

## Research Article

# The Association Between Lymphocyte/Neutrophil Ratio and Clinical Course in Intensive Care Patients

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### Abstract

**Objectives:** Hemogram parameters and basic ratios, such as the lymphocyte-to-neutrophil ratio (LNR), in addition to other biochemical factors, have been examined for their potential role in the inflammatory process. In this study, the aim was to explore an association between hemogram parameters and clinical course in patient admitted to the intensive care unit (ICU).

**Methods:** The data of 109 patients who were hospitalized for at least 10 days in the ICU were investigated retrospectively and divided into 2 groups: those who died in the ICU (n=68) and those who were transferred to a ward (n=41). Demographic features, hospitalization indications, length of time in the ICU, and laboratory data were analyzed using independent sample t-testing.

**Results:** The LNR was significantly higher in the patients who were transferred to a ward ( $0.32 \pm 0.4$  vs  $0.16 \pm 0.20$ ;  $p=0.03$ ). There was no significant difference in the other variables, including age, days in ICU, NLR and mean platelet volume. LNR was an independent factor for the duration of stay in the ICU.

**Conclusion:** The LNR may be helpful in the management and evaluation of patients in the ICU.

**Keywords:** Intensive care unit, lymphocyte/neutrophil ratio

The primary aim in intensive care units is to reduce mortality and hospital stay by providing clinical improvement based on clinical status of the patient. Along with correct diagnosis, appropriate treatment and good care, it is suggested that disease-specific or routine laboratory tests performed on intensive care patients can be used for this purpose. The prognostic value of commonly used inflammatory markers including albumin, c-reactive protein (CRP) and procalcitonin in addition to biochemical parameters such as lactate dehydrogenase and bilirubin have been confirmed in various studies.<sup>[1, 2]</sup> Prognostic significance of hemogram parameters, particularly in malignancies and inflammatory diseases, have been emphasized.

Mean platelet volume (MPV) have been associated with poor prognosis in bladder cancers, RDW have been found to predict survival in breast and prostate cancers.<sup>[3, 4, 5]</sup> It was also reported that both parameters were associated with sepsis and irritable bowel syndrome.<sup>[6, 7]</sup>

Inflammatory processes affect total leucocyte count and particularly absolute neutrophil, absolute lymphocyte and absolute monocyte counts. A reduction in lymphocyte and monocyte levels is observed as neutrophil count is elevated.<sup>[8, 9]</sup> New parameters for estimating leucocyte subtypes have been developed in recent years. The neutrophil/lymphocyte ratio (NLR) which can be easily obtained by automated blood

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**Submitted Date:** May 18, 2018 **Accepted Date:** June 13, 2018 **Available Online Date:** November 15, 2018

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count devices has been extensively studied particularly in solid organ tumors. Clinical implications of assessment with a combination of neutrophil count and neutrophil/lymphocyte ratio have been demonstrated in lung cancers, gastrointestinal system cancers and renal cancers.<sup>[10, 11, 12]</sup> There are also studies reporting association with mortality in acute coronary syndrome and pulmonary embolism.<sup>[13]</sup> It has been reported that short- and long-term mortality in emergency department critical care patients and post-operative complication risk in colorectal surgery patients can be predicted.<sup>[14, 15]</sup>

This study was aimed to investigate the relation between clinical course and hematological parameters in cases admitted to intensive care unit with various conditions.

## Methods

In our study, medical files of patients who were admitted to Konya Training and Research Hospital, Internal Medicine Intensive Care Unit for various conditions in the past year have been reviewed retrospectively. The medical records of patients who stayed at the unit for minimum 10 days were reviewed to obtain information on demographic data, hospitalization indication, duration of hospitalization and parameters including hemoglobin (Hb), hematocrit (Htc), red cell distribution width (RDW), mean corpuscular volume (MCV), total leucocyte count, absolute neutrophil count, absolute lymphocyte count, neutrophil/lymphocyte ratio (NLR) and lymphocyte/neutrophil ratio (LNR) and mean platelet volume (MPV). Additionally, values for serum biochemistry parameters (Serum glucose, creatinine, urea, electrolytes) and inflammatory markers (C reactive protein, erythrocyte

sedimentation rate) were evaluated. Patients divided into two groups as those who died in the intensive care unit and those who were transferred to the clinic.

