










ORIGINAL PAPER

## The role of the hematological inflammatory index and systemic immuno-inflammation index in acute cholecystitis

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### ABSTRACT

**Introduction and aim.** Acute cholecystitis is one of the most common hepatobiliary emergencies. We aimed to investigate the role of the initial hematological inflammatory index and systemic immuno-inflammation index in predicting short-term mortality in patients with acute cholecystitis.

**Material and methods.** This study with a retrospective observational design was conducted at the emergency department of a tertiary teaching hospital. Patients admitted to our clinic between June 15, 2021, and March 15, 2022, according to the Tokyo criteria were included in the sample. The hematological inflammatory index and systemic immuno-inflammation index were calculated using the hematological test results of the patients evaluated at the emergency department. Survivor and non-survivor groups were formed according to all-cause 30-day mortality. The differences between survivor and non-survivor groups were investigated.

**Results.** A total of 194 patients were included in the final analysis. The median age of the study population was 59 (25<sup>th</sup>–75<sup>th</sup> percentiles: 46.75–72) years. The rate of all cause-short-term mortality was 7.7. There were significant differences between the survivor and non-survivor groups in terms of the neutrophil count and the systemic immuno-inflammation index ( $p=0.007$ ,  $0.034$ , respectively; Mann-Whitney U test). No significant difference was found in the remaining laboratory parameters (lymphocyte count, platelet count, and hematological inflammatory index) ( $p=0.220$ ,  $0.489$ ,  $0.367$  respectively; Mann-Whitney U test).

**Conclusion.** The systemic immuno-inflammation index was determined to be significantly higher in the non-survivor group than in the survivor group among the patients with acute cholecystitis. However, there was no significant difference between these two groups in relation to the hematological inflammatory index.

**Keywords.** acute cholecystitis, neutrophil, lymphocyte, platelet, mortality

### Introduction

Acute cholecystitis is a disease caused by the acute inflammation of the gallbladder. Inflammatory changes that occur in this disease can range from a mild symptomatic to a severe clinical picture, including acute pancreatitis, acute cholangitis, and even empyema or gangrene.<sup>1</sup> Acute cholecystitis constitutes approxi-

mately 1–3% of patient presentations with abdominal pain. The cause is gallstones in 90–95% of cases.<sup>1,2</sup> To diagnose acute cholecystitis, it is necessary to evaluate the medical history, physical examination findings, laboratory results, and radiological imaging findings together. There is not a single clinical or laboratory parameter that will diagnose or exclude the diagno-

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sis. The Tokyo criteria (TG18 Diagnostic Criteria and Severity Grading of Acute Cholecystitis) published in 2007 and updated in 2013 and 2018 are used as diagnostic criteria.<sup>3</sup>

In infections, trauma, inflammatory diseases, and similar conditions, a series of changes occur as a response at or away from the inflammation area. This response is called the acute phase response, including neuroendocrine, hematopoietic, and metabolic changes.<sup>4</sup> Proteins with increasing or decreasing serum concentrations (acute phase reactants) and some hematological parameters are used in the clinical evaluation of the inflammatory acute phase response and response to therapy. The most studied hematological parameters are the neutrophil count, white blood cell count, and lymphocyte count. To determine the ideal marker, researchers have worked on a combination of these parameters.<sup>5</sup> The hematological inflammatory index (HII) and systemic immuno-inflammation (SII) are newly developed inflammatory indexes.<sup>6,7</sup> To the best of our knowledge, there is no study in the literature evaluating the role of HII and SII in acute cholecystitis.

## Aim

The aim of our study was to investigate the role of the initial SII and HII in predicting short-term mortality in patients presenting to the emergency department with acute cholecystitis.

## Material and methods

### Design of study

The current study with a retrospective observational design was conducted at the adult emergency department of a tertiary teaching hospital, serving a population of approximately one million and having an average of 1,000 admissions per day.

### Patient sampling

The data of patients with the acute cholecystitis ICD code, who presented to the Emergency Department of University of Health Sciences Umraniye Training and Research Hospital between June 15, 2021, and March 15, 2022, were obtained from the hospital computer-based patient information system. Patients who did not meet the Tokyo 2018 criteria and those with incomplete data were excluded from the study.

