

Efficacy of blood parameters as indicators of the need for overdue urgent cholecystectomy in elderly patients with acute cholecystitis

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ABSTRACT

BACKGROUND: Although early cholecystectomy is recommended for patients with acute cholecystitis, conservative treatment followed by delayed cholecystectomy (DC) is a highly preferred modality, especially in older adult patients. However, some severe cases require overdue urgent cholecystectomy (OC). This study aimed to evaluate the ability of laboratory findings and Tokyo severity classification (TokyoSC) to differentiate those with the need for OC among elderly patients.

METHODS: Laboratory/radiological/clinical findings of geriatric patients with acute cholecystitis on admission and TokyoSC were retrospectively analyzed. The DC and OC groups were compared.

RESULTS: The mean age of the 164 patients was 72.3±6.4 years. White blood cell, neutrophil (NEU), immature granulocyte (IG), C-reactive protein, neutrophil-to-lymphocyte ratio (NLR), and TokyoSC parameters were all significant at P<0.001 in differentiation. NLR had a specificity of 98%, and TokyoSC had a sensitivity of 98%.

CONCLUSION: NLR, NEU, IG, and TokyoSC were effective in differentiating patients who needed OC while planning conservative treatment + DC for older adult patients who were followed up due to acute cholecystitis. If the NLR is >9.9 and TokyoSC is moderate/high, early cholecystectomy should be preferred instead of conservative treatment + DC in aged patients.

Keywords: Acute cholecystitis; aged; cholecystectomy; c-reactive protein; neutrophil-to-lymphocyte ratio; severity grading.

INTRODUCTION

The incidence of acute cholecystitis (AC), one of the most common causes of presentation to the emergency department among gastrointestinal pathologies, increases with advancing age.^[1] This increases the average age of patients who undergo cholecystectomy while increasing age leads to a higher risk of complications related to gallstones.^[2]

There is no consensus on which patients should be considered at high surgical risk, which scales should be used for risk assessment, and whether age is a factor to consider. Therefore,

indications and contraindications for treatment choices, especially in the advanced age group, do not offer well-defined limits. The choice of one or the other depends on the expertise and preference of the treating surgeon.^[3] Older adult patients presenting with acute pathologies are frailer and, therefore, are at a higher risk of post-operative complications.^[4,5]

Current guidelines recommend early cholecystectomy (EC) and early laparoscopic cholecystectomy as possible treatment methods for AC patients.^[6] EC should be performed within the 1st week of the presentation.^[7] The widely accepted traditional approach also suggests that EC should be performed

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within the initial 72 h of symptom onset.^[8] However, regression of the acute manifestation with conservative treatment followed by delayed cholecystectomy (DC) (cholecystectomy after >6 weeks of presentation) is still a treatment plan frequently preferred by some clinicians.^[9] The increased risk of complications in EC, especially in older adult patients with comorbidities, leads to hesitation in patients and surgeons, causing DC to become the treatment of choice.^[10]

While DC has been associated with low morbidity and mortality, some patients who are scheduled for this operation develop the need for overdue urgent cholecystectomy (OC) after the recommended time for EC (≤ 72 h following the onset of symptoms) is exceeded, but before the conservative treatment is completed, contrary to what has been planned.

The present study aimed to establish whether laboratory findings on initial admission and the Tokyo Guidelines severity classification (TokyoSC)^[11] can differentiate the patients developing the need for OC among those scheduled for conservative treatment and DC.

MATERIALS AND METHODS

Patient Population

The study included geriatric patients (≥ 65 years old) who presented to the emergency departments of two different tertiary care centers between January 2018 and June 2021 with AC symptoms. AC was diagnosed according to the criteria specified in Tokyo guidelines. Patients who were diagnosed or operated outside the study centers had comorbidities with potential effects on the treatment like diabetes, who died during the follow-up, who underwent EC within ≤ 72 h of presentation with AC symptoms, or who underwent percutaneous cholecystostomy for various reasons were excluded from the study (Fig. 1).

Treatment Protocol

Appropriate conservative treatments (including intravenous fluids, antibiotics, analgesics, and restriction of oral intake) were administered to all patients with AC. Patients who improved with the treatment were discharged and underwent elective DC after >6 weeks. Those without the expected improvement with the treatment or who developed complications (perforation, abscess, etc.) underwent OC (>72 h following the presentation with AC symptoms). Operations were initiated laparoscopically in all the patients; those that could not be completed laparoscopically were converted to open surgery. All patients underwent surgery according to the principles of a safe cholecystectomy.

