Submitted: 11 July, 2024 Accepted: 14 August, 2024 Published: 08 February, 2025 DOI:10.22514/sv.2024.134

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ORIGINAL RESEARCH

Predictive value of inflammatory indices in acute cholecystitis: a retrospective study of gallstone detection and outcome assessment

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Abstract

Background: This retrospective observational study investigates the predictive value of inflammatory indices Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and Systemic Inflammatory Index (SII) for detecting gallstones and forecasting outcomes in patients with acute cholecystitis (AC). **Methods**: Conducted from 01 September 2022, to 01 September 2023, the research involved patients aged 18 and older diagnosed with AC in an emergency department, excluding those with overlapping pathologies or insufficient data. The study employed hemogram-based indices to explore their correlation with the presence of gallstones and the severity of AC, assessing outcomes such as hospitalization duration and the necessity for surgical intervention. **Results**: Findings demonstrated that high NLR and SII values significantly correlated with severe outcomes and increased hospitalization rates, while SII exhibited the highest accuracy in predicting mortality. Moreover, the study uniquely identified the Systemic Inflammatory Response Index (SIRI) as a significant marker for gallstone presence. **Conclusions**: Inflammatory indices like NLR, PLR and SII can be practical prognostic tools in managing AC, potentially guiding clinical decisions regarding immediate surgical needs and overall patient management. This suggests a broader application for these indices in emergency and surgical settings, improving diagnostic accuracy and treatment strategies.

Keywords

Acute cholecystitis; Gallstones; Systemic inflammatory index; Systemic inflammatory response index; Neutrophil-lymphocyte ratio; Platelet-lymphocyte ratio

1. Introduction

Acute cholecystitis (AC) is the gradual inflammation of the gallbladder due to gallstones blocking the cystic duct. Symptoms range from congestion and swelling to bleeding and tissue death [1]. Failure to promptly address the issue can result in heightened morbidity, as it may progress to severe cholecystitis, characterized by gangrenous alteration, abscess development, and gallbladder perforation [2]. AC is more likely to occur in individuals who are over the age of 60, male, have cardiovascular disease, diabetes mellitus or a history of cerebrovascular injury [3].

AC is primarily caused by inflammation and typically follows a mild symptomatic course; it can also manifest with an additional severe symptomatic course, leading to increased mortality and morbidity, mainly when there are delays in diagnosis [4]. The diagnosis of AC can be promptly established through clinical and medical examinations, laboratory tests, and imaging procedures [5]. While imaging techniques for diagnosing the disease are advancing, there is still a need for additional diagnostic methods to accurately determine both the diagnosis and the extent of the disease [4, 5].

Although access to radiological methods like computed tomography (CT) and ultrasonography (USG) is more accessible today, many centers need to be aware of alternative imaging methods. Especially in primary healthcare institutions [6], it is challenging to diagnose abdominal pain differently.

In acute abdominal pain, biochemical values such as Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), amylase, and lipase may take time to increase [7]. In these cases, we do not have a supporting parameter other than examination for patients with right upper quadrant pain and Murphy (+) on examination. In the absence of a firm evidence-level diagnosis, the physician needs help with referral. Loss of time in this process may lead to undesirable situations, such as complications of the patient's abdominal pain.

There is ongoing research on rapid and straightforward diagnostic markers, as the significance of early prediction of AC diagnosis is well recognized. To predict the prognosis of inflammatory conditions, several scores have been suggested,

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such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR), systemic inflammatory index (SII) and systemic inflammatory response index (SIRI), are widely used in the diagnostic procedure [8–10]. The release of arachidonic acid metabolites and platelet-activating factors caused by inflammation leads to an increase in neutrophils. In contrast, the stress induced by cortisol leads to a decrease in lymphocytes. Therefore, the ratio of this parameter accurately reflects the underlying inflammatory process [11].

Cholesterol gallstones are linked to heightened inflammation and a thickened mucus layer in the gallbladder wall, indicating that inflammation is an initial occurrence in the development of gallstones [12]. The severity of oxidative stress in patients with choledocholithiasis is correlated with inflammation parameters and biochemical markers of cholestasis [13].

In this study, we aim to discover the best prognostic parameters between the inflammatory indexes for acute cholecystitis and to detect the predictive power of the presence of gallstones with inflammatory index ratios.

2. Materials and methods

2.1 Study design

This study was designed as a retrospective observational study. The study included patients admitted to the emergency department between 01 September 2022 and 01 September 2023.

2.2 Study population

Our study included patients aged 18 years and older who presented to the emergency department and were diagnosed with acute cholecystitis. Among these patients, we excluded patients with additional pathologies that may cause abdominal pain, additional infections, pregnant and/or lactating women, lack of data, history of any malignancy or hematologic disease, bone marrow pathology and history of anti-inflammatory and/or immunosuppressive drug use. Patients referred to an external center and for whom no outcome information was available were also excluded.

