

An investigation into the predictive role of serum inflammatory parameters in the diagnosis of complicated acute cholecystitis

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ABSTRACT

BACKGROUND: Gallbladder gangrene and perforation are an important complication of acute calculous cholecystitis and are difficult to detect preoperatively. Therefore, in this study, we aimed to evaluate whether serum inflammatory parameters are predictive factors for complicated cholecystitis (CC).

METHODS: In the present study, histopathological findings of 250 patients who were operated on with the diagnosis of acute cholecystitis (AC) in the emergency department between 2014 and 2019 were evaluated and the cases were divided into two groups as AC and CC. Parameters, including age, gender, body mass index, white blood cell (WBC) count, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), and platelet distribution width (PDW), were examined for their ability to predict CC.

RESULTS: The findings obtained in this study showed that WBC, CRP, and NLR were significantly higher in the CC group ($p < 0.05$). WBC > 9.000 cells/ml, CRP > 29.0 , and NLR > 4.3 were the factors that could predict CC. There was no significant difference between the two groups concerning MPV and PDW ($p > 0.05$). CC was observed more frequently in patients over 65 years of age, but there was not a statistically significant difference ($p = 0.468$).

CONCLUSION: WBC, CRP, and NLR are valuable biochemical markers in predicting complicated AC. Advanced age may be a helpful predictive factor for CC. These factors may be helpful in making an early cholecystectomy decision.

Keywords: Acute cholecystitis; complicated cholecystitis; gangrenous cholecystitis; predictive factors.

INTRODUCTION

The prevalence of gallstones in the adult population is approximately 10–15% and approximately 20% of these cases show symptoms or complications.^[1] Gallstones may cause many severe complications, such as pancreatitis, Mirizzi syndrome, pericholecystic abscess, perforation, and especially acute cholecystitis (AC).^[1–4] Many clinical studies recommend early cholecystectomy as the most important measure to avoid these complications.^[5] Laparoscopic cholecystectomies performed in the period known as golden hours (the first

72–96 h) can reduce the complications of cholecystitis, shorten the length of hospital stay, and decrease the rate of laparotomies and perioperative complications.^[6] Thus, early planning of emergency cholecystectomy by predicting complicated cholecystitis (CC) at the first admission in the emergency department can decrease morbidity and mortality. For this purpose, although there are studies in the literature investigating the predictive roles of laboratory and radiological findings in CC, there is no consensus on this subject.^[6–8] The increase in leukocyte white blood cell (WBC) count, the decrease in lymphocyte count, and the increase in C-reactive

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protein (CRP) are all indicators of the inflammatory response to infection. Neutrophil/Lymphocyte ratio (NLR) is also an important indicator of inflammation.^[9] However, it is controversial in which value ranges or above which levels all these inflammatory parameters should be a warning for surgeons in the diagnosis of CC.

In this study, we aimed to investigate the role of inflammatory parameters, such as WBC, NLR, and CRP, in predicting CC.

MATERIALS AND METHODS

In our study, 250 consecutive cases of cholecystectomy with the indication of AC (non-complicated) and CC who applied to the Emergency Surgery Department of Emergency Surgery, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa between January 2014 and July 2019 were analyzed retrospectively. Ethics Committee approval was obtained for this study (11/03/2020-41300). Patients older than 18 years of age who were operated on with the diagnosis of AC and CC were included in this study. Patients under 18 years of age, those who underwent elective or delayed cholecystectomy, had acalculous cholecystitis, took antibiotherapy, had a malignant or hematological disease, were using chemotherapeutic or immunomodulatory agents, were intubated, had previously been hospitalized with the diagnosis of AC, and who underwent cholecystostomy were excluded from this study.

The demographic characteristics of the patients, pre-operative laboratory tests and post-operative pathology findings were evaluated. The patients were divided into two groups as AC and CC according to the surgical findings and histopathological findings of the cholecystectomy materials. Age, gender, body mass index (BMI), WBC (cells/ml), NLR, mean platelet volume

(MPV), platelet distribution width (PDW), and CRP (mg/dL) levels were compared between the groups. For the inflammatory parameters of the cases, the values before the first antibiotherapy and initial reference values were taken as a basis.

Patients with clinical findings (positive Murphy's sign, peritoneal reaction or right upper quadrant mass), inflammation parameters (fever, leukocytosis $>10,000/\text{mm}^3$, or increased CRP >3 mg/dL), and data consistent with cholecystitis in an imaging test were assumed to have AC according to the 2018 Tokyo Criteria.^[10] Gangrenous, perforated, and emphysematous cholecystitis was defined as CC on histopathological evaluation. All patients were operated on within the first 72–96 h.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data for statistical analysis. The distribution of variables was measured by the Kolmogorov–Smirnov test. Mann–Whitney U test was used to analyze quantitative independent data. Chi-square test was used in the analysis of qualitative independent data. The effect level and cutoff value were investigated using the ROC curve. SPSS 27.0 program was used in the analysis and $p < 0.05$ for statistical significance.

