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The Neutrophil-to-Lymphocyte Ratio at the Time of Admission: A New Prognostic Indicator for Hospital Mortality of Trauma Patients

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ABSTRACT

The elevated neutrophil-to-lymphocyte ratio (NLR) is associated with poor clinical outcomes, especially in pro-inflammatory states such as surgical injuries and severe hemorrhages. Therefore, it was hypothesized whether NLR value at the time of admission could be a prognostic indicator of hospital mortality in trauma patients.

This retrospective cohort study was conducted on 865 trauma patients referred to Rajaee Hospital between April 2016 and July 2019. The NLR value was calculated at the time of admission, and receiver operating characteristics (ROC) curve analysis was used to determine the cut-off point value of admission NLR related to hospital mortality of trauma patients. Furthermore, Kaplan-Meier survival analysis and Cox regression models have been applied to determine the effectiveness and prognostic potential of the admission NLR in the hospital mortality of trauma patients.

The median age of the trauma patients was 32 years with an interquartile range (IQR) of 23 to 48 years, and most of them were male (83.9%). Also, trauma patients had a median injury severity score (ISS) of 9 (IQR=4-16) and a median Glasgow coma scale (GCS) of 14 (IQR=9-15). The cut-off value for admission NLR was 5.27 (area under the curve: 0.642, 95%CI: 0.559-0.726, p=0.001). In Kaplan-Meier survival analysis, the admission NLR>5.27 was an indicator of hospital mortality in trauma patients (p=0.001). Multivariate Cox regression models demonstrated that trauma patients with an admission NLR>5.27 had a 2.33-fold risk of hospital mortality (hazard ratio=2.33, 95%CI: 1.02-5.38, p=0.041). Furthermore, the admission NLR>5.27 was associated with a higher risk of hospital mortality in trauma patients with age≥65 years, systolic blood pressure≤90 mmHg, blood potassium>4.5 mmol/L, blood sodium>144 mEq/L, blood potential hydrogen (pH)≤7.28, GCS≤8, ISS>24 and blood base excess≤-6.1 mEq/L.

The NLR value greater than 5.27 at the time of admission was associated with poorer outcomes, and it can be considered an independent prognostic indicator of hospital mortality in trauma patients.

Keywords: Inflammation; Mortality; Trauma

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INTRODUCTION

Trauma is one of the most important health problems worldwide, with higher incidence rates in low- and middle-income countries.[1] About 4.8 million annual deaths are recorded due to trauma, accounting for approximately 9% of the global mortality rate.[2] Based on the current trends, it is supposed that the global burden of injuries will increase in the future. Moreover, trauma is the second leading cause of death in Iran, mainly due to road traffic collisions.[3,4]

Trauma-related deaths can occur in three phases: i) immediate phase occurring within minutes to one hour after injury, ii) early phase occurring within 24 hours after injury, and iii) late phase occurring days to months after injury.[5] In terms of immunology, the immediate and early deaths after trauma are associated with pro-inflammatory responses of the immune system, whereas late trauma-related deaths commonly depend on anti-inflammatory responses.[5,6] Accordingly, over-activation of the immune system after severe injuries is associated with extensive systemic inflammatory response syndrome (SIRS) characterized by over-production and secretion of pro-inflammatory mediators into the peripheral blood and is considered a potentially life-threatening complication in the immediate and early phases of trauma-related deaths. High levels of pro-inflammatory mediators are followed by compensatory increases of anti-inflammatory mediators to maintain hemostasis, a process that leads to compensatory anti-inflammatory response syndrome (CARS).[7] These unbalanced immune responses-related disorders (SIRS and/or CARS) result in multi-organ dysfunction syndrome (MODS) and sepsis associated with late mortality in severe trauma patients.[8] In recent years, several studies have been conducted on the prognostic properties of the pro- and anti-inflammatory mediators such as C-reactive protein (CRP), procalcitonin (PCT), interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, IL-4, IL-10, chemokines, and eicosanoids, which may be used as the predictive biomarkers of trauma outcomes.[9-11] White blood cells (WBCs) are the major sources of pro- and anti-inflammatory mediators, and WBC count is a simple, rapid, and inexpensive prognostic laboratory indicator of injury outcome.[12]

Neutrophils and mononuclear cells rapidly increase in injured tissue in response to high concentrations of inflammatory mediators and damage-associated molecular patterns (DAMPs). Accordingly, the neutrophil-to-lymphocyte ratio (NLR) may be associated with poor clinical outcomes, especially in pro-inflammatory states.[13] Several studies have shown that elevated NLR is an important predictor of mortality in subjects with pro-inflammatory features such as patients with cancers,[14] coronary artery disease,[15] infections,[16] MODS,[17] surgical injuries,[18] and severe hemorrhage.[19] Therefore, it seems that NLR can be considered a useful prognostic indicator to predict trauma-related hospital mortality. In addition, various demographic, clinical, and paraclinical criteria have been evaluated in trauma victims to determine their prognostic values. In this regard, previous studies have shown that hypo- and hyperthermia, tachycardia, tachypnea, hyperglycemia, water-electrolytes imbalances, acid-base disorders, and coagulopathy are important indicators for the management and prediction of adverse outcomes in trauma patients.[20-22]

Our study aimed to evaluate the prognostic value of NLR at the time of admission and its association with hospital mortality in trauma patients. Moreover, this prognostic value was determined regarding other demographic, clinical, and paraclinical criteria.