2.3 Outcomes

The primary outcome of this study is the predictability of the presence of stones in patients with acute cholecystitis using inflammatory indices. The secondary outcome is to investigate the usefulness of inflammatory indices as prognostic indicators in patients with acute cholecystitis and the most robust index in between.

2.4 Data collection

Patient records were accessed through the hospital information management system to determine which patients should be included in the study. In order to identify patients diagnosed with acute cholecystitis in the emergency department during the specified date range, a search was performed using acute cholecystitis diagnosis codes in the hospital information management system. A total of 288 patients were identified. Of these patients, 39 were excluded because of a history of malignancy, 21 because of missing data, seven because of a history of hematologic disease, two because of pregnancy and one because of receiving immunosuppressive therapy. The remaining 218 patients were included in the study. Age, gender, laboratory data, imaging data, length of hospitalization, mortality and comorbidities of all patients were recorded on the data recording form for statistical analysis.

2.5 Calculation of data

In the study, calculations were performed using the hemogram results obtained for each case. The marked parameters were peripheral platelet (P), neutrophil (N), lymphocyte (L) and monocyte (M) counts. The ratios calculated based on these values are NLR (N/L), PLR (P/L), MLR (M/L), SII ((P $\times$ N)/L), SIRI (N $\times$ M/L), Multi Inflammatory Index (MII-1) (NLR $\times$ CRP), MII-2 (PLR $\times$ CRP) and MII-3 (SII $\times$ CRP).

2.6 Statistical analysis

After the data collection process, the data will be digitized and statistically analyzed. IBM SPSS Statistics 28.0 (IBM Corporation, Armonk, NY, USA) will be used for all analyses. p values less than 0.05 were considered significant, and all statistics were performed at a 95% confidence interval. Descriptive statistics will be presented as frequency, percentage, mean, standard deviation, median, minimum and maximum values. The Shapiro-Wilk test will test normality assumptions, skewness, kurtosis values and Quantile-Quantile (Q-Q) plots. The participant's data will be compared with the Independent Samples t Test to if they fit the normal distribution and with the Mann-Whitney U Test if they do not.

3. Results

A total of 218 patients were included in the study, and 94 (43.12%) were female. The mean age of the whole group was 59.49 $\pm$ 15.79 years. 183 (83.94%) patients had stones on USG. Hospitalization was given to 176 (80.73%) of the patients. 28 (12.84%) patients needed an urgent operation, and 4 (1.83%) patients ended up as exitus. All descriptive characteristics of the patients are presented in Table 1.

The results of the Receiver Operating Characteristic (ROC) curve analysis for the usefulness of all values in predicting outcomes are presented in Table 2 and Fig. 1. NLR, PLR, SII, MII-1, MII-2 and MII-3 are appropriate and statistically significant for this purpose. Table 2 presents the optimum cutoff values for predicting the endpoints of all variables and the sensitivities and specificities for these cutoff values.

Table 3 and Fig. 2 present an ROC curve analysis of all inflammatory parameters for predicting the presence or absence of stones on USG. Among all variables, SIRI was found to be the only statistically significant marker for predicting the presence of stones on USG. The optimum cutoff value for the SIRI variable in predicting the presence of stones on USG was >5.924, with a sensitivity of 61.75% and a specificity of 65.71%.

Table 4 and Fig. 3 present the ROC curve analysis of inflammatory parameters in predicting hospitalization or discharge of

TABLE 1. Descriptive statistics of patients.

	Statistics
Age	59.49 ± 15.79
Gender	
Male	124 (56.88%)
Woman	94 (43.12%)
Systolic BP	137.09 ± 25.34
Diastolic BP	73.58 ± 12.29
Pulse	94.12 ± 55.63
Fire	37.54 ± 4.66
WBC	14.51 ± 5.68
NEU	11.67 ± 5.54
LYM	1.64 ± 1.38
MONO	1.06 ± 0.65
PLT	274.95 ± 90.94
HMG	13.08 ± 1.95
BUN	18.14 ± 11.64
CRE	1.44 ± 3.97
NA	136.10 ± 3.93
CRP	104.49 ± 99.69
Stone on USG	
Yes	183 (83.94%)
None	35 (16.06%)
Pericholecystic Fluid on USG	
Yes	90 (41.28%)
None	128 (58.72%)
Hydropic sac on USG	
Yes	143 (65.60%)
None	75 (34.40%)
Sac wall thickness increase on USG	
Yes	193 (88.53%)
None	25 (11.47%)
Discharge/Admission	
Discharge	30 (13.76%)
Admission	176 (80.73%)
Treatment Refusal	12 (5.50%)
Service/ICU	
Service	166 (93.26%)
ICU	12 (6.74%)
Operation	
Performed	28 (12.84%)
None	190 (87.16%)
Time spent in the emergency room (h)	6.39 ± 3.61
Time spent in the ward/ICU (d)	7.45 ± 8.90
Outcome Discharge/Exitus	
Discharge	214 (98.17%)
Exit	4 (1.83%)

BP: arterial blood pressure; WBC: White Blood Cell; NEU: Neutrophil; LYM: lymphocyte; MONO: Monocyte; PLT: platelet; HMG: hemoglobin; BUN: blood urea nitrogen; CRE: Creatinine; NA: sodium; CRP: C-reaktif protein; USG: ultrasonography; ICU: intensive care unit.

