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Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Percentage Ratio as Predictors of In-hospital Mortality in Sepsis. An Observational Cohort Study

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ABSTRACT

Background: Sepsis remains a major public health problem with increased incidence of mortality. As early recognition and prompt treatment in the first 'golden hour' remain the cornerstone of the septic patient approach, there is a real need for rapid and cost-effective reliable markers. **Objective**: The aim of the study was to evaluate the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte percentage ratio (PL%R) in patients with sepsis who were initially treated in the Emergency Department and investigate their predictive ability regarding in-hospital mortality and performance comparing them to SOFA, APACHE II, and SAPS II score. **Methods**: A retrospective observational study in the Emergency Department and Internal Medicine Department in a Mediterranean University Hospital. A total of forty-three patients suffering from sepsis were enrolled in the study. Demographic information, past medical history with pre-existing co-morbidities, physical examination findings, and radiological data were reviewed. Neutrophil to lymphocyte ratio and platelets to lymphocyte percentage ratio was calculated from the complete blood count (CBC). Disease severity was evaluated by calculating SOFA, SAPS II and APACHE II score on admission. The outcome of patients was noted as a primary endpoint. **Results**: Values of NLR and PL%R were statistically significantly higher in the group of non-survivors and correlate with sepsis prognostic scores. **Conclusion**: Calculation of NLR and PL%R is easy, fast, and inexpensive in the assessment of patients with sepsis. Their role as prognostic indexes and their validity in the Emergency Department setting should be evaluated with large prospective studies.

Keywords: Sepsis, neutrophil to lymphocyte ratio, platelet to lymphocyte percentage ratio, organ dysfunction scores, prognosis.

1. BACKGROUND

Sepsis, a syndrome of clinical and pathophysiologic abnormalities induced by infection, remains a major public health problem with increased incidence of mortality (1, 2). Several biomarkers have been used as diagnostic and/or prognostic tool, alone or combined to sepsis severity scores. Currently, the Sequential Organ Failure Assessment (SOFA) and the q-SOFA scores are widely accepted in the evaluation of organ dysfunction due to sepsis, alone or in combination with the already used Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology II (SAPS II) scores (3-6).

Among the plethora of biomarkers available to clinicians investigating septic patients in the Emergency Department (ED), white blood cell count (WBC) and C-reactive protein (CRP) are always taken into consideration due to their availability and low cost. Serial measurement of

CRP, is useful for clinicians' decision-making, as its serum levels correlate with the syndrome evolution (7). Neutrophil-to-lymphocyte ratio (NLR) calculated from the complete blood count seems to be a reasonable tool for assessment during the sepsis course (8, 9).

Almost all human body systems are affected during the progression of sepsis syndrome. Regarding the haemostatic system, several abnormalities are recognized, such as dysfunction of the clotting cascade, release of cytokines with either pro- or anti-inflammatory effects, stimulation of plasminogen and activation of antithrombin-III. All the above seem to result in a hypercoagulative state clinically manifested with microvascular thrombosis and bleeding diathesis. Thrombocytopenia is also well recognized in sepsis as a result of several mechanisms, including peripheral non-immune destruction, production of cytokines and bone marrow suppression (10-12). Based on these alterations, there is a trend towards investigating the role of platelets to lymphocyte percentage ratio (PL%R) as a possible prognostic index in the field of sepsis (13, 14).

