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CLINICAL STUDY

Evaluation of inflammatory biomarkers affecting mortality in acute cholecystitis in the emergency department

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ABSTRACT
OBJECTIVES: The aim of this study was to investigate the effectiveness of *pan*-immune inflammation value (PIV), systemic immune-inflammatory index (SII), and systemic inflammation response index (SIRI) in predicting mortality in acute cholecystitis (AC).
BACKGROUND: Abdominal pain is one of the most frequent complaints encountered by physicians at emergency department (ED).
METHODS: This clinical study is a cross-sectional study among patients admitted to the emergency department of a tertiary hospital and diagnosed with AC. Total survival curves were estimated by the Kaplan–Meier method. Differences according to risk groups were determined by the log-rank test.
RESULTS: A total of 789 patients (survival: 737, non-survival: 52) diagnosed with AC were enrolled in the study. NLR and SII had an excellent diagnostic power in predicting 30-day mortality in the receiver operating characteristic (ROC) analysis, while the diagnostic power of SIRI and PIV was acceptable. It was observed that the probability of survival period decreased in the presence of NLR (>11.07), SII (>2315.18), SIRI (>6.55), and PIV (>1581.13) above the cut-off levels. The HRs of NLR, SII, SIRI, and PIV were 10.52, 7.44, 6.34, and 5.6, respectively.
CONCLUSION: NLR, SII, SIRI, and PIV may be useful markers in predicting 30-day mortality in patients with AC *(Tab. 3, Fig. 5, Ref. 25)*. Text in PDF www.elis.sk
KEY WORDS: cholecystitis, *pan*-immune inflammation value, systemic immune inflammatory index, systemic inflammatory response index, emergency department.

Introduction

Abdominal pain is one of the most frequent complaints encountered by physicians at the emergency department (ED). Acute cholecystitis (AC) is an acute surgical condition that should always be considered in patients presenting with right upper quadrant (RUQ) discomfort. AC accounts for 3–10% of abdominal pain causes, with cholecystolithiasis being the primary cause in 90–95% of cases in patients over 50 years (1). AC is an inflammation of the gallbladder that is commonly caused by gallstones obstructing the gallbladder neck or cystic duct (2). Despite the predominantly younger age range, cholecystitis remains associated with a 3.6% mortality risk (3).

According to the Tokyo Guideline 2018 (TG18), the diagnosis of a patient with suspected AC is made based on the presence of at least one of the two local inflammation symptoms (Murphy's sign or mass/pain/tenderness in RUQ) plus one of the systemic inflammation symptoms (fever, high level of c-reactive protein (CRP) or high white blood cell count (WBC)) (4). Specific imaging findings are also required for the conclusive diagnosis of AC. Clinical severity is determined based on the TG18 criteria, which include a variety of clinical findings such as the patient's history (duration of symptoms), physical examination, laboratory testing, and imaging modalities following the diagnosis (4, 5). In terms of rapidly implementing the most effective treatment protocol for a patient, assessment of the severity of AC is as essential as making the correct diagnosis (6). In addition, a quick, simple, and low-cost mortality predictor is essential for determining the institution where the patient ought to be treated (first contact clinic or specialized healthcare centers) and the intensity of treatment.

Laboratory parameters such as ischemia-modified albumin, percentage of immature granulocytes, monocyte distribution width, CRP, WBC, and neutrophil-to-lymphocyte ratio (NLR) were found to be markers closely related to the clinical severity of AC (7–10). Pan-immune inflammation value (PIV), systemic immune-inflammatory index (SII), and systemic inflammation response index (SIRI) are new inflammatory biomarkers that are associated with the clinical prognosis of inflammatory conditions (such as sepsis, acute pancreatitis, and encephalopathy) (11–13).

The aim of this study was to investigate the effectiveness of PIV, SII, and SIRI in predicting mortality in acute cholecystitis.

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Materials and methods

Study design and settings

This clinical study is a cross-sectional study conducted in the emergency department of a tertiary hospital. The local ethics committee approved the study, which waived the obligation to obtain informed consent (ethics committee decision number: 2023/86, date: March 20, 2023). The current study was carried out in accordance with the Helsinki Declaration.

