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The role of serum and urıne neopterın levels on the determınatıon of acute cholecystıtıs severity

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Abstract

Objective Acute cholecystitis (AC) is one of the most common causes of hospital admissions due to abdominal pain. Early diagnosis and prompt initiation of treatment positively impact morbidity and mortality in AC. The aim of our study was to determine serum and urine concentrations of additional biomarkers at different stages of the disease, beyond those currently used in acute cholecystitis severity staging, and to evaluate their potential inclusion as new staging parameters.

Methods This study prospectively analyzed data from 63 patients diagnosed with acute cholecystitis and treated by the same surgical team in 2020. In patients with AC, WBC, CRP, and PCT values, as outlined in the TG18 guidelines, showed an increasing trend. These values are commonly used to determine disease stage.

Results A correlated increase in these infectious parameters was observed as disease severity progressed. The mean S-NEO value in Stage 1–2 patients was 20.082 ± 9.517 nmol/L, while the mean U-NEO value was 3.46 ± 2.95 µmol/L. In Stage 3 patients, the mean S-NEO value was 40.92 ± 7.878 nmol/L, and the mean U-NEO value was 4.4 ± 2.42 µmol/L. The Mann–Whitney *U* test revealed a significant difference in S-NEO values between Stage 1–2 and Stage 3 groups ($p < 0.001$). However, no significant difference was observed between these groups in terms of U-NEO values ($p = 0.18$).

Conclusion In patients with acute cholecystitis, S-NEO and U-NEO levels can serve as complementary biomarkers alongside existing diagnostic and staging parameters. Particularly in staging severity, S-NEO levels may play a crucial role in early diagnosis and timely initiation of treatment, given their high specificity and sensitivity at defined cut-off values.

Keywords Acute cholecystitis, Serum neopterin (S-NEO), Urine neopterin (U-NEO), Biomarker for inflammation, Inflammatory markers in cholecystitis

Introduction

Acute cholecystitis (AC) is one of the most common causes of hospital admissions due to abdominal pain. Early diagnosis and prompt initiation of treatment positively influence morbidity and mortality associated with AC [1]. The diagnosis is typically established through a combination of nonspecific local and systemic inflammatory findings observed during physical examination and laboratory tests, along with characteristic local signs such as Murphy's sign and ultrasonographic findings. Staging the severity of acute cholecystitis is crucial for

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determining the appropriate treatment modality, including timely initiation of therapy and planning for early cholecystectomy [1–4].

AC, an acute inflammatory condition of the gallbladder, arises from obstruction in the gallbladder neck or cystic duct. Among patients with asymptomatic gallstones, 1–3% may experience mild to moderate symptoms annually, while 1–2% may develop severe complications, including AC, acute cholangitis, or acute pancreatitis (AP) [5].

Neopterin, also known as 2-amino-4-hydroxy-6-(D-erythro-1′,2′,3′-trihydroxypropyl)-pteridine, is a pteridine derivative produced by activated monocytes, macrophages, dendritic cells, and endothelial cells through guanosine triphosphate (GTP) metabolism via the enzyme guanosine triphosphate cyclohydrolase 1 (GTPCH-1). It is also produced in smaller amounts by renal epithelial cells, fibroblasts, and vascular smooth muscle cells in response to stimulation by interferon-gamma (IFN-gamma). As an important indicator of monocyte activation in the inflammatory response, neopterin levels have been shown to increase in conditions where inflammation plays a significant role in pathogenesis [6, 7].

Previous studies have investigated changes in serum neopterin (S-NEO) and urinary neopterin (U-NEO) levels in various infectious and inflammatory diseases, chronic conditions such as diabetes mellitus, and malignancies [8–13]. However, no global studies have specifically examined the role of neopterin levels in staging the severity of acute cholecystitis.

