High Platelet-Lymphocyte Ratio is a Risk Factor for 30-day Mortality In In-Hospital Cardiac Arrest Patients: A Case-Control Study

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Research

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Abstract

Background: Early identification of risk factors for short-term mortality in patients with in-hospital cardiac arrest (IHCA) is crucial for early prognostication. This study aimed to explore the association of early dynamic changes in inflammatory markers with 30-day mortality in IHCA patients.

Methods: This study retrospectively collected demographic and clinical characteristics and relevant laboratory indicators within 72 h after recovery of spontaneous circulation (ROSC) of IHCA patients from December 2015 to December 2020 at the First Affiliated Hospital of Chongqing Medical University. The outcome was 30-day mortality. A linear mixed model was used to analyze the dynamic changes in laboratory indicators within 72 h after ROSC, and Cox regression was used to identify the independent risk factors for 30-day mortality.

Results: Overall, 85 IHCA patients were included. The 0-72h and 0-30day cumulative mortality rates were 25.88% and 57.65%, respectively, and the median survival time was 13.79 days. There was no association of inflammatory markers before IHCA with mortality. Within 72 h after ROSC, inflammatory markers showed various changes: the absolute monocyte count (AMC) showed no significant change trend, and the absolute lymphocyte count (ALC) showed an overall upward trend, while the absolute neutrophil count (ANC), white blood cell (WBC) count, platelet (PLT) count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) showed an overall downward trend. Cox multivariate analysis showed that Charlson comorbidity index (CCI) (HR = 2.366, 95%CI (1.084, 5.168)), APACHE II score (HR = 2.550, 95% CI (1.001, 6.498)), abnormal Cr before IHCA (HR = 3.417, 95% CI (1.441, 8.104)) and PLR within 72 h after ROSC (HR = 2.993, 95% CI (1.442, 6.214)) were independent risk factors for 30-day mortality. When $PLR \geq 180$, the risk of 30-day mortality increased by 199.3%.

Conclusions: This study clarified the dynamic change trends of inflammatory markers within 72 h after ROSC. The PLR was an independent risk factor for 30-day mortality in IHCA patients; it can be used as a predictor of short-term mortality and provide a reference for early prognostication.

Trial registration: ChiCTR1800014324

1 Background

The prognosis of patients with in-hospital cardiac arrest (IHCA) essentially depends on the organization of the chain of survival. With the improvement of cardiopulmonary resuscitation (CPR) quality and the development of advanced life support technology that can be used in the early stage, the successful resuscitation rate of IHCA patients has greatly increased, and the survival time has also been prolonged, but the short-term survival rate has not been significantly improved (only approximately 25%) [1, 2]. In 2019, JAMA's latest review on IHCA [3] pointed out that two-thirds of patients with out-of-hospital cardiac arrest (OHCA) with successful resuscitation die of neurological causes, while the cause of short-term mortality in IHCA patients is different: in these patients, multiorgan dysfunction drives mortality.

Therefore, early intervention for organ dysfunction is the first step for reducing multiple organ injury and improving clinical outcomes in IHCA patients [4].

A potential pathological process of early organ failure in IHCA patients is the development of post cardiac arrest syndrome (PCAS) [5]. Four phases are thought to occur in the development of PCAS [6], and the first two stages, which occur 0–72 h after resuscitation, are the crucial periods that determine the prognosis of patients. During this period, ischemia and hypoxia during cardiac arrest and reperfusion injury after resuscitation lead to comprehensive activation of the immune system and the coagulation pathway [7], which can lead to "sepsis-like syndrome" and eventually to multiorgan dysfunction and even poor prognosis [6, 8]. Sugita et al. [9] further pointed out that the inflammatory response is closely related to reperfusion injury. Prolonged hypoxia can lead to activation of endothelial cells, and comprehensive activation of multiple inflammatory pathways can lead to systemic inflammatory response syndrome, which can eventually lead to multiple organ failure and even death of patients [10]. Therefore, strengthening the monitoring of early inflammatory markers and administering targeted treatment and intervention probably improve the organ function and prognosis of patients [11–13].