Sample size

According to the cross-sectional study design, between March 20, 2019, and March 20, 2023, 789 patients who met the inclusion criteria were included in this study.

Selection of participants

The patients' demographic, history, physical examination, laboratory, and imaging findings were retrospectively scanned from the hospital information system. The results of the patients at the time of admission to ED were evaluated. The imaging scans of all patients were evaluated by an experienced radiologist. Patients were evaluated using the TG18 criteria, and the definitive diagnosis of AC was established. (4). Patients over 18 and diagnosed with AC who sought care at the ED were included in the study.

Exclusion criteria encompassed connective tissue diseases, other acute and chronic infections, recent surgeries, recent burns and trauma, a history of hematological and chronic liver disease, the use of anticoagulants and steroids, malignancy, concurrent pancreatitis or cholangitis, age below 18 years, and incomplete data. A total of 789 patients meeting these criteria were selected, with 47 subsequently excluded.

The world-wide acknowledged severity-grading criteria of TG 18, were used to rate the severity of AC (4). We divided patients with AC into three clinical severity grades: grade 1 (mild), grade 2 (moderate), and grade 3 (severe). The relationship between inflammation biomarkers (PIV, SII, SIRI, and NLR) and mortality in survival and non-survival patients was statistically analyzed.

Laboratory analyses

An automated hematology analyzer (Coulter Gen-S Hematology Analyzer; Beckman Coulter Corp, Hialeah, FL, USA) was used to determine the full blood count (FBC). Hematological parameters total leucocyte count and differential, hemoglobin, hematocrit, platelet levels, NLR, PIV, SII and SIRI values were recorded. The NLR, PIV, SII and SIRI were defined as "neutrophil count/lymphocyte count", "neutrophil count × platelet count × monocyte count/lymphocyte count", "neutrophil count × platelet count/lymphocyte count", and "neutrophil × monocyte/lymphocyte count", respectively.

Statistical analysis

Parametric tests were used without conducting the normality test due to the compatibility of the central limit theorem (14). In the analysis of the data, the mean and standard deviation, and minimum and maximum values of the features were used while performing the statistics of continuous data. Categorical variables were defined using frequency and percentage values.

Tab. 1. Comparison of basic and laboratory characteristics of surviving and deceased patients.

	Total (n=789)	Non-survival (n=52)	Survival (n=737)	p
	x̄±SD	x̄±SD	x̄±SD	
Age (year)	64.5±17.6	77.4±13.1	63.6±17.5	<0.001*
	n (%)	n (%)	n (%)	
Sex				
Female	397 (50.03)	34 (65.3)	363 (49.3)	0.03**
Male	392 (49.67)	18 (34.7)	374 (50.7)	
Grade				
1	495 (62.7)	0 (0)	495 (67.2)	
2	198 (25)	6 (11.5)	192 (26.1)	<0.001**
3	96 (12.2)	46 (88.5)	50 (6.7)	
Features	x̄±SD	x̄±SD	x̄±SD	
Glucose	151.67±70.05	150.5±69.7	151.7±70.1	0.91*
Serum sodium (mEq/L)	136.26±4.84	135.4±6.3	136.1±4.58	0.62*
Serum potassium (mEq/L)	4.19±0.68	4.45±0.74	4.18±0.67	0.004*
Urea (mg/dL)	48.91±22.44	80.17±21.02	46.7±29.92	<0.001*
Creatinine (mg/dL)	1.21±0.98	1.68±1.11	1.18±0.82	0.006*
AST (U/L)	126.48±96.81	126.63±84.51	126.47±92.83	0.98*
ALT (U/L)	116.74±92.12	94.04±84.32	118.35±98.95	0.48*
Bilirubin total (mg/dL)	2.28±1.63	3.48±2.79	2.21±1.52	0.65*
Bilirubin direct (mg/dL)	1.37±1.65	2.41±1.41	1.29±0.58	0.24*
Bilirubin indirect (mg/dL)	0.91±0.46	1.06±0.85	0.91±0.43	0.46*
CRP (mg/L)	79.67±53.1	125.99±45.82	76.41±52.18	<0.001*
INR	1.24±0.61	1.47±0.64	1.22±0.59	0.08*
WBC (10^3mcL)	13.72±5.51	19.66±3.81	13.31±5.36	<0.001*
PLT (10^3mcL)	264.9±86.71	266.29±70.47	264.8±87.78	0.91*
NEU (10^3mcL)	11.26±5.24	16.44±4.71	10.89±5.09	<0.001*
LYM (10^3mcL)	1.41±0.81	0.91±0.51	1.44±0.82	<0.001*
MON (10^3mcL)	0.72±0.41	0.71±0.36	0.72±0.41	0.69*
NLR	12.22±9.33	24.01±15.8	11.39±7.63	<0.001*
SII	3,161. ±2353.63	6,261.09±3310.45	2,942.52±1166.64	<0.001*
SIRI	8.69±6.15	16.11±10.08	8.16±5.8	<0.001*
PIV	2,332.23±1981.81	4,259.1±2408.42	2,196.28±1904.05	<0.001*

