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Table 1. Baseline characteristics of the study population.

Characteristics	Deceased discharged patients (n=202)		Survival discharged patients (n=236)		*P* value
Age, years	63.12	(±17.14)	54.41	(±16.24)	<0.001
Female	77	(38.12)	69	(29.24)	0.062
Past medical history					
Diabetes mellitus	73	(36.14)	67	(28.39)	0.098
Hypertension	77	(38.12)	93	(39.41)	0.499
Cause of arrest					0.003
Cardiogenic	59	(29.20)	92	(38.98)	
Respiratory	34	(16.83)	40	(16.95)	
Metabolic	31	(15.34)	16	(6.78)	
Toxin-related	4	(1.98)	6	(2.54)	
Anaphylaxis	1	(0.96)	6	(2.54)	
Asphyxia	36	(17.82)	34	(14.41)	
Unspecified	37	(18.31)	42	(17.80)	
Resuscitation factor					
Witnessed	139	(68.81)	181	(76.69)	0.179
Bystander CPR	138	(68.32)	180	(76.27)	0.107
AED apply	40	(19.80)	88	(37.29)	<0.001
Initial shockable rhythm	33	(16.33)	80	(33.90)	<0.001
Presumed cardiogenic arrest	59	(29.21)	92	(38.98)	0.041
No-flow time	0.00	(0.00-9.00)	0.00	(0.00-5.00)	0.002
Total CPR time	34.94±17.62		21.63±15.01		<0.001
TTM factors					
TTM method					0.074
Arctic sun	128	(63.37)	159	(67.37)	
Intravascular	14	(6.93)	27	(11.44)	
Cooling pad	60	(29.70)	50	(21.19)	
Target temperature					0.693
From 32°C to 34°C	145	(71.78)	173	(73.31)	
From 35°C to 37°C	57	(28.22)	63	(26.69)	
Sepsis-related factors					
SOFA scores					
Total SOFA score	11.32	(±3.38)	9.25	(±2.68)	<0.001
Cardiovascular system	3.54	(±1.51)	3.11	(±1.41)	<0.001
Neurological system	3.88	(±0.35)	3.69	(±0.51)	<0.001

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Table 1 continued. Baseline characteristics of the study population.

Characteristics	Deceased discharged patients (n=202)		Survival discharged patients (n=236)		*P* value
Hematologic system	0.52	(±0.91)	0.28	(±0.57)	<0.001
Respiratory system	2.06	(±1.40)	1.42	(±1.31)	<0.001
Hepatic system	0.32	(±0.69)	0.10	(±0.37)	<0.001
Renal system	1.18	(±1.26)	0.67	(± 1.25)	<0.001
Lactate, mmol/L	10.32	(±4.83)	7.24	(±4.42)	<0.001
CRP, mg/dL	0.61	(0.08-4.84)	0.29	(0.06-2.67)	0.010

Values are presented as number (%), mean (±standard deviation), or median (interquartile range). CPR – cardiopulmonary resuscitation; AED – automatic external defibrillator; TTM – target temperature management; SOFA – sequential organ failure assessment; CRP – c-reactive protein.

Table 2. Logistic regression models for survival outcomes.

	Univariate OR (95% CI)	*P* value	Multivariable OR (95% CI), Model including SOFA score & lactate level***	*P* value	Multivariable OR (95% CI), Model including SOFA score#	*P* value	Multivariable OR (95% CI), Model including lactate level##	*P* value
Age	0.98 (0.94-0.99)	<0.001	0.98 (0.96-1.00)	0.091	0.98 (0.96-1.00)	0.159	0.97 (0.95-0.99)	0.012
Initial shockable rhythm	2.91 (1.82-4.71)	<0.001	0.81 (0.25-2.60)	0.448	0.62 (0.16-2.30)	0.486	0.84 (0.21-3.19)	0.810
Use of AED	2.40 (1.56-3.73)	<0.001	3.51 (1.03-13.04)	0.049	2.89 (0.89-10.00)	0.082	3.39 (1.01-12.30)	0.052
Cardiogenic etiology	0.76 (0.64-0.89)	<0.001	1.37 (0.59-3.16)	0.452	1.50 (0.66-3.39)	0.323	1.11 (0.49-2.48)	0.794
No-flow time*	0.96 (0.93-0.98)	<0.001	0.94 (0.90-0.98)	0.014	0.94 (0.90-0.97)	0.003	0.95 (0.92-0.99)	0.033
Total CPR time**	0.96 (0.95-0.97)	<0.001	0.95 (0.93-0.97)	<0.001	0.94 (0.92-0.96)	<0.001	0.94 (0.92-0.96)	<0.001
SOFA score	0.79 (0.73-0.85)	<0.001	0.77 (0.6-0.88)	<0.001	0.76 (0.67-0.86)	<0.001	-	-
Lactate	0.86 (0.82-0.90)	<0.001	0.85 (0.81-0.94)	0.002	-	-	0.87 (0.81-0.94)	<0.001

