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Serum alkaline phosphatase levels and their association with neurological outcomes post-cardiac arrest

Wu-Jie Xia[1] and Jing Song[1*]

Abstract

Background Alkaline phosphatase (ALP) has been associated with an increased risk of cardiovascular events and is strongly correlated with adverse cerebrovascular outcomes. However, the relationship between ALP and neurological outcomes post-cardiac arrest (CA) remains underexplored. This study aims to investigate the association between serum ALP levels and 3-month neurological outcomes in patients who have experienced CA.

Methods A retrospective review of 354 CA patients was conducted. Data for the study population were sourced from the DRYAD Digital Repository. Participants were categorized into three groups based on ALP level tertiles. Neurological outcomes were assessed at 3 months, with unfavorable neurological outcomes defined as a Cerebral Performance Categories (CPC) score of 3 to 5.

Results After adjusting for covariates, elevated ALP levels were independently associated with an increased risk of unfavorable neurological outcomes post-CA (odds ratio = 1.095, 95%confidence interval: 1.021–1.174; $P = 0.011$). Compared to the low ALP tertile, the high ALP tertile exhibited a 1.54-fold increased risk of unfavorable neurological outcomes.

Conclusion Elevated serum ALP levels were correlated with a higher risk of suboptimal neurological outcomes within 3 months following CA.

Keywords Alkaline phosphatase, Neurological outcome, Cardiac arrest, Risk factors, Predictor

Background

Cardiac arrest (CA) remains a leading cause of global mortality and morbidity. Despite advances in medical therapy, post-CA survival rates are still relatively low, ranging between 10 and 25% [1, 2]. A significant proportion of survivors experience neurological impairments, which contribute substantially to morbidity, primarily due to hypoxic-anoxic ischemic brain damage [3, 4]. Identifying reliable prognostic indicators is essential for optimizing patient care and improving neurological outcomes after CA.

Various prognostic markers, including clinical assessments, biomarkers such as neuron-specific enolase (NSE), imaging studies, and electrophysiological tests, have been employed to predict outcomes following CA. However, accurate prediction of neurological outcomes remains challenging, emphasizing the need for additional biomarkers.

Alkaline phosphatase (ALP), first identified in 1923 [5], is an enzyme involved in the hydrolysis of pyrophosphate from nucleotides and proteins. ALP plays a crucial role in vascular calcification [6] by inhibiting pyrophosphate, a potent inhibitor of medial vascular

*Correspondence:
Jing Song
jing_song1983@hotmail.com
[1] Department of Cardiology, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China

mineralization. Additionally, its modulatory effect on the immune system links ALP to systemic inflammation. Elevated ALP levels have been associated with various cerebrovascular and cardiovascular pathologies. High ALP concentrations have been observed in individuals with end-stage renal disease undergoing hemodialysis, those with metabolic syndrome or hypertension, and as a predictor of myocardial infarction [7–9]. Furthermore, ALP has been shown to serve as a reliable marker for cerebrovascular disease recurrence and post-stroke mortality [10, 11]. However, the relationship between serum ALP levels and neurological outcomes following CA remains underexplored.

This study, therefore, aims to investigate the association between serum ALP levels and 3-month neurological outcomes in post-CA patients through a secondary analysis of existing data.

Methods

Study population

This study is a secondary analysis of data from a retrospective study conducted by Lesu et al. (2018) in the intensive care unit (ICU) of Erasme Hospital, Brussels, Belgium [12]. The dataset used in this analysis was generously provided by Dr. Fabio Silvio Taccone and is archived in the "DRYAD" database, where it is freely accessible for further research and analysis (https://doi.org/10.5061/dryad.qv6fp83). The original study received approval from the local Ethical Committee (Comité d'Ethique Hospitalo-Facultaire Erasme-ULB), which waived the requirement for informed consent due to the retrospective nature of the research.