This study aims to explore the association of dynamic changes in routine inflammatory markers within 72 h after recovery of spontaneous circulation (ROSC) with the 30-day mortality of IHCA patients. The goal is to further clarify the immunopathological process of PCAS by understanding the early changes of routine inflammatory markers and to provide promising candidate biomarkers for predicting the 30-day mortality of IHCA patients.

2 Methods

2.1 Study design and participants

This study was a case-control study. The subjects were patients with IHCA at the First Affiliated Hospital of Chongqing Medical University from December 2015 to December 2020. When an IHCA event occurred, junior residents performed CPR immediately. Experienced senior residents and attendants participated in the following processes, including but not limited to CPR, airway management, vasopressor administration, defibrillation and other advanced resuscitation measures, performed according to the guidelines of advanced cardiac life support (ACLS) [14]. After ROSC, the patient was admitted to the intensive care unit for further treatment. This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Inclusion criteria: (1) age $\geq$ 18 years old; (2) CPR for at least 5 minutes (this time point was selected given that patients with IHCA undergoing conventional CPR for less than 5 min have a greater than 70% survival with favorable neurologic outcome) [15]; (3) sustained ROSC; and (4) informed consent form signed by the patient or an authorized family member. **Exclusion criteria:** (1) incomplete data; (2) withdrawal of treatment immediately after ROSC due to delayed confirmation of do not resuscitate order;

(3) autoimmune diseases or use of immunosuppressants (such as corticosteroids) in the last 3 months; and (4) major trauma or surgical operation affecting hematological parameters (see Fig. 1).

2.2 Outcome

The outcome was 30-day mortality. Survival was censored at 30 days following IHCA, and patients discharged prior to this time point were subsequently contacted by phone to ascertain survival status. The patients were divided into a death group and a survival group.

2.3 Data collection

The clinical and laboratory indicators of 85 IHCA patients were collected retrospectively. If a patient had multiple cardiac arrest events during hospitalization, only the first event was recorded [16].

1) Clinical indicators: age, sex, Charlson comorbidity index (CCI), pulmonary infection before cardiac arrest, etiology of IHCA (cardiogenic or noncardiogenic), initial rhythm (e.g., ventricular fibrillation, ventricular tachycardia, asystole, bradycardia, or pulseless electrical activity), resuscitation method, use of extracorporeal membrane oxygenation therapy, time to ROSC, GCS score within 24 h after ROSC, and APACHE II score within 24 h after ROSC.

2) Laboratory indicators: all indicators were collected 0–24 h before cardiac arrest and 0–72 h after ROSC (0–12, 12–24, 24–48, and 48–72 h), including lactate (Lac), albumin (Alb), total bilirubin (TB), creatinine (Cr), hemoglobin (Hb), mean platelet volume (MPV), red blood cell distribution width (RDW) and routine inflammatory markers. The routine inflammatory markers included absolute monocyte count (AMC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), white blood cell (WBC) count, platelet (PLT) count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII).

All the data were collected by two research assistants through the electronic medical record system. After data collection, the patient's name and medical record number were deleted, and the patient was given a unique study number. The statistical analyst reviewed all the data to confirm the accuracy and manually verified the incongruent or out-of-range values. Before statistical analysis, the data set was verified and cleaned up to prevent any further changes and ensure the consistency and integrity of the statistical records and analysis data. All the researchers who collected and collated the data were blinded to the research content.

2.4 Definition of relevant variables

2.4.1 Clinical indicators

All IHCA and CPR outcome reports complied with the Utstein style of reporting IHCA research [14]. Sustained ROSC was defined as a ROSC duration ≥ 20 minutes without CPR. Time to ROSC was defined as the time from cardiac arrest to the first recording of sustained ROSC [17]. Pulmonary infection was

defined according to the diagnostic criteria; clinicians made this diagnosis and uploaded it to the electronic case system to generate a code. In this study, the recorded diagnostic code was used to determine whether the patient had pulmonary infection before IHCA. The CCI was calculated according to the medical history of patients before IHCA [18]. The GCS score within 24 h after ROSC was used. If there were multiple scores, the lowest was selected. The APACHE II score within 24 h after ROSC was used. If there were multiple scores, the highest was selected [19].

