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Assessment of systemic immune–inflammatory index and other inflammatory parameters in predicting mortality in patients with acute cholecystitis: A retrospective observational study

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ABSTRACT

Objective: To investigate the effectiveness of the systemic immune-inflammatory (SII) index and other inflammatory parameters in predicting mortality among patients with acute cholecystitis (AC).

Methods: 279 Patients presented to the emergency department with abdominal pain and diagnosis of AC between September 2021 and September 2023 were included in the study. Demographic data, laboratory parameters, clinical follow-ups, and outcomes of the patients were recorded.

Results: The mean age of the patients was (55.0±16.3) years and 36.6% were male. 63.8% Had gallbladder/choledochal stones and 49.5% underwent surgery. The mortality rate was 6.1%. Advanced age ($P=0.170$) and prolonged hospitalization ($P=0.011$) were statistically significant risk factors for mortality. Decreased lymphocyte count ($P=0.020$) and increased C-reactive protein (CRP) levels ($P=0.033$) were found to be risk factors for mortality. According to the mortality predictor ROC analysis results, the cut-off for SII index was 3 138 (AUC=0.817, sensitivity=70.5%, specificity=84.7%), the cut-off for neutrophil count was $15.28 \times 10^3/\text{mm}^3$ (AUC=0.761, sensitivity=52.9%, specificity=95.0%), the cut-off for leukocyte count was $19.0 \times 10^3/\text{mm}^3$ (AUC= 0.714, sensitivity=52.9%, specificity=98.0%), cut-off for CRP was 74.55 (AUC=0.758, sensitivity=70.5%, specificity=79.0%), cut-off for aspartate transaminase (AST) was 33.0 IU/L (AUC=0.658, sensitivity=82.3%, specificity=50.3%).

Conclusions: The SII index may be a good predictor of mortality with high sensitivity and specificity. Elevated levels of neutrophils, leukocytes, CRP, and AST are other inflammatory parameters that can be used to predict mortality associated with AC.

KEYWORDS: Abdominal pain; Acute cholecystitis; Systemic immune-inflammatory index; Mortality; Inflammation; Emergency department

1. Introduction

Acute cholecystitis (AC) constitutes approximately 1%-3% of patients presenting to the emergency department with abdominal pain[1]. Although mild symptoms including abdominal pain, nausea, and vomiting may be observed in this disease, the clinical picture

Significance

It is important to predict mortality in patients presenting to the emergency department with acute cholecystitis. Neutrophils, leukocytes, systemic immune inflammatory (SII) index, C-reactive protein, and aspartate transferase values were found to be diagnostic in predicting mortality in these patients. SII index may be a good predictor of mortality with high sensitivity and specificity.

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may progress to sepsis, shock, multiple organ failure, and death[2]. Mortality due to AC has been reported to be approximately 3%[3].

AC is an acute inflammation of the gallbladder. In 90%-95% of these cases, the cause of AC is gallstones[4]. The diagnosis of the disease is made using clinical and physical examination, laboratory tests, and imaging methods. AC treatment method is determined according to the severity of the disease. While medical treatment may be suitable for uncomplicated AC, complicated AC requires surgical or invasive intervention[5]. Therefore, prediction of the severity of the disease is important for the correct planning of the patient's treatment.

Since the pathology and prognosis of AC are based on inflammation, inflammatory parameters are frequently taken into account in prognosis prediction. Various indices have been created with some formulas and calculations from hematologic and inflammatory parameters that can be obtained from routine blood tests. Many studies have suggested that the systemic immune-inflammatory (SII) index provides valuable information in predicting the prognosis of inflammatory diseases[6,7]. It has been reported to be diagnostically important in many systemic and local inflammatory diseases such as coronary artery disease, diabetes mellitus, arthritis, and ulcerative colitis, and especially the platelet/lymphocyte ratio can be used as a marker in ovarian, colon, and breast cancer[8-10].

This study aims to investigate the effectiveness of the SII index and other inflammatory markers in predicting mortality among patients with AC in the emergency department. Thus, we aim to contribute to clinicians making more accurate clinical decisions by providing early prognostic information.

