İstanbul Med J 2024; 25(3): 223-8
DOI: 10.4274/imj.galenos.2024.94467

Effectiveness of Preoperative Biomarkers: Role of the C-Reactive Protein/Albumin Ratio and Systemic Immune-Inflammation Index in Predicting Acute Cholecystitis Severity

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ABSTRACT

Introduction: The 2018 Tokyo Guidelines are insufficient for preoperative prediction of severe acute cholecystitis (AC) preoperatively. The Parkland Grading Scale (PGS) aids in intraoperative assessment but lacks preoperative utility. Biomarkers like C-reactive protein/albumin ratio (CAR) and systemic immune-inflammation index (SII) were explored for preoperative prediction of severe AC. The present study aimed to investigate the efficacy of biomarkers against severe AC.

Methods: A retrospective analysis at the University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital covered patients undergoing early laparoscopic cholecystectomy for AC from January 2014 and January 2023. AC was defined according to the 2018 Tokyo Guidelines criteria. Patients were categorized into two groups based on the PGS for intraoperative findings: Group 1 (grades 1-3) for mild AC and group 2 (grades 4-5) for severe AC. Clinical parameters, intraoperative findings, postoperative outcomes, and biomarkers, including CAR and SII, were analyzed.

Results: Of 141 patients, 93 were included in group 1 and 48 in group 2. Group 2 exhibited longer operation times, higher rates of conversion to open cholecystectomy, and complications, and prolonged hospital stays. Clinical parameters such as age, sex, symptom duration, and ASA score were varied between the groups. Biomarkers including C-reactive protein and white blood cell count differed significantly between the groups, with CAR and SII identified as predictive factors for severe AC. The cut-off points were 1.86 for CAR and 1327.69 for SII.

Conclusion: Preoperative biomarkers, particularly CAR and SII, can effectively predict severe AC. Levels exceeding 1.86 for CAR and 1327.69 for SII indicate increased conversion to open cholecystectomy and postoperative complication risk.

Keywords: Severe acute cholecystitis, C-reactive protein/albumin ratio, systemic immune-inflammation index, Parkland Grading Scale

Introduction

It is important to accurately evaluate the severity of acute cholecystitis (AC) in patients to improve treatment outcomes and prognosis (1). The Tokyo Guidelines 2018 (TG18) are recommended for evaluating the risk level of patients with AC to determine the most suitable treatment approach. According to the TG18, the diagnostic criteria for AC include duration of symptoms, physical examination findings, laboratory results, such as C-reactive protein (CRP) and white blood cell (WBC) levels, and radiological evaluation. The TG18 uses CRP levels only for diagnosing AC and not as a decisive marker in assessing the severity of AC. The WBC count was used as a criterion for determining disease severity (2). Nevertheless, the 2013 Tokyo Guidelines were found to be insufficient to predict conversion to open cholecystectomy (CC) but sufficient to predict mortality in the literature (3). Additionally, WBC count was not found to predict CC (4). Moreover, there is no difference in the rates of CC and complications between patients undergoing early laparoscopic cholecystectomy, even when the symptom duration exceeds 72 hours (5).

The Parkland Grading Scale (PGS) is based on intraoperative patient observations, and cholecystectomy becomes increasingly challenging from grades 1 to 5 (6). Lee et al. (7) reported that CRP and WBC counts, operation time, intraoperative complications, postoperative complications, and length of hospital stay were all the highest in patients classified as grade 5 on the PGS. In the same study, 87.2% of grade 5 cases on the PGS corresponded to grades 1 and 2 on the TG18. Cripps and Weber (8) found the PGS and the American Association for Surgery of Trauma Grading Scale to be superior to the TG18. They concluded that

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Cite this article as: Güneş Y, Teke E, Taşdelen İ, Ağar M, Şahinoğulları H, Aydın MT. Effectiveness of Preoperative Biomarkers: Role of the C-Reactive Protein/Albumin Ratio and Systemic Immune-Inflammation Index in Predicting Acute Cholecystitis Severity. İstanbul Med J. 2024; 25(3): 223-8

Received: 07.04.2024
Accepted: 04.06.2024

the PGS is the best grading system for AC. However, in the preoperative period, evaluating the severity of AC using PGS is challenging due to its intraoperative nature.

