The Diagnostic Role of Immature Granulocyte in Differentiating Acute Calculous Cholecystitis From Biliary Colic

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Abstract

Objective: Acute biliary cholecystitis (ABC) is a significant cause of abdominal pain in emergency department. In this study, we investigated the role of immature granulocytes (Ig) as markers of inflammatory response in distinguishing between biliary colic and ABC.

Materials and Methods: This retrospective study included 150 patients who presented with abdominal pain and were found to have or were diagnosed with gallstones. Patients were divided into biliary colic and ABC groups. Laboratory values of the patients, such as age, white blood cell count (WBC), hemoglobin, platelet, mean platelet volume, red cell distribution width, neutrophil (Neu), lymphocyte, Ig%, Ig number, and C-reactive protein (CRP) were recorded in the study form. Receiver operating characteristic and regression analysis were performed for the diagnosis of ABC.

Results: We found that the WBC, Neu, and Ig counts were statistically significantly higher in patients with ABC than in those with biliary colic. However, in the regression analysis, only the Murphy's sign and CRP value were found to be significant in the diagnosis of ABC [p<0.001, odds ratio (OR): 0.119 [95% confidence interval (CI): 0.053-0.268], p=0.002, OR: 1.007 (95% CI: 1.002-1.011), respectively].

Conclusion: Although the Ig number was statistically significant in distinguishing between ABC and biliary colic, we believe that the CRP value and Murphy's sign are superior parameters.

Keywords: Acute biliary cholecystitis, biliary colic, gallstones, immature granulocytes, abdominal pain

Introduction

Acute cholecystitis is the inflammation of the gallbladder caused by infection and is a common cause of patients presenting to the emergency department. This condition can lead to severe complications and requires rapid diagnosis and effective treatment [1,2]. It is crucial to ascertain whether patients presenting with abdominal pain alongside gallstones are experiencing an attack of cholecystitis because this has significant implications for the individual's clinical management and subsequent follow-up [3].

The discovery of new diagnostic methods and markers can aid in the early diagnosis and management of this disease. Some laboratory parameters, such as white blood cell count (WBC), neutrophil (Neu), Neu/lymphocyte ratio (NLR), C-reactive protein (CRP), and the CRP/albumin ratio play a significant role in determining whether patients will be admitted for observation [4-6]. Additionally, clinical signs, such as Murphy's sign, assist in developing diagnostic and treatment strategies [7]. However, there are still uncertainties in the current literature regarding the specificity and sensitivity of these markers and signs.

Immature granulocytes (Ig) are forms of Neus in the blood circulation that has not yet fully matured. We observed that they are produced in increased amounts when the body experiences infections, inflammation, or certain malignancies. An increase in Ig levels typically reflects bone marrow activation in response to active infection or other pathological conditions.

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In recent years, there has been a growing interest in using the percentage of Ig as a potential marker, especially in the early diagnosis and prognosis evaluation of infected patients [8-14].

This study aimed to investigate the potential role of Ig number and Ig% in the differential diagnosis of acute biliary cholecystitis (ABC) and biliary colic patients and in determining the need for inpatient follow-up while treating patients in line with the literature.

Materials and Methods

This retrospective single-center study was designed after receiving approval from our University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital's Ethics Committee (approval number: KAEK/2022.04.81, date: 07.04.2022). Between January 1, 2021, and January 1, 2022, all patients presenting to the emergency department with abdominal pain and detected gallstones had their WBC, platelet, Neu, hemoglobin, mean platelet volume, red cell distribution width, Ig number and percentage, and CRP results recorded from the hospital information management system. Because all data were obtained retrospectively from the hospital automation system, informed consent was not required.

After examining discharge reports, patients without available background information, those with a history of hematological diseases, malignancies, those under 18 years of age, pregnant, or using anti-inflammatory or immunosuppressive drugs were excluded from the study. After excluding 31 patients with abdominal pain and gallstones who received a diagnosis other than biliary colic and ABC, the study was conducted with a total of 150 patients. The examination and test results were evaluated according to the Tokyo 2018 criteria, and a distinction was made between ABC and biliary colic [2]. In total, 52 patients were included in the ABC group, and 98 were included in the biliary colic group.

