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Evaluation of prognosis of acute colangitis patients via hematological parameters

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Abstract

Early differentiation of cases with severe acute cholangitis is important for optimal treatment. In this study, it was aimed to elucidate the prognosis with complete blood count parameters among patients with acute cholangitis. Clinical and laboratory findings of 200 patients with acute cholangitis at Ankara City Hospital between February 2019 and October 2019 were retrospectively analyzed. Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, red cell distribution width and mean platelet volume levels were recorded from blood analysis at the time of admission. According to Tokyo guidelines, patients were divided into 3 groups as mild, moderate and severe acute cholangitis. In order to evaluate the prognosis, the length of hospital stay, the status of hospitalization in the medical intensive care unit and blood culture growth were investigated with hematological parameters. Of the 200 patients, 109 (54.5%) were male and 91 (45.5%) were female. According to Tokyo criteria, 17 patients' status was evaluated as severe, 70 as moderate and 113 as mild acute cholangitis. The area under the receiver operating characteristics curve for neutrophil-lymphocyte ratio measurements was statistically significant in distinguishing the mild vs moderate disease (AUC=0.694; 95% Confidence Interval (CI):0.586-0.802 and p=0.008), with a diagnostic accuracy rate of 59.5%. The diagnostic accuracy rate of red cell distribution width (AUC=0.603; 95% CI: 0.523-0.683 and p=0.013) was 61.5% and the diagnostic accuracy rate of mean platelet volume (AUC=0.582 95% CI: 0.502-0.662 and p=0.047) was 57.5% achieving a statistical significance. Neutrophil-lymphocyte ratio, red cell distribution width and mean platelet volume analysis is routinely obtained from complete blood count almost in every patient. These are inexpensive and easily accessible diagnostic markers and thus, might be useful in the differentiation of mild and severe acute cholangitis patients and their prognosis.

Keywords: Acute cholangitis, neutrophil-lymphocyte ratio, red cell distribution width, mean platelet volume

Introduction

Acute cholangitis is defined as a bacterial infection of the biliary system that develops as a result of obstruction of the bile ducts for various reasons [1,2]. Endotoxins and microorganisms in the infected biliary system may enter the systemic circulation and cause bacteremia and sepsis [3,4]. The prognosis of acute bacterial cholangitis has a wide spectrum that can progress from a self-limiting course to an emergency or fatal disease [5].

Treatment of acute bacterial cholangitis should be determined in accordance with the severity of the disease. Patients with mild or moderate cholangitis should be followed up with antibiotics and general supportive treatment and biliary drainage treatment when necessary. Patients with severe disease should be followed up in the medical intensive care unit (ICU) with biliary drainage and organ support therapy [6,7]. It is very crucial to detect cases with high-risk acute cholangitis, which can result in death, at an early stage and to initiate treatment without any delay [8].

There is still a need for markers that can detect these cases early with easy or routine examinations at the time of first admission.

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In the literature, the relationship of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV) and red cell distribution width (RDW) have not been clearly identified as prognostic factors of acute cholangitis such as the severity of and length of hospital stay. The aim of this current study was to elucidate the effectiveness of NLR, PLO, MPV and RDW hematological parameters in the evaluation of severity and prognosis of acute cholangitis disease.

Material and Methods

Study design and patient selection

The study was conducted between February 2019 and October 2019 in the Internal Medicine Service of Ankara City Hospital.

Diagnostic criteria were organized according to the Tokyo guideline, which was revised in 2018. Patients with a definite diagnosis of acute cholangitis according to these parameters (systemic inflammation, cholestasis, imaging) were included in the study.

Endoscopic retrograde cholangiopancreatography (ERCP) has been performed in 1879 patients and 396 of them had cholangitis according to 2018 Tokyo guidelines. This research was approved by Ankara City Hospital Ethics Committee (E1/091/2019).

A total of 196 individuals have been excluded due to malignancy, collagen tissue disease, chronic renal failure, heart failure, chronic liver disease, inflammatory bowel disease, use of antithrombotic drugs or pregnancy. Data of 200 hospitalized cases were collected retrospectively through the hospital database.

