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Inflammatory indices as an indicator of acute pancreatitis severity

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Abstract

Objective: The present study aimed to compare C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), neutrophil/albumin ratio (NAR), platelet/leukocyte ratio (PLR), systemic immune inflammation (SII), systemic inflammation response index (SIRI) and Ranson criteria associated with inflammation in acute pancreatitis (AP). Thus, the study aimed to analyze the significance ranking of these parameters in terms of disease severity.

Method: The present retrospective study was conducted after the ethics committee approval was obtained. The study included 221 AP patients visited hospital between 01.01.2018 and 31.12.2023. The patients were categorized into two groups based on Ranson criteria: Group 1 (Ranson≤2, n=147) and Group 2 (Ranson≥3, n=74). Basic participant demographics, laboratory reports, CRP, NLR, NAR, PLR, SII, SIRI and hospitalization periods were recorded in a data form, and the findings were analyzed.

Results: There was no difference between the groups based on gender (p=0.094). The Group 2 patients were older (p<0.001) than the ones in Group 1. Furthermore, CRP (p=0.001), NLR (p<0.001), NAR (p<0.001), PLR (p<0.001), SII (p<0.001) and SIRI (p<0.001) were higher in Group 2 patients when compared to Group 1. Also, the hospitalization period was significantly longer in Group 2 (p<0.001) compared to Group 1.

Conclusion: In the study, it was determined that the CRP, NAR, PLR, NLR, SII and SIRI findings were significantly higher in AP patients with a Ranson criteria ≥ 3, and a positive correlation was found between Ranson criteria and inflammatory parameters.

Keywords: Acute pancreatitis, systemic immune inflammation, systemic inflammation response index, hematological parameters

INTRODUCTION

Although the pathogenesis of acute pancreatitis (AP) is multifactorial, pancreatic enzyme activation plays a key role in local pancreatic damage. Based on the severity of inflammation induced by enzyme activation, the pathology of the disease can range between local peripancreatic edema to severe hemorrhagic gangrene and necrosis (1,2).

Early detection of AP severity is important to provide curative treatment and early identification of potential complications. Although various scoring systems have been developed, studies focusing on seeking more practical and result-oriented laboratory parameters continue to increase in the literature.

Previous studies reported that inflammation markers neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios could be employed as prognostic factors in several diseases (SLE, infections, rheumatic diseases, etc.), including certain types of cancer (3-5). Recently, the neutrophil/albumin ratio (NPAR), an inflammatory parameter calculated by dividing the neutrophil ratio by serum albumin concentration, was considered as an inflammatory prognostic factor in several diseases (6-8). However, there is no sufficient evidence on the prognostic value of Neutrophil / Albumin Ratio (NAR) in AP.

Systemic immune inflammation (SII) and systemic inflammation response index (SIRI) are integrated inflammatory biomarkers that could demonstrate local immune response and systemic inflammation throughout the human body (9,10). A recent study examined the predictive value of SII in severe acute pancreatitis and showed that patients with SII values above 1660.36 were more likely to develop severe acute pancreatitis. In another study, the power of SII in the diagnosis of acute pancreatitis was examined and

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it was shown that SII could be used in the diagnosis of acute pancreatitis with 78.7% sensitivity and 46% specificity. (11,12).

Hematological indices have been employed in several studies in recent years due to their non-invasive, rapid, low cost, high sensitivity properties. The present study aimed to investigate the impact of inflammatory parameters during the initial hospitalization of AP patients on disease severity and the duration of hospitalization.