Student's t test*, chi-square test** (p<0.05 significance)
AST – aspartate aminotransferase; ALT – alanine aminotransferase; CRP – c-reactive protein; INR – international normalized ratio; WBC – white blood cells; PLT – platelets; NEU – neutrophil; LYM – lymphocyte; MON – monocyte; NLR – neutrophil-to-lymphocyte ratio; SII – systemic immune inflammation index; SIRI – systemic inflammation response index; PIV – *pan*-immune inflammation value

Student's t-test statistics were used to compare survival patients and non-survival patients. Chi-square test statistics were used to evaluate the relationship between two independent categorical variables. The cut-off value in diagnostic measurements was determined using the receiver operating characteristic (ROC) analysis. Statistical significance was determined by the statistics of sensitivity and specificity. The area under the curve (AUC) in ranges of 0.5–0.6, 0.6–0.7, 0.7 0.8, 0.8/0.9, and >0.9 were interpreted as poor, fair, acceptable, excellent, and outstanding, respectively. Total survival curves were estimated by the Kaplan–Meier method. Differences between NLR, SII, SIRI, and PIV risk groups were determined by the log-rank test. The results are expressed as hazard ratio and 95% confidence interval. Statistical significance is considered when $P < 0.05$. New York software (e-picos, New York, NY, USA, www.e-picos.com) and the MedCalc statistical package program (MedCalc Software Ltd., Ostend, Belgium) were used for data evaluation.

Results

A total of 789 patients (survival: 737, non-survival: 52) admitted to the ED and diagnosed with AC were enrolled in the study. The mean age of the patients was 64.5±17.6 years. Non-survival patients (77.4±13.1 years) were older than survival patients (63.6±17.5 years) ($p<0.001$), and 50.03% of patients were female. Table 1 summarizes the patients' details, specifically mean age, gender, clinical severity levels, laboratory parameters, as well as mean and standard deviation values of inflammatory biomarkers. Higher mean values of serum potassium, urea, creatinine, CRP, WBC, neutrophil, NLR, SII, SIRI, and PIV were observed in non-survivor patients (Table 1). Conversely, mean lymphocyte levels were significantly higher in surviving patients (Tab. 1).

Table 2 presents the details of diagnostic accuracy of biomarkers crucial in predicting non-survival patients in the ROC analysis (Tab. 2, Fig. 1).

SIRI and PIV exhibited acceptable diagnostic power in predicting 30-day mortality (AUC: 0.756 and 0.750, respectively). Using a cut-off value of 6.55 for SIRI, the sensitivity and specificity were 86.5% and 70.2%, respectively. For PIV, a cut-off value of 1,581.13 resulted in sensitivity and specificity of 84.6% and 68.9%, respectively (Tab. 2).

NLR and SII demonstrated excellent diagnostic power to predict 30-day mortality (AUC: 0.809 and 0.808, respectively). Using a cut-off value of 11.07 for NLR, the sensitivity and specificity were 90.04% and 70.8%, respectively. For SII, a cut-off value of 2,315.18 led to sensitivity and specificity of 94.2% and 65.1%, respectively (Tab. 2).

