Observational Study

Medicine

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Relationship between serum lactate dehydrogenase and mortality after cardiac arrest

A retrospective cohort study

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Abstract

Serum lactate dehydrogenase (LDH) has been identified as an independent risk factor for predicting all-cause mortality in patients with multiple diseases. However, the prognostic value of LDH levels in post-cardiac arrest patients remains uncertain. This study aimed to assess the association between LDH and mortality in intensive care unit (ICU) patients after cardiac arrest. This retrospective observational study is based on data from the Dryad Digital Repository, which included 374 consecutive adult patients after cardiac arrest. Patients were divided into 2 groups based on median LDH values. A multivariate Cox proportional hazards model was established to assess the independent relationship between LDH and ICU mortality. Cumulative mortality was compared using Kaplan–Meier curves. The cohort included 374 patients, of which 51.9% (194/374) died in the ICU. The overall death rate from cardiac arrest was significantly higher for patients with LDH ≥ 335 IU/L (59.6%) than for those with LDH < 335 IU/L (44.1%). In multiple Cox regression models, hazard ratios (HR) and corresponding 95% confidence intervals (CI) for logLDH and the 2 LDH groups were 1.72 (1.07, 2.78) and 1.42 (1.04, 1.93), respectively. Participants with LDH ≥ 335IU/L had a higher incidence of ICU mortality than LDH < 335 IU/L, as shown by the Kaplan–Meier curves (P = .0085). Subgroup analysis revealed that the association between LDH and ICU mortality was vitally stable, with all P interactions from different subgroups >.05. Serum LDH levels are positively associated with ICU mortality in patients after cardiac arrest, especially for patients with LDH ≥ 335 IU/L.

Abbreviations: CI = confidence intervals, HR = hazard ratios, ICU = intensive care unit, LDH = lactate dehydrogenase, ROSC = recovery of spontaneous circulation.

Keywords: cardiac arrest, intensive care unit, lactate dehydrogenase, mortality

1. Introduction

The majority of cardiac arrest patients were already dead at the time of the incident. Even after successful cardiopulmonary resuscitation efforts and survival through intensive care unit (ICU) admission, the short-term mortality of such patients remains as high as 40% to 60%.[1–3] In patients with initial recovery of spontaneous circulation (ROSC) following cardiac arrest, significant morbidity and mortality rates are largely attributable to multiple system dysfunctions resulting from prolonged systemic ischemia and hypoxia. These symptoms have been attributed to post-cardiac arrest syndrome, which comprises cerebral injury, systemic ischemia/reperfusion response, myocardial dysfunction after cardiac arrest, and persistent precipitating cause of arrest.[4,5]

Serum lactate dehydrogenase (LDH) is a ubiquitous enzyme best known as a marker of disease and tissue damage that catalyzes the reversible conversion of pyruvate to lactate.[6] LDH testing can be easily and quickly implemented and is available at a low cost to patients in almost every emergency room and ward; therefore, LDH levels are routinely tested during clinical assessments for a variety of diseases. When the body experiences acute hypoxia or inflammation, levels of LDH in serum will rise significantly. Additionally, Li C. found that LDH levels are related to mortality rate in patients with coronavirus disease caused by viruses.[7] Furthermore, LDH has been shown to be a highly accurate prognostic factor for diseases involving multiple organ injuries, including sepsis, acute heart failure, hemodialysis and severe acute pancreatitis.[8–11] However, the prognostic value of LDH in patients after cardiac arrest remains unclear.

Post-cardiac arrest syndrome mainly affects the lungs, in addition to other tissues and organs, and can result in hypoxia, inflammation, thrombogenesis and organ injury.[5,12] Theoretically, elevated LDH levels are an important laboratory indicator for

This study was partly funded by Wenzhou Science and Technology Bureau: No. Y20220488.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Supplemental Digital Content is available for this article.

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How to cite this article: Lin L, Gao R, Chen L, Wu Z, Wei X, Xie Y. Relationship between serum lactate dehydrogenase and mortality after cardiac arrest: A retrospective cohort study. Medicine 2022;101:45(e31499).

