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RESEARCH ARTICLE

Prognostic Value of the Ratio of Hemoglobin to Red Blood Cell Distribution Width in Patients with Out-of-Hospital Cardiac Arrest: A Retrospective Study

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Abstract

Background The ratio of hemoglobin to red blood cell distribution width (HRR) can reflect the degree of oxidative stress and systemic inflammatory response in the body, and is a potential indicator to predict the prognosis of patients with cardiac arrest (CA).

Methods We retrospectively analyzed 126 patients successfully resuscitated after out-of-hospital cardiac arrest. Patients were grouped according to their survival status at discharge: 35 survived and 91 died. Binary logistic regression was used to analyze the independent factors affecting the prognosis of patients after cardiopulmonary resuscitation (CPR). A receiver operating characteristic (ROC) curve was used to analyze the predictive value of each independent factor for the prognosis of patients after CPR.

Results The HRR in death group was lower than that in the survival group ($P<0.05$), which was closely related to the prognosis of patients after CPR. The ROC curve showed that HRR < 8.555 ($AUC=0.733$, sensitivity 87.5%, specificity 40.7%, $P<0.001$) indicated poor prognosis after CPR.

Conclusions The HRR is an independent risk factor for the prognosis in patients who underwent CPR after out-of-hospital cardiac arrest. After successful resuscitation, HRR lower than 8.555 indicates poor prognosis.

Keywords Cardiac arrest · After cardiopulmonary resuscitation · Hemoglobin · Red blood cell distribution width · Ratio · Prognosis

1 Introduction

Cardiac arrest (CA) is a major global public health problem [1]. Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide [2]. The discharge survival rate of patients with OHCA in the United States is approximately 10% [3]. In China, the rates of discharge survival and good neurological function in OHCA patients are only 1.3% and 1%, respectively [4]. During CA, severe hypoxia and ischemia occur and inflammatory factors are released in the body, leading to the accumulation of various metabolites in the body. Reperfusion injury occurs after the return of spontaneous circulation (ROSC), resulting in multiple organ dysfunction or a disorder called post cardiac arrest syndrome (PCAS) [5].

Early identification of PCAS, of its severity, and early intervention measures are very important for the prognosis of patients with CA. In recent years, the red blood cell distribution width (RDW) has been found to be associated with the prognosis of CA in and out of hospital [6]. Hemoglobin (Hb) levels are associated with survival and neurological function prognosis after ROSC [7]. The ratio of hemoglobin to red cell distribution width (HRR) is a recently proposed

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composite parameter and novel inflammatory marker that can reflect the degree of oxidative stress and systemic inflammatory responses [8, 9]. Recent studies have shown that it plays an important role in predicting the prognosis of patients with cancer and lymphoma [10]. However, HRR has not yet been reported to predict the prognosis of patients with PCAS. HRR can be obtained quickly and economically. Therefore, this study aimed to explore the prognostic value of HRR in patients underwent CPR after OHCA and provide new insights for the clinical identification of PCAS.

2 Materials and Methods

2.1 Participants

We conducted a retrospective study of 126 patients with successful resuscitation for OHCA admitted to the ICU from the emergency room of the First Affiliated Hospital of Zhengzhou University between August 2016 and December 2022. The inclusion criteria were: (1) patients admitted to the ICU from the emergency room of our hospital after successful cardiopulmonary resuscitation after OHCA and (2) ≥ 18 years old. The exclusion criteria were: (1) Patients with less than 24 h in the ICU, (2) CA due to various traumas, (3) successful CPR for > 6 h, (4) history of blood transfusion within 3 months, (5) history of hematological or immune system diseases, (6) previous tumors and chemotherapy, and (7) missing medical records. Patients' personal information was anonymized while collecting and analyzing the data. This study conformed to the standards of medical ethics and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Approval #:2022-KY-1411).

