

# Can fibrinogen level be a criterion in choosing the treatment option in patients with acute cholecystitis?

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**Abstract. – OBJECTIVE:** We aimed to investigate whether there is a relationship between blood fibrinogen levels during hospitalization of patients hospitalized for conservative treatment due to acute cholecystitis (AC) in our clinic. Patients underwent surgery and were discharged with medical treatment.

**PATIENTS AND METHODS:** The files of 118 patients who were hospitalized due to the diagnosis of AC and planned for conservative medical treatment in our clinic between January 2018 and February 2020 were recorded, prospectively. The patients were divided into two groups as those who responded to conservative treatment (Group 1), and those who were operated urgently despite conservative treatment (Group 2). Increase in gallbladder wall thickness, presence of pericholecystic fluid and hydrops sac on ultrasound and computed tomography (CT) were considered significant for the diagnosis of acute cholecystitis. Blood fibrinogen levels were measured in all patients during hospitalization.

**RESULTS:** The mean age of 118 patients included in the study was 58.32 (19-96) years. There were 77 patients in Group 1 and 41 patients in Group 2. Serum fibrinogen level was found to be 298.34±111.7 mg/dl in Group 1 and 637±124.5 mg/dl in Group 2, and a statistically significant difference was found ( $p<0.001$ ). When the cut-off value for the fibrinogen level was taken as 564.50 mg/dl, the sensitivity and specificity of the test were found to be 75.6% and 61%, respectively in showing surgical treatment.

**CONCLUSIONS:** As a result of our study, we concluded that when the data obtained are evaluated, it should be kept in mind that despite medical treatment, there is an urgent need for an operation in patients with acute cholecystitis, and in patients with high plasma fibrinogen level (cut-off) at first admission.

*Key Words:*

Acute cholecystitis, Fibrinogen, Surgery.

## Introduction

Acute cholecystitis (AC) is an inflammation of the gallbladder that occurs as a result of long-term obstruction of the cystic duct<sup>1</sup>. The most common cause of obstruction is gallstones. Obstruction caused by gallstones may develop edema, ischemia, necrosis and ulcer in the gallbladder. In many patients, the disease can be self-limiting with no excessive symptoms. In addition, it may cause complications such as perforation, abscess, peritonitis and sepsis in patients with ongoing cystic duct obstruction. A positive Murphy sign as well as local inflammation findings such as palpable mass, pain or tenderness in the right upper quadrant of the abdomen are expected in the diagnosis of this disease. Local inflammation is often accompanied by fever, increased white blood cells (WBC) and elevated C-reactive protein levels. Radiologically, ultrasonography (US) and computed tomography (CT) can be used for diagnosis.

Severity assessment criteria have been determined in order to reduce mortality and morbidity rates in patients with acute cholecystitis and to provide early and most appropriate treatment. To optimize the treatment and provide a better prognosis in patients, clinically accurate assessment of the severity of AC is required. Updated Tokyo Guidelines 2018 (TG18)<sup>2</sup> for risk classification of patients with AC are used to plan the appropriate treatment strategy and to identify useful predictors for prognosis.

Despite being the gold standard treatment for AC, the timing of laparoscopic cholecystectomy (LC) is still being debated today. Basically, there are 2 approaches in the treatment of AC. The first one is the early surgical method and the second

one is the conservative treatment method. In the conservative treatment method, antibiotics are used until the inflammation is completely healed, followed by delayed LC 4-6 weeks later<sup>3</sup>. In conservative treatment, clinic does not regress in some of the patients despite medical treatment and emergency LC is performed<sup>4</sup>.

Several laboratory parameters have been examined<sup>5</sup> in the literature for the evaluation of AC severity and diagnosis. Fibrinogen, a polar phase reactant, is synthesized by hepatocytes and is a soluble glycoprotein weighing 340 kDa<sup>6</sup>. It consists of three polypeptide chains called  $\alpha$ ,  $\beta$  and  $\gamma$  and has plasma levels of 150-400 mg/dl<sup>7</sup>. The serum fibrinogen level is generally increased in any acute inflammatory condition and is expected to increase in AC as well<sup>8</sup>.

In our study, we aimed to investigate whether or not there is a relationship between the blood fibrinogen levels in patients during hospitalization and the blood fibrinogen levels in patients who underwent conservative treatment in our clinic due to AC, but the clinical symptoms did not improve despite medical treatment and were operated.