The original cohort included comatose patients (Glasgow Coma Scale score < 9) who experienced either in-hospital or out-of-hospital CA between January 2007 and December 2015. Exclusion criteria comprised patients with incomplete liver function data or those who died within 24 h of ICU admission. In accordance with contemporary resuscitation protocols, all patients who achieved a persistent return of spontaneous circulation (ROSC) received standard post-CA care [13]. Notably, CA survivors who remained comatose underwent a 24-h targeted temperature management (TTM) protocol, with the body temperature maintained between 32–34 °C. Details of the comprehensive post-resuscitation management protocol used at institution have been described in prior publications [14].

Data collection

Data were systematically collected to capture a comprehensive range of parameters. These included demographic details such as age, sex, and weight, as well as a variety of comorbidities, including hypertension, coronary artery disease, chronic heart failure, diabetes mellitus, chronic renal failure, antecedent neurological diseases, liver cirrhosis, chronic obstructive pulmonary disease, asthma, ongoing corticosteroid therapy, and persistent anticoagulation. In addition, extensive information on cardiopulmonary resuscitation (CPR) was gathered, differentiating between in-hospital and out-of-hospital CA events. We also recorded details regarding the initiation of bystander CPR, time to return of ROSC, total epinephrine dosage, instances of non-shockable rhythms, witnessed arrest scenarios, and non-cardiac causes of arrest.

To assess disease severity during the initial 24 h post-admission, we utilized the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II score [15, 16]. Blood samples collected at the time of admission—immediately following ROSC—were processed according to local laboratory protocols. These samples, collected within the first 24 h, provided key biochemical indicators, including lactate, C-reactive protein (CRP), creatinine, serum aspartate (AST) and serum alanine (ALT) transaminases, gamma-glutamyl transpeptidase (GGT), total bilirubin, ALP, protein content, glucose, lactate dehydrogenase (LDH), activated partial thromboplastin time (APTT), prothrombin time (PT), pH values, arterial partial pressures of both oxygen (PaO_2) and carbon dioxide ($PaCO_2$), and mean arterial pressure (MAP). Lastly, patients may have received specialized treatments, such as TTM, mechanical ventilation, continuous renal replacement therapy (CRRT), intra-aortic balloon pumping (IABP), and extracorporeal membrane oxygenation (ECMO).

Definitions

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the ongoing use of antihypertensive medications [17]. Diabetes mellitus was identified through any of the following criteria: a documented history of diabetes, newly detected hyperglycemia, a fasting serum glucose level of ≥ 7.0 mmol/L (≥ 126 mg/dL), a hemoglobin A1c value ≥ 6.2%, or the active prescription of hypoglycemic agents [18]. Acute kidney injury (AKI) was diagnosed using the AKIN criteria, which focus on changes in serum creatinine levels during hospitalization [19]. Shock was defined as a systolic arterial pressure < 90 mmHg, despite appropriate fluid resuscitation, or the need for vasopressors (e.g., dopamine, dobutamine, adrenaline) for more than 6 h. For the purposes of this study, appropriate fluid resuscitation was determined based on cardiac filling pressure measurements, such as central venous pressure. Specifically, shock was considered to

be present if vasopressor support was required for more than 6 h.