2.2 Diagnostic Criteria

OHCA is defined as a loss of consciousness, disappearance of arterial pulsation, respiratory arrest or sighing breathing, which is the clinical basis of OHCA. In addition, prehospital diagnosis of OHCA requires reference to ECG changes. CPR follows the 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation. The CPR success criteria were: patient's heart rate, blood pressure (systolic blood pressure ≥ 60 mmHg), and autonomic or pacemaker rhythm were restored after cardiac compressions and remained so until admission.

2.3 Date Collection

The following clinical data were collected from the 126 patients included in the study: gender, age, medical history, and ICU length of stay (days); initial score after admission to ICU, including the acute physiology and chronic health evaluation II score (APACHE II) and Glasgow coma scale (GSC); and initial vital signs after admission to ICU including heart rate, body temperature, respiration and mean arterial pressure (MAP). Additionally, blood gas analysis indexes, including arterial pH (pH), arterial partial oxygen pressure (PaO_2), blood lactic acid (Lac), 6 h lactic acid (6 h Lac), 12 h lactic acid (12 h Lac), 6 h lactic acid clearance, and 12 h lactic acid clearance; and serological indicators, including glomerular filtration rate (GFR), white blood cell count (WBC), red blood cell RBC, Hb, RDW and HRR were assessed. The above biochemical indices were determined by the Emergency Laboratory of the First Affiliated Hospital of Zhengzhou University. Patients were grouped according to their survival status at the time of discharge: 35 survived and 91 died.

2.4 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 and GraphPad Prism, version 8.0. The Kolmogorov–Smirnov method was used to test the normality of the quantitative data. Quantitative data conforming to normal distribution were represented by Mean ± SD, comparisons between groups were performed by independent sample *t* tests, and quantitative data not conforming to normal distribution were represented by median (quartile) [M (P25, P75)]. The Mann–Whitney U test was used for comparisons between groups. Disorderly classification data were expressed as frequency (%). Group comparisons between the χ^2 inspections and binary logistic regression were used to analyze independent prognostic factors for patients who underwent CPR after OHCA. A receiver operating characteristic (ROC) curve was used to analyze the evaluation value of independent influencing factors on the prognosis of patients after CPR and the value corresponding to the most approximate entry index was taken as the best cut-off value. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Demographics and Clinical Characteristics

A total of 126 patients (average age: 58.21 years; men: 85) with successful CPR after OHCA were included. Hypertension was present in 42.1% of the patients, diabetes in 22.2%, coronary heart disease in 22.2%, cerebrovascular disease in 9.5% and other system diseases in 36.5%. There were no statistically significant differences in age or medical history between the survival and death groups. Compared to the death group, patients in the survival group were younger and spent more days in the ICU ($P<0.05$). The characteristics of the patients in both groups are presented in Table 1.

3.2 Comparison of Initial Scores, Vital Signs and Laboratory Results on Admission to ICU

The initial vital signs, PaO_2 and WBC count of patients admitted to the ICU were not significantly different between the two groups (Table 2). The APACHE II score of the survival group was significantly lower than that of the death group, GSC score of the survival group was significantly higher than that of the death group. The laboratory indexes pH, 6 h lactic acid clearance, 12 h lactic acid clearance, GFR, RBC, Hb, HRR of the survival group were significantly higher than those of the death group, while the Lac, 6 h Lac, 12 h Lac, and RDW were significantly lower than that of death group ($P<0.05$).

3.3 Binary Logistic Regression Analysis of the Initial Admission Index

Indicators with significant differences in the univariate analysis of the 126 patients were assessed in a binary multivariate logistic regression analysis. The results included sex, ICU stay, APACHE II score, GSC score, pH, Lac, 6 h Lac, 6 h lactate clearance, 12 h Lac, 12 h lactate clearance, GFR, RBC, Hb, RDW, and HRR. HRR, 6 h lactic acid clearance rate, and APACHE II score were independent risk factors for prognosis after CPR (Table 3).