## Statistical Analysis

Statistical analysis was performed using IBM SPSS software version 22. Based on Kolmogorov-Smirnov test, parametric data showing normal distribution were presented as mean and standard deviation. Data of the two groups were compared using independent samples t-test. Statistical significance was set at  $p < 0.05$ .

## Results

Overall 109 patients were included in the study; 48 were female and 61 were male. No significant difference was found between female and male patients in terms of hematological parameters while serum creatinine levels were significantly lower in women compared to men (women:  $1.5 \pm 0.8$  mg/dL, men  $2.2 \pm 2.1$ ,  $p = 0.02$ ). Among the cases, 68 (62.4%) formed the group who died at the intensive care unit and 41 (37.6%) formed the group who were transferred to the clinic. Mean age was  $74.4 \pm 13.2$  years for the death group and  $74.7 \pm 12.9$  for the clinic transfer group; duration of hospitalization was  $20 \pm 10$  days and  $17 \pm 8$  days, respectively. Based on independent samples t-test, no difference was detected between the two groups in terms of age, duration of hospitalization, Hb, Htc, MCV, RDW, WBC, absolute neutrophil count, NLR, PLT and MPV values (Table 1). On the other hand, mean LNR was significantly higher in the clinic transfer group ( $p = 0.04$ ). Cox

**Table 1.** Distribution of Group Datas

	<b>Dead (n=68)</b>	<b>Discharged to the clinic (n=41)</b>	<b>p</b>
Age	74.4±13.2	74.7±12.9	0.91
During at ICU (Day)	20±10	17±8	0.24
Hb (g/dL)	10.7±2.8	11±3	0.6
WBC (µL)	11650±6370	11310±6900	0.79
PLT (µL)	240000±123000	237000±114000	0.91
Absolute lymphocyte (µL)	1150±871	1740±1690	0.04
LNR	0.16±0.20	0.32±0.4	0.03
NLR	11.2±7.8	8.6±9.4	0.12
MPV (fL)	10.3±1.1	10.7±0.9	0.07
RDW (%)	17.7±2.9	17±3.9	0.28
MCV (fL)	86.4±9.1	87.8±11.8	0.49
CRP (mg/dL)	103±82	83±68	0.2

\* Values are expressed as "Mean±Standard Deviation"

\* Bold values signifies  $p < 0.05$ .

Abbreviation: ICU; Intensive Care Unit, Hb; Hemoglobin, WBC; White Blood Cell, PLT; Thrombocyte, LNR; Absolute lymphocyte/Neutrophyl ratio, NLR; Absolute neutrophyl/Lymphocyte ratio, MPV; Mean Platelet Volume, RDW; Red Cell Distribution Width, MCV; Mean Corpuscular Volume, CRP; C-Reactive Protein.

hazard regression analysis indicated that duration of intensive care stay was independently predicted by LNR and intubation status. High LNR was associated with longer intensive care stay ( $p=0.01$ ), non-intubated patients had shorter stay at the intensive care unit ( $p=0.001$ ).

## Discussion

In many intensive care units, routine tests including complete blood count, various biochemical tests (Serum glucose, urea, creatinine, electrolytes, albumin, lactate dehydrogenase, gamma-glutamyl transferase, alkaline phosphatase etc.) and inflammatory markers such as CRP and pro-calcitonin are performed on patients upon admission. Test follow-up is generally coordinated based on patient's clinical features and the underlying disease. Can these parameters and some ratios simply derived from them predict clinical course?

Among the hemogram parameters, MPV has been recently studied in various disease groups. Some studies have shown MPV is a marker of inflammatory processes (e.g., inflammatory bowel diseases, sepsis, pneumonia).<sup>[16, 17, 18]</sup> It was also reported that low MPV values can be associated with poor prognosis in bladder carcinoma and renal cell carcinoma.<sup>[3, 19]</sup> Review of studies in intensive care patients has revealed different findings. For instance, in the study by Karagoz et al., high MPV values were associated with reduced survival and the meta-analysis conducted by Tajareernmuang et al. has indicated that first measurement was not predictive while MPV values measured after the third day could be significant.<sup>[20, 21]</sup> In our study, no difference was found in terms of MPV values between the patients who died at the intensive care unit and those who were transferred to the clinic ( $p=0.07$ ).