Received: 21 July 2022 / Received in final form: 30 September 2022 / Accepted: 3 October 2022

http://dx.doi.org/10.1097/MD.0000000000031499

evaluating post-cardiac arrest syndrome. Therefore, we conducted a retrospective cohort study in patients who experienced cardiac arrest to investigate the association between LDH and ICU mortality.

2. Materials and methods

2.1. Study population

All original data are deposited in the Dryad Digital Repository (10.5061/dryad.qv6fp83). 374 patients were recruited from a single site from 1/2007 to 12/2015. Full details on the study population and design have been previously reported.[13] This retrospective observational cohort study included patients who were hospitalized in the ICU of Erasme Hospital, Brussels (Belgium) after experiencing cardiac arrest. The local ethics committee approved this study (protocol 2017/264; Comité d'Ethique Hospitalo-Facultaire Erasme-University Libre Bruxelles). Due to the nature of the retrospective cohort study, written informed consent from participants was not needed.

2.2. Inclusion criteria

Patients who were comatose at time of inclusion (Glasgow Coma Scale score ≤ 8) and who had suffered cardiac arrest. Patients were excluded if they died within 24 hours of ICU admission; information regarding cardiac arrest/cardiopulmonary resuscitation history was not available; information about serum LDH levels was not available. According to the current guidelines for resuscitation, patients with continuous ROSC after cardiac arrest are assessed and examined.[4,14] Management of standardized agency scenarios post-resuscitation has been previously described.[15] Comatose patients after ROSC received targeted temperature management that was normally deceased to 32 to 34°C for 24 hours (Fig. 1).

2.3. Data collection

Essential clinical data was collected, including sex, age, cardiac arrest location, witness status, and characteristics of arrest. Sequential organ failure assessment score[16] and Acute Physiology and Chronic Health Evaluation (APACHE) II score[17] were calculated within 24 h of ICU admission. Blood samples were routinely collected upon ICU admission, and all laboratory data were measured immediately after ROSC in accordance with on-site standards. Levels of serum aspartate aminotransferase (normal limits: <41 IU/L), serum alanine transaminases (normal limits: <37 IU/L), serum gamma-glutamyl transpeptidase (normal limits: 8–38 IU/L), serum total bilirubin (normal limits: ≤1.2 mg/dL), serum LDH (normal limits: <200 IU/L), and platelets (normal limits: 150–350 × 10^3/mm^3) were determined using routine laboratory methods. Comorbidities included hypertension, diabetes, coronary artery disease, liver cirrhosis, and chronic obstructive pulmonary disease.

2.4. Statistical analysis

Serum LDH levels were natural log-transformed to achieve a normal distribution. We also present data on LDH levels as a continuous variable (per natural-log unit increase). For normally distributed variables, continuous variables are described as mean ± standard deviation, and non-normally distributed variable are described with median (25th–75th percentile) values. Baseline characteristics were compared across groups and tested using the Mann–Whitney rank sum test for continuous variables or the chi-square used for categorical variables. No missing data imputation was performed. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards models. Both non-adjusted and multivariate-adjusted models were produced. To minimize confusion, we included baseline covariates into the Cox regression model or

