Original Article

Neutrophil-to-lymphocyte ratio relation to sepsis severity scores and inflammatory biomarkers in patients with community-acquired pneumonia: A case series

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ABSTRACT

Background and Objectives: Neutrophil to lymphocyte ratio (NLR) as calculated from the white cell differential blood count is considered a promising marker for the prognosis of patients with various diseases, including sepsis. This study was designed to assess the possible use of neutrophil-to-lymphocyte ratio in the prediction of survival outcomes in patients with community acquired pneumonia (CAP). A secondary objective was to compare the prognostic accuracy of NLR with the commonly used severity scores of sepsis SOFA, APACHE II and SAPS II. **Methods:** This was a retrospective study based on data extracted from 26 patients suffering from acute CAP. The study period was from February 01, 2017 until April 30, 2017. All patients with CAP were presented in the Emergency Department (ED) of the University Hospital of Patras, Greece and were treated after admission in the Internal Medicine Department. The neutrophil-to-lymphocyte ratio (NLR) was calculated from the white blood cell count (WBC) values measured from a peripheral venous blood specimen drawn on admission. It was then compared with C-reactive protein (CRP) serum levels and the sepsis calculated prognostic scores APACHE II, SAPS II and SOFA. The impact of the above parameters was evaluated in relation to the final outcome. **Results:** The mean period of hospitalization for the enrolled patients was 9.3 days (SD 5.8 days). Twenty-four patients (92.3%) got finally discharged from the hospital and two (7.7%) died during the hospitalization. Mean NLR and serum CRP values on admission were 10.2 ± 8.8 (min 1.4; max 34.7) and 11.4 ± 11 mg/dL (min 0.4; max 42.6) respectively. Based on the correlation analysis, serum CRP was more strongly positively correlated with NLR (r = 0.543, P = 0.004), than total WBC (r = 0.454, P = 0.02). None of the biomarkers of inflammation measured or computed in the study (CRP, WBC, NLR) showed any correlation with either the days of hospitalization or the sepsis prognostic scores. **Conclusions:** NLR shows a statistical significant correlation to the commonly used inflammatory markers CRP and total WBC in the small sample size of patients with CAP that we assessed. Although NLR is a simple, cheap and rapidly available measurement in the ED, future, larger prospective studies are warranted to confirm its possible value as a prognostic index in sepsis patients with CAP.

Key words: neutrocyte-to-lymphocyte ratio (NLR), sepsis, community acquired pneumonia (CAP), SOFA, APACHE II

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INTRODUCTION

Sepsis and the related multiple organ failure remains a worldwide problem leading to high morbidity and mortality rates. The currently available organ failure scoring systems, such as the Sequential Organ Failure Assessment (SOFA), the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology II (SAPS II) scores are useful in the assessment of organ dysfunction over time and have been established as clinically useful indexes of severity and prognosis. The neutrophil-to-lymphocyte ratio (NLR) calculated easily from the complete blood

count is an assessable index, which has already been used as a prognostic tool in several clinical conditions including sepsis. The aim of this retrospective study was to assess the potential relation of the NLR in patients presenting in the Emergency Department (ED) suffering from a lower respiratory chest infection with the final outcome and the established sepsis calculated prognostic scores.

METHODS

Study population and design

This observational study enrolled 26 patients who presented in the Emergency Department of the University Hospital of Patras, Greece and were finally admitted with a lower respiratory tract infection diagnosis. The study included patients that were admitted from February 01, 2017 until April 30, 2017, and the study protocol was approved by the University Hospital of Patras, Greece Research and Ethics Committee. Depending on patient's condition, verbal consent for participation in the study was obtained from each one or a designated family member and was documented in writing. Data were de-identified and stored in an electronic database in a secure, locked computer. The research team included Consultants and resident physicians. All enrolled patients were finally admitted to the Internal Medicine Department of the Hospital.

Data collection

For the purpose of this study, the physicians completed a data form in the Emergency Department, which included information regarding the history, physical examination, laboratory tests and radiological imaging studies for each patient. After the clinical assessment, a chest X-ray of all the participants was obtained. Patients with suspected community acquired pneumonia (CAP) were defined as those with recent-onset respiratory symptoms, abnormal infiltrates on chest X-ray, and the absence of a recent hospitalization (3 months). The clinical suspicion of sepsis in these patients was based on the following criteria (2 or more): fever (> 38°C); increased respiratory rate; tachycardia (heart rate >90); hypotension (systolic blood pressure < 90 mmHg). Ten milliliters of blood were drawn from each patient and the samples were sent to the Hospital's laboratory for a complete blood count (CBC) and a biochemical analysis. Arterial blood gas analysis was performed in all participants and the PaO2/FiO2 ratio was calculated. The neutrophil to lymphocyte ratio (NLR) was computed from the CBC. The sepsis severity scores SOFA, APACHE II, and SAPS II were calculated after collecting all the required parameters. After discharge from the hospital, the total days of hospitalization for each patient were documented.