Study Parameters

The hospital management system was used to assess and record the patients' demographic data, laboratory findings (white blood cells [WBC], hemoglobin [HGB], platelets [PLT], neutrophils [NEU], lymphocytes [LEN], immature granulocytes [IG], alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBIL], C-reactive protein [CRP], neutrophil-to-lymphocyte ratio [NLR], and platelet-to-lymphocyte ratio [PLR]), radiological findings (gallbladder wall thickness and pericholecystic fluid), pathological findings (acute/chronic/gangrenous), surgical methods (laparoscopic/open), post-operative length of stay, and TokyoSC results (mild/moderate/high). For laboratory results, the results of the patients' first tests performed in the emergency department at presentation with AC symptoms were recorded.

cytes [IG], alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBIL], C-reactive protein [CRP], neutrophil-to-lymphocyte ratio [NLR], and platelet-to-lymphocyte ratio [PLR]), radiological findings (gallbladder wall thickness and pericholecystic fluid), pathological findings (acute/chronic/gangrenous), surgical methods (laparoscopic/open), post-operative length of stay, and TokyoSC results (mild/moderate/high). For laboratory results, the results of the patients' first tests performed in the emergency department at presentation with AC symptoms were recorded.

Statistical Method

Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and ratio. The Kolmogorov–Smirnov test was used to test whether the variables were normally distributed. The Mann–Whitney U test was used to analyze the quantitative independent variables. The Chi-square test was used to analyze the qualitative independent variables. Statistical significance was set at $p < 0.05$. The effect size was examined using univariate and multivariate regression analyses. All analyses were performed using the SPSS v27.0 (IBM, New York, NY, USA) program.

Ethical Approval

All data collection and analyses were carried out with the approval of the Institutional Ethics Committee (date: January 26, 2022, no:01-03). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was

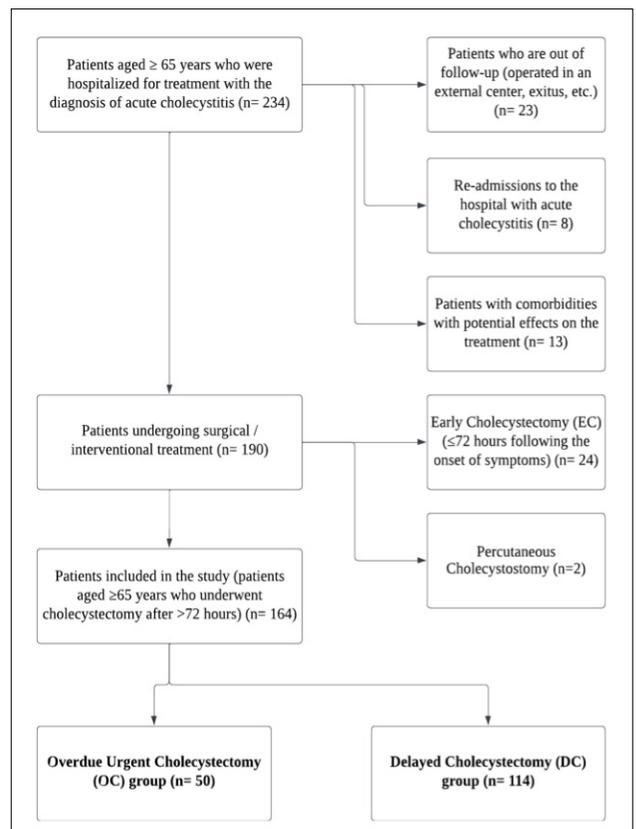


Figure 1. Flowchart. Patients included in the study.

approved by the ethics committee. Informed consent was obtained for experimentation with human subjects.

RESULTS

The mean age of the 164 study patients who were diagnosed with AC and scheduled for conservative treatment and DC after presenting to the emergency department was 72.3 ± 6.4 years. Of the patients, 56.7% (n=93) were female. OC was performed in 30.5% (n=50) of the patients. Conservative treatment was successful, and DC was performed in 69.5% (n=114). Regarding the TokyoSC results of the study patients, 22.0% (n=36) had mild, 68.3% (n=112) had moderate, and 9.8% (n=16) had severe AC. Laparoscopic cholecystectomy was performed in 73.8% of the patients.