Evaluation of neurological function

Neurological function was assessed at 3 months post-CA using the Cerebral Performance Categories (CPC) score. The CPC score was categorized as a favorable neurological outcome (CPC scores of 1–2) and unfavorable neurological outcome (CPC scores of 3–5) [15, 20]. These assessments were conducted by medical professionals who were blinded to the specifics of the study. The neurological evaluation, performed three months after CA, utilized the CPC scale, with scores ranging from 1 (indicating minimal to no neurological disability) to 5 (representing death). CPC evaluations were carried out during follow-up medical appointments or through telephone interviews with the primary care provider. A CPC score of 1–2 was considered a favorable neurological outcome, while a score of 3–5 was classified as unfavorable.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean ± standard deviation (SD) or as median with interquartile ranges (25th-75th percentile). To assess differences across the ALP tertile groups, we employed the chi-square test, one-way ANOVA, and Kruskal–Wallis H. Multivariable logistic regression was used to explore the relationship between ALP levels and neurological outcomes, with odds ratios (OR) and 95% confidence intervals (CI) calculated. Covariables included in the regression model were selected based on established association with the outcomes of interest or if their inclusion resulted in a change in the effect estimate exceeding 10%. Potential covariables included age, sex, ICU length of stay, SOFA score, APACHE II score, witnessed arrest, bystander CPR, time to ROSC, adrenaline, non-cardiac etiology, non-shockable rhythm, previous neurological disease, IABP, ECMO, shock, AKI, lactate, GGT, MAP, and hypoxic hepatitis. To gain a more nuanced understanding of the data, we conducted interaction and stratified analyses focusing on variables such as age, sex, witnessed arrest, bystander CPR, non-cardiac etiology, non-shockable rhythm, out of hospital arrest, chronic renal failure, liver cirrhosis, TTM, IABP, ECMO, and presence of shock.

All statistical analyses were performed using the R software package (available at http://www.R-project.org, courtesy of The R Foundation) in combination with Empower-Stats (available at http://www.empowerstats.com, provided by X&Y Solutions, Inc., Boston, MA). All tests were two-sided, and a *P* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of the study participants

Among the 435 CA patients initially assessed, 51 experienced early mortality, and 30 had incomplete data. As a result, the final analysis included 354 patients, of whom 71.5% were male and 28.5% were female. These patients were categorized into three groups based on the tertiles of their serum ALP levels. Table 1 presents the baseline clinical characteristics of the study cohort. The mean age of participants was 61.9 ± 15.3 years. Demographic characteristics were similar across the three groups, except that the high ALP group had a higher proportion of patients with non-shockable rhythms and a history of chronic renal failure.

Additionally, the high ALP group exhibited a greater incidence of shock and AKI during their ICU stay. In contrast, the low ALP group had a higher prevalence of treatments such as IABP and ECMO. Significant differences were observed in laboratory parameters across the three groups, particularly in CRP, LDH, GGT, total bilirubin, APTT, PT, and protein levels (all $P < 0.05$). The occurrence of hypoxic hepatitis was similar across the groups. ICU and hospital mortality rates varied significantly, with the highest rates observed in the high ALP group. These findings suggest that patients in the high ALP tertile are more likely to experience unfavorable neurological outcomes.

Univariate analysis

The results of the univariate analysis are summarized in Table 2 (see S1 Table for a full list of parameters). This analysis identified several factors positively associated with unfavorable neurological outcomes, including age, ICU length of stay, APACHE II score, SOFA score, time to ROSC, adrenaline administration, non-cardiac etiology, non-shockable rhythm, a history of neurological disease, shock, AKI, hypoxic hepatitis lactate, CRP, ALP, GGT, total bilirubin and MAP. In contrast, witnessed arrest and bystander CPR were negatively correlated with unfavorable neurological outcomes, suggesting a protective effect.

Multivariate analysis

Multivariate regression analysis (see Table 3) revealed that for every 10 IU/L increase in serum ALP levels, the risk of unfavorable neurological outcomes increased by 10%, even after adjusting for potential confounders (OR = 1.095, 95%CI: 1.021–1.174; $P = 0.011$).