METHOD

For the study, ethical permission was received from the Fırat University Non-Interventional Research Ethics Committee, dated March 05, 2024 and numbered 2024/04-16. The study included the clinical records of 221 AP patients who visited the hospital between 01.01.2018 and 31.12.2023 and fit the inclusion criteria (Figure 1). The patients were categorized into two groups based on Ranson criteria: Group 1 (Ranson≤2, n=147) and Group 2 (Ranson≥3, n=74). Basic participant demographics, laboratory reports, C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), neutrophil/albumin ratio (NAR), platelet to leukocyte ratio (PLR), systemic immune inflammation (SII), and systemic inflammation response index (SIRI) and hospitalization periods were recorded in a data form, and the findings were analyzed. AP was diagnosed based on the presence of at least two of the following three criteria: (i) abdominal pain consistent with the disease, (ii) biochemical evidence of pancreatitis (serum amylase and/or lipase level more than three times the upper limit), and (iii) characteristic abdominal imaging findings (13). The patients who were 18 years old or older, and without an advanced cardiovascular, malignant, metabolic or liver disease, hematological pathology, acquired immunodeficiency syndrome, and not pregnant were included in the study. Patients, who were younger than 18, with advanced cardiovascular, metabolic, liver, chronic inflammatory diseases, cancer, or acquired immunodeficiency syndrome, or pregnant, were excluded from the study.

Statistical analysis

The study data were analyzed with SPSS 21.0 (IBM Corporation, Armonk, NY, USA) software. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were conducted to determine the normal distribution of continuous variables. Parametric numerical data were presented in means ± standard deviations, and qualitative data were presented in percentages. Student's t-test was employed to compare the independent groups. Chi-Square test (cross-tab) was used to compare categorical variables between the groups. Receiver operating characteristic (ROC) curve analysis was conducted on the CRP, NAR, PLR, NLR, SII and SIRI findings between

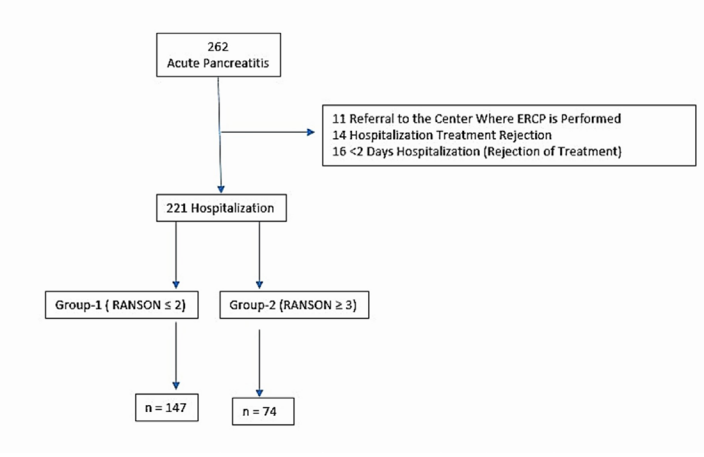

Figure 1. Study patient flow chart

the groups. ROC curve analysis results were presented as % specificity, % sensitivity (area under the ROC curve [AUC], p, 95% confidence interval [CI]). P < 0.005 was accepted as statistically significant in all analyses.

RESULTS

There was no significant difference in gender distribution between Group 1 (n=147, female (F)/male (M)=78/69) and Group 2 (n=74, F/M=48/26) participants (n=221) (p=0.094). However, the mean age was significantly different between the groups, with Group 1 having a mean age of 53.3±17.9 years and Group 2 having a mean age of 74.5±11.9 years (p<0.001). Laboratory parameters showed notable differences between the groups. In Group 2, CRP (p=0.001), NAR (p<0.001), PLR (p<0.001), NLR (p<0.001), SII (p<0.001), SIRI (p<0.001), and the hospitalization period (p<0.001) were significantly higher compared to Group 1 (Table 1). Additionally, Group 2 had significantly higher glucose (p<0.001), creatinine (p<0.001), AST (p=0.004), total bilirubin (p=0.001), direct bilirubin (p=0.001), LDH (p<0.001), white blood cell count (p<0.001), and neutrophil count (p<0.001), whereas the lymphocyte count was significantly lower (p<0.001) (Table 1).