### Data collection

Demographic data, comorbidities, and laboratory parameters were gathered from the patient information system of the hospital. Comorbidities were noted as congestive heart failure, diabetes mellitus, asthma, hypertension, chronic obstructive pulmonary disease, and chronic renal failure. The white blood cell count, hemoglobin, red cell distribution width, neutrophil count,

lymphocyte count, platelet count, mean platelet volume, blood urea nitrogen, creatinine, and albumin values were documented. The neutrophil lymphocyte ratio, SII, and HII were calculated. HII was calculated by multiplying the platelet count by 100 and dividing the result by the product of the neutrophil count and lymphocyte count. SII was calculated by multiplying the neutrophil-lymphocyte ratio by the platelet count.

### Statistical analysis

Statistical analysis was performed using Jamovi (The Jamovi Project, Version 1.6.21.0; 2020). The fit of the parameters to the normal distribution was determined with the Shapiro-Wilk test. Categorical data were presented as numbers and percentages, and continuous data as median and 25<sup>th</sup> and 75<sup>th</sup> percentile values. The correlation between categorical data and mortality was investigated using the chi-square test, and the relationship between continuous data and mortality was determined with the Mann-Whitney U test. The ability of the variables to predict mortality was examined using the receiver operating characteristic (ROC) analysis. The results of this analysis were presented with positive and negative predictive values, and the cut-off point specified as the area under the curve (AUC). Values above 0.7 were considered significant as promising AUC values.<sup>8,9</sup> Values above 0.05 were accepted for the significant p value.

### Ethics

Ethical approval for the study was obtained from the University of Health Sciences Umraniye Training and Research Hospital ethics committee with 03.31.2022 date and 114 number. Informed consent was waived within the knowledge of the local ethics committee, as the study did not include any personal information of the patients and had a retrospective design.

## Results

A total of 194 patients were included in the final analysis. The median age of the study population was 59 (25<sup>th</sup>–75<sup>th</sup> percentiles: 46.75–72) years, and 93 (47.9%) patients were female. The rate of all cause-short-term mortality was 7.7. The descriptive data of the study population and comparison of these characteristics between the survivor and non-survivor groups are presented in Table 1.

There were significant differences between the survivor and non-survivor groups in terms of the neutrophil count [10.23 (7.48–13.97) versus 14.78 (9.46–23.2)  $10^3/\mu\text{L}$ ,  $p = 0.007$ ] and SII [1726.37 (974.21–2746.58) versus 2381.1 (1509.74–6835.21),  $p = 0.034$ ] (Mann-Whitney U test). No significant difference was observed between the two groups in relation to the remaining laboratory parameters: lymphocyte count

**Table 1.** Baseline characteristics and laboratory parameters of the enrolled patients and their comparison between the survivor and non-survivor groups

