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Lymphocyte count and NLR as predictive value for the severity of acute cholangitis

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Abstract. – OBJECTIVE: Acute cholangitis is a serious infectious condition in which systemic complications occur and can lead to mortality. In this study, we tried to elucidate the relationship between lymphocyte count and neutrophil-lymphocyte ratio (NLR) with disease severity in patients with acute cholangitis.

PATIENTS AND METHODS: In this retrospective analysis, 633 patients who met the definitive diagnosis criteria for acute cholangitis were enrolled as the study group. In the same period, 155 patients without acute cholangitis who had normal inflammatory markers and underwent endoscopic retrograde cholangiopancreatography (ERCP) were included in the study as the control group. The lymphocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) of the acute cholangitis group, the control group, and the acute cholangitis group were compared according to the severity of cholangitis.

RESULTS: There was a statistically significant correlation between the severity of cholangitis and the degree of lymphocytopenia ($p<0.05$). It was observed that as the disease severity increased, the proportion of patients with normal lymphocytopenia degree decreased, and abnormal findings increased. It was seen that the NLR and PLR results of the patients increased as the severity of cholangitis increased.

CONCLUSIONS: As a result, one can conclude that the increase in the severity of cholangitis caused an increase in NLR and PLR and a decrease in lymphocytes. Although the increase in NLR and lymphocytopenia results were considered statistically significant, the increase in PLR was not at an acceptable level.

Key Words:
Acute cholangitis, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Lymphocytopenia.

Introduction

Acute cholangitis (AC) is the infection of the bile ducts due to various etiological factors. The result is that there is stasis and bacterial colonization in the biliary system. It is a serious infectious condition in which systemic complications occur and can lead to mortality[1]. Acute cholangitis was defined by systemic inflammation, cholestasis, and imaging findings described by the Tokyo 2018 Guidelines[2]. Clinical findings are non-specific. Nausea, vomiting, mild hepatomegaly, and accompanying right upper quadrant of the abdomen are present. Although the organ is in the epigastrium, the pain can radiate to the right shoulder[1].

There are two forms of cholangitis. Ascending cholangitis is a milder type, and it is the type that occurs with the occasional mixing of bacteria that multiply after partial obstruction into the blood. Suppurative cholangitis, on the other hand, is the more severe form and progresses with rapid bacterial growth because of complete obstruction. This form causes bacteremia, septic shock, multi-organ failure, and mortality in 70% of cases. Mortality rates have been reported as 10-30% in the literature[3].

Among the factors causing acute cholangitis are biliary tract obstruction, stasis, and bacterial proliferation[4]. Normally, the gallbladder is sterile, and the sphincter of Oddi is one of the protective mechanisms that block bacterial passage through the duodenum. Another protective factor is bile secretion, which has a bacteriostatic effect. Secretory IgA and biliary mucosa help maintain the sterility of bile flow. The presence of stone facilitates bacterial colonization[5].

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In some studies, it has been shown that biliary tract obstruction causes immunosuppression, cellular failure, and anergy[7]. Bacterial colonization increases with the concomitant flow of bile salts to the intestines. Distension, congestion, and edema develop due to obstruction of the bile ducts for any reason[6]. As a result, the clearance of hepatic cells decreases due to increased pressure, and accordingly, there is an increased release of immunomediators[6,7].

At the same time, there is an increase in vascular permeability with increased pressure, which allows the translocation of bacterial toxins. Generally, the increased pressure is around >20 cm H_2O[8]. The bacteria colonizing bile ducts increase the amount of bile and inhibit hepatocyte transport activity, reducing the amount of bile acid and bilirubin and causing the release of inflammatory mediators (TNF, IL-1, IL-6, IL-8). Bacteria can enter the bloodstream through veins and lymphatic systems due to increased pressure and mediators, leading to bacteremia[9].

Several studies[10,11] have investigated predictors of acute cholangitis severity, suggesting procalcitonin, presepsin, IL-7, and the delta neutrophil index (DNI) as prognostic markers, but these cannot be performed routinely due to their high cost or dependence on specific analyzers.