The primary aim of this study was to evaluate the effectiveness of serum and urine neopterin levels in determining the severity of acute cholecystitis. Additionally, this study compared these markers with established inflammatory parameters, such as white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT), to assess their potential as supplementary tools for staging acute cholecystitis. Furthermore, the study explored whether these markers could enhance the differentiation between Stage 1, 2, and 3 patients based on the Tokyo Guidelines 2018 criteria [14].

Materials and methods

This study prospectively analyzed data from 63 patients diagnosed with acute cholecystitis who received inpatient treatment under the care of the same team at the Department of General Surgery, Gazi University Medical Faculty Hospital, in 2020. The study was approved by the Gazi University Clinical Research Ethics Committee (Decision No. 177, 24–02–2020). The diagnosis of acute cholecystitis was established according to the Tokyo Guidelines 2018 (TG18), which require the presence of at least one local inflammation finding, one systemic inflammation finding, and characteristic imaging findings.

This study was prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research [15]. The design, inclusion and exclusion criteria, statistical analyses, and results were structured according to the STROBE checklist, which has been submitted alongside the manuscript.

During 2020, a total of 85 patients presenting with suspected acute cholecystitis were assessed for eligibility. Of these, 22 patients were excluded based on the following criteria: concurrent acute cholangitis or pancreatitis, presence of active infectious diseases (e.g., respiratory or urinary tract infections), untreated malignancies, autoimmune diseases, or HIV infection. The remaining 63 patients met the inclusion criteria and were enrolled in the study. According to the Tokyo Guidelines 2018 classification, the included patients were categorized into Stage 1 ($n=$ 37), Stage 2 ($n=$ 18), and Stage 3 ($n=$ 8) (Fig. 1).

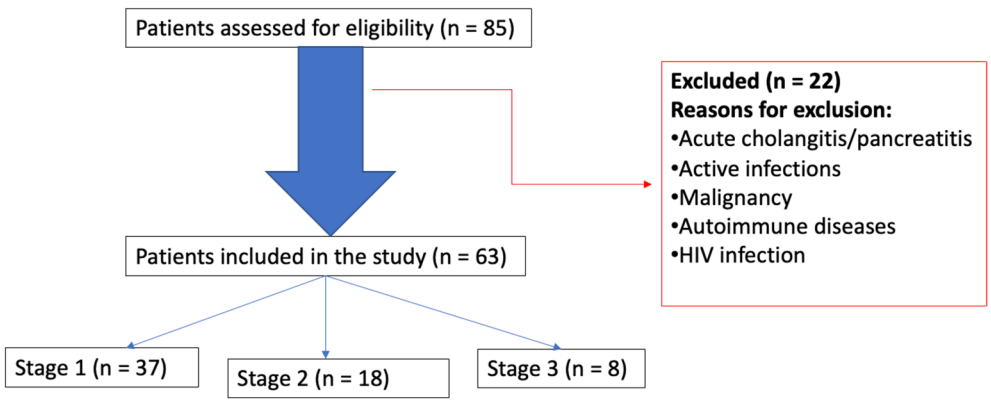


Fig. 1 Flow diagram of patient inclusion and exclusion in the study

A non-sterile midstream urine sample and 10 cc of peripheral venous blood were collected in yellow gel tubes from each consenting patient at the time of diagnosis. Blood and urine samples were stored at room temperature for a maximum of 4 h**,** then centrifuged at 3000 rpm for 15 min. The processed serum and particle-free urine were transferred to Eppendorf tubes and stored at − 20 °C until analysis.

Measurement of serum neopterin levels

Serum neopterin levels were measured using the Neopterin ELISA Kit (Immunoguide, IG-AB501SP) in the laboratories of the Gazi University Faculty of Medicine, Department of Immunology. The kit's microplate was pre-coated with a neopterin-specific antibody.

