

# Pre-operative neutrophil/lymphocyte and platelet/lymphocyte ratios are effective in predicting complicated acute cholecystitis

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## ABSTRACT

**BACKGROUND:** Acute cholecystitis is a severe disease that requires urgent operation in some cases. To select suitable patients for a conservative approach, there is a need for an affordable and reliable marker for determining complication risk. Evaluation of systemic inflammatory markers in combination with other parameters such as white blood cell and the C-reactive protein might help to decide the appropriate treatment option. This study aims to evaluate the diagnostic value of the neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (PLR) in determining the risk of complicated acute cholecystitis and to compare with intraoperative and pathological findings.

**METHODS:** A total of 229 patients operated on for acute cholecystitis were included in this study. Intraoperative and pathologically complicated acute cholecystitis in 78 cases and controls group was 151 cases. The two groups were compared in terms of inflammation markers. Then, we used the receiver operating characteristic curve analysis to determine the optimal value for NLR and PLR concerning the severity of cholecystitis. Then, the differences in clinical symptoms were investigated according to the cutoff value for NLR and PLR.

**RESULTS:** The NLR and PLR levels were found to be significantly higher in the complicated group ( $4.18 \pm 4.53$  vs.  $15.23 \pm 20.99$ ,  $145.34 \pm 87.58$ , and  $251.92 \pm 245.93$ , respectively,  $p < 0.01$ ). The best cutoff value for NLR and PLR was 5.5 and 146.90, respectively. Sensitivity for NLR was 80% and specificity was 80.1%. Sensitivity for PLR was 66.7% and specificity was 66.2%.

**CONCLUSION:** Systemic inflammation markers can be used to predict the risk of complicated acute cholecystitis. They are inexpensive tools that can be used to make surgical decisions, especially in resource scarce environments.

**Keywords:** Acute cholecystitis; inflammation; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio.

## INTRODUCTION

Acute cholecystitis is one of the most common surgical conditions affecting people in most countries, which is also a major reason for emergency room admissions. Perforation, gangrenous cholecystitis, and emphysematous cholecystitis are serious complications that increase morbidity and mortality, requiring urgent surgery.<sup>[1]</sup> Antibiotics, drainage, or pain relievers may be used to treat acute cholecystitis.<sup>[2]</sup> A limited

number of studies support conservative treatment in patients with acute cholecystitis without complications.<sup>[3-6]</sup> However, to proceed with this treatment, it should be seen as a bridge to surgery rather than as a definitive solution or as a repetition of routine emergency surgery.

Laparoscopic cholecystectomy (Lap-C) can be performed when conservative treatment is selected for various patients with mild disease, according to the Tokyo criteria, as well as

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having no response to the first treatment within 24 h: the patient's performance status is good, with <7 days passing since the onset of symptoms. If the patient with moderate cholecystitis demonstrates good performance, early Lap-C can be considered. If the patient is in poor condition, immediate/early drainage or elective Lap-C may alternatively be selected. Urgent biliary drainage should be performed when there is a high surgical risk of severe acute cholecystitis. If the patient does not have negative predictive factors, early Lap-C can be selected to be done in a developed center.<sup>[7]</sup>

The complete blood count is a simple, fast, and inexpensive test. Values such as white blood cell count, neutrophil-lymphocyte levels, and platelet count are typically used as inflammatory markers and parameters indicating disease severity.<sup>[8-10]</sup> Recent studies show that neutrophil-lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) can be used as reliable inflammatory markers in diseases such as chronic inflammation, systematic lupus erythematosus (SLE), appendicitis, rupture risk in tubal ectopic pregnancies, ulcerative colitis, and most malignancies.<sup>[9,11-14]</sup>

The aim of the present study is to evaluate the diagnostic value of NLR and PLR in determining the complication in acute cholecystitis and to compare with the intraoperative and pathological findings. This would tend to prevent morbidity and mortality with early intervention.