ROC analysis was performed to evaluate the diagnostic value of CRP, NAR, PLR, NLR, SII, and SIRI in distinguishing Group 1 and Group 2 patients. The analysis demonstrated that the specificity of CRP was 54.10%, NAR was 89.80%, PLR was 72.79%, NLR was 57.82%, SII was 68.71%, and SIRI was 76.19% (Table 2). Among these markers, NAR showed the highest specificity (89.80%), while SIRI had a specificity of 76.19%, indicating their potential utility in distinguishing between the patient groups. Additionally, NLR demonstrated the highest sensitivity (79.73%), followed by SII (63.51%) and CRP (66.67%). These findings suggest that systemic immune-inflammatory indices, particularly NLR, SII, and SIRI, may serve as useful indicators for differentiating between the groups.

Table 1: Patient and control demographics and laboratory data

	Group 1	Group 2	p
N (F/M)	147(78/69)	74(48/26)	0.094
Age	53.36 ±17.93	74.55 ±11.91	<0.001
Glucose (mg/dL)	131.74±46.41	168.83±71.17	<0.001
Creatinine (mg/dL)	0.92±1.06	1.64±1.85	<0.001
Albumin (g/L)	38.43±4.57	38.77±21.40	0.856
AST (U/L)	160.82±211	271.45±355.43	0.004
ALT (U/L)	154.55±198.83	169.60±179.19	0.584
Total Bilirubin (mg/dL)	1.27±1.36	2.12±2.39	0.001
Direct Bilirubin (mg/dL)	0.57±0.87	1.07±1.42	0.001
Amylase (U/L)	1650.93±2499.1	1515.68±1436.28	0.667
Lipase (U/L)	4168.57±6228.13	3050.63±3577.06	0.154
LDH (U/L)	330.13±220.13	692.32±1020.70	<0.001
C-reactive protein (mg/dL)	45.61±55.13	83.51±101.49	0.001
White blood cell (103/mm3)	10.95±3.40	12.99±5.17	<0.001
Lymphocyte (10e3/µL)	1.76±1.06	1.10±0.72	<0.001
Neutrophil (10e3/µL)	8.19±3.34	10.78±5.05	<0.001
Monocytes (10e3/µL)	0.83±1.02	0.96±1.13	0.367
Hemoglobin (mg/dL)	15.21±18.11	12.6±2.23	0.218
Platelet (10^3/mm3)	266.93±85	242.90±88.29	0.052
NAR	0.2158±0.09265	0.3166±0.18095	<0.001
PLR	210.554±160.2084	369.7904±457.99764	<0.001
NLR	7.1494±6.74104	15.440±14.68	<0.001
SII	1894.97±2015.82	3908.43±4325.60	<0.001
SIRI	5.14±4.98	15.93±26.18	<0.001
Hospitalization period	6.24±4.74	12.32±13.75	<0.001

N (F/M): Number of patients (Female/Male), AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate Dehydrogenase, NLR: Neutrophil / Lymphocyte Ratio, NAR: Neutrophil / Albumin Ratio, PLR: Platelet to leukocyte ratio, SII: Systemic Immune Inflammation, SIRI: Systemic Inflammation Response Index, p < 0.005 was accepted as statistically significant in all analyses.

Furthermore, the significantly prolonged hospitalization period in Group 2 suggests a potential association between these inflammatory markers and disease severity (Table 2).

DISCUSSION

It was determined that CRP (p = 0.001), NAR (p<0.001), PLR (p<0.001), NLR (p<0.001), SII (p<0.001), SIRI (p<0.001) and length of hospitalization were significantly higher in Group 2 (p<0.001).

AP is an inflammatory disease that can progress from local abdominal pain to mortality. Various scoring systems aim to determine disease severity and prognosis (14,15). The most frequently used system is the Ranson criteria. The limitation of the Ranson criteria is that its measurements become significant only after 48 hours (16,17). Thus, studies on several scoring systems or biomarkers that aim to predict mortality and disease severity at the time of the admission have been increasing. The most frequently used biomarkers are the inflammatory biomarkers.