2. Patients and methods

2.1. Study setting and design

This retrospective observational study was carried out from September 2021 to September 2023 in the emergency department. The demographic characteristics, laboratory data, radiologic imaging results, and outcomes of patients over the age of 18 diagnosed with AC were obtained through the hospital automation system and recorded on the patient registration form. Using the hemogram parameters of neutrophils ($10^3/\text{mm}^3$), lymphocytes ($10^3/\text{mm}^3$), and platelets ($10^3/\text{mm}^3$), the systemic immune inflammation index was calculated using the formula [(platelet count $\times$ neutrophil count) / lymphocyte count][7].

2.2. Ethical approval

The study was approved by University of Health Sciences, Bozyaka Training and Research Hospital, İzmir, Turkey with the approval

number of 2023/177.

2.3. Inclusion and exclusion criteria

Patients over 18 years of age with AC who presented to the emergency department with abdominal pain during the study period were included in the study. Patients with abdominal pain due to non-AC causes, breastfeeding and pregnant patients, and patients whose outcome information could not be obtained due to referral to an external center were excluded from the study.

2.4. Statistical analysis

Data were evaluated using IBM SPSS Statistics Standard Concurrent User Version 26 (IBM Corp., Armonk, New York, USA) and MedCalc Version 11 statistical package programs. Descriptive statistics were given as the number of units, percentage, mean $\pm$ standard deviation, median, Q1, and Q3 values. The normal distribution of the numerical variables was evaluated by Shapiro-Wilk normality test. Homogeneity of variances was evaluated by Levene's test. When the values in the groups met the parametric test prerequisites, they were compared using the independent two-sample *t*-test, and when they did not, they were compared using the Mann-Whitney *U* test. Pearson and Fisher's exact tests were used to compare categorical variables with each other. A multivariate logistic regression analysis was performed with the data that were statistically significant in the comparative analyses. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values for the parameters considered predictive of mortality. $P < 0.05$ was considered statistically significant.

3. Results

279 Patients who met the study criteria were included (Figure 1). The mean age of these patients was (55.0 $\pm$ 16.3) years and 36.6% ($n=102$) were male. Gallbladder or choledochal stones were found in 63.8% ($n=178$) of the patients. 49.5% ($n=138$) underwent surgical intervention. 6.1% ($n=17$) were deceased. Demographic characteristics of the patients and mean values of the parameters considered in the study are listed in Table 1.

After analyzing the risk factors for mortality, advanced age ($P < 0.001$), being hospitalized in the general surgery service ($P=0.031$), emergency operation ($P < 0.001$), being followed up in the intensive care unit ($P < 0.001$) and long hospitalization ($P < 0.001$) were found to be statistically significant for mortality (Table 2).

A comparison of laboratory values according to mortality is presented in Table 2. Accordingly, a statistically significant difference was found between neutrophil ($P < 0.001$), lymphocyte ($P < 0.001$), leukocyte ($P=0.003$), SII index ($P=0.001$), eosinophil