2.4.2 Laboratory indicators

All laboratory indicators were tested by the laboratory of the First Affiliated Hospital of Chongqing Medical University, and test values were uploaded to the electronic medical record system. According to the time at which the blood samples were obtained, the test values were collected 0–24 h before IHCA and at 0–12, 12–24, 24–48, and 48–72 h after ROSC. In this study, the normal reference values for relevant laboratory indicators were as follows: Lac: 0.5–2.2 mmol/L; Alb 35–50 g/L; TB 3–22 μ mol/L; Cr: female 41–97 μ g/L, male 57–106 μ g/L; Hb 130–175 g/L; MPV 7.6–13.2 fL; RDW 12%–16%; AMC $0.10\text{--}0.60 \times 10^9$ /L; ALC $1.10\text{--}3.20 \times 10^9$ /L; ANC $1.80\text{--}6.30 \times 10^9$ / L; WBC $3.50\text{--}9.50 \times 10^9$ /L; and PLT $85\text{--}303 \times 10^9$ /L. Recently, increasing evidence has indicated that there are strong interactions not only between inflammatory factors but also between inflammatory factors and PLTs in the pathophysiological development of PCAS after CPR [20]. Therefore, this study included an analysis of relevant routine composite inflammatory markers, including the NLR, PLR and SII. The NLR, PLR and SII values were calculated with the same blood sample from each patient, and the calculation formulas were as follows: $\text{NLR} = \text{ANC} / \text{ALC}$; $\text{PLR} = \text{PLT} / \text{ALC}$ and $\text{SII} = \text{PLT} \times \text{NLR}$.

The classification cutoff values for continuous variables were as follows: age: 65 years old; Cr: the diagnostic value of our hospital; Lac: mean; PLR: median; and other continuous variables: median.

2.5 Statistical analysis

Categorical variables are expressed as rates (n, %). Continuous variables with a normal distribution are expressed as the mean $\pm$ standard deviation (). Skewed continuous variables are expressed as the median and interquartile range (IQR). A linear mixed model was used to analyze the dynamic change trend of laboratory indicators of 85 patients within 72 h after ROSC. The repeated test values of AMC, ALC, ANC, WBC, PLT, NLR, PLR and SII at 0–12 h, 12–24 h, 24–48 h, and 48–72 h after ROSC were regarded as time-dependent variables. Variables with $P < 0.05$ in the univariate Cox regression analysis were included in the multivariate Cox regression analysis, and multivariate Cox regression was used to identify the independent risk factors for 30-day mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess the association of risk factors with 30-day mortality. Statistical analysis was performed using SAS 9.4. When the two-tailed P value was < 0.05 , the difference was considered statistically significant.

3 Results

3.1 Association of demographic, clinical and laboratory indicators before IHCA with 30-day mortality

The association of demographic characteristics, clinical characteristics, and laboratory indicators before IHCA with 30-day mortality is shown in Table 1. A total of 85 patients with IHCA were included in this study. Of them, 54 patients died, and 31 survived during the 30-day follow-up. The 0-72h cumulative mortality was 25.88%, the 0-30day cumulative mortality was 57.65%, and the median survival time was 13.79 days. The mean age of IHCA patients was 61.41 years old, and 54.12% were male. Of the 85 IHCA patients, 37.65% had cardiogenic causes, and noncardiogenic causes accounted for 62.35% of cases. 13 patients presented initial rhythm as ventricular fibrillation and ventricular tachycardia when IHCA occurred, and of them, 12 patients received CPR and an automated external defibrillator for resuscitation. Of the 85 patients, only 3 patients received the treatment of extracorporeal membrane oxygenation, and their 30-day survival rate was 100%. The median time to ROSC was 20 minutes, but it was not associated with 30-day mortality ($P > 0.05$). Age, CCI, APACHE II score and Cr before IHCA were associated with 30-day mortality (all $P < 0.05$). Overall, 48.24% of patients had pulmonary infection before IHCA, but there was no association of inflammatory markers before IHCA with 30-day mortality ($P > 0.05$).

Table 1

Association of demographic, clinical and laboratory indicators before IHCA with 30-day mortality.

