ORIGINAL ARTICLE

Association of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios with in-hospital mortality in the early phase of severe trauma

Dong Hun Lee, M.D.,[1] Byung Kook Lee, M.D.,[1] Sung Min Lee, M.D.,[1] Yong Soo Cho, M.D.,[1] Seong Woo Yun, M.D.[2]

[1]Department of Emergency Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju-*South Korea*

[2]Department of Emergency Medical Technology, Namseoul University, Chungnam-*South Korea*

ABSTRACT

BACKGROUND: This study aimed to examine the relationship between the immediate and early complete blood count-based scores and prognosis in trauma patients.

METHODS: This retrospective observational study included adult patients admitted for severe trauma between January 2014 and December 2018. Multivariate logistic regression analysis was conducted to assess the association between the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), and in-hospital mortality.

RESULTS: Among the 288 patients included in the study, in-hospital mortality was 26.4% (n=76). Immediately after emergency department (ED) arrival, non-survivors had lower NLR (3.28 vs. 4.73) and PLR (55.73 vs. 87.21) and higher LMR (4.91 vs. 3.91) than survivors. At 6 h after ED arrival, non-survivors had lower NLR (4.98 vs. 8.37) and PLR (58.23 vs. 123.74) and higher LMR (2.88 vs. 1.69) than survivors. Results of multivariate regression analysis revealed that NLR (odds ratio [OR], 0.926; 95% confidence interval [CI], 0.881–0.973) and PLR (OR, 0.994; 95% CI, 0.990–0.998) at 6 h after ED arrival were independently associated with in-hospital mortality.

CONCLUSION: Lower NLR and PLR at 6 h after ED arrival were associated with in-hospital mortality in cases of severe trauma.

Keywords: Neutrophil-to-lymphocyte ratio; prognosis; trauma.

INTRODUCTION

Trauma is the leading cause of death in individuals who in their most productive years of life.[1] The central nervous system (CNS) disorders or exsanguination is responsible for death in the early phase of trauma. Meanwhile, multiple organ failure (MOF) or sepsis is the main cause death in the late phase of trauma.[2]

Several scores using inflammatory cells such as neutrophils, monocytes, lymphocytes, and platelets have been developed as indicators of clinical systemic inflammation.[3] These scores have been reported to be useful in predicting outcomes in critically ill patients.[4–8] Studies have reported on the relationship between these scores and prognosis in trauma.[9,10] High neutrophil-to-lymphocyte ratios (NLRs) on the 2nd and 5th days of hospitalization were associated with in-hospital mortality in critically ill trauma patients.[9] Another study showed that a high NLR on the 10th day of hospitalization was associated with higher in-hospital mortality in trauma patients who received massive transfusion.[10] Trauma-related ischemic/inflammatory response develops immediately after trauma, and critical resuscitation effort is provided within a few hours after arrival at the hospital.[11] Thereby, NLR early

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Address for correspondence: Byung Kook Lee, M.D.
42, Jebong-ro, Donggu Gwangju - South Korea
Tel: +82 62-220-6809 E-mail: bbukkuk@hanmail.net

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after trauma can be an early marker for predicting survival in severe trauma patients. However, the previous studies have not addressed the role of NLR in the early phase of trauma.

We hypothesized that the immediate and early complete blood count (CBC)-based scores have a prognostic role in trauma patients. To address the prognostic role of CBC-based scores in trauma, the association between CBC-based scores and prognosis in trauma patients was examined.

MATERIALS AND METHODS

Study Design and Population

A retrospective observational study was conducted including adult patients (≥18 years) with severe trauma who visited the emergency department (ED) from January 2014 to December 2018, within an hour after injury, and those who underwent CBC testing immediately at ED visit and 6 h after ED arrival. Severe trauma was defined as having an injury severity score (ISS) >15.[12] The following exclusion criteria were applied: Age <18 years; trauma mechanisms, such as drowning or hanging; cardiac arrest following trauma; and missing data. Our hospital's Institutional Review Board approved the study. Informed consent was waived since this was a retrospective study.

Data Collection

The following variables were obtained for each patient: Age, sex, mechanism of trauma (such as blunt or penetrating), vital signs at ED arrival (systolic blood pressure [mmHg], heart rate, and respiratory rate), initial Glasgow Coma Scale (GCS), laboratory data on ED arrival and 6 h after ED arrival (white blood cell count, hemoglobin, platelet count, neutrophil count, lymphocyte count, and monocyte count), 24 h mortality, and in-hospital mortality. The abbreviated injury scale (AIS) score and ISS were measured during the ED visit. The revised trauma score (RTS) was measured using the GCS and vital signs. NLR, lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) were calculated using CBC obtained immediately at ED arrival and 6 h after ED arrival. The primary outcome was in-hospital mortality, and the secondary outcome was 24 h mortality.