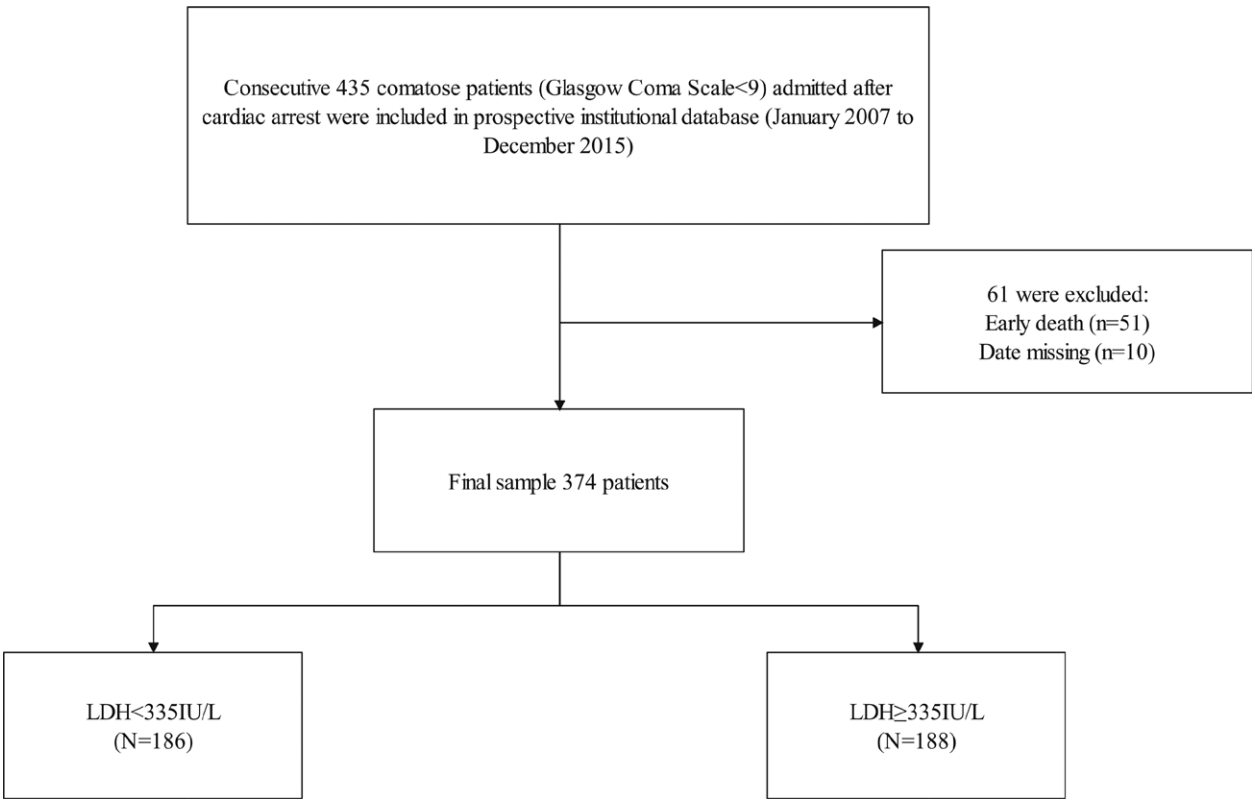

Figure 1. Flowchart of the study population with inclusion and exclusion criteria.

eliminated covariates in the complete model step by step, then compared the regression coefficients. Covariates were included in the final models as potential confounding factors if they altered estimates of the relationship between serum LDH and ICU mortality by >10%. A correlation test based on Schoenfeld residuals was used to verify the proportional hazards assumptions. Model 1 included no covariates. Model 2 was a minimally adjusted model with demographic characteristics. Model 3 was an adjusted model with Model 2 and arrest characteristics. Model 4 was adjusted for all potential confounding covariates.

We performed subgroup analyses by age, sex, whether the arrest was witnessed, bystander cardiopulmonary resuscitation, non-shockable rhythm, occurrence out of hospital, time to ROSC, and mean arterial pressure. The Wald test was performed for cross-product terms of trend variables and subgroup membership to evaluate heterogeneity across subgroups.

Date analysis was performed using Free Statistical versions 1.1 and R statistical software 3.3.2 (http://www.R-project.org, The R Foundation). A two-tailed $P < .05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics of study participants by categories of serum LDH levels