For these reasons, some researchers have turned to biomarkers to assess the severity of AC in the preoperative period. Several studies have identified CRP as a reliable predictor of difficult cholecystectomy or CC (1,9-11). Moreover, various biomarkers, such as procalcitonin, visfatin, and neopterin, have been investigated although their utility is limited (12-14). Biomarkers that are easy to use and inexpensive, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), CRP/albumin ratio (CAR), systemic immune-inflammation index (SII), systemic immune response index (SIRI), prognostic nutritional index (PNI), and Glasgow prognostic score (GPS), have recently been studied. However, conflicting evidence exists regarding the predictive value of these biomarkers in AC and the threshold values that can be used in management (15-27).

The objective of this study was to evaluate the efficacy of preoperative biomarkers for predicting difficult cholecystectomy during early laparoscopic cholecystectomy for AC.

Methods

We retrospectively analyzed patients who underwent early laparoscopic cholecystectomy for AC at the University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of General Surgery between January 2014 and January 2023. The University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital Local Ethics Committee approved this study (approval number: FSM EAH-KAEK 2023/184, date: 14.12.2023). All participants received written explanations of the study objectives and methods. AC was defined as the presence of at least one feature from each systemic, local, and radiological finding according to the TG18 (2).

Groups

The characteristics of the gallbladder from the operation notes of the patients included in the study (such as normal gallbladder, adhesion of surrounding tissues to the gallbladder, location of adhesion, hyperemia, pericholecystic fluid, hydrops, grade 1-3 abnormal liver anatomy, intrahepatic gallbladder, Mirizzi syndrome, perforation, and necrosis) were recorded. The grade of each patient was calculated according to the PGS, as defined by Madni et al. (6), based on the intraoperative findings. Patients were classified from 1 to 5. Grades 1, 2, and 3 were grouped into group 1, representing mild cholecystitis and easier cholecystectomy, while grades 4 and 5 were grouped into group 2, indicating severe cholecystitis and more difficult cholecystectomy.

Clinical Parameters, Intraoperative Findings, and Postoperative Outcomes

Preoperatively, the following information was collected from each patient: Demographic characteristics (age, gender), radiological findings (gallbladder wall thickness, presence of pericholecystic fluid), and clinical findings [severity of AC according to the TG18, American Society of Anesthesiologists (ASA) score]. To ensure the accuracy of the classification (as the groups were established based on mild and severe cholecystitis), intraoperative findings and postoperative results were initially documented. Intraoperative findings included the operation time, type of surgery, and presence of any complications. The postoperative and total hospital stays were documented in the postoperative results.

Biomarkers

CRP, leukocyte and neutrophil counts, lymphocyte and monocyte counts, platelet and albumin counts, mean platelet volume (MPV), and red cell distribution width (RDW) were recorded for each patient during admission. Subsequently, the following ratios and indices were calculated using the recorded values: NLR, PLR, MLR, CAR, SII, SIRI, PNI, and GPS. SII was calculated by multiplying the monocyte count by the neutrophil count and dividing the result by the lymphocyte count. SIRI was calculated by multiplying the platelet count by the neutrophil count and dividing the result by the lymphocyte count. To calculate PNI, the formula PNI = 10 × albumin (g/dL) + 0.005 × lymphocyte count was used. The GPS was calculated based on CRP and albumin levels. A score of two is assigned if CRP is >10 mg/L and albumin is <3.5 g/dL. A score of one is assigned if only one of these values reaches these levels. A score of 0 was assigned if neither CRP nor albumin meet these levels.

