ORIGINAL ARTICLE

Can neutrophil-to-lymphocyte ratio and proatherogenic risk factors improve the accuracy of pneumonia severity index in the prediction of community acquired pneumonia outcome in healthy individuals?

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ABSTRACT

Aim To investigate influence of neutrophil-to-lymphocyte ratio (NLR) and proatherogenic risk factors to improve the accuracy of pneumonia severity index (PSI) in the prediction of community acquired pneumonia (CAP) outcome in healthy individuals.

Methods A retrospective observational cross-sectional study conducted at the Clinic for Pulmonary Diseases and Tuberculosis "Podhrastovi", University Clinical Centre Sarajevo, included 83 patients with the diagnosis of CAP during the period March 2019-March 2021. Once diagnosed with CAP, PSI score was calculated and according to its value the need for hospital treatment was identified. Patients were divided in two groups: low risk of CAP (PSI <90), and high risk of CAP (PSI> 90).

Results The overall average hospital stay was 22.76±10.154 days. In the patients diagnosed with CAP, a positive correlation was established between the following parameters PSI score and age (r=0.670; p<0.01), C-reactive protein-CRP (rho=0.287; p<0.01), leukocytes (rho=0.406; p<0.01), NLR (rho=0.313; p<0.01) and platelet to lymphocyte ratio (PLR) (0.296; p<0.05). CRP, leukocytes, NLR and PLR were statistically significantly higher in patients with high risk of CAP compared to patients with low risk of CAP. Diastolic blood pressure, lymphocytes, eosinophils were significantly lower in patients with high risk of CAP (p<0.05;) compared to patients with low risk of CAP (p<0.01). The optimal cut-off value of NLR for CAP patients was 3.089 with an estimated area under curve (AUC) of 0.664.

Conclusion Proatherogenic parameters such as age, systolic blood pressure and leukocytes in combination with neutrophil-lymphocyte count ratio could improve accuracy of the pneumonia severity index in community acquired pneumonia outcome.

Key words: atherosclerosis, inflammation, lung

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INTRODUCTION

Community acquired pneumonia (CAP) is a serious and potentially fatal illness caused by a certain microbial etiologic factor and classified according to the severity by different scoring systems (1,2). Severe morbidity and mortality are identified not only during the acute phase of the infection, but CAP is identified as an increased risk factor for complications appearing years after the acute episode (3,4). This occurs mostly as a consequence of cardiovascular damage caused by the infection and inflammatory host response, all of it leading to chronic sequelae predisposing cardiovascular events (5).

The underlying pathophysiological mechanisms of cardiovascular events (CVE) include inflammation, platelet activation, endothelial dysfunction with specific pathogen-associated damage, hypoxemia often with myocardial invasion (5-7). Different severity scoring systems and clinical assessment tools are associated with better patient outcomes (5). The PSI has shown accuracy in identification of low-risk patients suitable for ambulatory treatment (8), however, with lack of studies proving its efficacy in high-risk patients. In such patient population mortality prediction itself does not always lead to accurate stratification, especially in cases of intensive care unit (ICU) admissions (8,9).

Neutrophilia along with absolute lymphocytopenia (lymphocyte count below 1.0×10^9/L) is a significant marker in infectious disease management, and in the prediction of bacteremia (10-13). Neutrophil-lymphocyte count ratio (NLCR) as an infection marker in ICU patients has been found to correlate well with disease severity and outcome, according to the Acute Physiology and Chronic Health Evaluation (APACHE-II) and Sequential Organ Failure Assessment (SOFA) scores (10). Prevalence, timing and risk factors of cardiac complications in patients with CAP are becoming understood for patients who are previously diagnosed with coronary artery disease or chronic heart failure. The influencing risk factors that can play a role in predicting the course of the disease are proatherogenic risk factors (such as age, systolic and diastolic blood pressure, laboratory parameters including cholesterol, triglycerides, high and low-density lipoproteins), as well as its inflammatory component (such as C-reactive protein - CRP, WBC and platelet count - PLT). Defence against infection and hyperactivation of PLT both contribute to pro-inflammatory and prothrombotic systemic stage as etiologic factors of CVEs (14). In order to assess usefulness of CRP in the CAP diagnosis and severity assessment, it has been noticed that a combination of PSI and CURB 65 scores improves the 30-day short-term mortality prediction (15). High levels of CRP at admission are linked to an increased risk of complications and short-term mortality (16,17). Elevated CRP levels maintained at 3–4 days are related to treatment failure and 30-day mortality (17,18). The CRP may be useful for cardiovascular risk assessment in healthy women (19). Increased CRP level failed to predict the occurrence of CVE in the short or long-term follow-up in CAP patients (20,21).