When compared to the DC group, the OC group had a significantly higher age ($P=0.031$), male-to-female ratio ($P=0.012$), rate of open surgery ($P<0.001$), rate of acute pathology types ($P<0.001$), higher TokyoSC severity grade ($P<0.001$), and longer stay ($P<0.001$). There was a significant difference in the surgical method ($P<0.001$), the radiological thickness of the gallbladder wall ($P=0.001$), and the rate of pericholecystic fluid ($P<0.001$) between the groups (Table 1).

With regard to laboratory findings, WBC ($P<0.001$), NEU ($P<0.001$), IG ($P<0.001$), CRP ($P<0.001$), NLR ($P<0.001$), and TBIL ($P=0.034$) were significantly higher in the OC group than in the DC group. In contrast, HGB, PLT, LEN, ALT, AST, and PLR did not significantly differ between the OC and DC groups ($P>0.05$) (Table 1).

Table 1. Comparison of the delayed cholecystectomy (DC) and overdue urgent cholecystectomy (OC) groups

	OC Group		DC Group		P-value
	Mean \pm SD/n (%)	Median	Mean \pm SD/n (%)	Median	
Age (years)	74.8 \pm 8.5	72.5	71.2 \pm 4.9	70.5	0.031 m
Gender					
Male	29 (58.0%)		42 (36.8%)		0.012 X ²
Female	21 (42.0%)		72 (63.2%)		
Surgery Type					
Open	32 (64.0%)		11 (9.6%)		<0.001 X ²
Laparoscopic	18 (36.0%)		103 (90.4%)		
Pathology					
Acute	25 (50.0%)		18 (15.8%)		<0.001 X ²
Chronic	18 (36.0%)		96 (84.2%)		
Gangrenous	7 (14.0%)		0 (0.0%)		
Tokyo Severity Classification					
Mild	1 (2.0%)		35 (30.7%)		<0.001 X ²
Moderate	37 (74.0%)		75 (65.8%)		
Severe	12 (24.0%)		4 (3.5%)		
WBC (10 ³ /uL)	14.1 \pm 6.8	14.1	8.5 \pm 3.1	8.1	<0.001 m
HGB (g/dl)	13.8 \pm 1.9	14.1	13.4 \pm 1.4	13.5	0.132 m
PLT (10 ³ /uL)	245.7 \pm 68.6	236.5	265.4 \pm 74.8	256.5	0.119 m
NEU (10 ³ /uL)	55.7 \pm 31.5	63.8	34.1 \pm 27.9	41.2	<0.001 m
LEN (10 ³ /uL)	10.4 \pm 10.8	5.3	15.9 \pm 14.9	10.8	0.059 m
IG (10 ³ /uL)	0.157 \pm 0.269	0.060	0.058 \pm 0.201	0.020	<0.001 m
AST (IU/L)	67.9 \pm 119.7	24.0	77.2 \pm 140.2	22.0	0.893 m
ALT (IU/L)	56.0 \pm 80.9	19.0	64.3 \pm 110.5	21.0	0.564 m
TBIL (mg/dl)	1.12 \pm 0.75	0.91	0.97 \pm 0.87	0.71	0.034 m
CRP (mg/dl)	6.05 \pm 8.42	2.05	1.08 \pm 3.17	0.20	<0.001 m
NLR	12.1 \pm 9.2	12.8	3.2 \pm 2.3	2.3	<0.001 m
PLR	110.6 \pm 141.7	42.1	78.1 \pm 82.8	21.5	0.218 m
Radiological thickness of the gallbladder wall (mm)	4.7 \pm 2.7	4.0	3.6 \pm 1.5	3.0	0.001 m
Radiological thickness of the gallbladder wall					
\geq 4mm	26 (52.0%)		19 (16.7%)		<0.001 X ²
< 4mm	24 (48.0%)		95 (83.3%)		
Pericholecystic fluid					
(+)	12 (24.0%)		6 (5.3%)		<0.001 X ²
(-)	38 (76.0%)		108 (94.7%)		
Hospitalization (days)	7.7 \pm 4.6	6.5	3.1 \pm 1.6	3.0	<0.001 m