When ALP levels were treated as categorical variables, a graded positive association was observed between ALP groups and the risk of unfavorable neurological outcomes (P for trend < 0.001). In the unadjusted model, compared

Table 1 Baseline characteristics of the patients according to tertiles of ALP levels

Variables	ALP tertile, IU/L			*P*-value
	Low (< 63.0) (*n* = 113)	Middle (63.0 -91.0) (*n* = 122)	High (> 91.0) (*n* = 119)	
Age (years)	59.8 ± 16.1	63.4 ± 15.0	62.6 ± 14.6	0.168
Sex (male), *n* (%)	77 (68.1%)	96 (78.7%)	80 (67.2%)	0.092
Weight (kg)	76.1 ± 15.7	77.9 ± 12.7	76.9 ± 15.0	0.625
ICU length of stay (days)	5.0 (3.0–9.0)	4.0 (2.0–8.8)	4.0 (2.0–9.0)	0.578
APACHE II score	25.4 ± 5.8	23.2 ± 8.0	23.8 ± 6.9	0.051
SOFA score	11.6 ± 3.5	10.7 ± 3.7	11.2 ± 3.5	0.110
Witnessed arrest, *n* (%)	98 (86.7%)	100 (82.0%)	103 (86.6%)	0.504
Bystander CPR, *n* (%)	79 (69.9%)	80 (65.6%)	80 (67.2%)	0.775
Time to ROSC (min)	15.0 (7.0–27.0)	15.0 (7.0–25.0)	15.0 (8.0–24.5)	0.846
Adrenaline (mg)	3.0 (2.0–6.0)	3.0 (1.0–5.0)	3.0 (2.0–5.0)	0.437
Out of hospital, *n* (%)	69 (61.1%)	75 (61.5%)	58 (48.7%)	0.079
TTM, *n* (%)	104 (92.0%)	107 (87.7%)	104 (87.4%)	0.453
Non-cardiac etiology, *n* (%)	43 (38.1%)	48 (39.3%)	50 (42.0%)	0.819
Non-shockable rhythm, *n* (%)	57 (50.4%)	69 (56.6%)	82 (68.9%)	0.014
Corticosteroids, *n* (%)	21 (18.6%)	21 (17.2%)	35 (29.4%)	0.044
Chronic anticoagulation, *n* (%)	24 (21.2%)	17 (13.9%)	20 (16.8%)	0.330
Chronic heart failure, *n* (%)	25 (22.1%)	23 (18.9%)	29 (24.4%)	0.580
Chronic renal failure, *n* (%)	15 (13.3%)	15 (12.3%)	30 (25.2%)	0.013
Hypertension, *n* (%)	49 (43.4%)	51 (41.8%)	51 (42.9%)	0.970
Coronary artery disease, *n* (%)	49 (43.4%)	49 (40.2%)	40 (33.6%)	0.297
Diabetes, *n* (%)	21 (18.6%)	28 (23.0%)	35 (29.4%)	0.148
COPD/Asthma, *n* (%)	15 (13.3%)	25 (20.5%)	19 (16.0%)	0.322