A total of 374 participants were included for analysis in our final data set (Fig. 1). Participant characteristics are shown according to serum LDH categories in Table 1. The median serum LDH level was 335 IU/L (range 110–17010 IU/L; IQR 240.0 to 488.0 IU/L). The average age of participants was 61.8 years old (standard deviation = 15.4). 270 patients (72.2%) were male, 208 (55.6%) experienced out-of-hospital cardiac arrest, and 221 (59.1%) had non-shockable initial rhythm. The typical length of ICU stay was 4 (2–9) days, and 194 patients (51.9%) died in the ICU. Notably, we observed a mortality rate of 59.6% (112/188) for patients with LDH ≥ 335 IU/L, which was higher than the 44.1% (82/186) mortality rate found for the LDH < 335 IU/L group. The distribution of comorbidities showed no significant differences. Patients in the LDH ≥ 335 IU/L group exhibited significantly longer time to ROSC, as well as higher levels of adrenaline, creatinine, aspartate aminotransferase, alanine transaminases, and gamma-glutamyl transpeptidase, compared with LDH < 335 IU/L, and the difference between groups was statistically significant ($P < .05$). We observed a much higher ICU mortality rate in the LDH ≥ 335 IU/L group compared to the LDH < 335 IU/L group ($P = .004$). Furthermore, patients in the LDH ≥ 335 IU/L group were much younger and had a lower rate of bystander cardiopulmonary resuscitation. Univariate analysis showed that age, witnessing of the arrest, bystander cardiopulmonary resuscitation, time to ROSC, adrenaline levels, out of hospital status, non-shockable rhythm, gamma-glutamyl transpeptidase levels, mean arterial pressure, Acute Physiology and Chronic Health Evaluation II score, and sequential organ failure assessment score were independently associated with ICU mortality (see Table S1, http://links.lww.com/MD/H811, Supplemental Content, Characteristics of the study population according to ICU mortality.).

3.2. Association between serum LDH levels and mortality in ICU patients

To analyze the independent effects of ICU mortality according to log LDH and LDH ≥ 335 IU/L, we established 4 models in this study. After adjustment for multivariate analysis, serum

Table 1

Baseline characteristics of the study participants.

DEMOGRAPHICS	Total	LDH < 335 IU/L	LDH ≥ 335 IU/L	*P* value
N	374	186	188	
Age, yr	61.8 ± 15.4	63.7 ± 15.9	60.0 ± 14.7	.021
Male, n (%)	270 (72.2)	141 (75.8)	129 (68.6)	.151
Hypertension, n (%)	159 (42.5)	80 (43)	79 (42)	.929
Coronary artery disease, n (%)	146 (39.0)	75 (40.3)	71 (37.8)	.689
Diabetes, n (%)	91 (24.3)	43 (23.1)	48 (25.5)	.672
Chronic pulmonary obstructive disease, n (%)	63 (16.8)	37 (19.9)	26 (13.8)	.153
Liver cirrhosis, n (%)	17 (4.5)	12 (6.5)	5 (2.7)	.131
Adrenaline, mg	3.0 (2.0, 5.0)	3.0 (1.0, 5.0)	4.0 (2.0, 6.2)	<.001
Noncardiac cause, n (%)	153 (40.9)	81 (43.5)	72 (38.3)	.354
Nonshockable rhythm, n (%)	221 (59.1)	106 (57)	115 (61.2)	.473
Time to ROSC, min	15.0 (7.0, 25.0)	11.5 (5.0, 21.0)	16.0 (10.0, 28.0)	<.001
Witnessed arrest, n (%)	320 (85.6)	164 (88.2)	156 (83)	.2
Bystander cardiopulmonary resuscitation, n (%)	254 (67.9)	140 (75.3)	114 (60.6)	.004
Out of hospital, n (%)	208 (55.6)	99 (53.2)	109 (58)	.412
Mean arterial pressure, mm Hg	90.6 ± 21.4	91.1 ± 22.1	90.2 ± 20.7	.704
ICU length of stay, days	4.0(2.0,9.0)	5.0(3.0,9.0)	4.0(2.0,9.2)	.299
Targeted temperature management scored, n (%)	332 (88.8)	165 (88.7)	167 (88.8)	1
Creatinine, mg dL-1	1.2 (0.9, 1.6)	1.1 (0.9, 1.5)	1.2 (1.0, 1.8)	.021
Aspartate aminotransferase, IU/L	95.0 (47.0, 192.5)	53.0 (33.2, 87.8)	175.0 (103.8, 326.5)	<.001
Alanine aminotransferase, IU/L	68.0 (32.0, 152.8)	39.5 (23.0, 72.0)	133.0 (60.5, 250.0)	<.001
Gamma-glutamyl transpeptidase, IU/L	68.0 (42.0, 103.0)	65.0 (38.0, 89.0)	77.0 (45.5, 117.5)	.002
LDH,IU/L	335(240.0,488.0)	239.5(198.0,280.0)	488.0(400.0,629.2)	<.001
Platelets, mm [3]	201.0 (138.2, 266.2)	203.0 (141.0, 260.8)	193.0 (135.8, 267.2)	.621
Total bilirubin, mg dL-1	0.5 (0.3, 0.9)	0.5 (0.3, 0.8)	0.5 (0.4, 0.9)	.333
Proteins, mg dL-1	5.6 (5.0, 6.2)	5.7 (5.1, 6.1)	5.6 (5.0, 6.3)	.54
APACHE II score	24.3 ± 7.0	23.9 ± 6.9	24.6 ± 7.1	.335
SOFA score	11.2 ± 3.5	11.1 ± 3.5	11.2 ± 3.6	.709
ICU mortality, n (%)	194 (51.9)	82 (44.1)	112 (59.6)	.004