PATIENTS AND METHODS

Patient Selection and Data Collection

This retrospective cohort study was conducted on 865 trauma patients≥15 years old referred to Rajaee Hospital between April 2016 and July 2019. Rajaee Hospital is one of the referral trauma centers in southern Iran (level I trauma center). The inclusion criteria were all patients injured in traffic accidents (pedestrian, motorbike, and car accidents), falling, or violence-related events who were admitted to the emergency department (ED). Exclusion criteria were sports, burns, and surgical injuries. We also excluded subjects with a positive history of cancer, autoimmunity, allergy, inflammatory, or infectious diseases in the last 3 months. Subjects were screened for inclusion/exclusion criteria, and different demographic data, including gender, age, admission date, and the causes of injuries were recorded by the admission staff. Furthermore, clinical data, including the level of consciousness, systolic and diastolic blood pressure (SBP and DBP), pulse rate (PR), and respiratory rate (RR) were collected at the admission time. Laboratory tests including blood sugar (BS),

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hemoglobin (Hb), hematocrit (Hct), creatinine (Cr), blood urea nitrogen (BUN), international normalized ratio (INR), sodium (Na), potassium (K), the potential of hydrogen (pH), and base excess (BE) were taken at the time of admission, and their results were documented subsequently (10-120 minutes after trauma). All patients were followed-up clinically during hospitalization and their outcomes (surviving or death) were recorded. The data were coded with the international classification of diseases (ICD)-10 injury diagnostic code system and entered into the center's data bank. Injury severity score (ISS), the Glasgow coma score (GCS), and other information of patients upon registration were recoded according to the ICD-10 coding system, as previously described by Yadollahi M et al.[23]

WBC count at the time of admission was used to calculate NLR as an indicator of systemic inflammation. NLR was obtained by dividing the absolute neutrophil count (cells/mm^3) by the absolute lymphocyte count (cells/mm^3). ROC curve analysis was used to determine the optimal cut-off value of the admission NLR. Patients were then classified into the two groups based on the calculated admission NLR cut-off point value; high and low NLR groups who had admission NLR higher and lower than the cut-off point, respectively. These two groups were evaluated regarding their demographic, clinical, and paraclinical criteria. In addition, the overall survival was compared between the high NLR group (as exposure group) and the low NLR group. In the survival analysis of trauma patients, the time of hospital admission was considered as the starting point of the study. The endpoints were the death and discharge time for the dead patients and survivors, respectively. Also, the prognostic value of the other variables at the time of admission was evaluated for hospital mortality in trauma patients.

This study was conducted in compliance with the provisions of the Helsinki Declaration. All procedures were approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.MED.REC.1397.380).

Statistical Analysis

The Kolmogorov-Smirnov (K-S) test was performed to evaluate the normal distribution of quantitative variables. Accordingly, quantitative variables with and without a normal distribution were reported as medians with interquartile range (IQR) and mean±standard deviations (SD), respectively.

The optimal cut-off point values of demographic, clinical, and paraclinical criteria of trauma patients were determined by ROC curve analysis according to the maximum Youden Index [sensitivity-(1-specificity)].[24] Quantitative variables transformed into dichotomous ones based on the related cut-off points, and Chi-square (χ^2) and Fisher's exact (expected cells value less than 5) tests were used for comparison of qualitative variables.

The Kaplan–Meier survival test was applied to estimate whether the calculated cut-off point for admission NLR can be useful as a prognostic indicator of hospital mortality in trauma patients.

The effects (prognostic value) of the calculated cut-off point for admission NLR and other criteria on hospital mortality of trauma patients were evaluated by univariate Cox regression analysis. Then, the variables with prognostic value (p-value≤0.2) were re-analyzed in multivariate Cox regression models for adjusting all confounding variables and determining the independent effects of admission NLR on hospital mortality of trauma patients. The results of multivariate Cox regression analysis were reported as hazard ratios (HR) and 95% confidence intervals (95%CI).

All statistical analyses were conducted using SPSS statistical software 19 (SPSS Inc, Chicago, IL, USA), and p-value<0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and paraclinical criteria of the studied population are shown in Table 1. None of the studied subjects had received any packed red blood cells (pRBC) and fresh frozen plasma (FFP) before evaluating neutrophil and lymphocyte counts.

