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Relationship of the systemic immuno-inflammation index and hematological inflammatory index with mortality and hospitalization in acute pancreatitis: a cross-sectional study

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Abstract: **Objective:** This study was conducted to reveal the relationship of the hematological inflammatory index (HII) and systemic immuno-inflammation index (SII) with short-term and prolonged hospitalization in cases of acute pancreatitis.

Methods: This single-center cross-sectional study was conducted in the emergency department (ED) of an educational hospital. The study population contained cases who untaken to the ED with acute pancreatitis between August 15, 2021, and May 15, 2022. Cases discharged from the ED, those referred to another center for hospitalization, and those with absent information were excluded from the study. The patients were grouped according to the length of hospital stay (expected and prolonged) and short-term mortality (survivor and died). We constructed a receiver operating characteristic (ROC) curve for short-term mortality and prolonged hospitalization and obtained the area under the curve (AUC) values for SII and HII.

Results: One hundred seventy-seven patients were included in the study. There was no significant difference between the expected and prolonged hospitalization groups in the terms of SII and HII (P=0.649 and P=0.084, respectively). There was also no significant difference between the survivor and died groups in the terms of these indexes (P=0.070 for HII and P=0.138 for SII). The AUC values for the SII and HII in the prediction of 30-day mortality were 0.616 and 0.642, respectively. The AUC values for the SII and HII in the prediction of prolonged hospitalization were 0.580 and 0.642, respectively.

Conclusion: The outcomes of the present study showed no significant difference among the expected and prolonged hospitalization groups or the survivor and died groups in the terms of SII and HII. We recommend the validation of our results in multicenter studies with larger samples.

Keywords: Blood Platelets; Lymphocytes; Neutrophils; Pancreatitis

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1. Introduction

The acute pancreatitis is a pancreatic disease characterized by abdominal pain and elevation of pancreatic enzyme levels, in which pancreatic digestive enzymes are activated by any etiological factor and widespread inflammation occurs in the pancreas and surrounding tissues. The diagnosis of acute pancreatitis is made by evaluating clinical signs, pancreatic enzyme levels, and radiological findings (1).

The local inflammatory response in the pancreas causes the secretion of cytokines such as platelet activating factor, interleukin (IL)-1, free oxygen radicals, IL-8, tumor necrosis factor (TNF)-alpha, and IL-6. These mediators play a central role in the transition from local inflammatory reaction to systemic disease (2). Oxygen free radicals are effective in the early and late stages of acute pancreatitis by causing damage to the cell membrane and functions through their direct effect on lipids and proteins, as well as damage to pancreatic cells by the release of lysosomal enzymes (3). In addition, the proinflammatory cytokines, development of inflammatory response, and oxidative stress trigger similar signal transmission pathways, causing a vicious circle in acute pancreatitis (4).

The systemic immune inflammation index (SII) and hematological inflammatory index (HII) are biomarkers that have been shown to be associated with inflammatory processes in the literature (5,6). Based on these data, we speculated that SII and HII might be involved in acute pancreatitis. Therefore, this study designed to reveal the relationship of SII and HII with short-term mortality and prolonged hospitalization in cases of acute pancreatitis.

2. Methods

2.1. Study design

The current study with a cross-sectional, single-center design was conducted in the emergency department of University of Health Sciences, Umraniye Training and Research Hospital that is an educational hospital in a metropolitan area of Istanbul, Turkey with an average of 665 non-traumatic adult emergent presentations per day (throughout the study dated). Ethical approval of current study was obtained from the scientific studies ethics committee of University of Health Sciences, Umraniye Training and Research Hospital. The personal data of the patients were not used; therefore, consent was not obtained from the cases until the awareness of the committee.

2.2. Study population

The study population contained cases who untaken to emergency department (ED) with acute pancreatitis between August 15, 2021, and May 15, 2022. The presence of two signs and symptoms of acute pancreatitis criteria [(i) persistent and severe abdominal pain, often radiating to the back; (ii) a threefold increase in serum lipase level above the upper limit of the normal value; (iii), and typical imaging manifestations of acute pancreatitis on ultrasonography or computed tomography] was considered as diagnosis for acute pancreatitis. Cases discharged from the ED, those referred to another center for hospitalization, and those with absent information were excluded from the study (Figure 1).

