Changes in neutrophil-to-lymphocyte ratios in postcardiac arrest patients treated with targeted temperature management

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ABSTRACT

Objective: The prognostic value of changes in neutrophil-to-lymphocyte ratios (NLR) in cardiac arrest survivors receiving targeted temperature management (TTM) is unknown. The current study investigated NLR in postcardiac arrest (PCA) patients undergoing TTM.

Methods: This retrospective single-center study included 95 patients (59 males, age: 55.0±17.0 years) with in-hospital and out-of-hospital cardiac arrests who underwent TTM for PCA syndrome within 6 h of cardiac arrest. Hypothermia was maintained for 24 h at a target temperature of 33°C. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

Results: Of the 95 patients, 59 (62%) died during hospital stay. Fewer vasopressors were used in patients who survived. Out-of-hospital cardiac arrest was more frequent in decedents (p=0.005). Length of stay in the hospital and intensive care unit were significantly longer in patients who survived (p=0.0001 and p=0.001, respectively). NLR on admission and during rewarming did not differ between survivors and decedents. NLR during cooling was significantly higher in decedents (p=0.014). Delta NLR cut-off of 13.5 best separated survivors and decedents (AUC=0.68, 95% CI: 0.57–0.79, p=0.003 with a sensitivity and specificity of 64% and 67%, respectively). In multivariate logistic regression analysis, larger increase in NLR was significantly associated with decreased survival (OR: 0.96, 95% CI: 0.94–0.99, p=0.008).

Conclusion: Changes in NLR are an independent determinant of survival in patients with return of spontaneous circulation PCA treated with TTM. An NLR change can be used to predict survival in these patients. (Anatol J Cardiol 2017; 18: 215-22)

Keywords: neutrophil-to-lymphocyte ratio, targeted temperature management, predictor of mortality

Introduction

The postcardiac arrest (PCA) syndrome reflects a complex pathophysiology, which involves acute ischemia and then reperfusion. These events activate apoptosis, cause mitochondrial dysfunction, increase neuroexcitotoxicity and free radical production, activate inflammatory and coagulation pathways, increase vascular permeability, and disrupt the blood–brain barrier (1). These patients are at risk for severe neurological injury and multiorgan failure. Targeted temperature management (TTM) is the standard of care in PCA survivors; hypothermia reduces the activation of these pathways and improves neurological outcomes (2). Hypothermia suppresses inflammation in patients undergoing TTM, e.g., decreases plasma cytokine levels after traumatic brain injury (3). In neonates with hypoxic ischemic injury, TTM is associated with altered circulating leukocytes and systemic immunosuppression (4). The neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, has been shown to predict mortality in acute coronary syndromes and sepsis. However, the prognostic value of NLR and changes in NLR (delta NLR) in cardiac arrest survivors receiving TTM is unknown. Dynamic changes in NLR could reflect changes in inflammation and/or responses to treatment interventions. Correlation of these changes with important clinical outcomes could provide a simple predictor of relevant outcomes. In the current study, we investigated NLR and delta NLR in PCA patients undergoing TTM.

Methods

Patient characteristics

The medical records department at the University Medical Center in Lubbock, TX, USA identified 137 patients who were treated with TTM between November 1, 2012 and May 31, 2015 to establish the case log for this retrospective single-center study. Forty-two patients were excluded due to inappropriate timing of blood count draws to calculate NLR (see below for details). The final study population included 95 patients who underwent TTM for PCA syndrome with return of spontaneous circulation. All
patients were admitted to intensive care units under the care of physicians in the pulmonary and critical care division and cardiologists. All patients were aged >18 years. Patients with intracranial hemorrhage, major surgery within the past 14 days, systemic infection or sepsis, ongoing severe shock with likely recurrent arrest and resuscitative efforts, trauma, and pregnant patients were excluded from the study. Patients who had shockable rhythm, defined as ventricular fibrillation or hemodynamically unstable ventricular tachycardia, were cardioverted or defibrillated. Patients were started on vasopressor infusions (usual order of use: norepinephrine, epinephrine, dopamine, and vasopressin), which were titrated to keep the mean arterial pressure >60 mm Hg. Refractory shock was defined as persistent hypotension (mean arterial pressure <60 mm Hg) despite aggressive fluid resuscitation and the use of two different vasopressors. Renal impairment was defined as the increase in serum creatinine 25% above the baseline. Renal replacement was performed either with hemodialysis or with continuous renal replacement therapy managed by nephrologists. None of the patients received diuretics during TTM. The institutional Review Board approved this research protocol and waived the requirement for written informed consent (IRB approval number 00000096, and date June 6, 2016).