Data presented are mean ± standard deviation, median (25th–75th percentile), or N (%).

APACHE = acute physiology and chronic health evaluation, ICU = intensive care unit, LDH = lactate dehydrogenase, ROSC = return of spontaneous circulation, SOFA = sequential organ failure assessment.

LDH levels were independently associated with all-cause mortality in ICU patients (HR = 1.72 [95%CI 1.07–2.78]), such that each unit increase in the log-transformed serum LDH group was associated with a 72% increase in ICU mortality. ICU mortality in the group with LDH ≥ 335 IU/L was associated with non-adjusted increased mortality risk (HR = 1.45 [95%CI 1.09–1.93]; P = .011) compared with the LDH < 335 IU/L group. In the fully adjusted model, the HR with 95% CI was 1.42 (1.04–1.93). All models showed highly similar results, indicating that the statistical results are robust (Table 2). We have further demonstrated the relevance of this association using a Kaplan–Meier survival curve analysis for crude cumulative ICU mortality (Fig. 2). Participants with LDH ≥ 335 IU/L group had a higher incidence of ICU mortality compared to those with LDH < 335 IU/L (P = .0085).

3.3. Subgroup analysis

Subgroup analyses of the associations between LDH and ICU mortality are presented in Table 3. Subgroup analyses examined the relationships between serum LDH levels and ICU mortality according to age, sex, witnessing of the arrest, bystander cardiopulmonary resuscitation, non-shockable rhythm, out of hospital status, time to ROSC, and mean arterial pressure. To test for interactions, Cox proportional hazards regression modeling was used to estimate HR between analyzed subgroups, with all P interactions from different subgroups >.05.

4. Discussion

Our results show that serum LDH levels are positively associated with ICU mortality after cardiac arrest, and this conclusion remained unchanged after adjusting for covariates. Based on Kaplan–Meier Survival analysis, participants in the LDH ≥ 335 IU/L group had a higher incidence of ICU mortality than those in the LDH < 335 IU/L group (P = .0085). Subgroup analysis could help us to better understand the interactions between different populations. For several ICU subgroups, we find that the results of this study support a stable association between serum LDH levels and ICU mortality, and none of the subgroup interaction terms were statistically significant (P for interaction >.05).

Cardiac arrest is among the most common cause of mortality in critically ill patients, and the short-term mortality of such patients remains as high as 40% to 60%,[1–3] consistent with the results observed in our study (51.9%). We discovered that higher numbers of epinephrine doses administered during cardiopulmonary resuscitation and longer resuscitation durations have been associated with higher LDH levels. Other studies have also corroborated this observation.[18,19] In addition, Hagihara et al[20] suggested that a positive association exists between prehospital epinephrine and ROSC before hospital arrival in patients who experience cardiac arrest. Furthermore, Robert et al[21] suggested that a longer duration of cardiopulmonary resuscitation and higher number of epinephrine doses during cardiopulmonary resuscitation are associated with lower rates of ROSC and reduced survival to hospital discharge. However, adjustment for epinephrine and time to ROSC did not reverse the LDH–ICU mortality association. It therefore appears that higher serum LDH levels are independently associated with ICU mortality in patients after cardiac arrest.