Statistical Analysis

Categorical data are expressed as numbers and percentages. Normality analysis of continuous variables was performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests and skewness and kurtosis values. The t-test was used for the analysis of data with a normal distribution, and the Mann-Whitney U test was used for non-normally distributed data, and data were shown as mean ± standard deviation and median (minimum-maximum), respectively. Receiver operating characteristic (ROC) analysis was performed for independent variables that were found to be significant between groups to determine the cut-off values. Sensitivity and specificity values were calculated for these cut-off values. Logistic regression analysis was performed to determine the role of independent variables in the diagnosis of ABC. Statistical significance was defined as

p<0.05 and 95% confidence interval. The data obtained were analyzed using SPSS 26.0 Statistics (IBM Corporation, Armonk, New York, USA).

Results

Of the 98 patients (65.3%) included in the study, they were discharged with a diagnosis of biliary colic, while 52 patients (34.7%) were hospitalized with a diagnosis of ABC. We found no statistically significant differences between the groups regarding the age or gender of the patients. When laboratory values were compared, WBC, Neu, Ig, and CRP values were significantly higher in the ABC group than in the biliary colic group. We found a statistically significant relationship between the presenting complaints of the patients and the presence of Murphy's sign; however, this relationship was only evident in patients with ABC and those who showed positivity for Murphy's sign (Table 1).

Independent variables that created a statistically significant difference between the biliary colic and ABC groups had cut-off values calculated using ROC analysis for the diagnosis of ABC (Figure 1). Sensitivity and specificity values were calculated for the determined cut-off values (Table 2). Logistic regression analysis of significant variables was performed to demonstrate their effect on the diagnosis of ABC (Table 3).

Discussion

In this study, the diagnostic role of markers such as Ig count and Ig percentage in distinguishing patients with ABC from those with biliary colic was examined, revealing that they do not have a significant relationship.

Karakulak et al. [15] elucidated the crucial correlation between elevated Ig percentage levels and severity, as well as the in-hospital mortality rates, in acute pancreatitis cases. This pivotal study underscores the significant role of Ig% as both a diagnostic and prognostic marker in the context of acute pancreatitis, offering valuable insights into patient outcomes [15]. In the study of Ünsal et al. [16] in 2022 investigated the predictive value of Ig count and delta Neu index (DNI) in the diagnosis of complicated acute cholecystitis. The findings indicate that both the Ig count and DNI have high diagnostic value in acute complicated cholecystitis. In particular, in the ROC analysis, a sensitivity of 68.8% and specificity of 86.9% were found for the Ig count, and 49.3% sensitivity and 96.2% specificity were found for DNI. These results suggest that Ig may play a significant role in assessing the risk of complications in acute cholecystitis [16]. In our study, although the Ig count was significantly higher in patients with ABC, its sensitivity was determined as 65.4% and specificity as 60.2%. Although there was statistical significance in group comparison, we determined that the Ig value did not play a role in distinguishing between

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Table 1. Distribution of patient characteristics according to clinical follow-up