Based on the ROC analysis, the optimal cut-off point value of admission NLR for the prediction of hospital mortality in trauma patients was 5.27 with 68.89% sensitivity and 52.93% specificity (area under the curve (AUC): 0.642, 95%CI: 0.559–0.726, and p=0.001; Figure 1). We found that 48.8% (422/865) of patients had the admission NLR>5.27 (greater than the cut-off point). Also, the optimal cut-off value for each of the demographic, clinical, and paraclinical features of trauma patients at the time of admission is demonstrated in Table 2.

Table 1. Demographic, clinical, and paraclinical criteria of trauma patients at the time of admission

Patients Features	Value
Gender	
Male, n (%)	726/865 (83.9)
Female, n (%)	139/865 (16.1)
Age, Median (IQR range)	32 (23-48)
≥65 years, n (%)	91/865 (10.5)
ISS, Median (IQR range)	9 (4-16)
>24, n (%)	17/170 (10.0)
GCS, Median (IQR range**)**	14 (9-15)
≤8, n (%)	203/865 (23.5)
SBP, Median (IQR range)	126 (113-138)
≤90 mmHg, n (%)	44/865 (5.1)
DBP, Median (IQR range)	80 (70-88)
≤64 mmHg, n (%)	131/864 (15.2)
PR, Median (IQR range)	97 (82-112)
>110 beats/minute, n (%)	224/865 (25.9)
RR, Median (IQR range)	18 (17-21)
>23 breaths/minute, n (%)	114/740 (15.4)
BS mg/dL, Mean±SD	153.00±65.16
Hb g/dL, Mean±SD	13.50±3.05
Hct percent, Mean±SD	38.44±7.24
Cr mg/dL, Mean±SD	1.46±5.84
BUN mg/dL, Mean±SD	16.00±9.53
INR, Mean±SD	1.25±1.28
Na+ mEq/L, Mean±SD	140.05±6.50
K+ mmol/L, Mean±SD	3.94±1.46
pH, Mean±SD	7.36±0.08
BE, Median (IQR range)	-2.4 (-4.6- -0.2)
≤-6.1 mEq/L, n (%)	120/838 (14.3)
NLR, Median (IQR range)	5.05 (2.5-9.2)
Hospital LOS, days, Median (IQR range**)**	9 (4-16)
ICU LOS, days, Median (IQR range)	3 (1-8)
Hospital mortality, n (%)	45/865 (5.2)

BE, base excess; BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; GCS, Glasgow coma scale; Hb, hemoglobin; Hct, hematocrit; ICU, intensive care unit; INR, international normalized ratio; ISS, injury severity score; K+, potassium; LOS, length of stay; Na+, sodium; NLR, neutrophil-to-lymphocyte ratio; pH, potential hydrogen; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure.

Kolmogorov-Smirnov (K-S) test was used; Quantitative variables with and without normal distribution were reported as Mean±SD and medians (IQR), respectively.

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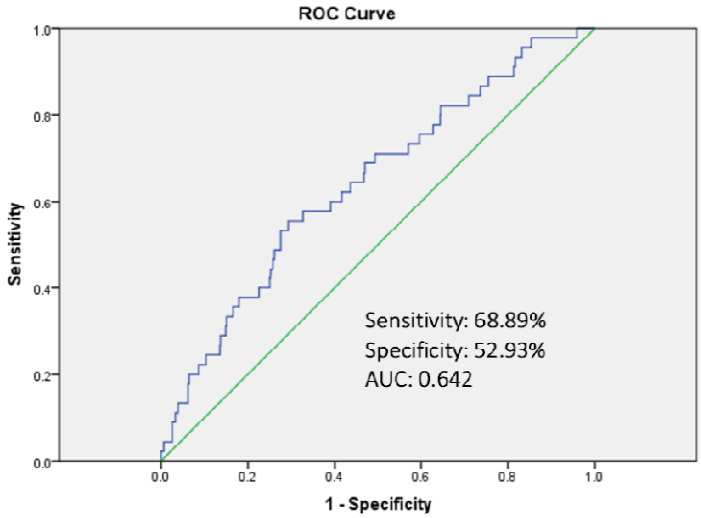

Figure 1. ROC curve analysis. The optimal cut-off point value of admission neutrophil-to-lymphocyte ratio (NLR) in trauma patients

Table 2. The optimal cut-off point for each of the demographic, clinical, and paraclinical criteria of trauma patients at the time of admission