Statistical Analysis

Continuous variables are presented as median with interquartile ranges and categorical variables as frequencies and percentages. Continuous variables that showed a non-normal distribution were analyzed using the Mann–Whitney U-test. Fisher's exact test was used to analyze the categorical variables. The receiver operating characteristic (ROC) analysis was used to examine the prognostic performance of NLR, LMR, and PLR for in-hospital mortality and 24 h mortality.

A multivariate logistic regression analysis was conducted to assess the association between NLR, LMR, and PLR and in-hospital mortality. All variables with p<0.20 in the univariate analysis were included in the multivariate regression analysis. The backwards stepwise approach was used to establish the final adjusted regression model, thereby sequentially eliminating variables with a threshold of p>0.10. Finally, age, RTS, and hemoglobin at 6 h after ED arrival were used as adjusted variables. NLR, LMR, and PLR were placed separately into the final model to independently perform the analysis. The logistic regression analysis results were presented as odds ratio (OR) and 95% confidence interval (CI). Data were analyzed using SPSS software, version 18 (IBM Inc., Chicago, IL, USA). The ROC curves were created and compared using MedCalc version 16.1 (MedCalc Software bvba, Ostend, Belgium). A two-sided significance level of 0.05 was used for statistical significance.

RESULTS

Patient Population and Baseline Characteristics

A total of 288 patients were studied. The median age was 55.1 (range, 42.3–68.1) years, and the median ISS was 22 (range, 17–27). The in-hospital mortality rate was 26.4% (n=76). Non-survivors were older and had higher ISS and lower RTS and GCS than survivors (Table 1).

Non-survivors had higher lymphocyte count from samples taken immediately after ED arrival. Meanwhile, their hemoglobin levels and neutrophil count were lower than survivors (Table 2). Non-survivors had lower NLR (3.28 [range, 1.61–6.71] vs. 4.73 [range, 1.64–9.85]) and PLR (55.73 [range, 37.85–88.42] vs. 87.21 [range, 56.14–141.57]) and higher LMR (4.91 [range, 2.50–8.71] vs. 3.91 [range, 1.49–7.35]) in blood samples taken immediately after ED arrival, than survivors (Table 2).

At 6 h after ED arrival, non-survivors had higher lymphocyte counts and lower hemoglobin levels and platelet counts than survivors (Table 2). In addition, non-survivors had lower NLR (4.98 [range, 2.11–8.58] vs. 8.37 [range, 4.64–13.89]) and PLR (58.23 [range, 36.33–89.24] vs. 123.74 [range, 73.87–201.29]) and higher LMR (2.88 [range, 1.56–6.69] vs. 1.69 [range, 1.02–3.89]) than survivors at 6 h after ED arrival (Table 2).

Logistic Regression Analysis for Predicting In-hospital Mortality

Table 3 shows the association of NLR, LMR, and PLR individually, with in-hospital mortality. After adjusting for confounders, NLR (OR, 0.926; 95% CI: 0.881–0.973) and PLR (OR, 0.994; 95% CI: 0.990–0.998) at 6 h after ED arrival were independently associated with in-hospital mortality (Table 3). NLR, LMR, and PLR immediately after ED visit and LMR 6 h after ED arrival were not associated with in-hospital mortality, as per results of multivariate logistic regression analysis.

Prognostic Performances of NLR, LMR, and PLR for In-hospital Mortality

Immediately after ED arrival, the areas under the curve

Table 1. Comparison of baseline characteristics according to in-hospital mortality