2.3. Data collection

Study data were gotten from the computer-based patient information registry system of hospital. Patients with high serum lipase values were screened and the files of these patients were reviewed by the researchers. Patients with acute pancreatitis-related clinical or radiological findings were included in the study. The patients' demographics, comorbidities (past medical history), in-hospital mortality, length of hospital stay, and laboratory parameters were recorded. Chronic obstructive pulmonary disease, cerebrovascular disease, hypertension, coronary artery disease, heart failure, active malignancy, diabetes mellitus and chronic renal failure were noted as past medical history. White blood cells count, indirect bilirubin, amylase, blood urea nitrogen, neutrophils count, glucose, lymphocytes count, hemoglobin, total bilirubin, albumin, hematocrits, platelets count, direct bilirubin, red cell distribution width, creatinine, aspartate transaminase, lipase, and alanine transaminase were recorded as laboratory parameters.

Patients that were hospitalized for longer than seven days were included in the prolonged hospitalization group. An expected hospital stay was defined as staying at hospital for seven days or less after admission (7-10). SII was computed by multiplying the neutrophil-to-lymphocyte ratio by the platelet count, and HII was computed by dividing the platelet-to-lymphocyte ratio by the neutrophil count and multiplying the result by 100. The neutrophil-to-lymphocyte ratio (NLR), aspartate aminotransferase-to-platelet ratio index (APRI), and platelet-to-lymphocyte ratio (PLR) were also calculated by the researchers.

2.4. Statistical analysis

SPSS version 25.0 (IBM Corp, Armonk, NY, USA) was used for data examination. The conformity of the data to the normal distribution was tested with the Shapiro Wilk test. Continuous data that did not fit the normal distribution were stated as median and 25^{th} and 75^{th} percentiles and categorical data were stated as percentages. Chi-squared test was used for the intergroup assessment of categorical statistics. Mann-Whitney U test was conducted to the intergroup comparison of continuous data that did not conform to the normal distribution.

We also constructed a receiver operating characteristic curve (ROC) for short-term mortality and prolonged hospitalization and obtained the area under the curve (AUC) values for SII and HII. Results of ROC analysis was presented as AUC, 95% confidence interval (CI), cut-off value, positive predictive value (PPV), negative predictive value (NPV). The odds ratios (OR) were calculated for SII and HII according to the optimum cut-off values obtained from the ROC analysis and presented with 95% CI. A P-value less than 0.05 was considered as significant.

3. Results

The data of one hundred seventy-seven cases were included for final analysis. Excluded cases are shown in figure 1. Median age of the included cases, was 58 years (25^{th} -75^{th} percentiles: 45-72 years). Ninety-one (52.9%) patients were women. The patients' demographic data, comorbidities, and hematological and biochemical parameters are given in table 1. Rate of prolonged hospitalization was 29.1%, and that of mortality rate was 8.8%. The comparison of the demographics, comorbidities, laboratory parameters, and mortality data between the expected and prolonged hospitalization groups and also between the survivor and died groups are shown in tables 1 and 2, respectively. Significant differences were found among expected and prolonged hospitalization groups considering the serum creatinine [0.8 (0.7-1.1) vs. 1 (0.8-1.7) mg/dL, P=0.013] and serum albumin [43 (39.0-45.5) vs. 41.2 (37-44) g/dL, P=0.043] levels (Mann-Whitney U test). Significant differences were detected among survivor and died groups in relation to the serum albumin [43.0 (38.9-45.4) vs. 38 (34.2-40.6) g/dL, P=0 .002], serum creatinine [0.8 (0.7-1.1) vs. 1.2 (0.8-3.8) mg/dL, P=0.013], and blood urea nitrogen [30.9 (24.5-47.8) vs. 68.3 (35.4-120.8) mg/dL, P=0.001] values (Mann-Whitney U test). With regard to the remaining results, including demographics, comorbidities, SII, HII, APRI, NLR, and PLR there was no significant difference according to the length of hospital stay or mortality status.

