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Value of Platelet to Lymphocyte Ratio in Predicting in-hospital Death of Patients with Sepsis

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ABSTRACT

Objective: The aim of this study was to evaluate the value of platelet-to-lymphocyte ratio (PLR) in predicting in-hospital death in patients with sepsis.

Material and Methods: In this study, 260 patients with sepsis were examined. The APACHE II score was calculated in the first 24 hours of patient admission. The ability of three models (APACHE II, APACHE II with the addition of PLR, and PLR alone) in predicting in-hospital death of patients was compared according to the final outcome (death or discharge).

Results: The mean PLR in the surviving and deceased groups was 349 ± 617 and 376 ± 677, respectively (P = 0.74). The Brier score was determined for APACHE II (0.332±0.32), followed by APACHE II with PLR (0.19 ± 0.18) and PLR (0.25 ± 0.01). The AUROC number for these three prediction criteria was 0.70 ± 0.03, 0.77 ± 0.02 and 0.49 ± 0.03, respectively. In evaluating the calibration of these three prediction models, the p value was significant for APACHE II (P < 0.05). However, this value was not significant for APACHE II with PLR and PLR alone (P = 0.782 and P = 0.786), respectively Sensitivity, specificity, positive and negative predictive values for APACHE II were determined to be 68, 63, 65 and 67%, respectively. Furthermore, these values for APACHE II along with PLR were 60, 85, 80 and 68%, respectively. In addition, these values were calculated for the PLR to be 22, 84, 58, and 52%, respectively.

Conclusion: The PLR is an important risk factor for in-hospital death in patients with sepsis. Adding this to the criteria of the APACHE II system is capable of improving the accuracy of this method in predicting in-hospital death of patients.

KEYWORDS

Platelets, Lymphocytes, Death Prediction.

Introduction

Sepsis is defined as the host response to infection. The invasive agent and host-activated inflammatory mediators disrupt the immune and regulatory systems, thereby disrupting the body's homeostasis (1). Sepsis is currently the tenth most common cause of death in the United States. It is estimated that 571,000 patients with severe sepsis are referred to emergency departments in the United States each year (2). Sepsis accounts for about four in every 1,000 visits to US emergency departments, and mortality from sepsis is estimated at 20 – 50 percent. The incidence of sepsis is also increasing as a cause of hospitalization, especially in people over 65 years of age (1, 3).

The most common main manifestations of the systemic response to sepsis are tachycardia, tachypnea, fever or hypothermia, and immune system activation (leukocytosis or leukopenia) (1). Collectively, these symptoms are often named as the systemic inflammatory response syndrome (SIRS) (1). The definition of SIRS is that the patient has at least two of the following features: 1- Hypothermia (mouth temperature less than 35) or fever (mouth temperature more than 38), 2- The number of breaths more than 20 times per minute or PaCO2 less than 32, 3- heart rate more than 90 beats per minute, 4- leukocytosis (WBC > 12000) or leukopenia (WBC < 4000) or band more than 10%. If SIRS is associated with a proven or suspected microbial origin, it is defined as sepsis.

Sepsis is referred to as severe sepsis if it is accompanied by one or more of the symptoms of: organ dysfunction, hypoperfusion, or hypotension, such as metabolic acidosis, acute mental retardation, oliguria, or acute respiratory

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distress syndrome (ARDS) (1). However, efforts to evaluate the validity of this classification system in patients referred to the emergency department have shown that the concept of sepsis, when defined solely on the basis of the SIRS criterion, is highly sensitive but nonspecific and cannot show an increased risk of mortality in patients (2).

The high prevalence of factors affecting the increase in the incidence of sepsis and septic shock includes: the administration of immunosuppressive and anti-cellular drugs, increasing the use of invasive intravenous equipment, increasing the mean age of the population, and increasing the incidence of seborrheic dermatitis, the increasing incidence of infections caused by resistant microorganisms and the increasing incidence of sepsis. These factors highlight the need for new strategies in the diagnosis and management of septic patients. However, despite the introduction of new theories related to the pathogenesis and pathophysiology of sepsis and the introduction of very strong antibiotics and antifungal drugs, there is still little success in definitively reducing incidence (4).

Defining accurate methods is one of the important factors that can be very helpful in this regard, because they can determine the prognosis of patients with sepsis, especially critically ill patients Finally, their use can be helpful in determining the type of treatment and prioritization of patients. Prognostic classification systems such as APACHE II show that factorization of patient age, underlying condition, and various physiological variables can provide an estimate of the risk of death from severe sepsis. Among the variables, the severity of the underlying disease has a greater impact on the risk of death. Septic shock is also a strong predictor of short- and long-term mortality. The mortality rate for severe sepsis is similar to that of positive and negative cultures (5).