As illustrated in Figures 2–5, it was observed that the probability of survival (%) decreased in accordance with risk groups.

The number of patients who died within the period of 0 to 30 days was 52 (6.59%), while the number of patients who survived was 737 (93.41%). The mean survival time was 28.8 days (95% CI: 28.5–29.2 days) (Tab. 3).

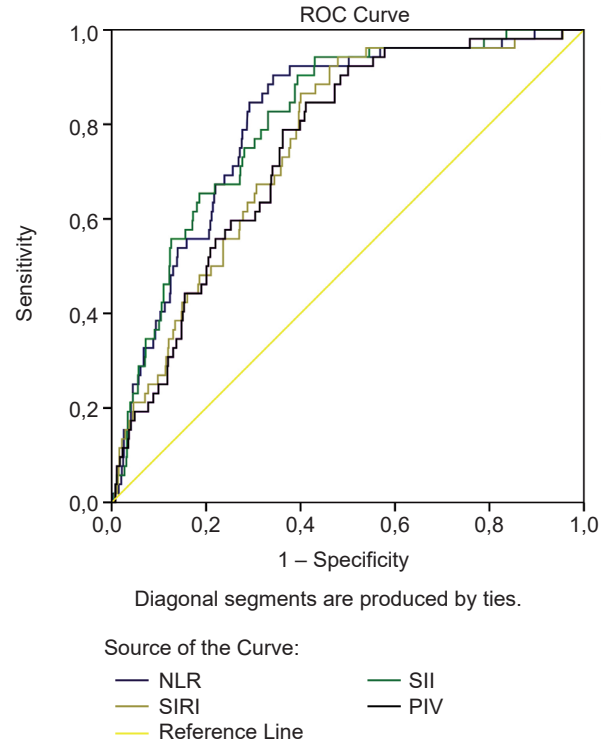

Fig. 1. The receiver operating characteristic (ROC) curves of biomarkers for predicting survival in acute cholecystitis. NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune inflammation index; SIRI, Systemic Inflammation Response Index; PIV, *pan*-immune inflammation value.

In patients with NLR >11.07, the mean survival range was 27.2 days (95% CI: 26.3–27.9 days), while in those with NLR ≤11.07, it was 29.9 days (95% CI: 29.8–30.02 days) (Tab. 3).

In patients with SII >2,315.18, the mean survival range was 27.6 days (95% CI: 26.9–28.3 days), while in those with SII ≤2,315.18, it was 29.9 days (95% CI: 29.8–30.02 days) (Tab. 3).

In patients with SIRI >6.55, the mean survival range was 27.7 days (95% CI: 26.9–28.4 days), while in those with SIRI ≤6.55, it was 29.8 days (95% CI: 29.5–29.9 days) (Tab. 3).

In patients with PIV >1,581.13, the mean survival range was 27.69 days (95% CI: 26.9–28.4 days), while in patients with PIV ≤1,581.13, it was 29.8 days (95% CI: 29.6–30.0 days) (Tab. 3).

Tab. 2. Diagnostic accuracy of inflammatory parameters to predicting non-survival patients.

Non-survival: 52 Survival: 737	AUC	Cut-off value	Sensitivity %	Specificity %	AUC 95% CI	p
NLR	0.809	>11.07	90.04	70.8	0.78-0.84	<0.001
SII	0.808	>2,315.18	94.2	65.1	0.78-0.83	<0.001
SIRI	0.756	>6.55	86.5	70.2	0.73-0.79	<0.001
PIV	0.750	>1,581.13	84.6	68.9	0.72-0.78	<0.001

AUC – area under curve; SE – standard error; PPV – positive predictive value; NPV – negative predictive value; CI – confidence interval; NLR – neutrophil-to-lymphocyte ratio; SII – systemic immune inflammation index; SIRI – systemic inflammation response index; PIV – *pan*-immune inflammation value