Previous neurological disease, *n* (%)	11 (9.7%)	17 (13.9%)	23 (19.3%)	0.113
Liver cirrhosis, *n* (%)	2 (1.8%)	3 (2.5%)	7 (5.9%)	0.175
IABP, *n* (%)	11 (9.7%)	10 (8.2%)	2 (1.7%)	0.029
ECMO, *n* (%)	22 (19.5%)	8 (6.6%)	15 (12.6%)	0.012
Shock, *n* (%)	60 (53.1%)	51 (41.8%)	79 (66.4%)	< 0.001
Mechanical ventilation, *n* (%)	112 (99.1%)	120 (98.4%)	117 (98.3%)	0.847
CRRT, *n* (%)	15 (13.3%)	15 (12.3%)	26 (21.9%)	0.085
AKI, *n* (%)	58 (51.3%)	65 (53.3%)	86 (72.3%)	0.001
Lactate (mmol/L)	5.0 (3.9–7.8)	4.9 (3.9–6.6)	5.2 (4.4–8.6)	0.130
CRP (mg/dL)	30.0 (10.0–67.8)	31.5 (10.0–72.3)	49.0 (22.5–110.0)	< 0.001
Creatinine (mg/dL)	1.2 (0.9–1.5)	1.2 (0.9–1.6)	1.3 (1.0–2.0)	0.082
AST (IU/L)	78.0 (39.0–161.0)	100.5 (50.3–189.0)	108.0 (57.0–236.0)	0.058
ALT (IU/L)	62.0 (28.0–123.0)	81.0 (39.3–174.5)	63.0 (32.0–141.0)	0.081
LDH (IU/L)	293.0 (222.0–396.0)	335.0 (246.3–500.8)	413.0 (260.5–530.5)	< 0.001
GGT (IU/L)	51.0 (26.0–79.0)	70.5 (46.3–95.8)	82.0 (59.5–143.0)	< 0.001
Total bilirubin (mg/dL)	0.5 (0.3–0.7)	0.6 (0.4–1.0)	0.6 (0.4–1.0)	0.001
APTT (sec)	34.1 (26.9–53.0)	30.3 (26.1–39.3)	34.2 (28.6–44.2)	0.016
PT (%)	54.0 (42.0–77.0)	69.0 (55.0–84.0)	63.0 (47.5–77.0)	0.007
Proteins (mg/dL)	5.5 (4.8–6.0)	5.8 (5.2–6.6)	5.8 (5.2–6.7)	< 0.001
Glucose (mg/dL)	205.0 (150.0–290.0)	218.5 (169.3–312.8)	190.0 (152.0–265.0)	0.131
pH	7.30 (7.24–7.39)	7.29 (7.20–7.38)	7.29 (7.19–7.36)	0.390
PaO_2 (mmHg)	115.0 (87.0–175.0)	118.5 (89.5–177.5)	108.0 (84.0–181.0)	0.676
$PaCO_2$ (mmHg)	37.0 (33.0–44.0)	38.5 (32.0–45.0)	37.0 (33.0–43.0)	0.588
MAP (mmHg)	90.1 ± 19.0	92.6 ± 21.2	90.3 ± 24.0	0.619
Hypoxic hepatitis, *n* (%)	6 (5.3%)	7 (5.7%)	13 (10.9%)	0.183
Unfavorable neurological outcome, *n* (%)	57 (50.4%)	70 (57.4%)	86 (72.3%)	0.002
ICU mortality, *n* (%)	50 (44.3%)	60 (49.2%)	74 (62.2%)	0.018
Hospital mortality, *n* (%)	55 (48.7%)	64 (52.5%)	82 (68.9%)	0.004