Patients features	Cut-off	AUC	Sensitivity (%)	Specificity (%)	*p*
Age	≥65 years	0.72	92.0	38.4	**<0.001**
ISS	>24	0.75	90.2	65.6	**<0.001**
GCS	≤8	0.76	77.8	61.1	**<0.001**
SBP	≤90 mmHg	0.62	92.9	52.2	**<0.001**
DBP	≤64 mmHg	0.61	83.48	49.05	**0.002**
PR	>110 beats/minute	0.60	71.2	48.5	**0.005**
RR	>23 breaths/minute	0.61	84.1	42.3	**0.028**
BS	>165 mg/dL	0.70	69.6	62.0	**<0.001**
Hb	>12.8 g/dL	0.64	61.5	63.8	**<0.001**
Hct	>34.7 %	0.63	72.9	52.8	**<0.001**
Cr	>1.25 mg/dL	0.70	69.3	64.5	**<0.001**
BUN	>16.8 mg/dL	0.63	66.6	54.0	**<0.001**
INR	>1.27	0.71	70.5	62.5	**<0.001**
Na+	>144 mEq/L	0.63	90.1	56.6	**<0.001**
K+	>4.5 mmol/L	0.63	92.2	51.2	**<0.001**
pH	≤7.28	0.66	86.6	46.0	**<0.001**
NLR	>5.27	0.64	68.9	52.9	**0.001**
BE	≤-6.1 mEq/L	0.63	81.7	50.3	**<0.001**

AUC, area under the curve; BE, base excess; BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; GCS, Glasgow coma scale; Hb, hemoglobin; Hct, hematocrit; INR, international normalized ratio; ISS, injury severity score; K+, potassium; Na+, sodium; NLR, neutrophil-to-lymphocyte ratio; pH, potential hydrogen; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure.

ROC curve analysis was used; Bold text indicates statistical significance (p<0.05).

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Table 3. The comparison of demographic, clinical, and paraclinical criteria between trauma patients with neutrophil-to-lymphocyte ratio (NLR)≤5.27 and NLR>5.27 at the time of admission

Patients features		Admission NLR≤5.27	Admission NLR>5.27	*p*
Gender	Male, n (%)	388/443 (87.6)	338/422 (80.1)	**0.003**
Age	≥65 years, n (%)	42/443 (9.5)	49/422 (11.6)	0.307
ISS	>24, n (%)	7/87 (8.0)	10/83 (12.0)	0.385
GCS	≤8, n (%)	88/443 (19.9)	115/422 (27.3)	**0.010**
SBP	≤90 mmHg, n (%)	22/443 (5.0)	22/422 (5.2)	0.869
DBP	≤64 mmHg, n (%)	57/442 (12.9)	74/422 (17.5)	0.057
PR	>110 beats/minute, n (%)	106/443 (23.9)	118/422 (28.0)	0.176
RR	>23 breaths/minute, n (%)	72/409 (17.6)	42/331 (12.7)	0.066
BS	>165 mg/dL, n (%)	112/442 (25.3)	123/420 (29.3)	0.193
Hb	>12.8 g/dL, n (%)	316/443 (71.3)	225/422 (53.3)	**<0.001**
Hct	>34.7 %, n (%)	347/429 (80.9)	274/403 (68.0)	**<0.001**
Cr	>1.25 mg/dL, n (%)	124/443 (28.0)	122/420 (29.0)	0.731
BUN	>16.8 mg/dL, n (%)	132/443 (29.8)	166/422 (39.3)	**0.003**
INR	>1.27, n (%)	98/439 (22.3)	145/421 (34.4)	**<0.001**
Na+	>144 mEq/L, n (%)	44/441 (10.0)	45/422 (10.7)	0.740
K+	>4.5 mmol/L, n (%)	32/440 (7.3)	48/421 (11.4)	**0.037**
pH	≤7.28, n (%)	51/433 (11.8)	46/406 (11.3)	0.839
BE	≤-6.1 mEq/L, n (%)	60/433 (13.9)	60/405 (14.8)	0.692

BE, base excess; BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; GCS, Glasgow coma scale; Hb, hemoglobin; Hct, hematocrit; INR, international normalized ratio; ISS, injury severity score; K+, potassium; Na+, sodium; NLR, neutrophil-to-lymphocyte ratio; pH, potential hydrogen; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure. Chi-square or Fisher's exact test (expected cells value less than 5) was used; Bold text indicates statistical significance (p<0.05).

Table 4. The comparison of outcome variables between patients with admission neutrophil-to-lymphocyte ratio (NLR)≤5.27 and NLR>5.27

Patients outcomes	admission NLR≤5.27	admission NLR>5.27	*p*
ICU LOS, days, Median (IQR range)	3 (1-7)	4 (1-10)	**<0.001**
Hospital LOS, days, Median (IQR range)	7 (3-13)	10 (6-19)	**<0.001**
Mortality, n (%)	5 (1.1)	36 (9.5)	**<0.001**

ICU, intensive care unit; LOS, length of stay; NLR, neutrophil-to-lymphocyte ratio. Bold text indicates statistical significance (p<0.05). Mann-Whitney U test (Median (IQR)) and Chi-square were used; Bold text indicates statistical significance (p<0.05).