Several studies have been conducted on CRP, the most commonly used inflammation indicator, in AP. Although it was demonstrated that CRP levels and disease severity were associated with the prognosis of AP and could guide the treatment, Rau et al. compared procalcitonin and CRP values and reported that procalcitonin was more valuable as a marker of early diagnosis and prognosis (18,19). Similar to previous findings, our study demonstrated that the CRP level increases with disease severity and is a significant parameter. However, it can be suggested that the lack of significant findings in a comparative ROC study conducted with other inflammatory parameters revealed two significant consequences for us. The first one is the fact that CRP could not be demonstrated to be specific or sensitive to any inflammatory event. The second one is to serve as an additional indicator for the transparency of the findings in this study.

Table 2: Receiver operating characteristic analyses on CRP, NAR, PLR, NLR, SII, and SIRI in the Groups 1 and 2

	Cut Off (ng/mL)	AUC	95% CI	Sensitivity	Specificity	PPD	NPD	p
CRP	>19.8	0.615	0.541 - 0.685	66.67	54.10	44.0	75.0	0.0080
NAR	>0.32	0.682	0.616 - 0.743	41.89	89.80	67.4	75.4	<0.001
PLR	>245.74	0.659	0.592 - 0.721	55.41	72.79	50.6	76.4	<0.001
NLR	>5.70	0.734	0.670 - 0.791	79.73	57.82	48.8	85.0	<0.001
SII	>2024	0.687	0.621 - 0.747	63.51	68.71	50.5	78.9	<0.001
SIRI	>7	0.694	0.629 - 0.754	55.41	76.19	53.9	77.2	<0.001

Abbreviations: CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte Ratio, NAR: Neutrophil/Albumin Ratio, PLR: Platelet to leukocyte ratio, SII: Systemic Immune Inflammation, SIRI: Systemic Inflammation Response Index, AUC: Area Under the Curve, PPD: Positive Predictive Value, NPD: Negative Predictive Value, p < 0.005 was accepted as statistically significant in all analyses.

Hematological inflammatory parameters or indices have been studied in inflammatory diseases since they are fast, available in several centers, and could be calculated easily. Whereas NLR and PLR have been the most commonly used hematological inflammatory parameters, NAR, SII, and SIRI inflammatory indices have just been investigated recently.

Neutrophils are precursor cells of the immune system defense, and it was reported that they are responsible for the synthesis of cytokine, chemokine, and growth factor, in addition to the production of antimicrobial agents (20). They stimulate cytokine secretion in platelets, much like neutrophils, during the early stages of inflammation. High cytokine levels have been reported to play a crucial role in linking inflammation to microvascular dysfunction by promoting the production of new neutrophils and platelets (21,22). Several studies demonstrated that NLR levels were high in pancreatitis. Suppiah A. et al. reported that elevation in NLR during the first 48 hours of admission was significantly associated with severe AP and an independent negative prognostic indicator of AP (23). Similarly, PLR was demonstrated to increase in inflammatory events and AP. Consistent with the literature, it was elevated in severe AP in the present study. This significant difference between the Groups 1 and 2 was quite interesting. The Ranson criteria scores were higher in the Group 2, and although this finding was due to the severity of AP, the mean age was higher in the Group 2 when compared to the Group 1. Since the immune response occurs later in the elderly, this significant difference is likely associated with the severity of pancreatitis.