	Biliary colic (98)	Acute biliary cholecyctitis (52)	p
Age	54.91±17.90	55.17±16.87	0.930
WBC, 10³/μL	10.29 (3.67-27.21)	12.99 (4.12-27.73)	**0.001**[*]
Hemoglobin, g/dL	12.98±1.66	13.25±1.96	0.380
Platelet, 10³/μL	251.41±76.69	259.33±71.85	0.540
MPV, fL	9.74±1.11	9.58±0.90	0.385
RDW, %	13.60 (11.90-17.80)	13.75 (12.00-18.70)	0.991[*]
Neutrophile, 10³/μL	8.06±3.98	10.05±3.86	**0.004**
Lymphocyte, 10³/μL	1.75 (0.20-4.50)	1.60 (0.40-14.90)	0.674[*]
Ig, %	0.00 (0.0-0.40)	0.00 (0.0-0.10)	0.158[*]
Ig count, 10³/μL	0.01 (0.00-0.19)	0.02 (0.00-0.30)	**0.009**[*]
CRP, mg/L	9.15 (0.46-343.12)	32.58 (1.17-386.79)	**<0.001**[*]
	n (%)	n (%)	
Gender, female	59 (60.2)	26 (50)	0.230[a]
Nausea	11 (11.2)	9 (17.3)	0.297[a]
Vomitting	9 (9.2)	6 (11.5)	0.647[a]
Murphy (+)	17 (17.3)	33 (63.5)	**<0.001**[a]
Abdominal pain	93 (94.9)	51 (98.1)	0.321[b]
Constipation	92 (93.9)	51 (98.1)	0.233[b]

Student t-test, [*]: Mann-Whitney U test, [a]: Pearson's chi-square test, [b]: Fisher's exact test

WBC: White blood cells, MPV: Mean platelet volume, RDW: Red cell distribution width, CRP: C-reactive protein, Ig: Immature granulocytes
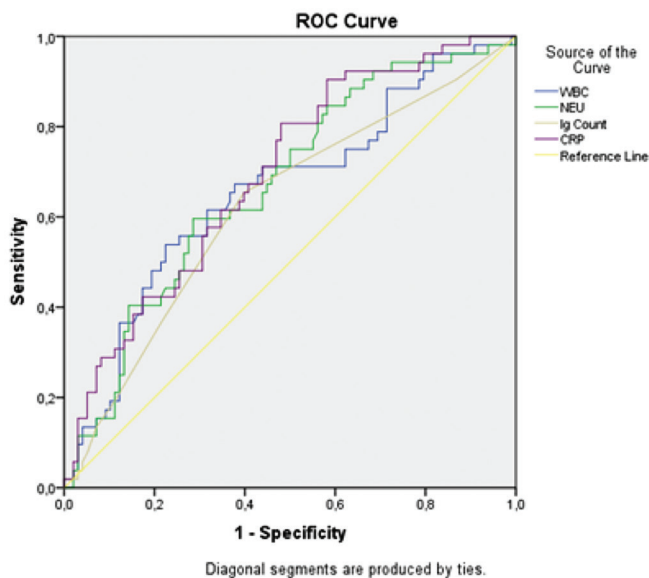

Figure 1. ROC curve of significant independent variables

ROC: Receiver operating characteristic, WBC: White blood cells, Neu: Neutrophil, Ig: Immature granulocytes, CRP: C-reactive protein

biliary colic and ABC in the regression analysis. It would not be appropriate to mention statistical significance and differences from the literature because many studies in the literature did not perform regression analysis.

A study conducted by Mahmood et al. [5] stated that the clinical diagnosis of distinguishing between complicated acute cholecystitis and simple acute cholecystitis is challenging. In this study, the potential use of inflammatory markers like CRP and NLR, to differentiate these two conditions was assessed. In this study, in which 176 patients were treated with emergency laparoscopic cholecystectomy, it was found that patients' age [odds ratio (OR): 1.047; p=0.003], high CRP (OR: 1.005; p=0.012), and NLR (OR: 1.094; p=0.047) values were independently associated with the severity of cholecystitis. The ROC analysis for CRP showed an area under the ROC curve value of 0.773 and indicated that a value above 55 mg/L for CRP is associated with predicting complicated cholecystitis with a sensitivity of 73.9% and specificity of 73.1%. These results suggest that CRP and NLR could be useful markers to predict the risk of complicated acute cholecystitis during emergency admission [5]. In our study, we found that CRP levels above 9.88 mg/L for ABC had a sensitivity of 80.8% and specificity of 52%. This is similar to the literature; however, we believe the difference in specificity may be due to the fact that all patients had gallstones and presented with abdominal pain.