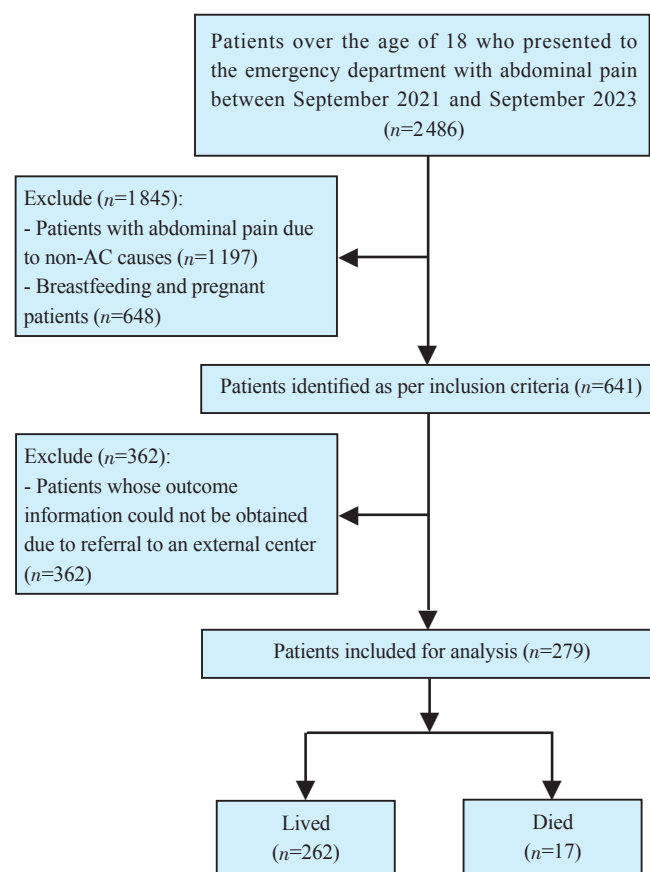


Figure 1. Study flowchart.

($P=0.001$), C-reactive protein (CRP) ($P<0.001$), aspartate transferase (AST) ($P=0.029$), and total bilirubin ($P=0.001$) levels in surviving and died patients (Table 2).

According to the results of the multivariate logistic regression analysis, positive statistically significant associations were found between mortality and age ($OR=1.097$, $P=0.017$), CRP ($OR=1.013$, $P=0.033$), and length of hospital stay ($OR=1.388$, $P=0.011$). It was shown that with each increase in age, the risk of mortality increased by 9.7%, and that an increase in CRP levels and length of hospital stay also increased the risk of mortality. A negative statistically significant association was found between lymphocyte count and mortality ($\beta=-3.903$, $OR=0.020$, $P=0.020$) (Table 3).

The cut-off value for the SII index was 3 138 (AUC=0.817, sensitivity=70.5%, specificity=84.7%), which was found to be a strong biomarker in terms of both sensitivity and specificity for predicting mortality. The cut-off value for neutrophil count was $15.28 \times 10^3/\text{mm}^3$ (AUC=0.761, sensitivity=52.9%, specificity=95.0%) and was shown to have limited sensitivity with high specificity for mortality prediction. The cut-off value for leukocyte count is

$19.0 \times 10^3/\text{mm}^3$ (AUC= 0.714, sensitivity=52.9%, specificity=98.0%), which has been found to have a very high specificity and limited sensitivity in predicting mortality. The cut-off value for C-reactive protein (CRP) was 74.55 (AUC=0.758, sensitivity=70.5%, specificity=79.0%) and was found to be a reasonable biomarker in terms of both sensitivity and specificity. The cut-off value for aspartate transferase (AST) was 33.0 IU/L (AUC=0.658, sensitivity=82.3%, specificity=50.3%) and was found to have high sensitivity and low specificity in predicting mortality (Table 4) (Figure 2).

Table 1. Demographic, clinical, and laboratory results of the patients ($n=279$).

Variables	
Sex, n, %	
Male	102 (36.6)
Female	177 (63.4)
Age, years, mean$\pm$SD	
	55.0 $\pm$ 16.3
Diagnostic imaging, n, %	
Ultrasonography	216 (77.4)
Computed tomography	63 (22.6)
Gallbladder/choledochal stone, n, %	
None	101 (36.2)
Have	178 (63.8)
Follow-up, n, %	
No	27 (9.7)
Yes	252 (90.3)
Operation, n, %	
No	141 (50.5)
Yes	138 (49.5)
Outcome, n, %	
Discharged	29 (10.4)
Services hospitalization	227 (81.4)
Intensive care hospitalization	6 (2.1)
Dead	17 (6.1)
Length of hospitalization, days, mean$\pm$SD	
	5.9 $\pm$ 4.4
Laboratory results	
Neutrophil, $\times 10^3/\text{mm}^3$, median, Q1,Q3	7.23 (4.92, 11.0)
Lymphocyte, $\times 10^3/\text{mm}^3$, median, Q1,Q3	1.51 (1.10, 2.32)
Leukocyte, $\times 10^3/\text{mm}^3$, median, Q1,Q3	9.82 (7.54, 12.7)
Platelets, $\times 10^3/\text{mm}^3$, median, Q1,Q3	276 (228, 332)
SII index, median, Q1,Q3	1 227 (736, 2 460)
Eosinophil, median, Q1,Q3	0.09 (0.03, 0.21)
Hemoglobin, g/dL, median,Q1,Q3	13.0 (11.6, 14.2)
CRP, mg/dL, median, Q1,Q3	11.7 (4.26, 68.3)
AST, IU/L, median, Q1,Q3	37.0 (19.0, 148)
ALT, IU/L, median, Q1,Q3	31.0 (16.5, 173)
Total bilirubin, mg/dL, median, Q1,Q3	0.78 (0.46, 1.55)
Direct bilirubin, mg/dL, median, Q1,Q3	0.72 (0.37, 1.30)
Indirectbilirubin, mg/dL, median, Q1,Q3	0.49 (0.40, 0.80)