TABLE 2. Cutoff scores, AUC value, sensitivity, selectivity and statistical significance of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters by endpoint group.

Test Result Variables	Cutoff	AUC	Std. Error	*p*	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
					Lower Bound	Upper Bound		
NLR	>12.391	0.835	0.039	**0.022**	0.759	0.912	100.0	74.3
PLR	>266.666	0.856	0.035	**0.015**	0.788	0.925	100.0	78.0
MLR	>0.698	0.652	0.055	0.298	0.545	0.759	100.0	50.5
SII	>4631.293	0.891	0.023	**0.007**	0.847	0.936	100.0	86.0
SIRI	>10.873	0.741	0.048	0.099	0.646	0.835	100.0	62.1
MII-1	>1921.642	0.874	0.042	**0.010**	0.791	0.957	100.0	77.1
MII-2	>39,629.729	0.904	0.038	**0.006**	0.830	0.978	100.0	79.4
MII-3	>619,804.707	0.924	0.030	**0.004**	0.865	0.984	100.0	83.6

AUC: Area Under the Curve; Std.: standard; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index. Statistically significant ones are written in bold.

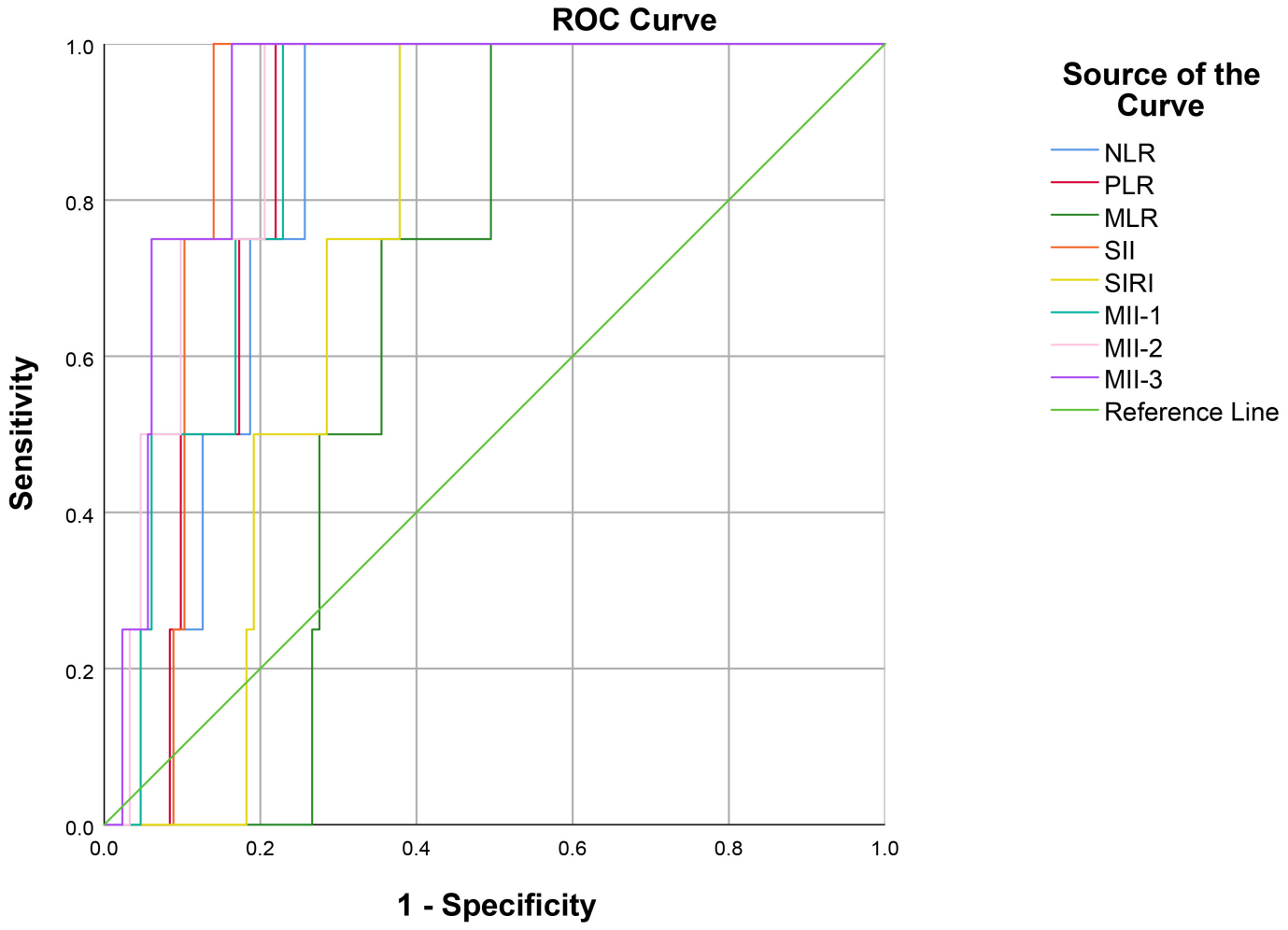

FIGURE 1. ROC curve analysis of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters plotted according to outcome. ROC: Receiver Operating Characteristic; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index.