There is a need for a new, inexpensive, and simple predictor of severe acute cholangitis, to stratify patients for urgent biliary drainage, close monitoring, and selective transfer to the intensive care unit (ICU) as early as possible. The neutrophil-lymphocyte ratio (NLR) is reported to be predictive of adverse outcomes in acute pancreaticobiliary diseases[10,11]. Additionally, lymphocyte count can be used as an inflammatory biomarker, and it could be used not only for diagnosis but also to provide outcomes while monitoring patient response to antimicrobial therapy and biliary drainage[11].

Lymphocyte count is an easily accessible and inexpensive parameter that is routinely obtained in patients with acute cholangitis. We assume that the lymphocyte count decreases as the severity of acute cholangitis increases, and the severity of acute cholangitis can be determined using this single parameter. Although there are few studies[10,11] showing the relationship between lymphopenia and acute cholangitis in the literature, there is no study showing the relationship between NLR and lymphopenia and the severity of acute cholangitis. Clinical research[10,11] confirmed the sensitivity of the NLR for the diagnosis/stratification of systemic infection, sepsis, and bacteremia, as well as its robust predictive and prognostic value. The NLR is predictive of disease severity, septic shock, organ failure, or ICU admission in acute pancreatitis and cholecystitis.

Various hematological and biochemical parameters such as white blood cell (WBC), c-reactive protein (CRP), and albumin were utilized in the diagnosis and severity grading of acute cholangitis. However, no study has yet investigated the association of the NLR and lymphocyte level with severe acute cholangitis. In this study, we tried to elucidate the relationship of NLR and lymphocyte count with disease severity in patients with acute cholangitis. Additionally, the utilization of lymphocyte count in the diagnosis of acute cholangitis, and the relationship of lymphocyte level with mortality have been evaluated.

Patients and Methods

In this retrospective analysis, 633 patients who were followed up in Ankara City Hospital Gastroenterology Clinic between February 2019 and December 2020 and met the definitive diagnosis criteria for acute cholangitis according to the Tokyo 2018 Guideline[2] were enrolled as the study group. In the same period, 155 patients without acute cholangitis who had normal inflammatory markers and underwent endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis, stent removal, or stent replacement were included in the study as the control group.

Patients age, gender, ultrasonography (USG) or computed tomography (CT) findings, hemogram, renal function tests, liver function tests, CRP, severity and source of acute cholangitis, outcome of acute cholangitis attack (discharge or exitus) data have been recorded from the hospital database.

Patients aged >18 years who meet the definitive diagnostic criteria for acute cholangitis according to the Tokyo 2018 guideline and have no other focus of infection have been included in the study[2]. According to the Tokyo 2018 guideline, those with possible acute cholangitis and other infectious diseases (pneumonia, urinary tract infection, soft tissue infection, etc.) and hematological diseases have not been included in the study[2].

Laboratory and radiological findings of the patients before biliary drainage and at the time of admission to the hospital were recorded.

The patients were divided into groups as grade 1 (mild), grade 2 (moderate), and grade 3 (severe) acute cholangitis according to Tokyo 2018 guideline[2]. The lymphocyte count was grouped as grade 1 (800-1200/mm^3), grade 2 (500-800/mm^3), grade 3 (200-500/mm^3), and grade 4 (<200/mm^3) according to the grouping system recommended by the World Health Organization. The lymphocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) of the acute cholangitis group, the control group, and the acute cholangitis group were compared within themselves according to the severity of cholangitis.

Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration. Informed consent was obtained from all participants. The Ethics Committee approval has been granted on 27.10.2020 with protocol number E1/1210/2020.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences [SPSS 23.0 (IBM Corp., Armonk, NY, USA)] for the Windows 23.0 package program. Frequency and percentage were given for categorical data and median, minimum, and maximum descriptive values for continuous data. The compatibility of the data with the Gaussian distribution was examined with the Kolmogorov-Smirnov test. For comparisons between groups, the Mann-Whitney U test was used for two groups, the Kruskal-Wallis H test for more than two groups, and the Chi-Square or Fisher's Exact test was used for comparison of categorical variables. The results were considered statistically significant when the *p*-value was lower than 0.05.