In the preparation phase, 50 µl of the sample, 100 µl of enzyme conjugate, and 100 µl of assay buffer were added to a polypropylene cup and homogenized. From this homogenized mixture, 200 µl was transferred to the monoclonal antibody-coated wells of the ELISA plate. The plate was then covered with black adhesive tape to prevent light exposure and incubated at room temperature for 90 min.

After incubation, the plate was washed four times using 350 µl of washing liquid in a BIOTEK ELx50 washing device. Tetramethylbenzidine (TMB) substrate (100 µl) was then added, and the plate was incubated in the dark for 15 min. To stop the reaction, stop solution was added, changing the color in the wells from blue to yellow. Optical density (OD) was measured at 450 nm, and neopterin levels were calculated by comparison with the standard curve. Serum neopterin levels below 10 nmol/L were considered normal in healthy individuals.

Measurement of urine neopterin levels

Urine neopterin levels were measured using the Neopterin ELISA Kit (Immunoguide, IG-AB501U). Urine samples were centrifuged at 600 *g* for 10 min and diluted 1:100 with dilution fluid (10 µl urine + 990 µl dilution fluid).

During preparation, 50 µl of the sample, 100 µl of enzyme conjugate, and 100 µl of assay buffer were added to a polypropylene cup and homogenized. From this homogenized mixture, 200 µl was transferred to the monoclonal antibody-coated wells of the ELISA plate. The plate was covered with black adhesive tape to avoid light exposure and incubated at room temperature for 90 min.

Following incubation, the plate was washed and then incubated with **T**MB substrate for 15 min. Afterward, stop solution was added, changing the color from blue to yellow. OD was measured at 450 nm, and results were converted to µmol/L by multiplying by 100 to account for the dilution.

Serum WBC, CRP, and PCT levels

Serum white blood cell (WBC), C-reactive protein (CRP), and procalcitonin (PCT) levels were measured as part of the study. WBC levels were considered normal within the range of 3900–10,900/mL. Values below 3900/mL were classified as neutropenia, while values above 10,900/mL were considered leukocytosis. CRP levels greater than 5 mg/L were classified as elevated, and PCT levels above 0.5 ng/mL were considered abnormally high.

Statistical analysis

All statistical analyses of the data obtained in the study were performed using IBM SPSS (Statistical Package for Social Sciences) Statistics Version 23.0 program. Before starting the analyses, the conformity of continuous variables to normal distribution was tested using the"Kolmogorov Smirnov Normality Test". Descriptive statistics were presented as'mean ± standard deviation'and'median (minimum–maximum)'for continuous variables and'frequency (percentage)'for categorical variables. Pearson, Chi-Square, Student t-test, Mann Whitney U test, Spearman test, One Way ANOVA, Receiver Operating Characteristic (ROC) curve analysis were used as statistical methods. Student's t-test data are explained with the relevant'p value and t value', while Mann–Whitney U Test data are explained with the relevant'p value and Z value'. Relationships between continuous variables were described by'Pearson'or'Spearman correlation coefficient (r) and the corresponding p value'. Predictive value, sensitivity and specificity values were calculated using ROC analysis. Statistical significance was accepted as $p < 0.05$.

Results

The study included 63 patients diagnosed with acute cholecystitis. The mean age was 52.93 years (± 14.31), with 39.6% ($n = 25$) female and 60.4% ($n = 38$) male. Based on the Tokyo Guidelines 2018 (TG18), 58.7% ($n = 37$) of patients were classified as Stage 1, 28.6% ($n = 18$) as Stage 2, and 12.7% ($n = 8$) as Stage 3. Elevated WBC, CRP, and PCT levels were observed in 71.4%, 93.6%, and 84% of patients, respectively. Significant differences in these markers were found across the stages ($p < 0.01$). Leukocytosis was most frequent in Stage 2 (100%) and Stage 3 (87.5%), compared to Stage 1 (54.1%) (Table 1).