Targeted temperature management protocol

All patients underwent TTM at the University Medical Center, a tertiary care hospital in Lubbock, TX, USA within 6 h of cardiac arrest using a previously published protocol (5). Hypothermia was achieved and maintained for 24 h at a target temperature of 33°C. Rewarming was performed with a 0.25°C increase per hour. Bladder and/or transesophageal temperatures were recorded every 15 min until the goal temperature was achieved and hourly thereafter during TTM and rewarming. TTM was performed with the surface cooling device Arctic Sun Temperature Management System (Medivance, Louisville, CO). All the patients received propofol and fentanyl infusions for sedation and pain control. Neuromuscular blockade was obtained with either rocuronium or vecuronium at the physician’s discretion.

Timing of leukocyte counts and neutrophil-to-lymphocyte ratios

Total and differential leukocyte counts were recorded from samples of peripheral complete blood counts (CBC). NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The neutrophil-to-lymphocyte ratio 1 (NLR1) was calculated from CBC drawn prior to the initiation of cooling. The neutrophil-to-lymphocyte ratio 2 (NLR2) was calculated from samples of CBC obtained at least 12 h post initiation of hypothermia. The neutrophil-to-lymphocyte ratio 3 (NLR3) was calculated from samples of CBC obtained at least 12 h after the rewarming had been started. Changes in NLR (Delta NLR) were calculated with samples from the cooling and rewarming stages of TTM as follows: NLR during hypothermia minus the admission NLR (NLR2–NLR1), NLR during hypothermia minus NLR during rewarming (NLR2–NLR3), and NLR during admission minus NLR during rewarming (NLR1–NLR3). Study investigators (TR, PA, and JN) collected variables without knowledge of the outcomes of the patients.

Statistical analysis

Continuous variables are reported as the mean±standard deviation. Categorical data are reported as percentages and compared using the chi square or Fischer’s exact test as appropriate. The Kolmogorov–Smirnov test was used to assess normal distributions of continuous variables. Student t-tests were used for normally distributed data; Mann–Whitney U tests were used for non-normal distributions. Pre- and post-hypothermia data were compared with paired t-test or Wilcoxon t-test for paired samples. All significant parameters identified by univariate analysis were evaluated by multiple logistic regression analysis. Data were analyzed using SPSS 20.0 software package (Armonk, New York, USA). For the delta NLR, the cut-off value with the highest sensitivity and specificity was determined using receiver operator curve analysis to discriminate between outcomes (survival or death).

Results

This study included 95 patients; patient characteristics are reported in Table 1. Seventy-nine patients (83.2%) had out-of-hospital cardiac arrests and 16 patients (16.8%) had in-hospital cardiac arrests. The mean age was 55.0±17.0 years. Thirty-three patients were Hispanic, 52 were non-Hispanic white, and 10 patients were African-Americans. Forty-three patients (45%) had diabetes, 63 (66%) had hypertension, 8 (8.4%) were on renal replacement therapy with hemodialysis or continuous renal replacement therapy, 39 (41.1%) had known coronary artery disease, and 23 (24.1%) had a history of systolic heart failure. The initial rhythm was shockable (ventricular fibrillation or hemodynamically unstable ventricular tachycardia) in 43 patients (45%), and a mean of 1.7±1.7 shocks was delivered to these patients. The time for return of spontaneous circulation was 18.0±12.4 min. TTM was initiated within 135.9±106.2 min of hospital admission. Eight-six patients (90.5%) required at least one vasopressor; 1.6±0.9 vasopressors were used to maintain a mean arterial pressure of ≥60 mm Hg during the intensive care unit stay. Patients remained on ventilators for 7.1±7.6 days. The total length of stay in intensive care unit and hospital were 8.2±8.2 days and 10.8±11.6 days, respectively.

