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Neutrophil to high-density lipoprotein cholesterol ratio as a potential inflammatory marker for predicting all-cause mortality in out-of-hospital cardiac arrest survivors

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Out-of-hospital cardiac arrest (OHCA) survivors have more than one-third mortality rate. Numerous inflammatory indicators are available, and it should be feasible to identify a fast and accurate way to aid medical decisions. This retrospective cohort study included 247 patients with OHCA, hospitalized between January 2015 and August 2024. The study was conducted in the intensive care unit of China Medical University Hospital, Taichung, Taiwan. A variety of inflammatory markers, including interleukin-6, neutrophil to high-density lipoprotein cholesterol ratio (NHR), and C-reactive protein, were screened at 24 h after OHCA. The primary endpoint was the 90-day all-cause mortality. Receiver operating characteristic (ROC) curves and Kaplan–Meier survival curves of NHR were analyzed. Possible risk factors for all-cause mortality were estimated by Cox regression modeling. NHR and interleukin-6 were similarly predictive of all-cause mortality in inflammatory response, and both were superior to C-reactive protein at 24 h after OHCA ($p < 0.001$). The area under the ROC curve of NHR was 0.74 (95% confidence interval [CI]: 0.66–0.81, $p < 0.001$), sensitivity: 0.68, and specificity: 0.68, and NHR = 16.1. The 90-day all-cause mortality rate for NHR > 16.1 compared to those with NHR ≤ 16.1 was 0.51 and 0.21, respectively, according to Kaplan–Meier curves analysis. The hazard ratio for NHR > 16.1 was 2.54 (95% CI: 1.68–3.82, $p < 0.001$). An NHR > 16.1 at 24 h after OHCA is a potential inflammatory marker for predicting all-cause mortality.

Keywords Neutrophils, High-density lipoprotein cholesterol, Neurological outcomes, Systemic inflammatory response, Cardiac arrest

Abbreviations

AISI	Aggregate index of systemic inflammation
CAHP	Cardiac arrest hospital prognosis
CI	Confidence interval
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LOX-1	Lectin-type oxidized low-density lipoprotein receptor 1

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NET	Neutrophil extracellular trap
NHR	Neutrophil to high-density lipoprotein cholesterol ratio
NLR	Neutrophil-to-lymphocyte ratio
OHCA	Out-of-hospital cardiac arrest
PCSK-9	Proprotein convertase subtilisin/kexin type 9
ROC	Receiver operating characteristic
SAA	Serum amyloid A
SII	Systemic immune-inflammation index
SIRI	Systemic inflammation response index
VIS	Vasoactive-inotropic score

Out-of-hospital cardiac arrest (OHCA) occurs at a rate of 50 to 100 per 100,000 person-years worldwide. 70% of all cardiac arrests are of cardiac origin, with most associated with ischemic heart disease[1]. When cardiac arrest occurs, brain damage is the most common problem[2]. Heart, brain damage or multiple organ failure will result in mortality. Assessment of the mortality outcomes after cardiac arrest is an important issue for further decision-making.

Cardiac arrest triggers ischemia-reperfusion injury, which leads to a massive systemic inflammatory response manifested by interleukin-6 signaling through monocyte-derived macrophages. Interleukin-6 has been the predictor of OHCA mortality[3–5]. Owing to the time and expense of the interleukin-6 enzyme-linked immunosorbent assay, a simpler method of categorizing white blood cells has been attempted. Interluekin-6 after ischemia and reactive oxidative stress after reperfusion trigger the innate immune system, resulting in neutrophil recruitment and aggregation, followed by lymphopenia. The neutrophil-to-lymphocyte ratio (NLR) has been attempted as a potential predictor of clinical outcomes after OHCA[6,7]. Additionally, several modifications of neutrophil-associated inflammatory markers, such as neutrophil times platelet or monocyte-to-lymphocyte ratio (SII or SIRI), or neutrophil times platelet and monocyte-to-lymphocyte ratio (AISI) have been used to improve predictive accuracy[8].

Oxidized low-density lipoprotein (ox-LDL) leading to atherosclerotic cardiovascular disease has been documented for decades. Lectin-like ox-LDL receptor-1 (LOX-1) is the surface receptor for ox-LDL found in endothelial cells, macrophages, and smooth muscle cells. Ox-LDL/LOX-1 complexes trigger leukocytes, platelets, and foam cells, leading to unstable lipid plaques and a high risk of acute myocardial infarction[9]. Due to the high positive correlation between LDL-cholesterol and ox-LDL, we usually treat with statins or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors based on LDL-cholesterol levels[10]. Unlike chronic inflammation, which promotes cholesterol synthesis in the liver, cholesterol is rapidly catabolized and excreted in the bile after cardiac arrest due to the acute systemic inflammatory response. This often results in a significant reduction of total and LDL-cholesterol levels[11].

High-density lipoprotein (HDL) is composed of apolipoprotein A1 released by the liver and cholesterol released by peripheral vascular macrophages. Mature HDL directly protects LDL from oxidation by free radicals and removes oxidized lipids from LDL[12]. Low HDL-cholesterol has been widely used as a neurological predictor after cardiac arrest due to the anti-inflammatory and antioxidant properties of mature HDL[13,14]. During severe acute inflammatory response triggered by cardiac arrest, the liver releases serum amyloid A (SAA)-1 that binds to the lipid surface of HDL particles, resulting in dysfunctional HDL[15]. Besides SAA-1, neutrophil recruitment, and neutrophil extracellular trap (NET) release, including myeloperoxidase, occurs after systemic inflammatory responses[16]. Neutrophils and NET formation are involved in the pathogenesis of inflammation in cardiovascular disease[17]. NETosis, which inhibits cholesterol efflux and promotes HDL oxidation, further leads to HDL dysfunction[18–20].

Given the lack of clear and reliable results on the relationship between neutrophils, HDL-cholesterol, and mortality, this study was designed to investigate the potential mortality prediction of the neutrophil-to-HDL-cholesterol ratio (NHR) in patients experiencing cardiac arrest.