Variable	Total	Survival group (n = 31)	Death group (n = 54)	HR (95%CI)	P
Baseline characteristics					
Age	61.41 ± 19.26	56.03 ± 21.2	64.5 ± 17.52	1.016 (1.002, 1.031)	0.028
Sex					
Male	46 (54.12%)	18 (58.06%)	28 (51.85%)	1.0 (reference)	
Female	39 (45.88%)	13 (41.94%)	26 (48.15%)	1.292 (0.757, 2.204)	0.348
CCI	5 (2, 7)	3 (1, 5)	6 (2, 7)	1.094 (1.016, 1.178)	0.018
Pulmonary infection					
No	44 (51.76%)	19 (61.29%)	25 (46.30%)	1.0 (reference)	
Yes	41 (48.24%)	12 (38.71%)	29 (53.70%)	1.396 (0.818, 2.385)	0.222
Etiology					
Cardiogenic	32 (37.65%)	10 (32.26%)	22 (40.74%)	1.0 (reference)	
Noncardiogenic	53 (62.35%)	21 (67.74%)	32 (59.26%)	0.779 (0.452, 1.342)	0.368
Initial rhythm					
ventricular tachycardia	5 (5.88%)	2 (6.45%)	3 (5.56%)	1.0 (reference)	
ventricular fibrillation	8(9.41%)	2 (6.45%)	6 (11.11%)	1.444 (0.381, 5.465)	0.589
Asystole	38 (44.71%)	9 (29.03)	29 (53.70)	1.798 (0.577, 5.605)	0.312

Note: CCI = Charlson comorbidity index; CPR = Cardiopulmonary resuscitation; AED = Automated external defibrillator; ECMO = Extracorporeal membrane oxygenation; ROSC = Recovery of spontaneous circulation; GCS = Glasgow coma score; Lac = Lactate; Alb = Albumin; TB = Total bilirubin; Cr = Creatinine; Hb = Hemoglobin; MPV = Mean platelet volume; RDW = Red blood cell distribution width; AMC = Absolute monocyte count; ALC = Absolute lymphocyte count; ANC = Absolute neutrophil count; WBC = White blood cell; PLT = Platelet; NLR = Neutrophil-lymphocyte ratio; PLR = Platelet-lymphocyte ratio; SII = Systemic immune-inflammation index.

Variable	Total	Survival group (n = 31)	Death group (n = 54)	HR (95%CI)	P
Bradycardia	28 (32.94%)	15 (48.39%)	13 (24.07%)	0.746 (0.223, 2.491)	0.634
pulseless electrical activity	6 (7.06%)	3 (9.68%)	3 (5.56%)	0.773 (0.17, 3.522)	0.739
Resuscitation method					
CPR	73 (85.88%)	25 (80.65%)	48 (88.89)	1.0 (reference)	
CPR + AED	12 (14.12%)	6 (19.35%)	6 (11.11%)	0.707 (0.302, 1.653)	0.423
Use of ECMO					
No	82 (96.47%)	28 (90.32%)	54 (100.00%)	1.0 (reference)	
Yes	3 (3.53%)	3 (9.68%)	0 (0.00%)	0.157 (0.009, 2.616)	0.197
Time to ROSC	20 (10, 35)	20 (7, 30)	21.5 (13, 40)	1.008 (0.997, 1.019)	0.169
GCS score	3 (3, 6)	5 (3, 8)	3 (3, 5)	0.906 (0.82, 1.002)	0.055
APACHE II score	26 (18, 32)	22 (13, 26)	28.5 (22, 34)	1.029 (1.011, 1.046)	0.001
Laboratory indicators before IHCA					
Lac	2.3 (1.1, 4.3)	1.93 (1, 3.8)	2.55 (1.25, 4.6)	1.087 (0.999, 1.184)	0.054
Alb	35 (32, 38)	33 (31, 38)	35 (33, 39)	1.005 (0.97, 1.042)	0.772
TB	12.2 (8, 17.3)	11.4 (8.2, 15.8)	12.55 (7.7, 19.8)	1.011 (0.998, 1.025)	0.090
Cr	71 (58, 116)	61 (51, 87)	86.5 (64, 130)	1.002 (1, 1.004)	0.017