## MATERIALS AND METHODS

Patients who were operated on with acute cholecystitis diagnosis in the Ankara Kecioren Training and Research Hospital between 05 January 2010 and 25 September 2019 were retrospectively analyzed. The necessary approval was obtained from the ethics committee of Ankara Kecioren Training and Research Hospital with the approval number 2012-KAEK-15/2190. Demographic data and clinical characteristics were collected from patient cards and hospital computer records. Consent was obtained from all patients to use the data. Moreover, 229 patients were included in the study, diagnosed with acute cholecystitis; the diagnosis and management decision is made by physical examination, as well as laboratory and ultrasound results.

Patients with acalculous cholecystitis were excluded from the study. Exclusion criteria were comprised acalculous cholecystitis and any chronic inflammatory or autoimmune disease, while blood values indicating inflammation at the time of surgery were a function of other issues, versus acute cholecystitis and gallbladder cancer, or another type of cancer. Other exclusion criteria included having another surgery during the same session, blood diseases causing high or low platelet values, and the use of anticoagulant medication.

A total of 310 patients had the diagnosis of acute cholecystitis preoperatively. Twenty-one of them were excluded because

of acalculous cholecystitis. Sixty patients were excluded due to other exclusion criteria. Perforation, gangrenous cholecystitis, and emphysematous cholecystitis were evaluated as complicated acute cholecystitis. The diagnosis of complicated acute cholecystitis was made by intraoperative and pathological evaluation.

The surgery decision was made with the Tokyo criteria. Conservative and medical treatment options were considered in clinically stable patients and those without signs of complications. Patient gender, age, comorbidities, vital signs (fever, respiratory rate, pulse rate, and blood pressure), and physical examination findings were analyzed in conjunction with the patient's files. Creatinine levels, lymphocytes, platelets, white blood cells, hemoglobin, and neutrophil counts in laboratory tests were collected. All blood results were analyzed in the same laboratory. Perforated, gangrenous, and emphysematous gallbladder cases became more complicated after intraoperative and pathological evaluations.

The patients included in the study were divided into two groups for statistical analysis: Those who were intraoperatively and pathologically diagnosed as having complications were selected for the study group, while patients without complications were selected for the control group. NLR and PLR were calculated by neutrophil and platelet counts, divided by the absolute lymphocyte count. Both groups were compared for NLR and PLR.

## Statistical Analysis

Continuous variables are presented as mean and standard deviation. Categorical variables are presented as frequency and percentage. Continuous variables in two groups were compared using Student's t-test, and categorical variables were compared using the Chi-square test, which do not display normal distribution properties; therefore, hypothesis testing is managed with non-parametric prediction methods. The relationship between clinical-pathological parameters, such as NLR/PLR, was analyzed with the Mann-Whitney U-test (dual-sample Wilcoxon rank-sum) test. Optimal cutoff values of the NLR and PLR were calculated by the receiver operating curve analysis (ROC).

## RESULTS

In the final analysis, the data of a total of 229 patients were examined. According to the operation and final histopathological reports, there were 34.06% (78 patients) with complicated acute cholecystitis and 65.94% (151) of patients without any complications. There were 45 perforated gallbladders, 31 necrotic gallbladders, and two emphysematous gallbladders patients in the complicated group. Comparison of demographic and hematological parameters, NLR and PLR rates between groups are given in Table 1. Leukocyte and neutrophil ( $10.08 \pm 5.09$  and  $7.04 \pm 4.87$ ) levels were lower in

**Table 1.** Comparing demographic characteristics and laboratory findings in acute cholecystitis

	Total (n=229)	Non-complicated (n=151)	Complicated (n=78)	p-value*
	Mean±SD	Mean±SD	Mean±SD	
Age, years	56.47±15.79	53.42±15.03	62.36±15.63	0.981
Platelet, K/mL	264.13±88.73	267.51±80.10	257.60±103.66	0.262
Leukocyte, K/mL	12.60±6.49	10.08±5.09	17.46±6.16	<b>0.008</b>
Neutrophil, K/mL	9.67±6.32	7.04±4.87	14.78±5.66	<b>0.014</b>
Lymphocyte, K/mL	2±1.08	2.20±0.90	1.61±1.28	0.119
NLR	7.94±13.78	4.18±4.53	15.23±20.99	<b>&lt;0.001</b>
PLR	181.64±167.44	145.34±87.58	251.92±245.93	<b>&lt;0.001</b>

Statistically significant values are indicated in bold. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SD: Standard deviation. \*P-value shows the comparison of complicated and uncomplicated acute cholecystitis.