Materials and methods

Study design and population

This observational, retrospective cohort study included 247 patients with OHCA, consecutively admitted to the intensive care unit of China Medical University Hospital, Taichung, Taiwan, between January 2015 and August 2024. Patients with non-cardiac origin or metastatic cancer were excluded (STROBE flow chart shown in Fig. 1). The study design conformed to the ethical guidelines of the institutional review board of the China Medical University Hospital (CMUH104-REC3-058 and CMUH112-REC3-016).

Adult hospitalized patients with OHCA from January 2015 to August 2024 enrolled a total of 532 patients for further evaluation; 125 patients with non-cardiac origin were excluded, and 398 eligible patients were analyzed. However, several patients did not have lipid profiles. Finally, the survival group had 163 patients for a 90-day follow-up, and the mortality group had 84 patients for a 90-day follow-up. OHCA, out-of-hospital cardiac arrest; CPC, cerebral performance categories.

Variables, data, sources, and measurements

Data were retrieved from electronic hospital records and included the following covariables: age, sex, cardiopulmonary resuscitation (CPR) duration, initial shockable or non-shockable rhythm, the first 24-h vasoactive-inotropic score (VIS), previous chronic medication, data of coronary angiography and mechanical circulatory support (e.g., intra-aortic balloon pump or extracorporeal membrane oxygenation). Patients were divided into two groups, including survival and mortality. In survival group, cerebral performance categories (CPCs) of 1–4 used for neurological outcomes assessment. In mortality group, CPC of 5 was classified.

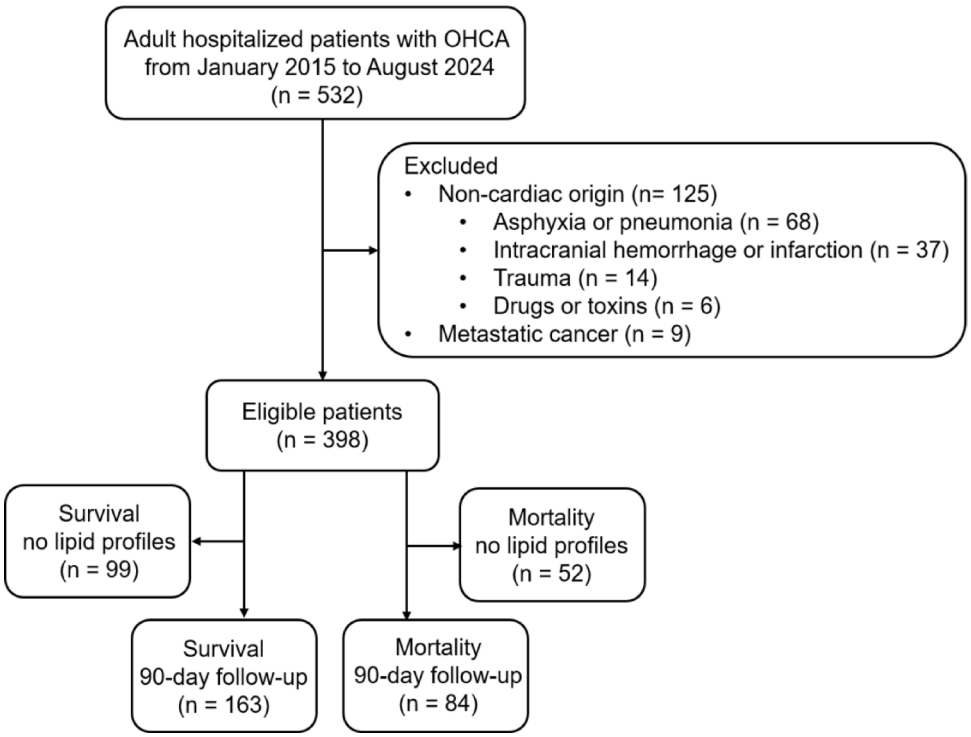

Fig. 1. STROBE flow chart of OHCA survivors.

CPR duration, initial rhythm, and CAHP score

Delays in the initiation of CPR (no-flow time) of > 5 min were excluded from the analysis to minimize statistical error. CPR duration is the duration from CPR to return of spontaneous circulation (low-flow time) independent of member type or mode. Initial shockable rhythm means that the monitor initially detects a shockable rhythm, including pulseless ventricular tachycardia or ventricular fibrillation. Other initial rhythms, including pulseless electrical activity or asystole, are referred to as non-shockable rhythms. Finally, the cardiac arrest hospital prognosis (CAHP) score was estimated according to a formula including age, setting, initial rhythm, duration from collapse to when CPR began, duration from CPR to return of spontaneous circulation, admission pH, and total epinephrine administered. A CAHP score < 150 predicts a low risk of poor neurological outcomes, but a CAHP score ≥ 150 predicts a high risk of poor neurological outcomes.

The first 24-h VIS and left ventricular ejection fraction measurement

The first 24-h VIS, including the sum of the maximal flow rate of vasoactive-inotropic agents within 24 h after OHCA, was calculated. A VIS ≤ 100 (e.g., total epinephrine dose < 3 mg during CPR) and lactate level < 5 mmol/L at 24 h after OHCA suggests cardiogenic pre-shock. In contrast, a VIS > 100 (e.g., total epinephrine dose ≥ 3 mg during CPR) and lactate level > 5 mmol/L at 24 h after OHCA suggests cardiogenic shock. Data of left ventricular ejection fraction (LVEF) at 24 h after OHCA acquired by echocardiography with the Simpson method under apical 4-chamber view was confirmed by two specialists. LVEF > 40% indicates diastolic heart failure, but LVEF ≤ 40% indicates systolic heart failure.

Laboratory tests of complete blood count, biochemistries, and inflammatory markers

Complete blood count parameters, including white blood count, red blood count, hemoglobin, and platelet count, were measured. Different counts of white blood cells, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils, were also obtained.

Markers related to heart, liver, and kidney function were measured, including N-terminal pro-B-type natriuretic peptide (NT-pro BNP), Troponin-I, aspartate aminotransferases, alanine aminotransferase, blood urea nitrogen, and creatinine. Metabolic biochemistry tests, including fasting blood glucose, lactate, albumin, and lipid profiles, were also performed. Lipid profiles included total cholesterol, triglyceride, LDL-cholesterol, and HDL-cholesterol.