The comparison of demographic, clinical, and paraclinical criteria between trauma patients showed that the frequency of female patients, as well as, patients with GCS≤8, BUN>16.8 mg/dL, INR>1.27, and K>4.5 mmol/L were significantly higher in patients with NLR>5.27 compared to NLR≤5.27 (for all, p<0.05; Table 3). Conversely, the frequency of patients with Hb>12.8 g/dL and Hct>34.7% were significantly lower (for both, p<0.001; Table 3).

Comparison of the survival by the log-rank test demonstrated a statistically significant difference between the high and low NLR groups (p=0.001; Figure 2). Accordingly, survival was lower in trauma patients with the admission NLR>5.27.

In addition, the comparison of outcome variables between patients with NLR≤5.27 and NLR>5.27 at the time of admission showed that the admission NLR values greater than 5.27 were significantly associated with longer length of stay (LOS) in the intensive care units (ICU), longer hospital LOS and higher mortality (for all, p<0.001; Table 4).

Univariate Cox analysis of demographic, clinical, and paraclinical criteria showed that age≥65 years, ISS>24, SBP≤90 mmHg, K>4.5 mmol/L, NLR>5.27, pH<7.28, Na>144 mEq/L, Cr>1.25 mg/dL, GCS≤8, BUN>16.8 mg/dL, and INR>1.27 at the time of admission were the effective factors (prognostic indicators) to predict the hospital mortality of trauma patients (for all, p<0.05; Table 5). After adjusting for all confounding variables using multivariable Cox regression hazard models, hospital mortality risk in trauma patients remained significantly associated with age≥65 years, SBP≤90 mmHg, Na>144 mEq/L, NLR>5.27, ISS>24, and GCS≤8 at the time of admission (HR=11.89, 6.69, 3.21, 2.33, 2.19, and 1.79, respectively; for all, p<0.05; Table 5).

After determining the independent prognostic value of demographic, clinical, and paraclinical criteria, Cox regression hazard models were used to evaluate the prognostic value of NLR>5.27 in combination with each of the above criteria. As shown in Table 6, after adjusting for all confounding variables using multivariable Cox regression hazard models, the prognostic value of NLR>5.2 at the time of admission (HR=2.33; Table 5) was increased in combination with other demographic, clinical, and paraclinical prognostic indicators such as age≥65 years, SBP≤90 mmHg, K>4.5 mmol/L, Na>144 mEq/L, pH<7.28, GCS≤8, ISS>24, and BE≤-6.1 mEq/L (HR=13.60, 6.82, 4.52, 4.40, 3.99, 3.51, 3.19, and 2.39, respectively; for all, p<0.05; Table 6).

Our results demonstrated that the admission NLR value was significantly higher in patients with ISS≥16 compared to patients with ISS<16 (4.635 [2.395–8.438] and 5.575 [3.57–12.75], respectively; p=0.012; Figure 3).

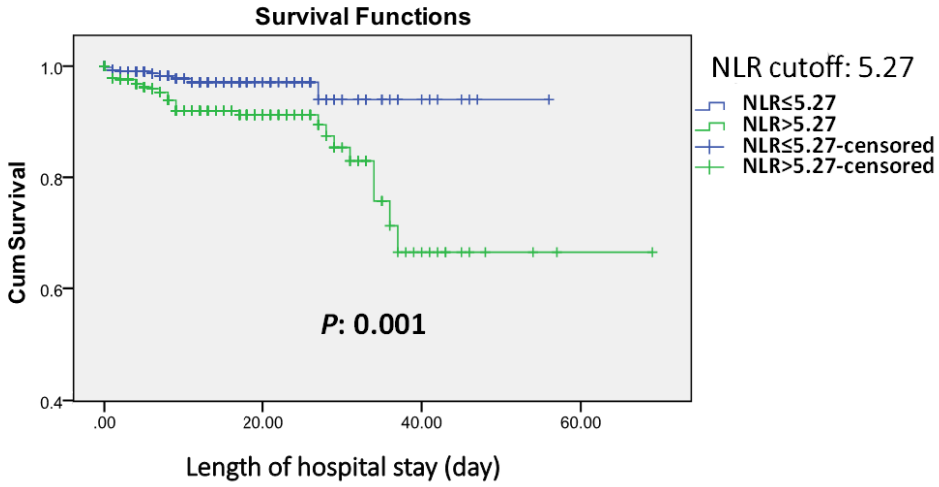

Figure 2. Kaplan-Meier survival curves. The patients with the admission neutrophil-to-lymphocyte ratio (NLR)>5.27 versus admission NLR≤5.27

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Table 5. The prognostic value of demographic, clinical, and paraclinical criteria at the time of admission for prediction of hospital mortality in trauma patients