The analysis of the ROC curve was performed to determine

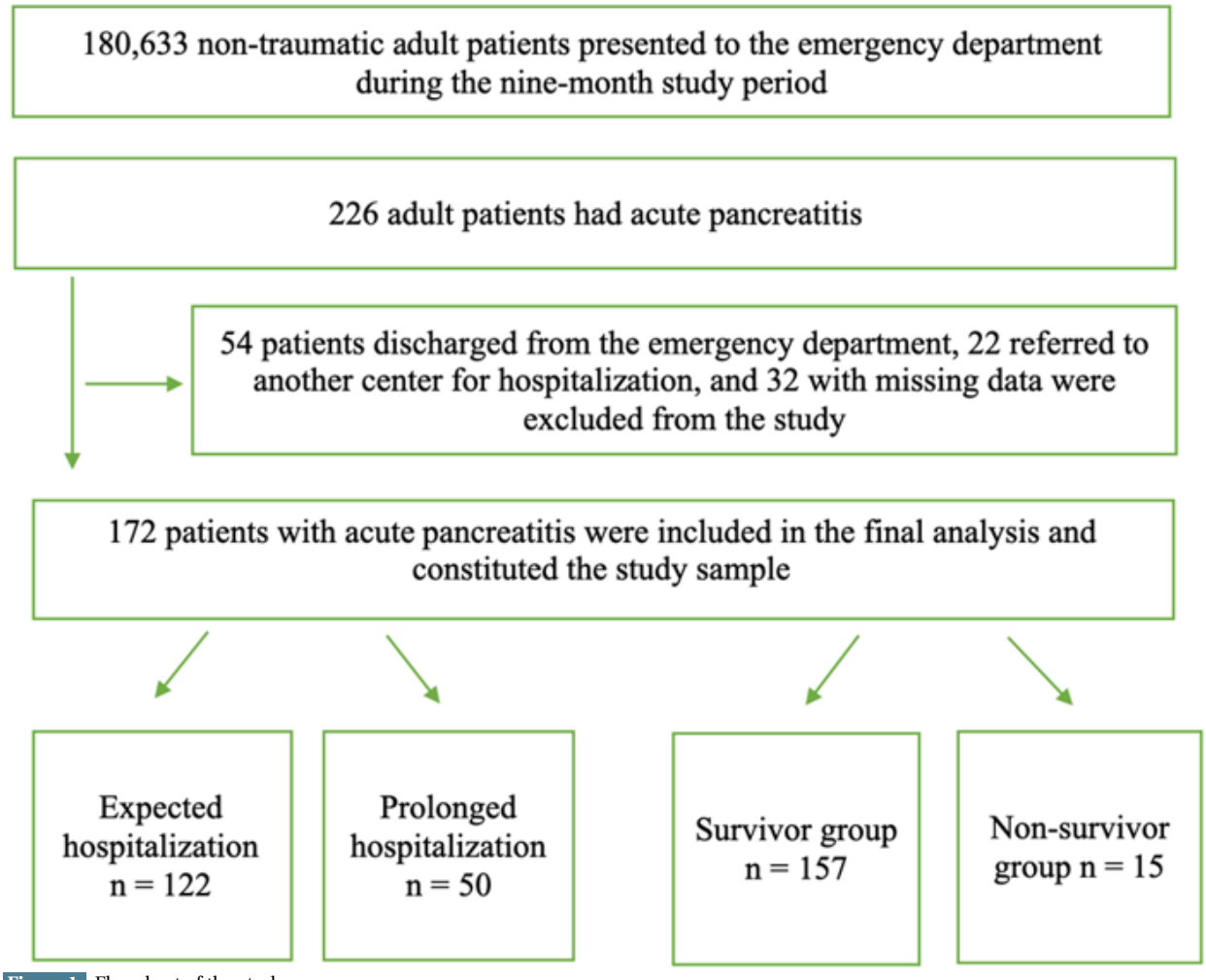

Figure 1 Flowchart of the study

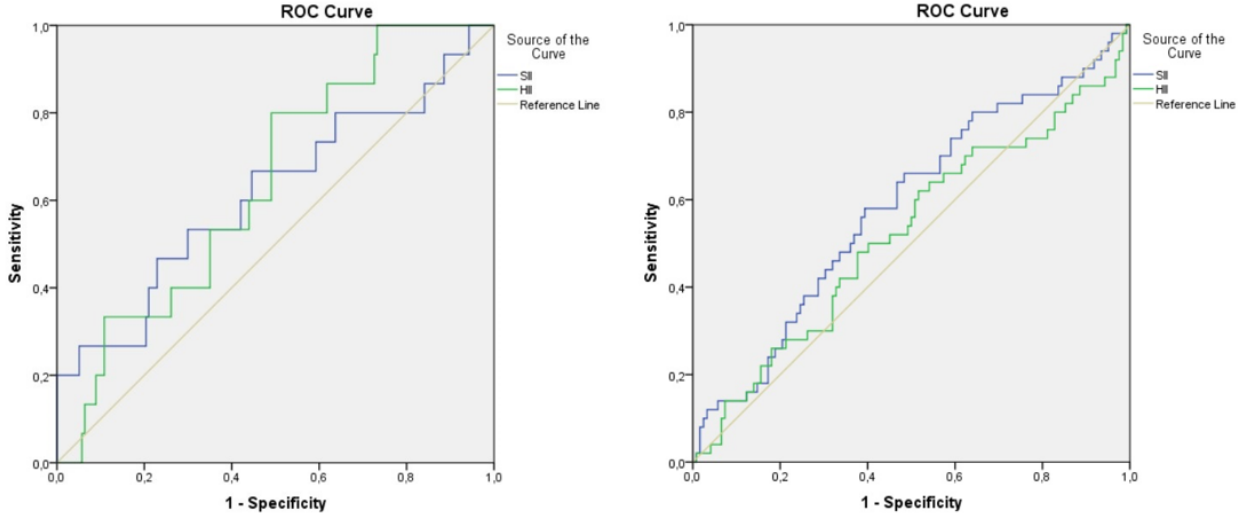

Figure 2 Receiver operating characteristic curves for systemic immuno-inflammation index (SII) and hematological inflammatory index (HII) for the prediction of 30-day mortality (left) and prolonged hospitalization (right) in patients with acute pancreatitis

Table 1 Baseline characteristics and laboratory parameters of the enrolled patients and their comparison between the expected and prolonged hospitalization groups

