Original Research
JCAM

Relationship of neutrophil-to-lymphocyte ratio with presence and severity of pneumonia

Relation of neutrophil to lymphocyte ratio and pneumonia severity

Yasemin Kaya[1], Nilay Taş[2], Ebru Çanakçı[2], Zübeyir Cebeci[2], Muhammet Özbilen[3], Havva Keskin[4], Berna Botan Yıldırım[5]
[1]Department of Internal Medicine, Ordu University Medical School, Ordu,
[2]Department of Anesthesiology and Reanimation, Ordu University Medical School, Ordu,
[3]Department of Internal Medicine, Ministry of Health and Ordu Univesrty Education and Research Hospital, Ordu,
[4]Department of Internal Medicine, Medeniyet University Medical School, Istanbul,
[5]Department of Chest Diseases, Ordu University Medical School, Ordu, Turkey

Abstract

Aim: Today, community-acquired pneumonia remains one of the causes of high mortality and morbidity. In this study, we aimed to demonstrate the relationship between NLR, which was found to be a marker related to the systemic inflammation in the recent studies, and PSI, CURB-65, and PIRO, which were developed to predict hospitalization, being taken to an intensive care unit, and prognosis in patients with community-acquired pneumonia, and mortality. Material and Method: 100 patients admitted to the department and intensive care unit with the diagnosis of community-acquired pneumonia were included in the study. The patients underwent physical examinations and their medical histories were taken when admitted to the hospital. The biochemistry, hemogram, arterial blood gas examinations were analyzed. Their Pneumonia Severity Index (PSI), CURB-65 (Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age ≥65), and PIRO (Predisposition, Infection, Response, Organ dysfunction) scores were calculated. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. Results: 67 of the patients in the department and another 33 in the intensive care unit were followed. The average age of patients followed in the intensive care unit was 75.3±10.3 and the average age of patients followed in the department was 66.8±12.5. A positive correlation was found between NLR and CURB-65, PIRO, and PSI scores (respectively: r: 0.354 p<0.001, r: 0.290 p: 0.003, r: 0.302 p: 0.002). In the ROC curve analysis, for the estimation of CURB-65 > 2 score, NLR had a 6.26 predictive value (AUC:0.762, 95% CI:0.662-0.863, p<0,001), 76% sensitivity and 60% specificity; for the estimation of PIRO 4-5-6 score, NLR had a 6.67 predictive value (AUC:0.687, 95% CI:0.569-0.806, p=0.013), 67% sensitivity and 60% specificity; for the estimation of PSI score, NLR had a 5.55 predictive value (AUC:0.637, 95% CI:0.523-0.750, p<0,001), 62% sensitivity and %58 specificity. Patients who died had significantly higher NLR levels in proportion to the survivors (13.5+9 vs 7.9+6.8, p=0.010). However, in the ROC curve analysis for the estimation of death, NLR was not superior to CURB, PIRO, and PSI scores. Discussion: NLR, a non-specific inflammatory marker that can be calculated quickly and easily in the routine hemogram examination, and is closely related to the scores regarding the severity of patients with CAP. Although it is not superior to the score systems in the estimation of death, it can be used for the same purpose as the score systems.

Keywords

Neutrophil to Lymphocyte Ratio; Community; Acquired Pneumonia; PSI; CURB; 65-PIRO

DOI: 10.4328/JCAM.5817 Received: 12.03.2018 Accepted: 30.03.2018 Published Online: 04.04.2018 Printed: 01.09.2018 J Clin Anal Med 2018;9(5): 452-7
Corresponding Author: Yasemin Kaya, Department of Internal Medicine, Ordu University Medical School, 52000, Ordu, Turkey.
T.: +90 4522252342 F.: +90 4522250190 E-Mail: ysmnkcmz@gmail.com
ORCID ID: 0000-0001-7360-8090

Introduction

Community-acquired pneumonia (CAP) is a potentially life threatening illness and is an important cause of morbidity and mortality [1,2]. It also has a high treatment cost and places an economic burden on health care systems [2]. Although pneumonia takes sixth place among the causes of death in England and the United States, it is in first place among the causes of death due to infections [3,4]. While the mortality is 1-5% for outpatients, the average mortality rises to 12% for inpatients, and to 40% for patients who require intensive care support [5]. In the previous studies, various scoring systems have been defined to indicate hospitalization and intensive care unit (ICU) admission with the diagnosis of pneumonia, and to estimate the mortality rate. The most frequently used pneumonia severity scoring systems are the Community-Acquired Pneumonia Severity Index (PSI), the Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age ≥65 (CURB-65), and the Predisposition, Infection, Response, Organ dysfunction (PIRO) [6-8].

