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Neutrophil to Lymphocyte Ratio as a Predictive Factor for Evaluation of Outcome in Critically Ill Patients

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Abstract

***Background & Aims*:** Morbidity and mortality are higher in intensive care units (ICU). In this study hematological indexes such as NLR (Neutrophil to lymphocyte ratio) and PLR (platelet to lymphocyte ratio) were investigated in the ICU patients.

Materials & Methods: We did a retrospective study on ICU patients older than 18 years between June 2019 and July 2019. We gathered medical and laboratory data in the first 24 hours of ICU hospitalization and analyzed them. There were two groups of survived and un-survived. The primary outcome measure was death in ICU.

***Results*:** We included 194 patients whose mean age was 66.7 ± 20.1 years, and 105(54%) patients were male. 76 (39%) patients were non-survivors. Non-survivors had significantly higher NLR value (mean, 16 ± 15.1) than the survivors (mean, 10.5 ± 14, p = .015). The PLR of survivors and non-survivors was 240.3 ± 156.7 and 320.3 ± 269.1, respectively. PLR was not different between groups (p >0.05).

***Conclusion*:** These results suggest that NLR at admission is associated with higher mortality in the ICU among critically ill patients over 18 years old. Therefore, NLR at admission may be an alternative indicator of disease severity.

***Keywords*:** Critical Care; Neutrophils; Lymphocytes; Inflammatory Marker; Mortality

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Introduction

The number of ICU admission in hospitals is expected to grow in the coming years, including the large section that will eventually die. Recent studies declared that ICU mortality in their studied population varies from 10.1 to 27.3% (1-3).

Mortality and morbidity rates in the ICU patients are much higher than in another one who does not require treatment in this section. Therefore, alternative markers have been developed for mortality prediction in the ICU. Several screening tools have been developed to identify the risk of increased adverse outcomes, but these risk

assessment tools do not appear to have sufficient prognostic accuracy (3).

Recently, the use of hematologic inflammatory markers is increasing. Several hematologic markers have been suggested that relate to inflammatory conditions and outcomes in the literature (2-5). Neutrophil to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two new markers produced by routine hematology tests.

Inflammatory status of patient can be assessed by neutrophil to lymphocyte ratio (NLR). This simple indicator is inexpensive, reproducible, fast, and readily available. The prognosis of infection-related diseases, such as sepsis, bacteremia and appendicitis (4) and noninfectious diseases, such as acute myocardial infarction, stroke and several types of cancers (5) have been associated with NLR.

Although the mechanism is not exactly clear, the neutrophil increment could lead to systemic inflammation that affects atherosclerosis and tumor progression. Lymphocytes play the opposite role.

Therefore, NLR is a marker and predictive factor of risk and outcome in systemic inflammation and many other diseases. Also, it predicts better than total WBC count or neutrophil count (6).

According to recent studies, NLR (7) and PLR (8) were considered as a prognostic and inflammatory predictor in critically ill patients.

Further studies should be done to confirm the association between mortality in critically ill patients and NLR and PLR. We hypothesize that NLR and PLR are associated with mortality in critically ill patients. So we performed an observational study using unselected adult critically ill patients to test this hypothesis.

Method and Material

This retrospective observational study was conducted on consecutive patients who were admitted to ICU, between June 2019 and July 2019. It was carried out in a referral academic hospital after approval of the Ethics committee of Iran University of Medical Science. All patients provided informed consent before participating.

Inclusion criteria were patients older than 18 years who were admitted to the medical ICU with different medical problems. Patients with a trauma-related injury, hematologic disease, or incomplete blood count (CBC) test were excluded. Our diagnosis was confirmed according to laboratory tests and radiographic data.

Patients were observed until they were discharged from ICU or died. In the first 24 hours of hospitalization, hematological biomarkers such as hemoglobin, RBC, WBC and platelet count, RDW, PDW, and troponin were measured. If these tests were done more than one time in a day, the less number was archived. NLR and PLR were calculated for every patient by division of the neutrophil/platelet count by the lymphocyte count. Also, we recorded demographic data (age and sex), comorbid diseases, length of stay (LOS), and mortality in the ICU. Our primary and secondary objectives were mortality and loss in the ICU, respectively.