Results

A total of 788 participants, including 633 cholangitis and 155 control group patients were included in this retrospective analysis. The distribution of demographic and clinical findings of the participants are given in Table I. When the table was examined, no statistically significant relationship was found between the groups in terms of individuals' gender distribution ($p>0.05$). There was a statistically significant difference between the two groups in terms of age ($p<0.05$). The mean age of the cholangitis group was higher than the mean age of the individuals in the control group. There was a statistically significant difference between the two groups in all laboratory parameters ($p<0.05$).

The results of the Chi-square analysis evaluating whether there was a relationship between the cholangitis or control group and the degree of lymphocytopenia of the participants were given in Table II. When the table was examined, a statistically significant correlation was found between the individuals in the cholangitis or control group and the degree of lymphocytopenia ($p<0.05$). While most of the control group had a normal lymphocyte count, the majority of the cholangitis group had lymphocytopenia.

The results of the Chi-square analysis evaluating whether there was a relationship between the severity of cholangitis and the degree of lymphocytopenia of the participants were given in Table II. When the table was examined, a statistically significant relationship was found between the severity of cholangitis and the degree of lymphocytopenia ($p<0.05$). It was observed that as the disease severity increased, the proportion of patients with normal lymphocytopenia degree decreased, and abnormal findings increased.

The results of the Chi-square analysis evaluating whether there is a relationship between the final status of the participants and the degree of lymphocytopenia are given in Table II. When the table was examined, no statistically significant relationship was found between the final status of the individuals and the degree of lymphocytopenia ($p>0.05$).

The Mann-Whitney U test results, which evaluate whether there was a significant difference between the NLR and PLR results according to the final status of the participants, were given in Table III. When the table was examined, it was determined that there was a statistically significant difference between the NLR results according to the final status of the individuals ($p<0.05$). There was no statistically significant difference between PLR results according to the final status of the individuals ($p>0.05$). NLR and PLR results of individuals who had deceased were found to be higher than the results of individuals who were discharged.

Table I. Distribution of demographic and clinical findings of the patients.

Characteristics (n = 788)	Total (n = 788) n (%) or median (min-max)	Control (n = 155) n (%) or median (min-max)	Cholangitis (n = 633) n (%) or median (min-max)	p
Male	430 (54.6)	75 (48.4)	355 (56.1)	
Female	358 (45.4)	80 (51.6)	278 (43.9)	
Age, year	67 (19-99)	61 (22-89)	68 (19-99)	< 0.001
Cholangitis severity				
Control	155 (19.7)	155 (100)	NA	
Mild	270 (34.3)	NA	270 (42.7)	
Moderate	156 (19.8)	NA	156 (24.6)	
Severe	207 (26.3)	NA	207 (32.7)	
Cholangitis Source Hospital-associated	162 (25.6)	NA	162 (25.6)	
Nosocomially-acquired	48 (7.6)	NA	48 (7.6)	
Community-acquired	423 (66.8)	NA	423 (66.8)	
Laboratory				
Glucose (mg/dL)	115 (22-815)	99 (61-331)	119 (22-815)	< 0.001
Creatinine (mg/dL)	0.91 (0.32-6.20)	0.76 (0.46-1.99)	0.96 (0.32-6.20)	< 0.001
AST (U/L)	109 (6.7-2,537)	25.5 (7-758)	133 (6.7-2,537)	< 0.001
ALT(U/L)	123.5 (2-1,496)	32 (2-899)	145 (5-1,496)	< 0.001
GGT (U/L)	361 (8-2,415)	77 (8-1,524)	442 (15-2,415)	< 0.001
ALP (U/L)	241 (17-2,084)	119 (17-877)	274.5 (31-2,084)	< 0.001
Total Bilirubin (mg/dL)	4 (0.2-31.3)	0.8 (0.2-18.9)	4.6 (0.4-31.3)	< 0.001
Direct Bilirubin (mg/dL)	2.8 (0.1-24.1)	0.3 (0.1-16.2)	3.3 (0.1-24.1)	< 0.001
INR	1.2 (0.8-10)	1 (0.9-2.7)	1.2 (0.8-10)	< 0.001
WBC (10^6/L)	10,085 (3,900-55,790)	6,870 (3,650-12,680)	11,630 (3,900-55,790)	< 0.001
Neutrophil (10^6/L)	8,295 (529-51,250)	4,000 (529-10,540)	9,780 (1,360-51,250)	< 0.001
Lymphocyte (10^6/L)	995 (80-10,000)	1,820 (970-3,900)	790 (80-10,000)	< 0.001
NLR	9.4 (0.4-119.1)	2 (0.4-7.4)	13.5 (0.7-119.1)	< 0.001
PLR	0.2 (0-3.9)	0.2 (0-0.3)	0.3 (0-3.9)	< 0.001
Platelet (10^9/L)	230 (17-883)	269 (66-572)	218 (17-883)	< 0.001
CRP (mg/L)	62.8 (0.7-443.9)	3.2 (0.7-9.8)	87.4 (3-443.9)	< 0.001