Inflammatory markers measured included NHR, interleukin-6, C-reactive protein, LOX-1, and SAA-1. NHR was defined as a neutrophil (10^9/uL) to HDL-cholesterol (mmol/L) ratio.

Statistical analysis

Values were expressed as mean ± standard deviation (SD) or absolute number and percentages. The student's *t*-test was used to determine *p*-values, with *p*-value < 0.05 considered statistically significant. Further analysis of NHR data was conducted, including receiver operating characteristic (ROC) curves and Kaplan-Meier 90-day

survival curves. Multivariable Cox logistic regression analysis was performed to identify the independent risk factors of OHCA mortality. The model passed the proportional hazards hypothesis test and the variance inflation factor of these covariates all < 10 to avoid multicollinearity. The 90-day hazard ratio, 95% confidence interval (CI), and related significant values obtained from regression are reported. Statistical significance was set at 5%. Statistical analyses were performed using SPSS version 30 for Windows (Armonk, NY, USA).

Results

Baseline clinical characteristics

The baseline clinical characteristics of the study population according to 90-day all-cause mortality after OHCA are shown in Table 1. The mean age at diagnosis was 60.4 ± 14.7 years, and most patients were male (79.4%). The primary medical history included hypertension, hyperlipidemia, diabetes mellitus, chronic heart failure, coronary artery disease, and end-stage renal disease as possible risk factors for OHCA. The survival group had a higher proportion of initial shockable rhythm and lower CPR duration than the mortality group.

In terms of the etiology of cardiac OHCA, the leading cause was coronary heart disease (76.1%), including left main stem disease (9.7%) and three-vessel disease (38.1%). Percutaneous coronary intervention (60.3%) was performed for ST-segment elevation myocardial infarction (34.4%) or non-ST-segment elevation myocardial infarction with hemodynamic instability (25.9%). About 23.9% of patients received intra-aortic balloon pumps, and approximately 38.5% received extracorporeal membrane oxygenation for mechanical circulatory support.

		Survival ($n = 163$)	Mortality ($n = 84$)	p-value
Age (y), mean ± SD		59.1 ± 13.8	62.9 ± 16.1	0.01
Male sex, n (%)		131 (80.4)	65 (77.4)	0.51
BMI (kg/m^2), mean ± SD		26.3 ± 4.4	25.8 ± 5.1	0.30
Medical history, n (%)	Hypertension	77 (47.2)	35 (41.7)	0.33
	Hyperlipidemia	53 (32.5)	33 (39.3)	0.21
	Diabetes mellitus	49 (30.1)	26 (31.0)	0.91
	Chronic heart failure	40 (24.5)	19 (22.6)	0.72
	Coronary artery disease	31 (19.0)	20 (23.8)	0.24
	End-stage renal disease	26 (16.0)	9 (10.7)	0.15
	Cerebrovascular disease	8 (4.9)	5 (6.0)	0.70
	Chronic obstructive pulmonary disease	6 (3.7)	2 (2.4)	0.42
Lipid profiles (mg/dL) before admission, mean ± SD	Total cholesterol	169.5 ± 46.6	188.2 ± 63.3	0.21
	Triglyceride	143.5 ± 66.8	158.8 ± 83.4	0.39
	LDL-cholesterol	106.7 ± 35.1	122.2 ± 44.8	0.17
	HDL-cholesterol	36.3 ± 8.9	34.2 ± 7.7	0.54
Witnessed cardiac arrest, n (%)		134 (82.2)	65 (77.4)	0.46
Bystander CPR, n (%)		105 (64.4)	45 (53.6)	0.26
Initial shockable rhythm, n (%)		125 (76.7)	48 (57.1)	< 0.001
CPR duration (min), mean ± SD		20.2 ± 18.0	31.7 ± 23.9	< 0.001
CAHP score, mean ± SD		158.3 ± 38.6	216.6 ± 41.1	< 0.001
The first blood data at ED, mean ± SD	Arterial blood pH	7.10 ± 0.21	6.98 ± 0.17	< 0.001
	Lactate (mmol/L)	11.0 ± 5.8	15.0 ± 6.7	< 0.001
	White blood cells (10^3 cells/μL)	13.2 ± 4.6	12.8 ± 5.6	0.53
	Neutrophil (10^3 cells/μL)	7.6 ± 4.5	7.7 ± 4.6	0.87
CHD, n (%)	Coronary angiography	123 (75.5)	65 (77.3)	0.71
	Left main disease	15 (9.2)	9 (10.7)	0.31
	Triple vessel disease	61 (37.4)	33 (39.3)	0.81
AMI, n (%)	Percutaneous coronary intervention	97 (59.5)	52 (61.9)	0.49
	ST-elevation myocardial infarction	56 (34.3)	29 (34.5)	0.87
Intra-aortic balloon pump, n (%)		35 (21.5)	24 (28.6)	0.10
Extracorporeal membrane oxygenation, n (%)		51 (31.3)	44 (52.4)	< 0.001
Targeted temperature management, n (%)		115 (70.4)	55 (65.4)	0.13
The first 24-hour VIS, mean ± SD		108.5 ± 114.6	246.8 ± 194.7	< 0.001
LVEF at 24 h after OHCA (%), mean ± SD		41.9 ± 14.7	31.6 ± 14.4	< 0.001

Table 1. Baseline clinical characteristics of the study population according to 90-day all-cause mortality after OHCA. *AMI* acute myocardial infarction, *BMI* body mass index, *CAHP* cardiac arrest hospital prognosis, *CHD* coronary heart disease, *CPR* cardiopulmonary resuscitation, *ED* emergency department, *LVEF* left ventricular ejection fraction, *VIS* vasoactive-inotropic score.

The survival group had lower CAHP score, first 24-h VIS, and higher LVEF at 24 h after OHCA compared to the mortality group.