All comparisons were unpaired, and all tests of significance were 2-tailed. Provided data were analyzed by SPSS 20 (statistical product and service solutions, Chicago, IL, USA). Statistical analysis is presented by mean +SD. We used $\chi 2$ test or Fisher's exact test for analysis of categorical data. Continuous data were analyzed by Student t-test or Mann-Whitney U test. We determined cutoff levels for NLR as predictors of mortality by Receiver operating characteristic (ROC) curve analysis. P-value less than 0.05 was defined as statistically significant.

Result

In this study, a total of 194 patients admitted to the medical ICU at the time of emergency admission were evaluated. Among them, 118 (61%) were survivors and 76 (39%) were non-survivors. The mean age was 63.8 ±21.3 years old in the survived group and 71.3±17.5 years old in the un-survived group.

The patients in the un-survived group were significantly older than patients in the survived group (p=0.018). Among survived and un-survived group, 52% and 55% were men, respectively. Gender was not significantly different between these two groups (p=0.86). Survivors had a significantly shorter length of

stay in ICU than the un-survived group (6 ± 0.5 versus 13.6± 1.9 days, $p < 0.001$).

The most prevalent underlying diseases were hypertension, anemia, diabetes, cerebrovascular accident, and end-stage renal disease (ESRD) with a rate of 37.8%, 30.9%, 28.4%, 18.4%, and 14.4%, respectively. Also, 36.1% of all patients experienced sepsis. Clinical characteristics between the ICU survivors and non-survivors are presented in Table 1.

Hemoglobin, RDW, PDW, and troponin in the survivor group were not significantly different from those in the un-survived group ($p > 0.05$ for all).

The mean level of NLR in survived and un-survived subjects were 10.5±14 and 16.06±15.1, respectively. The un-survived group had higher NLR compared to the survived group (p=0.015). The level of platelet was significantly lower in survived group than un-survived group (244.4 ± 109.2 vs. 207.8 ± 98.9 u/mm3. p=0.03). However, there was no significant difference between the PLR of the survived group (240±156.7) and the un-survived group (320±269.1), (p=0.2). WBC count was significantly higher ($p<0.001$) and the lymphocyte count was significantly lower in the un-survived group compared to the survived group (p=0.04). Serum biomarker characteristics between ICU survivors and non-survivors are indicated in Table 2.

The best cutoff value of NLR was 9.2 with 64% sensitivity and 66% specificity in predicting mortality (AUC: 0.65, $p<0.015$) (Fig.1).

Patients were divided into two groups based on the NLR cutoff (9.2) and their outcomes were compared (Table3). Mortality rate of NLR above 9.2 was 51% (N =54) and below 9.2 was 25% (N= 22) (p=0.03). Length of stay in the ICU was significantly higher in patients with NLR above 9.2 compared to NLR below 9.2 (p=0.019) (Table.3).