Survival and neutrophil-to-lymphocyte ratio

Fifty-nine patients (62%) died during their hospital stay. Patients who survived were younger (50.2±19.7 years vs. 57.9±14.6 years, p=0.085). There were no statistically significant differences in sex, ethnicity, BMI, time to achieve return of spontaneous circulation, and time to initiate TTM between survivors and decedents. Refractory shock, the presence of AKI at 24 h or 48 h, and ventilator duration did not differ between survivors and
The need for vasopressor support was determined by the senior intensive care unit (ICU) critical care fellows and attending physicians. Vasopressor use at any time during ICU stay did not differ between survivors and decedents; however, fewer vasopressors were used in patients who survived (1.29±0.83 vs. 1.76±0.97, \( p=0.019 \)). Outcomes associated with cardiac arrest location (in-hospital vs. out-of-hospital) were significantly different; 54 out of 79 patients (68%) who had out-of-hospital cardiac arrest died, whereas five out of 16 patients (31%) who had in-hospital cardiac arrest died (\( p=0.005 \)). The total length of stay in the hospital and ICU were significantly longer in patients who survived compared with decedents (p=0.0001 and p=0.001, respectively). Serum \( \text{Na}^+ \) level was lower in patients who survived (135.4±6.2 mEq/L vs. 138.3±4.6 mEq/L, \( p=0.015 \)); however, there were no significant differences in serum potassium, chloride, bicarbonate, glucose, creatinine, BUN, ALT, and AST levels between survivors and decedents. Total protein (6.5±1.1 gm/dL vs. 5.7±1.1 gm/dL, \( p=0.004 \)) and albumin (3.7±0.7 gm/dL vs. 3.2±0.6 gm/dL, \( p=0.006 \)) were higher in patients who survived compared with decedents.

The neutrophil-to-lymphocyte ratios (NLR1, NLR2, and NLR3) are reported in Table 2. There was no difference in NLR1 and NLR3 between patients who survived and decedents (NLR1: 13.2±20.9 vs. 6.6±8.5, \( p=0.07 \); NLR3: 13.8±11.1 vs. 14.9±8.3, \( p=0.23 \)). NLR-2 was significantly higher in decedents than survivors (24.9±24.9 vs. 17.5±17.7, \( p=0.014 \)) (Fig. 1). The delta NLR was negative (NLR1>NLR2) in 18 patients, of whom seven died and 11 survived (p=0.024). Receiver operator characteristic curve analysis demonstrated that a delta NLR \( 2 \) cutoff of 13.5 has a sensitivity and specificity of 64% and 67% respectively to separate survival vs death.

### Table 1. Baseline characteristics of the study population

| Parameter (n=95) | Value |
|-----------------|-------|
| Age, years      | 55.0±17.0 |
| Total length of hospital stay, days, median (IQR)* | 7.5 (9) |
| ICU stay, days, median (IQR)* | 6 (5) |
| Male sex, %    | 59 (62.1) |
| Ethnicity       |       |
| Hispanic, %     | 33 (34.7) |
| Non-Hispanic white, % | 52 (54.7) |
| African-American, % | 52 (54.7) |
| Diabetes mellitus, % | 43 (45) |
| Hypertension, % | 63 (66) |
| Chronic kidney disease, % | 15 (16) |
| Renal replacement therapy, % | 8 (8.4) |
| Coronary artery disease, % | 39 (41.1) |
| History of systolic heart failure, % | 23 (24.2) |
| Previous myocardial infarction, % | 24 (25.3) |
| Alcohol use disorder, % | 13 (13.7) |
| History of smoking, % | 48 (50.5) |
| BMI             | 29.5±7.2 |
| Patients with shockable initial rhythm, % | 43 (45) |
| Number of shocks delivered, median (IQR)* | 1 (2) |
| Left ventricular EF, median (IQR)* | 50 (25) |
| Location of cardiac arrest, n (%) |       |
| In-hospital     | 16 (16.8) |
| Out-of-hospital | 79 (83.2) |
| Time elapsed for ROSC, min, median (IQR)* | 15 (13) |
| TTM initiated within, min, median (IQR)* | 105 (128) |
| Days on ventilator, median (IQR)* | 5 (6) |
| Number of vasopressors used, median (IQR)* | 1 (1) |