*SII index: systemic immune-inflammatory index; CRP: C-reactive protein; AST: aspartate transferase; ALT: alanine rransaminase.

Table 2. Comparison of patient characteristics according to mortality groups.

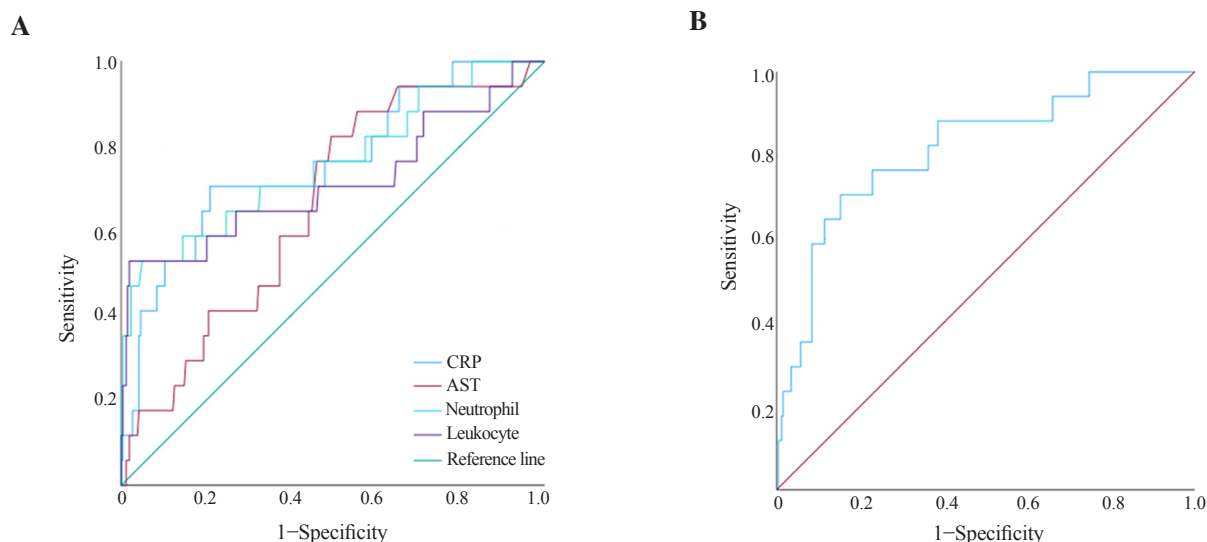
Variables	Lived (n=262)	Died (n=17)	$t/\chi^2/Z$	P
Sex, n, %				
Male	94 (35.9)	8 (47.1)	0.86 ^c	0.354
Female	168 (64.1)	9 (52.9)		
Age, years, mean±SD	53.8±15.9	73.4±11.9	-4.99 ^t	<0.001
Diagnostic imaging, n, %				
Ultrasonography	205 (78.2)	11 (64.7)	1.67 ^c	0.196
Computed tomography	57 (21.8)	6 (35.4)		
Gallbladder/choledochal stone, n, %				
None	97 (37.0)	4 (23.5)	1.25 ^c	0.262
Have	165 (63.0)	13 (76.5)		
Outcome, n, %				
Discharged	29 (11.1)	0 (0.0)	94.78 ^c	<0.001
Services hospitalization	227 (86.6)	7 (41.2)		
Intensive care hospitalization	6 (2.3)	10 (58.8)		
Length of hospitalization, days, mean±SD	5.55±3.69	11.94±8.45	-3.09 ^t	0.001
Laboratory results				
Neutrophil, ×10 ³ /mm ³ , median, Q1, Q3	7.08 (4.84, 10.2)	15.5 (7.47, 18.6)	-3.612 ^Z	<0.001
Lymphocyte, ×10 ³ /mm ³ , median, Q1, Q3	1.58 (1.13, 2.34)	0.95 (0.50, 1.21)	4.068 ^Z	<0.001
Leukocyte, ×10 ³ /mm ³ , median, Q1, Q3	9.75 (7.50, 12.3)	19.1 (8.44, 20.6)	-2.949 ^Z	0.003
Platelets, ×10 ³ /mm ³ , median, Q1, Q3	276 (229, 332)	263 (186, 320)	1.152 ^Z	0.249
SII index, median, Q1, Q3	1 162 (702, 2240)	4478 (2344, 6669)	4.377 ^Z	<0.001
Eosinophil, median, Q1, Q3	0.10 (0.04, 0.21)	0.02 (0.01, 0.05)	3.190 ^Z	0.001
Hemoglobin, g/dL, median, Q1, Q3	13.0 (11.7, 14.3)	12.2 (10.9, 14.0)	1.019 ^Z	0.308
CRP, mg/dL, median, Q1, Q3	11.1 (4.11, 51.7)	159 (12.0, 270)	-3.570 ^Z	<0.001
AST, IU/L, median, Q1, Q3	32.5 (19.0, 136)	73.0 (42.0, 255)	-2.183 ^Z	0.029
ALT, IU/L, median, Q1, Q3	30.5 (16.0, 168)	78.0 (24.0, 219)	-1.367 ^Z	0.171
Total bilirubin, mg/dL, median, Q1, Q3	0.74 (0.45, 1.42)	1.82 (0.98, 4.38)	-3.459 ^Z	<0.001
Direct bilirubin, mg/dL, median, Q1, Q3	0.54 (0.36, 0.72)	1.30 (1.10, 7.35)	1.045 ^Z	0.095
Indirect bilirubin, mg/dL, median, Q1, Q3	0.42 (0.32, 0.48)	0.80 (0.73, 3.75)	1.045 ^Z	0.095

