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Evaluation of progranulin and inflammatory markers in the diagnosis of acute cholecystitis

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Abstract

This study aimed to investigate the role of inflammatory markers and progranulin levels in diagnosing cholecystitis, assessing their potential as diagnostic biomarkers. The research involved 54 patients diagnosed with acute cholecystitis in the emergency department. Routine complete blood count and biochemistry analyses were conducted. Blood samples were obtained, centrifuged, and stored at -80°C. Progranulin levels in sera were assessed using a spectrophotometric method. Statistical analysis was carried out using SPSS v.22.0, revealing significant variances between patients and healthy controls. Acute cholecystitis patients exhibited elevated levels of inflammatory markers (white blood cells, C-reactive protein, procalcitonin) and decreased progranulin levels compared to controls. Progranulin showed a high sensitivity (86.5%) and specificity (87.5%) in diagnosing acute cholecystitis. Other markers had varying sensitivity and specificity values. Inflammatory markers, particularly progranulin, show promise in diagnosing cholecystitis. Evaluating these markers together can enhance diagnostic accuracy. Further studies are needed to validate these findings and explore progranulin's specificity to cholecystitis.

Keywords: Acute cholecystitis, inflammatory markers, c-reactive protein, procalcitonin, progranulin

Introduction

Acute cholecystitis (AC) is characterized by inflammation of the gallbladder and is a common condition that requires emergency surgical intervention. It typically arises due to the blockage of the bile duct by gallstones and biliary sludge. Additionally, biliary tract issues, tumors, severe illnesses, and certain infections can also lead to cholecystitis [1-3]. In the pathophysiology of AC, both chemical and bacterial inflammation of the gallbladder are frequently observed. Among individuals with gallstones, 1-4% may present with AC, gallstone pancreatitis and choledocholithiasis. Obstruction of the gallbladder leads to the accumulation of bile, gallstones, and biliary sludge, increasing the pressure within the gallbladder. Patients typically present with symptoms such as right upper quadrant pain, nausea, vomiting, and fever. In the emergency department, clinical and laboratory parameters such as Murphy's sign and elevated leukocytes are used for diagnosis. However, these parameters alone are insufficient. Biochemical markers such as C-reactive protein (CRP), procalcitonin (PCT), white blood cell count (WBC) and the neutrophil/lymphocyte ratio (NLR) are considered potential predictors in the diagnosis of AC [1-4].

Progranulin (PGRN) is a glycoprotein-based growth factor involved in various physiological (e.g., wound healing) and pathological processes. PGRN is highly expressed by neutrophils and is converted into granulins, which attract additional neutrophils to the site of inflammation. Neutrophils, as the first line of defense, produce reactive oxygen species and secrete granule contents that kill infections, providing rapid responses to tissue damage and microbes. The secretory leukocyte protease inhibitor (SLPI) binds to PGRN, playing a crucial role in controlling inflammation [5,6].

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Progranulin is known as a critical protein that plays a role in various biological processes and modulates the inflammatory response. In recent years, research on the role of progranulin in the pathogenesis of inflammatory diseases has increased. In this context, the effect of progranulin levels on the acute inflammatory response and disease progression has been found to be notable.

Although numerous studies have explored the use of various inflammatory biomarkers in diagnosing acute cholecystitis, there is limited data on the use of progranulin levels for this purpose. A better understanding of the inflammatory response and the identification of new biomarkers for diagnosing acute cholecystitis are crucial for providing early and accurate treatment to patients.

This study aimed to investigate the role of inflammatory markers and progranulin levels in the diagnosis of acute cholecystitis, evaluating their potential as diagnostic biomarkers. The findings may offer significant insights into the use of new and effective biomarkers for acute cholecystitis.

In this context, examining the relationships between progranulin and other inflammatory markers is considered an important step in the clinical management of patients.