Although we know that better patient outcome originates from the addition of a severity score to clinical assessment, comparative analyses of different scores are scarce (21). Despite the association of CAP with a significant mortality rate in hospital conditions, a review of available research in Bosnia and Herzegovina has not yielded results.

The aim of this study was to investigate influence of neutrophil-to-lymphocyte ratio (NLR) and proatherogenic risk factors to improve the accuracy of pneumonia severity index in the prediction of community acquired pneumonia outcomes in healthy individuals.

PATIENTS AND METHODS

Patients and study design

A retrospective observational cross-sectional study was conducted in a two-year period between March 2019 and March 2021 at the Clinic for Pulmonary diseases and Tuberculosis "Podhrastovi", University Clinical Centre Sarajevo (90 hospital beds, tertiary level of healthcare for the Federation of Bosnia and Herzegovina and the secondary healthcare level for Canton Sarajevo), including 83 patients with the diagnosis of CAP.

Methods

All patients at initial examination were assigned with the diagnosis of CAP according to the disease history, physical examination, chest X-ray or cross-sectional computed tomography scan (CT) findings, and laboratory parameters. Once diagnosed with CAP, PSI score was calculated as a clinical prediction rule for calculation of the probability of morbidity and mortality among pa-

tients with CAP and severity of illness. According to a PSI value, the need for hospital treatment was identified. The PSI score consisted of the following values: age, gender, history of nursing home residency, neoplastic disease, chronic liver disease, congestive heart failure (CHF), cerebrovascular disease (CVD), chronic renal disease related to creatinine clearance value, altered mental status, respiratory rate (RR), systolic blood pressure (SBP), body temperature, heart rate (HR), pH value of arterial blood gas analysis, blood urea nitrogen (BUN), sodium, glucose and haematocrit level, partial pressure of oxygen in arterial blood (PaO_2), and pleural effusion. To each of these parameters a numerical value was assigned. Once the PSI score was calculated, the patient's state was stratified in one of its five risk classes. First three classes were classified as low risk accounting point values of <70, equal 70, and 71-90 points, respectively); the fourth class implies moderate risk (91-130 points), and the fifth class high risk patients (>130 total points). The patients were divided into two groups using 90 points as a cut-off value: the first group with low-risk CAP with PSI score ≤90, and the second group with high-risk CAP with PSI score was >90.

Beside PSI score parameters, the following laboratory parameters were evaluated in each patient: complete blood cell count (CBC), differential blood cell count including neutrophil granulocytes (Neu), lymphocytes (Lym), monocytes (Mono), basophil granulocytes (Bas) and eosinophil granulocytes (Eos), CRP, cholesterol and triglyceride value, and acid base analysis, according to the reference range values. On the day of admission a physical examination was performed including measurements of vital parameters such as heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) values.

The patients were followed during hospital stay with repeated/daily notification of vital parameters values and timed lab test analysis according to objective clinical improvement or deterioration of the patient's condition.

Statistical analysis

Data were evaluated by standard statistical procedures and presented in tables. For the evaluation of normal distribution of continuous variables, Shapiro-Wilk test was used. The results were statistically evaluated and presented as mean value (X) and standard deviation (SD) for normally distributed variables, as well as median value and interquartile rank for non-normally distributed variables. Coefficient of correlation (r) was determined according to Spearman and Pearson. Independent t test was used to compare normally distributed variables, and the Mann-Whitney U-test was used to compare non-normally distributed variables. To determine optimal cut-off values of potential biomarkers for differentiation between low-risk CAP patients and high-risk CAP patient's receiver operating characteristic (ROC) curve and corresponding areas under the curve (AUC) were used. The accuracy rate for ROC curves was calculated with the 95% confidence interval (95% CI). The $p<0.05$ was considered as statistically significant.

RESULTS

Out of 83 patients with CAP, 49 (59.04%) were males and 34 (40.96%) females. Average age of all patients was 59.18±15.56 years. Average hospital stay for all patients was evaluated as 22.76 ± 10.154 days. The mean values of the systolic and diastolic blood pressure were 128.43±20.32 mmHg and 80 (70 - 80) mm Hg, respectively, with an average heart rate of 89/min. Leucocytes of $8.42x10^9$ and predomination of neutrophils with the mean value of 62.4% were found. Mean values of lymphocytes, monocytes, basophils and eosinophils were 19.1%, 6.4%, 0.44% and 1.4%, respectively. The mean value of CRP was 31.6 (5.9 - 118) mg/dL. The mean value of PSI score in patients with CAP was 80.89 ± 35.43 (Table 1).