Patients features		Univariate Cox Regression		Multivariate Cox Regression	
		p	HR; (95%CI)	*p*	HR; (95%CI)
Gender	F		1		1
	M	0.335	0.70; (0.34-1.45)	NA	NA
Age	<65 years		1		1
	≥65 years	**<0.001**	5.24; (2.89-9.50)	**<0.001**	11.89; (4.59-30.91)
ISS	≤24		1		1
	>24	**0.019**	4.48; (1.27-15.77)	**0.022**	2.19; (1.09-4.34)
GCS	>8		1		1
	≤8	**0.003**	2.49; (1.37-4.55)	**0.033**	1.79; (1.02-4.84)
SBP	>90 mmHg		1		1
	≤90 mmHg	**0.002**	3.92; (1.65-9.34)	**0.025**	6.69; (1.19-36.38)
DBP	>64 mmHg		1		1
	≤64 mmHg	0.069	1.92; (0.95-3.89)	0.419	1.80; (0.43-7.42)
PR	≤110 beats/minute		1		1
	>110 beats/minute	0.336	1.36; (0.73-2.52)	NA	NA
RR	≤23 breaths/minute		1		1
	>23 breaths/minute	0.341	1.51; (0.65-3.55)	NA	NA
BS	≤165 mg/dL		1		1
	>165 mg/dL	0.561	1.20; (0.65-2.21)	NA	NA
Hb	≤12.8 g/dL		1		1
	>12.8 g/dL	0.183	1.53; (0.82-2.85)	0.470	1.59; (0.41-5.89)
Hct	≤34.7 %		1		1
	>34.7 %	0.650	1.17; (0.60-2.28)	NA	NA
Cr	≤1.25 mg/dL		1		1
	>1.25 mg/dL	**0.002**	2.55; (1.40-4.64)	0.509	1.33; (0.54-2.99)
BUN	≤16.8 mg/dL		1		1
	>16.8 mg/dL	**0.007**	2.26; (1.25-4.09)	0.072	2.09; (0.96-4.76)
INR	≤1.27		1		1
	>1.27	**0.025**	1.96; (1.09-3.53)	0.453	1.10; (0.60-2.11)
Na+	≤144 mEq/L		1		1
	>144 mEq/L	**0.001**	3.01; (1.55-5.86)	**0.018**	3.21; (1.22-8.48)
K+	≤4.5 mmol/L		1		1
	>4.5 mmol/L	**<0.001**	3.43; (1.77-6.65)	0.179	4.35; (0.50-33.33)
pH	>7.28		1		1
	≤7.28	**0.001**	3.10; (1.62-5.94)	0.297	3.78; (0.31-46.03)
NLR	≤5.27		1		1
	>5.27	**0.001**	3.29; (1.58-6.86)	**0.041**	2.33; (1.02-5.38)
BE	>-6.1 mEq/L		1		1
	≤-6.1 mEq/L	0.122	1.74; (0.86-3.53)	0.166	2.07; (0.74-5.75)

BE, base excess; BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; GCS, Glasgow coma scale; Hb, hemoglobin; Hct, hematocrit; INR, international normalized ratio; ISS, injury severity score; K+, potassium; NA, non-applicable/not available; Na+, sodium; NLR, neutrophil-to-lymphocyte ratio; pH, potential hydrogen; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure.

Univariate and multivariate Cox Regression models were used; HR, hazard ratio; 95%CI, 95% confidence interval; Bold text indicates statistical significance ($p<0.05$).

Table 6. The prognostic value of demographic, clinical, and paraclinical criteria at the time of admission for prediction of hospital mortality in trauma patients with admission neutrophil-to-lymphocyte ratio (NLR)>5.27