m Mann-Whitney u test/X² Chi-square test; WBC: White Blood Cell; HGB: Hemoglobin; PLT: Platelet; NEU: Neutrophil; LEN: lymphocyte; IG: Immature Granulocyte; AST: Aspartate transaminase; ALT: Alanine transaminase; TBIL: Total Bilirubin; CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 2. Assessment of the efficacy of laboratory/clinical/radiological parameters and Tokyo Severity Classification in the DC/OC differentiation by logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Age	1.092	1.035–1.152	0.001			
Gender	0.422	0.214–0.832	0.013			
Hospitalization (days)	1.740	1.433–2.111	<0.001			
Surgery Type	0.060	0.026–0.140	<0.001			
Pathology	0.453	0.232–0.884	0.020			
Radiological thickness of the gallbladder wall	1.335	1.083–1.646	0.007			
Pericholecystic fluid	0.176	0.062–0.501	0.001			
WBC	1.260	1.157–1.373	<0.001			
HGB	1.157	0.928–1.443	0.196			
PLT	0.996	0.991–1.001	0.115			
NEU	1.025	1.013–1.038	<0.001	1.011	1.011–1.048	0.001
LEN	0.970	0.945–0.996	0.022			
IG	7.303	1.107–48.155	0.039			
AST	0.999	0.997–1.002	0.684			
ALT	0.999	0.996–1.003	0.629			
TBIL	1.212	0.829–1.773	0.322			
CRP	1.196	1.087–1.316	<0.001			
NLR	1.363	1.228–1.513	<0.001	1.337	1.191–1.501	<0.001
PLR	1.003	1.000–1.006	0.074			
Tokyo Severity Classification	8.707	3.365–22.532	<0.001	4.116	1.400–12.104	0.010

Logistic Regression (Forward LR); WBC: White Blood Cell; HGB: Hemoglobin; PLT: Platelet; NEU: Neutrophil; LEN: lymphocyte; IG: Immature Granulocyte; AST: Aspartate transaminase; ALT: Alanine transaminase; TBIL: Total Bilirubin; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 3. Assessment of the efficacy of blood parameters and Tokyo severity classification in the DC/OC differentiation by ROC analysis

	Area under the curve	Confidence interval 95%	P-value
WBC	0.735	0.636–0.834	<0.001
NEU	0.745	0.662–0.828	<0.001
IG	0.768	0.687–0.849	<0.001
CRP	0.743	0.656–0.831	<0.001
NLR	0.825	0.750–0.899	<0.001
PLR	0.561	0.465–0.656	0.218
Tokyo Severity Classification	0.709	0.627–0.792	<0.001

WBC: White Blood Cell; NEU: Neutrophil; IG: Immature Granulocyte; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

The univariate model showed that age, sex, length of stay, surgical method, pathology type, gallbladder wall thickness, pericholecystic fluid, WBC, NEU, LEN, IG, CRP, NLR, NPR, and TokyoSC were significantly effective ($P<0.05$) in differentiating between the OC and DC groups (Table 2). On the contrary, the multivariate reduced model revealed significant independent ($P<0.05$) efficacy of NEU, NLR, and TokyoSC in differentiating between OC and DC groups (Table 2).

The receiver operating characteristics analysis of the efficacy of the laboratory findings and TokyoSC in the differentiation between OC and DC groups showed that WBC,

NEU, IG, CRP, NLR, and TokyoSC parameters were all significant at $P<0.001$. Among these, NLR was the most effective ($AUC=0.825$) and TokyoSC was the least effective ($AUC=0.709$) parameter (Table 3).

DISCUSSION

Surgery is the gold standard treatment for AC. The updated guidelines of the World Society of Emergency Surgery based on available knowledge recommend EC (preferably laparoscopic cholecystectomy) for the older adult patient group presenting with AC;^[6] however, surgery in the acute period

is associated with a higher mortality rate in older adults and other high-risk patients.^[12] Therefore, some surgeons may avoid EC, especially considering that mortality and morbidity will increase. Older adult AC patients with comorbidities and functional disorders can benefit from conservative treatment.^[13] Supporting this choice, Wiggins et al. reported a lower mortality rate in the patient group receiving conservative treatment as the preferred method than in those undergoing surgery as the preferred method.^[14] While this patient- and surgeon-specific choice is not incorrect, the presentation of AC does not regress in some of the patients who are scheduled for DC and initiated on conservative treatment, resulting in the need for urgent surgery. Similar situations with worsening despite receiving medical treatment may lead to what we call OC.^[15]