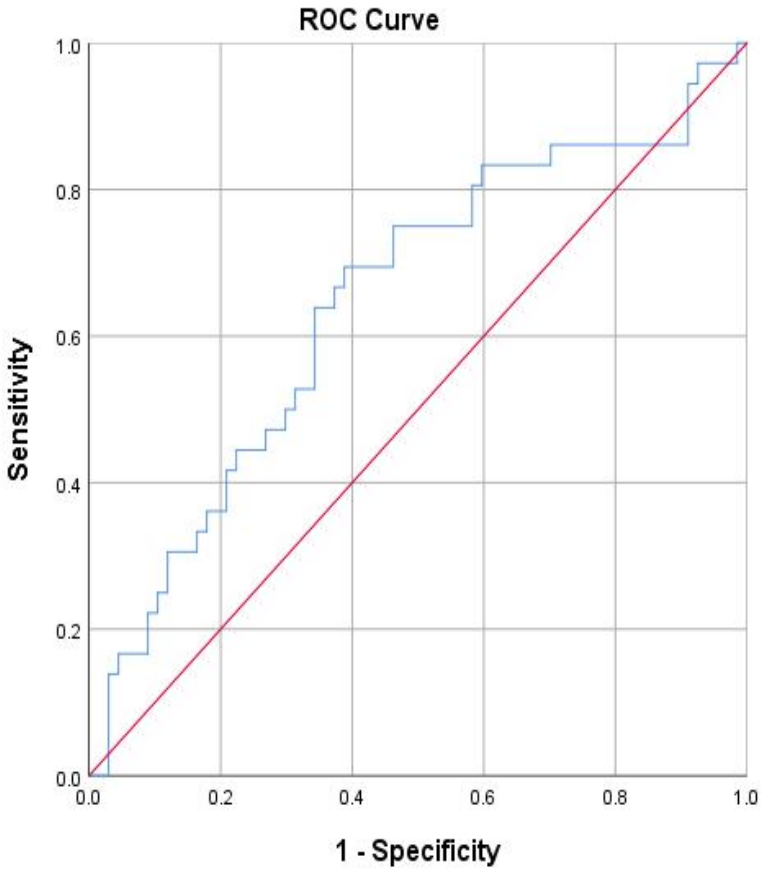

Figure 1. Prognostic value of the NLR for the prediction of ICU patient outcome (AUC: 0.646; 95% CI: 0.531–0.760)

Table 1. Demographic Data of the Study Participants

Characteristic	Total, N=194	Survivors, N= 118	Un-Survivors, N= 76	P-value
AGE, year	66.7 ± 20.1	63.6 ± 21.3	71.3± 17.5	0.018
GENDER				
Men/Women, n (%)	105(54%) /89(46%)	62(53%) /56(47%)	42(55%) /34(45%)	>0.0.05
Admission Cause				
IHD, n (%)	11 (5.7%)	6 (5.3%)	5 (6.8%)	>0.0.05
Sepsis, n (%)	70 (36.1%)	48 (43.8%)	22 (31.6%)	>0.0.05
GIB, n (%)	21 (10.8%)	13(10.5%)	8 (6.8%)	>0.0.05
Pneumonia, n (%)	21 (10.8%)	8 (6.7%)	13 (13.3%)	>0.0.05
Comorbidity				
Anemia, n (%)	60 (30.9%)	32 (28.9%)	28 (37%)	>0.0.05
CKD/ESRD, n(%	28 (14.4%)	13 (12.3%)	15 (19.2%)	>0.0.05
HTN, n (%)	73 (37.8%)	39 (34.2%)	34 (45.5%)	>0.0.05
CVA, n (%)	35 (18.4%)	22 (20%)	13 (18.8%)	>0.0.05
DM	55 (28.4%)	32 (27.8%)	23 (28.8%)	>0.0.05
ICU stay ,days	8.8 ± 10.9	6 ± 0.5	13.6 ± 1.9	<0.001

[a] *Continuous variables were analyzed by Student's t-test or Mann-Whitney U test, and categorical data by Chi-square test*

[b] *IHD: ischemic heart disease; GIB: gastro intestinal bleeding; CKD: chronic kidney disease; ESRD: end stage renal disease; and HTN: hypertension*

[c] *Variables are expressed as mean (standard deviation) and categorical data are expressed as number (percentage)*

Table 2. Serum biomarkers characteristics between ICU survivors and non-survivors

Characteristic	Survivors (n=118)	Non-Survivors (n=76)	P-value
WBC count ,u/mm3	10.1 ± 4.8	12 ± 6	0.019
Hb, g/dl	12.1 ± 3.1	11.9 ± 3.3	>0.05
RDW	15.6 ± 3	16.3 ± 3	>0.05
Plt, u/mm3	244.4 ± 109.2	207.8 ± 98.9	0.036
Neutrophil count ,u/mm3	10.5 ± 5.1	16.06 ± 6	>0.05
Lymphocyte count ,u/mm3	1.4 ± 0.9	1.2 ± 1	0.04
PDW	11.1± 2	11.3 ± 1.6	>0.05
PLR	240.3 ± 156.7	320.3 ± 269.1	>0.05
NLR	10.5 ± 14	16 ± 15.1	0.015
Troponin, ng/ml	107.6 ± 322.3	171 ± 580.4	>0.05

[a] *Continuous variables were analyzed by Student's t-test or Mann-Whitney U test*

[b] *ICU: intensive care unit; WBC: white blood cell; Hb: hemoglobin; RDW: red cell distribution width; Plt: platelet, PDW: platelet cell distribution width; PLR: platelet to*

Lymphocyte ratio; NLR: neutrophil to lymphocyte ratio.