Material and Methods

The study is a cross-sectional observational epidemiological study aiming to determine the sensitivity and specificity of new biomarkers that can be used in the diagnosis of acute cholecystitis. The study was conducted between March 2023 and June 2023. Patients who visited the emergency department, were over 18 years old, had no other serious comorbidities, and were diagnosed with acute cholecystitis were included in the study. The control group was selected by matching the age and gender of the patient group. Patients under 18 years old and patients over 18 years old who were not diagnosed with acute cholecystitis were excluded from the study. This study included 54 patients diagnosed with acute cholecystitis and 24 healthy individuals.

The diagnosis of patients presenting to the emergency department with suspected acute cholecystitis was made using routine diagnostic methods, including complete blood count, CRP, and medical imaging. Blood samples from patients with acute cholecystitis and from healthy individuals in the control group were collected into tubes without anticoagulant. After allowing the blood to clot, the samples were centrifuged at 4000 rpm for 10 minutes, and the serum portion was separated. The serum samples were stored frozen at -80°C until analysis. On the day of analysis, the samples were thawed. Progranulin levels in these sera were then measured and evaluated using a spectrophotometric method.

Statistical analysis was performed using SPSS v.22.0. Qualitative data were presented as frequencies and percentages, while numerical data were presented as means and standard deviations. Parametric assumptions were assessed for the One Sample T-test, while the One Sample Wilcoxon Signed Rank Test was used for non-parametric data. The t-test or Mann-Whitney U test was used for comparing quantitative data between two groups. The Chi-square ($\chi 2$) test was used for comparing qualitative data.

Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic characteristics of the biomarkers. Cut-off values in ROC analysis were determined using the Youden index. Sensitivity, specificity, positive, and negative likelihood ratios were calculated. Statistical significance was set at $p<0.05$ for AUC in ROC analysis and $p<0.01$ for other analyses.

The study was approved by the decision of Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee session no: 2022/26, decision no: 05, dated 27.09.2022. The study is consistent with the principles of the Declaration of Helsinki.

Results

This study included 54 patients diagnosed with acute cholecystitis and 24 healthy control individuals. The results present a detailed analysis of the hemogram and biochemical test results between the two groups.

Demographic Characteristics

The mean age of patients with acute cholecystitis was 57.9±19.87 years, while the mean age of the control group was 50.67±9.83 years. The age range for the cholecystitis group was between 22 and 97 years, and for the control group, it was between 32 and 79 years (Table 1).

Clinical and Laboratory Findings

White Blood Cell Count: The average white blood cell count in acute cholecystitis patients was 11238 mm³ (±4724.94). In the control group, the average WBC count was 7399 mm³ (±1629.60) (Table 1). This indicates a significantly higher white blood cell count in the cholecystitis patients compared to the control group.

Neutrophil Count: The average neutrophil count in cholecystitis patients was 8783 mm³ (±4700.52). In the control group, it was 4175 mm³ (±1197.58). The percentage of neutrophils in cholecystitis patients was on average 75.7% (±11.94), compared to 55.97% (±7.37) in the control group. This shows that neutrophil count and percentage are significantly elevated in the cholecystitis patients.

Platelet Count: The average platelet count in cholecystitis patients was 240000 (±90.000). In the control group, the platelet count was 267000 (±62000). No significant difference was observed in platelet count between the two groups.

C-Reactive Protein: The average CRP level in acute cholecystitis patients was 74.9 mg/dL (±108.41). In the control group, the average CRP level was 4 mg/dL. This result indicates that CRP levels are significantly higher in cholecystitis patients compared to the control group.

Procalcitonin: The average procalcitonin level in cholecystitis patients was 3.0 µg/L (±6.38). These values indicate that

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procalcitonin levels are significantly elevated in cholecystitis patients. The procalcitonin values for the control group were not specified in this study.

Progranulin: The average progranulin level in acute cholecystitis patients was 118.2 ng/mL (±36.34). In the control group, the average progranulin level was 248.61 ng/mL (±186.34). These findings show that progranulin levels are significantly lower in cholecystitis patients compared to the control group.

