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Diagnostic value of acute phase reactants and scores used in the diagnosis of cholangitis in patients with purulent cholangitis

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Abstract

Acute cholangitis is a clinical condition that occurs due to stasis and infection of the biliary system, which can recur if left untreated and may lead to life-threatening consequences. Early diagnosis, severity scoring based on the Tokyo Criteria at the time of diagnosis, and prompt initiation of treatment can help prevent mortality. This article aims to retrospectively review patients diagnosed with acute cholangitis by observing pus drainage during Endoscopic Retrograde Cholangiopancreatography (ERCP), determine the diagnostic values and prognostic effects of data obtained from complete blood counts and evaluate the diagnostic and severity criteria of acute cholangitis, including 331 patients who underwent the procedure and exhibited pus drainage, along with 300 healthy volunteers. We observed that the most common cause in the etiology of acute cholangitis was choledocholithiasis. There was a statistically significant difference between the healthy control group and the acute cholangitis group in terms of leukocyte count (WBC), red cell distribution width (RDW), platelet count (PLT), mean platelet volume/platelet count (MPV/PLT), neutrophil count/lymphocyte count ratio (NLR), and platelet count/lymphocyte count ratio (PLR) values. ROC analysis revealed that RDW, NLR, and PLR values had high sensitivity and specificity in distinguishing the acute cholangitis group from the healthy group. When we compared acute cholangitis severity groups, there was a statistically significant difference between the groups in terms of WBC, RDW, PLT, MPV/PLT, NLR, and PLR values. Due to the high sensitivity and specificity and easy accessibility of WBC, RDW, PLT, NLR, and PLR tests in diagnosing cholangitis, a closer and careful evaluation of these tests would be beneficial for early diagnosis and effective treatment of the disease. Additionally, this study confirms the high accuracy of the Tokyo Criteria in diagnosing acute cholangitis, highlighting the inadequacies of other clinical scoring systems.

Keywords: Acute cholangitis, Endoscopic Retrograde Cholangiopancreatography (ERCP), Tokyo Criteria

1. Introduction

Acute cholangitis is a condition that arises from the stasis and infection of the biliary system, which can lead to life-threatening consequences. A cholangitis attack can result in fatality, may recur if the causing obstruction remains untreated, and can progress to liver abscess or biliary cirrhosis (1). The pathogenesis of acute cholangitis involves choledocholithiasis, benign or malignant strictures, biliary-enteric anatomical anomalies, and the failure of a permanent biliary stent to function (2).

In a study on populations in Europe and North America, researchers found that symptomatic gallstone disease developed in 20% of patients with common bile duct stones, while only 0.2% experienced acute bacterial cholangitis (3).

In 1887, the clinical presentation characterized by fever, right upper quadrant pain, and jaundice coined the term Charcot's Triad. Subsequently, in 1959, the altered mental status and signs of septic shock accompanying this clinical picture led to the term Reynolds' Pentad. Despite the high specificity, the described Charcot's Triad and Reynolds' Pentad have low sensitivity, leading to the establishment of the Tokyo Criteria in 2007, 2013, and 2018 (2, 3). The Tokyo Criteria aims to provide a more accurate diagnosis of acute cholangitis and categorize it into three groups based on severity (4). Determining the severity of a patient's condition in acute cholangitis and initiating early medical treatment (fluid support, appropriate antibiotic therapy) is crucial in all cases.

Subsequently, identifying the underlying cause and ensuring biliary drainage is necessary (3, 5). In severe cases accompanied by organ failure, intensive care support should be administered (3). In encountered cases, healthcare providers should conduct laboratory tests, including a complete blood count, renal and hepatic biochemical tests, acute-phase reactants (such as erythrocyte sedimentation rate, CRP [C-Reactive Protein]), and INR. Obtaining a blood culture before starting antibiotic therapy is recommended (6). The mean platelet volume (MPV), MPV/PLT ratio, neutrophil count/lymphocyte count ratio (NLR), red cell distribution width (RDW), and platelet count/lymphocyte count ratio (PLR) obtained from the complete blood count is critical and easily accessible indicators aiding in the early detection of critical illness (7, 8).