The neutrophil-lymphocyte ratio (NLR) is used to evaluate systemic inflammation and is a laboratory marker that can be easily measured. In many of the previous studies, it was demonstrated that NLR could be used as a good marker related to the progression and the mortality of diseases, such as cardiovascular diseases, acute appendicitis, acute pancreatitis and oncologic diseases [9-12].

We hypothesized that the increased systemic inflammation assessed by NLR in the initial assessment of CAP might help clinicians identify the patients who will require ICU admission. This would determine whether NLR could predict for hospitalization and ICU admission through the severity criteria defined by PSI, CURB-65, and PIRO in the patients with CAP. We also assessed the relationship between NLR and patients' outcomes.

Material and Method

We followed 100 consecutive patients (aged 18 and above) hospitalized with the diagnosis of CAP. Pneumonia was defined on the admission chest radiograph as a newly developing pulmonary infiltrate and cough, dyspnea, fever, and/or pleuritic chest pain, the symptoms and signs of lower respiratory tract infection. The exclusion criteria were hospital admission in the previous two weeks, receiving an antibiotherapy treatment for any cause, being accompanied by any infection or acute coronary syndrome, and immunosuppressive cases (e.g. neutropenia due to chemotherapy, due to corticosteroid, or cytotoxic drug use).

From among the patients diagnosed with CAP, the ones indicated for ICU admission were followed in ICU and the others were followed in the patient clinic. The decision for ICU admission was made if the patient had one major or at least three minor criteria. The major criteria were invasive mechanical ventilation necessity and septic shock requiring vasopressor. The minor criteria were recognized as respiratory rate ≥30/min., PaO2/FiO2 ≤250, multilobar infiltrates on the chest radiography, confusion/disorientation, uremia (BUN ≥20 mg/dL), leucopenia (Leucocyte <4000 /mm3), thrombocytopenia (Thrombocyte <100 000 / mm3), hypothermia (<36°C), and hypotension requiring liquid loading. The decision for admission to an ICU or service was made by the attending physicians. The study was approved by the ethics committees.

Age, gender, smoking status, drug use and coexistent diseases (neurological and neoplastic diseases, liver, heart, lung, renal, diabetes mellitus, and hypertension) of all patients were recorded on admission to the hospital. Detailed physical examinations of all patients were performed and the clinical symptoms (fever, pleuritic chest pain, cough, dyspnea, and mental confusion) and the clinical findings (blood pressure, body temperature, respiratory rate, and heart rate) were recorded.

The blood samples for complete blood count and biochemistry were taken from all of the patients on admission to the hospital. The blood samples were collected in gel tubes, which did not include anticoagulant, for blood biochemistry analysis. The blood samples were centrifuged at 1800*g for 15 minutes and the plasma and serum samples were obtained and measured cholorometrically using an Abbott original reagent on Abbott Architect 8000 auto analyzer. The blood samples from all patients were taken to K3 EDTA tubes to count hemoglobin, total white blood cells (WBC), neutrophils and lymphocytes, and were analyzed on the Abbott Cell-Dyn 3700 Hematology device. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. The artery was reached via the percutaneous route and the blood was taken by heparin injector for blood gas measurement. The sample was taken to the laboratory on an ice pack within 5 minutes and was studied on an ABL800 FLEX blood gas analyzer (Radiometer) device.

Pneumonia Severity Index (PSI) [6], CURB-65 (Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age ≥65) [7], and PIRO (Predisposition, Infection, Response and Organ dysfunction) [8] scores of all patients at the time of admission were calculated.

Statistics

Numeric variables were expressed as mean ± SD and the categorical variables were expressed as percentage. To test the difference of the numeric variables between groups, Student's T-test or Mann-Whitney U test was used. To test the difference of the categorical variables between the groups, the Chi-square test was used. For correlation analysis between the variables, Pearson or Spearman correlation test was used. NLR was used for predicting the severity of PSI, CURB-65, and PIRO scores and ROC analysis was used for determining the best cut-off value. P value <0.05 was recognized as the limit of significance. SPSS 20.0 SPSS Inc., Chicago, Illinois) packet program was used for all statistical analysis.