AST: aspartate aminotransferase; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; INR: international normalized ratio; WBC: white blood cells; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; CRP: c-reactive protein.

The results of the Kruskal-Wallis H test, which evaluates whether there was a significant difference between the NLR and PLR results according to the severity of cholangitis, were given in Table IV. When the table was examined, it was determined that there was a statistically significant difference between the NLR and PLR results according to the cholangitis severity of the individuals ($p<0.05$).

It was seen that the NLR and PLR results of the patients increased as the severity of cholangitis increased. When the association between the correlation analysis and the severity of cholangitis and the results of NLR and PLR was examined, it was observed that there was a positive relationship in both ratios ($p<0.05$). While the relationship between cholangitis severity and NLR was low (r=0.414), the relationship between PLR and PLR was not found at an acceptable level (r=0.101).

As a result, it was determined that the increase in the severity of cholangitis caused an increase in the degree of lymphocytopenia, NLR, and PLR results. Although the increase in the degree of lymphocytopenia and NLR was considered statistically significant, the increase in PLR was not at an acceptable level.

Discussion

Systemic inflammation is regulated *via* lymphocytes, and a decrease in their concentration causes disease progression. Inflammatory status in the body leads to lymphopenia, regarding this, it may be said that any fluctuation of NLR could elaborate the immuno-inflammatory changes in acute cholangitis. At this stage, it is disguising why the usefulness of the NLR, and

Table II. Evaluation of the relationship between the degree of lymphocytopenia and the study groups.

Grade of lymphocytopenia	Study groups (n = 633)		p
	Control (n=155) n (%)	Cholangitis (n=633) n (%)	
Normal	144 (92.9)	184 (29.1)	< 0.001
Grade 1 (Lower limit of normal -800)	11 (7.1)	130 (20.5)	
Grade 2 (500-800)	0 (0)	167 (26.4)	
Grade 3 (200-500)	0 (0)	133 (21.0)	
Grade 4 (< 200)	0 (0)	19 (3.0)	
Grade of lymphocytopenia	**Severity of cholangitis (n = 633)**		**p**
	Mild (n = 270) n (%)	Moderate (n = 156) n (%)	Severe (n = 207) n (%)	
Normal	107 (39.6)	42 (26.9)	35 (1.9)	< 0.001
Grade 1 (Lower limit of normal -800)	68 (25.2)	33 (21.2)	29 (14.0)	
Grade 2 (500-800)	59 (21.9)	42 (26.9)	66 (31.9)	
Grade 3 (200-500)	33 (12.2)	38 (24.4)	62 (30.0)	
Grade 4 (< 200)	3 (1.1)	1 (0.6)	15 (7.2)	
Grade of lymphocytopenia	**Status (n = 591)**		**p**
	Discharged (n = 559) n (%)	Deceased (n = 32) n (%)	
Normal	156 (27.9)	7 (21.9)	0.307
Grade 1 (Lower limit of normal -800)	119 (21.3)	4 (12.5)	
Grade 2 (500-800)	149 (26.7)	14 (43.8)	
Grade 3 (200-500)	118 (21.1)	6 (18.8)	
Grade 4 (< 200)	17 (3.0)	1 (3.1)	