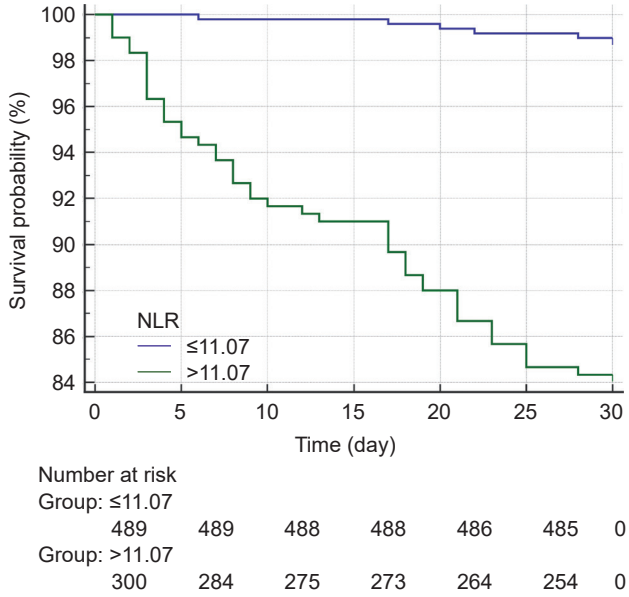

Fig. 2. Kaplan–Meier curve for 30-day survival by NLR risk factor.

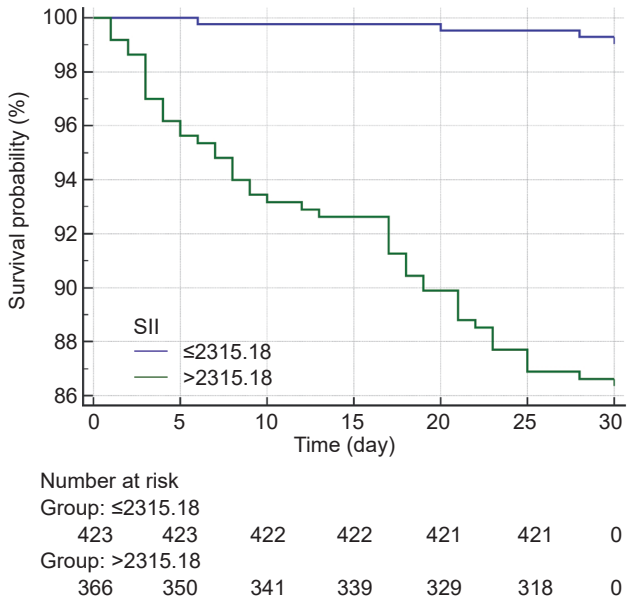

Fig. 3. Kaplan–Meier curve for 30-day survival by SII risk factor.

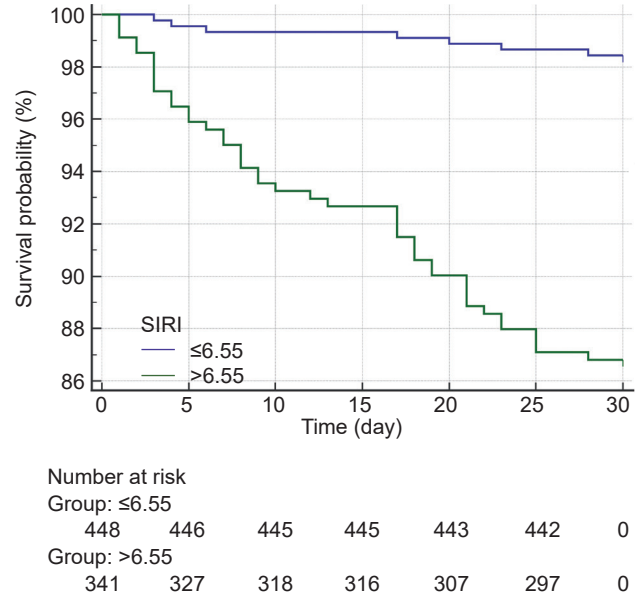

Fig. 4. Kaplan–Meier curve for 30-day survival by SIRI risk factor.