Data are expressed as n (%) or mean ± SD or medians (interquartile range:25th to 75th percentiles)

Abbreviations: *AKI* Acute kidney injury, *ALP* Alkaline phosphatase, *ALT* Alanine aminotransferase, *APACHE* Acute physiology and chronic health evaluation, *APTT* Activated partial thromboplastin time, *AST* Aspartate aminotransferase, *COPD* Chronic obstructive pulmonary disease, *CPR* Cardiopulmonary resuscitation, *CRP* C-reactive protein, *CRRT* Continuous renal replacement therapy, *ECMO* Extracorporeal membrane oxygenation, *GGT* Gamma-glutamyltransferase, *IABP* Intra-aortic balloon pump, *ICU* Intensive care unit, *LDH* Lactate dehydrogenase, *MAP* Mean arterial pressure, *PT* Prothrombin time, *ROSC* Return of spontaneous circulation, *SOFA* Sequential Organ failure assessment, *TTM* Targeted temperature management

to individuals in the low ALP tertile, those in the high ALP tertile had a 1.56-fold increased risk of unfavorable neurological outcomes (OR = 2.560, 95%CI: 1.485–4.416; $P < 0.001$). However, the risk in the middle ALP tertile was not significantly associated with unfavorable neurological

Table 2 The results of univariate analysis

	Statistics	OR (95% CI)	*P*-value
Age	61.9 ± 15.3	1.0 (1.0, 1.0)	0.004
Sex			
Female	101 (28.5%)	Ref	
Male	253 (71.5%)	0.9 (0.6, 1.5)	0.768
ICU length of stay	7.9 ± 9.5	1.0 (1.0, 1.0)	0.023
APACHE II score	24.1 ± 7.0	1.0 (1.0, 1.1)	0.015
SOFA score	11.2 ± 3.6	1.2 (1.1, 1.3)	< 0.001
Witnessed arrest			
No	53 (15.0%)	Ref	
Yes	301 (85.0%)	0.4 (0.2, 0.8)	0.007
Bystander CPR			
No	115 (32.5%)	Ref	
Yes	239 (67.5%)	0.5 (0.3, 0.7)	0.002
Time to ROSC	18.4 ± 14.2	1.0 (1.0, 1.1)	0.001
Adrenaline	4.1 ± 3.7	1.2 (1.1, 1.3)	< 0.001
Non-cardiac etiology			
No	213 (60.2%)	Ref	
Yes	141 (39.8%)	1.6 (1.0, 2.5)	0.043
Non-shockable rhythm			
No	146 (41.2%)	Ref	
Yes	208 (58.8%)	3.4 (2.2, 5.3)	< 0.001
Previous neurological disease			
No	303 (85.6%)	Ref	
Yes	51 (14.4%)	2.1 (1.1, 4.2)	0.026
Shock			
No	164 (46.3%)	Ref	
Yes	190 (53.7%)	1.9 (1.3, 3.0)	0.003
AKI			
No	145 (41.0%)	Ref	
Yes	209 (59.0%)	2.1 (1.4, 3.3)	< 0.001
Hypoxic hepatitis			
No	328 (92.7%)	Ref	0.003
Yes	26 (7.4%)	8.8 (2.1, 38.0)	
Lactate	6.3 ± 3.4	1.1 (1.0, 1.2)	0.014
CRP	63.4 ± 74.1	1.0 (1.0, 1.0)	0.035
ALP	93.6 ± 67.5	1.0 (1.0, 1.0)	< 0.001
GGT	99.9 ± 138.0	1.0 (1.0, 1.0)	0.009
Total bilirubin	0.9 ± 1.4	1.6 (1.1, 2.3)	0.015
MAP	91.0 ± 21.5	1.0 (1.0, 1.0)	0.001

outcomes (OR = 1.323, 95%CI: 0.791–2.212; $P = 0.287$). In multivariable regression model II, participants in the high ALP tertile had a 1.54-fold increase risk (OR = 2.535, 95%CI:1.093–5.875; $P = 0.030$) compared to the reference group. However, the risk of unfavorable neurological outcomes was not significantly associated with the middle ALP tertile (OR = 1.311, 95%CI: 0.610–2.819; $P = 0.488$). Despite this, the P for trend of 0.03 suggests a potential incremental increase in risk across the ALP tertiles, indicating a complex, dose-dependent relationship between ALP levels and neurological outcomes.

Table 3 The results of multivariate analysis

	Non-adjusted model	Model I	Model II
ALP, per 10-unit increase	1.087 (1.034, 1.142) < 0.001	1.083 (1.031, 1.138) 0.001	1.095 (1.021, 1.174) 0.011
ALP (tertile)			
Low	Ref	Ref	Ref
Middle	1.323 (0.791, 2.212) 0.287	1.252 (0.740, 2.115) 0.402	1.311 (0.610, 2.819) 0.488
High	2.560 (1.485, 4.416) < 0.001	2.461 (1.418, 4.270) 0.001	2.535 (1.093, 5.875) 0.030
P for trend	< 0.001	0.001	0.03

Model I adjusted for age and sex. Model II adjusted for age, sex, ICU length of stay, SOFA score, APACHE II score, witnessed arrest, bystander CPR, time to ROSC, adrenaline, non-cardiac etiology, non-shockable rhythm, previous neurological disease, IABP, ECMO, shock, AKI, lactate, GGT, MAP, hypoxic hepatitis

Subgroup analysis

A subgroup analysis was performed to explore potential confounding factors that could influence the relationship between serum ALP levels and neurological outcomes. However, no significant interactions were identified (see Table 4).