Variables	Total n = 194	Survivor n = 179 (92.3%)	Non-survivor n = 15 (7.7%)	p
	n (%) / Median (25 <sup>th</sup> -75 <sup>th</sup> percentiles)	n (%) / Median (25 <sup>th</sup> -75 <sup>th</sup> percentiles)	n (%) / Median (25 <sup>th</sup> -75 <sup>th</sup> percentiles)	
Age	59 (46.75 – 72)	58 (45 – 69)	79 (72 – 86)	<0.001
<65 years	122 (62.9%)	120 (98.4%)	2 (1.6%)	<0.001
≥65 years	72 (37.1%)	59 (81.9%)	13 (18.1%)	
Gender				
Female	93 (47.9%)	85 (91.4%)	8 (8.6%)	0.663
Male	101 (52.1%)	94 (91.3%)	7 (6.9%)	
Comorbidities				
Chronic obstructive pulmonary disease	10 (5.2%)	8 (80%)	2 (20%)	0.175
Hypertension	83 (42.8%)	74 (89.2%)	9 (10.8%)	0.161
Diabetes mellitus	47 (24.2%)	43 (91.5%)	4 (8.5%)	0.818
Coronary artery disease	39 (20.1%)	33 (84.6%)	6 (15.4%)	0.085
Congestive heart failure	14 (7.2%)	11 (78.6%)	3 (21.4%)	0.081
Asthma	12 (6.2%)	11 (91.7%)	1 (8.3%)	0.936
History of malignancy	8 (4.1%)	8 (100%)	0	0.403
Hyperlipidemia	41 (21.1%)	38 (92.7%)	3 (7.3%)	0.911
Laboratory parameters				
White blood cell count (10 <sup>3</sup> /μL)	13.1 (10.07 – 17.06)	12.97 (9.88 – 16.8)	16.8 (12.3 – 25.6)	0.012
Neutrophil count (10 <sup>3</sup> /μL)	10.38 (7.53 – 14.24)	10.23 (7.48 – 13.97)	14.78 (9.46 – 23.2)	0.007
Lymphocyte count (10 <sup>3</sup> /μL)	1.59 (0.49 – 0.71)	1.61 (1.17 – 2.18)	1.24 (0.98 – 2.12)	0.22
Hemoglobin (g/dL)	10.5 (11.8 – 14.9)	13.6 (12 – 14.9)	11.2 (9.3 – 12.8)	<0.001
Hematocrit (%)	40.5 (36.3 – 44.5)	40.9 (37.1 – 44.7)	33 (28.1 – 37)	<0.001
Red blood cell distribution width (%)	13.6 (13.1 – 14.5)	13.5 (13 – 14.2)	17.2 (16.9 – 19.3)	<0.001
Platelet count (10 <sup>3</sup> /μL)	270 (225 – 321)	271 (229 – 321)	244 (197 – 370)	0.489
Mean platelet volume (fL)	9.7 (8.97 – 10.5)	9.8 (9.1 – 10.6)	8.12 (7.26 – 9.53)	<0.001
Plateletcrit (%)	0.26 (0.22 – 0.32)	0.26 (0.22 – 0.32)	0.21 (0.15 – 0.27)	0.03
Blood urea nitrogen (mg/dL)	30.6 (22.2 – 40.1)	29.6 (21.5 – 37.3)	55.6 (36.3 – 70.6)	<0.001
C-reactive protein, (mg/dL)	51.64 (8.5 – 154.88)	45.8 (8.1 – 145.9)	135 (112 – 188)	0.006
Albumin (g/dL)	42.9 (38.7 – 45)	43 (39.4 – 45)	30 (23 – 33)	<0.001
Total bilirubin (mg/dL)	0.84 (0.53 – 1.43)	0.81 (0.51 – 1.39)	1.2 (0.77 – 3.56)	0.018
Direct bilirubin (mg/dL)	0.27 (0.15 – 0.55)	0.26 (0.14 – 0.51)	0.55 (0.27 – 2.61)	0.006
Indirect bilirubin (mg/dL)	0.48 (0.31 – 0.79)	0.48 (0.3 – 0.78)	0.86 (0.43 – 1.24)	0.025
Neutrophil-lymphocyte ratio	6.51 (3.95 – 10.05)	6.37 (3.89 – 9.53)	12.31 (9.27 – 16.58)	0.002
Platelet-lymphocyte ratio	162.62 (119.65 – 240.16)	162.29 (12.83 – 233.98)	201.02 (100.67 – 365)	0.559
C-reactive protein/albumin ratio	1.22 (0.2 – 4.03)	1.08 (0.17 – 3.52)	4.3 (3.95 – 7.45)	<0.001
Blood urea nitrogen/albumin ratio	0.71 (0.51 – 0.99)	0.69 (0.48 – 0.94)	2.06 (1.4 – 3.03)	<0.001
Systemic immune-inflammation index	1764.96 (1001.77 – 2778.77)	1726.37 (974.21 – 2746.58)	2381.1 (1509.74 – 6835.21)	0.034
Hematologic inflammatory index	1.68 (1.08 – 2.5)	1.7 (1.13 – 2.54)	1.5 (0.92 – 2.46)	0.367

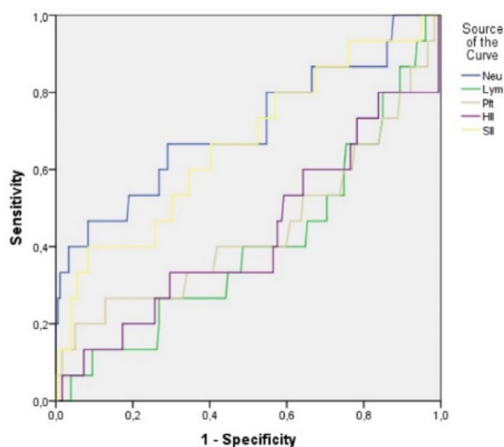
[1.61 (1.17-2.18) versus 1.24 (0.98-2.12) 10<sup>3</sup>/μL, p = 0.220], platelet count [3 (1-22) versus 9 (2-21) 10<sup>3</sup>/μL, p = 0.489], and HII [1.7 (1.13-2.54) versus 1.5 (0.92-2.46), p = 0.367] (Mann-Whitney U test). The initial laboratory parameters of the enrolled patients and their comparison between the survivor and non-survivor groups are shown in Table 1.