3.4 ROC Curve Analysis of HRR and 6 h Lactic Acid Clearance to Predict Prognosis of Patients After CPR

With the prognosis (survival = 1) of patients discharged after CPR as the state variable and HRR, 6 h lactate clearance rate, and their combination as the test variables, the ROC curve was used to analyze the predictive value of HRR, 6 h lactate clearance rate, and their combination in predicting the prognosis of patients after CPR. The cut-off value for the initial HRR of patients admitted to the ICU was 8.555 ($AUC=0.733$, sensitivity 87.5%, specificity 40.7%, $P<0.001$; Table 4 and Fig. 1), the cut-off value of lactic acid clearance at 6 h was 28.947, ($AUC=0.701$, sensitivity 88.6%, specificity 35.8%, $P<0.001$; Table 4 and Fig. 2), and the combined cut-off value was 0.296($AUC=0.802$, sensitivity 71.4%, specificity 51.4%, $P<0.001$; Table 4 and Fig. 3).

4 Discussion

CA is the sudden termination of the cardiac ejection function, disappearance of arterial pulsation and heart sounds, and severe ischemia and hypoxia of vital organs such as the brain, leading to the end of life, which is a common clinical emergency [11]. A significant proportion of patients with ROSC after CPR die in the early stages of post-resuscitation care due to their unique and complex pathophysiological process known as "post-cardiac arrest syndrome" or PCAS [12]. Once a patient with CA develops ROSC, a chain of events occurs, characterized by ischemic hypoxic brain injury, cardiac dysfunction, and systemic ischemia–reperfusion response. Ischemia–reperfusion causes widespread activation of the immune and clotting pathways, thereby increasing the risk of multiple organ failure and infection [13]. The inflammatory response after CPR is similar to that of sepsis, hence the name" septicemia like syndrome" [14]. Patients may exhibit abnormal inflammatory regulation, myocardium and adrenal gland dysfunction, coagulation dysfunction, and endothelial dysfunction following CA [5, 15]. Capillary endothelial cell dysfunction results in increased capillary permeability, capillary leakage, proteins, and other substances from the blood vessels into the tissue

Table 1 Baseline characteristics of the survival and death groups

	All (n = 126)	Survival (n = 35)	Death(n = 91)	$t/Z/\chi2$	P
Gender (male)	85 (67.5)	29 (82.9)	56 (61.5)	5.234	0.022
Age (year)	58.21 ± 15.16	54.17 ± 12.97	59.76 ± 15.72	− 1.871	0.064
Hypertension	53 (42.1)	12 (34.3)	41 (45.1)	1.203	0.273
Diabetes	28 (22.2)	7 (20.0)	21 (23.1)	0.138	0.710
Coronary heart disease	28 (22.2)	11 (34.1)	17 (18.7)	2.376	0.123
Cerebrovascular	12 (9.5)	2 (5.7)	10 (11.0)	0.816	0.366
Other	46 (36.5)	12 (34.3)	34 (37.4)	0.103	0.748
ICU days	6.50 (3.00,12.25)	11.00 (6.00,18.00)	5.00 (2.00,11.00)	− 3.382	0.001

All included Patients were grouped according to their survival status at the time of discharge: 35 survived and 91 died. ICU days, mean ICU stay in days

Table 2 Comparison of initial scores, vital signs and laboratory results on ICU admission between survival and death groups