AED – automatic external defibrillator; CPR – cardiopulmonary resuscitation; SOFA – sequential organ failure assessment; OR – odds ratio; CI – confidence interval. * No-flow time: time from collapse to resuscitation administration. ** Total CPR time: time from resuscitation to return of spontaneous circulation (BLS time+ACLS time). *** Hosmer-Lemeshow X squared=14.94, df=8, *P* value=0.06, indicating a good model fit. 6 of 10. # Hosmer-Lemeshow X squared=9.48, df=8, *P* value=0.30, indicating a good model fit. ## Hosmer-Lemeshow X squared=8.91, df=8, *P* value=0.35, indicating good model fit.

Analysis of Factors Associated with Survival Outcomes

In the univariate analysis, lower SOFA score and lactic acid level were associated with survival discharged outcomes: SOFA score (odds ratio (OR), 0.79; 95% confidence interval (CI), 0.73-0.85; *P*<0.001) and lactic acid (OR, 0.86; 95% CI, 0.82-0.90; *P*<0.001). Furthermore, in the univariate analysis, other factors, such as younger age, shockable state of initial rhythm, use of AED, cardiogenic etiology, shorter no-flow time, and total CPR time, were associated with survival-to-discharge

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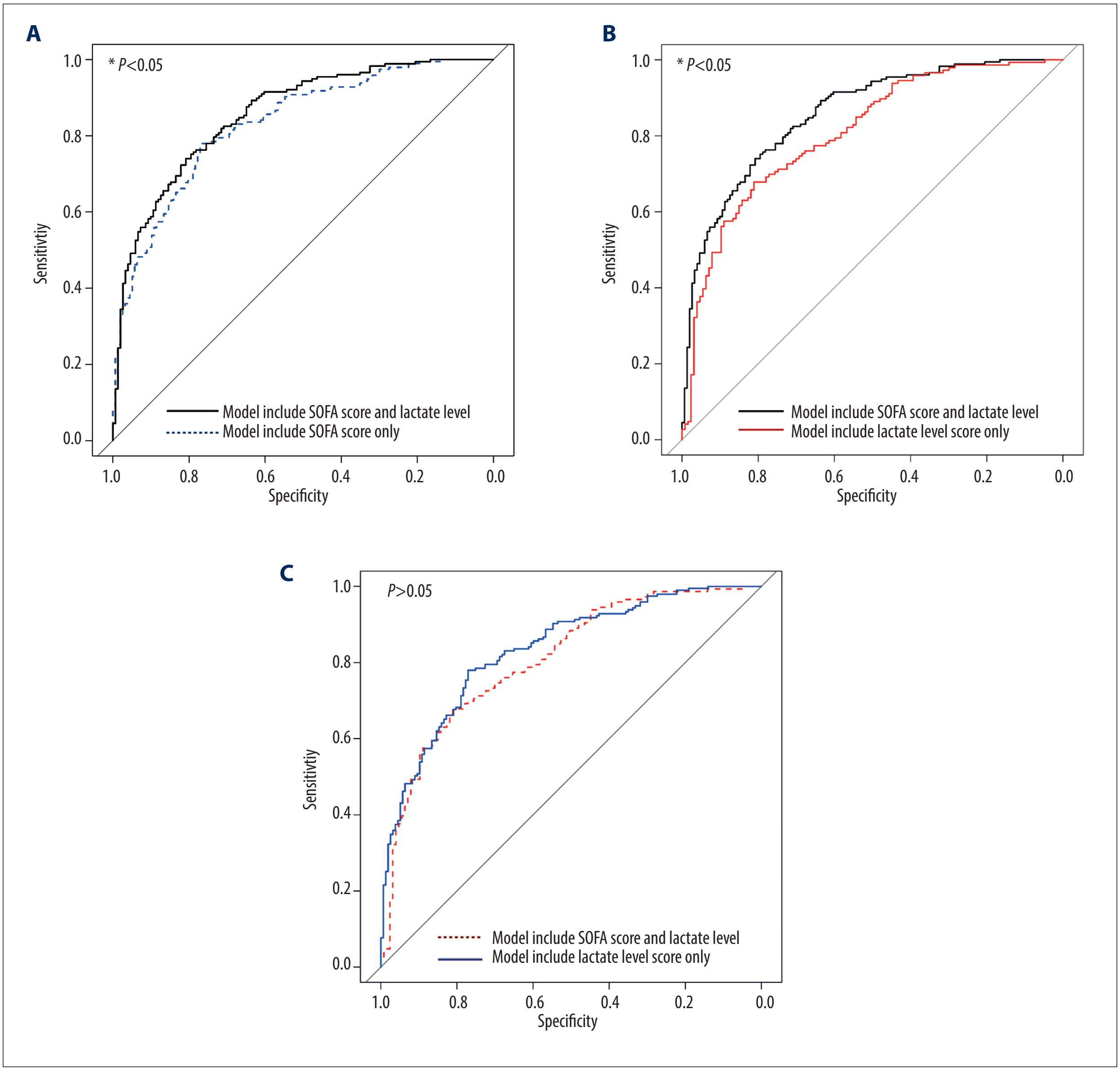