Discussion

This study explored the potential relationship between serum ALP levels and neurological outcomes following CA. Our findings demonstrated that elevated ALP levels were independently associated with unfavorable neurological outcomes after a CA event. This association persisted even after adjusting for various confounding factors. Specifically, patients in the high ALP tertile had a 1.54-fold increased risk of poor neurological outcomes compared to those in the low ALP tertile.

Recent literature has highlighted the importance ALP, particularly in relation to cerebrovascular disease. ALP activity is increasingly recognized as an indicator of vascular calcification. Previous research has shown a strong relationship between elevated ALP levels and poorer functional outcomes and increased mortality in cerebrovascular disease [21]. For instance, studies have indicated that higher serum ALP levels correlate with a greater risk of early mortality in patients with acute ischemic stroke [22]. Long-term observations have suggested that elevated ALP levels can predict 1-year mortality, recurrent vascular events, and both vascular and all-cause mortality up to three years following the initial incident. Yamashita et al. [23] proposed that ALP

Table 4 Results of subgroup analysis and interaction analysis

Subgroup	OR (95% CI)	*P*-value	*P* for interaction
Sex			0.524
Female	1.066 (0.959, 1.185)	0.237	
Male	1.112 (1.020, 1.213)	0.016	
Age			0.961
< 60 year	1.097 (0.991, 1.213)	0.075	
≥ 60 year	1.093 (0.997, 1.198)	0.057	
Witnessed arrest			0.691
No	1.158 (0.862, 1.555)	0.330	
Yes	1.091 (1.016, 1.172)	0.017	
Bystander CPR			0.519
No	1.061 (0.950, 1.184)	0.294	
Yes	1.110 (1.022, 1.206)	0.013	
Non-cardiac etiology			0.433
No	1.075 (0.990, 1.166)	0.086	
Yes	1.139 (1.003, 1.293)	0.045	
Non-shockable rhythm			0.767
No	1.080 (0.962, 1.212)	0.194	
Yes	1.103 (1.014, 1.199)	0.023	
Out of hospital			0.366
No	1.120 (1.029, 1.220)	0.009	
Yes	1.049 (0.933, 1.179)	0.424	
Chronic renal failure			0.082
No	1.059 (0.988, 1.136)	0.107	
Yes	1.228 (1.039, 1.452)	0.016	
Liver cirrhosis			0.984
No	1.086 (1.015, 1.161)	0.017	
Yes	1.075 (0.399, 2.895)	0.887	
TTM			0.164
No	1.226 (1.007, 1.493)	0.043	
Yes	1.072 (0.994, 1.156)	0.072	
IABP			0.881
No	1.096 (1.021, 1.176)	0.011	
Yes	1.059 (0.695, 1.614)	0.789	
ECMO			0.683
No	1.092 (1.014, 1.177)	0.020	
Yes	1.058 (0.921, 1.215)	0.428	
Shock			0.349
No	1.145 (1.000, 1.311)	0.051	
Yes	1.066 (0.991, 1.147)	0.085	

Note 1: Above model adjusted for age, sex, ICU length of stay, SOFA score, APACHE II score, witnessed arrest, bystander CPR, time to ROSC, adrenaline, non-cardiac etiology, non-shockable rhythm, previous neurological disease, IABP, ECMO, shock, AKI, lactate, GGT, MAP, hypoxic hepatitis

Note 2: In each case, the model is not adjusted for the stratification variable

levels could be used as a valuable prognostic marker for a range of brain injuries, including post-resuscitation encephalopathy, ruptured cerebral aneurysms, acute subdural hematoma, contusion, and non-traumatic intracerebral hemorrhages. Additionally, a large-scale retrospective study of 226 adult patients who suffered refractory out-of-hospital CA and underwent extracorporeal CPR found a significant association between serum ALP levels and neurological status at hospital discharge [24]. Similarly, Lee et al. [25] suggested that elevated serum ALP levels may reflect compromised cerebral microcirculation.