Results

67 of the patients were followed in the patient clinic of internal medicine or pulmonology and the other 33 were followed in the intensive care unit. The baseline characteristics of the patients in ICU and in the patient clinic are summarized in Table 1. 77% of the patients scored 3-4-5 on CURB-65, 72% scored 4-5-6-on PIRO, and 61% scored 4-5 on the PSI. A positive correlation was found between NLR and CURB- 65, PIRO, and PSI scores (r: 0.354 p<0.001, r: 0.290 p: 0.003, r: 0.302 p: 0.002, respectively) (Figure 1-2-3, respectively). In ROC curve analysis, a cut-off NLR value of 6,26 had 76% sensitivity and 60% specificity in prediction of CURB-65 3-4-5 (AUC:0,762, 95% CI:0,662-0,863, p<0,001). (Figure-4-A); for estimation of PSI 3-4-5 score, NLR had 5,55 predictive value (AUC:0,637, 95% CI:0,523-0,750,

Table 1. Comparison of base line characteristics of patients admitted to inpatient clinic and intensive care unit.

	Inpatient clinic Patients (n=67)	Intensive care unit Patients (n=33)	P value
Age	66,8±12,5	75,3±10,3	0,001
Gender (male) %	62,7	75,8	0,191
Diabetes Mellitus, %	18	53,8	<0,001
Hypertension, %	37	38	0,287
COPD, %	32	50	0,078
Cigarette, %	48	73	0,020
PSI-median	3	5	<0,001
PIRO-median	2	4	<0,001
CURB-65-median	2	4	<0,001
Hemoglobin	12,3±2,01	10,8±2,1	0,003
White blood cells	13,4±6,1	15,0±9,3	0,899
RDW	15,7±2,3	17,7±3,1	0,004
NLR	8,1±6,4	15,5±10,8	0,004
Blood Sugar	140±61	141±48	0,981
Creatinine (mg/dl) (mean±SD)	3,1±17,02	1,37±0,96	0,637
BUN (mg/dl)(mean±SD)	21,4±10	41,6±35,8	0,016
ALT (mg/dl)(mean±SD)	19,1±13,5	31,9±36,8	0,144
AST (mg/dl)(mean±SD)	21,2±8,6	49,1±57,4	0,043
CRP (mean±SD)	13,6±10,5	15,9±9,9	0,381
Cure (%)	100	55,2	<0,001
Mortality (%)	0	44,8	<0,001
Respiratoryrate>30 (%)	0	65,2	<0,001
Multi-lobular infiltration (%)	37,3	60	0,051
Confusion (%)	4,5	52	<0,001
Uremia (%)	19,4	60	<0,001
Leukopenia (%)	0	12	<0,001
Thrombocytopenia (%)	0	23,8	<0,001
PaO2/ FiO2 <250 (%)	13,4	52,2	<0,001
Hypothermia (%)	0	4	0,100
Hypotension (%)	0	24	<0,001

PSI: Pneumonia Severity Index, **CURB-65:** Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age ≥65, **PIRO:** Predisposition, Infection Response, Organ dysfunction, **COPD**: Chronic obstructive pulmonary disease, **RDW:** Red cell distribution width, **NLR**: Neutrophil-lymphocyte ratio, **CRP:** C-reactive protein, **BUN:** Blood urea nitrogen, **ALT:** Alanine Aminotransferase, **AST:** Aspartate Aminotransferase

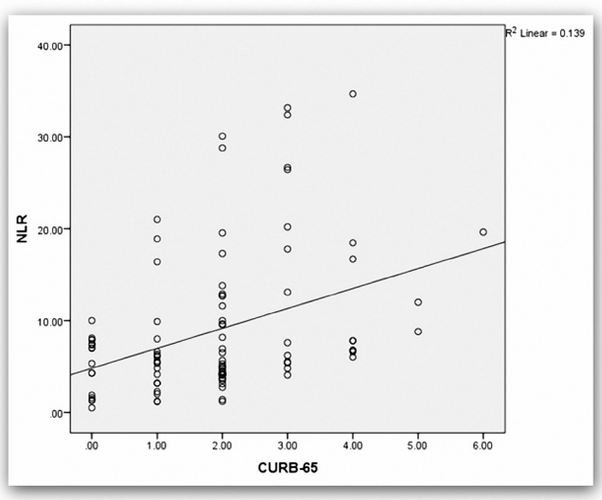


Figure 1. Correlations of NRL with CURB-65

p<0,001), 62% sensitivity and 58% specificity (Figure-4-B); for estimation of PIRO 4-5-6 score, NLR had 6,67 predictive value (AUC:0,687, 95% CI:0,569-0,806, p=0,013), 67% sensitivity and 60% specificity [Figure-4-C]. Also, a positive correlation was detected between NLR and the number of minor diagnostic criteria (r: 0,230, p: 0,037) [Figure-5].