Follow-up of laboratory tests on the day of admission

The results of laboratory tests at 24 h after OHCA are shown in Table 2. A complete blood count was done on the day of admission. On the first day after an OHCA, there was an increase in white blood cells, mainly neutrophils. Hemoglobin and platelet count typically decrease due to inflammation-related consumption. The survival group had lower levels of indices such as NLR, SII, SIRI, or AISI compared to the mortality group ($p < 0.001$, shown in Table 2).

In biochemical indices, markers related to heart, liver, and kidney function were significantly higher due to organ damage after OHCA. In the lipid profile analysis, total cholesterol, LDL-cholesterol, and HDL-cholesterol were higher in the survival group than in the mortality group, except for triglycerides and remnant cholesterol. Fasting blood glucose level and the lactate-to-albumin ratio were elevated after OHCA, especially in the mortality group ($p < 0.001$).

Combined with the complete blood count and biochemical indicators, we used NHR as a new inflammatory indicator. After a series of investigations, LOX-1, SAA-1, and C-reactive protein increased after OHCA, but there was no significant difference between the two groups. NHR and interleukin-6 were significantly elevated after OHCA, especially in the mortality group.

Sub-analysis of cholesterol and NHR according to CPC levels

Total cholesterol, LDL-cholesterol, and HDL-cholesterol decreased gradually according to increasing CPC levels in the neurological outcome sub-analysis. Total cholesterol was 154.7 ± 50.9 mg/dL in the survival (CPC 1–4) group and 115.1 ± 36.4 mg/dL in the mortality (CPC 5) group. LDL-cholesterol was 96.3 ± 45.5 mg/dL in the survival group and 65.8 ± 26.8 mg/dL in the mortality group. HDL-cholesterol was 35.7 ± 10.3 mg/dL in the survival group and 26.4 ± 11.2 mg/dL in the mortality group ($p < 0.001$, Table 2; Fig. 2A). There was no significant

		Survival ($n = 163$)	Mortality ($n = 84$)	p-value
Complete blood count				
White blood cells (10^3 cells/μL), mean ± SD		13.9 ± 4.6	14.5 ± 4.8	0.39
Neutrophil (10^3 cells/μL), mean ± SD		11.8 ± 4.4	13.1 ± 4.7	0.03
Hemoglobin (g/dL), mean ± SD		11.9 ± 2.5	10.8 ± 2.6	< 0.001
Platelet count (10^3 cells/μL), mean ± SD		174.2 ± 74.8	135.3 ± 89.4	< 0.001
Neutrophil-to-lymphocyte ratio (NLR)		7.3 ± 16.6	16.7 ± 125.7	< 0.001
Systemic immune-inflammation index (SII)		1266.9 ± 3276.1	2254.7 ± 14472.7	< 0.001
Systemic inflammation response index (SIRI)		2.8 ± 6.6	7.4 ± 26.9	< 0.001
Aggregate index of systemic inflammation (AISI)		495.9 ± 1035.0	1003.7 ± 5936.9	< 0.001
Biochemistries				
NT-pro BNP (ng/mL), mean ± SD		5.5 ± 8.3	9.5 ± 9.2	0.05
Troponin-I (ng/mL), mean ± SD		42.3 ± 69.1	60.7 ± 81.7	0.03
Aspartate aminotransferase (U/L), mean ± SD		406.0 ± 728.7	1248.4 ± 2828.2	< 0.001
Alanine aminotransferase (U/L), mean ± SD		190.4 ± 293.5	479.1 ± 1241.5	0.001
Blood urea nitrogen (mg/dL), mean ± SD		27.6 ± 17.7	36.2 ± 21.7	< 0.001
Creatinine (mg/dL), mean ± SD		2.1 ± 2.0	2.6 ± 1.8	0.03
Fasting blood glucose (mg/dL), mean ± SD		291.6 ± 119.4	346.9 ± 206.1	0.003
Lactate (mmol/L), mean ± SD		3.1 ± 2.0	9.6 ± 7.4	< 0.001
Albumin (g/dL), mean ± SD		3.3 ± 0.6	2.8 ± 0.7	< 0.001
Lipid profiles (mg/dL) after admission, mean ± SD	Total cholesterol	154.7 ± 50.9	115.1 ± 36.4	< 0.001
	Triglyceride	131.0 ± 82.2	110.3 ± 92.4	0.62
	LDL-cholesterol	96.3 ± 45.5	65.8 ± 26.8	< 0.001
	HDL-cholesterol	35.7 ± 10.3	26.4 ± 11.2	< 0.001
Inflammatory markers				
NHR (10^9/mmol), mean ± SD		12.8 ± 6.4	19.2 ± 10.3	< 0.001
Interleukin-6 (pg/mL), mean ± SD		1242.3 ± 2205.6	2153.8 ± 3005.0	0.007
LOX-1 (pg/mL), mean ± SD		102.3 ± 88.3	109.6 ± 94.4	0.78
SAA-1 (μg/mL), mean ± SD		210.7 ± 119.9	208.8 ± 127.4	0.96
C-reactive protein (mg/dL), mean ± SD		2.3 ± 3.0	3.1 ± 3.3	0.08

Table 2. Complete blood count, biochemistries, and inflammatory markers at 24 h after OHCA of the study population according to 90-day all-acuse mortality. *HDL* high-density lipoprotein, *NHR* neutrophil to HDL-cholesterol ratio, *LDL* low-density lipoprotein, *LOX-1* lectin-like ox-LDL receptor-1, *NT-pro BNP* N-terminal pro-B-type natriuretic peptide, *SAA-1* serum amyloid A-1.