(*) Indicates non-normally distributed data. BMI - body mass index; EF - ejection fraction; ICU - intensive care unit; IQR - interquartile range; ROSC - return of spontaneous circulation; TTM - targeted temperature management; Vasopressors, norepinephrine, vasopressin, epinephrine, dopamine. Numbers in parenthesis indicate percentages.
Variables assessed in multivariate analysis

There were no statistically significant differences in the changes in NLR from admission to rewarming (delta NLR1–NLR3) and from cooling to rewarming (delta NLR2–NLR3) between survivors and decedents (p=0.27 and p=0.18, respectively). A bigger increase in NLR between admission and cooling (delta NLR2–NLR1) was significantly associated with decreased survival [OR=0.96, 95% CI (0.94–0.99), p=0.008] (Fig. 3). After excluding in-hospital cardiac arrest patients from the analysis, delta NLR2–NLR1 still predicted mortality [OR=0.96, 95% CI (0.93–0.99), p=0.014]. Mortality risk increased independently 1.15 times with every day spent in ICU. Age, location of cardiac arrest (in-hospital vs. out-of-hospital), number of vasopressors used (quantitative), serum albumin, total protein, and serum creatinine on admission were not independent predictors of survival. Higher serum sodium levels on admission were independently associated with improved survival (Table 3).
It may also be considered for out-of-hospital cardiac arrest patients with non-shockable initial rhythms or for patients with in-hospital cardiac arrests (6, 7). The American Heart Association Guidelines recommend TMM for all comatose patients with return of spontaneous circulation PCA (8). In a recent systematic review and meta-analysis, conventional cooling improved survival by 30% (RR: 1.32, 95% CI: 1.10–1.65) following resuscitation PCA (9). Hypothermia has multiple effects on the pathways activated during ischemia–reperfusion injuries. In particular, it reduces cerebral metabolism, programmed cell death, and acute inflammation resulting in the migration of neutrophils into the damaged tissue and maintains the vascular and blood–brain integrity.

NLR is a readily available inflammatory marker, which has been associated with plaque burden in coronary artery disease, percutaneous coronary intervention outcomes in acute coronary syndrome, COPD severity, and outcomes associated with various cancers (10–16). In experimental models of brain injury, parenchymal neutrophil infiltration occurs, and neutrophil infiltration into the ischemic brain has been implicated in posts ischemic brain injury (17). An ischemic insult and subsequent reperfusion initiate an inflammatory cascade and the recruitment of leukocytes into the cerebral microcirculation. Peripheral leukocytes respond quickly to ischemic insults, and bone marrow activation augments new leukocyte recruitment into circulation, which usually takes up to 4 h (18). After hypoxic ischemic insult, the neutrophil counts increase and lymphocyte counts decrease in peripheral circulation. Stroke infarct size has been correlated with lymphocytopenia (19). These changes in cell counts reflect bone marrow stimulation and cell release, margination and demargination of leukocytes in the microcirculation, the sequestration the cells in various tissues, apoptotic pathways, and leukocyte migration into the damaged tissue. Lymphocyte count typically decreases during acute stress events, and this may decrease the control of inflammation provided by regulatory lymphocytes. Consequently, the absolute number of circulating leukocytes provides important information about the level of acute distress, and the ratio of neutrophils to lymphocytes may provide composite integrated information about the overall inflammatory process. These changes occur over several days, and dynamic changes in leukocyte numbers and ratios provide an index of ongoing acute inflammation and responses to therapeutic interventions.

There is limited information on the possible effects of sedatives and opioids on dynamic changes in NLR. Huetteeman et al. (20) reported that propofol did not have a significant effect on neutrophil function in patients requiring long-term sedation. However, changes in NLR were not investigated in this study. In a study reported by Kim et al. (21), sedation and pain control with propofol and remifentanil, respectively, lowered NLR during laparoscopic surgery. In their study, there was a signifi-
cant increase in NLR at the end of surgery, 2 h after surgery and 24 h after surgery when compared with preinduction values in both the propofol–remifentanil group and inhaled anesthetic group. Although there was an increase from baseline, NLR in the propofol–remifentanil group was significantly lower 2 h after surgery than in the inhaled anesthetic group. There were no surgical interventions in our patients, and inhaled anesthetics were not used. There are no studies that have investigated the possible effects of rocuronium or vecuronium on NLR. However, since all patients in our study received these nondepolarizing neuromuscular blocking agents, there should have been a uniform effect, if any, on peripheral blood counts in both survivors and decedents.