The ROC curve analysis was performed to determine the predictive ability of the neutrophil count, lymphocyte count, platelet count, SII, and HII for short-term mortality. The cut-off values of these parameters according to the best Youden's index, as well as their sensitivity, specificity, AUC, and 95% confidence interval values are presented in Table 2 and Figure 1.

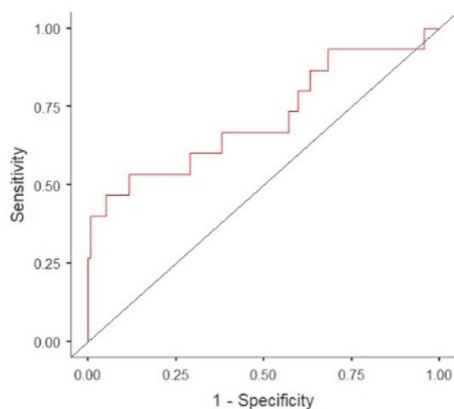
**Table 2.** Accuracy of the investigated laboratory parameters in predicting short-term mortality in patients with acute cholecystitis<sup>a</sup>

Variables	AUC	Accuracy	95% CI	Cut-off value	Sensitivity	Specificity	PPV	NPV	PLR	NLR	p value
Neutrophil count	0.708	0.933	0.639–0.771	>16.82	46.67	91.62	31.8	95.3	5.57	0.58	0.014
Lymphocyte count	0.596	0.923	0.523–0.665	≤1.39	60.00	64.80	12.5	95.1	1.70	0.62	0.246
Platelet count	0.554	0.923	0.481–0.625	≤230	46.67	73.74	13.0	94.3	1.78	0.72	0.574
Systemic immuno-inflammation	0.666	0.918	0.593–0.884	>4049.3	40.00	91.62	28.6	94.8	4.77	0.65	0.041
Hematological inflammatory index	0.570	0.923	0.498–0.641	≤1.53	66.67	56.42	11.4	95.3	1.53	0.59	0.428

<sup>a</sup> AUC – area under the curve, CI – confidence interval, PPV – positive predictive value, NPV – negative predictive value, PLR – positive likelihood ratio, NLR – negative likelihood ratio



**Fig. 1.** Receiver operating characteristic curves of the hematological inflammatory index (HII), systemic immuno-inflammation index (SII), neutrophil count (Neu), lymphocyte count (Lym), and platelet count (Plt) for the prediction of short-term mortality in patients with acute cholecystitis



**Fig. 2.** Receiver operating characteristic curve of the multivariate logistic regression model for the prediction of short-term mortality in patients with acute cholecystitis

With the multivariate regression model created for the prediction of short-term mortality, the AUC value was calculated as 0.714 (accuracy: 0.943, sensitivity: 0.999, and specificity 0.267,  $p < 0.001$ ) (Figure 2).

## Discussion

In the current study, we investigated the role of the initial SII and HII values in predicting short-term mortality in patients with acute cholecystitis. According to the results of the univariate analysis, there was no significant difference in the HII value between the survivor and non-survivor groups. The SII value was found to be significantly higher in the mortality group, and it was able to predict short-term mortality in acute cholecystitis with high specificity (91.62%). Another valuable finding for the literature was that the created multivariate regression model detected the risk of short-term mortality in acute cholecystitis with high accuracy (0.943).

Neutrophils, one of the primary response agents to acute inflammation, constitute 50–70% of circulating leukocytes, and an increase in neutrophils is usually expected in acute cholecystitis.<sup>10</sup> In a study by Naidu et al., it was shown that the neutrophil count was higher in the patient group whose histology was compatible with acute cholecystitis among patients who had undergone cholecystectomy for acute cholecystitis compared to those without this disease (10.1 K/uL versus 6.0 K/uL).<sup>11</sup> In another study, Sato et al. reported that the neutrophil values of patients with acute cholecystitis significantly differed between the three groups formed according to disease severity determined by the TG18 criteria.<sup>12</sup> In the current study, the neutrophil count was found to be significantly higher in the mortality group. These results show that the neutrophil value can be used as a guide for both the diagnosis of acute cholecystitis and the determination of severity and prediction of mortality.