Furthermore, the development of post-cardiac arrest syndrome itself may lead to an increase in serum LDH levels. The primary underlying mechanisms are described as follows. Cardiac arrest leads to hypoxia, anaerobic metabolism, lactic acidosis, depletion of cellular adenosine triphosphate, ion pump malfunction, intracellular Ca++ ion accumulation, and cellular edema.[22] LDH is a redox-active enzyme which is widely expressed across various cells and tissues, primarily including the heart, skeletal muscle, liver, and brain.[23] After cells or tissues are damaged, LDH is rapidly released into the peripheral blood. For this reason, increased LDH has been associated with a number of different conditions, such as hypoxia, hemolysis, cancer, tissue injury and necrosis.[24] LDH can reversibly catalyze pyruvic to lactate during the process of glycolysis, in addition to playing a major role in anaerobic cellular metabolism.[25–27] The transcription factor hypoxia-inducible factor enhances transcription of the LDH gene when the cellular oxygen supply is inadequate.[28] Subsequent ROSC can further aggravate these injuries.[29] Meanwhile, a phase of secondary injury after ROSC is caused by the production of oxygen-free radicals, directly causing oxidative damage to cell membranes and promoting inflammation.[30] Previously published reports have suggested

Table 2

Factors during LDH associated with ICU mortality in patients after cardiac arrest by multivariate Cox regression analyses.

	Non-adjusted	Adjust I	Adjust II	Adjust III
Log LDH (per-unit increase)	1.85 (1.20, 2.86)	2.25 (1.45, 3.50)	1.90 (1.20, 3.00)	1.72 (1.07, 2.78)
Binary variable				
LDH < 335 IU/L	Reference	Reference	Reference	Reference
LDH ≧ 335 IU/L	1.45 (1.09, 1.93)	1.60 (1.20, 2.15)	1.42(1.05, 1.92)	1.42 (1.04, 1.93)
P	0.011	0.002	0.021	0.027

Data presented are HR and 95% CI.

Adjust I model adjusts for age and gender.

Adjust II model adjusts for adjust I + Adrenaline + Witnessed Arrest + Bystander cardiopulmonary resuscitation + Out of Hospital + Non-shockable Rhythm + Time to ROSC.

Adjust III model adjusts for adjust II + Mean arterial pressure + Gamma-glutamyl transpeptidase + APACHE II + SOFA.

APACHE = acute physiology and chronic health evaluation, CI = confidence intervals, HR = hazard ratios, ICU = intensive care unit, LDH = lactate dehydrogenase, ROSC = return of spontaneous circulation, SOFA = sequential organ failure assessment.

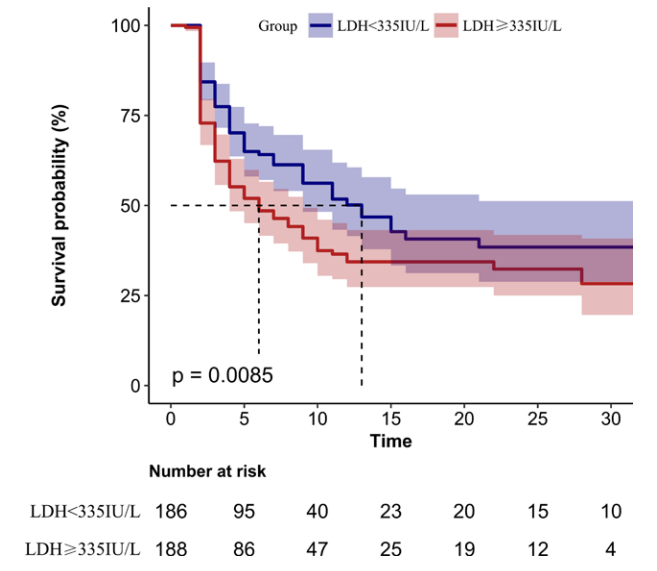

Figure 2. Mortality among groups was plotted over time on a Kaplan–Meier survival curve.

Table 3

Subgroup analyses of the association between serum LDH levels and ICU mortality in patients after cardiac arrest.