While the mortality rate in the patient clinic was 0%, the mortality rate among the ICU patients was 44,8%. The patients who died had significantly higher NLR levels than the patients who survived (13.5+9 vs 7.9+6.8, p=0.010). However, in the ROC curve analysis, NLR was not superior to CURB, PIRO, and PSI scores in the prediction of death. [Figure-6 and Table-2].

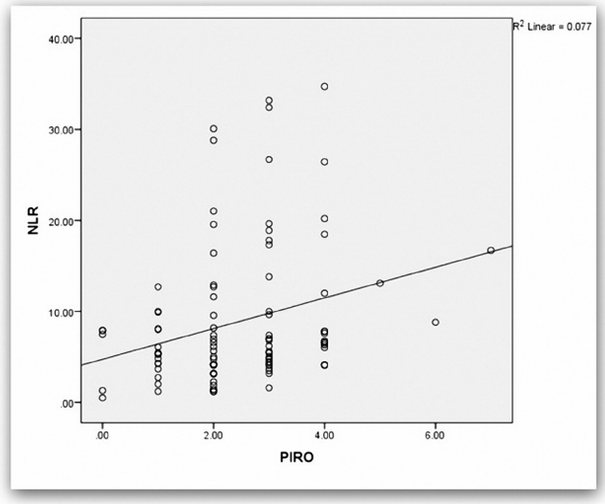


Figure 2. Correlations of NRL with PIRO

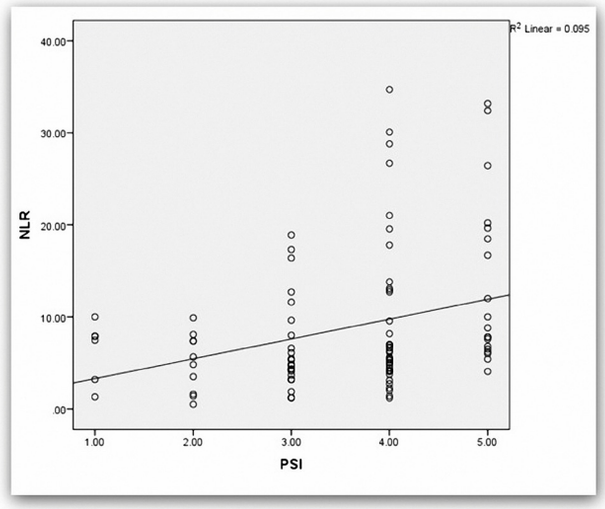
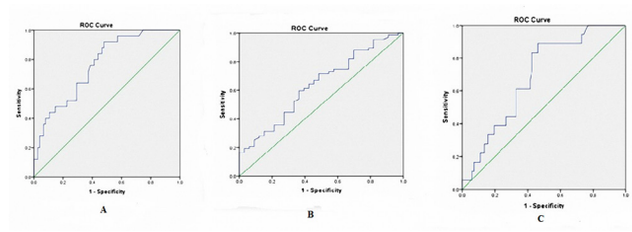


Figure 3. Correlations of NRL with PSI



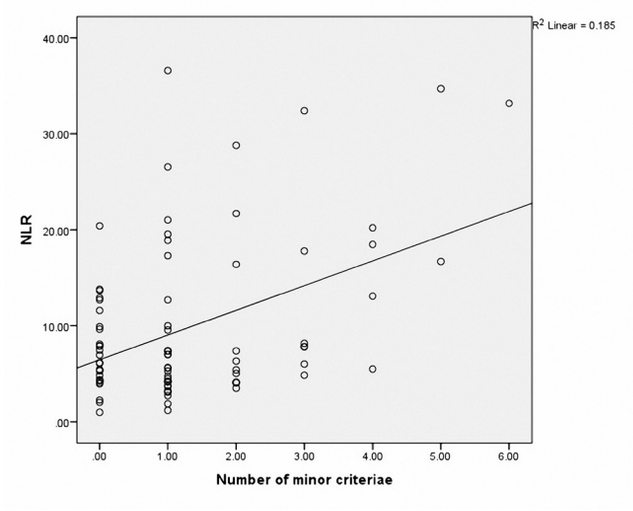


Figure 5. Receiver–operating characteristic (ROC) curve analysis plot to determine the cut-off value of neutrophil-to-lymphocyte ratio in the PIRO