	All (n = 126)	Survival (n = 35)	Death (n = 91)	χ^2/t	*P*
APACHE II	23.00 (18.00, 28.00)	17.00 (15.00, 21.00)	25.00 (21.00, 29)	−6.122	< 0.001
GSC	3.00 (3.00, 3.00)	3.00(3.00, 8.00)	3.00 (3.00, 3.00)	−4.018	< 0.001
HR	106.75 ± 277.97	103.89 ± 26.49	107.85 ± 28.58	−0.711	0.479
T	36.5 (36.0, 36.6)	36.5 (36.1, 36.6)	36.4 (36.0, 36.6)	−1.130	0.259
R	16 (15, 20)	17 (15, 21)	15.00 (15.00, 20.00)	−1.820	0.069
MAP (mmHg)	82.33 (68.00, 96.58)	82.00 (73.33, 97.33)	83.33 (65.66, 96.33)	−0.477	0.634
pH	7.25 (7.11, 7.35)	7.32 (7.20, 7.41)	7.22 (7.03, 7.33)	−2.969	0.003
PaO_2 (mmHg)	118.50 (80.80, 209.00)	128.00 (82.00, 182.00)	118.00 (80.00, 210.00)	−0.112	0.911
Lac(mmol/L)	9.55 (2.60, 7.30)	6.80 (3.70, 10.50)	10.1 (5.60, 14.3)	−2.623	0.009
6 h Lac (mmol/L)	3.95 (2.60, 7.30)	2.70 (1.60, 3.90)	5.50 (3.10, 8.70)	−4.922	< 0.001
6 h lactic acid clearance	45.85 (18.78, 66.27)	58.62 (41.79, 72.41)	32.35 (5.00, 58.67)	−3.478	0.001
12 h Lac (mmol/L)	2.80 (1.58, 5.53)	1.60 (1.10, 2.90)	3.10 (2.00, 7.00)	−4.220	< 0.001
12 h lactic acid clearance	61.30 (33.92, 78.23)	73.17 (58.62, 81.08)	55.17 (25.93, 75.29)	−3.165	0.002
GFR	73.20 (51.80, 95.18)	87.13 (64.15, 100.23)	71.27 (43.62, 91.24)	−2.541	0.011
WBC ($\times 10^9$ /L)	15.95 ± 6.48	16.46 ± 5.87	15.75 ± 6.69	0.547	0.586
RBC ($\times 10^9$/ L)	4.09 ± 0.82	4.37 ± 0.70	3.98 ± 0.84	2.443	0.016
Hb (g/L)	124.66 ± 25.62	136.57 ± 18.60	120.09 ± 26.55	3.364	0.001
RDW (fl)	13.90 (13.10, 15.03)	13.20 (12.70, 14.00)	14.10 (13.40, 15.73)	−3.871	< 0.001
HRR	8.83 (7.70, 10.62)	10.29 (8.80, 11.52)	8.29 (7.13, 9.93)	−4.050	< 0.001

APACHE II, mean acute physiology and chronic health evaluation II score; GSC, mean Glasgow coma scale; MAP, mean arterial blood pressure; 6 h lactic acid clearance, mean (Initial blood lactic acid concentration − after 6 h)/initial blood lactic acid concentration * 100%; 12 h lactic acid clearance, mean (Initial blood lactic acid concentration − after 12 h)/initial blood lactic acid concentration *100%; HRR, mean hemoglobin to red blood cell distribution width ratio

Table 3 Binary logistic regression analysis of the first admission index

	β	SE	Wald	*P*	OR	95% CI	
						Lower limit	Upper limit
HRR	0.443	0.143	9.663	0.002	1.558	1.178	2.060
6 h lactic acid clearance	0.028	0.011	7.142	0.008	1.029	1.008	1.050
APACHE II	−0.274	0.061	20.035	< 0.001	0.760	0.674	0.857
constant	−0.612	1.893	0.105	0.764	0.542		

HRR mean hemoglobin to red blood cell distribution width ratio; 6 h lactic acid clearance, mean (Initial blood lactic acid concentration -after 6 h)/initial blood lactic acid concentration *100%; APACHE II, mean acute physiology and chronic health evaluation II score

Table 4 Predictive value of HRR, 6 h lactic acid clearance and their combination on prognosis of patients after cardiopulmonary resuscitation

	AUC	95% CI	Yoden index	Cut-off value	Specificity	Sensitivity	*P*
HRR	0.733	0.641–0.826	0.407	8.555	0.407	0.875	< 0.001
6 h lactic acid clearance	0.701	0.605–0.797	0.358	28.947	0.358	0.886	< 0.001
Combination	0.802	0.723–0.881	0.514	0.296	0.514	0.714	< 0.001

HRR, mean hemoglobin to red blood cell distribution width ratio; 6 h lactic acid clearance, mean (Initial blood lactic acid concentration -after 6 h)/initial blood lactic acid concentration * 100%; Combination, mean HRR combined with 6 h lactic acid clearance

space [16–19]. Ischemia–reperfusion injury leading to a systemic inflammatory response, CA ischemia-hypoxic encephalopathy, and myocardial dysfunction are the major factors leading to PCAS. Systemic inflammatory responses and significantly elevated levels of circulating cytokines occur after CA [14].