Statistical Analysis

IBM SPSS 25 software was used for statistical analysis. Means, standard deviations, frequencies, and percentages were used to describe the data. To compare qualitative data between groups, the Pearson's chi-squared test and the Fisher's exact test were employed. The distribution of quantitative data was assessed using the Shapiro-Wilk test. Univariate analysis involved comparing quantitative data between groups using the Student's t-test and the Mann-Whitney U test. Logistic regression analysis was performed to evaluate positive data in the univariate analysis. In logistic regression analysis, statistically significant data were evaluated using the receiver operating characteristic curve (ROC), and the area under the curve (AUC), cut-off points, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were determined. Statistical significance was considered at $p<0.05$.

Results

Early laparoscopic cholecystectomy for AC was performed in 141 patients. Of these, 93 patients were categorized into group 1 and, while 48 patients into group 2.

Intraoperative Findings and Postoperative Outcomes

The mean operation time was 71.3±24.45 minutes in group 1 and 102.5±40.55 minutes in group 2 ($p<0.001$). CC was necessary for 1 (1.1%) patient in group 1 and 8 (17%) patients in group 2 ($p=0.001$). Complications were not observed in patients in group 1, whereas 3 patients (6.14%) in group 2 experienced complications ($p=0.038$). Obstructive jaundice resulting from a common bile duct stone was observed in the postoperative period in the first patient, whereas bile leakage from the cystic duct occurred in the remaining two patients. Endoscopic retrograde cholangiopancreatography was performed, and a biliary stent was placed in each of the three patients. The total length of hospital stay was 3.52±2.83 days in group 1 and 6.04±4.24 days in

group 2 (p<0.001). The postoperative hospital stay was 2.22±2.43 days in group 1 and 4.31±3.61 days in group 2 (p<0.001) (Table 1).

Clinical Parameters

The mean age of patients was 46.6±12.77 years in group 1 and 52.2±16.72 years in group 2 (p=0.027). 60.2% of the patients in group 1 and 37.5% in group 2 were female (p=0.010). The mean symptom duration from symptom onset to admission was 2.15±2.52 days in group 1 and 2.43±2.13 days in group 2 (p=0.064). The mean symptom duration from symptom onset to surgery was 3.46±3.02 days in group 1 and 4.10±2.82 days in group 2 (p=0.037). The mean gallbladder wall thickness on preoperative abdominal ultrasonography was 4.28±1.64 mm in group 1 and 4.51±1.66 mm in group 2 (p=0.441). Pericholecystic fluid was present in 21.5% of patients in group 1 and 45.8% of patients in group 2 (p=0.003). According to the TG18, grade 1 AC was present in 72% of patients in group 1 and 52.1% in group 2, grade 2 AC was present in 26.9% of patients in group 1 and 33.3% in group 2, and grade 3 AC was present in 1.1% of patients in group 1 and 14.6% in group 2 (p=0.001). In group 1, 87% of patients were classified as ASA 1-2 and 13% as ASA 3-4. In group 2, 70.2% of patients were ASA 1-2 and 29.8% were ASA 3-4 (p=0.017) (Table 2).

Biomarkers

Significant differences were observed between the groups in CRP, WBC count, neutrophil count, lymphocyte count, albumin, NLR, PLR, MLR, CAR, SII, SIRI, PNI, and GPS (p<0.05). However, no statistically significant differences in other biomarkers (platelet count, monocyte count, MPV, and RDW) (p>0.05) (Table 2).