Variables	Total N=172	Expected hospitalization N=122 (70.9%)	Prolonged hospitalization N=50 (29.1%)	P-value
	N (%)/median (25^{th}-75^{th} percentiles)	N (%)/median (25^{th}-75^{th} percentiles)	N (%)/median (25^{th}-75^{th} percentiles))	
Age	58.0 (45.0-72.0)	57.0 (44.2-70.8)	60.5 (48.0-73.8)	0.249
<65 years	109 (63.4%)	81 (66.4%)	28 (56%)	0.276
≥65 years	63 (36.6%)	41 (33.6%)	22 (44%)	
Gender				
Female	91 (52.9%)	64 (52.5%)	27 (54.0)	0.988
Male	81 (47.1%)	58 (47.5%)	23 (46.0)	
Comorbidities				
Chronic obstructive pulmonary disease	16 (9.3%)	8 (6.6%)	8 (16.0%)	0.100
Hypertension	80 (46.5%)	52 (42.6%)	28 (56.0%)	0.153
Diabetes mellitus	45 (26.2%)	28 (23.0%)	17 (34.0%)	0.192
Coronary artery disease	34 (19.8%)	23 (18.9%)	11 (22.0%)	0.795
Congestive heart failure	11 (6.4%)	7 (5.7%)	4 (8.0%)	0.836
Active malignancy	26 (15.1%)	26 (15.1%)	26 (15.1%)	0.363
Cerebrovascular disease	9 (5.2%)	5 (4.1%)	4 (8.0%)	0.505
Chronic renal failure	18 (10.5%)	10 (8.2%)	8 (16.0%)	0.214
Laboratory parameters				
White blood cell count (10^3/μL)	10.3 (8.1-13.1)	9.7 (8.1-12.1)	11.2 (8.8-15.0)	0.062
Neutrophil count (10^3/μL)	7.6 (5.8-10.6)	7.2 (5.8-9.6)	9.2 (5.9-12.9)	0.050
Lymphocyte count (10^3/μL)	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.6 (0.4-0.7)	0.267
Hemoglobin (g/dL)	12.9 (11.5-14.2)	12.9 (11.7-14.3)	12.6 (11.1-13.8)	0.230
Hematocrit (%)	39.6 (34.8-42.8)	39.8 (35.6-42.8)	38.1 (34.2-42.6)	0.216
Red cell distribution width (%)	14.0 (13.2-15.3)	14.0 (13.2-15.3)	14.0 (13.2-14.8)	0.755
Platelet count (10^3/μL)	252.5 (205.0-317.2)	249.5 (202.8-315.0)	256.5 (222.0-320.2)	0.239
Blood urea nitrogen (mg/dL)	32.0 (24.8-54.8)	30.9 (23.9-47.1)	36.6 (27.4-66.7)	0.059
Creatinine (mg/dL)	0.8 (0.7-1.2)	0.8 (0.7-1.1)	1 (0.8-1.7)	0.013
Albumin (g/dL)	43.0 (38.1-45.3)	43.0 (39.0-45.5)	41.2 (37.0-44.0)	0.043
Glucose (mg/dL)	128.5 (104.8-164.8)	124.5 (103.2-160.0)	135.5 (107.0-172.2)	0.239
Amylase (mg/dL)	560.5 (277.0-1548.0)	646.0 (271.2-1639.5)	495.5 (311.0-1496.8)	0.649
Lipase (mg/dL)	1185.2 (551.6-2906.4)	1208.1 (531.3-2902.5)	1185.2 (557.4-2878.4)	0.649
Total bilirubin (mg/dL)	1.0 (0.5-2.5)	1.0 (0.5-2.4)	1.0 (0.5-2.6)	0.882
Direct bilirubin (mg/dL)	0.5 (0.2-1.6)	0.6 (0.2-1.5)	0.4 (0.1-1.6)	0.643
Indirect bilirubin (mg/dL)	0.4 (0.2-0.8)	0.4 (0.2-0.7)	0.4 (0.2-0.9)	0.524