Since the specific pathway leading to rhabdomyolysis is not yet known in inflammatory pathways or processes in sepsis, we aimed to use the APACHE model of two platelet to lymphocyte ratios (PLR) for predicting in-hospital mortality in patients suffering from sepsis.

Materials and Methods

Study Setting

This study was a prospective cohort study that was performed on patients with an initial diagnosis of sepsis (based on the presence of at least 2 of the 4 symptoms of SIRS) (1), and the presence of an infectious disease as diagnosed by a physician. The study was performed from the beginning of April to the end of March 2017 in the emergency room of Imam Reza Hospital, Mashhad University of Medical Sciences. After obtaining informed consent from eligible individuals, demographic information including gender, age, medical history, and patient's clinical symptoms were collected and recorded based on APACHE II scores. In this system, the patient's clinical information was numbered at the time of admission. This information includes body temperature, arterial pH, heart rate, sodium, potassium, mean arterial pressure, respiration rate, and white blood cell count. The APACHE II score in the first 24 hours of patient admission was calculated and completed using the standard APACHE II form (revised in 1999). This system was introduced in 1985 by Kenas et al. which consists of three parts. The first part is the acute physiological score, consisting of 12 parameters. Eleven parameters are defined in a certain range and a special score (between 0 and 4) is considered for each range, which is scored depending on the distance of these ranges from the normal limit. Parameter 12 is the patient's level of consciousness based on the Glasgow Coma Scale (GCS), the difference values of which are reduced from 15 (normal limit) and the score of this parameter is added to the score of the previous 11 parameters, forming the acute physiological score. This score is added to the score obtained from the other two parts (chronic underlying disease matching score and age matching score) and finally the APACHE II score is determined. Scoring in the APACHE II system is from 0 to 71, which is mostly related to the increased probability of patient death (6).

In addition to measuring APACHE II, we added a PLR criterion and measured the predictive power of this model relative to the APACHE II system. Finally, the collected information was entered into SPSS 20 software. Mann-Whitney, Chi-square and regression tests were used to analyze the data. Statistical significance was considered to be the value of 0.05.

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Results

Patient Demographic Information

In this study, 260 patients with sepsis were included, 130 of whom died in the hospital and 130 others who survived. The mean age of patients in the surviving group was 66.27 ± 19.36 years and in the deceased group was 72.43 ± 15.35 years (P < 0.001). In the surviving group, there were 43.8% male patients, and in the deceased group there were 44.6% male patients, with the rest in each group being females. (P = 0.056).

The mean PLR was 349 ± 617 in the surviving group and 376 ± 677 in the deceased group. The results of a Mann-Whitney test showed that the mean ratio of platelets to lymphocytes in patients based on outcome (death / discharge) was not significantly different (P = 0.74).

The mean PLR was 349 ± 617 in the surviving group and 376 ± 677 in the deceased group. The results of a Mann-Whitney test showed no significant difference in the mean ratio of platelets to lymphocytes in patients based on outcome (death / discharge) (P = 0.74).

All criteria involved in calculating the APACHE II score in patients were evaluated and each was compared separately between the two groups.

There were a range of parameters that were compared across the two groups. The mean age (P < 0.001), pulse rate (P = 0.01), respiratory rate (P = 0.02), FiO2 (P = 0.01), urea (P < 0.001), creatinine (P = 0.04) and white blood cell count (P = 0.06) and the number of patients requiring mechanical ventilation (P < 0.001) in the surviving group was significantly less than the deceased group.

In contrast, the mean of SaO2 (P = 0.07), GCS (P <0.001), urine volume (P = 0.02), PH (P < 0.001) and HCo3 (P = 0.07) in the surviving group were significantly higher than in the deceased group. However, when comparing other parameters, the observed difference across the two groups was not significant. Brier scores calculated for APACHE II, APACHE II with PLR and PLR were 0.332 ± 0.32, 0.19 ± 0.18 and 0.25 ± 0.01, respectively. The AUROC number for these three prediction criteria was 0.70±0.03, 0.77 ±0.02 and 0.49 ± 0.03, respectively (Table 1 and Figure 1).