Table III. Evaluation of NLR and PLR results according to the recent status of the participants.

	Status	N	Median	Min-Max	p
NLR	Discharged	559	**13.28**	**0.70-119.10**	**< 0.001**
	Deceased	32	**22.54**	**1.89-112.81**	
PLR	Discharged	558	0.27	0.02-3.86	0.324
	Deceased	32	0.32	0.02-1.55	

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

Table IV. Evaluation of participants' NLR and PLR results by cholangitis severity.

	Cholangitis	N	Median	Min-Max	p
NLR	Mild	270	**7.42**	**0.99-56.35**	**< 0.001**
	Moderate	156	**17.68**	**0.65-102.71**	
	Severe	207	**21.64**	**0.70-119.10**	
PLR	Mild	270	**0.24**	**0.05-3.86**	**< 0.001**
	Moderate	156	**0.31**	**0.02-1.42**	
	Severe	207	**0.28**	**0.02-2.88**	

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

lymphopenia has rarely been investigated in acute cholangitis. Beliaev et al[12] reported that lymphocyte count, NLR, and CRP had the highest discriminative power among all laboratory parameters in patients with acute cholangitis. On the contrary, WBC and albumin had the poorest predictive value. They stated their cut-off levels for the diagnosis of acute cholangitis as $\geq 9.6 \times 10^9$/L for WBC, $\geq 4.9 \times 10^9$/L for neutrophil count, $\leq 1.3 \times 10^9$/L for lymphocyte count, ≤30.5 g/L for albumin, ≥23.5 mg/L for CRP and ≥5.3 for NLR.

Lymphocyte count and NLR could be utilized to identify patients who need close monitoring and urgent biliary drainage on admission[13]. Additionally, it can guide the medical team to transfer patients from the emergency service to the intensive care unit. Lymphocyte count and NLR can provide supportive data on the clinical status of the patient at the early stage (1-4 days). Lymphocyte count and NLR have a dynamic course with the severity of acute cholangitis. Normalizing values indicate a mild to moderate clinical status, while elevated NLR and decreased lymphocyte count indicate severe disease[13,14]. In this study, we found a statistically significant correlation between the individuals in the cholangitis or control group and the degree of lymphocytopenia ($p<0.05$). While most of the control group had a normal lymphocyte count, the majority of the cholangitis group had lymphocytopenia.

Due to its availability and ease of calculation using patients' normal blood cell counts, the NLR has gained attention as a possible biomarker of inflammatory disorders and malignancy prognosis. Even after accounting for additional predictive indicators, NLR's impact on outcomes held true in terms of both magnitude and direction. Given the strong correlation between inflammation and cancer development, enhanced tumor-associated neutrophils (TAN), or neutrophils infiltrating tumors, may have potential as a predictive biomarker[15].

However, one should bear in mind that the prognostic value of NLR is not limited to malignancies such as colorectal cancer, prostate cancer, bladder cancer, gastric cancer, metastatic renal cell carcinoma, metastatic melanoma, and advanced non-small-cell lung cancer[16]. Mounting evidence in previous studies[17] elaborated that increased lymphocytes in peripheral blood were associated with better prognosis, whereas elevated neutrophils correspond to poor prognosis. NLR is assumed to reflect the balance between activation of the inflammatory pathway and immune function.