In alignment with these previous studies, our results reinforce the notion that higher ALP levels are linked to poorer neurological prognosis post-CA. This suggests that ALP play a pivotal role in the pathophysiological processes affecting neurological after CA.

Several mechanisms could explain the impact of ALP on neurological outcomes following CA. Elevated ALP levels may serve as a marker of systemic inflammation. For instance, increased ALP is often seen in conditions such as sepsis [26], which is associated with a dysregulated inflammatory response. Inflammation can compromise the blood–brain barrier, impair tissue reperfusion, and induce microvascular coagulation and complement- mediated brain damage, all of which could contribute to adverse neurological outcomes following CA, such as stroke or hemorrhage. Another potential mechanism involves disruptions in vascular homeostasis. ALP levels might influence vascular balance, and endothelial progenitor cells (EPCs), which are essential for vascular repair, could be reduced in patients with elevated ALP. Given that EPCs play a crucial role in maintaining vascular integrity, a reduction in these cells could increase the risk of unfavorable neurological outcomes [27].

Despite these promising findings, our study has several limitations. As a retrospective observational endeavor, it lacks the rigor of randomized controlled trials, which limits our ability to establish causal relationships between ALP levels and neurological outcomes. Additionally, our analysis was based on a relatively small sample size, which may have constrained our statistical power to detect more subtle associations. Another key limitation is that we only considered ALP levels measured within the first 24 h post-admission, without accounting for potential fluctuations in ALP levels over time. These variations could provide valuable insights into the dynamic role of ALP in predicting neurological outcomes. Furthermore, our study was limited by the data available from the original source, resulting in the exclusion of potentially relevant variables, such as defibrillation timing, post-CPR intervals, and other clinical interventions that may have influenced outcomes. Therefore, to strengthen the generalizability of our

findings, future multicenter studies with larger sample sizes and more comprehensive data are needed.

Conclusion

This study identifies a significant association between elevated serum ALP levels and unfavorable neurological outcomes in patients following CA. Patients with higher ALP levels, particularly those in the high ALP tertile, exhibited a 1.54-fold increased risk of poor neurological outcomes at 3 months post-CA. These findings suggest that ALP could serve as a valuable prognostic marker for neurological recovery in post-CA patients.

Abbreviations

AKI	Acute kidney injury;
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APACHE	Acute physiology and chronic health evaluation
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CA	Cardiac arrest
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
ECMO	Extracorporeal membrane oxygenation
GGT	Gamma-glutamyltransferase
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
LDH	Lactate dehydrogenase
MAP	Mean arterial pressure
PT	Prothrombin time
ROSC	Return of spontaneous circulation
SOFA	Sequential organ failure assessment
TTM	Targeted temperature management

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04785-7.

Supplementary Material 1.

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Clinical trial number

Not applicable.

Authors' contributions

W.J.X. played a significant role in drafting the manuscript, data analysis, and interpretation. J.S. was instrumental in conceptualizing the study, meticulously revising the manuscript, data analysis, and interpretation, and endorsed the final version submitted. Both authors thoroughly reviewed and approved the final manuscript.

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Data availability

Datasets employed and/or assessed during this research are accessible from the "DRYAD" database, with the following dataset link: https://doi.org/https://doi.org/10.5061/dryad.qv6fp83.

Declarations

Ethics approval and consent to participate

Our research involves a secondary analysis leveraging a previously published retrospective study conducted at the ICU of Erasme Hospital, Brussels, Belgium. The original research was granted approved by the local Ethical Committee (Comite' d'Ethique Hospitalo-Facultaire Erasme-ULB). Additionally, all participants in the original study furnished written informed consent.

Consent for publication

Not required.

Competing interests

The authors declare no competing interests.

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