Note: CCI = Charlson comorbidity index; CPR = Cardiopulmonary resuscitation; AED = Automated external defibrillator; ECMO = Extracorporeal membrane oxygenation; ROSC = Recovery of spontaneous circulation; GCS = Glasgow coma score; Lac = Lactate; Alb = Albumin; TB = Total bilirubin; Cr = Creatinine; Hb = Hemoglobin; MPV = Mean platelet volume; RDW = Red blood cell distribution width; AMC = Absolute monocyte count; ALC = Absolute lymphocyte count; ANC = Absolute neutrophil count; WBC = White blood cell; PLT = Platelet; NLR = Neutrophil-lymphocyte ratio; PLR = Platelet-lymphocyte ratio; SII = Systemic immune-inflammation index.

Variable	Total	Survival group (n = 31)	Death group (n = 54)	HR (95%CI)	P
Hb	106.12 ± 26.57	105.77 ± 30.19	106.31 ± 24.55	0.999 (0.989, 1.009)	0.837
MPV	11 (10.2, 11.8)	11 (10.2, 11.9)	11.15 (10.2, 11.8)	1.005 (0.988, 1.023)	0.575
RDW	14.3 (13.2, 15.8)	14 (13.1, 15.3)	14.6 (13.4, 16.3)	1.134 (0.986, 1.304)	0.078
AMC	0.53 (0.35, 0.86)	0.48 (0.35, 0.86)	0.53 (0.35, 0.86)	1.116 (0.666 ~ 1.87)	0.676
ALC	0.87 (0.56, 1.33)	0.95 (0.73, 1.46)	0.87 (0.52, 1.29)	0.749 (0.451, 1.243)	0.264
ANC	7.58 (4.81, 10.49)	7.9 (4.81, 10.31)	7.45 (4.66, 10.54)	1.002 (0.94, 1.069)	0.943
WBC	9.86 ± 4.69	9.8 ± 3.6	9.89 ± 5.24	0.992 (0.933, 1.055)	0.801
PLT	185 (127, 272)	208 (146, 302)	167 (107, 272)	0.999 (0.996, 1.001)	0.349
NLR	8.24 (4.95, 13.24)	8.36 (3.59, 14.5)	8.09 (5.07, 13.24)	1.016 (0.987, 1.047)	0.287
PLR	19.64 (13.95, 35.63)	18.8 (15.25, 32.74)	19.82 (12.64, 42.45)	1.005 (0.993, 1.017)	0.423
SII	14.46 (8.12, 29.61)	14.55 (8.12, 29.61)	14.15 (6.88, 31.57)	1.005 (0.993, 1.018)	0.401
Note: CCI = Charlson comorbidity index; CPR = Cardiopulmonary resuscitation; AED = Automated external defibrillator; ECMO = Extracorporeal membrane oxygenation; ROSC = Recovery of spontaneous circulation; GCS = Glasgow coma score; Lac = Lactate; Alb = Albumin; TB = Total bilirubin; Cr = Creatinine; Hb = Hemoglobin; MPV = Mean platelet volume; RDW = Red blood cell distribution width; AMC = Absolute monocyte count; ALC = Absolute lymphocyte count; ANC = Absolute neutrophil count; WBC = White blood cell; PLT = Platelet; NLR = Neutrophil-lymphocyte ratio; PLR = Platelet-lymphocyte ratio; SII = Systemic immune-inflammation index.					

3.2 The dynamic change trends of laboratory indicators within 72 h after ROSC and its association with 30-day mortality

The repeated test values of laboratory indicators of 85 IHCA patients at 0–12 h, 12–24 h, 24–48 h, and 48–72 h after ROSC were regarded as time-dependent variables. The analysis results of the dynamic change trends are shown in Appendix 1. The differences in inflammatory markers (AMC, ALC, ANC, WBC count, PLT count, NLR, PLR and SII) at different periods within 72 h after ROSC were statistically significant (all $P < 0.05$).