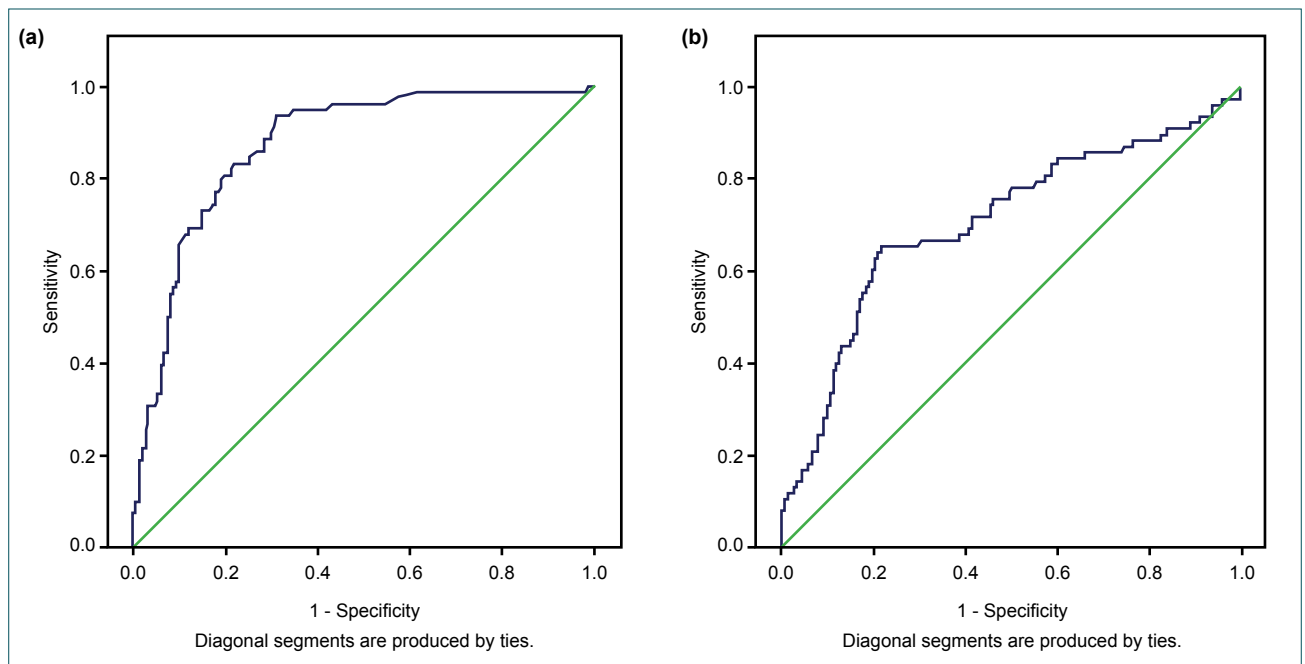
**Table 2.** ROC curve characteristics of discriminative factors

	AUC	p-value	Cutoff value	Sensitivity, %	Specificity, %
Neutrophil-to-lymphocyte ratio	0.873	<0.001	5.50	80.8	80.1
Platelet-to-lymphocyte ratio	0.704	<0.001	146.90	66.7	66.2

Statistically significant values are indicated in bold. ROC: Receiver operating characteristics; AUC: Area under the curve.

the non-complicated group ( $p<0.05$ ). NLR levels were found to be significantly lower in the non-complicated group. PLR and NLR levels were significantly lower in non-complicated patients than corresponding levels in the complicated group ( $p<0.001$ ). The optimal cutoff values of NLR and PLR were determined by ROC curve analysis (Fig. 1).

Given the ROC analysis for NLR and PLR levels for diagnostic performance for complicated gallbladder and surgery indications, the area under the curve was 0.893 and 0.704, respectively (Table 2). The best cutoff value for NLR and PLR was 5.5 and 146.90, respectively, with 80% sensitivity and 80.1% specificity for NLR and 66.7% and 66.2% for PLR.