Data collection

Demographic information (age and sex) of the cases, physical examination findings at admission, hematological parameters as leukocyte counts, hemoglobin levels, red cell distribution width, mean platelet volume, absolute neutrophil count (ANC), lymphocyte count, platelet count were obtained. Additionally, derived parameters such as NLR (neutrophil/lymphocyte ratio) and PLR (platelet/lymphocyte ratio) were calculated by hematology analyzer. Biochemical parameters (total and direct bilirubin, International Normalized Ratio (INR), albumin, urea, creatinine) were recorded to determine clinical severity. The cases' ultrasound imaging (USG) findings, magnetic resonance imaging cholangiopancreatography (MRCP), computerized tomography (CT) imaging and ERCP reports were analyzed. Severity of the disease, blood culture growth, length of stay in hospital and medical ICU, and mortality during the hospitalization were recorded according to the Tokyo guidelines.

Statistical analysis

The normal distribution of continuous numerical variables was examined with Kolmogorov-Smirnov analysis. Homogeneity of variances was analyzed by Levene's test. Descriptive statistics were shown as median (minimum–maximum) for continuous numeric variables. Categorical variables were expressed as number of cases and (%). Mann Whitney U test, Kruskal Wallis test and Dunn-Bonferroni tests were utilized to investigate the differences between the groups. Categorical data were analyzed via Pearson's Chi-Square test and Fisher's test. It was investigated whether laboratory measurements such as NLR, PLR, MPV, RDW were statistically significant in distinguishing cases according to disease severity, by calculating the area under the receiver operating characteristics (ROC) curve and 95% confidence intervals. The correlation between continuous numerical variables was analyzed using the Spearman correlation test.

The factor(s) that were the most determinant in estimating the change in length of hospital stay were examined by multivariate linear regression analysis. The combined effects of all possible factors that were thought to be determinative in predicting the positivity of culture among all cases and in cases where culture could be taken were investigated by multivariate logistic regression analysis. Data analysis was performed in IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA) package program. A 'p' value<0.05 was considered statistically significant.

Results

Of 200 cases included in this study, 109 were male and 91 were female. According to Tokyo criteria, 113 (56.5%) of the individuals had mild cholangitis, 70 (35%) had moderate to severe diseases, and 17 (8.5%) had severe cholangitis. Regarding the data 3 (1.5%) of the subjects deceasedd during their follow-up. Growth was detected in 22 (34.9%) of 65 cases.

The average hospitalization period was 8 days, the average medical ICU stay was 3 days. The characteristics of the patients were leaborated in Table 1 and Table 2. The relationship between demographic and laboratory characteristics of the cases regarding to disease seriousness was summarized in Table 3.

Table 1. Characteristics of the patients

	n=200
Age (year)	63.0±18.1
Age range (year)	19-99
Gender	
Male	109 (%54.5)
Female	91 (%45.5)
Culture growth	
No	41 (%65.1)
Yes	22 (%34.9)
Disease activity	
Mild	113 (%56.5)
Moderate	70 (%35.0)
Severe	17 (%8.5)
Length of hospital stay (days)	8 (2-47)
Number of patients admitted to ICU	14 (%7.0)
ICU length of stay (days)	3 (1-17)
Deceased	3 (%1.5)

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Table 2. Frequency distributions of the cases in terms of etiology

	n	%
Choledocholithiasis	181	90.5
Postoperative benign stenosis	11	5.5
Cyst compression	2	1.0
Mirizzi syndrome	2	1.0
Stenosis secondary to pancreatitis	2	1.0
Lemmel syndrome	1	0.5
Pancreatic cyst	1	0.5
Total	200	100.0

The area under the ROC curve regarding NLR was statistically significant in distinguishing the group with mild-moderate disease and severe course (area under the curve (AUC)=0.694; 95% (CI): 0.586-0.802 and p=0.008) (Figure 1). The best cut-off point for NLO has been detected as 11.05, with 82.4% sensitivity and of 57.4% specificity. Positive and negative predictive valueswere 15.2% and 97.2% respectively, and the diagnostic accuracy rate was 59.5%.

The AUC of RDW measurements was statistically significant in distinguishing the group with mild-moderate disease severity from the group with severe disease (AUC=0.737; 95% confidence ınterval: 0.613-0.862 and p<0.001) (Figure 1).