NLR has been studied in various malignancy and it was reported to be an independent prognostic factor for colon and breast cancer.<sup>[11, 22]</sup> Cho et al. have reported that NLR in combination with CA125 could be used diagnostically and that high NLR was associated with poor prognosis.<sup>[23]</sup> Additionally, NLR was associated with higher mortality in the analysis of cases who were transferred to the intensive care unit either from the emergency department or any clinic for various indications.<sup>[14]</sup> In etiology-based analyses including particularly sepsis, a significant relation was not found between reason for ICU admission and NLR.<sup>[24]</sup> In this respect, the etiological variability of the cases included in our study has limited subgroup analysis. The fact that no difference for NLR was found between our patient groups (death and clinical transfer groups) is suggested to be related to small sample size.

LNR was the significant parameter in our study. Data related to LNR in the literature appears to be obtained primarily from restricted samples. For example, increased LNR was found, along with high adenosine deaminase levels, in pleural fluid

samples of patients with pulmonary tuberculosis. Additionally, increased LNR indicating tissue lymphocyte infiltration was associated with prolonged survival in advanced non-small cell lung cancer.<sup>[25, 26]</sup> Choi et al. have reported higher blood LNR levels in the non-rejected heart transplantation group compared to the acute rejection group at 3 months of transplantation.<sup>[27]</sup> Since lymphocytes are known to act at different stages of both natural and acquired immunity from antigen delivery to antibody response, these findings can be explained by the role of lymphocytes in immunity and suppressed immunity of ICU patients. Immunosuppression can lead to sepsis, opportunistic infections, organ dysfunctions and even death.<sup>[28, 29, 30]</sup>

Many factors that cause immunosuppression can be present in ICU conditions and their suppressive potentials may be variable. For example in cases who have undergone surgery, immunity is suppressed during the post-operative period.<sup>[31]</sup> Central nervous system (CNS) trauma causes immunosuppression due to directly the trauma and/or secondary infections. The pathophysiology involves inflammation and changes in release of mediators active in immune response.<sup>[32]</sup> Additionally, the primary indication for admission to ICU such as sepsis and treatment-related factors such as broad spectrum antibiotic use can also induce immunosuppression. Anti-neoplastic agents used for treatment of malignancies, post-transplantation immunosuppressive agents and corticosteroid use are among the medical factors. In the prospective study including pediatric ICU patients, Muszynski et al. have reported that erythrocyte concentrates with long storage time showed unfavorable effects on natural immunity.<sup>[33, 34]</sup>

Results of our study indicating higher LNR values in the group transferred to a clinic from ICU, longer ICU stay in the higher LNR group according to Cox regression analysis suggests cases with higher LNR may have a more intact immune system compared to those with lower LNR. As indicated with the above mentioned literature, immunosuppression in ICU conditions is multifactorial. Considering common factors including indication for ICU admission, co-morbidities, organ functions, medications and infection status predict progression, studies on larger case samples that analyze etiology-based subgroups would be more favorable. We consider this as the major limitation of our study. We suggest our study can provide a unique perspective with regard to significant results obtained with LNR assessment in peripheral blood samples.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship contributions:** Concept – A.T., O.B., Z.E.A.K., H.K.; Design – A.T., O.B., Z.E.A.K., H.K.; Supervision – A.T., O.B., Z.E.A.K., H.K.; Materials – A.T., O.B., Z.E.A.K., H.K.; Data collection &/or processing – A.T., O.B., Z.E.A.K., H.K.; Analysis and/or interpretation – A.T., O.B., Z.E.A.K., H.K.; Literature search – A.T., O.B., Z.E.A.K., H.K.; Writing – A.T.; Critical review – A.T.

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