RESULTS

In this study, there were 250 patients and 51.6% ($n=129$) of them were female and 48.4% ($n=121$) of them were male. About 63.2% of the patients (168) were under 65 years of age and 36.8% ($n=92$) were over 65 years of age. The mean age of all patients was 59.9 ± 16.6 years. The demographic data of the patients and the distribution of serum parameters are shown in Table I.

Table I. Comparison of age, gender, body mass index and serum parameters between groups

	Acute cholecystitis	Complicated cholecystitis	Total	P
	Mean \pm SD/n (%)	Mean \pm SD/n (%)	Mean \pm SD/n (%)	
Age	59.6 \pm 17.1	61.4 \pm 14.5	59.9 \pm 16.6	0.513 ^a
<65	128 (64.3)	30 (58.8)	158 (63.2)	0.468 ^b
>65	71 (35.7)	21 (41.2)	92 (36.8)	
Gender				
Female	105 (52.8)	24 (47.1)	129 (51.6)	0.467 ^b
Male	94 (47.2)	27 (52.9)	121 (48.4)	
Body mass index	26.5 \pm 4.7	27.5 \pm 4.4	26.7 \pm 4.6	0.150 ^a
Mean platelet volume	8.6 \pm 5.5	8.1 \pm 1.0	8.5 \pm 4.9	0.131 ^a
Platelet distribution width	16.9 \pm 0.7	16.9 \pm 0.7	16.9 \pm 0.7	0.485 ^a
White blood cell count	8.6 \pm 3.5	11.6 \pm 5.5	9.2 \pm 4.2	0.000 ^a
C-reactive protein	42.2 \pm 71.5	84.7 \pm 79.5	50.9 \pm 75	0.000 ^a
Neutrophil-to-lymphocyte ratio	4.9 \pm 7.2	8.2 \pm 7.8	5.6 \pm 7.4	0.000 ^a

^aMann-Whitney U test; ^bChi-Square test. SD: Standard deviation.

Table 2. The area under the ROC curve (AUC) for the diagnosis of complicated cholecystitis

Variables	AUC	Cut-off point	CI 95%	p
WBC	0.684	9.0	0.599–0.768	0.000 ^c
CRP	0.740	29.0	0.669–0.811	0.000 ^c
NLR	0.698	4.3	0.621–0.775	0.000 ^c

^cROC analysis. ROC: Receiver Operating Characteristic; AUC: Area under curve; CI: Confidence interval; WBC: White blood cell count; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio.

In the examination of histopathology results, 79.6% (n=199) of the cases were AC, 20.4% (n=51) were CC. There was no significant difference in age, gender, BMI, MPV, and PDW parameters between AC and CC groups (p>0.05). Mean WBC, CRP, and NLR values were significantly higher in the CC group than in the AC group (p<0.05) (Table 1).

Significant efficacy of WBC (AUC 0.684 [0.599–0.768]), CRP (AUC 0.740 [0.669–0.811]), and NLR (AUC 0.698 [0.621–0.775]) was observed in the distinction between AC and CC. For the WBC cutoff value of 9.000 µl, positive predictive value was 35.1%, negative predictive value was 88.5%, sensitivity was 64.7%, and specificity was 69.3%. For the CRP: 29.0 mg/L cutoff value, these rates were 37.4%, 90.7%, 72.5%, and 68.8%, respectively. The cutoff value for NLR was 4.3 and the positive predictive value was 35.1, the negative predictive value 88.5, the sensitivity 64.7, and the specificity 69.3 (Table 2 and Fig. 1).

When we examined the cases by age groups, the rate of CC was higher in the >65 age group, but this numerical difference

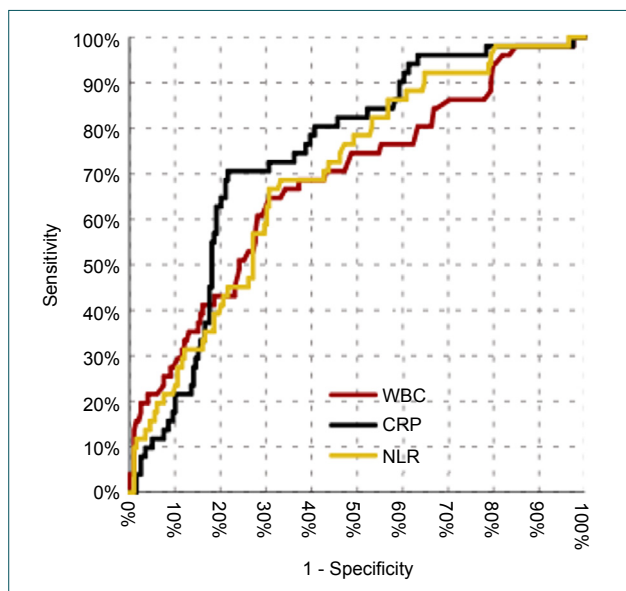


Figure 1. ROC curve of WBC, CRP, and NLR for distinguishing between acute and complicated cholecystitis, with the AUC of 0.684, 0.740, and 0.698, respectively. WBC: White blood cell, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio.