**Figure 1.** Complicated acute cholecystitis group: ROC curves (a), NLR (b), and PLR (c). NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; ROC: Receiver operating characteristics.

## DISCUSSION

Our study's significant finding is that higher NLR and PLR levels were associated with elevated complication risk in cholecystitis. We found that these rates provide valuable data that can be used to predict gallbladder complications in patients with a definitive diagnosis of acute cholecystitis in any hospital; this tends to prevent morbidity and mortality with early intervention.

Acute cholecystitis is a prominent reason for emergency admissions.<sup>[15]</sup> For these patients, treatment was performed conservatively or surgically. The topic is controversial as to which patients will have the conservative treatment applied as a bridge to surgery. The Tokyo criteria for this controversial issue are revised periodically.<sup>[16]</sup>

The most common form of severe cholecystitis is gangrenous cholecystitis or gallbladder perforation: The former occurs in up to 30% of patients.<sup>[17]</sup> In this case, surgery is required versus conservative treatment. To make this decision, new, inexpensive, and easy-to-use methods support the imaging approaches and examination findings although NLR and PLR are involved in the prediction of various inflammatory conditions.

Inflammatory markers, such as leukocytes and C-reactive protein (CRP), are increasingly used to measure the severity of acute cholecystitis. In addition, these new markers are inexpensive and good indicators of inflammation but could not assess the clinical severity of the disease; it has rarely been reported that they are associated with complicated cases of acute cholecystitis. Ares et al.<sup>[18]</sup> reported that NLR levels above 5 are correlated with acute gangrenous cholecystitis. One other study noted that NLR levels above 4.18 increased the probability of severe cholecystitis.<sup>[19]</sup> A recently published study showed that NLR and PLR levels are associated with a diagnosis of acute cholecystitis.<sup>[20]</sup> Another study showed that NLR and PLR could guide the CRP and leukocyte values, which we routinely assess as inflammatory markers in acute cholecystitis. However, no information was given as to whether it is complicated or not.<sup>[21]</sup> This results are correlated with our study. As a result of our study, an NLR value above 5.5 was significant in the complicated group, including gangrenous cholecystitis. The NLR value can be used with other diagnostic parameters with its high sensitivity and specificity. Using this value can be predicted that the gallbladder is perforated, emphysematous, or gangrenous before surgery, and conservative treatment can be avoided. Thus, severe situations that may develop in the future are prevented. Beliaev et al.<sup>[22]</sup> concluded that the differential power of the NLR was more accurate in the diagnosis of mild acute cholecystitis: It was also found that the NLR would be considered as a potential inflammatory biomarker for acute cholecystitis. One more study showed that it could predict severe cholecystitis with 70.5% sensitivity and 70.0% specificity, mainly

when the NLR value is above 3. Higher NLR values (well over 3) show that age, male gender, ED admission, longer operative time, post-operative complications, and prolonged hospital stay were significant variables.<sup>[23]</sup>

A recently published study showed that the NLR could be used as a diagnostic marker for diagnosing acute appendicitis and can also assist in the clinical evaluation of perforated/gangrenous appendicitis.<sup>[24]</sup> Our study showed that this value could also be used to diagnose perforated or gangrenous cholecystitis, and the PLR value can also be used as a supportive one.

NLR and PLR, as reported in several studies, show how they can be important in determining the prognosis of many kinds of cancers.<sup>[12,13,25]</sup> Zhang et al.<sup>[26]</sup> reported that the other studies (pre-operative NLR and PLR) were closely related to the prognosis of patients with bladder cancer and could also be useful in evaluating patients' prognosis with gallbladder cancer. We found two patients with gallbladder cancer in our study: PLR levels were above the cutoff value (PLR: 213.3 and 194.3), but NLR values were below it (NLR: 2.23 and 3.42). It is not statistically significant, given that the number is so small.