The length of hospital stay, need for open surgery, need for emergency surgery, and medical care costs have been reported to be higher in older adult patients presenting with symptomatic gallstones.^[2] We found that our data from patients aged ≥ 65 years were consistent with the literature in terms of the length of hospital stay, need for open surgery, and need for emergency surgery.^[16] Janssen et al., in their study with no age restriction, initiated AC patients on conservative treatment, and emergency surgery was required in 6% of the patients, while elective surgery was performed in 69% of patients.^[15] Similarly, the rate of need for emergency surgery was 30% in our study cohort that was initiated with conservative treatment. We believe that this was mainly because our study group included older adult patients with lower physiological capacity. In our study patients, all of whom were over the age of 65 years, those who had to discontinue conservative treatment and undergo OC also had a significantly higher mean age than those in the DC group ($P=0.031$).

TokyoSC classifies AC cases into three severity grades: mild, moderate, and severe.” This classification is based on organ/system dysfunction, limited laboratory findings, and clinical findings.^[11] Our study assessed this classification, which is considered the best indicator of conversion from laparoscopic to open surgery,^[17] in terms of predicting the need for OC in AC patients aged ≥ 65 years, who were initiated on medical treatment, and found it to have sufficient efficacy ($AUC=0.709$, $P<0.001$). However, the level of efficacy was lower than that of the laboratory parameters used in our study. We believe that this is mainly because the TokyoSC criteria may vary in the older adult patient population, especially due to comorbidities. Among our findings, the most important benefit of TokyoSC was that the need for OC was predictable, with a sensitivity of 98% in patients classified as having “moderate or severe” AC. However, the low specificity (31%) suggests that DC may not be a safe enough choice in patients classified as having “mild” AC.

WBC, NEU, and IG, which were assessed in our study, increase significantly in infectious processes due to an increased inflammatory response.^[18] Similarly, we established that AC

patients had high levels of these parameters upon admission. We also found that these parameters were significantly higher in cholecystitis cases requiring OC. IG count has been reported to be an early indicator of severe AC.^[19] In our study, the IG count, among the laboratory findings, was the most effective parameter after NLR, suggesting that it can be used in the selection of AC patients who should not waste time with conservative treatment. CRP has been reported as the most important inflammatory marker for conversion to advanced AC and open surgery and is superior to WBC and NLR.^[20] Our study found CRP to be effective in predicting the need for OC in the older adult patient group with AC, showing a sensitivity of 52.0% and a specificity of 87.7% ($P<0.001$, $AUC=0.743$). However, high serum CRP levels may result from an underlying chronic inflammatory process associated with frailty syndrome in older adults.^[21] Therefore, we believe that the lower efficacy of CRP compared to NLR and IG might be related to these chronic inflammatory processes.

Recently, several studies have used the ratios of blood parameters to each other (NLR, PLR, etc.) in the prediction of disease diagnosis and disease severity.^[22] The meta-analysis by Kler et al. stated that NLR could predict the diagnosis of AC, but no study had enough power to differentiate the severity of the disease.^[23] Despite this finding, a study concluded that an NLR of 4.18 could predict severe cholecystitis with 78.3% sensitivity and 74.3% specificity.^[24] A similar study, which was conducted in the older adult population presenting to the emergency department, reported an NLR of >9.9 which was significantly associated with severe AC.^[25] Although our study was not intended to predict the severity of AC, we also established a cutoff point of >9.9 NLR, which is a similar finding. We found that NLR had a sensitivity of 58% and a specificity of 98% in predicting the need for OC in the older adult patient group. Given that our results are correlated with TokyoSC, we conclude that NLR is a predictor of AC severity. The present study mainly examined the effect of NLR on the need for OC, which is the next step, rather than severity differentiation. The efficacy of NLR in such differentiation was found to be the highest among the study parameters ($P<0.001$, $AUC=0.825$).