Table 3. Comparison of inflammatory parameters in the distinction between complicated cholecystitis and acute cholecystitis by age groups

	Acute cholecystitis	Complicated cholecystitis	P
	Mean±SD	Mean±SD	
Age <65			
MPV	8.8±6.8	8.1±0.9	0.612 ^a
PDW	16.8±0.6	16.7±0.6	0.403 ^a
WBC	8.7±3.7	12.2±5.9	0.003 ^a
CRP	36.2±63.1	74.4±78.7	0.000 ^a
NLR	4.6±7.6	6.7±4.4	0.000 ^a
Age >65			
MPV	8.4±1	8±1.2	0.069 ^a
PDW	17.1±0.8	17.1±0.8	0.776 ^a
WBC	8.2±3.3	10.9±4.9	0.004 ^a
CRP	53.1±83.9	99.4±80.2	0.000 ^a
NLR	5.4±6.5	10.3±10.8	0.012 ^a

^aMann-Whitney U test. MPV: Mean platelet volume; PDW: Platelet distribution width; WBC: White blood cell count; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; SD: Standard deviation.

was not statistically significant (p=0.468, Table 1). In addition, there was no significant difference in MPV and PDW between AC and CC groups in both patients under 65 years of age and over (p>0.05). WBC, CRP, and NLR were significantly higher in CC patients in all age groups (p<0.05) (Table 3).

DISCUSSION

AC is an acute inflammation of the gallbladder, usually caused by cystic duct obstruction, and gallstones are responsible for 95% of cases.^[11] In addition to causing AC, gallstones may lead to complications, such as xanthogranulomatous cholecystitis, emphysematous cholecystitis, gallbladder wall perforations, pericholecystic abscesses, Mirizzi syndrome, cholecystoenteric fistulas, choledocholithiasis, gallstone pancreatitis, gallstone pancreatitis, porcelain gallbladder, and gallbladder malignancies.^[4] In the treatment of AC, early cholecystectomy has come to the fore as a safer and cost-effective treatment with shorter hospital stay compared to delayed cholecystectomy.^[12,13] Early diagnosis and early cholecystectomy are critically important in this patient group given that CC is associated with increased morbidity and mortality compared to non-CC. However, it is often challenging to diagnose CC in the pre-operative period, as there are no specific diagnostic criteria.

WBC has been reported as the only biomarker criterion for the evaluation of AC severity.^[10] Studies have shown that increased WBC count is more due to an intense inflammatory response to necrotic changes in the gallbladder wall than

bacterial invasion.^[14] Teefey et al.^[15] reported that the probability of developing necrotizing gangrenous cholecystitis is 30% in the case of WBC count $>17 \times 10^3/\mu\text{L}$. Portinari et al.^[16] created a nomogram to distinguish between AC and severe AC and reported WBC count $\geq 12.4 \times 10^3/\mu\text{L}$, CRP ≥ 9.9 mg/dl and increased gallbladder wall thickness on ultrasound as important predictive factors for the development of gangrenous cholecystitis. In our study, the WBC count >9.000 cutoff value was determined as the predictive factor for CC. This cutoff value was lower than other studies in the literature. We think that this is because the WBC counts on which the study is based were made on samples collected at the first application of the patients to the emergency department.

The Tokyo guidelines have used CRP of >3 mg/dL as one of the diagnostic criteria but have not used it with different cutoffs for diagnosing severity.^[10] Mok et al.^[17] reported that CRP elevation alone is a predictive factor for gangrenous cholecystitis and that the cutoff value is >200 . Bouassida et al.^[8] also found that the high levels of CRP (cutoff value >60.5 mg/dL) are an important marker for advanced AC and conversion to open surgery. Beliaev et al.^[18] found out in a large-scale cohort study that the discriminative power of serum CRP was superior to WBC in predicting CC. In our study, we found that the high CRP (cutoff value of 29.0 mg/dL) is a predictive factor for CC, in line with the literature.

Neutrophils are an important part of the inflammatory response and the NLR is a current parameter for the literature that gives an idea of the severity of an inflammatory or infectious condition. There are many studies in the literature reporting that NLR has an important prognostic role in malignancy, cardiac diseases, peripheral vascular diseases, and rheumatic diseases.^[19–22] NLR has been reported to be a predictive factor for CC and the cutoff value range is 4.17–10.25.^[8,9,23,24] Consistent with the literature, we found the NLR in our study as 4.30. We concluded that NLR has predictive value in the differentiation of complicated/un-CC. There are a limited number of studies on this subject in the literature and the results are in line with our study.