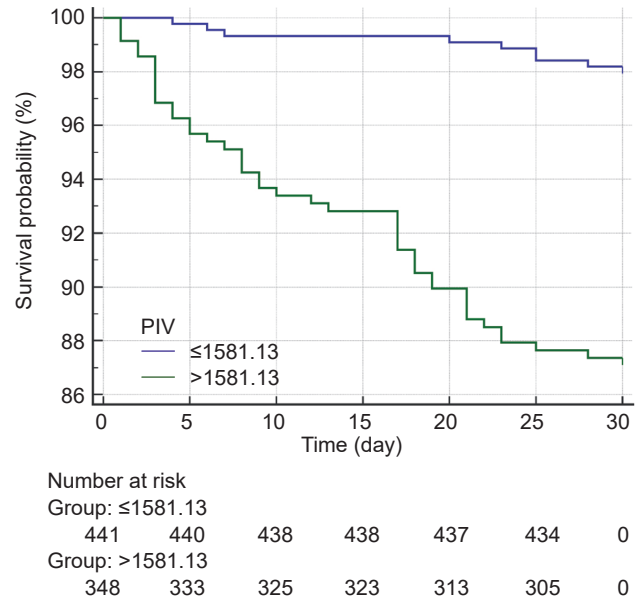

Fig. 5. Kaplan–Meier curve for 30-day survival by PIV risk factor.

As shown in the summary of results of the comparison of survival curves (log-rank test) (Tab. 3), 47 out of 300 patients with NLR> 11.07 and 5 of 489 patients with NLR<11.07 died (p<0.001). In patients with NLR >11.07, the mortality risk was significantly higher compared to those with NLR ≤11.07, specifically 10-fold (95% CI: 5.97–18.54; p<0.05).

Forty-nine of 366 patients with SII >2,315.18 and 3 of 423 patients with SII <2,315.18 died (p<0.001). Mortality risk in patients with SII >2,315.18 was significantly higher than in those with SII ≤2,315.18, specifically 7.44-fold (95% CI: 4.32–12.86; p<0.05).

Forty-five of 341 patients with SIRI >6.55 and 7 of 448 patients with SIRI ≤ 6.55 died (p<0.001). Mortality risk in patients with SIRI >6.55 was significantly higher than in those with SIRI ≤ 6.55, specifically 6.34-fold (95% CI: 3.65–11.01; p<0.05).

Forty-four of 348 patients with PIV >1.581.13 and 8 of 441 patients with PIV ≤1.581.13 died (p<0.001). Mortality risk in patients with PIV >1,581.13 was significantly higher than in those

with PIV ≤ 1.581.13, specifically 5.6-fold (95% CI: 3.23–9.71; p<0.05).

Tab. 3. Comparison of survival curves (Log-rank test).

	Non-survival n (%)	Survival n (%)	Mean survival (% 95 CI)	Hazard ratio (% 95 CI)	Log-rank p
NLR					
>11.07 (n:300)	47(15.67)	253(84.33)	27.2(26.3–27.9)	10.52(5.97–18.54)	**<0.001**
≤11.07(n:489)	5(1.02)	484(98.98)	29.9(29.8–30.1)		
SII					
>2315.18 (n:366)	49(13.39)	317(86.61)	27.6(26.9–28.3)	7.44(4.32–12.86)	**<0.001**
≤2315.18 (n:423)	3(0.71)	420(99.29)	29.9(29.8–30.1)		
SIRI					
>6.55 (n:341)	45(13.2)	296(86.8)	27.7(26.9–28.4)	6.34(3.65–11.01)	
≤ 6.55(n:448)	7(1.56)	441(98.44)	29.8(29.5–29.9)		**<0.001**
PIV					
>1581.13 (n:348)	44(12.64)	304(87.36)	27.69(26.9–28.4)	5.6(3.23–9.71)	**<0.001**
≤1581.13 (n:441)	8(1.81)	433(98.19)	29.8(29.6–30.0)		
Overall	52(6.59)	737(93.41)	28.8(28.5–29.2)	–	–

CI – confidence interval; NLR – neutrophil-to-lymphocyte ratio; SII – systemic immune inflammation index; SIRI – systemic inflammation response index; PIV – *pan*-immune inflammation value