Aspartate transaminase (U/L)	104.5 (28.0-212.0)	129.0 (30.2-215.0)	51.5 (25.2-197.8)	0.112
Alanine transaminase (U/L)	62.0 (24.8-207.2)	69.5 (27.0-207.8)	44.5 (17.2-194.5)	0.118
Aspartate aminotransferase-to-platelet ratio index (APRI)	0.4 (0.1-0.9)	0.4 (0.1-1.0)	0.2 (0.1-0.7)	0.054
Neutrophil-to-lymphocyte ratio	5.0 (3.1-8.6)	4.6 (3.0-8.5)	5.7 (3.9-10.1)	0.103
Platelet-to-lymphocyte ratio	164.2 (119.4-267.2)	149.2 (116.2-259.2)	185.4 (134.9-293.9)	0.170
Hematological inflammatory index	2198.1 (1539.0-3627.5)	2129.3 (1579.4-3553.1)	2463.8 (1444.2-3818.4)	0.649
Systemic immuno-inflammation index	1255.0 (745.2-2342.0)	1136.6 (713.8-2148.5)	1488.9 (886.7-2879.3)	0.084
Mortality	15	9 (60%)	6 (40%)	0.498

the discriminative ability of the two hematological parameters in terms of 30-day mortality. In the group of patients with acute pancreatitis, according to the best Youden's index, the cut-off value for SII was 2456.3 [sensitivity: 46.67% (95% CI: 21.27,73.41), specificity: 77.07% (95% CI: 69.7,83.39)], and the AUC value was 0.616 (95% CI: 0.450,0.782) (PPV: 16.28, NPV: 93.8). In the same group, according to the best Youden's index, the cut-off value for HII was 2139.1 [sensitivity: 80% (95% CI: 51.91,95.67), specificity: 50.96% (95% CI: 42.86,59.01)], and the AUC value was 0.642 (95% CI: 0.510,0.768) (PPV: 13.48, NPV: 93.39). According to ROC analysis accuracy of SII and HII were calculated as 0.91 and 0.91.

The analysis of the ROC curve was performed to determine the discriminative ability of the two hematological parameters in terms of prolonged hospitalization (Figure 2). In study group, according to the best Youden's index, the cut-off value for SII was 1388.5 [sensitivity: 58% (95% CI: 43.21,71.81), specificity: 60.66% (95% CI: 51.41,69.38)], and the AUC value was 0.580 (95% CI: 0.450,0.782, PPV: 37.66, NPV: 77.89). In the same group, according to the best Youden's index, the cut-off value for HII was 2063.2 [sensitivity: 62% (95% CI: 47.18,75.35), specificity: 47.54% (95% CI: 38.43,56.78)], and the AUC value was 0.642 (95% CI: 0.515,0.768, PPV: 32.63, NPV: 75.32). According to ROC analysis accuracy of SII and

Table 2 Baseline characteristics and laboratory parameters of the enrolled patients and their comparison between the survivor and died groups