The dynamic change trends of inflammatory markers with time are shown in Fig. 2. Within 72 h after ROSC, the AMC showed no significant change trend (Fig. 2A), the ALC showed an overall upward trend

(Fig. 2B), and the ANC, WBC, PLT, NLR, PLR and SII showed an overall downward trend (Fig. 2C-H); in addition, the PLR and SII tended to be stable with time.

Univariate Cox regression analysis based on time-dependent variables showed that of the laboratory indicators tested within 72 h after ROSC, Lac and PLR were associated with 30-day mortality (both $P < 0.05$), as shown in Table 2.

Table 2

Univariate analysis of the association of laboratory indicators measured within 72 h after ROSC with 30-day mortality.

Variable	β	SE	HR (95% CI)	P
Lac (< 8 vs $\geq$ 8)	0.050	0.025	1.052 (1.002, 1.104)	0.042
Alb (< 30 vs $\geq$ 30)	-0.015	0.336	0.985 (0.510, 1.903)	0.965
TB (< 14.5 vs $\geq$ 14.5)	0.414	0.338	1.513 (0.779, 2.936)	0.221
Cr (< 130 vs $\geq$ 130)	0.530	0.336	1.700 (0.879, 3.285)	0.115
Hb (< 100 vs $\geq$ 100)	-0.306	0.338	0.736 (0.379, 1.429)	0.365
MPV (< 11.2 vs $\geq$ 11.2)	-0.275	0.336	0.760 (0.393, 1.467)	0.413
RDW (< 14.8 vs $\geq$ 14.8)	0.435	0.338	1.545 (0.796, 2.999)	0.198
AMC (< 0.56 vs $\geq$ 0.56)	0.092	0.334	1.096 (0.569, 2.111)	0.783
ALC (< 0.84 vs $\geq$ 0.84)	-0.462	0.337	0.630 (0.326, 1.220)	0.171
ANC (< 12 vs $\geq$ 12)	0.004	0.350	1.004 (0.505, 1.994)	0.992
WBC (< 14 vs $\geq$ 14)	0.363	0.340	1.437 (0.738, 2.797)	0.286
PLT (> 150 vs $\leq$ 150)	-0.495	0.364	0.610 (0.299, 1.243)	0.174
NLR (< 13 vs $\geq$ 13)	0.524	0.336	1.689 (0.874, 3.263)	0.119
PLR (< 180 vs $\geq$ 180)	0.699	0.339	2.012 (1.035, 3.911)	0.039
SII (< 1900 vs $\geq$ 1900)	0.574	0.338	1.775 (0.915, 3.446)	0.090

Note: Lac = Lactate; Alb = Albumin; TB = Total bilirubin; Cr = Creatinine; Hb = Hemoglobin; MPV = Mean platelet volume; RDW = Red blood cell distribution width; AMC = Absolute monocyte count; ALC = Absolute lymphocyte count; ANC = Absolute neutrophil count; WBC = White blood cell; PLT = Platelet; NLR = Neutrophil-lymphocyte ratio; PLR = Platelet-lymphocyte ratio; SII = Systemic immune-inflammation index.

3.3 Multivariate analysis of 30-day mortality

The variables with $P < 0.05$ in the univariate analysis were included in multivariate analysis: including age, CCI, APACHE II, Cr before IHCA, Lac within 72 h after ROSC and PLR within 72 h after ROSC (all $P < 0.05$) (Tables 1 and 2). After adjusting for confounding variables in the Cox multivariate regression analysis, the multivariate results showed that $PLR \geq 180$ had a 199.3% increased risk of 30-day mortality in IHCA patients (HR = 2.993, 95% CI (1.442, 6.214)). IHCA patients with a $CCI \geq 5$ had a 136.6% increased risk of 30-day mortality (HR = 2.366, 95% CI (1.084, 5.168)). When $APACHE II \geq 26$, the risk of 30-day mortality increased by 155% (HR = 2.550, 95% CI (1.001, 6.498)). Abnormal Cr before IHCA increased the risk of 30-day mortality by 241.7% (HR = 3.417, 95% CI (1.441, 8.104)) (Fig. 3).