	Survivors	Non-survivors	P
N	28	15	
Gender (M/F)	17/11	8/7	ns
Age (±SD)	64.5 (54-78)	85 (78-88)	p<0.05
UTI (n)	4	4	ns
Chest Infection (n)	18	8	ns
Cholecystitis (n)	4	0	ns
Peritonitis (n)	2	2	ns
Cellulitis (n)	0	1	ns
Mean WBC (±SD)	16046 (5336)	19975 (7157)	p<0.05
Mean PLT (±SD)	275 (91)	285 (146)	ns
Mean CRP (±SD)	12.7 (9)	16 (11)	ns
Mean Length of stay (IQR)	5 (3,25-10,75)	5 (2-8)	ns
Mean SOFA (IQR)	3 (1,25-3,75)	6 (3-8)	p<0.05
Mean SAPS II (±SD)	33.54 (11)	50.73 (12)	p<0.05
Mean APACHE II (±SD)	9.67 (4)	16.6 (5)	p<0.05
Mean NLR (IQR)	9,1 (5,2-15,5)	25,3 (8,9-31,4)	p<0.05
Mean PLT/Lymph% Ratio (IQR)	24,6 (17,7-40,5)	51,6 (25,9-105)	p<0.05
Mean CRP/Alb Ratio (IQR)	3,5 (1,7-7,1)	4,9 (2,7-7,7)	ns

Table 1. Patient baseline characteristics. UTI: urinary tract infections, WBC: white blood cells, PLT platelets, CRP: C reactive protein, SOFA: sequential organ failure assessment, APACHE: acute physiology and chronic health evaluation, NLR: neutrophil to lymphocyte ratio, PLT: platelets, Lymph%: lymphocyte percentage, Alb: albumin.

2. OBJECTIVE

This is a retrospective study based on patients diagnosed with sepsis, initially assessed and treated in the Emergency Department of a Mediterranean tertiary center, aiming to investigate NLR and PL%R predictive ability regarding in-hospital mortality and performance comparing them to SOFA, APACHE II and SAPS II score.

3. PATIENTS AND METHODS

3.1. Study population and design

A total of 43 consecutive patients with the diagnosis of sepsis were included in this retrospective study. The study period was from October 01 2019 to December 30 2019. Diagnosis was established according to international criteria and sepsis-3 definitions. All patients received appropriate treatment in the Emergency Department of the University Hospital of Patras, Greece. The Ethics Committee of the University Hospital approved the study protocol. For this retrospective observational study all data were collected from a secure electronic database and no patient consent was required. The research team comprised from Consultants, resident physicians and medical students. After initial assessment in the ED all included patients were finally admitted to the Internal Medicine Department of the Hospital for further treatment.

3.2. Data collection

Patient data contained demographic information, past medical history with pre-existing co-morbidities, physical examination findings, and radiological data were reviewed. Neutrophil to lymphocyte ratio and platelets to lymphocyte percentage ratio were calculated from the complete blood count (CBC). Disease severity was evaluated by calculating SOFA, SAPS II and APACHE II score on admission. The outcome of patients (survivor or non-survivor) was noted as primary endpoint. Exclusion criteria for the studied population were: corticosteroid therapy, antibiotic use before admission, hematologic disorders, malignant diseases, chemotherapy or radiotherapy within the previous month.

3.3. Statistical analysis

Data analysis was performed with the help of descriptive statistics tools. Continuous variables were expressed as means (±SD) and differences between groups were tested using Student's t-test or Mann–Whitney U test. The NLR and PL%R discriminating ability regarding in-hospital mortality was expressed as the area under the receiver operating characteristic curve (ROC). Logarithmic transformation of NLR and L%R data was carried out to reduce positive skewness and normalize the distribution of data. Correlations of NL and PL% ratios with SOFA, APACHE II and SAPS II scores were studied using the Pearson correlation coefficient. All tests were two-tailed, and a P value <0,05 was considered statistically significant. All data were analyzed using the IBM SPSS Statistics software (version 24).