Table 1. Comparison of intraoperative findings and postoperative outcomes among the study groups

	Group 1, (n=93)	Group 2, (n=48)	p-value
Operation time, mean (minute)	71.3±24.45	102.5±40.55	<0.001[1*]
Conversion to open cholecystectomy, n (%)	1 (1.1)	8 (16.7)	0.001[2*]
Complication, n (%)	0	3 (6.3)	0.038[2*]
Total hospital stay, mean (days)	3.52±2.83	6.04±4.24	<0.001[1*]
Postoperative hospital stay, mean (days)	2.22±2.43	4.31±3.61	<0.001[1*]

[1]Mann-Whitney U test, [2]Fisher's exact test, *p<0.05 significant

Table 2. Comparison of clinical parameters and biomarkers among the groups in the univariate analysis

	Group 1, (n=93)	Group 2, (n=48)	p-value
Age, mean (year)	46.6±12.77	52.2±16.72	0.027[1*]
Gender, n (%)			
Female	56 (60.2)	18 (37.5)	0.010[2*]
Male	37 (39.8)	30 (62.5)	
Symptom duration, mean (days)			
From onset to admission	2.15±2.52	2.43±2.13	0.064[3]
From onset to surgery	3.46±3.02	4.10±2.82	0.037[3*]
Radiological findings			
Gallbladder wall thickness, mean (mm)	4.28±1.64	4.51±1.66	0.441[3]
Pericholecystic fluid, n (%)	20 (21.5)	22 (45.8)	0.003[2*]
Grade by TG18, n (%)			
1, mild	67 (72)	25 (52.1)	0.001[2*]
2, moderate	25 (26.9)	16 (33.3)	
3, severe	1 (1.1)	7 (14.6)	
ASA score, n (%)			
1-2	80 (87)	33 (70.2)	0.017[2*]
3-4	12 (13)	14 (29.8)	
Biomarkers			
CRP level, mean (mg/L)	4.57±6.06	13.26±10.57	<0.001[3*]
WBC count, mean (10^3/uL)	11.93±4.03	14.80±5.16	0.001[3*]
Neutrophil count, mean (10^3/uL)	8.81±3.67	11.93±5.19	0.001[3*]
Lymphocyte count, mean (10^3/uL)	2.28±0.86	1.88±1.06	0.010[3*]
Platelet count, mean (10^3/uL)	270.72±77.66	277.66±90.22	0.707[3]
Monocyte count, mean (10^3/uL)	0.70±0.32	0.83±0.53	0.075[3]
MPV, mean (fL)	8.61±1.53	8.48±1.66	0.659[1]

Table 2. Continued

	Group 1, (n=93)	Group 2, (n=48)	p-value
RDW (%)	14.05±1.43	14.5±1.48	0.051[3]
Albumin, mean (g/dL)	4.31±0.29	4±0.59	0.003[3*]
NLR, mean	4.5±2.94	9.96±6.36	<0.001[3*]
PLR, mean	131.83±48.97	206.01±169.56	0.002[3*]
MLR, mean	0.34±0.21	0.54±0.41	0.005[3*]
CAR, mean	1.07±1.42	5.35±12.13	<0.001[3*]
SII, mean	1172.86±701.48	2741.97±3176.0	<0.001[3*]
SIRI, mean		4	0.001[3*]
PNI, mean	3.31±3.13	7.95±9.21	0.005[3*]
GPS, mean	38.02±14.27	34.23±15.31	<0.001[3*]
	0.63±0.48	1.09±0.53	

[1]Student's t-test, [2]Pearson's chi-square test, [3]Mann-Whitney U test, TG18: Tokyo Guidelines 2018, CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, CAR: CRP-albumin ratio, SII: Systemic immune-inflammation index, SIRI: Sysytemic inflammatory response index, PNI: Prognostic Nutritional index, GPS: Glasgow prognostic score, *p<0.05 significant

Multivariate Analysis and Cut-off Points

Significant clinical parameters and biomarkers in the univariate analysis during the preoperative period were further evaluated by multivariate binary logistic regression analysis. In the multivariate analysis, only CAR and SII were found to be predictive of early laparoscopic cholecystectomy for AC (p<0.05) (Table 3). Subsequently, ROC analysis was conducted for both variables. For CAR, the AUC was 0.780 (p<0.001), the sensitivity was 68.29%, the specificity was 81.71%, the positive predictive value was 65.12%, the negative predictive value was 83.75%, the cut-off point was 1.86, and the accuracy rate was 77.24%. For the SII, the AUC was 0.694 (p<0.001), the sensitivity was 60.42%, the specificity was 75.27%, the positive predictive value was 55.77%, the negative predictive value was 78.65%, the cut-off point was 1327.69, and the accuracy rate was 70.21% (Figure 1).