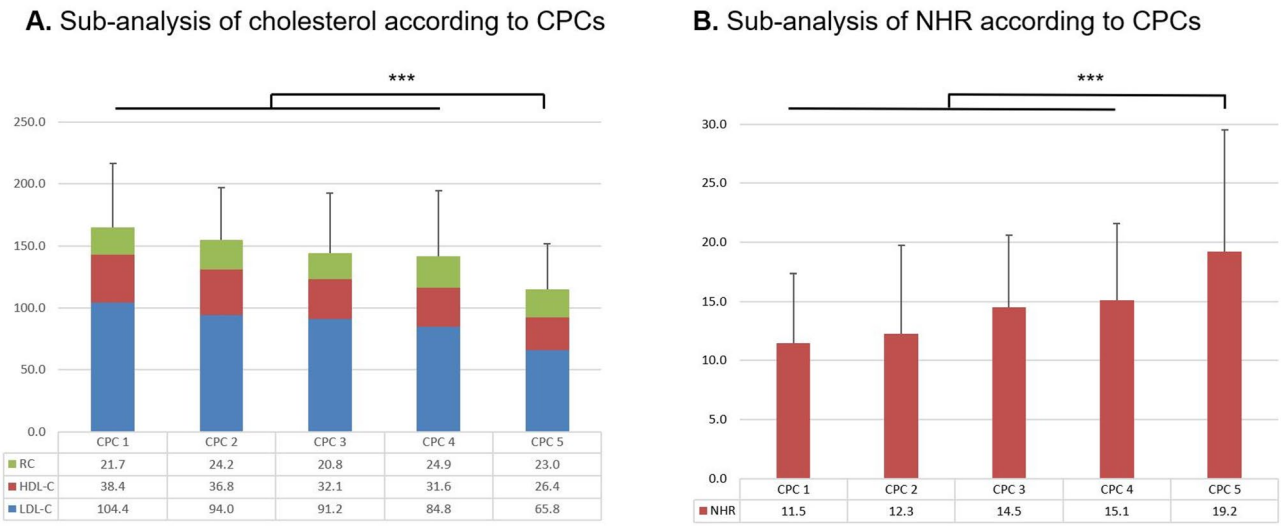

Fig. 2. Sub-analysis of cholesterol and NHR according to CPC. (**A**) Sub-analysis of cholesterol according to CPC. CPC 1–4 vs. CPC 5 data of cholesterol as below: RC: 22.7 ± 13.2 vs. 23.0 ± 13.4 mg/dL, $p = 0.85$; HDL-C: 35.7 ± 10.3 vs. 26.4 ± 11.2 mg/dL, $p < 0.001$; LDL-C: 96.3 ± 45.5 vs. 65.8 ± 26.8 mg/dL, $p < 0.001$. (**B**) Sub-analysis of NHR according to CPC. CPC 1–4 vs. CPC 5 data of NHR as below: 12.8 ± 6.4 vs. 19.2 ± 10.3, $p < 0.001$. *NHR* neutrophil to high-density lipoprotein-cholesterol ratio, *CPC* cerebral performance categories, *RC* remnant-cholesterol, *HDL-C* high-density lipoprotein-cholesterol, *LDL-C* low-density lipoprotein-cholesterol.

influence in triglycerides or remnant cholesterol according to CPC levels. In the neurological outcome sub-analysis, NHR increased gradually with the increase of CPC level. NHR was lower in the survival (CPC 1–4 group than in the mortality (CPC 5) group (12.8 ± 6.4 vs. 19.2 ± 10.3, $p < 0.001$, Table 2; Fig. 2B).

ROC curves of inflammatory markers and Kaplan–Meier survival curves of NHR

The area under the ROC curve for NHR was 0.74 (95% CI: 0.66–0.81, $p < 0.001$), that of interleukin-6 was 0.69 (95% CI: 0.62–0.76, $p < 0.001$) and that of C-reactive protein was 0.58 (95% CI: 0.51–0.63, $p = 0.18$). NHR and interleukin-6 have acceptable similar areas under the ROC curve for prediction better than C-reactive protein. NHR = 16.1 with maximal Youden index, sensitivity was 0.68, and specificity was 0.68. Interleukin-6 = 890.72 pg/mL with maximal Youden index, sensitivity was 0.63 and specificity was 0.62 (Fig. 3A). Further analysis of NHR was conducted using Kaplan-Meier survival curves. After 90-day follow-up, the survival rate was 0.79 for NHR ≤ 16.1 but only 0.49 for NHR > 16.1 (log-rank $p < 0.001$, Fig. 3B).

Ninety-day mortality rate-adjusted covariables using Cox regression model

Figure 4 shows several covariables analyzed as risk factors for 90-day mortality. Risk factors in descending order, were a lactate > 5 mmol/L (hazard ratio: 5.41, 95% CI: 3.71–7.89), the first 24-h VIS > 100 (hazard ratio: 2.88, 95% CI: 1.91–4.34), NHR > 16.1 (hazard ratio: 2.54, 95% CI: 1.68–3.82), CPR duration ≥ 15 min (hazard ratio: 1.99, 95% CI: 1.31–3.02), and age ≥ 75 years (hazard ratio: 1.51, 95% CI: 1.06–2.15). There was no significant influence of sex or coronary heart disease. The initial shockable rhythm was the only protective factor (hazard ratio: 0.58, 95% CI: 0.42–0.81) under a short no-flow time < 5 min.

Several covariables analyzed as risk factors for 90-day mortality. Covariables include Age ≥ 75 years (hazard ratio: 1.51, 95% CI: 1.06–2.15), male sex (hazard ratio: 0.90, 95% CI: 0.61–1.33), coronary heart disease (hazard ratio: 1.11, 95% CI: 0.76–1.60), CPR duration > 15 min (hazard ratio: 1.99, 95% CI: 1.31–3.02), initial shockable rhythm (hazard ratio: 0.58, 95% CI: 0.42–0.81), the first 24-hour VIS > 100 (hazard ratio: 2.88, 95% CI: 1.91–4.34), lactate > 5 mmol/L (hazard ratio: 5.41, 95% CI: 3.71–7.89), and NHR > 16.1 (hazard ratio: 2.54, 95% CI: 1.68–3.82). CPR, cardiopulmonary resuscitation; VIS, vasoactive-inotropic score; NHR, neutrophil to high-density lipoprotein cholesterol ratio; OHCA, out-of-hospital cardiac arrest.

Discussion

This study evaluates the potential of inflammatory markers to predict all-cause mortality after OHCA. NHR has similar efficacy to interleukin-6, a major pro-inflammatory cytokine. An NHR > 16.1 at 24 h after OHCA would predict a 90-day all-cause mortality and suggest that the patient will need more intensive care.