Variables	Total (n=288)	Survivors (n=212)	Non-survivors (n=76)	p
Age (years)	55.1 (42.3–68.1)	54.1 (40.3–65.0)	61.1 (47.3–75.1)	0.005
Male, n (%)	214 (74.3)	159 (75.0)	55 (72.4%)	0.766
Mechanism of trauma, n (%)				0.172
Blunt	274 (95.1)	199 (93.9)	75 (98.7)	
Penetrating	14 (4.9)	13 (6.1)	1 (1.3)	
Injury Severity Score	22 (17–27)	22 (17–25)	25 (20–33)	<0.001
Head/neck AIS	3 (0–4)	2 (0–4)	4 (3–5)	<0.001
Face AIS	0 (0–0)	0 (0–0)	0 (0–0)	0.960
Chest AIS	2 (0–3)	2 (0–3)	2 (0–3)	0.221
Abdomen AIS	0 (0–3)	0 (0–3)	0 (0–2)	0.328
Extremity/pelvic AIS	2 (0–3)	2 (0–3)	2 (0–3)	0.564
External AIS	0 (0–1)	0 (0–1)	0 (0–0)	0.003
Revised Trauma Score	6.90 (5.03–7.84)	7.11 (5.97–7.84)	5.03 (4.09–6.38)	<0.001
Glasgow Coma Scale	14 (7–15)	15 (9–15)	6 (3–12)	<0.001
Systolic BP, mmHg	100 (80–120)	100 (80–120)	90 (60–140)	0.276
Diastolic BP, mmHg	60 (40–80)	60 (50–80)	60 (30–90)	0.202
Respiratory rate, /min	20 (20–22)	20 (20–22)	20 (20–22)	0.710
Pulse rate, /min	88 (78–100)	88 (78–100)	93 (80–110)	0.063

AIS: Abbreviated injury scale; BP: Blood pressure.

Table 2. Comparison of complete blood count characteristics according to in-hospital mortality

Variables	Survivors (n=212)	Non-survivors (n=76)	p
Immediately after emergency department visit			
White blood cell count, $\times 10^9$/L	12.6 (9.4–17.1)	12.7 (8.7–17.9)	0.826
Hemoglobin, g/dL	12.5 (10.9–13.9)	11.4 (9.3–13.7)	0.003
Neutrophil count, $\times 10^9$/L	9.2 (5.3–13.6)	8.1 (5.5–12.8)	0.012
Lymphocyte count, $\times 10^9$/L	2.0 (1.2–4.1)	2.8 (1.4–5.1)	0.046
Monocyte count, $\times 10^9$/L	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.389
Platelet count, $\times 10^9$/L	193 (145–243)	174 (108–226)	0.619
Neutrophil-to-lymphocyte ratio	4.73 (1.64–9.85)	3.28 (1.61–6.71)	0.045
Lymphocyte-to-monocyte ratio	3.91 (1.49–7.35)	4.91 (2.50–8.71)	0.025
Platelet-to-lymphocyte ratio	87.21 (56.14–141.57)	55.73 (37.85–88.42)	<0.001
6 h after emergency department visit			
White blood cell count, $\times 10^9$/L	13.6 (10.1–17.5)	12.9 (9.6–16.5)	0.421
Hemoglobin, g/dL	12.1 (10.8–13.4)	10.6 (8.4–12.9)	<0.001
Neutrophil count, $\times 10^9$/L	11.1 (7.6–14.5)	9.6 (7.2–13.1)	0.056
Lymphocyte count, $\times 10^9$/L	1.3 (0.8–2.2)	1.9 (1.3–3.4)	<0.001
Monocyte count, $\times 10^9$/L	0.7 (0.5–1.1)	0.7 (0.4–1.1)	0.532
Platelet count, $\times 10^9$/L	0.2 (0.1–0.2)	0.1 (0.1–0.2)	<0.001
Neutrophil-to-lymphocyte ratio	8.37 (4.64–13.89)	4.98 (2.11–8.58)	<0.001
Lymphocyte-to-monocyte ratio	1.69 (1.02–3.89)	2.88 (1.56–6.69)	<0.001
Platelet-to-lymphocyte ratio	123.74 (73.87–201.29)	58.23 (36.33–89.24)	<0.001

Table 3. Multivariate logistic regression analysis for predicting in-hospital mortality

	Adjusted OR (95% CI)[a]	p
Immediately after ED visit		
Neutrophil-to-lymphocyte ratio	0.969 (0.924–1.016)	0.190
Lymphocyte-to-monocyte ratio	1.007 (0.961–1.055)	0.776
Platelet-to-lymphocyte ratio	0.997 (0.993–1.001)	0.110
6 h after ED visit		
Neutrophil-to-lymphocyte ratio	0.926 (0.881–0.973)	0.002
Lymphocyte-to-monocyte ratio	1.039 (0.981–1.101)	0.195
Platelet-to-lymphocyte ratio	0.994 (0.990–0.998)	0.007

Each variable was individually entered into the final model and was independently analyzed. ED: Emergency department; OR: Odds ratio; CI: Confidence interval. [a]Adjusted for age, RTS, and hemoglobin at six hours after ED arrival.