Table 3. Predictors of severe acute cholecystitis according to multivariate binary logistic regression analysis

	B	S.E.	Wald	p-value	OR	95% CI
CAR	0.429	0.116	13.724	<0.001*	1.536	1.224-1.928
SII	0.001	<0.001	6.061	0.014*	1.001	1.000-1.001

CAR: CRP-albumin ratio, SII: Systemic immune-inlammation index, OR: Odds ratio, CI: Confidence interval, *p<0.05 significant

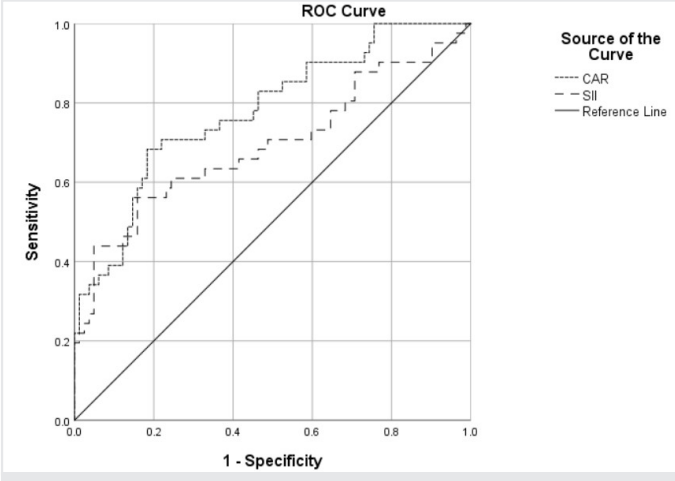

Figure 1. ROC curve analyses for CAR and SII
ROC: receiver operating characteristic, CAR: C-reactive protein/albumin ratio, SII: Systemic immune-inflammation index

Discussion

It is important to understand the severity of AC in the preoperative period. Because the severity of CC increases, the risk of CC and complications increases even in the best medical centers. In this study, we aimed to identify biomarkers that offer easier and a more practical use for preoperative assessment of the severity of AC. Although many studies have investigated biomarkers in the literature, the results have significantly varied. This variance can be attributed to the absence of standardized criteria for defining severe cholecystitis during data grouping and the limited utilization of biomarkers. For these reasons, most studies have biases. To mitigate potential biases, this study focused on accurately grouping patients with AC. To achieve this, we employed the PGS, which is a grading system based on intraoperative characteristics that provides a more comprehensive evaluation of AC severity (8). In our study, the intraoperative and postoperative results were significant in group 2, with longer operative times, more frequent surgical procedures, more complications, and longer hospital stays. These results confirm that PGS grades 4-5 indicate severe cholecystitis.

Furthermore, we included in the study most of the biomarkers used to predict severe cholecystitis in the preoperative period. Through an exhaustive literature review, we identified the most common biomarkers, such as CRP, WBC, neutrophil count, lymphocyte count, platelet count, monocyte count, MPV, RDW, albumin, NLR, PLR, MLR, CAR, SII, SIRI, PNI, and GPS, and included them in our study. As a result, our study identified CAR and SII as predictive factors for severe cholecystitis. CAR emerged as the most predictive factor, with an AUC of 0.780, accompanied by 77.24% AR and a cut-off value of 1.86. Additionally, SII emerged as the second most significant predictive value, with an AUC of 0.694, 70.21% AR, and a cut-off value of 1327.69.