Our ROC analysis results show that progranulin has high sensitivity and specificity in diagnosing AC (Figure 1).

Table 1. Demographic characteristics, hemogram and biochemistry analysis results of the patients diagnosed with acute cholecystitis and the healthy control group

	Patient				Control			
	Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
Age	57.9	19.87	22	97	50.6667	9.83	32	79
CRP*	74.9	108.41	1	470	4	0	-	-
WBC	11238	4724.94	4240	22530	7399	1629.60	4970	11010
Neutrophil count	8783	4700.52	1780	20320	4175	1197.58	2120	7120
Neutrophil percentage	75.7	11.94	42	93.1	55.9708	7.37	40.5	68.4
Lymphocyte count	1532	791.57	380	4410	2418	542.40	1480	3610
Lymphocyte percentage	16.0	9.56	2.2	38	33.2292	6.20	20.6	44.1
Platelet (10^3)	240	90	42	414	267	62	158	39
Procalcitonin*	3.0	6.38	0.02	23	0.046	0	-	-
Progranulin	118.2	36.34	69.16	267.5	248.61	186.34	124.63	1046.2

CRP: c-reactive protein, PCT: procalcitonin, SD: standard deviation. WBC: white blood count; *The relevant variables were not studied in the control group and were compared with normal values in the literature (Procalcitonin: <0.046, CRP: <4.0)

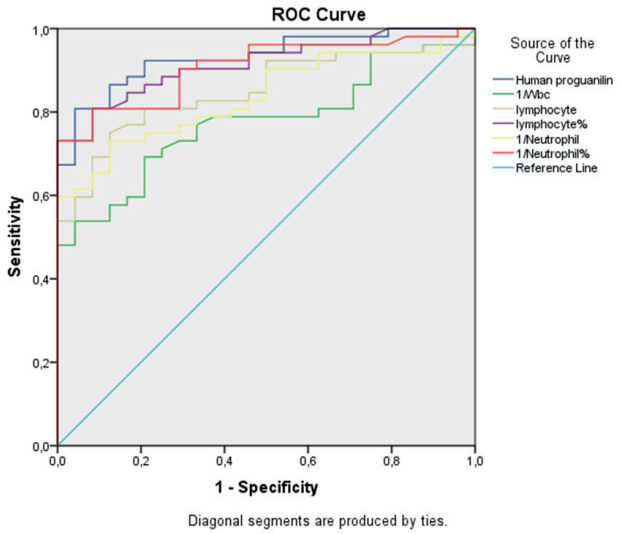

Figure 1. Roc Analysis of hemogram and biochemistry analysis results of the patients diagnosed with acute cholecystitis; Smaller test result indicates more positive test, Roc curve; Values in groups were calculated using the ROC curve

ROC Analysis and Test Performance

Progranulin: ROC analysis showed that progranulin has a high sensitivity (86.5%) and specificity (87.5%) for diagnosing acute cholecystitis. The cutoff value for progranulin was <144.54 ng/mL. The ROC curve indicates that progranulin could be an effective biomarker for improving diagnostic accuracy (Table 2 and Figure 1).

White Blood Cell Count: The cutoff value for WBC was 7520 mm³. At this threshold, the sensitivity was 77.4%, and the specificity was 66.7%. ROC analysis suggests that WBC contributes to diagnostic accuracy but has lower performance compared to other biomarkers.

Lymphocyte Count: The cutoff value for lymphocyte count was 2.105 mm³. Sensitivity at this level was 80.8%, and specificity was 79.2%. ROC analysis indicates that lymphocyte count significantly affects diagnostic value.

Lymphocyte Percentage: The cutoff value for lymphocyte percentage was 27.45%. Sensitivity at this level was 84.6%, and specificity was 83.3%. ROC analysis shows that lymphocyte percentage is effective in enhancing diagnostic accuracy.