Figure 2. Comparison of receiver operating characteristics (ROC) curves for predicting survival outcome in patients with post-cardiac arrest syndrome. (**A**) Comparison of the area under the ROC curve (AUROC) of the 2 models, the model including SOFA score and serum lactate level versus the model including SOFA score only (AUROC=0.86 versus 0.83, *P* value=0.028). (**B**) Comparison of AUROC of the 2 models, the model including SOFA score and serum lactate level versus the model including serum lactate level only (AUROC=0.86 vs 0.81, *P* value=0.004) (**C**) Comparison of the AUROC of the 2 models, the model including the SOFA score versus the model including the serum lactate level (AUROC=0.83 vs 0.81, *P* value=0.050).

outcomes ($P<0.001$). However, even after adjusting for multiple confounding factors, including age, initial shockable rhythm, use of AED, cardiogenic etiology, no-flow time, and total CPR time, SOFA score and serum lactic acid level were still associated with good survival outcomes: SOFA score (OR, 0.77; 95% CI, 0.67-0.88; $P<0.001$) and serum lactate level (OR, 0.85; 95% CI, 0.81-0.94; $P=0.002$) (**Table 2**).

Prediction of Survival Discharged Outcome

The model that combines the SOFA score and lactate level is more effective in predicting survival outcomes. DeLong's test was performed for 2 areas under the ROC curve (AUROC) of the multivariable models, which included the SOFA score, the serum lactate level, or both. All 3 multivariable models included variables with statistically significant ORs in the univariate analysis, such as age, initial shockable rhythm state, use of an

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Table 3. Different effects of serum lactic acid and sequential organ dysfunction assessment (SOFA) score on survival prognosis according to presumed cause of arrest.

Survival related factors	Presumed cause of arrest			
	Cardiogenic		Non-cardiogenic	
	Multivariable* OR (95% CI)	*P* value	Multivariable* OR (95% CI)	*P* value
Serum lactic acid	0.91 (0.82-1.00)	0.07	0.85 (0.79-0.92)	<0.001
SOFA score	0.75 (0.62-0.89)	0.001	0.84 (0.75-0.92)	<0.001

SOFA – sequential organ failure assessment; OR – odds ratio; CI – confidence interval. * Multivariable regression logistic model includes serum lactic acid or SOFA score with initial shockable rhythm, use of AED, no-flow time, and total CPR time.

AED, presumed cardiogenic etiology, no-flow time, and total CPR time. The model that included both the SOFA score and serum lactate level was superior in predicting survival compared to the models including either the SOFA score or the serum lactate level alone (0.86 vs 0.83, *P* value=0.028, 0.86 vs 0.81, *P* value=0.004, respectively). Additionally, there was no significant difference between the SOFA score-only and serum lactate level-only models (0.83 vs 0.81, *P* value=0.050) (**Figure 2**).

Effect of Serum Lactic Acid and SOFA Score According to Cause of Arrest

In patients with presumed non-cardiogenic cause of arrest, lower serum lactic acid level and SOFA score were still associated with good survival outcomes in multivariable logistic regression models including age, initial shockable rhythm, use of AED, no-flow time, and total CPR time: serum lactate level (OR, 0.85; 95% CI, 0.79-0.92; *P*<0.001), SOFA score (OR, 0.84; 95% CI, 0.75-0.92; *P*<0.001). In patients with presumed cardiogenic cause of arrest, lower SOFA score was associated with better survival prognosis (OR, 0.75; 95% CI, 0.62-0.89; *P*=0.001), but serum lactic acid level was not associated with survival prognosis (OR, 0.91; 95% CI, 0.82-1.00; *P*=0.07), (**Table 3**).