(AUCs) for NLR, LMR, and PLR were 0.665 (95% CI, 0.607–0.720), 0.626 (95% CI, 0.567–0.682), and 0.756 (95% CI, 0.702–0.805), respectively (Table 4). At 6 h after ED arrival, AUCs for NLR, LMR, and PLR were 0.718 (95% CI, 0.662–0.769), 0.666 (95% CI, 0.608–0.720), and 0.801 (95% CI, 0.750–0.846), respectively (Table 4).

DISCUSSION

In this retrospective cohort study, which included severe trauma patients, we found that non-survivors had lower NLR and PLR, immediately after and 6 h after ED arrival, than survivors. Low NLR and PLR 6 h after ED arrival were independently associated with higher in-hospital mortality.

The previous studies reported a relationship between NLR and outcome in trauma.[9,10,13] In a study of patients with traumatic brain injury, a high NLR at admission was related to increased 28-day mortality,[13] which was different from this study result. This study included patients who arrived within 1 h of injury to ED. Meanwhile, the time interval from injury to ED arrival was unknown in the previous study. Patients with various times from injury to ED arrival were included in the previous study. Hence, the immune response of trauma patients was mixed, within the first 24 h, which may have confounded the results.[13] In the previous study, NLRs of extended Glasgow Outcome Score (GOSE) 7 and 8 at admission were higher than those of GOSE 3–6.[13] In another study on trauma, NLR, which trends to increase through day 0–2, was related to the complications of trauma.[14] In this previous study, NLRs at 24 and 48 h in the group showing an increasing NLR trend were higher than those in the group showing a decreasing NLR trend.[14] NLR at admission in the group showing an increasing NLR was lower than that in the group showing a decreasing NLR trend, and this relationship was reversed at 24 and 48 h.[14] In the surgical intensive care unit setting, NLR of the trauma with sepsis subgroup was higher than that of the trauma without sepsis subgroup.[15] Although not statistically significant, the trauma with sepsis subgroup had higher mortality than the trauma without sepsis subgroup (31.3% vs. 23.9%).[15] In a study on the association between NLR and mortality in trauma patients, NLRs on the 2nd and 5th days of hospitalization were associated with in-hospital mortality.[9] The cause of death after the first 24 h or 5 days was sepsis or MOF, not bleeding or CNS problems.[16] Thus, as seen in medical diseases, such as sepsis and pancreatitis,[13,17,18] a high NLR may be associated with high mortality in trauma patients. In other words, the previous study did not analyze patients who died within the first 24 h. Since the mortality rate in the first 24 h was 25–30%,[16] the previous study may not reflect the overall mortality of trauma.[9] In addition, if a patient with a low NLR was misinterpreted as having a good prognosis, the patient's risk of dying in the early phase of trauma may be missed.

A high PLR was associated with a high incidence of post-operative complications and high mortality in cardiogenic pul-

Table 4. Prognostic performance of NLR, LMR, and PLR at 6 hours after ED arrival for predicting in-hospital mortality and 24-hour mortality

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
In-hospital mortality						
NLR	≤6.34	61.8	67.9	40.9	83.2	0.665 (0.607–0.720)
LMR	>4.87	43.4	79.7	43.4	79.7	0.626 (0.567–0.682)
PLR	≤90.63	79.0	64.6	44.4	89.5	0.756 (0.702–0.805)
24 h mortality						
NLR	≤5.19	72.0	69.6	18.4	96.3	0.718 (0.662–0.769)
LMR	>2.71	72.0	62.7	15.5	95.9	0.666 (0.608–0.720)
PLR	≤53.25	68.0	81.8	26.2	96.4	0.801 (0.750–0.846)

NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve; CI: Confidence interval; ED: Emergency department.

monary edema and malignancy.[19–21] In contrast to the previous studies, non-survivors had lower PLRs than survivors in this study, which showed a significant independent association. The possible explanations for this difference will now be described. The platelet count changes in cases of severe trauma. Several studies insisted that low platelet counts are associated with coagulopathy or disseminated intravascular coagulation and subsequently mortality.[22–24] Lymphocyte count also changes in severe trauma. Acute lymphocytosis in the early phase of trauma was related to injury severity, which was also related to mortality in the previous study.[25,26] In this study, lymphocyte counts were higher in non-survivors than in survivors, which is in line with the results of the previous study. In patients with severe trauma, a reduced platelet count with an increased lymphocyte count can be related to mortality. Thus, low PLR may have a significant relationship with mortality. In a recent study on pediatric trauma, PLR was lower in non-survivors than in survivors, and it remained as an independent predictor for mortality.[27]