This article aims to retrospectively review patients diagnosed with acute cholangitis by observing pus drainage during Endoscopic Retrograde Cholangiopancreatography

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(ERCP), determine the diagnostic values and prognostic effects of data obtained from complete blood counts, and evaluate the diagnostic and severity criteria of acute cholangitis.

2. Materials and Methods

After the Non-Interventional Studies Ethics Committee of Ondokuz Mayıs University Faculty of Medicine Hospital granted ethical approval with decision number 466 dated 13/10/2021, the study included a total of 331 patients who underwent ERCP with observed pus drainage during the procedure and 300 healthy blood donors between January 1, 2005, and August 1, 2021. The demographic characteristics of all patients enrolled in the study, their clinical presentations, laboratory tests at the time of diagnosis, and their admission statuses to the Intensive Care Unit (ICU) were examined. Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) V25. The Kolmogorov-Smirnov test was used to evaluate the suitability of standard distribution for quantitative data. The data comparing complete blood count parameters between the patient and healthy groups did not demonstrate normal distribution, so the researchers employed the Mann-Whitney U test for analysis.

In the groups categorized based on disease severity, the complete blood count parameters were evaluated using One-Way ANOVA for data conforming to the normal distribution and the Kruskal-Wallis H test for data that did not follow the normal distribution. The statistical significance of laboratory values that could differentiate acute cholangitis patients from the healthy group was determined by calculating the area under the ROC curve and the 95% confidence interval. A significance level of $p < 0.05$ was considered.

3. Results

This study involved 331 cases of acute cholangitis and 300 healthy volunteers. Among the acute cholangitis cases, 178 (53.8%) were male, and 153 (46.2%) were female. There was no statistically significant difference in terms of gender between the healthy control group and the acute cholangitis group. The average age of the patients was determined to be 50.5 ± 9.2 years.

Abdominal pain was present in 255 individuals (77.0%), and fever was observed in 158 cases (47.7%). Total bilirubin levels >2 mg/dL were considered jaundice and detected in 283 cases (85.0%). Eighteen patients (5.4%) required positive inotropic support, and altered consciousness was seen in 20 cases (6.0%). One hundred thirteen patients (33.5%) exhibited symptoms consistent with Charcot's triad, and seven (2.2%) showed symptoms in line with Reynold's Pentad.

Disease severity was evaluated based on the Tokyo Criteria classification and the need for intensive care unit (ICU) admission. In the first-degree cholangitis group, no patient required intensive care support. In the second-degree cholangitis group, 1 (0.7%) patient required intensive care unit admission, while in the third-degree group, 12 (20%) patients needed intensive care unit admission. A statistically significant difference in the need for ICU care was observed among the three groups ($p < 0.001$).

Acute cholangitis diagnosed cases revealed choledocholithiasis in 179 instances (54.1%), with 58 patients (17.5%) having a history of cholecystectomy and malignant stricture observed in eighty cases (24.2%). The analysis of the complete blood count statistics for the cases was conducted and presented in Table 1.

Table 1. Organizing descriptive data of patient group laboratory results

	n	Average	Std. Deviation	Median	Minimum	Maximum
WBC (10^9/L)	331	11,8	6,5			
RDW (%)	331			15	11,7	27
Monocyte (10^9/L)	328	0,62	0,46			
Lymphocyte (10^9/L)	328			1	0,15	5,7
MPV (fL)	324	9,2	1,7			
Neutrophil (%)	331			81	45	96
Neutrophil (10^9/L)	331	9,8	6,3			
PLT (10^9/L)	331	258,1	116,5			
NLR	328			8,3	1,1	78,7
PLR	328			248,7	11,5	1761,3
MPV/PLT	325			3,6	0	115,4

WBC:White blood cell count, RDW: Red cell distribution, MPV: Mean platelet volume, PLT: Platelet count, NLR: Neutrophil count/lymphocyte count ratio, PLR: Platelet count/lymphocyte count ratio, MPV/PLT:Mean platelet volume/platelet count ratio

Due to the non-normal distribution of the data, a comparison of complete blood count parameters between the patient group and the healthy control group is presented in median (minimum-maximum) format, as detailed in Table 2. Significant differences were found between the patient and control groups for WBC, RDW, lymphocyte, neutrophil, neutrophil percentage, PLT, NLR, PLR, and MPV/PLT values ($p<0.001$). However, there was no statistically significant difference between the two groups in terms of MPV value ($p=0.30$).