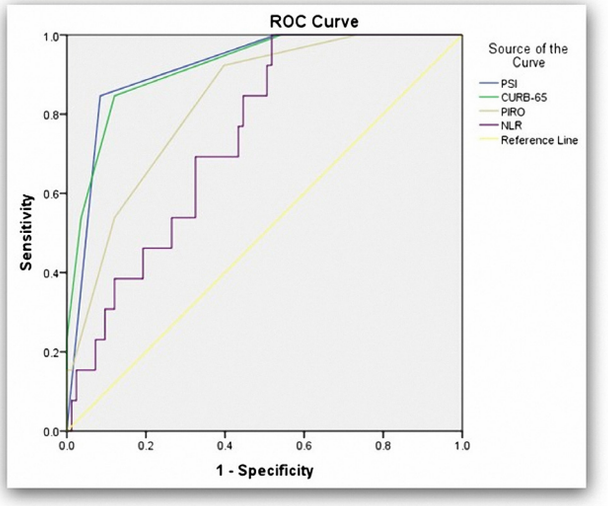


Figure 6. Receiver–operating characteristic (ROC) curve analysis plot to determine the cut-off value of neutrophil-to-lymphocyte ratio in PSI

Table 2. ROC curve analysis for risk scores and NLR in prediction of death.

	AUC	95% CI	P value
PSI	0,917	0,846-0,988	<0,001
CURB-65	0,863	0,742-0,984	<0,001
PIRO	0,709	0,537-0,881	0,016
NLR	0,743	0,627-0,860	0,005

PSI: Pneumonia Severity Index, **CURB-65:**Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age ≥65, **PIRO:** Predisposition, Infection, Response, Organ disfunction, **NLR:** Neutrophilto Lymphocyte Ratio

Discussion

In this study, we demonstrated that there was a positive correlation between NLR and CURB-65, PIRO, and PSI scores indicating the severity of pneumonia. In addition to the study results, we showed that the elevated basal levels of NLR in the patients with CAP were significantly associated with mortality. The ability of NLR, when compared with the scoring system, to predict mortality in the patients with community-acquired pneumonia had not been studied before. We showed in this study that NLR was not superior but not inferior to the scoring system.

The various scoring systems were developed to make a decision about outpatient or inpatient treatment of the patients with CAP, and to use to estimate mortality. The most widely-known and used systems are CURB- 65, PSI, and PIRO. CURB-65 is a point scoring system to separate the patients with a high risk of mortality and PSI is a scoring system aimed to prevent unnecessary hospital admissions [7, 13]. While the value of CURB-65 in predicting admission to ICU was lower than its value in predicting mortality, PSI was found more accurate in the estimation of mortality in ICU [14]. PIRO is mostly used in the estimation of risk and mortality in ICU. A correlation was shown between an increase in the PIRO score and the need for mechanical ventilation, and between the length of ICU stay and the mortality rate [15]. The guidelines indicate that patients with low scores may undergo outpatient treatment, but patients with a high score, such as 2 or higher on CURB-65 and PSI 4-5, should be treated as inpatients [16, 17].

Comorbid conditions and patient age are considerably effective in PSI scoring. Also, recording the required laboratory values and physical examination findings one by one makes the use of the PSI difficult in busy workplaces. CURB-65 is a more widely-used system as it evaluates a fewer number of parameters. While PSI has very high negative predictive value in the patients with a low risk of CAP, it is reported that CURB-65 has a higher positive predictive value in the at-risk group [18]. Chalmers et al. reported in a meta-analysis that no difference was determined between CURB-65 and PSI in predicting mortality in CAP [19].

The scoring systems were developed to decrease unnecessary hospital admissions and to help clinicians diagnose the high-risk patients. In the calculation of these scoring systems, a value is calculated by using the hemodynamic states and the various blood parameters of the patients as well as the individual characteristics like age and gender. In especially busy working centers, the use of the scoring systems is difficult because they require so many parameters. In our study, it was shown that there was a positive correlation between NLR and PIRO, PSI, and CURB-65. Similarly, a study by De Jager et al., found that NLR indicated a positive correlation with CURB-65 in demonstrating the severity of CAP [20]. In our study,, we also found that NLR was closely related with mortality in the patients with CAP. It was shown that NLR was as reliable and effective as the scoring systems in diagnosing the at-risk patients and predicting mortality rates. We suggest that NLR, which is quickly performed and cost-efficient, may be used for the same purpose as the scoring systems in determining high-risk patients with CAP. We also suggest that the use of NLR will be beneficial in easily diagnosing the high-risk patients, in contrast to the difficulties in calculating the scoring systems in daily routines and in busy workplaces.