To the best of our knowledge, there are not any studies examining MPV and PDW covered by routine hemogram tests in patients with CC in the literature. According to Sayit et al.,^[25] MPV was significantly lower in AC compared to the control group as an acute phase reactant that does not require additional cost. In the same study, PDW was significantly higher in the AC group.^[25] However, in our study, we did not find any statistically significant difference between the acute and CC groups regarding the levels of these two parameters.

Advanced age is a risk factor for AC and most cases occur in the elderly adult population.^[26] Many medical centers prefer to treat elderly patients conservatively and perform delayed cholecystectomy, which they consider safer for this patient

group.^[26,27] However, if CC develops, there is no doubt that mortality and morbidity will take a more severe dimension, especially in elderly patients. Therefore, it becomes critical to be able to predict the development of CC in this patient group. In the present study, the average age of the acute and CC groups was similar. CC was more common in patients >65 years of age, but this was not a statistically significant difference. In addition, when patients were examined as >65 and <65 years of age, we found that WBC, CRP, and NLR were higher in CC in all age groups. Sato et al.^[24] reported a significantly increased risk of gangrenous cholecystitis at the age of ≥ 80 years. Shirah et al.^[6] reported that gangrenous cholecystitis developed at a higher rate in the 41–60 and >60 age group compared to the 20–40 age group. Given this information in the literature and in our study, we think that age is a copredictive factor for CC and more attention should be paid concerning the development of gangrenous cholecystitis in elderly patients with AC.

Although the retrospective nature of our study is a limitation, the number of patients was much higher than many similar studies in the literature. We believe that performing emergency cholecystectomy can significantly affect the perioperative complications, morbidity, and mortality by correctly predicting the possibility of complications in AC through evidence-based predictive factors that do not require additional costs. Therefore, more multi-center, prospective, and controlled studies should be conducted to reach a consensus on the subject.

Conclusion

We concluded that WBC >9.000 count/ μL , CRP >29.0 (mg/dL) and NLR >4.3 are the factors that show statistically significant efficacy in predisposing gangrenous complicated AC. Given these risk factors, the urgency of patients for surgery can be decided in the emergency department. In addition, age, which is another risk factor, may be helpful in making decisions about early cholecystectomy.

Ethics Committee Approval: This study was approved by the Istanbul University Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 11.03.2020, Decision No: 41300).

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ORJİNAL ÇALIŞMA - ÖZ

Komplike akut kolesistit tanısında serum enflamatuvar parametrelerin öngörücü rolüne yönelik bir araştırma

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AMAÇ: Safra kesesi gangreni ve perforasyonu, akut taşlı kolesistitin önemli bir komplikasyonudur ve ameliyat öncesi olarak tespit edilmesi zordur. Bu nedenle bu çalışmada, serum enflamatuvar parametrelerin komplike kolesistit için prediktif faktör olup olmadığını değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Bu çalışmada acil serviste 2014–2019 yılları arasında akut kolesistit tanısıyla ameliyat edilen 250 hastanın histopatolojik bulguları değerlendirildi ve olgular akut kolesistit ve komplike kolesistit olarak iki gruba ayrıldı. Yaş, cinsiyet, vücut kitle indeksi, beyaz kan hücresi sayısı (WBC), C-reaktif protein (CRP), nötrofil-lenfosit oranı (NLR), ortalama trombosit hacmi (MPV) ve trombosit dağılım genişliği (PDW) gibi parametreler, komplike kolesistiti tahmin etme oranları açısından incelendi.

BULGULAR: Bu çalışmada elde edilen bulgular komplike kolesistit grubunda WBC, CRP ve NLR'nin anlamlı olarak daha yüksek olduğunu gösterdi ($p < 0.05$). WBC > 9.000 hücre/ml, CRP > 29.0 ve NLR > 4.3 , komplike kolesistiti öngörebilen faktörlerdi. MPV ve PDW açısından iki grup arasında anlamlı fark yoktu ($p > 0.05$). Altmış beş yaş üstü hastalarda komplike kolesistit daha sık görüldü, ancak istatistiksel olarak anlamlı bir fark yoktu ($p = 0.468$).

TARTIŞMA: WBC, CRP ve NLR, komplike akut kolesistiti tahmin etmede değerli biyokimyasal belirteçlerdir. İleri yaş, komplike kolesistit için yararlı bir prediktif faktör olabilir. Bu faktörler erken kolesistektomi kararı vermede yardımcı olabilir.

Anahtar sözcükler: Akut kolesistit; kangren kolesistit; komplike kolesistit; prediktif faktörler.

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