Table 1. Clinical and laboratory parameters' values in patients diagnosed with community acquired pneumonia

Variable (reference values)	Mean±SD Mean (min.-max.)
Age (years)	59.18±15.56
Hospital duration (days)	22.76±10.154
Systolic BP (mmHg)	128.43±20.32
Diastolic BP (mmHg)	80 (70-80)
HR (beat/min)	89 (76-100)
CRP (0-5mg/dL)	31.6 (5.9-118)
Leukocytes (3.4-9.7x109/L)	8.42 (6.4-12.2)
Neutrophil granulocytes (44-72%)	62.4 (43.65-78.29)
Lymphocytes (20-46%)	19.1 (7.55-32.7)
Eosinophil granulocytes (2-4%)	1.4 (0.2-3.1)
Basophil granulocytes (0-1%)	0.44 (0.16-0.73)
Monocytes (4-8%)	6.4 (3.9-8.71)
Thrombocytes (158-424x109/L)	252 (213-319)
Cholesterol (<5.0 mmol/L)	4.58±1.25
Triglycerides (<1.7mmol/L)	1.9 (1.2-2.4)
PSI score	80.89±35.43

SD, standard deviation; BP, blood pressure; HR, heart rate; CRP, C-reactive protein; PSI, pneumonia severity index; min., minimum; max., maximum;

In the population of patients diagnosed with CAP, a positive correlation of PSI score was established with age (r=0.670; p<0.01), CRP (rho=0.287; p<0.01), leukocytes (rho=0.406; p<0.01), NLR (rho=0.313; p<0.01) and PLR (0.296; p<0.05) and negative correlation with lymphocytes (rho=-0.277; p<0.05), eosinophils (rho=-0.281; p<0.05) and monocytes (rho=-0.023; p<0.05) (Table 2).

Table 2. Correlation of clinical and laboratory parameters with pneumonia severity index (PSI) in patients diagnosed community acquired pneumonia

Variable	Pearson's coefficient (r) / Spearman's coefficient (rho) of PSI score	p
Age (years)	0.670	0.000
Duration of hospitalization days	0.156	0.158
Systolic BP (mmHg)	-0.001	0.995
Diastolic BP (mmHg)	-0.209	0.058
HR (beat/min)	0.200	0.071
CRP (mg/dL)	0.287	0.009
Leukocytes (109/L)	0.406	0.000
Neutrophils (%)	0.192	0.084
Lymphocytes (%)	-0.277	0.012
Eosinophils (%)	-0.281	0.011
Basophils (%)	-0.139	0.223
Monocytes (%)	-0.223	0.048
Thrombocytes (109/L)	0.091	0.415
Cholesterol (mmol/L)	0.067	0.550
Triglycerides (mmol/L)	0.131	0.239
NLR	0.313	0.009
MLR	0.176	0.155
PLR	0.296	0.015

BP, blood pressure; CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; MLR, monocyte lymphocyte ratio; PLR, platelet lymphocyte ratio;

In order to compare the values of clinical - laboratory parameters between patients with low risk of CAP (PSI <90) and patients with high risk of CAP (PSI> 90), the age, CRP, leukocytes, NLR and PLR were statistically significantly higher in patients with high risk of CAP compared to patients with low risk of CAP (p<0.05); the variables of diastolic blood pressure, lymphocytes and eosinophils were significantly lower in patients with high risk of CAP compared to patients with low risk of CAP (p<0.01) (Table 3).

The ROC curve was used to evaluate the diagnostic value of NLR as a biomarker of severity of CAP. The optimal cut-off value of NLR for CAP patients was 3.089, with a specificity of 76% and sensitivity of 60%, positive predictive value of 65.1% and negative predictive value of 60% with an estimated AUC of 0.664 (CI 95%: 0.531 – 0.798).

Table 3. Clinical and laboratory parameters in community acquired pneumonia (CAP) patients according to pneumonia severity index (PSI)

Variable	Mean±SD Mean (min.-max.)		p
	Low risk PSI<90 (n=58)	High risk PSI>90 (n=25)	
Age (years)	55±14.70	70±9.98	0.000
Duration of hospitalization (days)	20.5±10	28±10.12	0.09
Systolic BP (mmHg)	130±19.66	120±21.36	0.296
Diastolic BP (mmHg)	80 (70-80)	80 (60-80)	0.018
HR (beat/min)	86 (76-95.75)	90 (80-100)	0.363
CRP (mg/dL)	21.5 (3.35-85.3)	46.5 (22.9-143.9)	0.037
Leukocytes (3.4-9.7x109/L)	7.37 (6.19-9.72)	12.1 (6.43-15.2)	0.015
Neutrophils (%)	56.4 (40.2-67.7)	66.6 (47.3-80.4)	0.147
Lymphocytes (%)	24.05 (10-33.4)	12.6 (6.7-26.3)	0.039
Eosinophils (%)	2.3 (0.3-3.34)	0.82 (0.04-2.7)	0.03
Basophils (%)	0.4 (0.19-0.7)	0.47 (0.07-0.8)	0.827
Monocytes (%)	6.75 (4.92-8.77)	4.59 (1.81-8.58)	0.128
Thrombocytes (158-424x109/L)	252 (213-318)	266 (217-344)	0.660
Cholesterol (mmol/L)	4.6±1.33	4.7±1.11	0.381
Triglycerides (mmol/L)	1.9 (1.2-2.17)	2 (1.2-3.3)	0.143
NLR	4.08±2.3	6.4±6.63	0.020
MLR	0.34±0.25	0.32±0.28	0.087
PLR	18.84±10.63	22.19±15.56	0.047

