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Neutrophil-Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Prediction of Severe Acute Pancreatitis: A Prospective Single Center Study

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ABSTRACT

Background: Acute pancreatitis (AP) was the most common discharge diagnosis of gastrointestinal disorder that places a substantial burden on the healthcare system. The clinical course of most patient with AP is often mild and it often resolves without sequelae. And yet a considerable percentage of people develop severe AP (SAP) that would greatly affect the outcome. The objective of the current study is to assess the value of neutrophil-lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in prediction of SAP.

Patients and methods: A prospective cohort study was conducted in the Department of Tropical Medicine and Gastroenterology of Assiut University Hospital in the Period between 2018 and 2020. A total of 100 patients with AP were enrolled in the study. Demographic, clinical, laboratory and outcome data of those patients were recorded. NLR and PLR were calculated.

Results: Out of the enrolled patients; based on the revised Atlanta Criteria, 19 (19%) patients had SAP and 81 (81%) patients had mild AP. Patients with SAP had significantly higher serum creatinine, NLR and PLR. Also, frequency of mortality and admission to intensive care unit was significantly higher in patients with SAP. NLR at cutoff point >2.43 had 100% overall accuracy in prediction of SAP with area under curve (AUC) was1 while PLR at cutoff >187.04 had 87% overall accuracy with AUC was 0.850.

Conclusion: patients with SAP had bad prognosis. Usage of NLR and PLR can help in prediction of those patients with NLR and PLR. Future studies to confirm such findings are recommended.

Keywords: Acute pancreatitis, Neutrophil-lymphocyte ratio, Platelet to lymphocyte ratio, Severe acute pancreatitis.

INTRODUCTION

One of the most prevalent gastrointestinal tract disorders, acute pancreatitis (AP), is a quickly developing pancreatic inflammatory condition that varies in severity and clinical appearance. Worldwide, there are between 4.9 and 73.4 instances of AP for per 100,000 people. Although the condition is moderate in the majority of patients and has a fair prognosis, 15% to 20% of AP patients experience a severe clinical course with increased rates of morbidity and mortality [(1,2)].

In addition to medications, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic metabolic abnormalities, drugs, trauma, ischemia, neoplasms, infections, and hereditary factors, the main risk factors for AP are gallstones and alcohol abuse. Uncertain mechanisms underlie the many etiological factors that cause an AP attack [(3,4)].

Recognizing individuals at risk of severe acute pancreatitis (SAP) at an early stage is crucial for prompt treatment and therapy optimization. To evaluate and categorize the severity of AP today, a number of severity rating systems have been presented and recognized. The ones that are most frequently used in standard clinical practice include the APACHE II system, Ranson criteria, and bedside index for severity in acute pancreatitis (BISAP) score [(5,6)].

Among several serum biochemical markers, serum procalcitonin (>1.8 ng/mL) and C-reactive protein (CRP) ≥ 150 mg/L at 48 hours post-admission have been adopted as prognostic factors for the management of AP [(7)]. Also, serum levels of the inflammatory mediators interleukin (IL) 6, 8, and IL-10 have been found to be accurate for predicting persistent organ dysfunction in AP patients [(8,9)].

However, these serum markers are expensive, not readily available, and cannot adequately predict the prognosis or severity of AP. Recently, neutrophil-lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been proposed as widely available markers that provide a rapid evaluation of the extent of the inflammatory process in AP patients. Secondary to paucity in our locality about use of NLR and PLR in prediction of SAP, the current study was conducted to evaluate such markers in patients with AP.

PATIENTS AND METHODS

Study design and setting:

A prospective cohort study was conducted in the Department of Tropical Medicine and Gastroenterology of Assiut University Hospital in the Period between 2018 and 2020.

Selection criteria:

Any patient with 18 years or above and met criteria for diagnosis of AP was eligible for the study. The following patients were excluded from this study: age <18 years old, patients with metastatic tumor, acquired immunodeficiency syndrome, uremia, late stage of liver

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cirrhosis, active tuberculosis, refractory heart failure, previous transplantation, immunosuppressive therapy and pregnancy, patients with chronic pancreatitis or pancreas carcinoma.