Subgroup	n	ICU mortality		HR (95%CI)	*P* for interaction
		LDH < 335 IU/L	LDH ≧ 335 IU/L		
Age (yr)					.557
<65	201	34 (37.8)	56 (50.5)	1.27 (0.80~2.00)	
≥65	173	49 (50.5)	55 (72.4)	1.59 (1.02~2.46)	
Sex					.204
Male	270	59 (41.5)	77 (60.2)	1.58 (1.08~2.29)	
Female	104	24 (53.3)	34 (57.6)	1.15 (0.63~2.09)	
Witnessed arrest					.517
YES	320	71 (43.0)	83 (53.5)	1.31 (0.93~1.85)	
NO	54	12 (54.5)	28 (87.5)	2.83 (1.21~6.60)	
Bystander cardiopulmonary resuscitation					.775
YES	254	58 (41.4)	59 (51.8)	1.27 (0.85~1.89)	
NO	120	25 (53.2)	52 (71.2)	1.61 (0.97~2.67)	
Nonshockable rhythm					.071
YES	221	56 (52.8)	83 (72.2)	1.58 (1.10~2.27)	
NO	153	27 (33.3)	28 (38.9)	0.97 (0.51~1.84)	
Out of hospital					.116
YES	208	47 (47.0)	66 (61.1)	1.18 (0.79~1.76)	
NO	166	36 (41.4)	45 (57.0)	1.82 (1.09~3.03)	
Time to ROSC (min)					.573
<30	306	71 (43.8)	82 (56.9)	1.44 (1.02~2.02)	
≥30	68	12 (48.0)	29 (67.4)	1.28 (0.59~2.82)	
Mean arterial pressure (mm Hg)					.468
<65	25	5 (45.5)	11 (78.6)	0.35 (0.05~2.30)	
≥65	242	76 (44.2)	99 (58.2)	1.47 (1.07~2.03)	

Adjusts for age + gender + Adrenaline + Witnessed Arrest + Bystander cardiopulmonary resuscitation + Out of Hospital + Non-shockable Rhythm + Time to ROSC + Gamma-glutamyl transpeptidase + Mean arterial pressure + APACHE II + SOFA.

APACHE = acute physiology and chronic health evaluation, CI = confidence intervals, HR = hazard ratios, ICU = intensive care unit, LDH = lactate dehydrogenase, ROSC = return of spontaneous circulation, SOFA = sequential organ failure assessment.

that LDH release from inflammatory cells is increased to such a degree that higher concentrations are measured in serum,[31] and serum LDH levels have also been associated with increased levels of other inflammatory markers.[32,33] In addition, systemic ischemia can lead to myocardial dysfunction, which may manifest as low cardiac output with hypotension, markedly elevated RV filling pressure and an overall decrease in myocardial contractility as observed by echocardiogram.[34] However, a study of patients with acute heart failure showed that higher LDH levels were significantly associated with 90-day, 180-day, and 365-day mortality rates.[10] Therefore, LDH tends to increase in patients after cardiac arrest, who are unable to limit endogenous acid production, leading to elevated LDH levels.[35] To the best of our knowledge, this study presents, for the first time, an independent positive association between LDH and all-cause mortality after cardiac arrest throughout the ICU stay. Serum LDH levels can assist clinicians in the early evaluation of patients after cardiopulmonary resuscitation. Clinicians should pay attention to serum LDH levels when patients are admitted to the ICU after cardiac arrest.

Our study has several limitations, including those related to its retrospective observational study design. Importantly, although we adjusted for potential confounding bias, residual confounding cannot be ruled out. For example, medical treatment may result in increased levels of serum LDH. In addition, the research subjects in the study are patients who initially exhibited ROSC after cardiac arrest. Therefore, there are shortcomings regarding the universality of our study results and their extrapolation. Finally, as comprehensive information on LDH isoforms is unavailable, we are unable to determine whether increased survival or mortality rates are associated with LDH diversity.

5. Conclusions

In summary, the study demonstrates that levels of serum LDH are positively associated with ICU mortality in patients after cardiac arrest. Future studies are required to identify the precise molecular mechanisms and causal pathways underlying this correlation between elevated LDH levels and mortality.

Acknowledgments

The authors thank all participants and staff members of our institution. We also thank Dr Jie Liu of the Department of Vascular and Endovascular Surgery, Chinese people's liberation army general hospital for comments regarding the manuscript, as well as his contributions regarding statistical support and study design consultations.

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