Table 1. Performance of APACHE II, plt/lym and APACHE II with plt/lym

MODELS	**Overall performance**	**Discrimination**				**Calibration**	
		AUROC	Std. Error	Confidence Interval 95%		Hosmer Lemshow-Test	P.value
	Brier Score [STD](Min-Max)			Lower Bound	Upper Bound		
APACHE_II	0.332 [0.32] (0-0.89)	0.709	0.032	0.648	0.771	X2(8)=202.08	<0.05
APACHEII With Plt/lym	0.190 [0.18] (0-0.81)	0.771	0.029	0.714	0.827	X2(8)=4.765	0.782
Plt/lym	0.25 [0.01] (0.18-0.35)	0.492	0.036	0.422	0.563	X2(8)=7.351	0.786

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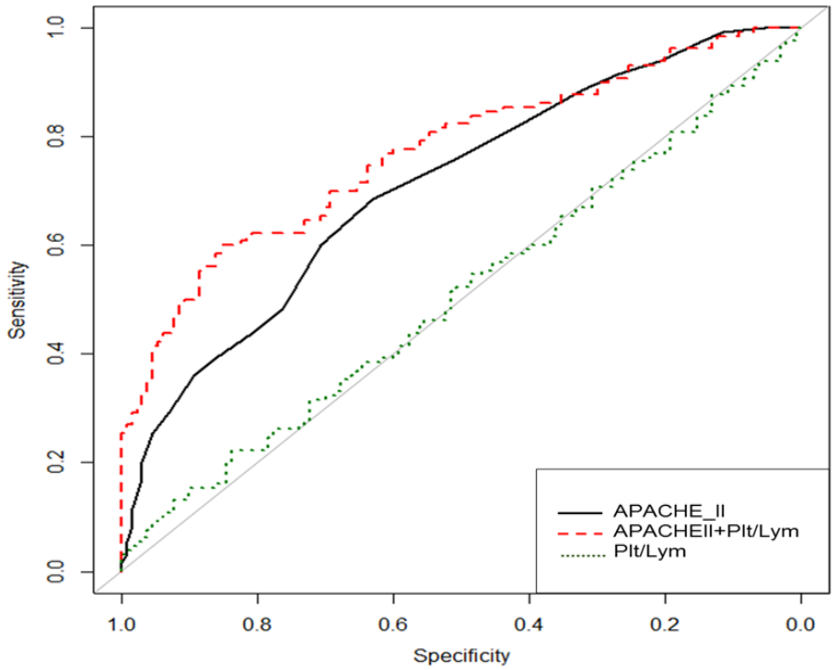

Figure 1. ROC curve drawn for three models APACHE II, plt/lym and Apache II with plt/lym in predicting in-hospital death due to sepsis

In evaluating the calibration of these three prediction models, P value was calculated using Hosmer Lemshow Test, where p value was significant for APACHE II ($P < 0.05$). However, this value was not significant for APACHE II with PLR and PLR ($P = 0.782$ and $P = 0.786$), respectively (Tables 1, Figures 2 and 3).

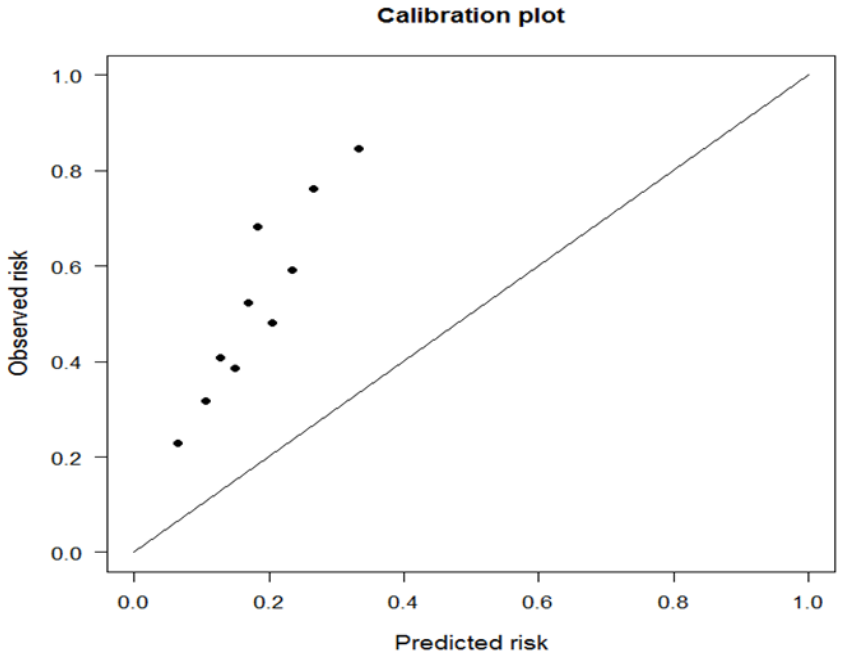

Figure 2. APACHE II calibration curve in predicting in-hospital death from sepsis