4 Discussion

This case-control study included a total of 85 IHCA patients and retrospectively analyzed demographics, clinical characteristics and relevant laboratory indicators within 72 h after ROSC. The results of the linear mixed model showed that within 72 h after ROSC, inflammatory markers showed different patterns: the AMC showed no significant change trend, the ALC showed an overall upward trend, and the ANC, WBC, PLT, NLR, PLR and SII showed an overall downward trend. After adjusting for confounding variables by Cox multivariate regression, PLR within 72 h after ROSC was an independent risk factor for 30-day mortality in IHCA patients. When $PLR \geq 180$, the risk of 30-day mortality of IHCA patients increased by 199.3% (HR = 2.993, 95% CI (1.442, 6.214)). The inflammatory biomarker PLR can be used as a predictor of 30-day mortality in IHCA patients with ROSC, and it can be a reference for early prognostication.

Early organ failure is a main cause of short-term mortality in IHCA patients, and its potential pathological process is the development of PCAS. In particular, the comprehensive activation of the immune system and coagulation pathway within 72 h can lead to coagulation disorders and multiorgan failure and eventually to the death of patients. Many studies have pointed out that the systemic inflammatory response plays an important role in the pathophysiological development of early PCAS and affects the prognosis of IHCA patients [6, 12]. Neutrophils are early determinants of the development of the systemic inflammatory response. Whole-body ischemia and reperfusion during CPR can activate neutrophils to release inflammatory mediators, such as elastase and heparin binding protein, which can lead to inflammatory tissue damage and therefore affect the prognosis of patients [21, 22]. Villois et al. [23] reported that a low ALC on admission is an independent predictor of poor prognosis in OHCA patients. In a large retrospective cohort study of > 1,000 OHCA patients, Weiser et al. [24] further showed that NLR on admission was a predictor of long-term mortality of patients with cardiogenic OHCA. OHCA patients with $NLR \geq 6$ had a higher risk of mortality. Additionally, PLTs have been proven to play an important immune role in the systemic inflammatory response and have an important impact on the prognosis of patients [20, 25]. Kim et al. [26] identified that a continuously decreased PLT count within 7 days is associated with a poor neurologic outcome and mortality at 6 months. Therefore, the early dynamic changes in routine inflammatory markers may reflect the immunopathological process of PCAS, which is closely

related to the prognosis of cardiac arrest. Therefore, these dynamic changes could be used as an important index for prognosis assessment.

This study analyzed the dynamic changes of inflammatory markers within 72 h after ROSC in 85 IHCA patients, and found that the AMC trend did not significantly change, the ALC showed an overall upward trend, and the ANC, WBC count, PLT count, NLR, PLR and SII showed an overall downward trend; in addition, the PLR and SII tended to be stable with time. Kim et al. [26] found that in OHCA patients treated with targeted temperature management, the PLT count continuously decreased within 72 h after cardiac arrest. Many recent studies on sepsis and other severe diseases [27–29] have shown that the NLR, PLR and SII can continue to decrease in the early stage of disease, which is consistent with the conclusion of our study. However, Ryzhov et al. [30] showed that the AMC increases briefly within 6 h after ROSC, the ALC shows a persistent decrease 6–72 h after ROSC, and the ANC and WBC count increase significantly within 48 h and 72–168 h after ROSC. These findings are inconsistent with the results of our study. First, these discrepancies can be explained by the heterogeneity of the study population; 80% of the patients had OHCA in Ryzhov's study [30], while the target population of our study was IHCA patients. In addition, the use of drugs in the early stage after cardiac arrest may affect the dynamic changes of related indicators; for example, corticosteroids can lead to lymphopenia after cardiac arrest [23]. Therefore, our study excluded patients using immunosuppressants, and these controversial results still need further verification.