Patients features		Univariate Cox Regression		Multivariate Cox Regression	
		p	HR; (95%CI)	*p*	HR; (95%CI)
Gender	F		1		1
	M	0.914	0.96; (0.42-2.18)	NA	NA
Age	<65 years		1		1
	≥65 years	**<0.001**	4.14; (2.11-8.12)	**<0.001**	13.60; (4.99-37.09)
ISS	≤24		1		1
	>24	**0.015**	5.01; (1.88-13.02)	**0.036**	3.19; (1.17-8.70)
GCS	>8		1		1
	≤8	**0.029**	2.11; (1.08-4.12)	**0.027**	3.51; (1.15-10.67)
SBP	>90 mmHg		1		1
	≤90 mmHg	**0.002**	4.72; (1.81-12.32)	**0.005**	6.82; (1.77-26.24)
DBP	>64 mmHg		1		1
	≤64 mmHg	0.103	1.95; (0.87-4.35)	0.897	1.08; (0.35-3.33)
PR	≤110 beats/minute		1		1
	>110 beats/minute	0.497	1.27; (0.64-2.55)	NA	NA
RR	≤23 breaths/minute		1		1
	>23 breaths/minute	0.103	2.19; (0.85-5.60)	0.094	2.40; (0.86-6.66)
BS	≤165 mg/dL		1		1
	>165 mg/dL	0.604	1.20; (0.61-2.37)	NA	NA
Hb	≤12.8 g/dL		1		1
	>12.8 g/dL	0.085	1.82; (0.92-3.60)	0.282	2.30; (0.49-10.82)
Hct	≤34.7 %		1		1
	>34.7 %	0.382	1.39; (0.67-2.91)	NA	NA
Cr	≤1.25 mg/dL		1		1
	>1.25 mg/dL	**0.020**	2.23; (1.13-4.37)	0.340	2.66; (0.36-19.84)
BUN	≤16.8 mg/dL		1		1
	>16.8 mg/dL	0.107	1.72; (0.89-3.32)	0.165	2.07; (0.74-5.75)
INR	≤1.27		1		1
	>1.27	**0.036**	2.03; (1.05-3.92)	0.868	1.09; (0.41-3.91)
Na+	≤144 mEq/L		1		1
	>144 mEq/L	**0.004**	2.93; (1.40-6.14)	**0.009**	4.40; (1.44-13.46)
K+	≤4.5 mmol/L		1		1
	>4.5 mmol/L	**0.001**	3.21; (1.58-6.52)	**0.011**	4.52; (1.66-12.33)
pH	>7.28		1		1
	≤7.28	**<0.001**	3.99; (1.98-8.03)	**0.001**	3.99; (1.43-13.42)
BE	>-6.1 mEq/L		1		1
	≤-6.1 mEq/L	**0.049**	2.14; (1.06-4.19)	**0.038**	2.39; (1.01-4.59)

BE, base excess; BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; GCS, Glasgow coma scale; Hb, hemoglobin; Hct, hematocrit; ICU, intensive care unit; INR, international normalized ratio; ISS, injury severity score; K+, potassium; LOS, length of stay; NA, non-applicable/not available; Na+, sodium; NLR, neutrophil-to-lymphocyte ratio; pH, potential hydrogen; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure. Univariate and multivariate Cox Regression models were used; HR, hazard ratio; 95%CI, 95% confidence interval; Bold text indicates statistical significance ($p<0.05$).

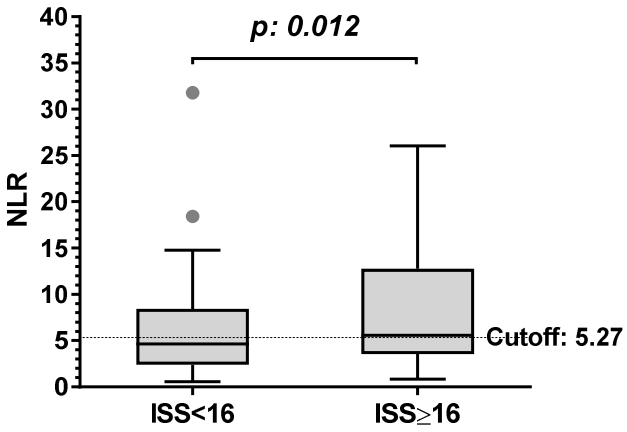

Figure 3. The Comparison of the admission neutrophil-to-lymphocyte ratio (NLR) value between trauma patients with injury severity score (ISS)<16 and ISS≥16. Mann-Whitney U test (Median (IQR)) was used; Bold text indicates statistical significance (p<0.05)

DISCUSSION

The results of our study demonstrated an association between NLR value at the time of admission and hospital mortality rate in trauma patients. Although our study highlighted the independent prognostic values of the admission NLR (10-120 minutes after trauma) to predict the hospital mortality in trauma patients, previous studies evaluated the values of NLR in the days after trauma. In this regard, two separate studies by Dilektasli et al, and Heffernan et al, have considered the NLR values at 2 and 7 days after the incidence of trauma as an independent prognostic indicator of mortality.[24,25] Furthermore, Duchesne et al, indicated that high levels of NLR were linked to higher mortality rates in patients with severe hemorrhage.[13] These findings suggest some abnormalities of the immune system in patients with trauma. Our results also revealed that patients with higher ISS had increased values of admission NLR. This result proposes the positive association between the severity of the injury and the intensity of the subsequent induced inflammatory responses.[26] In this regard, elevated NLR value after the injury is mainly due to the increased neutrophils count along with the decreased lymphocytes, monocytes, and eosinophils in peripheral blood, which has been reported as one of the earliest findings in the acute phase of inflammation.[25,27,28] Multiple organ failure occurs in patients with high level of NLR in response to severe injuries.[29] This phenomenon could be explained by the fact that neutrophils and macrophages are the first innate immune cells recruited to the site of injury in response to the high levels of chemokines such as chemokine (C-X-C motif) ligand (CXCL)1, CXCL2, CXCL8, CXCL10, chemokine (C-C motif) ligand (CCL)2, CCL3 and CCL8. These cells differentiate into inflammatory cells under the effects of cytokines derived from type 1 and 17 helper T (Th1 and Th17) cells such as interferon (IFN)-γ, IL-17F, and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as, other released inflammatory cytokines (such as IL-1β, TNF-α, and IL-6).[30,31] In steady-state conditions and non-severe injuries, entry of the anti-inflammatory cells, especially regulatory T (Treg) cells, type 2 helper T (Th2) cells, and myeloid-derived suppressor cells (MDSCs) into the site of injury, balances the immune responses, controls the systemic inflammation, and initiates tissue repairing under the influence of IL-4, IL-10, transforming growth factor (TGF)-β, and IL-33.[32-34] The imbalance between the pro- and anti-inflammatory systems plays a major role in the post-injury outcomes of severe traumatic injuries.[13] In this regard, over-activation of immune cells in sites of injury and subsequent systemic release of pro-inflammatory mediators, including inflammatory cytokines, chemokines, and enzymes (elastase, protease, and collagenase), promote SIRS that is the leading cause of systemic inflammation.[9,33,35] These processes enhance the release of DAMPs and