Comparison of inflammatory markers

The mean WBC values increased significantly across stages. Stage 1 patients had a mean WBC of 11,607 (± 2446)/mL, while in Stage 2, the mean WBC increased to

Table 1 Distribution of clinical and laboratory parameters by acute cholecystitis stages

	Stage 1($n=37$)	Stage 2 ($n=18$)	Stage 3 ($n=8$)	Total ($n=63$)	*p*
Age (years) Mean ± SD Median [min–max]	49.05 ± 14.48 48 [21–80]	57.94 ± 12.04 58 [35–76]	59.62 ± 13.73 61 [33–77]	52.93 ± 14.31 55 [21–80]	
Gender, n (%) Male Female	20 (54.1) 17 (45.9)	14 (77.7) 4 (22.3)	4 (50) 4 (50)		
WBC, (/mL)	11,607 (± 2446)	16,917 (± 3323)	23,738(± 18,110)	14,665.23	**< 0.01***
CRP, (mg/L)	71.44 (± 68.14)	233.08 (± 110.87)	195.03(± 131.01)	133.32	**< 0.01***
Procalcitonin (ng/mL)	0.12 (± 0.13)	0.86 (± 0.84)	7.41(± 15.68)	1.26	**0.04***
S-NEO*, (nmol/L)	15.78 ± 5.05****	28.91 ± 10.52	40.92 ± 7.82	22.72 ± 11.61	**< 0.01****
U-NEO*, (µmol/L)	3.06 ± 2.56	4.28 ± 3.57	4.40 ± 2.42	3.58 ± 2.89	**0.239***

Percentages are column percentages

* Results were obtained by ANOVA test

16,917 (± 3323)/mL, and in Stage 3, it further increased to 23,738 (± 18,110)/mL ($p < 0.01$). The mean CRP values were 71.44 (± 68.14) mg/L in Stage 1, 233.08 (± 110.87) mg/L in Stage 2, and 195.03 (± 131.01) mg/L in Stage 3, with significant differences noted between the stages ($p < 0.01$). The mean procalcitonin (PCT) levels also increased significantly across the stages, with values of 0.12 (± 0.13) ng/mL in Stage 1, 0.86 (± 0.84) ng/mL in Stage 2, and 7.41 (± 15.68) ng/mL in Stage 3 ($p = 0.04$). For serum neopterin (S-NEO) and urinary neopterin (U-NEO), a significant increase was observed across all stages ($p < 0.01$). However, while U-NEO showed an increasing trend, it did not reach statistical significance ($p = 0.239$) (Table 1).

Post hoc analysis

Significant differences in WBC, CRP, PCT, and S-NEO values were observed between Stage 1 and Stage 2–3 groups ($p < 0.001$). However, for U-NEO, no significant difference was noted between the groups ($p = 0.188$). In comparisons of Stage 1–2 versus Stage 3 groups, WBC, PCT, and S-NEO values showed significant differences ($p < 0.01$), while CRP and U-NEO levels did not ($p > 0.05$) (Table 2).

Cut-off values

ROC analysis determined the optimal cut-off values for markers in staging acute cholecystitis: For WBC, a level > 20.51/mL differentiated Stage 2–3 from Stage 1 with 88.5% sensitivity and 83.8% specificity (Fig. 2A). A level > 15.735/mL differentiated Stage 3 from Stage 1–2 with 87.5% sensitivity and 78.2% specificity (Fig. 2B). For CRP, a level > 176.5 mg/L differentiated Stage 2–3 from Stage 1 with 65.4% sensitivity and 94.6% specificity (Fig. 2C). For PCT, a level > 0.219 ng/mL had 88.5% sensitivity and 83.8% specificity for Stage 2–3 vs. Stage 1 (Fig. 2D). A level > 0.868 ng/mL differentiated Stage 3 from Stage 1–2

Table 2 Comparison of ınflammatory markers between stage 1–2 vs. stage 3 and stage 1 vs. stage 2–3 patients