Variables	Survivor group N=157 (91.2%) N (%)/median (25^{th}-75^{th} percentiles)	Died group N=15 (8.8%) N (%)/median (25^{th}-75^{th} percentiles)	P-value
Age	57.0 (44.0-71.0)	78.0 (65.5-85.5)	0.491
<65 years	106 (67.5%)	3 (20%)	0.498
≥65 years	51 (32.5%)	12 (80%)	
Gender			
Female	85 (54.1%)	6 (40%)	0.437
Male	72 (45.9%)	9 (60%)	
Comorbidities			
Chronic obstructive pulmonary disease	13 (8.3%)	3 (20%)	0.304
Hypertension	72 (45.9%)	8 (53.3%)	0.777
Diabetes mellitus	42 (26.8%)	3 (20%)	0.794
Coronary artery disease	30 (19.1%)	4 (26.7%)	0.717
Congestive heart failure	9 (5.7%)	2 (13.3%)	0.550
Active malignancy	24 (15.3%)	2 (13.3%)	0.999
Cerebrovascular disease	8 (5.1%)	1 (6.7%)	0.999
Chronic renal failure	16 (10.2%)	2 (13.3%)	0.999
Laboratory parameters			
White blood cell count (10^3/μL)	10.3 (8.1-13.0)	11.1 (8.3-14.1)	0.654
Neutrophil count (10^3/μL)	7.5 (5.8-10.2)	8.1 (6.6-12.5)	0.393
Lymphocyte count (10^3/μL)	0.5 (0.4-0.7)	0.5 (0.4-0.6)	0.265
Hemoglobin (g/dL)	12.9 (11.6-14.2)	12.0 (9.6-13.9)	0.088
Hematocrit (%)	39.7 (34.9-42.8)	36.0 (28.4-42.7)	0.117
Red cell distribution width (%)	14 (13.2-14.9)	14.6 (13.5-16.3)	0.222
Platelet count (10^3/μL)	252 (205-316.0)	258 (213.5-316)	0.700
Blood urea nitrogen (mg/dL)	30.9 (24.5-47.8)	68.3 (35.4-120.8)	**0.001**
Creatinine (mg/dL)	0.8 (0.7-1.1)	1.2 (0.8-3.8)	**0.013**
Albumin (g/dL)	43.0 (38.9-45.4)	38 (34.2-40.6)	**0.002**
Glucose (mg/dL)	127.0 (105.0-162.0)	137 (115-190)	0.366
Amylase (mg/dL)	653.0 (280.0-1663.0)	308 (242.0-429)	0.045
Lipase (mg/dL)	1289.8 (582.5-2953.9)	766 (459.4-1363.8)	0.056
Total bilirubin (mg/dL)	0.9 (0.5-2.5)	1.4 (1.0-3.1)	0.267
Direct bilirubin (mg/dL)	0.5 (0.2-1.5)	0.8 (0.1-1.8)	0.817
Indirect bilirubin (mg/dL)	0.4 (0.2-0.8)	0.4 (0.2-1.5)	0.348
Aspartate transaminase (U/L)	106.0 (30.0-212.0)	28 (22.5-263)	0.572
Alanine transaminase (U/L)	64.0 (26.0-208.0)	27 (16.0-142)	0.197
Aspartate aminotransferase-to-platelet ratio index (APRI)	0.4 (0.1-0.9)	0.3 (0.1-1.2)	0.635
Neutrophil-to-lymphocyte ratio	5 (3.1-8.4)	6.8 (4.2-20.6)	0.109
Platelet-to-lymphocyte ratio	161.5 (114.7-265.2)	230.2 (152.1-408.7)	0.051
Hematological inflammatory index	2093.6 (1489.6-3554.1)	2854.1 (2148.3-4966)	0.070
Systemic immuno-inflammation index	1232.3 (743.2-2190.9)	1945.8 (939.8-4521.3)	0.138
Length of hospital stay (days)	5 (3-8)	5 (2.5-12)	0.555

HII were calculated as 0.72 and 0.71.

The OR of SII (>2456.3) and HII (>2139.1) for 30-day mortality were determined as 2.94 (95% CI: 1,8.66), and 4.13 (95% CI: 1.13,15.3), respectively. The OR of SII (>1388.5) and HII (>2063.2) for prolonged hospitalization were determined as 1.96 (95% CI: 0.67, 5.78), and 4.16 (95% CI: 1.13,15.3), respectively.