4. RESULTS

Demographic characteristics of the patients (survivors and non-survivors), source of infection, mean values for inflammatory markers (WBC, CRP), mean values for NLR, PL%R, CRP to Albumin (CRP/alb) Ratio, and sepsis severity scores are shown in Table 1. Forty-three septic patients were included in the study, suffering from chest infection, urinary tract infection, cholecystitis, peritonitis and cellulitis. Upon study completion 15 died and 28 were successfully discharged from our hospital. Patients in the non-survivor group were older than the patients in the survivor group and

male to female ratio was 1.14 and 1.54 respectively. Upon admission to the ED non-survivors had higher WBC count, SOFA, SAPS II, APACHE II (10326 ± 9688 *10^6/mm^3, 5.6 ± 2, 50.73 ± 12, 16.6 ± 5, respectively) than survivors (4546 ± 7590 *10^6/mm^3, 3 ±2, 33.54 ± 11, 9.67 ± 4; p=0.006, p<0.001, p=0.002, p<0.001, respectively). Furthermore, NL and PL% ratios in the non-survivor group were higher (21.5 ± 13, 69 ± 68) than the survivor group (11.6 ± 9 and 38.2 ± 36; p=0.024 and p=0.034, respectively). No difference was found in mean length of hospital stay, PLTs, CRP and CRP to albumin ratio in both groups.

Using a receiver operating characteristic curve (ROC) analysis to distinguish patients with an unfavorable outcome from patients with a favorable outcome, Apache II, Saps II and SOFA area under the curve (AUC) was 0.852 (95% CI 0.737 – 0.968; p<0.001), 0.837 (95% CI 0.713 – 0.961; p<0.001), 0.783 (95% CI 0.631 – 0.936; p=0.002) respectively. NLR area under the curve (AUC) was 0.711 (95% CI 0.535 – 0.886; p=0.024) and PL%R AUC was 0.698 (95% CI 0.528 – 0.868; p=0.034) (Figure 1). Using a cutoff level of 19.93, NLR had a sensitivity of 60% and specificity of 89% in predicting an unfavorable outcome. PL%R had a sensitivity of 60% and a specificity of 82% with a cutoff value of 49.58. Finally, NLR was positively correlated with APACHE II (*r*=0.516; p<0.001), SAPS II (*r*=0.459; p=0.002) and SOFA score (*r*=0.556; p<0.001). PL% ratio had a weaker correlation with APACHE II (r=0.337; p0.027), SAPS II (r=0.386; p=0.011) and SOFA score (r=0.399; p=0.008).

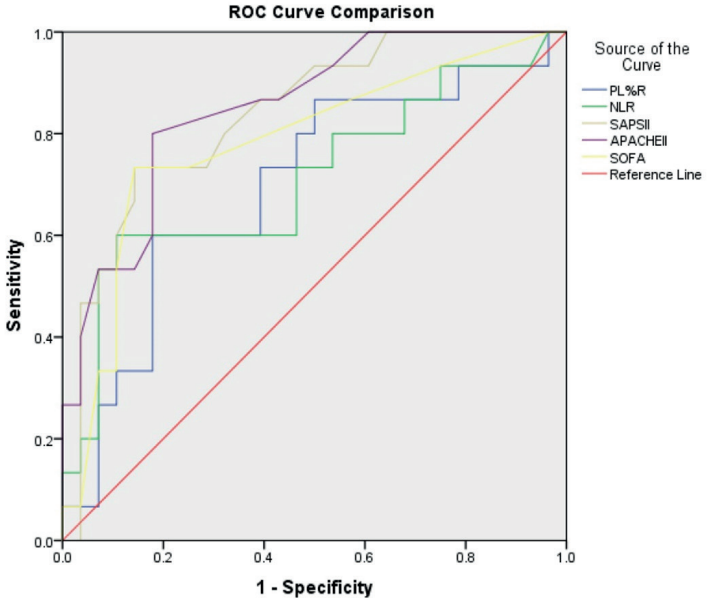

Figure 1: Receiver Operating Characteristic (ROC) Curve comparison for prediction of in-hospital mortality.