This study has several limitations. First, it was a retrospective and single-center study; therefore, further studies with larger sample sizes and prospective designs involving multiple centers are necessary. Second, this study only included trauma patients with ISS >15. Since immune response markers, such as NLR, LMR, and PLR, may vary depending on the degree of injury, studying the immune response of all trauma patients might be needed, including those with ISS 15 or less. In addition, this study only included the results of the CBC test immediately after ED arrival and 6 h after ED visit. Prospective research is needed, including the results of serial changes at the time when the visit exceeds 6 h after ED arrival. Finally, this study did not investigate the cause of in-hospital mortality. Immune responses may vary depending on exsanguination, CNS disorders, sepsis, and MODS, which may appear to be the cause of trauma-related death. Therefore, future studies on the relationship between causes of trauma-related death and immune response are needed.

Conclusion

Lower NLR and PLR at 6 h after ED arrival were associated with in-hospital mortality in severe trauma.

Ethics Committee Approval: This study approved by the Chonnam National University Hospital Institutional Review Board (CNUH-2019-372).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: D.H.L.; Design: D.H.L., B.K.L.; Supervision: B.K.L.; Resource: Y.S.C.; Materials: S.M.L.; Data: S.M.L., Y.S.C.; Analysis: D.H.L., S.W.Y.; Literature search: S.W.Y.; Writing: D.H.L. , B.K.L.; Critical revision: D.H.L., B.K.L.

Conflict of Interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Ağır travmanın erken evresinde nötrofil-lenfosit ve trombosit-lenfosit oranlarının hastane içi mortalite ile ilişkisi

Dr. Dong Hun Lee,[1] Dr. Byung Kook Lee,[1] Dr. Sung Min Lee,[1] Dr. Yong Soo Cho,[1] Dr. Seong Woo Yun[2]

[1]Chonnam Ulusal Üniversite Hastanesi, Chonnam Ulusal Üniversite Tıp Fakültesi, Acil Tıp Bölümü, Gwangju-*Güney Kore*
[2]Acil Tıp Teknolojisi Bölümü, Namseoul Üniversitesi, Chungnam-*Güney Kore*

AMAÇ: Bu çalışma, travma hastalarında acil ve erken tam kan sayımına dayalı skorlar ile prognoz arasındaki ilişkiyi incelemeyi amaçlamaktadır.
GEREÇ VE YÖNTEM: Bu geriye dönük gözlemsel çalışma, Ocak 2014 ile Aralık 2018 arasında ağır travma nedeniyle hastaneye başvuran yetişkin hastaları içermektedir. Nötrofil-lenfosit oranı (NLR), lenfosit-monosit oranı (LMR) ve trombosit-lenfosit oranı (PLR) ve hastane içi mortalite arasındaki ilişkiyi değerlendirmek için çok değişkenli lojistik regresyon analizi yapıldı.
BULGULAR: Çalışmaya alınan 288 hastada, hastane içi mortalite %26.4 (n=76) idi. Acil servise getirildikten hemen sonra, hayatta kalmayanlarda hayatta kalanlara göre daha düşük NLR (3.28'e karşı 4.73) ve PLR (55.73'e 87.21) ve daha yüksek LMR (4.91'e karşı 3.91) saptandı. Acil servise ulaştıktan altı saat sonra, hayatta kalmayanlar hayatta kalanlara göre daha düşük NLR (4.98'e karşı 8.37) ve PLR (58.23'e karşı 123.74) ve daha yüksek LMR (2.88'e karşı 1.69) değerine sahipti. Çok değişkenli regresyon analizinin sonuçları, acil servise gelişten altı saat sonraki NLR (Odds oranı [OR], 0.926; %95 Güven Aralığı [GA], 0.881–0.973) ve PLR (OR, 0.994; %95 GA, 0.990–0.998) değerlerinin hastane içi mortalite ile bağımsız olarak ilişkili olduğunu ortaya koymuştur.
TARTIŞMA: Şiddetli travma olgularında acil servise geldikten altı saat sonraki düşük NLR ve PLR değerleri, hastane içi mortalite ile ilişkilendirildi.
Anahtar sözcükler: Nötrofil-lenfosit oranı; prognoz; travma.

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