Table 3. Demographic and laboratory characteristics of cases according to disease seriousness

	Mild (n=113)	Moderate (n=70)	Severe (n=17)	p
Age (year)	60.0 (22.0-99.0)[a,b]	74.0 (19.0-98.0)[a]	76.0 (42.0-90.0)[b]	<0.001†
Gender				0.379‡
Male	60 (%53.1)	37 (%52.9)	12 (%70.6)	
Female	53 (%46.9)	33 (%47.1)	5 (%29.4)	
NLR	6.6 (1.3-45.4)[a,b]	18.4 (4.6-82.5)[a]	17.4 (6.6-57.0)[b]	<0.001†
PLR	231.5 (22.4-1058.3)[a]	315.3 (79.2-1096.1)[a,c]	206.7 (78.3-1376.2)[c]	<0.001†
MPV	7.9 (6.6-12.0)	8.3 (6.9-11.0)	8.6 (5.8-11.6)	0.088†
RDW	14.0 (5.2-20.2)[b]	14.3 (12.8-22.1)[c]	14.8 (12.8-25.3)[b,c]	0.002†

† Kruskal Wallis test, ‡ Pearson's Chi-Square test, a: mild-moderate (p<0.001), b: mild-severe (p<0.01), c: moderate-severe (p<0.05)

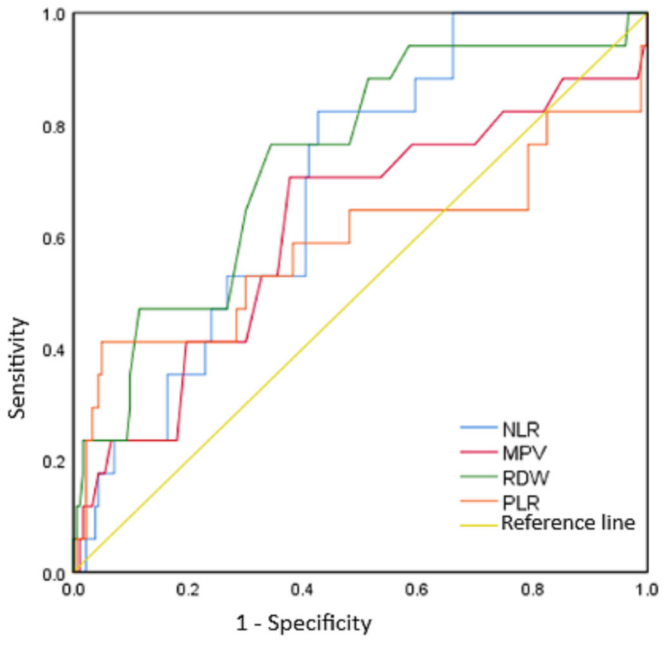

Figure 1. ROC analysis of hematological parameters in differentiating mild and moderate acute cholangitis patients from severe acute cholangitis patients

The best cut-off point for RDW is 14.55, the sensitivity of RDW is 76.5%; selectivity 65.6%; positive and negative predictive values, respectively; 17.1% and 96.8%, and the diagnostic accuracy rate was 66.5%.

The AUC regarding NLR measurements was statistically significant in distinguishing mild disease moderate to severe disease (AUC=0.865; 95% CI: 0.816-0.914 and p<0.001) (Figure 2). The cut-off point for NLR was 9.18, with a sensitivity of 87.4% and specificity of 72.6%. Positive and negative predictive values were 71.0% and 88.2% respectively, and the diagnostic accuracy rate was 79%.

The AUC regarding PLR measurements was statistically significant in distinguishing mild disease severity from moderate to severe disease (AUC=0.652; 95% CI: 0.573-0.731 and p<0.001) (Figure 2). The cut-off point for PLR was 424.907, with a sensitivity of 39.1% and specificity of 90.3%. Positive and negative predictive values were 75.6% and 65.8% respectively, and the diagnostic accuracy rate was 68%.