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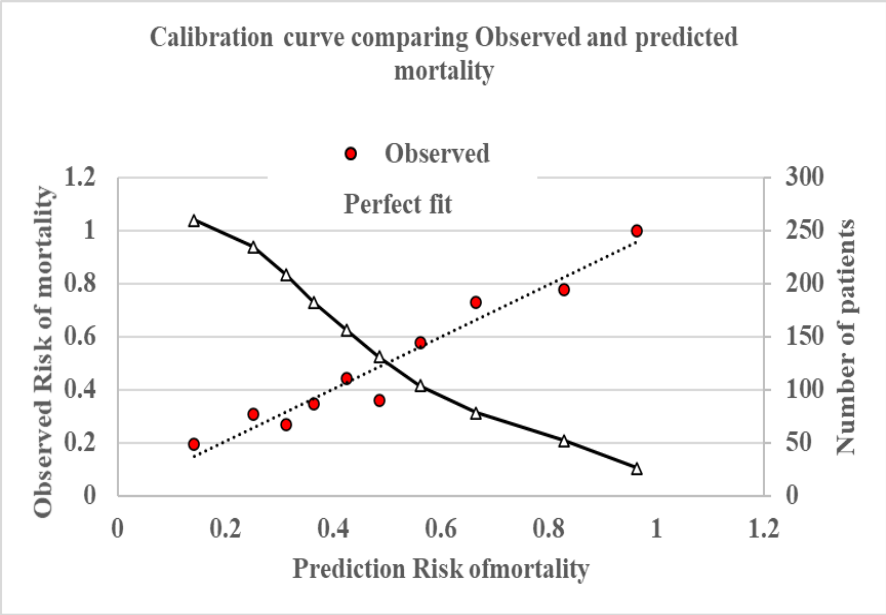

Figure 3. APACHE II + plt/lym calibration curve in predicting in-hospital death from sepsis

Sensitivity, specificity, positive and negative predictive values were determined with a possible threshold of 0.16 for APACHE II (68, 63, 65 and 67%, respectively). These values (Threshold: 0.19) for APACHE II with PLR were 60, 85, 80 and 68%, respectively. These values were calculated for the PLR to be 22, 84, 58, and 52%, respectively (Threshold probability model: 0.5), (Table 2).

Table 2. Comparison of sensitivity, specificity, positive predictive value and negative predictive value of APACHE II, plt/lym and APACHE II with plt/lym in predicting in-hospital death due to sepsis

COORDS_for all Models	Threshold	sensitivity	specificity	PPV	NPV	Accuracy
APACHE_II	0.16	68%	63%	65%	67%	66%
APACHEII With Plt/lym	0.54	60%	85%	80%	68%	73%
Plt/lym	0.5	22%	84%	58%	52%	53%

A pairwise comparison of these three prediction methods in DeLong's ROC test showed that there was a significant difference between these three models in all comparisons (Table 3).

Table 3. Comparison of three methods of predicting patient mortality using DeLong's ROC test

DeLong's ROC test	APACHE_II	APACHEII With Plt/lym	Plt/lym
APACHE_II	******	p-value = 0.027	p-value <0.001
APACHEII With Plt/lym	p-value = 0.027	******	p-value <0.001
Plt/lym	p-value <0.001	p-value <0.001	******

In an independent assessment of relationship of each APACHE II criteria with the prognosis of patients in the regression test, only creatinine (P = 0.033) and mechanical ventilation (P <0.001) had a significant relationship with the prognosis of patients. There was a marked decrease in the prognosis of patients with an increase in each.

Discussion

The results of this study showed that the ratio of platelets to lymphocytes alone could not be a good predictor of in-hospital death of patients with sepsis. APACHE II, along with the platelet-to-lymphocyte ratio, had an acceptable Brier score, calibration, sensitivity, specificity, and positive and negative predictive values, and was much more

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effective than the other two methods. The ratio of platelets to lymphocytes has recently been identified as a new inflammatory marker (7). The reason for this association with inflammation is probably due to a change in the white blood cell count that the body's inflammatory response can produce, leading to increased neutrophil, and decrease lymphocyte counts. Also, changes in leukocyte count are one of the criteria for determining the severity of SIRS due to its high importance. On the other hand, platelet is one of the proven indices in the evaluation of sepsis severity in patients and therefore is included in SOFA scores (8).