ROC analysis of NLO, PLO, RDW, and MPV/PLT values between the patient and control groups was performed, and the results are presented in Table 3 and Fig. 1. The value with the least difference between sensitivity and specificity in the analysis for each parameter was determined as the cutoff value.

Following the categorization of severity based on the Tokyo Criteria, a comparison of complete blood count data between the groups is presented in Table 4.

Table 2. Comparison of laboratory parameters according to groups

	Patient (n=331)	Control (n=300)	P
WBC (10^9/L)	10.3 (1.7-50.2)	6.5 (3.7-43)	***<0.001***
RDW (%)	15 (12-27)	13.9 (13-18)	***<0.001***
Monocyte (10^9/L)	0.52 (0.05-6.3)	0.5 (0.2-7)	***0.01***
Lymphocyte (10^9/L)	1 (0.15-5.7)	2.1 (1-4)	***<0.001***
MPV (fL)	9.2 (6-20)	9.1 (5-11)e	0.30
Neutrophil (%)	81 (45-96)	59.0 (38-75)	***<0.001***
Neutrophil (10^9/L)	7.9 (1.1-47.7)	3.9 (1.9-9.5)	***<0.001***
PLT (10^9/L)	244 (13-784)	217 (130-799)	***<0.001***
NLR	8.3 (1.1-78.7)	1.8 (0.7-4.5)	***<0.001***
PLR	248.7 (11.5-134.2)	100.9 (48.1-399.5)	***<0.001***
MPV/PLT	3.6 (1-115.4)	4.2 (1-251.3)	***<0.001***

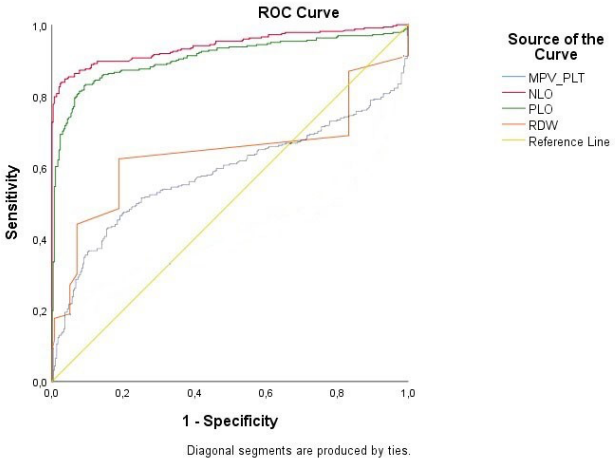

Fig. 1. ROC analysis grafics

Table 3. Diagnostic test results for acute cholangitis

	NLR	PLR	RDW	MPV/PLT
Cut Value	≥2.64	≥130.98	≥14.05	≥4.02
AUC (%95 CI)	0.94 (0.92-0.96)	0.91 (0.88-0.93)	0.65 (0.61-0.70)	0.59 (0.54-0.63)
Sensitivity	89 (85.1-92.2)	85.7 (81.1-89.3)	63.4 (58-68.6)	42.2 (36.7-47.7)
Specificity	88.6 (84.5-92)	85.6 (81.1-89.4)	81.2 (76.3-85.5)	42.1 (36.5-48)
PPV	89.6 (86.2-92.2)	86.7 (83.2-89.6)	79.0 (74.5-82.8)	44.2 (40.3-48.2)
NPV	88.4 (84.4-91)	84.5 (80.6-87.7)	66.7 (63.2-70)	40.1 (36.3-44.1)
Accuracy Rate	88.8 (86.1-92)	85.7 (82.6-88.3)	71.9 (68.2-75.3)	42.2 (38.2-46.1)

AUC: Area under curve, PPV:Positive predictive value, NPV:Negative predictive value