The AUC regarding MPV measurements was statistically significant in distinguishing mild disease patients from moderate to severe individuals (AUC=0.582; 95% CI: 0.502-0.662 and

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p=0.047) (Figure 2). The cut-off point for MPV was 7.95 with a sensitivity of 64.4% and a specificity of 52.2%. Positive and negative predictive values were 50.9% and 65.6% respectively; with a diagnostic accuracy of 57.5%.

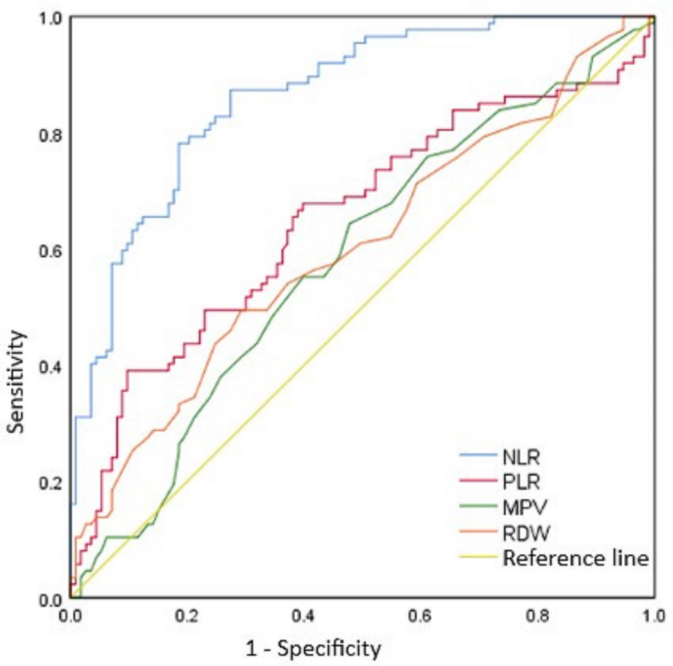

Figure 2. ROC curve of hematological parameters in distinguishing the group with mild disease from the group with moderate-severe disease

The AUC regarding RDW measurements was statistically significant in distinguishing mild disease group from the moderate to severe disease group (AUC=0.603; 95% CI: 0.523-0.683 and p=0.013) (Figure 2). The cut-off point for RDW was 14.55, with a sensitivity of 49.4% and specificity of 70.8%. Positive and negative predictive values were 56.6% and 64.5% respectively, and the diagnostic accuracy rate was 61.5%.

When the patients were evaluated according to ward and medical ICU admission, NLR and RDW levels were statistically significantly higher in patients hospitalized in the ICU (p<0.01). There was a statistically significant and same-sided correlation between the length of hospital stay and age, NLR and RDW (p<0.05).

NLR level of the group with growth in culture was statistically significantly higher (p=0.006). Regardless of disease severity, as NLR level increases, the probability of culture growth increases statistically significantly (OR=1.041; 95% CI: 1.005-1.078 and p=0.024).

Discussion

Acute cholangitis can present with various symptoms, ranging from a simple infection that responds to fluid replacement and antibiotic therapy to a severe situation requiring intensive care follow-up and emergency drainage [6].

Since acute cholangitis is a serious infection that can result in mortality, early diagnosis of the disease and initiation of antibiotic therapy, and providing emergency drainage treatment as early as possible is crucial [9,10].

Although mortality rates have decreased over the years, it is still high in severe acute cholangitis as 20-30% [11]. Previous literature elaborated the use of various inflammatory bio-markers in evaluating the severity and prognosis of infectious diseases. Some of these markers could be stated as NLR, PLO, MPV, RDW that obtained from simple blood count [12,13].

The utility of NLR, PLO, MPV and RDW hematological parameters to be leveraged as bio-markers to determine the severity of acute cholangitis and predict patients who need to be followed in the medical ICU have been emphasized for the first time in the literature in this research. Thus, it is predicted that these hematological parameters could be easily obtained during the first time of admission. This may be useful in distinguishing patients who will require close follow-up and early intervention, and in determining the treatment approach.

Neutrophils also play an important role in acute inflammation. They also indirectly take part in the regulation of the adaptive immune response [14]. Various physiological changes occur in the subgroups of circulating leukocytes under stressful conditions. Stress situations increase neutrophils and decrease lymphocytes [15]. Therefore, NLR has been investigated in various infectious and inflammatory conditions.