	Stage 1	Stage 2–3	*p*	Z	T
WBC, (/mL)	11,607(± 2446)	19,016 (± 10,471)	**< 0.001****	− 5.298**	
CRP, (mg/L)	71.44 (± 68.14)	221.37 (± 116.12)	**< 0.001****	− 5.040**	
Procalcitonin, (ng/mL)	0.12 (± 0.13)	2,87 (± 8.88)	**< 0.001****	− 5.782**	
S-NEO, (nmol/L)	15.786 ± 5.05	32.607 ± 11.16	**< 0.001***		− 8.079*
U-NEO, (µmol/L)	3.06 ± 2.56	4.31 ± 3.21	0.188*		− 1.725*
	Stage 1–2	**Stage 3**	***p***	**Z**	
WBC, (/mL)	13,345(± 3713)	23,738 (± 18,110)	**0.009****	− 2.622**	
CRP, (mg/L)	124.34 (± 113.24)	195.03 (± 131.01)	0.107**	− 3.418**	
Procalcitonin, (ng/mL)	0.36 (± 0.59)	7.41 (± 15.68)	**0.001****	− 1.610**	
S-NEO, (nmol/L)	20.082 ± 9.517	40.92 ± 7.878	**< 0.001****	− 4.087**	
U-NEO, (µmol/L)	3.46 ± 2.95	4.4 ± 2.42	0.180**	− 1.342**	