Patients with return of spontaneous circulation PCA frequently have severe neurological impairments and in-hospital complications related to their primary disease and multiorgan failure. The use of TTM complicates neurological assessment since these patients are ventilated, paralyzed, and sedated. Consequently, neurological assessments are unsatisfactory, and physicians must wait until the patient has completely recovered from hypothermia to make these assessments. Biomarkers have the potential to help clinicians predict outcomes, which should improve conversations with families. Shuetz et al. (22) studied 34 patients with cardiac arrests who were managed with therapeutic hypothermia. Twenty-five patients had a respiratory tract infection based on clinical evaluation, and 18 patients had positive microbiological cultures to confirm the diagnosis. They found that the procalcitonin level was highest on the first day after hypothermia and then trended downward. The C-reactive protein level trended upward after hypothermia. There was a little consistent change in white blood cell counts. This study demonstrates that biomarkers frequently used to identify infection are elevated in patients with cardiac arrest treated with hypothermia independent of an underlying infection. Storm et al. (23) measured neuron-specific enolase in cardiac arrest patients treated with hypothermia. This protein is a dimeric intracellular glycolytic enzyme present in neurons. It increases in patients with cardiac arrest, stroke, subarachnoid hemorrhage, and brain trauma. They prospectively studied 35 patients resuscitated from cardiac arrest. The absolute level neuron-specific enolase predicted outcomes at 48 h, and the change in levels between 24 and 48 h also predicted outcomes. Rundgren et al. (24) also measured neuron-specific enolase in PCA patients treated with hypothermia. This study included 107 patients. The absolute level at 72 h and the change in levels between 24 and 48 h were significantly higher in patients with poor outcomes. Aibiki et al. (3) measured systemic and internal jugular plasma IL-6 levels in patients following traumatic brain injury. This study included patients treated with either hypothermia or normothermia. There was a significant increase in IL-6 levels in all patients on admission. Hypothermia suppressed these levels throughout the following 6 days. Patients with poor outcomes had elevated levels during the hypothermic phase, the rewarming phase, and after rewarming. Coffelt et al. (25) postulated that dynamic changes in NLR may be more important to predict outcomes than the baseline value. To our knowledge, there are no studies that have investigated dynamic NLR changes in cardiac arrest patients undergoing TTM. Guo et al. (26) calculated longitudinal NLRs in patients who had a stroke treated with thrombolytic therapy. They found that NLR was a dynamic variable that helped predict hemorrhagic transformation of the stroke. NLR measured between 12–18 h following stroke and thrombolytic administration was the best predictor of hemorrhagic transformation. Bigger increases in NLR during TTM during the periprocedural period of percutaneous coronary intervention has been associated with adverse clinical outcomes (27). Our study also demonstrates that NLR is increased in patients with cardiac arrest during hypothermia and that the increase in NLR during hypothermia is significantly higher in decedents. Overall these studies suggest that biomarkers can help us understand the pathophysiology of neurological injury, such as CRP and cytokines, were not measured in the study. Prospective studies with larger number of patients are warranted.

Study limitations

This study was a retrospective single-center study with limited number of both out-of-hospital and in-hospital cardiac arrest patients. Information was collected from medical records, which were created by multiple physicians managing these patients. The medical records did not provide consistent information to determine the stability of coronary artery disease (unstable angina vs. stable coronary artery disease) and the NYHA heart failure functional class. Other markers of inflammation, such as CRP and cytokines, were not measured in the study. Prospective studies with larger number of patients are warranted.

Conclusions

In conclusion, NLR increases during hypothermia in patients with return of spontaneous circulation PCA treated with TTM. Mortality is increased in patients with a significant increase in NLR during the cooling phase. These results suggest that a significant increase in NLR during TTM may identify patients with poor prognoses. Based on the findings of this study, changes in NLR during hypothermia within 12 h can be used for prognosis estimation and as an indicator of treatment effect(s) in future studies.

Conflict of interest: None declared.
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