Table 4. Complete blood count parameters according to disease severity

	Disease Severity			Statistics	
	1. Degree (Mild)	2. Degree (Moderate)	3. Degree (Severe)	Test Statistics	P
WBC (10^9/L)	8.9±3.7[b]	13.1±6.3[a]	14.7±9.0[a]	30.555	***<0.001****
RDW (%)	14.7±2[b]	15.7±2.3[a]	15.8±2.2[a]	7.689	***<0.001****
Monocyte (10^9/L)	0.57±0.58	0.66±0.35	0.63±0.36	1.214	0.298*
Lymphocyte (10^9/L)	1.2 (0.19- 3.4)[a]	1 (0.15-5.7)[b]	0.74 (0.29-2.7)[c]	22.017	***<0.001^***
MPV (fL)	9.2±1.8[b]	9±1.6[b]	9.9±1.8[a]	6.356	***0.002****
Neutrophil (%)	74 (45-95)[a]	84 (53-96)[b]	88 (60-96)[b]	42.173	***<0.001^***
Neutrophil (10^9/L)	6.8±3.7[b]	11.1±6.2[a]	12.8±8.4[a]	33.199	***<0.001****
PLT (10^9/L)	273±105[b]	274.7±114.9[b]	186.7±118.4[a]	14.917	***<0.001****
NLR	4.7 (1.1 -72.8)[a]	9.7(1.2 -78.7)[b]	14.6 (1.9 -70)[b]	47.037	***<0.001^***
PLR	212 (54.7-989.5)[a]	265.3(22.1-1761.3)[b]	228.7 (11.5-835.7)[b]	8.092	***0.017^***
MPV/PLT	4.6±8.8[b]	3.8±1.8[b]	10.5±16.6[a]	5.145	***0.007****

a-c: There is no difference between groups with the same letter for each measurement value *One-Way ANOVA, ^Kruskal Wallis H Test

4. Discussion

Acute cholangitis is a potentially life-threatening condition arising from stasis and infection in the biliary system (1). Initially, reviewing vital signs in every patient suspected of acute cholangitis is advised. If signs indicating urgent intervention due to organ or system failure are identified, supportive therapy should be initiated without delaying a definitive diagnosis (25). An attack of cholangitis can lead to fatal consequences, and if the causing obstruction is left untreated, it can recur progress to liver abscess, or biliary cirrhosis (1).

The average age of acute cholangitis cases in the literature is reported to be between 50-60 years old, with no difference in the frequency of cholangitis between genders (9). Our study's average age of patients diagnosed with acute cholangitis is similar to the literature. Statistically, there is no significant difference between genders, consistent with the literature.

The most common cause of biliary tract obstructions is choledocholithiasis (28-70%), followed by benign or malignant strictures, strictures related to previous surgeries, sclerosing cholangitis, and past biliary stent obstructions (3, 5, 10). Acute or chronic pancreatitis, autoimmune cholangitis, and congenital anomalies cause benign strictures, pancreatic cancer, gallbladder cancer, cholangiocarcinomas, and liver metastases cause malignant strictures (11). Similarly to previous studies, our study found choledocholithiasis to be the most frequent etiology.

The most commonly observed symptoms and signs in patients diagnosed with acute cholangitis are fever, abdominal pain, and jaundice, also known as Charcot's Triad. The incidence of all three symptoms occurring together ranges from 15.4% to 72% of cases. In addition to Charcot's Triad, altered mental status and signs of shock (Reynolds' Pentad) are

observed in 3.5% to 7.7% of cases (2). Tokyo Criteria has been found to have a sensitivity of over 90% for diagnosing acute cholangitis (12). Consistent with the literature, we believe that while Charcot's Triad and Reynolds' Pentad describe a small portion of acute cholangitis cases, they are insufficient for diagnosis. Therefore, considering that all patients meet the Tokyo Criteria, we believe that the Tokyo Criteria have high sensitivity in diagnosing acute cholangitis.

In a study comparing patients with septic or non-septic acute cholangitis with an infectious non-control group conducted by Jiang et al., the white blood cell count was significantly higher in both septic and non-septic groups compared to the control group. However, no significant difference was observed between the septic and non-septic groups in acute cholangitis (13). In Boey et al.'s study, the white blood cell count was above 10x10^9/L in 82% of acute cholangitis cases (1). As seen in the literature, the white blood cell count is valuable in diagnosing and classifying the severity of acute cholangitis.