[c] *Variables are expressed as mean (standard deviation)*

Table 3. Comparison of outcomes in patients grouped according to NLR values

Outcome	NLR > 9.2 (n = 106)	NLR <9.2 (n = 88)	P-value
Days of stay in intensive care (mean ± SD)	12.2 ± 12.8	7.4 ± 12.5	0.019
Discharged, n (%)	52(49%)	66(75%)	0.004
Expired, n (%)	54(51%)	22(25%)	0.004

SD standard deviation, NLR neutrophil to lymphocyte ratio

Discussion

In the present study, the performance of several easily valuable hematologic parameters as predictors of short-term outcome in critically ill patients was evaluated. We showed that the high level of both NLR and WBC and low level in platelet count at admission time to ICU were associated with high mortality in critically ill patients. However, there were no significant differences between the survived and un-survival group in the terms of the number of neutrophils, MPV, PLR, hemoglobin, RDW, PDW, and troponin.

The severity of the patient and prognosis could be assessed using new technologies designed for healthcare. The need to choose a highly efficient approach to predict the patients' clinical prognosis and outcome in a short period in the ICU is still a challenge. Several inflammatory markers such as NLR, PLR, Prognostic Nutritional Index, and the Modified Glasgow Prognostic Score have been proposed to assess the prognosis of inflammatory conditions and malignancies (9, 10).

These markers could also be used in the early detection, risk classification, and decision making of high-risk critically ill patients. Among them, NLR, PLR, and Lymphocyte to CRP ratio are simple to calculate, and do not have an additional cost. (11)

NLR is obtained from the absolute number of neutrophils and lymphocytes. It shows the underlying inflammatory process. The release of arachidonic acid metabolites and platelet-activating factors leads to neutrophilia and thrombocytosis, and lymphopenia (12).

The association of NLR with outcomes could be due to the physiological link between neutrophilia and lymphopenia with systemic inflammation and stress. Zahorec et al. (13) reported that NLR reflects the patient's response to the inflammatory condition. Thus, neutrophils increase in response to stress, which, if high, causes lymphocyte apoptosis (14, 15). Also, Heffernan et al. reported lymphopenia and neutrophilia in trauma patients and patients with systemic inflammatory response syndrome (16).

Lymphocytes are important for regulating the proper inflammatory response. Apoptosis, cellular exhaustion, and down-regulation cause their persistence of a harmful inflammatory state (17). Overall, increased NLR may identify patients who are physiologically intolerant of inflammatory conditions and are more prone to death. (18).

NLR as a poor prognostic factor in various cancers, including breast, renal, hepatocellular carcinomas, colorectal, bladder, prostate, ovarian and testicular cancers is reported in several studies (17-24). Evidence supports the utility of the NLR in predicting the prognosis of inflammatory conditions, despite being a non-specific marker (11, 21, 25). It is found that the normal NLR values in an adult, non-geriatric, population in good health are between 0.78 and 3.53 (26). Normal PLR reference values for healthy individuals have not yet been described.

In our study, there was a significantly direct correlation between NLR level and mortality rate and length of ICU stay. When using the best cutoff value of

NLR, PPV and NPV were 64% and 66%, respectively. Patients with NLR value greater than 9.2 had higher mortality and length of ICU stay, based on our ROC curve analysis. This study is similar to studies conducted by Salciccioli et al. (7) and Yoldas et al. (8) that introduced NLR as a prognostic factor in critically ill patients. According to our study, PLR was not a useful predictor of mortality or morbidity in critically ill patients in contrast to the findings of the study conducted by Yoldas et al. (8). They concluded that the PLR was a simple and rapid marker of inflammatory stress in critically ill patients.

In this study, we had some limitations. Our study is a single-center retrospective study, should be repeated with larger prospective studies. Consistent with other retrospective studies, this study is limited by an inability to control for all measured and unmeasured confounders. All-cause mortality was our primary outcome in the ICU, so we could not analyze the cause of specific mortalities.

The role of underlying diseases was not described and they were not investigated as an independent factor for mortality in this study. Therefore, the role of hematologic indices was described in all critical patients. We also suggest further studies to investigate other parameters, such as hemodynamics, acid-base status (e.g., lactate), or common scoring systems (e.g., Sequential Organ Failure Assessment or Acute Physiology and Chronic Health Evaluation).

Conclusion

The NLR predicted mortality in critically ill patients. This marker is inexpensive and easy to evaluate. Physicians should be aware of elevations in the NLR and platelet in patients in ICUs.

Abbreviations and Symbols:

ICU: Intensive care units

NLR: Neutrophil to lymphocyte ratio

PLR: Platelet to lymphocyte ratio

CBC: Complete blood count

LOS: length of stay

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Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests.

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