The relation between the severity of pneumonia and the blood parameters has been widely studied. It has been found that from among the traditional infection markers, white blood cell count, neutrophil count, and C-reactive protein (CRP) have limited use in the early diagnosis of community-acquired bacteremia. It has also been reported that NLR is better at predicting bacteremia than CRP, white blood cell count, neutrophil count, and lymphocyte count [21].

NLR is a value obtained by the ratio of two inflammatory markers (neutrophil-lymphocyte), and has a stronger predictive value for bacteremia than neutrophil and lymphocyte counts [22]. In a study of CAP patients, NLR was found superior to CRP in predicting the mortality rate [20]. Goodman et al. suggested that NLR was beneficial in the diagnosis of patients with suspected appendicitis, and more sensitive in showing bacterial infection than WBC [23]. Also, NLR was studied as an infection marker in patients in intensive care units and it was found to correlate well with disease severity and outcome [24-26]. Zahorec et al. reported correlation between the severity of the clinical course and the grade of neutrophilia and lymphocytopenia in patients with severe sepsis and septic shock in an oncologic intensive care unit. They proposed using NLR as an additional marker of infection in the intensive care unit [9]. In our study, NLR was significantly higher in the patients with a high risk of mortality in the intensive care unit than the ones staying in the service. We believe that it is beneficial, especially when determining the severity of high-risk patients with CAP, to consider NLR as a new and strong parameter, in addition to those previously defined.

Approximately 10% of CAP cases require intensive care following admission [27] and itis known that any delay in admission to intensive care increases mortality rates [28]. 45% of CAP cases requiring intensive care are not admitted to ICU at first, and many of the delayed transfers are CAP cases with quick deterioration. Therefore, it is important to detect this kind of patient. While the scoring systems (PSI, CURB-65) have high sensitivity for the separation of hospitalization and outpatient treatment, they are not effective in distinguishing the necessity of intensive care [29]. The different admission criteria to ICU (one major or 3 minor) are implemented without regard to whether the patients have CAP or not. For admission to ICU, the major standards are the invasive mechanical ventilation necessity and the septic shock requiring vasopressor; the minor standards are respiratory rate ≥30/minutes, PaO2/FiO2 ≤250, multilobar infiltration, confusion-orientation disorder, uremia (BUN ≥20 mg/dl), leucopenia (leucocyte < 4000/mm3), thrombocytopenia (thrombocyte< 100000/mm3), hypothermia (body temperature<36°C) and hypotension requiring liquid loading[30]. Studies have shown that no single minor criteria is enough by itself to diagnose severe CAP, so at least three minor criteria are required for admission to ICU [29]. Ramírez et al. proposed that the inflammatory biomarkers could indicate the need for intensive care and to prevent the delay of admission to the ICU, so that especially patients with the minor criteria but normal level of inflammatory biomarkers could be followed in the service [28]. In our study, NLR values of patients followed in ICU were significantly higher than the values of patients followed in the service. Also, in this patient group, a significant correlation was observed between NLR and mortality. It was also determined again by our study that there was a positive relation between the increase in the number of minor criteria and NLR. It is known that for this patient group age and comorbid conditions increase the mortality rate. It is essential to diagnose the patients with a high risk of mortality early and to make a decision about the treatment. When considering that a delay in the decision about admission to ICU leads to an increase in the mortality rate, NLR gains more importance in this patient group as a systemic inflammatory marker that can be quickly evaluated. Although there are many factors to estimate the mortality for this patient group, we suggest that NLR can be used as an effective parameter in the estimation of mortality.

Limitations

This is an observational and single-institution study that has a relatively small sample size. Thus, it is subject to various unaccountable confusing factors natural to such an analysis. Additionally, we could not compare NLR with other inflammatory markers, fibrinogen, or myeloperoxidase, because they were not routinely measured in our study population.

Conclusion

NLR, which is a non-specific inflammatory marker that can be quickly and easily calculated via routine hemogram examination, is closely related to the scores demonstrating the severity of patients with CAP. Although it is not superior to the most commonly used scoring systems in estimating mortality, it can be used for the same purpose.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Kaya Y, Taş N, Çanakçı E, Cebeci Z, Özbilen M, Keskin H, Yıldırım BB. Relationship of neutrophil-to-lymphocyte ratio with presence and severity of pneumonia. J Clin Anal Med 2018;9(5): 452-7.