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Association between the neutrophil-to-lymphocyte ratio and neurological outcomes in patients undergoing targeted temperature management after cardiac arrest

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ABSTRACT

Purpose: This study aimed to elucidate the association between the neutrophil-to-lymphocyte ratio (NLR) and neurological outcomes in out-of-hospital cardiac arrest (OHCA) patients treated with targeted temperature management (TTM).

Materials and methods: A retrospective study was performed on patients treated with TTM after OHCA. Patients were divided into two groups according to their calculated NLRs (NLR < 6 and NLR ≥ 6). The primary outcome was poor neurological outcome at 6 months as defined by a Cerebral Performance Category between 3 and 5.

Results: A total of 216 were included and 131 subjects had poor neurological outcomes at 6 months. In the univariate model, NLRs ≥ 6 at 48 and 72 h after ROSC were associated with poor neurological outcomes (OR: 3.716, 95% CI: 1.243–11.114; OR: 7.429, 95% CI: 3.693–14.945, respectively). In the multivariate logistic regression analysis, an NLR ≥ 6 at 72 h was associated with poor neurological outcomes after adjusting for history of HTN, shockable rhythm, cardiac cause of arrest and time from collapse to ROSC and highest WBC, hs-CRP, lactate and pneumonia (OR = 3.299, 95% CI = 1.080–10.081).

Conclusions: An NLR ≥ 6 at 72 h after the ROSC is associated with poor neurological outcomes at 6 months after CA.

1. Introduction

Despite recent advances in critical care and targeted temperature management (TTM), out-of-hospital cardiac arrest (OHCA) is associated with subsequently high mortality and morbidity rates [1]. The major pathophysiological mechanism underlying these high rates following CA is ischemic-reperfusion injury. Post-cardiac arrest syndrome (PCAS), a systemic inflammatory syndrome following CA, occurs during the reperfusion period after the return of spontaneous circulation (ROSC). It shares several pathophysiological mechanisms with sepsis, and contributes to hypoxic ischemic brain injury, which is a leading cause of poor prognosis in post-CA patients [2]. Systemic inflammatory markers, such as C-reactive protein (CRP), procalcitonin and cytokines, have been studied for risk stratifications to poor outcomes in PCAS patients [3-5]. However, the relevance of these inflammatory markers to the outcome has not yet been fully investigated.

The neutrophil-to-lymphocyte ratio (NLR), which reflects the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses, is inexpensive, easy and rapidly determined by calculating white blood cell (WBC) differentials. The NLR has been used to predict adverse outcomes in many diseases, especially cardiovascular disease, stroke and malignancies [6-9], and has a better predictive value than total WBC or neutrophil counts in cardiovascular disease [10]. In a recent study, the NLR at admission was associated with mortality in OHCA patients [11]. However, the association of the NLR on the neurological outcomes of PCAS patients treated with TTM is still unknown.

This study tested the hypothesis that NLR is associated with the neurological outcomes of OHCA patients treated with TTM. We also investigated the time profiles of the NLR and its association with neurological outcomes.

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2. Method

2.1. Patients and setting

We performed a retrospective observational study based on a prospectively designed registry of OHCA patients in a single tertiary educational hospital in Seoul, Korea between January 2009 and December 2016. Data were collected according to the Utstein Style Criteria for reporting OHCA as follows [12]: age; sex; history of hypertension (HTN), diabetes mellitus and coronary artery disease; witnessed arrest; bystander CPR; first monitored rhythm; cause of arrest; and time from collapse to the ROSC. The inclusion criteria were patients older than 18 years of age who were resuscitated from OHCA and treated with TTM. Patients were excluded if their CA etiology was due to trauma; if hemorrhaging, such as intracranial bleeding and gastrointestinal bleeding, was detected; or if they expired within 72 h after the ROSC. The study outcome was a poor neurological outcome at 6 months post-CA, defined as a Cerebral Performance Category (CPC) between 3 and 5, and a telephone follow-up was used to make this assessment.

2.2. Post-cardiac arrest care

All patients who were mentality comatose after being resuscitated from CA were treated with TTM according to a previous post-CA care protocol published by our hospital [13]. The induction and maintenance of temperature were performed using an endovascular cooling device (Thermoguard, ZOLL Medical Corporation, Chelmsford, MA, USA) or ArticSun (Bard Medical, Louisville, CO, USA). A target temperature of 33 °C was induced and maintained for at least 24 h. After the maintenance phase, rewarming to 37 °C was performed at a rate of 0.25 °C/h. All patients were administered a sedative and neuromuscular blocking agents (NMBAs) before induction to control shivering, and these agents were infused continuously throughout the entire TTM phase.