TABLE 3. Cutoff scores, AUC value, sensitivity, selectivity, and statistical significance of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters by stone group on USG Tables should be placed in the main text near the first time they are cited.

Test Result Variables	Cutoff	AUC	Std. Error	*p*	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
					Lower Bound	Upper Bound		
NLR	>4.626	0.540	0.058	0.451	0.427	0.653	75.40	40.00
PLR	≤155.882	0.408	0.048	0.085	0.313	0.503	38.30	80.00
MLR	>0.698	0.554	0.056	0.309	0.445	0.664	53.60	62.90
SII	>1615.173	0.548	0.056	0.367	0.439	0.657	60.70	54.30
SIRI	>5.924	0.617	0.057	**0.029**	0.505	0.728	61.75	65.71
MII-1	>83.891	0.580	0.055	0.132	0.474	0.687	79.80	40.00
MII-2	>4157.608	0.552	0.053	0.332	0.447	0.656	72.68	42.86
MII-3	>30,214.035	0.587	0.053	0.102	0.483	0.692	76.50	45.71

AUC: Area Under the Curve; Std.: standard; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index. Statistically significant ones are written in bold.

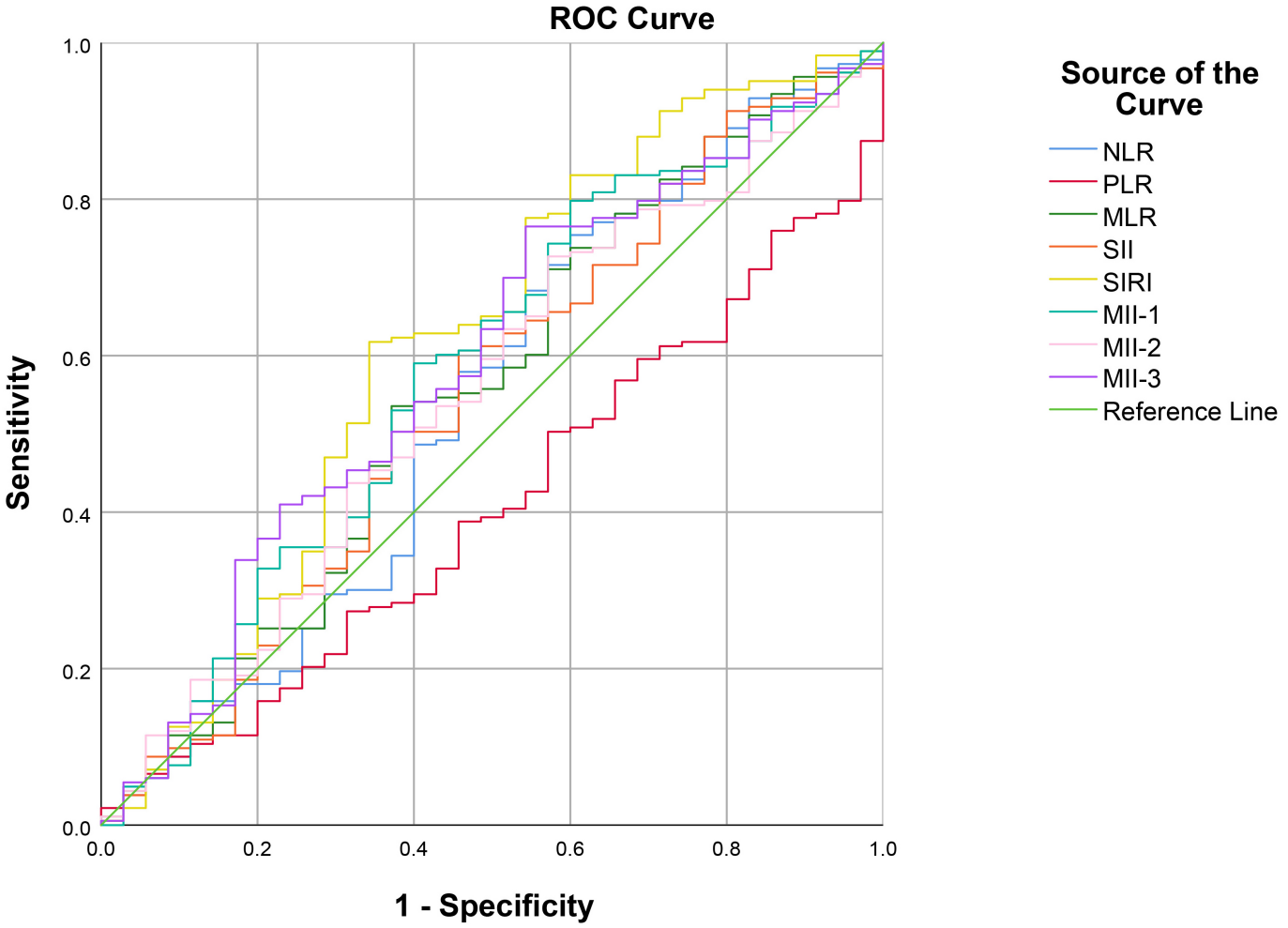

FIGURE 2. ROC curve analysis of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters according to the prediction of stone presence on USG. ROC: Receiver Operating Characteristic; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index.

TABLE 4. Cutoff scores, AUC value, sensitivity, selectivity, and statistical significance of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters by discharge/hospitalization group.

Test Result Variables	Cutoff	AUC	Std. Error	*p*	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
					Lower Bound	Upper Bound		
NLR	>3.797	0.672	0.057	**0.003**	0.561	0.783	86.90	43.30
PLR	>138.281	0.622	0.056	**0.032**	0.513	0.731	78.40	50.00
MLR	>0.431	0.645	0.063	**0.011**	0.521	0.768	80.10	56.70
SII	>1176.250	0.648	0.056	**0.010**	0.538	0.758	76.70	53.30
SIRI	>4.059	0.671	0.057	**0.003**	0.560	0.783	76.10	63.30
MII-1	>289.371	0.684	0.056	**0.001**	0.574	0.795	67.60	73.30
MII-2	>6082.444	0.680	0.055	**0.002**	0.572	0.787	72.70	66.70
MII-3	>79,350.717	0.687	0.055	**0.001**	0.580	0.794	65.30	76.70

AUC: Area Under the Curve; Std.: standard; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index. Statistically significant ones are written in bold.