One study found that NLR increased with the increasing severity of sepsis. The mean NLR values for patients who died were 25.49, and the mean NLR for surviving patients was 15.03 ( $p < 0.001$ ).<sup>[27]</sup> Our study's NLR measurements were consistent with these findings, as NLR cutoff values were higher with increasing inflammatory severity estimates. As far as we know, the literature indicates that the relationship between NLR/PLR and complications of acute cholecystitis is limited. This study concluded that higher NLR and PLR levels were independently associated with complicated acute cholecystitis. If the PLR value was above 146.90, the patient was known to have complications, with a sensitivity of 66.7% and a specificity of 66.2%.

This study has several limitations. The number of patients enrolled in this study was small, and it was retrospective. Furthermore, NLR and PLR values were not compared with parameters such as CRP and IL-6. On the other hand, this is the first retrospective study investigating the predictive value of PLR in acute cholecystitis and the difference between NLR and PLR in two subgroups of acute cholecystitis. The availability of almost complete data for every measured result coinciding with the fact that it was examined with pathological data; this includes intraoperative findings as its strengths.

## Conclusion

This study shows that both NLR and PLR were significant independent predictive factors of complications in acute cholecystitis cases. These inflammatory markers help decide to do surgery or stick with conservative treatment, which may lead

to a more accurate surgical decision. NLR and PLR values are calculated from a simple complete blood count. These tests do not add extra costs and are worth being worked on in larger groups. These markers can also be helpful in regions where advanced examination facilities are limited.

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**Ethics Committee Approval:** This study was approved by the Ankara Kecioren Trainin and Research Hospital Clinical Research Ethics Committee (Date: 11.11.2020, Decision No: 2012-KAEK-15/2190).

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**Conflict of Interest:** None declared.

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ORIJİNAL ÇALIŞMA - ÖZ

## Komplike akut kolesistiti öngörmeye preoperatif nötrofil/lenfosit ve trombosit/lenfosit oranları etkilidir

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**AMAÇ:** Akut kolesistit, bazı durumlarda acil ameliyat gerektiren ciddi bir hastalıktır. Konservatif yaklaşım ve komplikasyon riskini belirlemek için uygun hastaları belirlemede için uygun maliyetli ve güvenilir bir markera ihtiyaç vardır. Beyaz kan hücresi, C-reaktif protein gibi diğer parametrelerle birlikte sistemik inflamatuvar belirteçlerin kullanılması, uygun tedavi seçeneğine karar vermede yardımcı olabilir. Bu çalışma, komplike akut kolesistit riskini belirlemede nötrofil lenfosit oranı (NLO) ve trombosit lenfosit oranının (PLO) tanisal değerini değerlendirmeyi ve intraoperatif ve patolojik bulgularla karşılaştırmayı amaçlamaktadır.

**GEREÇ VE YÖNTEM:** Bu çalışmaya akut kolesistit nedeniyle ameliyat edilen toplam 229 hasta alındı. İntraoperatif ve patolojik olarak komplike 78 olgu ve kontrol grubu 151 olgu idi. İki grup iltihap belirteçleri açısından karşılaştırıldı. Daha sonra, kolesistitin ciddiyetine ilişkin NLO ve PLO'nun optimal değeri belirlemek için ROC karakteristik eğri analizini kullanıldı. NLO ve PLO için kesme değerine göre klinik semptomlardaki farklılıklar araştırıldı.

**BULGULAR:** NLO ve PLO düzeyleri komplike grupta anlamlı olarak yüksek bulundu (sırasıyla,  $4.18 \pm 4.53$  ve  $15.23 \pm 20.99$ ,  $145.34 \pm 87.58$  ve  $251.92 \pm 245.93$ ,  $p < 0.01$ ). NLO ve PLO için en iyi kesme değeri sırasıyla 5.5 ve 146,90 idi. NLR için duyarlılık %80, özgüllük %80.1 idi. PLR için duyarlılık %66.7 ve özgüllük %66.2 olarak bulundu.

**TARTIŞMA:** Sistemik enflamasyon belirteçleri, komplike akut kolesistit riskini tahmin etmek için kullanılabilir. Özellikle kaynak kıtlığı olan ortamlarda cerrahi kararlar almak için kullanılacak ucuz araçlardır.

**Anahtar sözcükler:** Akut kolesistit; enflamasyon; nötrofil-lenfosit oranı; trombosit-lenfosit oranı.

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