NAR is an effective biomarker calculated with neutrophil and albumin counts, providing a cost-effective and easily accessible indicator of systemic inflammation. Previous studies have shown that NAR can predict conditions such as acute kidney injury, cardiogenic shock, myocardial infarction, and cancer (7,24,25). However, there are only a few studies in the literature examining the relationship between NAR and disease severity in other inflammatory conditions, including pancreatitis. The prognostic significance of NAR in severe inflammation has been widely discussed in recent years (6,26). In our study, we found that NAR was significantly higher in Group 2 compared to Group 1 ($p<0.001$), suggesting its potential role as an indicator of disease severity. Moreover, ROC analysis demonstrated that NAR had the highest specificity (89.80%) among all inflammatory markers, emphasizing its predictive value. These findings are consistent with previous reports highlighting the role of NAR as a prognostic biomarker. The ability of NAR to distinguish between different patient groups with high specificity suggests that it may be a valuable tool in clinical decision-making, particularly in identifying patients with a more severe disease course. Furthermore, considering the easy accessibility and low cost of NAR measurement, its integration into routine clinical practice could enhance early risk stratification and management strategies. These findings reinforce the importance of systemic immune-inflammatory markers and suggest that NAR may serve as a clinically useful parameter in assessing disease severity.

Apart from CRP and the proportional parameters (NLR, PLR), the systemic immune inflammation index (SII) that includes a combination of neutrophil, lymphocyte, and platelet counts, and SIRI, formulated based on neutrophils, lymphocytes, and monocytes, were initially used by Hu et al. in 2014 to analyze the prognosis of hepatocellular carcinoma (27). In recent years, SII has been used as an indicator to predict and evaluate neurological and inflammatory diseases, and carcinomas (28-30). The prognostic value of SII was evaluated in a study conducted with 103 pediatric blunt abdominal trauma patients and it was found that higher SII scores were associated with increased mortality. The study reported that an SII intercept of 890.47×10^3/L had 95.7% sensitivity and 62.5% specificity in predicting mortality in these patients (31). In particular, high SII levels have been shown to be associated with disease severity in patients with AP. In another study conducted with 101 AP patients, patients with severe AP were found to have significantly higher SII values compared to patients with mild acute pancreatitis. The study revealed that SII could be an early indicator in distinguishing severe AP from mild AP with 92.9% sensitivity and 87.7% specificity (32). Yasak et al. reported that SII was significantly elevated with the increase in AP severity, and the sensitivity of SII was 72.73% and its specificity was 58.21% in the differentiation of severe AP (33). In another study, AP with higher SII was found more likely to be severe (sensitivity = 92.9%, specificity = 87.7%). The predictive power of SII for the severity of AP was more specific when compared to PLR (sensitivity = 82.1%, specificity = 84.9%) and NLR (sensitivity = 82.1%, specificity = 82.2%) (32). In the present study, it was determined that SII was more specific and sensitive compared to PLR, and it was more specific compared to NLR but demonstrated lower sensitivity. In a study conducted by Silva-Vaz et al., SIRI was employed for the first time as a new prognostic tool for AP severity (34). Similarly, in our study, it was observed that the SII could serve as a useful biomarker for assessing the severity of AP. When compared to PLR and NLR, SII demonstrated higher specificity, enabling a more reliable differentiation of AP severity. Additionally, while the prognostic value of SIRI has been previously established, our study found that SII exhibited a stronger predictive capacity for AP severity than SIRI. Our findings highlight the potential role of SII in clinical practice as a valuable tool for the rapid and accurate determination of AP severity.

Limitations of the study

The present retrospective study was conducted with a small sample size in a single center. Furthermore, the study is cross-sectional, preventing clear findings on causality. Due to the limitations of the current study findings, further studies should be conducted with larger samples in several centers to confirm these findings.

CONCLUSION

To prevent mortality and morbidity in AP patients induced by a chain of inflammatory events, early diagnosis, rapid treatment, and prediction of severe acute pancreatitis are significant in follow-up and prognosis. The inflammatory markers NLR, NAR, PLR, SII, and SIRI are easily accessible and rapid parameters that could be employed to predict AP severity. Among these parameters, NAR is more specific in whereas NLR is more sensitive in AP when compared to others.

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