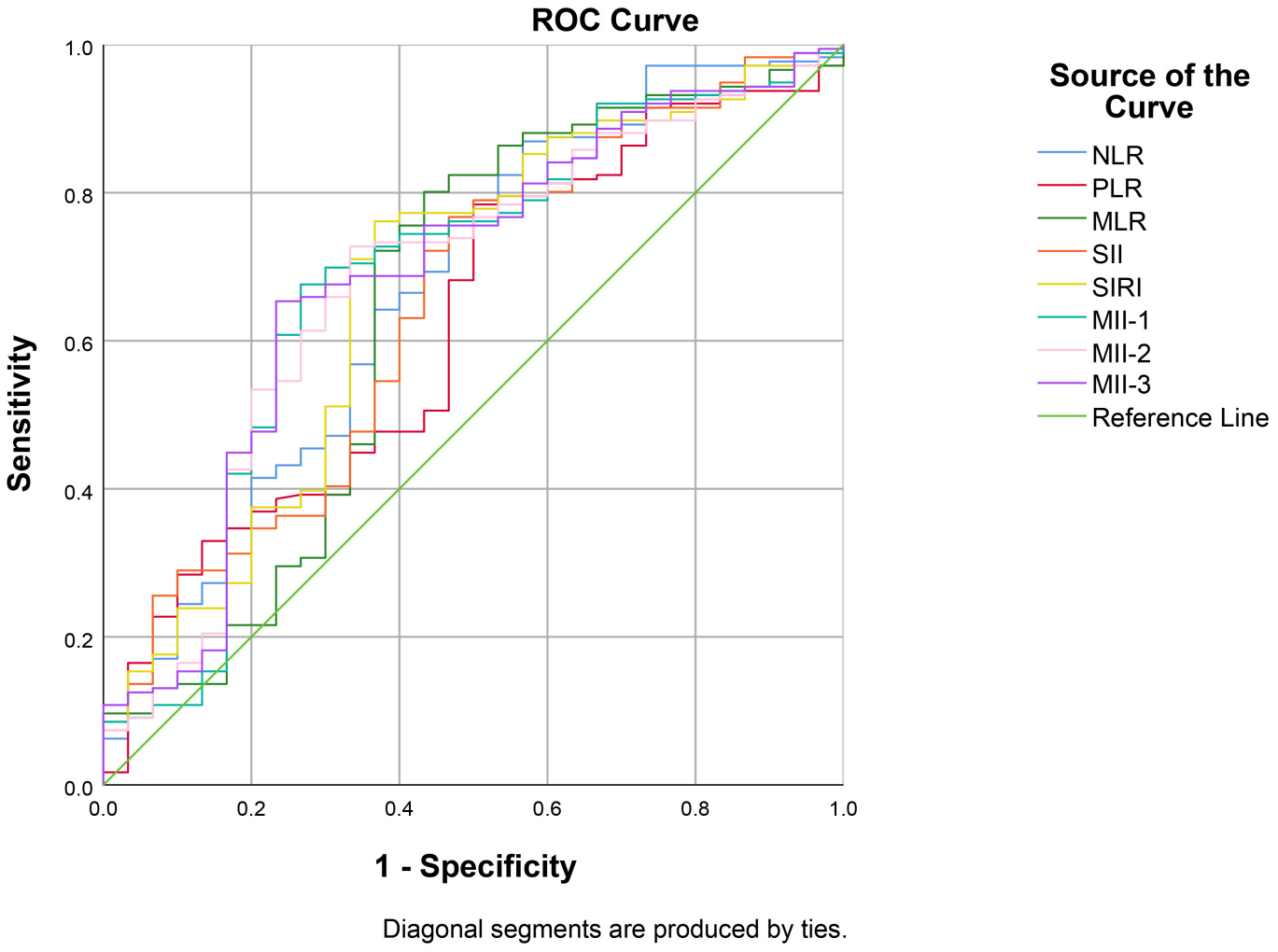

FIGURE 3. ROC curve analysis plotted according to NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters and discharge/admission group. ROC: Receiver Operating Characteristic; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index.

acute cholecystitis patients from the emergency department. The use of all parameters for this purpose is appropriate and statistically significant. Table 4 presents the optimum cutoff values for predicting the endpoints of all variables and the sensitivities and specificities for these cutoff values.

ROC curve analysis of inflammatory parameters in predicting hospitalization of acute cholecystitis patients to the ward or intensive care unit is presented in Table 5 and Fig. 4. The use of NLR, PLR, SII, MII-1, MII-2 and MII-3 for this purpose is appropriate and statistically significant. The optimum cutoff values for predicting the endpoints of all variables and the sensitivities and specificities for these cutoff values are presented in Table 5.

4. Discussion

Accurately evaluating the seriousness of acute cholecystitis is crucial for optimizing treatment results and minimizing adverse postoperative incidents [14–16]. Localized inflammation and surgical trauma trigger metabolic and systemic inflammatory reactions, potentially resulting in systemic complications [9]. Gaining comprehension of inflammation and addressing the potential systemic imbalances it can induce is crucial for averting unfavorable consequences and avoiding unnecessarily extended hospital stays in cases involving AC.

The current study involved a comparative analysis of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 in determining their effectiveness in predicting severe inflammation in acute cholecystitis, the risk of complication, and choledocholithiasis outcomes. Although computed tomography (CT) and ultrasonography (USG) techniques are available, supplementary diagnostic methods are still required to improve diagnostic precision, particularly in primary healthcare facilities with limited resources. Discovering alternative markers, such as indicators of inflammation, shows potential in this context. Although the algorithms of diagnostic and therapeutic methods for the diagnosis and etiology of AC are known [17], there is no simple, inexpensive, and non-invasive method for early diagnosis and treatment, especially in centers where conventional methods are unavailable. In a study by Gojayev *et al.