Neutrophil Count: The cutoff value for neutrophil count was 5005 mm³. Sensitivity at this level was 75.5%, and specificity was 79.2%. ROC analysis indicates that neutrophil count contributes to diagnostic accuracy.

Neutrophil Percentage: The cutoff value for neutrophil percentage was 64.65%. Sensitivity at this level was 81.1%, and specificity was 91.7%. ROC analysis reveals that neutrophil percentage significantly enhances diagnostic accuracy.

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Table 2. Cut-off, sensitivity and specificity values of hemogram and biochemistry analysis results of the patients with acute cholecystitis and the healthy control group

	Cut-off	Sensitivity	Specificity	AUC	95% CI	p[a]
Human progranulin	144.54	86.5	87.5	0.931	0.877-0.986	<0.001
WBC (10^3/µL)	7520	77.4	66.7	0.778	0.677-0.879	<0.001
Lymphocyte count	2105	80.8	79.2	0.850	0.765-0.935	<0.001
Lymphocyte percentage	27.45	84.6	83.3	0.915	0.854-0.976	<0.001
Neutrophil count	5005	75.5	79.2	0.840	0.754-0.926	<0.001
Neutrophil percentage	64.65	81.1	91.7	0.909	0.845-0.973	<0.001

[b]Smaller test result indicates more positive test

Discussion

Acute cholecystitis is the rapid and inflamed inflammation of the gallbladder. This condition often occurs due to gallstones and can lead to serious complications. Diagnosis is based on history, physical examination findings, laboratory tests, and imaging results [1-3]. Ultrasound and computed tomography can be used for diagnosis but may not be available in every hospital [1,3,4]. Therefore, some serological markers can also be helpful in diagnosis. Considering the role of inflammatory, ischemic, and oxidative stress markers, studies investigating these markers are important. These data demonstrate the importance of evaluating inflammatory markers (WBC, CRP, NLR, procalcitonin) in the diagnosis and management of patients diagnosed with acute cholecystitis. This study investigated the role of inflammatory markers and progranulin levels in the diagnosis of AC.

In the study by Fransvea et al., it was found that in patients, the white blood cell level was 10800 mm^3 (range: 8300-14900), CRP level was 25 mg/L (range: 11-40), and procalcitonin level was 0.11 ng/mL (range: 0.05-0.56) [7]. The study by Fransvea et al. supports the use of these markers in the diagnosis of acute cholecystitis, but it should be emphasized that evaluating these markers alone may not be sufficient.

In a study by Bouassida et al. [8], it was determined that in patients, the white blood cell level was 15015 mm^3 (range: 12500–39800), neutrophil/lymphocyte ratio was 5.04 (range: 0.82–11.9), and CRP level was 126 mg/L (range: 6–371). The findings of Bouassida et al. suggest that particularly high NLR and CRP levels may be determinants in the diagnosis of acute cholecystitis. This implies that these markers are important in assessing the severity of the disease and the degree of inflammatory response.

In the study by Gokce et al. [9], it was found that in patients diagnosed with acute cholecystitis, the neutrophil/lymphocyte ratio (range: 5.8±6.1), platelet/lymphocyte ratio (range: 172.3±91.1), white blood cell count (range: 9600±400 mm^3), and CRP level (range: 25.6±55.5 mg/L) were significantly higher compared to those without acute cholecystitis. The study by Gökçe et al. indicates that markers such as NLR, PLR, WBC, and CRP have a strong diagnostic value in patients diagnosed with acute cholecystitis, but evaluating these markers together may yield more accurate results.

Similarly, a study by Server et al. [10] found that in the acute cholecystitis group, WBC, CRP, and neutrophil/lymphocyte ratio were significantly higher (WBC>9000 mm^3, CRP>29.0, and NLR>4.3, respectively). The findings of Server et al. suggest that WBC, CRP, and NLR are important in acute cholecystitis. The combined evaluation of these markers may be more effective in the diagnosis and treatment process.