The ischemia-reperfusion injuries after OHCA significantly affect myocardial ischemia and cerebral hypoxia, including its precipitating factors, known as post-cardiac arrest syndrome[21]. Ischemia-reperfusion injuries trigger a series of severe systemic inflammatory responses. Monocyte-derived macrophages release inflammatory cytokines, including tissue necrosis factor-α and interleukin-1β. Interleukin-1β further triggers interleukin-6, which generates trans-signaling in addition to classic signaling[22]. Several studies have used interleukin-6 as a major pro-inflammatory marker and predictor of neurologic prognosis after OHCA at admission[3–5]. Targeted temperature management has become the standard of care to prevent fever and reduce brain metabolism and

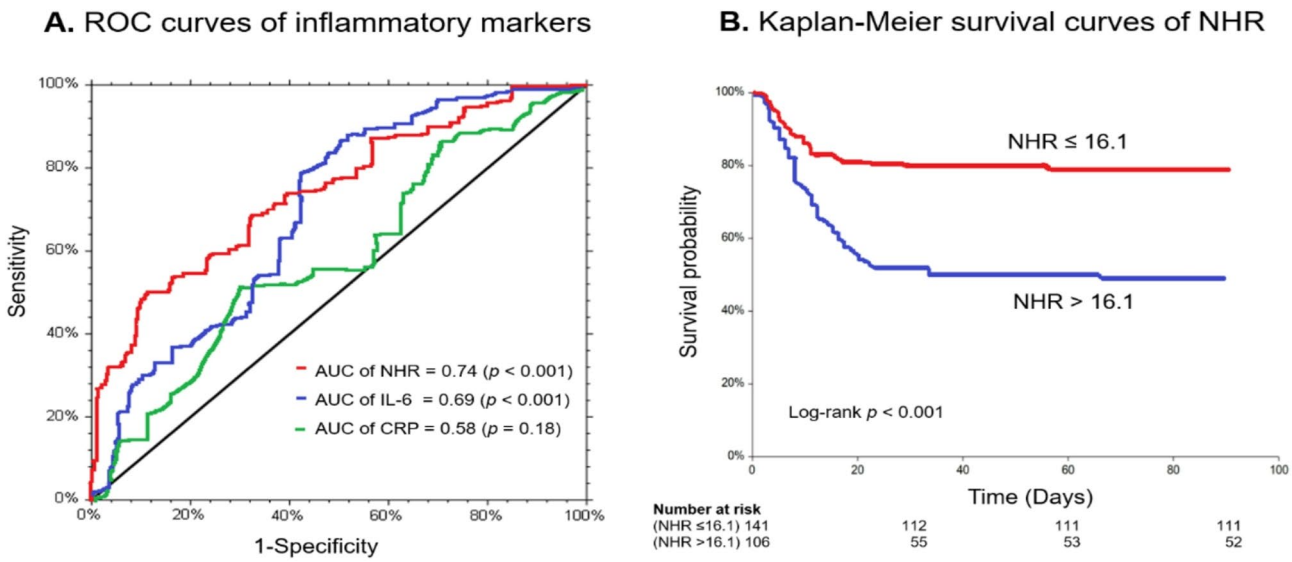

Fig. 3. ROC curves of inflammatory markers and Kaplan–Meier survival curves of NHR. (**A**) Area under the ROC curve of NHR = 0.74 (95% CI: 0.66–0.81, $p < 0.001$), similar as that of IL-6 = 0.69 (95% CI: 0.62–0.76, $p < 0.001$). The AUC of NHR or IL-6 all were better than that for CRP = 0.58 (95% CI: 0.51–0.63, $p = 0.18$). NHR = 16.1 with maximal Youden index, sensitivity = 0.68, and specificity = 0.68. (**B**) The 90-day survival rate for NHR ≤ 16.1 compared with that for NHR > 16.1 was 0.79 and 0.49, respectively, according to Kaplan-Meier curves analysis. *ROC* receiver operating characteristic curve, *NHR* neutrophil to high-density lipoprotein cholesterol ratio, *CI* confidence interval, *IL-6* interleukin-6, *AUC* the area under the ROC curve, *CRP* C-reactive protein.

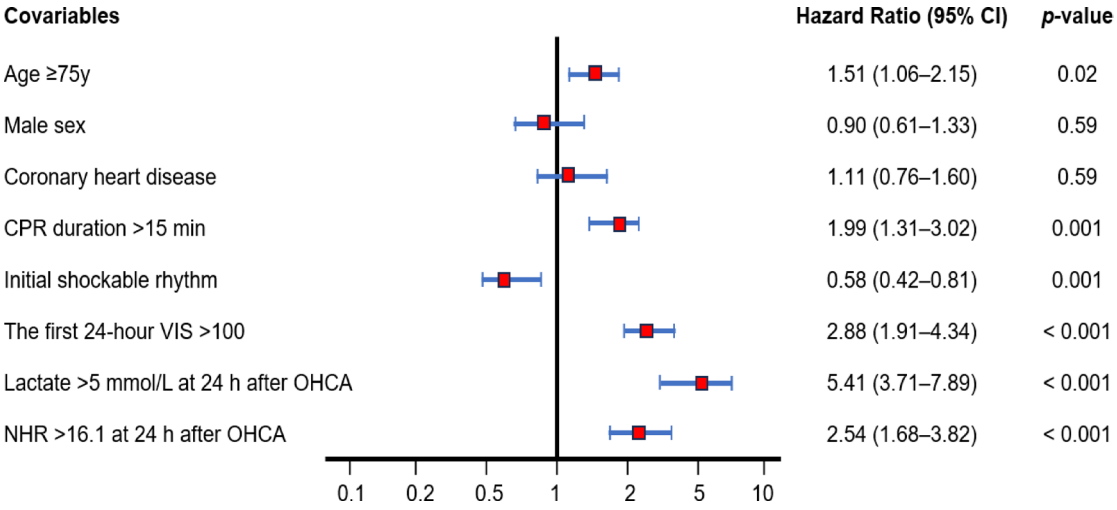

Fig. 4. Ninety-day mortality rate-adjusted covariables of OHCA survivors using the Cox regression model.

interleukin-6-induced inflammation[23]. To reduce the need for vasoactive-inotropic agents, adjunctive treatments such as high-dose steroids or interleukin-6 receptor antagonists on admission have been tried[24,25].