* [18], more than a thousand patients were evaluated for founding an early signal method for AC, and they describe that if the neutrophil-to-lymphocyte ratio (NLR) is higher than 5.65 and the total leukocyte count exceeds 8100/mm^3, complications are 92% likely. The results of a systematic review and meta-analysis demonstrate that the Neutrophil-to-Lymphocyte Ratio (NLR) is notably elevated in patients with AC compared to those without, and it can serve as a reliable indicator for the presence of AC. Nevertheless, NLR may not accurately forecast the seriousness of AC due to constraints in the study's statistical power [19]. On the other hand, in a study by Patel *et al.* [20], they describe a higher NLR as positively associated with an increased length of stay (LOS) in patients admitted with acute cholecystitis (AC), indicating that it can serve as a valuable indicator of the severity of the disease. In this study, we found that NLR greater than 3.797 were hospitalized to the service, >12.391 has a relation with mortality outcome and >13.67 has a relation with ICU hospitalization. This study's results align with other results and confirm other studies.

The NLR, the ratio of platelets to lymphocytes (PLR), and the systemic inflammatory index (SII) are valuable indicators for determining the severity of AC. Among these, the NLR is the most effective in predicting advanced inflammation and the likelihood of progressing to more severe forms of the condition, surpassing the predictive capabilities of both the PLR and SII. There is a strong correlation between high NLR values and the occurrence of postoperative complications and sepsis [9].

Our analysis revealed that the SII demonstrated the highest performance in predicting mortality in AC, achieving an AUC of 0.891 when using a cutoff value greater than 4631.293. It demonstrates a high sensitivity of 100% but a high specificity of 86%. The SII also exhibits a strong predictive capacity for hospitalization, as indicated by an area under the curve (AUC) value of 0.801 and a cutoff value of 3413.703. It demonstrates a high sensitivity of 83.3% but a high specificity of 77.7%.