Lymphocytes are among markers representing immunity.<sup>13</sup> In the current literature, there are conflicting results in studies evaluating the role of the lymphocyte count in acute cholecystitis. In a study by Sato et al., evaluating the effectiveness of the lymphocyte count in predicting the severity of acute cholecystitis, it was suggested that this parameter did not have a place in this prediction.<sup>12</sup> These results were later validated by Mahmood et al.<sup>14</sup> On the other hand, Ertok et al. found that

the lymphocyte count was significantly lower in patients with acute cholecystitis compared to the control group.<sup>15</sup> In our study, the lymphocyte counts, and mortality were unrelated. The results of the mentioned studies reveal that there is no relationship between acute cholecystitis and lymphocyte count.

Platelet plays a role in inflammation, in addition to being an important element of the coagulation cascade. The platelet count is a well-known predictor of many infectious diseases, especially sepsis.<sup>16</sup> On the other hand, there are controversial publications concerning the effects of platelets on acute cholecystitis. Contrary to expectations, Sayit et al. reported increased platelet values in patients with acute cholecystitis compared to the control group.<sup>17</sup> Sato et al. found a low platelet count in severe acute cholecystitis cases.<sup>14</sup> In contrast, Woo et al. revealed that the platelet count was not affected in patients with acute cholecystitis compared to severe cases.<sup>18</sup> In the current study, the platelet count was unaffected. The results of the mentioned studies indicate that there is no relationship between acute cholecystitis and platelet count.

SII and HII are new and inexpensive biomarkers that can be easily calculated using the neutrophil, platelet, and lymphocyte counts.<sup>19–22</sup> These two indexes are parameters that show the balance between inflammatory and immune responses. The role of SII has been investigated in many malignant diseases, asthma, coronary disease, ischemic stroke, and as a systemic inflammation and prognostic marker. High SII values have been associated with poor outcome in coronary diseases, stroke, and malignant diseases.<sup>19–21</sup> A logical explanation for this has been suggested in the literature as SII being a marker of a strong inflammatory response and a weak immune response. On the other hand, HII is a newly developed and less studied indicator compared to SII. Şahinli and Türker proposed HII as a new prognostic marker in patients that underwent resection for gastric cancer.<sup>22</sup> According to the best of our knowledge, our study is the first in the literature to evaluate the role of SII and HII in predicting short-term mortality in patients with acute cholecystitis.

There are several important limitations to our study. The retrospective design is the most important limitation. In addition, acute cholecystitis represents a heterogeneous group, including patients with or without stones, gangrenous cholecystitis, and gallbladder empyema. However, in the current study, we were not able to perform subgroup analyses. The limited sample and single-center design can be considered as other limitations that could limit the generalizability of our findings.

## Conclusion

In conclusion, SII was determined to be significantly higher in the non-survivor group than in the survivor group among the patients with acute cholecystitis.

In terms of HII, there was no significant difference between the survivor and non-survivor groups with acute cholecystitis. SII is an easily accessible, inexpensive parameter that assists clinicians in the clinical follow-up of patients with acute cholecystitis. However, we consider that our results should be validated through large multi-center studies to increase their generalizability.

## Declarations

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The authors declared that this study has received no financial support or any funding.

### Author contributions

Conceptualization, S.Ö. and İ.A.; Methodology, S.Ö., İ.A., A.A., M.M.İ. and A.Ö.; Software, S.Ö.; Validation, S.Ö., İ.A., A.A. and G.A.; Formal Analysis, S.Ö., M.M.İ., G.A. and S.E.E.; Investigation, S.Ö.; Resources, S.Ö., A.Ö., M.M.İ., A.A. and S.E.E.; Data Curation, S.Ö., İ.A., M.M.İ. and G.A.; Writing – Original Draft Preparation, S.Ö., İ.A., A.Ö., M.M.İ., A.A., S.E.E. and G.A.; Writing – Review & Editing, S.Ö., G.A. and S.E.E.; Visualization, S.Ö., İ.A., A.Ö., M.M.İ., A.A., S.E.E. and G.A.; Supervision, S.Ö., İ.A., A.Ö., M.M.İ., A.A., S.E.E. and G.A.; Project Administration, S.Ö.; Funding Acquisition, S.Ö., İ.A., A.Ö., M.M.İ., A.A., S.E.E. and G.A.

### Conflicts of interest

The authors declare no conflict of interest.

### Data availability

The datasets used and/or analyzed during the current study are open from the corresponding author on reasonable request.

### Ethics approval

Study was approved by the institutional review board, and a waiver of authorization was given (Ethics Committee decision no. 114, date: 03.31.2022).

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