Diagnosis and stratification of acute pancreatitis:

The presence of at least two of the following three symptoms was required for the diagnosis of AP: acute onset of the typical upper abdominal pain (which is persistent, severe, and frequently radiates to the back); elevated pancreatic enzyme levels (serum amylase and/or lipase > 3 times the upper limit of normal); and AP-suggestive findings on ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) [(10)].

To identify the severity of the condition and make the diagnosis of necrotic pancreatitis, CT pictures taken three to four weeks following the initial imaging were evaluated. Gallstones, alcohol, hypertriglyceridemia, and other factors (hypercalcemia, medications, trauma, autoimmune, endoscopic operations) were all included as the causes of AP [(10)]. The cause of the remaining instances was listed as uncertain. The updated Atlanta Criteria were used to divide the study group into mild-moderate and severe AP categories [(11)].

Data collection:

During the study period, a total of 100 patients with AP were eligible for the study. All patients were subjected to full history and thorough clinical evaluation. Demographics information of all enrolled patients were collected and recorded on admission. Clinical (blood pressure, respiratory rate, pulse rate) and laboratory parameters (white blood cell count, neutrophil count, lymphocyte count, hemoglobin level, platelet level, red cell distribution width (RDW) level, hematocrit (HCT), renal function, hepatic function, electrolytes, arterial blood gas) were assessed and recorded.

The Ranson score was calculated using data from the first 48 hours following admission. The presence of features of systemic inflammatory response syndrome was recorded within 24 hours of admission. NLR at admission and serum CRP level (mg/L) at 48 hours were also recorded.

Ethical consent:

Our study was approved by the Ethical Review Committee Faculty of Medicine at Assiut University. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study was registered on clinicaltrials.gov with NCT 03601325.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 20 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean and standard deviation (SD), and compared by Student's t test. While nominal data are expressed as frequency (percentage) and were compared by Chi-square test. The prognostic performance of NLR, and PLR were compared for severity according to the revised Atlanta Criteria. The data were also evaluated regarding the ability of each scoring system to predict AP severity by calculating receiver operator characteristic (ROC) curves using the MedCalc software (SolidWorks, Concord, MA). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each individual scoring system were calculated. The area under the ROC (AUROC) was used to evaluate the discriminative ability of NLR and PLR for predicting severity. A P-value ≤ 0.05 was considered significant.

RESULTS

Baseline data of the studied patients based on severity of AP (table 1):

Out of the enrolled patients; based on the revised Atlanta Criteria, 19 (19%) patients had SAP and 81 (81%) patients had mild AP. Patients with SAP had significantly higher creatinine CRP, APACHE-II, Ranson score and RDW with significantly lower albumin level in comparison to those with mild AP. Other baseline data showed no significant differences between both groups.

Table (1): Baseline data of the studied patients based on severity of AP.

Variable	Severity of AP		*P* value
	Mild (n= 81)	Severe (n= 19)	
Age (year)	49.59 ± 8.79	46.95 ± 6.84	0.22
Sex	48 (59.3%)	9 (47.4%)	0.24
Male	33 (40.7%)	10 (52.6%)	
Female			
Smoking	7 (8.6%)	3 (15.8%)	
Comorbidities			0.18
Nothing	69 (85.2%)	17 (89.5%)	
Diabetes mellitus	8 (9.9%)	0	
Ischaemic heart disease	2 (2.5%)	2 (10.5%)	
Chronic kidney disease	2 (2.5%)	0	
Aetiologies			0.21
Biliary	61 (75.3%)	19 (100%)	
Post-ERCP	10 (12.3%)	0	
Hypertriglyceridemia	4 (4.9%)	0	
Hypercalcemia	2 (2.5%)	0	
Unknown	4 (4.9%)	0	
Hemoglobin (g/dl)	11.56 ± 1.23	12.09 ± 0.67	0.08
Platelets (10^3/ul)	234.56 ± 51.98	240.98 ± 56.32	0.65
Leucocytes (10^3/ul)	6.98 ± 1.11	7.88 ± 1.71	0.76
Albumin (mg/dl)	39.98 ± 3.45	28.78 ± 4.44	< 0.001
Alanine transmarine (u/L)	46.87 ± 10.31	49.09 ± 10.68	0.76
Aspartate transaminase (u/L)	51.45 ± 5.55	50.50 ± 12.43	0.30
Creatinine (mg/dl)	1.09 ± 0.1	2.01 ± 0.41	< 0.001
C-reactive protein (mg/dl)	15.67 ± 3.63	30.87 ± 4.21	< 0.001
Ranson score	2.50 ± 0.51	4.98 ± 1.11	< 0.001
RDW (%)	11.11 ± 2.61	15.32 ± 0.96	0.03
APACHE-II score	4.88 ± 0.95	10.14 ± 2.21	< 0.001