The severity of the disease determines the management of acute cholangitis. While urgent biliary drainage is required for control of infection, early biliary drainage is recommended in moderate to severe patients [7]. Lee examined the relationship between disease severity and NLR in pneumonia patients, and NLR levels resulted higher in intensive care patients who were considered as severe [16]. Sato et al. conducted [17] a study on acute cholecystitis and classified participants according to Tokyo guideline. NLR resulted different between the patients. In addition, the cut-off point was calculated as 10.25 with 81.5% sensitivity and 57% specificity. Also, 93.3% sensitivity and 56.9% specificity were shown when the cut-off was accepted as 11.26 in severe patients [17].

Acute cholangitis cases were evaluated according to Tokyo Criteria fort he first time in our study in the literature. NLR was shown to be a diagnostic biomarker in the detection of both mild and severe cholangitis patients. Accordingly, NLR measurement at the time of first diagnosis may be useful in determining the prognosis of patients with acute cholangitis.

When the relationship between NLR and length of stay was evaluated, there was a statistically significant and same-sided correlation between length of hospital stay and NLR. However, when NLR was thought to be associated with disease severity and included in the regression model, NLR was not detected as a risk factor independent of possible risk factors.

Azab et al. reported that medical ICU admission was higher in

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the group with high NLR in patients with pancreatitis [18]. In our study, NLR was significantly higher in acute cholangitis patients admitted to the medical ICU. However, NLR was not an independent risk factor in the multivariate logistic regression analysis of all possible factors that were thought to be determinative in differentiating admission to the medical ICU.

An another paper examining the diagnosis of bacteremia in emergency room patients, it was emphasized that NLR could be as effective as procalcitonin [19]. In the current study, the NLR level of the group with growth in culture was statistically significantly higher than the group with no growth in culture. All possible factors that were thought to be determinative in distinguishing the groups with and without growth in culture were included in the multivariate logistic regression test. According to the test, as the NLR level increases, regardless of the severity of the disease, the probability of culture growth increases statistically. In our study, it was demonstrated that NLR could be a determinant in distinguishing groups with and without growth in culture fort he first time. Thus, taking blood cultures from patients with acute cholangitis with high NLR at the time of admission and early antibiotic therapy may be a guiding parameter.

In many studies, it has been shown that MPV was a marker of platelet generation and function, as well as reflecting inflammatory conditions. Data of prospective literature showed a correlation between the increase in MPV and the risk of thrombosis. Hence the reduction in MPV in patients with inflammation and reversal in the anti-inflammatory course [20].

Mean platelet volume has been found to be high in cases where cardiovascular diseases such as diabetes, hypertension, obesity, smoking, and hypercholesterolemia are accepted as risk factors [21].

RDW is a potent prognostic marker in many diseases such as cardiac/renal diseases, or viral hepatitis [22-27]. According to our results, RDW might be helpful in distinguishing patients with mild and severe acute cholangitis at admission.

PLR has a utility as an inflammatory sign [28]. Therefore, relationship of PLR with several diseases such as malign diseases, collagen tissue diseases, cardiovascular diseases has been the subject of previous studies [29-34].

It revealed a same-sided correlation between the length of hospital stay and age, NLR and RDW. According to the current results, age was found to be a factor independent of other factors in estimating the length of hospital stay.

Limitations

The main limitation of this research could be attributed to its retrospective nature, in a single center. In addition, in this study, all patients with a definite diagnosis of acute cholangitis were evaluated without any discrimination according to etiology. The relatively low number of sample size might have affected statistical analysis outcomes. There is a need to confirm our findings with multicenter, controlled studies.

Conclusion

In conclusion, NLR and RDW can be used as an indicator in the early detection and differentiation of both mild and severe patients, while MPV and PLR could be utilized in mild patients. In addition, this research have elaborated fort he first time in the literature that NLR could be a determinant in distinguishing groups with and without growth in culture, and it was shown that NLR is an independent risk factor in predicting bacteremia.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This research was approved by Ankara City Hospital Ethics Committee (E1/091/2019).

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