5. DISCUSSION

In this study we evaluated the usefulness of NLR and PL%R as predictive markers of survival in a case series of patients with sepsis, assessed in the Emergency Department. We found that both indexes had a positive correlation with the commonly used severity scores, with NLR showing a stronger positive correlation to all scores than PL% ratio. Also, both indexes were higher in the non-survivor group of septic patients. As there is no diagnostic 'gold standard' of sepsis, various indexes and scores have been used during the progression of the syndrome, but their sensitivity and specificity vary. Scores like SOFA, APACHE II and SAPS II are commonly applied in clinical practice and in our case series patients with unfavorable outcome had higher scores. Among several biomarkers, the white blood cell count and C-reactive protein as indexes of the underlying inflammatory progress, are worldwide used from clinicians in relation to sepsis severity scores. Additionally, the neutrophil-to-lymphocyte ratio, representing also the patients' inflammatory response, has been used as it is easily calculated from the complete blood count. We found higher levels of WBC and NLR in patients with worse outcome, a finding supported by the majority of the published literature (15-17).

PLR has already been used in the assessment of various diseases with several underlying mechanisms including thrombotic conditions, inflammatory states, and malignancies. There are plenty of reports in literature referring to significant association between increased PLR and adverse outcomes in cardiovascular diseases and malignancies such as pancreatic, colorectal and endometrial cancer (18,19).

Part of the complicated underlying pathophysiology of sepsis syndrome is clot formation and bleeding diathesis associated with disseminated intravascular coagulation (DIC), combined to platelet dysfunction. Thrombocytopenia in sepsis seems to be relevant to peripheral destruction, hemophagocytic disorders, secretion of cytokines and bone marrow suppression. Due to the above complexity, the role of several parameters derived from the peripheral blood count has been investigated. The diagnostic efficiency of red blood cell distribution width (RDW), platelet distribution width (PDW), and neutrophil-lymphocyte count ratio in sepsis have been reported in the study by Zhang (20). Results from the retrospective study by Loonen et al showed that NLR was a rapidly available biomarker, most promising in differentiating patients with blood stream infection (BSI) from those without BSI in the Emergency Care Unit (21). Increased NLR and PLR have been associated with inflammatory conditions and poor outcome in certain disease states, but PLR is yet not considered as a marker of routine evaluation of patients with sepsis as limited and conflicting literature exists regarding its value (13, 14, 22, 23). In the study by Biyikli, retrospective analysis of patients with sepsis revealed no statistical differences between the group of patients who died within 30 days of admission and those who did not (13).

In the era of COVID-19, NLR and PLR have emerged as easily calculated biomarkers that can predict the severity of the disease. These two indices significantly differ between cases and control and thus could be useful in the emergency department, especially in settings with limited resources (24). The combination of NLR with other easily available biomarkers such as CRP and platelets can provide addi-

tional prognostic information for the severity of COVID-19 (25). Moreover, NLR has been included in conjunction with additional respiratory parameters and LDH, in predictive score for the risk of invasive mechanical ventilation (26).

6. CONCLUSION

There is a realistic need for rapid and cost-effective reliable markers at least in the setting of the Emergency Department, where clinicians are obliged to work in a limited time manner. As early recognition and prompt treatment in the first 'golden hour' remain the corner stone of septic patient approach, adding indexes like NLR and PLR in the diagnostic setting might be helpful. Among the limitations of our study is the retrospective observational design and the relatively small sample size. Another issue that should be considered is the fact that in the multiplicative course of the syndrome, the number and type of white blood cells as well as the number and function of platelets vary, depending on the stage of sepsis, the patient's immunologic status, and the etiology of the infection. A demand for convenient, practical, low-cost indexes for detection, monitoring and prognostication of the sepsis syndrome is still warranted. Large prospective studies are needed to confirm the validity of the NLR and the PLR as acceptable markers in clinical practice.

- **Author's contribution:** V.K and T.P. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. S.K, F.M., E.O., N.N., N-D. P., and V.B. had a part in article preparing for drafting or revising it critically for important intellectual content. F.M., and D.V. gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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