BP, blood pressure; CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; MLR, monocyte lymphocyte ratio; PLR, platelet lymphocyte ratio; n, number of patients; min., minimum; max., maximum;

DISCUSSION

The evaluation of complete and differential blood cell count in 83 patients included in our study identified predomination of neutrophils in leukocyte count with mean value of 62.4%; mean values of other differential blood cell count components predominated with lymphocytes accounting of 19.1%, and the mean value of CRP was 31.6 (5.9 - 118). Clear differentiation of high-risk patients must be performed in predicting who will die from pneumonia and who has more probability of survival with determining (at admission) patients who need more than standard care (such as elderly or those with multiple comorbidities) (22). Patients who presented with the need of respiratory or inotropic support are easily triaged into rapid resuscitative care (22).

A growing interest for the host inflammatory response in the development of pneumonia and infection markers facilitates treatment decisions and improves the accuracy of clinical severity scores in patients admitted with CAP (23-25). The markers such as CRP, white blood cell (WBC) count and neutrophil count are still the most frequently used infection markers in daily clinical practice,

but the NLR proved to be a simple and even better marker in predicting bacteremia than non-specific inflammatory parameters (25). In the population of patients diagnosed with CAP in our study, a positive correlation was established between PSI score and age, CRP, leukocytes, NLR and PLR. Our results correlate with a study of Sahin et al., where positive correlation identified between leucocyte, neutrophil, NLR, PCT and uric acid levels on the 1st day with CURB-65 score and PSI score, however, no correlation was found between the CURB-65 score and the PSI score, and CRP, platelet and PLR on the 1st day. Sahin et al. study suggested that although there was no significant relationship between CURB-65 and PSI scores and CRP, there was a significant relationship between NLR and these scores. Leukocyte, NLR, CRP and PCT were found to be very useful in the follow-up of treatment response (25). The NLR and PLR were evaluated and shown to be a widely useful and cheap tool in the diagnosis and the prediction of 90-day mortality in patients with sepsis according to the study of Spoto et al. (25). However, Taboubi et al. study (26) identified NLR increase in 68.4% of patients, but it did not establish the association between NLR and outcome of CAP, which does not correlate with our results. In order to a diagnostic value of blood parameters for community-acquired pneumonia, Huang et al. (27) conducted a study enrolling 80 CAP patients and 49 healthy subjects and NLR and found higher diagnostic value for CAP comparing to MLR; NLR showed a significant correlation to PSI, indicating the disease severity of CAP, which correlates with results of our study. However, unlike our results they found no positive correlation between PLR and PSI score.

According to the results of our study, the age, CRP, leukocytes, NLR and PLR were significantly higher in patients with high risk of CAP (PSI> 90) compared to patients with low risk of CAP (PSI <90), while diastolic BP, lymphocytes, and eosinophils were significantly lower in patients with high risk of CAP compared to patients with low risk of CAP. In the study of Che-Morales et al. uni- and multivariate analysis showed that neutrophils and NLR could be surrogate of PSI III or higher, and NLR value ≥7.2 provided that probability (28). It is not clear if old or cumulative, acute or subacute inflammation correlate with arterial stiffness. Atherosclerosis due to low-grade inflammation is considered an inflammatory disease. An increased WBC has been associated with arterial stiffness and atherosclerotic events and stronger predictions of cardiovascular risk (29). The cross-sectional study of Khang et al. identified that the prevalence of acute myocardial infarction (AMI) during CAP hospitalization in geriatric patients is significant and has an impact on in-hospital mortality. Respiratory failure, pre-existing coronary artery disease, diabetes and urea levels were associated with the occurrence of AMI in the older patients after hospitalization with CAP (30).

Although a positive correlation was only established with age, systolic blood pressure and leucocytes, we believe that triglycerides and cholesterol and its fractions were not identified as significant due to small sample size. Probably, with the sample size increase, some other proatherogenic risk factors (such as cholesterol and triglycerides) may contribute even more to accuracy of PSI in the prediction of CAP clinical outcome. Further evaluation of proatherogenic factors on a larger sample will provide information to determine significance and sensitivity of NLR. In conclusion, the NLR and certain proatherogenic risk factors improve the accuracy of PSI and the prediction of unfavourable clinical outcomes in adult CAP patients.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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