TABLE 5. Cutoff scores, AUC value, sensitivity, selectivity and statistical significance of NLR, PLR, MLR, SII, SIRI, MII-1, MII-2 and MII-3 parameters by hospitalization to service /ICU Group.

Test Result Variables	Cutoff	AUC	Std. Error	*p*	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
					Lower Bound	Upper Bound		
NLR	>13.670	0.789	0.066	**0.001**	0.660	0.917	75.0	80.1
PLR	>266.666	0.834	0.040	**0.001**	0.756	0.912	83.3	78.9
MLR	>0.833	0.629	0.088	0.138	0.456	0.801	66.7	64.5
SII	>3413.703	0.801	0.053	**0.001**	0.697	0.905	83.3	77.7
SIRI	>15.620	0.635	0.093	0.119	0.453	0.817	58.3	77.1
MII-1	>1389.660	0.793	0.069	**0.001**	0.658	0.928	83.3	69.3
MII-2	>31,538.213	0.809	0.065	**0.001**	0.681	0.937	83.3	70.5
MII-3	>619,804.707	0.806	0.069	**0.001**	0.671	0.941	75.0	84.3

AUC: Area Under the Curve; Std.: standard; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index. Statistically significant ones are written in bold.

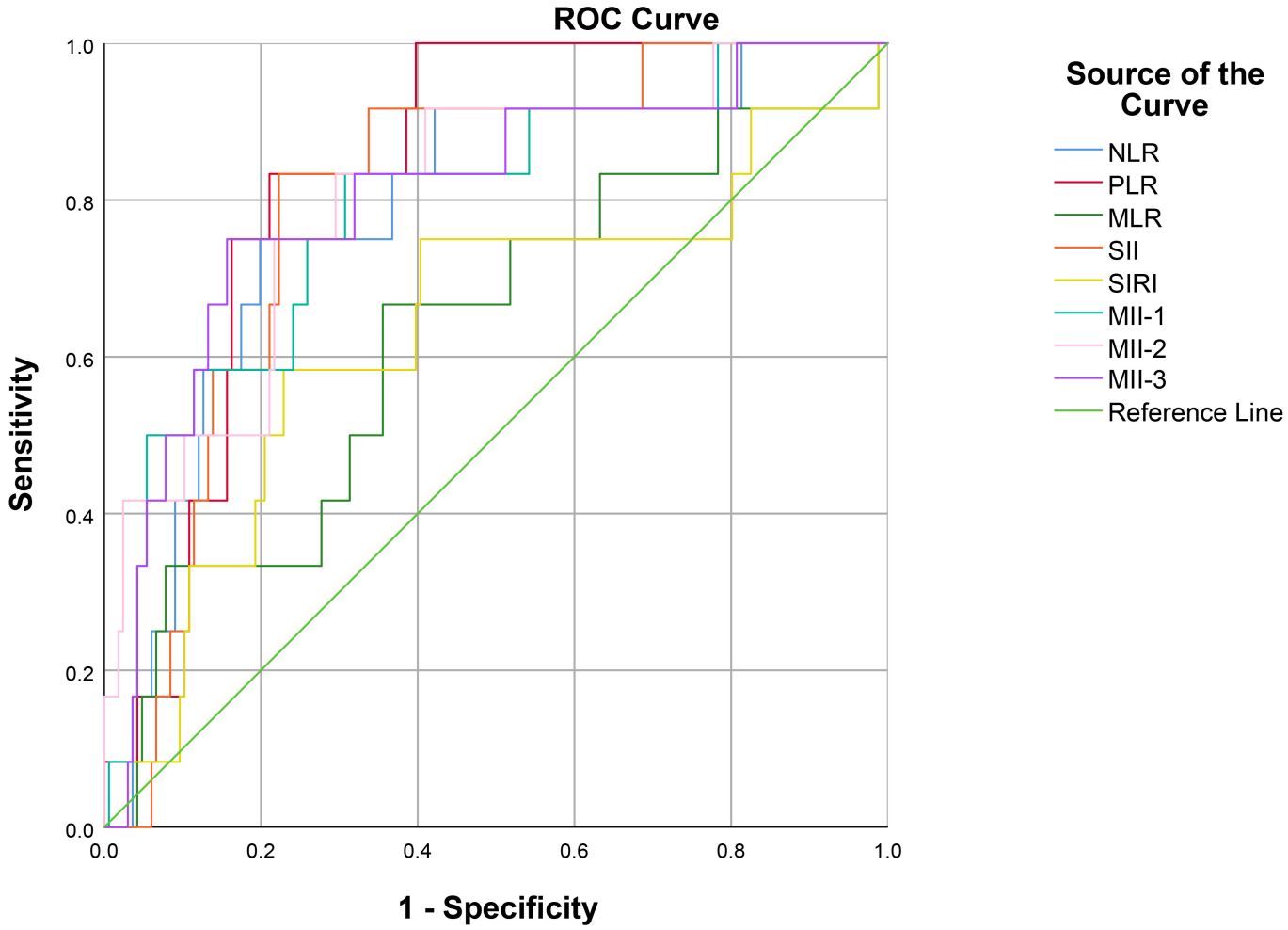

FIGURE 4. ROC curve analysis plotted according to NLR, PLR, SII, MII-1, MII-2 and MII-3 parameters and discharge/admission group. ROC: Receiver Operating Characteristic; NLR: Neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; SII: Systemic Immune-Inflammation; SIRI: Systemic Inflammation Response Index; MII: Multi Inflammatory Index.