Circulating neutrophils have been shown to contain and secrete vascular endothelial growth factors, tumor necrosis factor, and other cytokines that contribute to cancer progression[18]. Additionally, increased levels of neutrophils subsequently suppress the cytolytic activity of lymphocytes, leading to lymphocytopenia or decreased lymphocyte function[19]. Zahorec[20] published that there is a reciprocal association between neutrophils and lymphocyte counts. NLR reflects the balance of immune-inflammatory status, and any alleviation of neutrophil count results in the expression of pro-inflammatory cytokines, leading to systemic inflammatory response syndrome (SIRS) and septic shock in severe acute cholangitis[21]. In this study, we found a statistically significant relationship between the severity of cholangitis and the degree of lymphocytopenia ($p<0.05$). It was observed that as the disease severity increased, the proportion of patients with normal lymphocytopenia degree decreased, and abnormal findings increased.

Tokyo 2018 Guideline[2] has been used widely for the severity assessment of acute cholangitis. However, there are certain open points to be addressed. First of all, it is not user-friendly to perform it at the emergency service. Secondly, the guideline should be more comprehensive to cover six organ systems, requiring complex items such as vital signs and laboratory results, accompanied by diagnostic criteria for acute cholangitis[22]. The interpretation is not only based on clinical and imaging assessments but also on inflammatory markers such as WBC and CRP. According to TG18, mild disease is accompanied by WBC 10×10^9/L - 12×10^9/L and CRP 10 mg/L. Moderate disease is described as leucopenia WBC $<4.0 \times 10^9$/L or leuk,ocytosis with WBC exceeding $12.0 \times 10^9/L^2$. No value of CRP for moderate acute cholangitis has been established, although it is likely to require early intervention[23]. In clinical usage, these thresholds jeopardize the diagnostic accuracy of TG18. There is no convincing evidence that WBC $<4.0 \times 10^9$/L is a reliable inflammatory marker, and no lead exists for patients with normal WBC count (4×10^9/L - 11×10^9/L). The cut-off values of diagnostic biomarkers have not been clearly stated in TG18[24].

In this study, it was determined that the degree of lymphocytopenia, NLR, and PLR of the patients increased as the severity of cholangitis increased. When the association between the cor-

relation analysis and the severity of cholangitis and the results of NLR and PLR was examined, it was observed that there was a positive relationship in both ratios ($p<0.05$). While the relationship between cholangitis severity and NLR was low (r=0.414), the relationship between PLR and PLR was not found at an acceptable level (r=0.101). The initiation of antibiotherapy and biliary drainage at this early stage could provide a window of opportunity for the patient with severe acute cholangitis. There is a need for the designation of certain biomarkers to be used as predictive parameters. Lymphocyte count and NLR can be utilized as they are cheap, routinely measured in clinical practice, and can predict the severity of acute cholangitis with high accuracy.

The main limitation of this study could be attributed to its retrospective nature. On the contrary, the strength of the study lies beneath its relatively larger sample size. Additionally, statistical significance has been achieved in a majority of the parameters.

Conclusions

As a result, one can conclude that the increase in the severity of cholangitis caused an increase in NLR and PLR and a decrease in lymphocyte count. Although the increase in NLR and lymphocyte count was considered statistically significant, the increase in PLR was not at an acceptable level. Regarding these facts, we assume that lymphocyte count and NLR might have a predictive value on the disease severity of acute cholangitis. We recommend the use of lymphocyte count for grading acute cholangitis severity and providing early biliary drainage in patients with lymphopenia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

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Ethics Approval

The Ethics Committee approval has been granted on 27.10.2020 with protocol number E1/1210/2020 by Ankara City Hospital Scientific Research Assessment and Ethics Committee.. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

Informed Consent

Informed consent was obtained from all participants.

Authors' Contribution

Conception and design: B. Yeşil. Supervision: M. Yüksel. Providing: All Authors. Data Collection: All Authors. Analysis: All Authors. Literature Review: B. Yeşil and A. R. Çalışkan. Article Writing: B. Yeşil and A R. Çalışkan. Critical Review: M. Akdoğan Kayhan.

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