A pivotal study exploring the correlation between gallbladder wall thickness and the CRP/albumin ratio identified the latter as a potentially valuable biomarker for detecting gallbladder inflammation [6]. Further emphasizing the utility of CRP in gallbladder pathologies, another investigation identified CRP levels exceeding 200 mg/dL as critical for reliably predicting

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Table 2. ROC analysis, sensitivity, and specificity values of variables for ABC					95% confidence interval	
Variables	Area	Sensitivite	Spesifite	p	Lower bound	Upper bound
WBC, ≥10.785 10³/µl	0.658	71.2	56.1	**0.001**	0.565	0.752
Neutrophile, ≥9.105 10³/µl	0.671	59.6	71.4	**0.001**	0.581	0.760
Ig count, ≥0.015 10³/µl	0.624	65.4	60.2	**0.012**	0.529	0.719
CRP, ≥9.88 mg/L	0.694	80.8	52.0	**0.000**	0.608	0.780
ABC: Acute biliary cholecystitis, WBC: White blood cells, CRP: C-reactive protein, ROC: Receiver operating characteristic, Ig: Immature granulocytes						

Table 3. Results of regression analysis for ABC	Univariate		Multivariate	
	p	OR (95% CI)	p	OR (95% CI)
WBC	0.008	1.120 (1.030-1.219)	0.912	0.980 (0.684-1.404)
Neutrophile	0.006	1.132 (1.037-1.236)	0.576	1.113 (0.765-1.621)
Ig count	0.196	744.617 (0.033-16684194.55)		
CRP	0.002	1.007 (1.002-1.011)	0.044	1.005 (1.000-1.010)
Murphy (+)	<0.001	0.121 (0.056-0.261)	<0.001	0.119 (0.053-0.268)
ABC: Acute biliary cholecystitis, WBC: White blood cells, CRP: C-reactive protein, OR: Odds ratio, CI: Confidence Interval, Ig: Immature granulocytes				

the onset of gangrenous cholecystitis, marking a significant advancement in early diagnostic capabilities [17]. In our study, we observed a statistically significant increase in all inflammatory markers in the ABC group compared with the biliary colic group. These results are consistent with the literature.

The iconic Murphy's sign, steeped in clinical lore, maintains its pivotal stance in the diagnosis of gallbladder diseases. Our findings reaffirm the high-risk association between a positive Murphy's sign and acute cholecystitis, thus advocating for its undiminished value in tandem with modern diagnostic approaches [18]. In our study, we also identified that this sign plays a central role in patient management. These findings emphasize the importance of using clinical examination as a complementary tool to modern diagnostic methods.

Study Limitations

Our study has several limitations that should be acknowledged. First, the study is retrospective in nature, which implies that the data obtained were inherently limited, affecting the comprehensiveness of the analysis. Second, the small number of cases and the confinement of the analysis to a single center may limit the generalizability of our findings. Furthermore, we were unable to evaluate the time from the onset of symptoms to hospital admission, which might have an impact on the values of inflammatory markers.

Conclusion

This study highlights the synergistic utility of biomarkers, such as Ig, CRP, WBC count, and the clinical signs of Murphy's in the diagnosis and management of ABC. The integrated application of these markers may enhance the precision of diagnostic

processes and improve patient management. Our findings suggest the potential for a more efficient triage of patients presenting with abdominal pain in emergency settings, potentially expediting appropriate treatment decisions.

Although the results are promising, they should be interpreted with an understanding that they stem from a single-center study with a limited sample size. Confirmation of these findings in larger, multicentric studies is essential to solidify their place in clinical practice.

Future research expanding and refining these preliminary observations could pave the way for identifying the optimal combination of biomarkers and clinical signs for the diagnosis and treatment of gallbladder diseases. Adopting a more holistic and multifaceted approach in clinical practice is likely to enhance success rates in the management of biliary disorders and improve patient outcomes.

Ethics

Authorship Contributions

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or Interpretation: R.Y., M.U., M.K.A., S.D., Literature Search: R.Y., B.Y., A.F.B.K., Writing: R.Y., B.Y., A.F.B.K., S.D.

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