Discussion

We evaluated the effect of combined use of the SOFA score and serum lactate measurements on patient prognosis in PCAS, comparing the multivariable regression model AUROC of the combined SOFA score and serum lactate level with models including either the SOFA score alone or the serum lactate level alone. The combination of SOFA score and serum lactate level was significantly better in predicting survival-to-discharge outcomes in patients with PCAS. This finding adds to the results of previous studies that have examined the individual association of SOFA score and serum lactate level with the survival of patients with PCAS, and both the SOFA score and the serum lactate level have significant value in predicting prognosis in patients with PCAS [19,20]. The highest SOFA score over 72 h had an independent association with in-hospital mortality in patients with PCAS [19]. Patients with lower lactate level at specific times and greater percent decrease in lactate level over the first 12 h after cardiac arrest had better survival rates [20]. However, the 2 factors used in each study have not previously been combined to predict the survival of patients with PCAS. Our study demonstrates that the combination of these 2 factors is useful for predicting survival in patients with PCAS and is superior to models that use either factor alone.

Similar to sepsis, the SOFA score reflects the current state of organ failure in patients with PCAS and may be useful in predicting patient survival [21]. The SOFA score is used to assess the severity of organ dysfunction in critically ill patients. It evaluates the functions of 6 organ systems: respiratory, cardiovascular, hepatic, coagulation, renal, and neurological [22]. The SOFA score is commonly used in ICUs to estimate the clinical severity of disease in patients and to monitor the progression of organ failure during patient care [21]. After prolonged hypoxic/ischemic insults during cardiac arrest, patients usually experience a cascade of events, including systemic ischemia/reperfusion injury, dysregulated inflammation, and subsequent multi-organ dysfunction, known as PCAS, during the post-cardiac arrest period [19,24]. The extent of organ dysfunction and failure in patients with PCAS and the severity of the condition are reflected in the SOFA score at the time of measurement. Therefore, as in our study, a higher SOFA score in patients with PCAS indicates more severe organ damage or dysfunction at the time of scoring, which can predict a poor prognosis in terms of survival and discharge from the hospital.

Serum lactate levels, which show the state of energy metabolism and shock in patients with PCAS, indicate organ dysfunction or hypoperfusion and reflect dysregulated immune status in patients with PCAS. Lactate is a metabolic byproduct that accumulates in the body when there is an imbalance between oxygen supply and demand [25]. During cardiac arrest, blood flow to vital organs, including the brain and heart, is disrupted,

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leading to oxygen deprivation and initiation of anaerobic metabolism [26]. In addition, despite the return of blood flow and adjustment of the hypotensive status after ROSC, tissue perfusion may still be compromised because of impaired microcirculatory dysfunction caused by endothelial dysfunction, nitric oxide dysregulation, or hematologic abnormalities owing to an excessive inflammatory response, which can hinder the delivery of oxygen to tissues and cause persistent anaerobic glycolysis [27]. Elevated lactate levels can indicate aggravation of tissue hypoperfusion and anaerobic metabolism related to cardiac arrest and persistent PCAS [19]. Moreover, serum lactate levels correspond to several clinical variables that reflect the status of systemic inflammation and could serve as early biomarkers of the systemic inflammatory response in sepsis as a prelude to apparent organ dysfunction [28]. Therefore, hyperlactatemia after ROSC may be a predictor of myocardial dysfunction, pressor-dependent hemodynamic instability, microcirculatory failure, hematologic dysfunction, and subsequent multiple organ damage caused by aggressive systemic inflammation. Consequently, the systemic accumulation of lactic acid may be an indicator of hypoperfusion and aggressive inflammation in PCAS and is, therefore, related to poor survival in PCAS.

In addition, SOFA score and serum lactic acid level each have different effects on survival prognosis in patients with PCAS, as shown in the **Table 3**. This may mean that these 2 factors have different implications for clinical aspects in PCAS patients, and the combination of the 2 factors would have more significant impact on predicting survival in presumed non-cardiac arrest patients than in cardiac arrest patients.

This study had some limitations. First, it had a retrospective design and was conducted at a single institution in South Korea. Prospective studies involving diverse patient populations are warranted. Second, when comparing the basic characteristics of the patients enrolled in our study, there were significant differences in age, CPR time, and AED use. Although these factors were adjusted for during analysis, they may have acted as confounding factors. Third, we excluded patients who were not indicated for TTM or who did not apply for various reasons, which may have introduced a selection bias. After adjusting for these confounding factors, we found that SOFA scores and lactate levels were associated with survival. Fourth, the SOFA score uses the Glasgow Coma Scale (GCS), which has limitations in neurological assessment. The neurological component of the SOFA Score relies on the GCS, which has limitations, such as interobserver variability and reliance on subjective assessment [29].

Conclusions

Our study demonstrated that the combination of SOFA score and lactate level could be valuable in predicting survival in patients with PCAS who have undergone TTM in the ICU setting. SOFA score and lactate level each reflect and involve different clinical aspects in patients. Therefore, by combining these 2 factors, healthcare providers can better predict the survival prognosis in patients with PCAS and this may help clinicians provide appropriate explanations to caregivers. Prospective studies with larger sample sizes and a wider variety of patients are warranted.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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