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **AP**: acute pancreatitis; **ERCP**: endoscopic retrograde cholangio-pancreaticography; **RDW**: red cell distribution width; **APACHE-II**: acute physiology and chronic health evaluation II

NLR and PLR based on severity of AP (table 2):

Patients with SAP had significantly higher NLR (10.07 ± 3.37 vs. 1.29 ± 0.49; $p< 0.001$) and PLR (254.89 ± 94.75 vs. 125.38 ± 64.35; $p< 0.001$) in comparison to those with mild AP.

Table (2): NLR and PLR based on severity of AP

Variable	Severity of AP		*P* value
	Mild (n= 81)	Severe (n= 19)	
NLR	1.29 ± 0.42	10.07 ± 2.41	**<0.001**
PLR	125.38 ± 21.51	254.89 ± 51.11	**<0.001**

Data expressed as mean (SD). *P* value was significant if < 0.05. **AP**: acute pancreatitis; **NLR**: Neutrophil-lymphocyte ratio; **PLR**: platelet to lymphocyte ratio

Outcome among the studied patients based on severity of AP (table 3):

Patients with SAP had significantly prolonged hospital stay (17.63 ± 5.27 vs. 10.23 ± 4.27 (days); $p< 0.001$), significantly higher of intensive care unit admission (13 (68.4%) vs. 4 (4.9%); $p< 0.001$) and mortality (7 (36.8%) vs. 1 (1.2%); $p< 0.001$).

Table (3): NLR and PLR based on severity of AP

Variable	Severity of AP		*P* value
	Mild (n= 81)	Severe (n= 19)	
Hospital stay (days)	10.23 ± 2.31	17.63 ± 4.12	**< 0.001**
ICU admission	4 (4.9%)	13 (68.4%)	**< 0.001**
Mortality	1 (1.2%)	7 (36.8%)	**< 0.001**

Data expressed as mean (SD), frequency (percentage). *P* value was significant if < 0.05. **AP**: acute pancreatitis; **ICU**: intensive care unit

Accuracy of NLR and PLR in prediction of SAP (table 4, figure 1):

It was found that NLR at cutoff point > 2.43 had 100% overall accuracy in prediction of SAP with area under curve (AUC) was1 while PLR at cutoff > 187.04 had 87% overall accuracy with AUC was 0.850.

Table (4): Accuracy of NLR and PLR in prediction of SAP

Item	NLR	PLR
Sensitivity	100%	78.90%
Specificity	100%	88.90%
Positive predictive value	100%	62.5%
Negative predictive value	100%	94.7%
Accuracy	100%	87%
Cutoff point	> 2.43	> 187.04
Area under curve	1.00	0.85
P value	< 0.001	< 0.001

P value was significant if < 0.05. S**AP**: severe acute pancreatitis; **NLR**: Neutrophil-lymphocyte ratio; **PLR**: platelet to lymphocyte ratio