* Calculated by Student *t* test

**Calculated by Mann Whitney *U* test

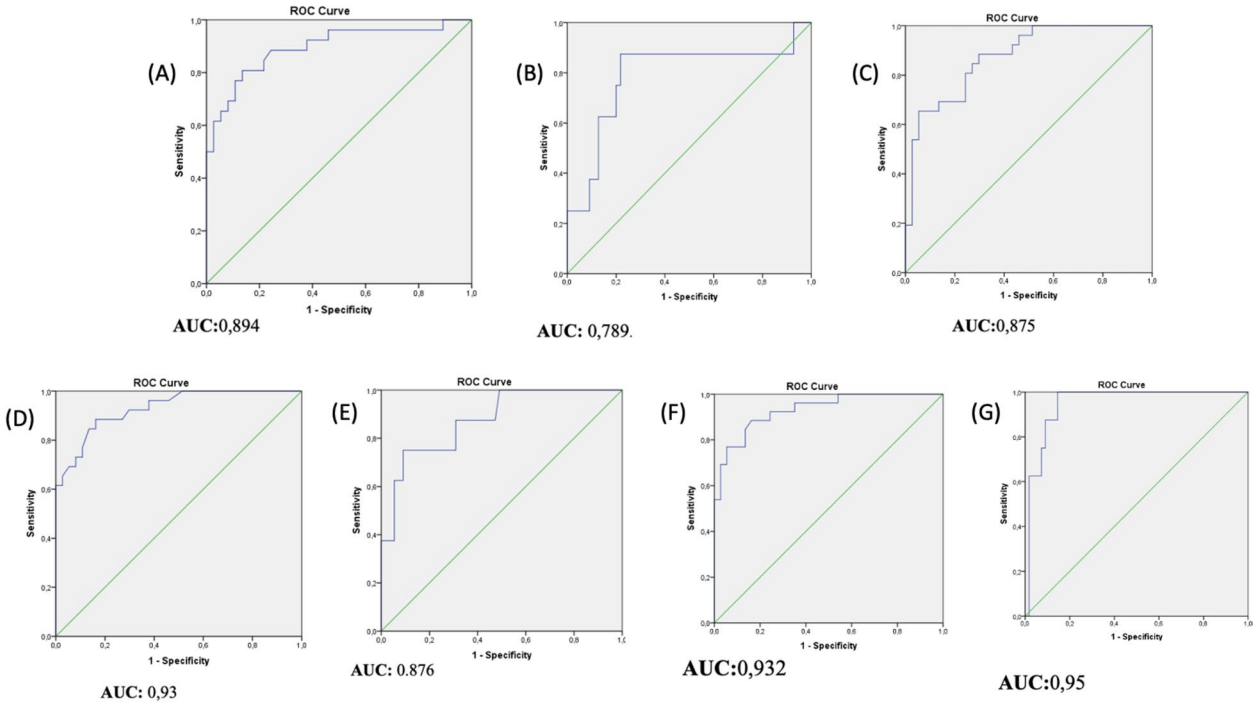


Fig. 2 ROC analysis of ınflammatory markers for acute cholecystitis severity staging

with 75% sensitivity and 90.9% specificity (Fig. 2E). For S-NEO, a level >20.51 nmol/L differentiated Stage 2–3 from Stage 1 with 88.5% sensitivity and 83.8% specificity (Fig. 2F). A level >27.6 nmol/L differentiated Stage 3 from Stage 1–2 with 100% sensitivity and 85.5% specificity (Fig. 2G).

Correlation analysis

The Spearman correlation test revealed statistically significant positive relationships between several inflammatory markers. A strong positive correlation was found between WBC and CRP ($r = 0.5$, $p < 0.001$), as well as between CRP and PCT ($r = 0.651$, $p < 0.001$). Similarly, a significant positive correlation was observed between PCT and S-NEO ($r = 0.684$, $p < 0.001$) and between S-NEO and U-NEO ($r = 0.400$, $p < 0.001$). However, no significant correlation was identified between WBC and U-NEO ($r = 0.198$, $p = 0.119$) (Table 3).

Discussion

Acute cholecystitis (AC) is a common cause of hospital admissions due to abdominal pain. Early diagnosis and timely initiation of treatment significantly reduce morbidity and mortality in AC [1]. Staging the severity of AC is essential for determining appropriate treatment modalities, such as early cholecystectomy planning [1–3]. One globally accepted guideline for staging the severity of AC is the Tokyo Guidelines 2018 (TG18) [14].

In a study conducted by Wright et al., involving 445 patients with AC, the mean age was 61.6 (± 19.1) years, with 56.4% ($n = 251$) male and 43.6% ($n = 194$) female. In comparison, our study's mean age was slightly lower at 52.93 (± 14.31) years, and the gender distribution was similar, with 57.1% ($n = 36$) male and 42.9% ($n = 27$) female [16].

WBC and CRP are widely used diagnostic markers for AC and are integral in staging disease severity. In a study by Ambe et al., including 138 patients, WBC and CRP levels increased progressively with disease severity. Significant differences were observed between stage 1 and 2 and between stage 1 and 3. However, no significant differences were found between stage 2 and 3 [17]. Similarly, in our study, WBC and CRP levels significantly increased with disease severity ($p < 0.001$), and significant differences were observed between stage 1 and 2 ($p < 0.001$ for both markers). Unlike Ambe et al., our study found no significant differences between stage 1 and 3 ($p = 0.210$ for WBC and $p = 0.087$ for CRP). This discrepancy may be attributed to the low number of stage 3 patients in our study, underscoring the need for larger sample sizes in future research.

Procalcitonin (PCT) is an inflammatory marker that increases within 3–4 h of bacterial infections and is detectable earlier than CRP [18]. Yüzbaşıoğlu et al. demonstrated significant differences in PCT levels between AC stages 1, 2, and 3. The study reported a

Table 3 Correlation analysis between ınflammatory markers in acute cholecystitis patients