4. Discussion

In present study, we assessed the role of HII and SII in predicting prolonged hospitalization and mortality in patients presenting to the emergency department with acute pancreatitis. The results revealed no significant difference between the expected and prolonged hospitalization groups or the survivor and died groups in terms of these indexes. As far as we know, this is the first research to investigate the role of HII in acute pancreatitis.

Acute pancreatitis is often a spontaneous self-limiting condition. However, 25% of patients can progress to serious disease. Mortality can increase up to 20% in the patient group with severe pancreatitis (11). To use health resources efficiently and identify patients in need of medical support early, studies have been carried out to predict serious illness and

bad outcome in acute pancreatitis cases. The Ranson score is the most well-known and studied scoring system (12). In addition, classification systems such as Balthazar have been industrialized to predict the radiological severity of the disease (13). Since hematological parameters are easily accessible and inexpensive, their ability to determine prognosis has also been investigated by many researchers (1,11,14-18). Yarkaç et al. (17) evaluated the ability of hematological parameters to predict acute pancreatitis and reported the areas under the curve of NLR and platelet count as 0.657 and 0.582, respectively. In same study, in prediction of severe acute pancreatitis, area under curve values of NLR and platelet count were determined as 0.937 and 0.532, respectively. Thus, the authors concluded that NLR was a good predictor of serious disease. In a study with 154 patients, Khan et al. (18) compared mild to moderate pancreatitis and severe pancreatitis groups in terms of lymphocyte, neutrophil, and platelet counts and found no significant difference among groups in terms of lymphocyte and platelet counts but it noted that the neutrophil count was significantly higher in the severe pancreatitis cases.

SII and HII are combined hematological indexes formed with the combination of lymphocyte, neutrophil, and platelet count. Both indexes were first developed for the evaluation of patients with malignancies. SII and HII, both associated with inflammation, were presented as new prognostic markers in the literature in 2014 and 2020, respectively (5,19).

In a study conducted with 218 cases of severe acute pancreatitis, Lu et al. showed that SII could predict acute kidney injury (20).

In another study conducted in 2022, authors investigated prediction ability of SII for short-term mortality in patients with acute cholecystitis, and they showed that SII value was significantly higher in the mortality group (21). Zhang et al. reported that SII could predict bad outcome in 513 cases followed up in intensive care unit with severe acute pancreatitis (22). In contrast, in the present research, no difference was detected in the SII values according to the mortality status or length of hospital stay. This discrepancy may be related to the samples of previous studies consisting of patients with severe pancreatitis. In these patients, SII may be affected due to the exaggerated inflammatory response. Our sample included all acute pancreatitis cases that presented to the ED. The ability of SII and HII to predict poor outcome in a population that includes all acute pancreatitis cases may be limited.

5. Limitations

The key limitation of current study was a retrospective design. As in other retrospective studies, our data were not sufficient to evaluate causality and confounding factors such as hyperlipidemia, and body mass index. The data mentioned, were not recorded in the hospital computer-based data system for all patients. Secondly, no scoring system was used to evaluate the severity of acute pancreatitis. However, considering that the mortality rate of our sample was 8.8%, when the mortality rate in cases of severe acute pancreatitis patients is reported to be around 20% in the literature, it can be suggested that our sample consisted mostly of moderate acute pancreatitis cases (11). Thirdly, nine of the patients in the mortality group died within seven days of hospital admission. Although these patients were included in the expected length of stay group, they had mortality. This is a factor that complicates the interpretation of our results. We think that the reason for this confusing situation may be that the onset time of the symptoms of the patients is not similar. The necessary data to circumvent this limitation, was not available in the hospital computer-based data system. Finally, our study had single-center design. Therefore, our results should be validated by multicenter studies with larger samples, because single-center design limits generalizability of current study.

6. Conclusion

In conclusion, the results of present study showed no significant difference between expected and prolonged hospitalization groups or survivor and died groups in terms of SII and HII. There is a need for multicenter studies to be carried out with a larger number of patients to confirm our results.

7. Declarations

7.1. Acknowledgement

None.

7.2. Authors' contribution

All the authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

7.3. Conflict of interest

We declare no conflict of interest.

7.4. Funding

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