Discussion

Predicting the prognosis in patients with an elevated mortality risk after an AC diagnosis in the ED is crucial for providing these patients with necessary therapy and facilitating timely referral from first-contact clinics to specialized healthcare centers, thereby decreasing the risk of negative outcomes. In a multicenter cohort study by Endo et al, age, body mass index, performance status, and Charlson Comorbidity Index were found to be predictive factors for 30-day mortality in Grade 1–2 AC (15). In Grade 3 AC, the predictive markers of 30-day mortality include performance status, jaundice, neurological dysfunction, and respiratory dysfunction (15). Biomarkers used in clinical classification of severity encompass WBC, platelet count, INR, creatinine, and some blood gas parameters (4). In this study, we investigated the potential of novel inflammatory indices (NLR, SII, SIRI, and PIV) to predict mortality. These inflammatory indices can be calculated from parameters commonly employed in the clinical settings.

NLR is a simple, inexpensive marker calculated by dividing absolute neutrophil count by the lymphocyte count. The manifestations of inflammatory response are neutrophilia and lymphopenia (16). In their study conducted on 214 patients diagnosed with AC, Polanco et al. found that with a cut off value of 12.48, NLR could predict mortality with 70% sensitivity, and 70% specificity (17). Furthermore, NLR was reported as an independent predictor of mortality in a multivariate analysis (17). In our study, we concluded that, with a cut-off value of 11.07, NLR had the potential to predict mortality with higher sensitivity. In addition, compared to other patients, the mortality risk in patients above this cut-off value was ten-fold higher. In this respect, this paper corroborates the results of previously published studies.

SII is a comprehensive indicator of the equilibrium between immune and inflammatory conditions. In a study by Peng et al., increased SII was associated with adverse survival outcomes in patients with bile duct cancer (18). In a meta-analysis involving 1,402 patients, high-levels of SII were associated with poor survival in patients undergoing invasive surgery due to cholangiocarcinoma (19). Şener et al found that SII is a parameter that might be used in the diagnosis of AC (20). In this study, we discovered that SII can be considered a predictive marker of mortality at an acceptable level (AUC: 0.808), contributing to the literature.

SIRI is a biomarker calculated from lymphocyte, neutrophil, and monocyte counts that have been demonstrated to be of prognostic value for malignancy. Qi et al showed its utility in predicting the survival of patients undergoing chemotherapy for pancreatic adenocarcinoma (21). In a study of patients after liver transplantation due to hepatocellular carcinoma, the 5-year survival rate was substantially higher among those with SIRI >1.25 compared to those with low SIRI values (22). In the study conducted by Cakcak et al. on hospitalized AC patients, the SIRI value was found to be nearly three times higher in patients who developed complications and underwent cholecystostomy than in those with no complications (23). In this study, mortality risk was found to be six times higher in AC patients with high SII values.

PIV is a novel inflammatory-based inclusive biomarker that incorporates NLR, platelet count, and monocyte count. Fuca et al predicted survival in patients with metastatic colorectal cancer and found PIV to outperform other biomarkers (24). In a systematic meta-analysis that included six studies, a high PIV value was found to be valuable in predicting poor survival in patients with colorectal cancer (25). In a study conducted on one type of non-small lung cancer cell, it was concluded that PIV could be a predictive marker for overall survival (26). In this study, it was found that PIV may also be utilized for predicting mortality in AC.

There are no studies evaluating the association between SII, SIRI, and PIV and mortality in patients with AC available in the current literature. This is the first study conducted on this subject.

Our study has some limitations. It is a retrospective single-center study conducted only on adult patients with isolated cholecystitis, excluding those with additional pathology (pancreatitis, cholangitis, malignancy, etc.). In addition, follow-up and post-treatment values of biomarkers were not assessed in the study. Although the conclusions of this study cannot be generalized due to these limitations, they can serve as a suggestion for new large-scale randomized controlled trials.

Conclusion

While SIRI and PIV were shown to have an acceptable diagnostic power to predict 30-day mortality, NLR and SII exhibited excellent diagnostic power. We found that increased values of

NLR, SII, SIRI, and PIV were predictive of decreased survival probability. In conclusion, these biomarkers might be beneficial in predicting 30-day mortality in patients with AC.

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