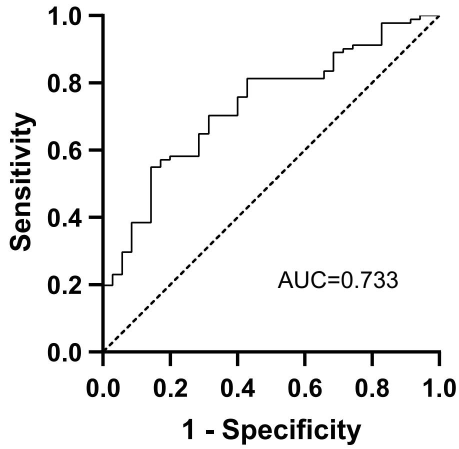

Fig. 1 ROC curve of HRR

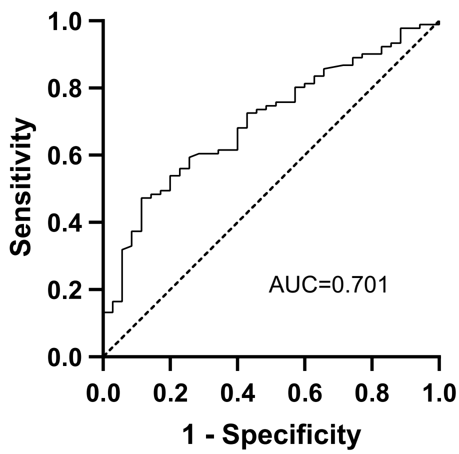

Fig. 2 ROC curve of 6 h lactic acid clearance

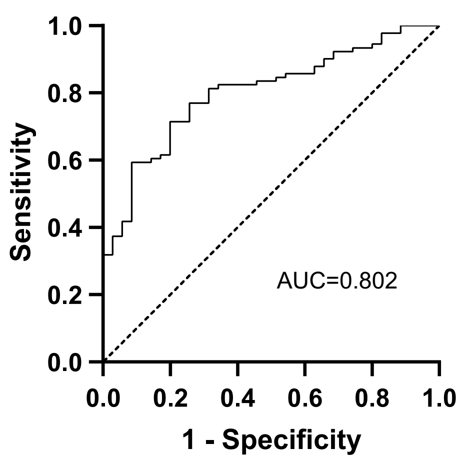

Fig. 3 ROC curve of HRR combined with 6 h lactic acid clearance

The RDW is a measure of the heterogeneity of circulating erythrocyte size. Oxidative damage and inflammatory responses can affect the RDW [20]. Recent studies have shown that an elevated RDW is a strong predictor of mortality in critically ill patients. Additionally, the RDW is a predictor of cardiac dysfunction and mortality in patients with congestive heart failure and acute coronary syndrome [21–24]. Kim et al. [12] conducted a retrospective study and found that the highest quartile of RDW (RDW > 15.4%) was independently associated with all-cause mortality at 30 days after CPR ($OR = 1.95$; 95% CI 1.05–3.60; $P = 0.034$), suggesting that the initial RDW was an independent predictor of all-cause mortality after resuscitation. Comparison of the baseline data in this study showed that the RDW in the death group was higher than that in the survival group ($P < 0.05$). This may be related to myocardial dysfunction after resuscitation. In addition, there is evidence of a significant relationship between higher Hb levels and the recovery of spontaneous respiratory circulation after CA (in conjunction with favorable neurological outcomes within hours of CA and survival to discharge) [25–27]. A study of Albaeni et al. [7] showed that Hb levels ≥ 10 g/dl after recovery of spontaneous respiratory circulation are associated with a good neurological prognosis for survival, while patients with high Hb levels have a shorter duration of good neurological prognosis. However, an index of the HRR combined with RDW and Hb has not been reported to predict the prognosis and neurological function of patients after CPR following OHCA. This study aimed to investigate the prognostic value of the HRR ratio in patients undergoing cardiopulmonary resuscitation after OHCA. The HRR is a new inflammatory marker that quickly reflects the degree of oxidative stress and systemic inflammatory responses [8, 9]. Recently, it has been used to predict the prognosis of various cancers and lymphomas [10, 28–30]. However, the relationship between the HRR and patient prognosis after CPR has not been reported. In this study, the survival group had a higher HRR than the death group ($P < 0.001$). Bivariate multivariate logistic regression analysis showed that the HRR was an independent factor influencing the prognosis of patients after cardiopulmonary resuscitation ($OR = 1.558$, 95% CI:1.178–2.060, $P < 0.05$). The ROC curve suggested that when the HRR was < 8.555, patients had a poor prognosis after cardiopulmonary resuscitation ($AUC = 0.731$, sensitivity 0.875, specificity 0.407). This may be related to oxidative stress and inflammation in tissues and organs caused by ischemia–reperfusion injury after ROSC during CA.