inflammatory cytokines, and chemokines in a variety of tissues that are far from the trauma sites and subsequently induce the influx of inflammatory cells. Over-activation of the recruited inflammatory cells under the influence of these inflammatory mediators leading to adverse events such as multiple organ dysfunction syndromes (MODS).[31] Chronic problems occur when CARS is elevated following high levels of SIRS in severe trauma. The persistence of SIRS and CARS after severe injuries result in the creation of PICS (persistent inflammatory-immunosuppressive and catabolic syndrome), which is characterized by immune system paralysis and predominance of anti-inflammatory conditions.[36] The weakened immune system increases susceptibility to infections and septicemia, which are positively associated with stronger SIRS and more severe MODS.[37]

The results of a study have shown that NLR value during the first 48 hours after injury is a predictive marker for the development of organ failure in the future.[38] This report was in line with our findings that trauma patients with an increasing NLR value (>5.27) at the time of admission had a higher risk (HR=2.33) of hospital mortality after traumatic injury. Our study showed that age≥65 years, SBP≤90 mmHg, Na>144 mEq/L, NLR>5.27, ISS>24, and GCS≤8 of trauma patients have independent effects (prognostic value) on hospital mortality of trauma patients. Multiple studies have supported our findings. They have shown that age was an important predictive factor for hospital mortality of trauma patients.[39,40] Also, a meta-analysis study indicated that the mortality was significantly higher in patients with lower GCS scores.[41] Furthermore, Aiyagari et al, reported that the mortality rate was increased in trauma patients with hypernatremia.[42] In addition, previous studies have demonstrated that BE can be a prognostic value for determining the trauma patients' outcomes. A large amount of lactic acid is generated by the activation of anaerobic metabolism following the bleeding and hypoxic conditions in injured tissues, which results in increasing base deficit (BD) levels (BE≤-6.1 mEq/L).[22,43,44] On the other hand, our results demonstrated that the prognostic value of admission NLR>5.27 was increased in the presence of other indicators such as age≥65 years, SBP≤90 mmHg, K>4.5 mmol/L, Na>144 mEq/L, pH≤7.28, GCS≤8, ISS>24, and BE≤-6.1 mEq/L.

The recent study has several limitations. First, our retrospective study was designed based on electronic medical records from a single center that may cause selection bias. Second, patients may have different post-traumatic care and support that may affect trauma-related outcomes. For example, the amount of fluid resuscitation may affect the level of admission NLR, at least in the acute phase of injury. Finally, we did not compare other inflammatory factors in the acute phase, including platelet-to-lymphocyte rate (PLR) and monocyte-to-lymphocyte rate (MLR). Therefore, we suggest that future studies must be carried out in multiple centers, with larger sample sizes, and at different time intervals after the trauma. Additional efforts should also be made to determine the effect of different post-traumatic care and supports on NLR value in trauma patients. Furthermore, the admission NLR may be more useful in combination with other markers such as PLR and MLR, as well as, inflammatory mediators to predict hospital mortality after severe trauma.

In conclusion, increased NLR value (>5.27) at the time of admission was associated with poorer outcomes in trauma patients. This study showed that the admission NLR>5.27 might have an independent prognostic value for the incidence of hospital mortality in trauma patients. In addition, the admission NLR>5.27 could have higher effects on the hospital mortality of trauma patients with age≥65 years, SBP≤90 mmHg, K>4.5 mmol/L, Na>144 mEq/L, pH≤7.28, GCS≤8, ISS>24, and BE≤-6.1 mEq/L.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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