^tIndependent two-sample *t* test; ^cchi-square test; ^ZMann-Whitney *U* test.**Table 3.** Multivariate logistic regression analysis results.

Predictors	β	SE	OR	95% CI	P
Age	0.092	0.039	1.097	1.027-1.204	0.017
Neutrophil	0.282	0.417	1.326	0.458-2.844	0.498
Lymphocyte	-3.903	1.688	0.020	0.000-0.333	0.020
Leukocyte	0.076	0.358	1.079	0.621-2.887	0.830
SII index	0.000	0.000	0.999	0.999-1.000	0.674
Eosinophil	0.079	0.166	1.082	0.781-1.500	0.633
CRP	0.013	0.006	1.013	1.000-1.028	0.033
AST	0.004	0.002	1.000	0.998-1.010	0.119
Total bilirubin	0.287	0.160	1.333	1.044-1.974	0.073
Length of hospitalization	0.328	0.129	1.388	1.125-1.890	0.011

Table 4. Receiver operating characteristic analysis of parameters in the prediction of mortality due to acute cholecystitis.

Variables	Cut-off	AUC	Sensitivity	Specificity
Neutrophil, $\times 10^3/\text{mm}^3$	15.28	0.761	52.94	95.04
Leukocyte, $\times 10^3/\text{mm}^3$	19.00	0.714	52.94	98.09
SII index	3 138	0.817	70.59	84.73
CRP, mg/dL	74.55	0.758	70.59	79.01
AST, IU/L	33.00	0.658	82.35	50.38

**Figure 2.** CRP, AST, neutrophil, leukocyte (A), and SII (B) values in the ROC curve for the prediction of mortality due to acute cholecystitis.