Beliaev *et al.* [21] claim that patients with AC exhibit elevated levels of systemic inflammation response index (SIRI) and SII compared to controls. This indicates that SIRI and SII can be helpful to diagnostic markers in addition to CRP [21]. Moreover, Cakcak *et al.* [22] found that inflammatory markers such as SIRI and SII can forecast the seriousness of AC and assist in determining whether cholecystostomy, a less invasive alternative to cholecystectomy, is a suitable course of action.

Cholesterol concentrated in the gallbladder can precipitate and form gallstones in some abnormal conditions. Excessive absorption of water from bile, excessive absorption of bile salts and lecithin from bile, excessive secretion of cholesterol into bile, inflammation of the gallbladder epithelium, factors that promote and inhibit crystallization in gallbladder bile, mucin, prostaglandins, calcium and lack of motility play a role in the development of cholesterol stones [23, 24]. Cholecystokinin receptor defects in the gallbladder smooth muscle membrane, oxidative stress and inflammatory mediators lead to smooth muscle dysfunction and decreased motility [25, 26]. As inflammation increases, especially fluid and bile salt, absorption in the bile wall increases, and cholesterol begins to precipitate. Accordingly, stone formation increases and increases, inflammation increases, and these events enter a vicious cycle. The SIRI and its related indices, such as SII, are useful prognostic tools for various diseases, including cardiovascular events [27], cancer [28] and conditions characterized by acute inflammation [29, 30], such as acute cholecystitis, as in this study.

Depending on our study, the SIRI is the single inflammatory parameter that indicates gallstones. SIRI probably shows the chronic inflammation process and results. In addition to predicting the likelihood of gallstones, SIRI was also found to be insignificant for mortality and significant forward admission and intensive care unit stay. In SII, it was found to be significant for all. The only difference in the SII and SIRI formulations is the platelet and lymphocyte multiplier in the ratio's denominator. This suggests that SIRI may be significant in chronic inflammatory processes leading to stone formation rather than acute inflammatory processes. As far as we know, this is the first time in the literature that a simple computable parameter such as SIRI has been used to assume the presence of gallstone.

This study shows that SIRI will be supportive in the absence of CT and USG, which are the gold standard for the diagnosis

[31], by looking at the hemogram, which is a simple and inexpensive test to give a clue about the presence of bile stones. In addition, high SII will give an idea about the severity and outcome of AC and will strengthen our hand in hospitalization and discharge.

This article has some limitations. First, it has a single-center and retrospective design, which constitutes the most important limitation. Second, the study's aim is to use inflammatory markers in primary health care centers, but it was conducted in a large research hospital. Studies that will include smaller centers are needed. In addition, the study was conducted on patients with a definitive diagnosis. Studies conducted with a control group may report more definitive results.

5. Conclusions

The results indicate that specific inflammatory markers, such as Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio and Systemic Inflammatory Index, show potential as prognostic indicators for acute cholecystitis. These markers can assist clinicians in making prompt decisions about patient management, such as assessing the necessity for immediate surgery or predicting the need for hospitalization. Moreover, this is the first study in which an inflammatory index was used to predict the existence of a foreign body like a gallstone. Further investigation may prioritize prospective studies with more extensive sample sizes to authenticate the results and investigate supplementary inflammatory markers.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

MGE, ESB, SMC, SK, AK—conceptualization. MGE, ESB—methodology, data curation. SMC, SK, AK—software. MGE, ESB, SMC—validation. MGE, SK—formal analysis. MGE, SMC, AK—investigation. ESB, SMC, SK—resources; visualization. MGE, ESB, AK—writing–original draft preparation, project administration. ESB, SK—writing–review and editing; supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki and approved by the Izmir Katip Celebi University Non-Interventional Research Ethics Committee (protocol code 0406 and date of approval: 21 September 2023). Consent for participation was obtained from all subjects.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Mehmet Göktuğ Efgan, Ejder Saylav Bora, Semih Musa Coşkun, Süleyman Kırık, Ahmet Kayalı. Predictive value of inflammatory indices in acute cholecystitis: a retrospective study of gallstone detection and outcome assessment. Signa Vitae. 2025; 21(2): 60-69. doi: 10.22514/sv.2025.021.