The role of platelets has been examined in a study by Klinger et al. (2004) (9). The authors found that platelets, in addition to homeostasis and tissue repair, played an active role in causing inflammation as well as in the host antibacterial defense. Although acute infection with viruses and bacteria can possibly inhibit the production of megakaryocytes, chronic inflammation is associated with reactive thrombocytosis.

Also, in 2013, Imani et al. (10) in a study of 30 patients with sepsis admitted to the intensive care unit of a hospital in Shahrekord reported that the platelet count during sepsis was significantly higher than before and after sepsis. They also measured WBC, CRP, and ESR with platelets before, during, and after sepsis, suggesting that these cheaper and more affordable methods could be used instead of more expensive and complex tests such as PCT for diagnosis of patients with sepsis.

Clinical studies conducted previously have shown that an increase in neutrophils, platelets, neutrophil to lymphocyte ratio (NLR) and PLR are associated with unpleasant clinical and pathological features and also with a poor patient prognosis (11-13). The efficiency of PLR has been evaluated in many studies in assessing the prognosis and predicting death of patients with various malignancies as well as cardiovascular diseases, where many positive results have been reported.

The results of a 2015 study by Hudzik et al. (14) in the Netherlands showed that in-hospital mortality and one-year mortality were higher in the group with PLRs greater than 124. Statistical results also showed the role of PLR as an independent risk factor in confirmation of short-term and long-term mortality in diabetic patients.

There have been a range of studies that have examined the role of the PLR as a predictive clinical parameter. Kundi et al. (15) found that PLR, pulmonary artery systolic pressure, right ventricular dysfunction, WBC level, D-dimer, lymphocytes, platelets, and neutrophils were significantly associated with higher SPESI scores in patients with acute pulmonary embolism. Oylumlu et al. (7) also stated in 2015 in Turkey that high levels of PLR are a good predictor of in-hospital mortality in patients with acute coronary syndrome. Raungkaewmanee et al. (16) in 2012 in a study of 166 patients with ovarian epithelial cancer reported that PLR has a high potential in predicting advanced stages of the disease and cases with poor surgical response. It is a strong predictor as compared to thrombocytosis and NLR. In contrast, Aldemir et al. (17) reported the predictive value of baseline PLR in determining the prognosis of patients with localized and progressive gastric cancer.

Therefore, the PLR can be used in the follow-up of inflammatory diseases and malignancies such as peripheral vascular system disorders, coronary artery disease and hepatobiliary malignancies in women (16-18). So far, very few studies have examined the predictive value of PRL in patients with sepsis. In one of these studies, Menezes et al. (8) examined the value of the PRL in predicting death in 195 patients with sepsis. Their study was performed only on patients admitted to the ICU and its statistical analysis method was different from our study. However, their work did show that the PLR could be a strong predictor of sepsis-induced death.

This criterion has also shown high efficiency in evaluating specific infections. Chen and colleagues (19) for example, used the PRL to diagnose *Mycobacterium tuberculosis* infection in patients with sepsis. They examined 87 patients with COPD and TB, and 83 patients with COPD, where PLR greater than 216.82 had a sensitivity of 92.4% and a specificity of 84.5% in determining TB infection in patients with COPD. Farah et al. (20) also reported that PLR in patients with *Helicobacter pylori* infection was significantly higher than a control group and asymptomatic individuals. Meng et al. (21) also showed that PLR was significantly associated with disease severity in patients with hepatitis C-related liver disease as well as disease recovery rate and good therapeutic response.

Overall, the results of this study could lead to the proposition of a cheap and affordable method for predicting in-

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hospital death due to sepsis in hospitalized patients. Using this method, high risk patients who need faster and more diagnostic and treatment measures can be identified and prioritized to receive services. This may lead to a reduction of the mortality rate of the disease among hospitalized patients.

Conclusion

In this study, we found that the PLR is an important risk factor for in-hospital death in patients with sepsis. Adding the PLR to the criteria of the APACHE II system can significantly improve the accuracy of this method in predicting in-hospital death in patients with sepsis. Unlike other markers and criteria for measuring inflammation, the PLR is a cheap and readily available biomarker for classifying the risk of death in patients with sepsis. Future work would be well-guided to conduct extensive studies with a large sample size to confirm the results of our study. The utility of using the PLR as a predictor for mortality in other inflammatory and infectious diseases also warrants further investigation. Ultimately it is hoped that work in this field will help lead to improved prediction of in-hospital mortality in septic patient cohorts.

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