During CA, the body is in a state of severe ischemia and hypoxia and the transmission of oxygen and metabolic substrates is interrupted, resulting in an anaerobic metabolic state of the mitochondria and dysfunction of the electron transport chain, and injury to mitochondria after CA. Anaerobic metabolism of tissues produces lactic acid, and the accumulation of a large amount of lactic acid can lead to metabolic acidosis and a decrease in PH. When spontaneous respiratory circulation is not restored during CA, tissues and organs undergo anaerobic metabolism to produce lactic acid because of hypoxia, and lactic acid accumulation leads to metabolic acidosis in the tissues and organs [31, 32]. The study of Seeger et al. [33] showed that lactic acid was an independent predictor for patients after CPR. In addition, two recent prospective studies shown that a greater lactate clearance was a predictor for lower mortality and better neurologic outcome after CA [34, 35]. The results of the binary logistic regression analysis in this study showed that the 6 h lactate clearance rate was an independent prognostic factor for patients with CPR after OHCA ($OR = 1.029$, 95% CI: 1.008–1.050, $P < 0.001$). When the 6 h lactate clearance rate was < 28.947, the prognosis after CPR was poor ($AUC = 0.701$, sensitivity: 0.886; specificity: 0.358). This study further explored the combined index of the HRR and 6 h lactic acid clearance, and the results showed that the combined index of the HRR and 6 h lactic acid clearance had a higher predictive value than each single index.

However, this study has some limitations. First, the sample size was small; therefore, there may have been some bias in the results obtained, and the sample size needs to be expanded for verification. Second, this was a retrospective observational study that only collected scores and laboratory indicators at a single time point upon admission and did not study dynamic changes in the HRR. Moreover, although the HRR is relatively mature in research on various cancers and lymphomas, further research on the mechanism of the HRR in CA as a newly proposed inflammatory indicator remains to be conducted. Finally, the data points in time collected in this study are indicators of the initial laboratory results of a patient with CA admitted to the ICU after successful CPR. Various indicators before hospital admission were not included; therefore, this study has certain limitations and further investigation is required.

5 Conclusions

HRR is an independent risk factor affecting the prognosis of patients undergoing CPR after OHCA. After successful resuscitation, an HRR of < 8.555 indicates poor prognosis. The 6 h lactate clearance rate is an independent risk factor affecting the prognosis of patients after resuscitation for OHCA. The 6 h lactate clearance rate of < 28.947 after successful resuscitation indicates poor prognosis. The combined index of 6 h lactate clearance rate and HRR has a higher predictive value for the prognosis of patients after resuscitation.

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Author's Contributions HW, YL and TZ conceived and designed the study. RL supervised the conduct of the study. HW, YL, YZ and RJ are responsible for data acquisition. HW, RL, LY and QZ analyzed the data and takes responsibility for the paper. HW, TZ, QZ, XJ and YZ assisted with literature review. HW and YL drafted the initial manuscript. RL, TZ, QL and CL reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Data Availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics Approval and Consent to Participate This study was approved by the First Affiliated Hospital of Zhengzhou University Ethics Committee (Approval #:2022-KY-1411).

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