Through analysis of the association of inflammatory markers within 72 h with prognosis, this study further found that only the PLR was associated with 30-day mortality. The PLR can be quickly calculated by obtaining the PLT count and ALC from routine clinical blood examinations. The PLR reveals changes in both the PLT count and the ALC caused by acute inflammation and a prethrombotic state. As a novel, simple and inexpensive routine composite inflammatory marker, the PLR has been proven to have value for predicting the prognosis of various disorders in recent years [31, 32]. A study on dynamic changes in the PLR in breast cancer patients identified that patients with a persistently low PLR after initial treatment have a significantly better prognosis in terms of late metastasis than other patients [31]. Shen et al. [33] showed that a high PLR on admission ($PLR > 200$) was significantly associated with increased mortality in patients with sepsis ($OR = 1.0002$, 95% CI [1.0001–1.0004]). Additionally, studies have also shown that a high PLR can be used to predict poor prognosis in relation to cardiovascular events [34]. In this study, when $PLR \geq 180$, the risk of 30-day mortality of IHCA patients increased by 199.3% ($HR = 2.993$, 95% CI (1.442, 6.214)). The reason for this pattern may be that PLTs play an important role in both the immunomodulatory and inflammatory processes in IHCA patients. They can contribute to the initiation or exacerbation of the inflammatory process by inducing the release of inflammatory cytokines and interacting with different kinds of bacteria and immune cells, including neutrophils, T lymphocytes, natural killer cells and macrophages. Higher PLT counts, to a certain extent, are associated with increased systemic inflammation [25], and a low ALC may represent a suppressed immune and inflammatory response [28, 35]. Therefore, a higher PLR reflects a more severe systemic inflammatory immune response in IHCA patients, which is closely related to the development of PCAS and death.

We acknowledge several limitations in our study. 1. This study is a single-center retrospective case-control study, and the sample size is relatively small, so it is necessary to verify the conclusions in a prospective study with an expanded sample size. 2. Since 0–72 h after ROSC is an important period for determining the prognosis of patients, we focused on the association of the dynamic changes in inflammatory markers in this period with the 30-day mortality of IHCA patients to identify routine inflammatory markers that can predict prognosis early. However, according to the results of our study, the median survival time of patients was 13 days, so future studies should include routine inflammatory marker data after 72 h to provide a clearer picture of the progression of PCAS and the association of the change trends of inflammatory markers with mortality. 3. This study didn't conduct combined analysis of inflammatory markers. In a future study, we will combine related inflammatory markers, such as the PLR and NLR, to further explore the relationship between the severity of inflammation and the mortality of IHCA patients.

5 Conclusions

In conclusion, early identification of the risk factors for short-term mortality in IHCA patients and exploration of the dynamic changes in routine inflammatory markers can provide a reference for clinicians to determine patient prognosis early. The PLR is simple and inexpensive and can be used as an effective prognostic predictor of 30-day mortality in IHCA patients. As such, the PLR is worthy of further verification and promotion.

Abbreviations

ACLS=Advanced cardiac life support; Alb=Albumin; ALC=absolute lymphocyte count; AMC=absolute monocyte count; ANC=absolute neutrophil count; CCI=Charlson Comorbidity Index; CI=confidence interval; CPR=Cardiopulmonary resuscitation; Cr=creatinine; Hb=hemoglobin; HR=Hazard ratio; IHCA=in-hospital cardiac arrest; Lac=lactate; MPV=mean platelet volume; NLR=neutrophil-lymphocyte ratio; OHCA=out-hospital cardiac arrest; PCAS=post cardiac arrest syndrome; PLR=platelet-lymphocyte ratio; PLT=platelet; RDW=red blood cell distribution width; ROSC=recovery of spontaneous circulation; TB=total bilirubin; WBC=white blood cell; SII=systemic immune-inflammation index.

Declarations

Ethical approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

All the coauthors have approved this version of the manuscript and consent to publication.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Feng Li and Lihong Huang designed the study and performed the experiments; Jingjing Peng and Xuefeng Wang analyzed the data; Lihong Huang wrote the manuscript; Feng Li reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow Chart.

Figure 2

The dynamic change trends of inflammatory markers within 72 h after ROSC. AMC=Absolute monocyte count; ALC=Absolute lymphocyte count; ANC=Absolute neutrophil count; WBC=White blood cell; PLT=Platelet; NLR= Neutrophil-lymphocyte ratio; PLR=Platelet-lymphocyte ratio; SII=Systemic immune-inflammation index.

Figure 3

Risk factors for 30-day mortality in the multivariate Cox regression model with time-dependent variables. Lac=Lactate; Cr=creatinine; CCI=Charlson comorbidity index; PLR= platelet-lymphocyte ratio.

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