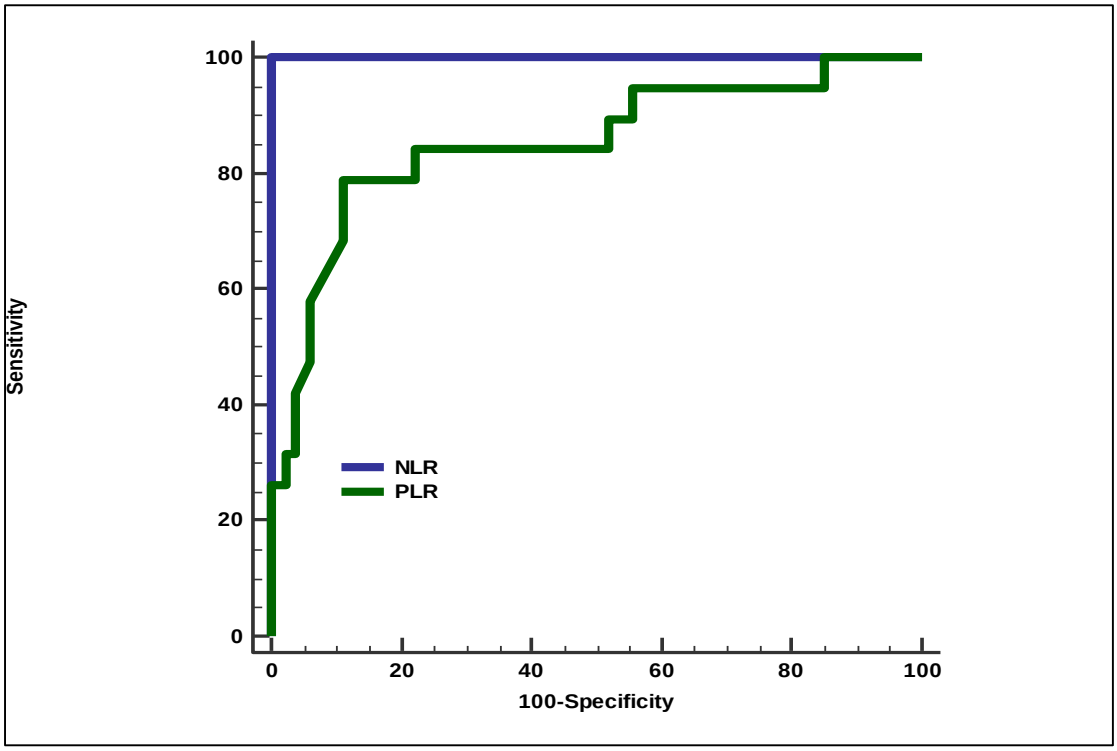

Figure (1): Accuracy of NLR and PLR in prediction of severe acute pancreatitis. **NLR**: Neutrophil-lymphocyte ratio; **PLR**: platelet to lymphocyte ratio**.**

DISCUSSION

The clinical extent of AP varies widely from no symptoms to systemic inflammatory response syndrome (SIRS), persistent organ failure (POF), and death. The clinical presentation of AP is both unreliable and nonspecific and exhibits a sensitivity less than 40% for the prediction of adverse outcomes [12,13].

Also, the underlying pathophysiology behind the progression of local pancreatic injury to SIRS is not fully understood. Due to the diverse presentations of AP and its unknown pathophysiology, multiple severity scoring systems have been designed to help clinicians in triaging AP patients and predicting their prognosis [14,15].

The Ranson score, the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, BISAP score, and the Glasgow-Imrie criteria are currently in wide use. However, these systems are time-consuming and difficult to apply to patients outside of intensive care settings because they use many variables. Also, they are unsuitable for the evaluation of patients at the time of admission or shortly thereafter [16,17].

In a recent review by **Shah *et al.*** [18] it was declared that the APACHE II scoring system had the highest accuracy for predicting severe AP when compared with other scoring systems. However, the APACHE II scoring system is exhaustive and cannot be widely adopted for AP patients outside the intensive care setting [19].

Also in a previous study, it was demonstrated that the APACHE II score had just a 67% PPV at 24 h after admission and was even less accurate for identifying patients with specific complications such as peripancreatic fluid collections or major organ failure [20].

In recent years, researchers have been interested in determining the most practical and accurate parameter indicative of the severity and prognosis of AP. Some researchers have found that no statistically significant pairwise differences were observed between the APACHE-II and the other scoring systems, including CRP value at 24 hours, BISAP, Ranson, and Balthazar scores [18, 21, 22].