There are limited studies exploring the relationship between AC, CAR, and SII. Three recent studies have reported a relationship between severe AC and CAR (22,25,26). Yilmaz et al. (25) reported an AUC of 0.742 and a cut-off point of 2.61 for CAR. Their study utilized grouping based on the TG18. In contrast, Utsumi et al. (26) found an AUC of 0.78 and a cut-off point of 5.54 for CAR. The grouping was based on laparoscopic cholecystectomy versus CC. However, grouping according to the TG18 in the first study did not compare intraoperative or postoperative outcomes, leaving uncertainty regarding the implications of the results. The TG18 score may not sufficiently denote severe cholecystitis, and it is unclear whether complications or risk escalation correlate with an increased grade. In our study, approximately half of the patients categorized under PGS grades 4-5 exhibited grade 1 AC according to the TG18. In another recent study, Sato et al. (22) found that CAR and NLR were the most effective inflammation-based prognostic scores for predicting grade ≥2 AC as per the TG18. However, the study did not provide insights into CC or complications. In our study, we observed that in group 2, corresponding to the PGS grades 4-5, there were increases in CC, complications, operation time, and hospital stay, with CAR emerging as the most predictive value.

The relationship between AC and SII has been investigated in two recent studies (23,24). Yildiz et al. (24) identified significant associations among NLR, SIRI, and SII. They reported an AUC of 0.742 for the SII using a cut-off point of 790.53. In their studies, the case group comprised patients with AC, and the control group comprised patients who visited the emergency department for any reason with complaints of abdominal pain. Similarly, Serban et al. (23) found that NLR and PLR were also significant, along with SII. They reported an AUC of 0.734 for the SII using a cut-off point of 949.6. Their study involved patients categorized based on intraoperative findings, similar to our study design. Severe AC was associated with prolonged hospitalization, conversion to open cholecystectomy, and increased rate of complications.

In our study, no significant relationship was identified between severe AC and CRP, WBC, albumin, NLR, PLR, MLR, SIRI, PNI, or GPS. Despite this, numerous studies in the literature have linked these biomarkers with severe AC (1,9-11,17-21,27). For instance, in the study conducted by Bouassida et al. (1) categorized patients with gangrenous cholecystitis, pericolic abscess, hepatic abscess, and biliary peritonitis as having advanced AC. Similar to our study, the authors observed a high rate of CC, complications, prolonged hospitalization, and operation time in this group. However, only WBC count, CRP level, and NLR were assessed as biomarkers, with CRP being identified as predictive.

Study Limitations

Our study has several limitations. First, the sample size is small, which may limit the generalizability of the findings. Second, being a retrospective study, it is susceptible to biases inherent in the study design. However, our study also possesses notable strengths. Specifically, severe AC was accurately defined, enhancing the reliability of our results. Additionally, our study examined the largest number of biomarkers, which contributed to a comprehensive analysis of the condition.

Conclusion

CAR and SII are the most effective biomarkers of severe AC during the preoperative period. If CAR >1.86 and SII >13.27.69, clinicians should suspect severe AC and anticipate a higher risk of CC and an increased risk of complications.

Ethics Committee Approval: The University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital Local Ethics Committee approved this study (approval number: FSM EAH-KAEK 2023/184, date: 14.12.2023).

Informed Consent: It was obtained.

Authorship Contributions: Surgical and Medical Practices - Y.G., E.T., İ.T., M.A., H.Ş., M.T.A.; Concept - Y.G., E.T., M.T.A.; Design - Y.G., E.T., M.T.A.; Data Collection or Processing - Y.G., E.T., M.A., H.Ş., M.T.A.; Analysis or Interpretation - Y.G., E.T., M.T.A.; Literature Search - Y.G., E.T., M.A., H.Ş., M.T.A.; Writing - Y.G., E.T., İ.T., M.T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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