Inflammation is closely related to immune response. Initially, NLR was used as a prognostic predictor in sepsis because of neutrophil bactericidal activity[26,27]. This stress triggers a systemic inflammatory response and generates large amounts of reactive oxygen radicals, thereby enhancing neutrophil-associated innate immunity. Although B or T lymphocytes are involved in the initial inflammation of adaptive immunity, apoptosis-related lymphopenia is common[28]. NLR has been documented as a predictor of outcomes after cardiac arrest with "sepsis-like" syndrome[6,29]. Neutrophils also interact extensively with platelets and monocytes frequently[30]. Neutrophils enhance platelet production and adhesion. Platelets enhance neutrophil activation, adhesion, and NET formation. Monocytes and neutrophils increase each other's recruitment, significantly amplifying the inflammatory response. We get used to using neutrophil times platelet or monocyte-to-lymphocyte ratio (SII or SIRI) to evaluate the severity of coronary heart disease or cardiovascular mortality[31,32]. Platelets interact

with circulating monocytes by directly attaching to their surface. Activated monocytes migrate to injured tissues, leading to monocyte-derived macrophage inflammatory responses. Platelet aggregation triggers tissue factor-related thrombus formation[33]. We are accustomed to using neutrophil times platelet and monocyte-to-lymphocyte ratio (AISI) to assess cardiovascular mortality after acute myocardial infarction[34]. As acute myocardial infarction is the leading cause of OHCA, we used these indices to assess the outcomes of OHCA survivors. How inflammatory markers are selected is important. As shown in Table 2, the candidates included NLR (p value: 9.10E-04), SII (p value: 4.71E-04), SIRI (p value: 5.64E-08), AISI (p value: 5.55E-05), and NHR (p value: 8.40E-13). Although all of these inflammatory indices had p-values less than 0.001, the NHR had the greatest discriminatory power.

Inflammation is also closely related to lipid metabolism. ox-LDLs have been recognized as a driver of inflammation. Chronic inflammatory conditions, such as metabolic syndrome, have been widely studied. After a high glycemic index, foods are absorbed into the intestines; glucose is converted to triglycerides by insulin and stored in visceral fat. The liver then secretes triglyceride-rich lipoproteins, which are converted to small, dense LDLs. If the patient has hypertension, hyperlipidemia, or diabetes mellitus, these small, dense LDLs can easily be modified into ox-LDLs and deposited in the blood vessel wall, resulting in atherosclerotic cardiovascular disease. If the amount of LDL-cholesterol is highly correlated with small, dense LDLs, we use statins or PCSK-9 inhibitors to lower LDL-cholesterol levels[35]. However, in extreme cases of acute inflammation, such as in patients with cardiac arrest who have achieved a return of spontaneous circulation, the large number of oxygen free radicals causes LDLs to be quickly converted to ox-LDL, further perpetuating the immuno-inflammatory response and thrombosis formation. This acute systemic inflammatory response also causes total cholesterol to be rapidly broken down and excreted into bile. We have found that the amount of LDL-cholesterol measured in patients having cardiac arrest after resuscitation is significantly lower due to the rapid oxidation of LDL involved in the inflammatory response[36]. Although low cholesterol or LDL-cholesterol levels predict poor outcomes in OHCA survivors[37,38], patients who had previously used statins showed better outcomes[39].

HDL plays an important role in predicting outcomes in patients having cardiac arrest due to its ease of crossing the blood-brain barrier[40]. Apoprotein A1 is the main HDL protein responsible for anti-inflammatory, antioxidant, and cholesterol efflux capacity[41]. However, in the acute inflammatory state following cardiac arrest, many oxidizing free radicals can render apoprotein A1 functionally inactive. During a systemic inflammatory response, liver-derived SAA is primarily found on HDL[15]. SAA completely deactivates HDL, creating what we refer to as dysfunctional HDL. This dysfunctional HDL is unable to fight the inflammatory response from macrophages or counteract the thrombotic effect of ox-LDL. In a state of massive oxidative inflammation, neutrophils not only accumulate in large numbers but also form NETs. NETosis releases neutrophil-specific myeloperoxidase, further forming ox-HDL to impair cholesterol efflux capacity[42,43]. Dysfunctional ox-HDL is highly susceptible to breakdown under these highly inflammatory and oxidizing conditions. Therefore, increased NETs or decreased apoprotein A1 had been documented in poor neurological prognosis after OHCA[14,19,20]. Although lower HDL cholesterol predicts poor outcomes, this phenomenon is not related to triglycerides or remnant cholesterol.

Figure 5; Table 3 show the differences in immune and metabolic responses related to chronic and acute inflammation. In the status of chronic persistent inflammation (e.g., metabolic syndrome), immune markers may be mildly increased except lymphocytes. Metabolic markers may be mildly increased except HDL-cholesterol[44]. In the status of acute systemic inflammation (e.g., cardiac arrest), neutrophils and monocytes increased, but platelets and lymphocytes decreased[6,7,29]. Glucose and triglycerides also increased, all of cholesterols decreased[13,14,37,38]. In addition to a reversed triglyceride-glucose index, ox-LDL and platelets are rapidly consumed due to macrophage-derived acute inflammatory response and reactive oxygen species. NHR, which combines increased neutrophils and decreased HDL-cholesterol has been identified as a novel