In the current study, we aimed to assess the use of NLR and PLR in prediction of severity of SAP. The study enrolled 100 patients with AP. Out of those patients, based on the revised Atlanta Criteria [11], 19 (19%) patients had SAP and 81 (81%) patients had SAP. In line with the current study, a previous study of 80 patients with AP stated that 19 (23.8%) patients had severe AP [10].

In another study of 406 patients with AP, 56 (13.7%) patients had SAP [6]. This low percentage of SAP in such study compared to our results may be explained by different sample size, study population and selection criteria.

Also, we found that Patients with SAP had significantly higher creatinine CRP, APACHE-II, Ranson score, RDW, NLR and PLR with significantly lower albumin level in comparison to those with mild AP. Patients with SAP had significantly prolonged hospital stay (17.63 ± 5.27 vs. 10.23 ± 4.27 (days); p< 0.001), significantly higher of intensive care unit admission (13 (68.4%) vs. 4 (4.9%); p< 0.001) and mortality (7 (36.8%) vs. 1 (1.2%); p< 0.001).

Gezer *et al.* [10] reported that regarding a variety of laboratory parameters, the NLR, PLR, RDW, glucose, and blood urea nitrogen (BUN) level of the SAP group were significantly increased compared to the MAP group on admission (P<0.001). The severity of AP increased as the NLR, SOFA, BISAP, and Ranson increased (P<0.01). The SAP group had significant lower albumin level compared to MAP group (P<0.001).

Also, another study concluded that that NLR, PLR, RDW, glucose, and BUN level of the SAP group were significantly increased compared to the mild acute pancreatitis (MAP) group on admission (*P*<.001). The severity of AP increased as the NLR, BISAP, and Ranson increased (*P*<0.01) [6].

Here, in the current NLR at cutoff point > 2.43 had 100% overall accuracy in prediction of SAP with area under curve (AUC) was1 while PLR at cutoff > 187.04 had 87% overall accuracy with AUC was 0.850. **Zhou *et al.* [6]** reported that The AUC values of NLR and PLR to predict SAP were 0.722, 0.621, respectively.

The NLR was 1st introduced as an easily measurable parameter evaluating systemic inflammation and stress in critically ill patients, while PLR was also proved to be an inflammatory marker and the role of platelet as a crucial link between inflammation and microvascular dysfunction has been investigated. A few of researches have explored the relationship between NLR, PLR, and AP [23-25].

Wang *et al.* [25] demonstrated that NLR had the highest discriminatory capacity for severe hypertriglyceridemia-induced AP. **Jeon and Park [26]** proved that elevated baseline NLR correlates with SAP and organ failure. Study by **Li *et al.* [27]** enrolled 359 patients and concluded that NLR had the largest AUC compared with RDW, CRP, lymphocyte-monocyte ratio, and prognostic nutritional index.

İlhan *et al.* [28] investigated 14 patients who developed AP in ongoing pregnancy and 30 healthy pregnant controls, an result indicated that NLR elevated significantly in AP group compared with controls, but there was no significant difference in terms of PLR.

Han *et al.* [29] declared that NLR on admission within 48h had the highest AUC for predicting severe AP, with a cut-off value of 6.66, and NLR was also significantly positively correlated with the Ranson score and hospital stays. **Zhang *et al.* [13]** suggested that high NLR is associated with persistent organ failure, extended duration of intensive care, and also a higher mortality rate. In line with their study, **Gezer *et al.* [10]** found that NLR had the highest value to predict mortality compared with other scoring systems and biomarkers.

Although activation and modulation of neutrophils and platelets play a central role in establishing host defenses in settings of systemic inflammation, excessive inflammatory response results in massive cell transmigration to the pancreas, which in turn results in the destruction of the pancreas and organ failure subsequent to release of aggressive defense molecules [30].

The main limitations of the current included, relatively small sample size, being conducted in single centers, didn't perfume comparison with other scores as APACHE-II and radiological scores, didn't assess effect of NLR and PLR on 28-day mortality.

In conclusion, each of NLR and PLR can be used in prediction patients with SAP but future studies on large scale with comparison between different clinical, laboratory and radiological scores are warranted to validate the best score that could be used.

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