Our study has a few limitations. First, this was a retrospective study. The patients' findings on admission to the emergency department were obtained from hospital records. Laboratory parameters were analyzed and recorded on the initial admission of patients to the emergency department. Therefore, the records had to be considered correct. Some patients had more than one emergency department admission due to AC. For such patients, the last admission before surgery was included in the assessment. The previous applications of these patients were excluded from the study ($n=8$). Since the study was carried out by different physicians in two centers; treatment of acute cholecystitis was not standard in all patients. The study was designed on the improvement of patients with multimodal conservative treatment. The study was designed

in the restricted age group (over 65 years). It can be thought that the response to conservative treatment will be better in younger patients. This hypothesis should be tested with further studies.

CONCLUSION

The recommended treatment for AC is EC within the 1st week (preferably within the first 72 h). However, conservative treatment plus DC is also a common treatment plan for various reasons and approaches, especially in older adult patients. We found that NLR, as well as NEU, IG, and TokyoSC, was effective in differentiating patients who needed OC while planning conservative treatment + DC for older adult patients who were followed up due to AC. If the NLR is >9.9 (98% specificity) and TokyoSC is moderate/high (98% sensitivity), EC should be preferred instead of conservative treatment + DC in older adult patients.

Ethics Committee Approval: This study was approved by the Alaaddin Keykubat University Ethics Committee (Date: 26.01.2022, Decision No: 01-03).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.K.; Design: M.K., S.Ş.; Supervision: M.K.; Resource: M.K.; Materials: M.K., S.Ş.; Data collection and/or processing: M.K., S.Ş.a.; Analysis and/or interpretation: M.K., S.Ş.a.; Literature search: M.K., S.Ş.; Writing: M.K., S.Ş., S.Ş.a.; Critical review: M.K., S.Ş.

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ORİJİNAL ÇALIŞMA - ÖZ

Akut kolesistitli yaşlı hastalarda gecikmiş acil kolesistektomi ihtiyacının göstergesi olarak kan parametrelerinin etkinliği**Dr. Mehmet Kubat,¹ Dr. Serkan Şengül,² Dr. Serdar Şahin³**¹Alanya Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Antalya, Türkiye²Alaaddin Keykubat Üniversitesi, Genel Cerrahi Ana Bilim Dalı, Antalya, Türkiye³Ahi Evran Üniversitesi, Genel Cerrahi Ana Bilim Dalı, Kırşehir, Türkiye

AMAÇ: Akut kolesistitli hastalarda erken kolesistektomi önerilmesine rağmen, konservatif tedaviyi takiben gecikmiş kolesistektomi (DC) özellikle yaşlı erişkin hastalarda oldukça tercih edilen bir yöntemdir. Bununla birlikte, bazı ciddi vakalar gecikmiş acil kolesistektomi (OC) gerektirir. Bu çalışma, laboratuvar bulgularının ve Tokyo şiddet sınıflandırmasının (TokyoSC) yaşlı hastalarda OK ihtiyacı olanları ayırt etme yeteneğini değerlendirmeyi amaçladı.

GEREÇ VE YÖNTEM: Akut kolesistitli geriatric hastaların başvuru sırasındaki laboratuvar/radyolojik/klinik bulguları ve TokyoSC geriye dönük olarak incelendi. DC ve OC grupları karşılaştırıldı.

BULGULAR: 164 hastanın yaş ortalaması 72.3 ± 6.4 idi. Beyaz kan hücresi, nötrofil (NEU), olgunlaşmamış granülosit (IG), C-reaktif protein, nötrofil-lenfosit oranı (NLR) ve TokyoSC parametrelerinin tümü farklılaşmada $p < 0,001$ 'de anlamlıydı. NLR'nin özgüllüğü %98 ve TokyoSC'nin duyarlılığı %98'dir.

SONUÇ: NLR, NEU, IG ve TokyoSC, akut kolesistit nedeniyle takip edilen yaşlı erişkin hastalarda konservatif tedavi + DC planlanırken OC ihtiyacı olan hastaları ayırt etmede etkiliydi. NLO >9.9 ve TokyoSC orta/yüksek ise yaşlı hastalarda konservatif tedavi + DC yerine erken kolesistektomi tercih edilmelidir.

Anahtar sözcükler: Akut kolesistit; C-reaktif protein; kolesistektomi, nötrofil-lenfosit oranı; şiddet derecelendirmesi; yaşlı.

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