Exclusion criteria for the study population were the use of antibiotics for more than 24 hours at the time of admission, conditions known to affect total and differential white blood cell count (WBC) counts such as treatment with steroids and medications proven to affect WBC, hematologic disorders, chronic inflammatory conditions, history of steroid use within 3 months prior to admission, and history of chemotherapy or radiotherapy within the previous 4 weeks.

Statistical analysis

Data were analyzed using descriptive statistical tools, including frequencies for discrete variables or means and standard deviations for continuous variables. Data analysis included a bivariate correlation analysis using the Pearson's r coefficient in search for significant correlations between NLR and serum CRP, age, admission PaO2/FiO2, days of hospitalization and the sepsis severity scores (SOFA, APACHE II and SAPS II). The significance level was set at a *P*-value of 0.05. All data analysis was conducted using the IBM SPSS Statistics version 23.0 software package.

RESULTS

Patient data and demographics

The minimum age of the patients was 21 years and the maximum age was 91 years (mean 72.5 years SD 15.5 years). Seventeen patients were male (65.4%) and nine (34.6%) were female. 92.3% of the patients had positive lower respiratory infection findings in the chest x-ray and 7.7 % did not. The mean period of hospitalization was 9.3 days with a SD of 5.8 days. Twenty-four patients (92.3%) got finally discharged from the hospital and two (7.7%) died during hospitalization. Mean NLR and serum CRP values on admission were 10.2 ± 8.8 (min 1.4; max 34.7) and 11.4 ± 11 mg/dL (min 0.4; max 42.6) respectively. Descriptive statistics along with the statistical data from the SOFA, APACHE II and SAPS II prognostic scores are presented in Table 1.

Descriptive statistical data

Bivariate correlation analysis

Based on the correlation analysis, we found that serum C-reactive protein (CRP) was more strongly positively correlated with NLR (r = 0.543, P = 0.004), than WBC (r = 0.454, P = 0.02). None of the markers of inflammation measured or computed in the study (CRP, WBC, NLR) showed any correlation with either the days of hospitalization or the sepsis prognostic scores. Age was strongly positively correlated with all the severity scores on admission (SOFA, r = 0.577, P = 0.002; APACHE II, r = 0.574, P = 0.002; SAPS II, r = 0.595, P = 0.001) and negatively correlated with the PaO2/FiO2 ratio (r = -0.6,

Table 1: Descriptive statistical data and the SOFA, APACHE II and SAPS II prognostic scores

	Minimum	Maximum	Mean	Std. Deviation
Age (years)	21	91	72.5	15.5
NLR	1.4	34.7	10.21	8.83
WBC (10^3/μL)	1,960	27,340	11,001.2	5,465.3
Serum CRP (mg/dL)	0.40	42.58	11.4	11.04
PaO_2/FiO_2	94	480	261.5	102.5
SOFA	0	7	3	2
APACHE II	6	27	14	6
SAPS II	19	50	33	10
Days of Hospitalization	3	28	9.3	5.8

NLR: neutrophil-to-lymphocyte ratio; WBC: white blood cell count; CRP: C-reactive protein.

$P = 0.001$). The PaO2/FiO2 ratio was also strongly associated with a worse prognostic score (SOFA, $r = -0.926$, $P < 0.001$; APACHE II, $r = -0.620$, $P = 0.001$; SAPS II, $r = -0.439$, $P = 0.025$). The only parameter that was correlated with a significant longer hospital stay was the APACHE II score ($r = 0.467$, $P = 0.016$) on admission.