In a study comparing neonates diagnosed with sepsis and a control group, the RDW level was significantly higher in the suspected or proven neonatal sepsis group compared to the control group (14). In a study on preterm and late-onset sepsis-diagnosed neonates, when the RDW threshold was set at 19.5, it was associated with 87% sensitivity and 81% specificity (15). Due to the significantly higher RDW value in acute cholangitis patients compared to healthy individuals and its correlation with the severity of acute cholangitis, RDW should be used as an adjunct laboratory value in diagnosing acute cholangitis

Qin et al.'s study indicated that a platelet count below 50x10^9/L in acute cholangitis cases indicates severe infection (16). In a study of critically ill patients, irrespective of the reason for admission, thrombocytopenia was found in 23% with PLT<100x10^9/L and 10% with PLT<50x10^9/L, showing a significant association with longer hospital stays and higher mortality (17). Another study on septic patients requiring vasopressors and monitoring in intensive care units found thrombocytopenia (<15x10^9/L) in 58% of cases (18). It has been observed that as the severity of the disease increases in acute cholangitis patients, the platelet count decreases. This suggests that the disease course might be severe if there is thrombocytopenia at the time of diagnosis or if thrombocytopenia develops during patient follow-up.

Golwala et al. observed a mortality rate of 65% in pediatric patients with an MPV/PLT ratio exceeding 3.45 (19). In a retrospective analysis of 1143 patients in an intensive care unit categorized by their 1-year mortality status, the deceased group showed a higher MPV/PLT ratio compared to the surviving group (8). Considering the decreased platelet count and increased precursor cell production from the bone marrow in acute cholangitis patients and the correlation of MPV/PLT ratio with the severity of the disease, we anticipate the MPV/PLT ratio to be high in acute cholangitis patients and increasing with disease severity.

In a study examining pediatric patients with bacteremia, NLR was identified as an indicator of sepsis and a determinant of antibiotic therapy duration (20). A meta-analysis of 14 studies investigating the relationship between NLR and prognosis in sepsis found a significant association between increased NLR and higher mortality. The threshold value for NLR ranged from 4.36 to 23.8 in the studies reviewed, with no definitive optimal value determined through meta-analysis (21). The high NLR value is significant in diagnosing acute cholangitis, correlating with disease severity and possessing high sensitivity and specificity, making it a usable parameter in diagnosing and following acute cholangitis.

A high PLR value can serve as an auxiliary test for early recognition of sepsis. In a study comparing neonates diagnosed with neonatal sepsis and a control group, the group diagnosed with neonatal sepsis showed significantly higher PLR (22). In a study comparing the 30-day mortality of patients operated for acute mesenteric ischemia, a significant association was found between high PLR and high mortality (23). In a study comparing patients diagnosed with community-acquired pneumonia and a control group, the inpatient or outpatient-treated group showed higher PLR levels than the control group. However, no difference was found between inpatients and outpatients (24). In a study investigating early prognostic parameters for septic shock in patients treated with granulocyte colony-stimulating factor (G-CSF) following chemotherapy, a significant association was found between high PLR levels and 1-month mortality (25). On the other hand, a study conducted on patients with emphysematous pyelonephritis found a significant association between low PLR levels and sepsis. The study used a PLR threshold of <18.4 and considered it an independent risk factor for septic shock (26). However, a retrospective analysis of 249 patients monitored in the intensive care unit following emergency abdominal surgery found no significant association between mortality and PLR (27). After evaluating the data of patients in our study and reviewing relevant literature examples, we advocate considering elevated PLR levels as an essential factor in diagnosing acute cholangitis due to their notably high sensitivity and specificity rates among these patients.

This study, assessing patients diagnosed with acute cholangitis through pus drainage during ERCP, asserts that the WBC, RDW, PLT, NLR, and PLR tests merit meticulous consideration. Their high sensitivity, specificity, and easy accessibility collectively support their potential to facilitate early disease detection and effective treatment strategies. Additionally, alongside the inadequacies of other clinical scoring systems, our study reaffirms the high accuracy rate of the Tokyo Criteria in diagnosing acute cholangitis.

Conflict of interest
The authors declared no conflict of interest.

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None to declare.

Authors' contributions
Concept: M.Ö.K., Design: M.Ö.K., Data Collection or Processing: M.Ö.K., Analysis or Interpretation: M.Ö.K., Ö.Y.Ç., Literature Search: M.Ö.K., Ö.Y.Ç., Writing: M.Ö.K.

Ethical Statement
Approval was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee, the study started. The ethics committee decision date is 13/10/2021 and the number of ethical committee decisions is 2021/466.

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