4. Discussion

AC is a common cause of abdominal pain in the emergency department[11]. When inflammation spreads outside the gallbladder, perforation, and intra-abdominal abscess formation, sepsis and multiple organ damage occur as a result of sepsis, coagulation disorders, and increased coagulation due to damage to blood vessels by inflammation. Exacerbation of inflammation in AC patients indicates that the inflammatory process in the gallbladder is progressing, complications are occurring, and inflammation is spreading throughout the body.

Since AC is an inflammatory disease, it leads to changes in liver enzyme levels and inflammatory parameters[12]. The SII index is a new and affordable biomarker that can be easily calculated using neutrophil, platelet, and lymphocyte counts, since in this situation, neutrophils, the white blood cells used by the body to fight infections increase rapidly, lymphocytes begin to decrease, and platelets begin to decrease due to consumptive coagulopathy. These changes in

parameters lead to an increase in the SII index value[12,13]. In our study, the SII index was found to have high sensitivity and specificity in predicting mortality. Similar to our study, Özdemir *et al.* found that the mortality rate in AC was 7.7%, and the cut-off value of the SII index 4 049.3 predicted short-term mortality with a specificity of 91.62%[14]. In addition, similar to our findings, increased neutrophil counts and decreased lymphocyte counts were also reported to be associated with mortality[14].

Studies also found that increased neutrophil and decreased lymphocyte counts have been associated with the diagnosis and severity of AC[11,12,15,16]. Among these studies, Uludağ *et al.* found that white blood cells, CRP, and neutrophil/lymphocyte ratio were higher in patients with complicated AC compared to uncomplicated AC[15]. Serban *et al.* reported that neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and SII index can be used to differentiate mild and complicated patients[17]. In our study, decreased lymphocyte count and elevated CRP were found to be significant risk factors for mortality. Although increased SII index was significant in univariate analysis, it was not statistically significant in multivariate analysis. It was found to have high sensitivity and specificity in

predicting mortality and the cut-off value was determined as 3 138. Although our sample size was adequate, the power of this finding was 51%. We think that the power of the finding is low due to the high difference in the number of people between the two groups ($n=262$ vs. $n=17$).

Another parameter we found to be associated with mortality was CRP. CRP cut-off value of 74.55 mg/dL predicted mortality with 70.59% sensitivity and 79.01% specificity. CRP is a protein produced by the liver. Its blood level increases in cases of inflammation. It is also an indicator of cell damage. Karakaş *et al.* reported that high CRP levels were associated with the severity of AC[5]. We speculate that increased CRP levels in AC cases resulting in death are associated with both severe inflammation and cell damage. Likewise, AST, one of the other parameters that we found to be significant in mortality evaluation, is an indicator of liver cell damage.

Stasis-causing acute cholecystitis creates a favorable environment for bacteria to proliferate. As stasis and inflammation increase, the pressure inside the pouch increases, leading to edema of the pouch wall and further stimulation of inflammation. In the early stage, an increase in neutrophils is observed. As inflammation progresses, blood lymphocyte counts begin to decrease. The high bilirubin levels are associated with mortality signals that the risk of death will increase when stasis is severe.

In addition to the lymphocyte and CRP parameters mentioned so far, the patient's age and length of hospital stay were also found to be statistically significantly different between patients who died and lived. Similar to the literature, advanced age and length of hospitalization also contribute to mortality[18].

AC provides a picture of activation of inflammation based on stasis of bile flow. The SII index is an indicator of a strong inflammatory response and a weak immune response. In our results, we found a higher mortality rate among those who were older and had a longer hospital stay. Cell damage indicators and inflammatory parameters were also found to be high in patients with mortality, indicating that severe stasis and inflammation are associated with death. Among these parameters, the SII index can be used as a good predictor of mortality with high sensitivity and specificity. Prospective studies with balanced numbers of patients in living and dead groups are needed.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

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Authors' contributions

All authors contributed to the conceptualization, methodology, supervision, writing, review and editing of this article. In addition, İK performed statistical analysis.

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