Finally, in the study by Şakalar et al. [11], it was found that the blood procalcitonin level of patients diagnosed with acute cholecystitis was 5.82±2.58 ng/mL (range: 0.1-221.3), white blood cell level was 12046±703 /mm^3 (range: 700-50370), and CRP level was 6.79±1.25 mg/L (range: 0.32-90.4). The study by Şakalar demonstrates that markers such as procalcitonin, WBC and CRP are associated with high values in the diagnosis of acute cholecystitis.

Proper evaluation of these markers can play an important role in managing the disease. However, it should be noted that they should be individually evaluated for each patient and considered in conjunction with clinical findings.

This study investigated the role of inflammatory markers and progranulin levels in the diagnosis of acute cholecystitis. Our findings indicate that inflammatory markers are elevated, while progranulin levels are decreased in AC. These results suggest that inflammatory markers and progranulin may aid in the diagnosis of AC.

The finding of low progranulin levels in AC patients is particularly interesting. Literature indicates that progranulin has anti-inflammatory properties and plays a role in regulating the inflammatory response. In this context, low progranulin levels in AC patients may suggest increased consumption of progranulin in states of heightened inflammatory response. This finding implies that progranulin could play a significant role in the inflammation process and may serve as a novel biomarker for the diagnosis of AC.

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Our ROC analysis results show that progranulin has high sensitivity and specificity in diagnosing AC. This suggests that progranulin, when used alongside other inflammatory markers, could improve diagnostic accuracy for AC. The high sensitivity and specificity of progranulin are particularly important in reducing false-negative and false-positive results in AC diagnosis.

These findings highlight the role of progranulin in the pathophysiology of AC. Progranulin is known to have anti-inflammatory properties. Therefore, low progranulin levels in AC patients may indicate excessive activation and uncontrolled spread of inflammation. This supports the use of progranulin as a potential biomarker to explain the inflammation-related complications of AC. Moreover, it suggests that progranulin could be an alternative to other diagnostic methods for AC, which are often costly and invasive.

Our study also examined the relationship between progranulin and common inflammatory markers used in the diagnosis of AC. Correlation analyses show a negative relationship between progranulin levels and WBC, CRP, and PCT. These results suggest that progranulin could be a comparable alternative or an additional biomarker to the existing inflammatory markers used in the diagnosis of AC.

The findings of our study indicate that evaluating inflammatory markers and progranulin together in clinical practice could enhance the diagnostic accuracy of AC. Inflammatory markers, particularly progranulin, show promise in diagnosing AC. Evaluating these markers together can enhance diagnostic accuracy. Further studies are needed to validate these findings and explore progranulin's specificity to AC.

This study is the first and important study to investigate the levels of progranulin in patients with acute cholecystitis. This study shows that there is a significant difference in progranulin levels between patients with acute cholecystitis and healthy individuals.

This research offers a notable contribution to the literature by examining the role of inflammatory markers and progranulin levels in the diagnosis and prognosis of acute cholecystitis. The study's findings highlight the potential of these biomarkers to enhance diagnostic accuracy and improve patient management.

Our study also has limitations. For example, being based on data from a single center may limit the generalizability of our findings. This situation limits the generalizability of the study results. Conducting multicenter studies may increase the applicability of the results to a larger population.

Conclusion

In the diagnosis of acute cholecystitis, leukocyte, C-reactive protein, and procalcitonin values were found to be significantly higher in patients diagnosed with cholecystitis compared to the control group. Progranulin levels were found to be lower in patients with acute cholecystitis. Overall, this study highlights the importance of inflammatory markers and progranulin in acute cholecystitis, suggesting that evaluating these markers together can guide clinicians in the diagnostic process.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval for our study was obtained from KSÜ Faculty of Medicine Ethics Committee (Date: 27.09.2022 Session No: 2022/26 Decision No: 05). Our study is consistent with the ethical guidelines of the 1975 Declaration of Helsinki.

Patient Informed Consent
Permission was obtained from the participants of the study with an informed consent form.

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