DISCUSSION

Sepsis is the clinical syndrome of life-threatening organ dysfunction caused by a dysregulated host response to an infection, leading potentially to increased mortality rates (> 40%). According to pathophysiology, several disorders develop during the process of septic syndrome and these are evaluated through the assessment of various biomarkers. According to the definition criteria, sepsis is characterized by abnormalities of the white blood count, this may be decreased (< 4,000/μL) or increased (> 12,000/μL) or the presence of more than 10% of immature white blood cells identified in the peripheral blood sample. During the course of sepsis, the number of white blood cells may vary, depending on the stage of sepsis or septic shock, the patient's immunologic status, and the etiology of the infection.[1]

Recently, new tests and markers that allow a more rapid and less costly detection of bacteremia and sepsis have been investigated. Beyond procalcitonin and C-reactive protein, which have been served as useful predictors in the assessment of sepsis patients in daily practice,[2] several other biomarkers related to the sepsis process have been investigated. However, only a few of them have been applied in clinical practice, especially in the setting of assessing a sepsis patient in the Emergency Department (ED).[3] Neutrophil-to-Lymphocyte ratio (NLR) is a readily accessible biomarker based on the calculation of the white cell blood count. This ratio has been used previously as a marker for the assessment of patients suffering from several clinical conditions.[4,5] However, there is a matter of debate regarding the usefulness of NLR in relation to the clinical prognosis in sepsis as conflicting data have been published up until now. Results from the study of Salciccioli *et al.* showed that after assessing 5,056 critically ill patients in the subgroup of sepsis patients, there was no statistically significant relationship between NLR and mortality.[6,7]

In the existence of an underlying infection, the response of the host is generally characterized by an increase in the neutrophil count and a decrease in the lymphocytes. However, NLR is not a sensitive marker in the diagnosis of sepsis. Elevated NLR levels have also been associated with trauma, surgery, pancreatitis, cardiac and rheumatic disorders,[8,9] but there are references in the recent bibliography proposing the use of NLR in sepsis. An observational, cohort study by Liu *et al.* published in 2016, after assessing 333 adults with sepsis, concluded that increased NLR levels were independently associated with an unfavorable clinical prognosis.[10] Results from the study by Hwang in 2017, after assessing 1395 patients with sepsis, revealed that the initial NLR measured at ED admission was independently associated with the 28-day mortality. Additionally, a change in the NLR may be used as a valuable prognostic marker.[11]

As the number of critically ill patients admitted to the emergency department increases daily worldwide, interventions and treatment should be conducted in a timely manner in order to decrease mortality. For that reason, more easily accessible tools are warranted to evaluate patients with sepsis. A total of 373 critically ill patients were assessed in a study by Akilli *et al.*, aiming to evaluate the predictive effect of the NLR to mortality. After assessing patients in the ITU, the authors concluded that the NLR can provide directions to emergency department physicians for interventions, particularly within a few hours after admission, in the critically ill patient group.[12]

In the current study, we evaluated the NLR on admission in patients with suspected CAP. A prospective clinical study

from Cataudella *et al.*, aimed to explore the performance of the neutrophil-to-lymphocyte ratio, as an index of systemic inflammation that predicts prognosis in elderly adults treated for CAP. The study enrolled 195 patients and results showed that NLR predicted 30-day mortality ($P < 0.001$) and performed better than pneumonia severity index (PSI), CURB-65, C-reactive protein, and white blood cell count to predict prognosis.[13] Our study found that NLR is correlating stronger with serum CRP than total WBC ($r = 0.543$, $P = 0.004$ *vs.* $r = 0.454$, $P = 0.02$, respectively), in this small group of patients with CAP. This correlation could indicate that NLR along with CRP could reflect the magnitude of the inflammatory response in these patients more accurately.

However, our study failed to show a statistical significant relationship between the NLR and the SOFA, APACHE II and SAPS II scores as well as with the total days of hospital stay. This could be partially attributed to the small sample size studied. Due to this limitation, a subgroup analysis (*e.g.*, specific age groups) could not be performed in order to identify potentially significant correlations between NLR and the sepsis severity scores.

CONCLUSIONS

Though WBC and serum CRP are simple tools that aid clinician's decision making in the Emergency Department, the simple calculation of the NLR that we found correlating stronger with serum CRP than total WBC, could be of help when assessing patients with CAP. These results may encourage clinicians to take into consideration NLR as a diagnostic and prognostic tool in the assessment of sepsis patients in daily practice. In the setting of limited financial and laboratory resources, the use of NLR seems to be a reasonable approach for the evaluation of patients with sepsis, at least in the small sample size of patients with pneumonia that we assessed. Further investigation is required to increase the understanding of pathophysiology of this relationship and to validate these findings with data collected prospectively. As the neutrophil-lymphocyte ratio (NLR) is a simple biomarker of inflammation, its consideration as a routine test for sepsis and the determination of the ideal cutoff value for bacteremia and sepsis is warranted.

Conflict of Interest

None declared.

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