Parameters		WBC	CRP	PCT	S-NEO	U-NEO
WBC	R	1.000	0.568	0.564	0.495	0.198
	p		**< 0.001**	**< 0.001**	**< 0.001**	**0.119**
	N	63	63	63	63	63
CRP	R	0.568	1.000	0.651	0.493	0.285
	p	**< 0.001**		**< 0.001**	**< 0.001**	**0.024**
	N	63	63	63	63	63
PCT	R	0.564	0.651	1.000	0.684	0.373
	p	**< 0.001**	**< 0.001**		**< 0.001**	**0.003**
	N	63	63	63	63	63
S-NEO	R	0.495	0.493	0.684	1.000	0.400
	p	**< 0.001**	**< 0.001**	**< 0.001**		**0.001**
	N	63	63	63	63	63
U-NEO	R	0.198	0.285	0.373	0.400	1.000
	p	**0.119**	**0.024**	**0.003**	**0.001**	
	N	63	63	63	63	63

R: correlation coefficient, p: Spearman correlation analysis

cut-off value of 0.52 ng/mL (95.45% sensitivity, 46.67% specificity) for distinguishing stage 1 from stages 2 and 3, and 0.8 ng/mL (72.4% sensitivity, 90.06% specificity) for distinguishing stage 3 from stages 1 and 2 [19]. In line with these findings, our study also showed significant differences in PCT levels between stages ($p = 0.04$). Additionally, PCT levels above 0.219 ng/mL had 88.5% sensitivity and 83.8% specificity for differentiating stage 1 from stages 2 and 3, while levels above 0.868 ng/mL had 75% sensitivity and 90.9% specificity for differentiating stage 3 from stages 1 and 2. These results support the utility of PCT as a biomarker for AC staging.

Neopterin, a pteridine derivative produced by activated monocytes, macrophages, dendritic cells, and endothelial cells, is known to increase in both intracellular and extracellular bacterial infections. These findings suggest that S-NEO may serve as a valuable adjunct biomarker, particularly in advanced stages of acute cholecystitis, where traditional markers may lack specificity or sensitivity.

In our study, serum (S-NEO) and urinary neopterin (U-NEO) levels were evaluated in AC patients. S-NEO levels showed a significant increase with disease severity ($p < 0.01$), with significant differences between stages 1 and 2, 1 and 3, and 2 and 3 ($p < 0.001$, $p < 0.001$, $p = 0.014$, respectively). Furthermore, significant correlations were observed between S-NEO levels and traditional biomarkers such as WBC, CRP, and PCT (Spearman, $p < 0.001$ for all).

While S-NEO levels showed promise as a marker for disease severity, U-NEO levels, though elevated in AC cases, did not correlate with disease severity. This discrepancy may be due to impaired renal clearance in severe cases, particularly in stage 3 patients.

Conclusion

In patients with acute cholecystitis, WBC, CRP, and PCT values used in the TG18 guideline increase. These values are used to determine the stage of the disease. In our study, a correlated increase in these infective parameters was observed as the severity of the disease increased.

In patients with acute cholecystitis, S-NEO and U-NEO levels can be used in addition to existing biomarkers for diagnosis and clinical staging. Especially in determining the stage of the disease, it is thought that S-NEO levels may be of great help in early diagnosis and rapid initiation of treatment, with cut-off values exhibiting high specificity and sensitivity.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02616-1.

Additional file 1

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Author contributions
M.Y., YF.A., R.K., M.Ş., C.A. wrote the main manuscript text. M.Y. prepared tables. YF.A. prepared figures. All authors reviewed the manuscript.

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Data availability
The database of this study is open to sharing. It can be obtained from the authors upon request.

Declarations

Ethics approval and consent to participate
Approval for this study was obtained from the Gazi University Faculty of Medicine Institutional Review Board Ethics Committee, and signed informed consent forms were obtained from all patients.

Animal and human rights statement
All procedures performed in this study were by the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards. No animal or human studies were performed by the authors for this article.

Scientific responsibility statement
The authors declare that they are responsible for the scientific content of the article, including study design, data collection, analysis and interpretation, writing, part or all of the outline, preparation and scientific review of the content, and approval of the final version of the article.

Consent for publication
Consent for publication was obtained from all participants.

Competing interests
The authors declare no competing interests.

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