2.3. Measurements

Venous blood samples were routinely collected at admission and at 24 h, 48 h and 72 h after the ROSC. Total WBC counts and neutrophil, lymphocyte, monocyte, eosinophil and basophil differentials were determined using an automated blood cell counter (Sysmex XE-2100, Sysmex Corp., Kobe, Japan). The NLR was calculated as the total neutrophil count divided by the total lymphocyte count in the same blood sample. Serum chemistry and/or arterial blood gas analyses were also performed simultaneously with the complete blood count (CBC). Laboratory parameters, such as high-sensitivity CRP (hs-CRP), and lactate, were also included. Early-onset pneumonia was defined by new infiltration on chest x-ray (persist for at least 48 h) associated with a positive quantitative culture of distal pulmonary secretion samples, obtained by endotracheal aspirates. In the absence of a bacteriological sample, he diagnosis was retained when the previous signs of were present and associated with purulent endotracheal aspirates and hypoxemia ($PaO_2/FiO_2 < 240$) not explained by pulmonary edema, pulmonary embolism, or atelectasis [14].

2.4. Statistical methods

Categorical variables are presented as counts and percentages, and continuous data are presented as the mean ± standard deviation. To compare the patients' characteristics and outcomes, chi-square tests or Fisher's exact tests were performed for categorical variables, and *t*-tests were performed for continuous variable. To evaluate the association of NLRs with neurological outcomes at 6 months after CA, the NLRs were divided into two categories: NLR < 6 and NLR ≥ 6. Recently, the NLR was studied using a cut-off value of 6 [11]. As this value agreed with mortality data in OHCA patients and other previous studies [15, 16], we chose to use the same cut-off value and created a common variable with two categories.

To evaluate the association between the NLR and poor neurological outcomes at 6 months after CA, univariate logistical regression and multivariate logistical regression analyses were performed. Demographic variables with p values < 0.2 in the univariate analysis were subjected to the multivariate logistical regression model. Demographic factors with p values < 0.05 in the multivariate logistical regression model were selected as covariates. To adjust for other inflammatory markers and infection, the WBC, hs-CRP, lactate and pneumonia were also selected as covariates. The highest levels of WBC, hs-CRP and lactate within 72 h after the ROSC were selected.

We estimated receiver operating characteristic (ROC) curves and compared the areas under the ROC curves (C-statistic with 95% CI) in the corresponding logistical models. We also compared the areas under the curve (AUCs) using the Delong test to assess equality.

Statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL, USA) and MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium), and p values ≤ 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

Of the 262 patients observed during the study period, 46 were excluded because they died within 72 h of the ROSC. Thus, a total 216 patients were finally included in this study. The mean age of the subjects was 53.0 (SD 16.4) years, and 157 (72.6%) patients were male. Ventricular fibrillation was the initial rhythm for 93 (43%) subjects, and 131 (60.6%) patients experienced poor neurological outcomes at 6 months after ROSC. Table 1 shows the demographic and laboratory characteristics of the patients according to their NLRs at 72 h after the ROSC. Subjects in the NLR < 6 group were younger, had a higher proportion of initial shockable rhythm and cardiac cause of arrest and had a shorter time from collapse to the ROSC than those of the NLR ≥ 6 group. Table 2 shows the demographic and laboratory characteristics of patients according to neurological outcome at 6 months after the ROSC. The proportion of NLR ≥ 6 subjects between the good and poor outcome groups was not statistically significant at admission or at 24 h after ROSC. However, the proportion of NLR ≥ 6 subjects was higher in the poor outcome group at 48 h and 72 h after ROSC [Fig. 1].

Table 1
Demographic findings according to the neutrophil-to-lymphocyte ratio at 72 h.

	NLR < 6 N = 54	NLR ≥ 6 N = 162	p
Age (year)	49.0 ± 13.7	54.3 ± 17.0	0.022
Sex, male	39 (72.2)	118 (0.73)	0.930
Past history			
HTN	11 (20.3)	51 (31.5)	0.118
DM	8 (14.8)	36 (22.2)	0.242
Witness	42 (77.8)	113 (70.0)	0.257
Bystander CPR	31 (57.4)	86 (53.1)	0.581
Shockable	35 (64.8)	58 (35.8)	<0.001
Cardiac cause of arrest	47 (87.0)	105 (64.8)	0.001
Time from collapse to ROSC, min	26.0 ± 23.5	33.5 ± 17.3	0.014
Poor neurological outcome at 6 months after ROSC	14 (25.9)	117 (72.2)	<0.001
WBC, G/l	13,826 ± 5845	16,306 ± 8396	0.045
hs-CRP, mg/dl	6.85 ± 6.70	12.77 ± 8.52	<0.001
Lactate, mmol/l	6.59 ± 6.19	7.33 ± 6.32	0.458
Pneumonia	25 (46.3)	112 (69.1)	0.003
Bacteremia	4 (7.4)	16 (9.9)	0.588

Abbreviation; NLR = neutrophil to lymphocyte ratio; HTN = hypertension; DM = diabetes mellitus; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; WBC = white blood cell; hs-CRP = high sensitivity C-reactive protein.