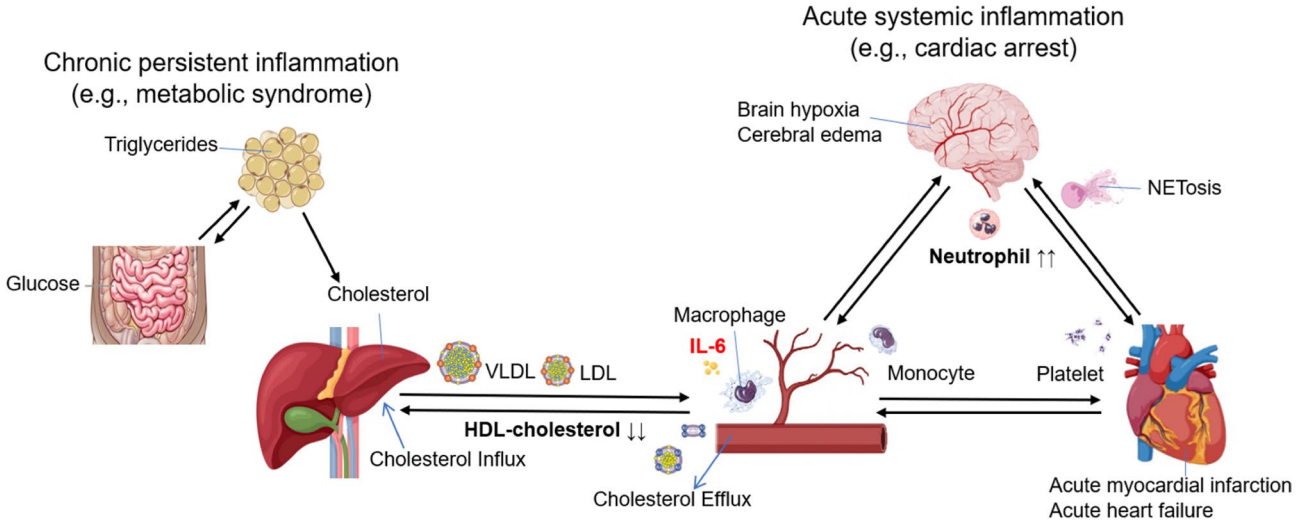

Fig. 5. The difference between chronic and acute inflammation-related immune and metabolic markers.

Immune markers according to complete blood count						
	White blood count	Neutrophils	Lymphocyte	Monocyte	Hemoglobin	Platelet
Chronic persistent inflammation	–/↑	–/↑	–/↓	–/↑	–/↓	–/↑
Acute systemic inflammation	↑	↑	↓	–/↑	↓	↓
Metabolic markers according to lipid profiles and glucose						
	Total cholesterol	LDL-cholesterol	HDL-cholesterol	RC	Triglyceride	Glucose
Chronic persistent inflammation	–/↑	–/↑	–/↓	–/↑	↑	–/↑
Acute systemic inflammation	↓	↓	↓	–/↑	–/↑	↑

Table 3. Differences in markers of immune and metabolic responses between chronic and acute inflammation. *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *RC* Remnant cholesterol.

inflammatory marker of cardiovascular events. NHR had been used to predict mortality outcomes of acute ischemic stroke[45,46] and acute myocardial infarction[47–49]. Based on blood data from the first blood draw in the emergency department to 24 h after OHCA blood was drawn in the cardiac intensive care unit (Tables 1 and 2). In the mortality group, white blood counts increased obviously from 12.8 to 14.5 (10^3 cells/μL) and neutrophils increased obviously from 7.7 to 13.1 (10^3 cells/μL). In the survival group, white blood counts increased mildly from 13.2 to 13.9 (103 cells/μL) and neutrophils increased mildly from 7.6 to 11.8 (10^3 cells/μL). Based on lipid profiles before and after admission (Tables 1 and 2). Total cholesterol decreased obviously from 188.2 to 115.1 (mg/dL) and HDL cholesterol decreased obviously from 34.2 to 26.4 (mg/dL) in the mortality group. In the survivor group, total cholesterol decreased mildly from 169.5 to 154.7 (mg/dL) and HDL cholesterol decreased mildly from 36.3 to 35.7 (mg/dL). Over time, neutrophil values are maximized 24 h after acute inflammation. The NHR measured 24 h after OHCA provides the novel and better predictive accuracy.

Reducing NHR through adjunctive anti-inflammatory strategies before admission may be a promising therapeutic goal. It would be valuable to investigate whether strategies such as statin therapy, anti-inflammatory agents (e.g., IL-6 receptor antagonists), or lipid-modulating interventions could improve prognosis. Prehospital administration of statins rather than fibrates improves survival in cardiac arrest patients[39]. Although either statins or fibrates increase HDL cholesterol levels, this opposite result is due to the fact that statins decrease homocysteine, whereas fibrates increase homocysteine concentrations[50]. Omega-3 fatty acids also have a statin-like effect, which means that HDL quality is more important than quantity in preventing sudden cardiac arrest[51]. Prehospital treatment of comatose OHCA patients with either high-dose methylprednisolone or IL-6 receptor antagonists inhibits the IL-6-induced acute systemic inflammatory response, thereby improving survival[24,25]. Interestingly, IL-6 but not neutrophil levels were significantly reduced with high-dose methylprednisolone, whereas neutrophil but not IL-6 levels were significantly reduced with IL-6 receptor antagonists[24,25].

This study has some limitations that should be noted. First, the patients with a lack of lipid profiles were excluded. Second, the study was conducted in a single center and had a limited sample size. Third, acute kidney injury or sepsis in about one-quarter of hospitalized patients also interferes with the accuracy of the 90-day mortality rate. Finally, we need plan on a prospective study design or randomized control trial to validate NHR's role in clinical decision-making, especially in cardiac OHCA including acute myocardial infarction or acute heart failure.

Conclusions

NHR is a potential inflammatory marker to predict all-cause mortality after OHCA. When NHR is > 16.1 at 24 h after OHCA, intensive care intervention should be considered to improve clinical outcomes. Reducing NHR through adjunctive anti-inflammatory strategies before admission may be a promising therapeutic target for OHCA survivors.

Data availability

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding authors.

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Author contributions
Conceptualization, D.C., Y.L.; methodology, D.C.; data curation, D.C., Y.L.; formal analysis, D.C.; investiga-tion, D.C.; writing—original draft, D.C.; writing—review & editing, G.W., K.C.; supervision, G.W., K.C. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study was approved by the institutional review board of the China Medical University Hospital (CMUH104-REC3-058 and CMUH112-REC3-016) for data collection and analysis.

Informed consent
Verbal and written informed consent have been obtained from all participant proxies.

Additional information
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