## Patients and Methods

This retrospective case-control study was approved by the Ethics Committee of the Harran University Faculty of Medicine (approval No.: 13.07.2017-07). The files of 118 patients who were hospitalized due to the diagnosis of AC and planned for conservative medical treatment in our clinic between January 2018 and February 2020 were recorded, prospectively. This study was performed in accordance with the Helsinki Declaration and current ethical guidelines and was approved by the institutional research and Ethics Committee. The patients were divided into two groups as those who responded to conservative treatment (Group 1), and those who were operated urgently despite conservative treatment (Group 2). The demographic characteristics of the patients such as age, gender, blood fibrinogen level, white blood cell count, type of surgery, hospitalization period, mortality and morbidity rates were recorded. After 4-6 weeks, the patients in Group 1 were discharged with the recommendation of cholecystectomy, due to improvement in clinical and physical examination findings after medical treatment. Since clinical and physical examination findings in patients in Group 2 did not improve during medical treatment, the patients

were operated under emergency conditions after obtaining their consent.

The patients in the emergency ward were diagnosed with acute cholecystitis; a sign of local inflammation (Murphy's sign or right upper quadrant tenderness/pain), systemic inflammation [fever, elevated C-reactive protein (CRP) level/white blood cell (WBC) count], and findings by abdominal computed tomography (CT) and ultrasound were evaluated. Increase in gallbladder wall thickness, presence of pericholecystic fluid and hydrops sac on ultrasound and CT were considered significant for the diagnosis of acute cholecystitis. Blood fibrinogen levels were measured in all patients during hospitalization.

Classic 4-port laparoscopic cholecystectomy was performed on the patients who underwent surgery. Cholecystectomy was performed with a right subcostal incision in other patients.

## Statistical Analysis

SPSS 20 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Numerical data were presented as mean  $\pm$  standard deviation. One-Sample Kolmogorov-Smirnov test was used to evaluate the distribution of numerical data. Independent Sample *t*-test was used to evaluate numerical data with normal distribution between groups. The Mann-Whitney U test was used to compare the data where the distribution was not normal. Chi-square test was used to compare non-numerical data. The difference was considered statistically significant when the *p*-value was found to be  $<0.05$ . The diagnostic performance of serum fibrinogen levels was evaluated by analyzing ROC curves.

## Results

The mean age of 118 patients included in the study was 58.32 (19-96) years. There were 77 patients in Group 1 and 41 patients in Group 2. There was no significant difference between the groups in terms of age and gender (Table I). Percutaneous cholecystostomy was performed in 7 of 41 patients who did not respond to medical treatment (Group 2) due to the high risk of surgery. The operation was completed laparoscopically in 31 patients who underwent surgery. The remaining 3 patients underwent open surgery due to severe adhesions and failure to reveal anatomical structures. In the operated group, wound infection was observed in 6 of the patients, post-op

**Table I.** Association between demographic variables and groups.

	Group 1 (n=77)	Group 2 (n=41)	p-value
Gender			
Female	47	22	
Male	30	19	0.439
Age (year)	59.8 (19-96)	55.4 (20-96)	0.255

atelectasis in 4 patients, biliary fistula in 1 patient, and mortality in 1 patient, respectively.

Serum fibrinogen level was found to be  $298.34 \pm 111.7$  mg/dl in Group 1 and  $637 \pm 124.5$  mg/dl in Group 2, and a statistically significant difference was found ( $p < 0.001$ ). When the cut-off value for the fibrinogen level was taken as 564.50 mg/dl, the sensitivity and specificity of the test were found to be 75.6% and 61% respectively in showing surgical treatment. The number of white blood cells was  $12.93 \pm 5.38$  in Group 1 and  $14.8 \pm 4.7$  in Group 2, and no statistically significant difference was found ( $p > 0.005$ ). Mean hospital stay was  $4.1 \pm 3.9$  days in Group 1 and  $4.85 \pm 3.2$  days in Group 2, and no statistically significant difference was found ( $p > 0.005$ ) (Table II). ROC curves were plotted to estimate the effectiveness of serum fibrinogen level in the diagnosis of acute cholecystitis (Figure 1).

## Discussion

AC is defined as gallbladder inflammation and is usually caused by obstruction of the cystic duct. AC may develop at any age, but its incidence is higher in the second and 8<sup>th</sup> decades of life<sup>9</sup>. The gold standard treatment for AC is laparoscopic cholecystectomy. Early diagnosis and treatment of AC play an important role in mortality and morbidity<sup>5</sup>. AC accounts for 14% to 30% of cholecystectomies<sup>10</sup>.

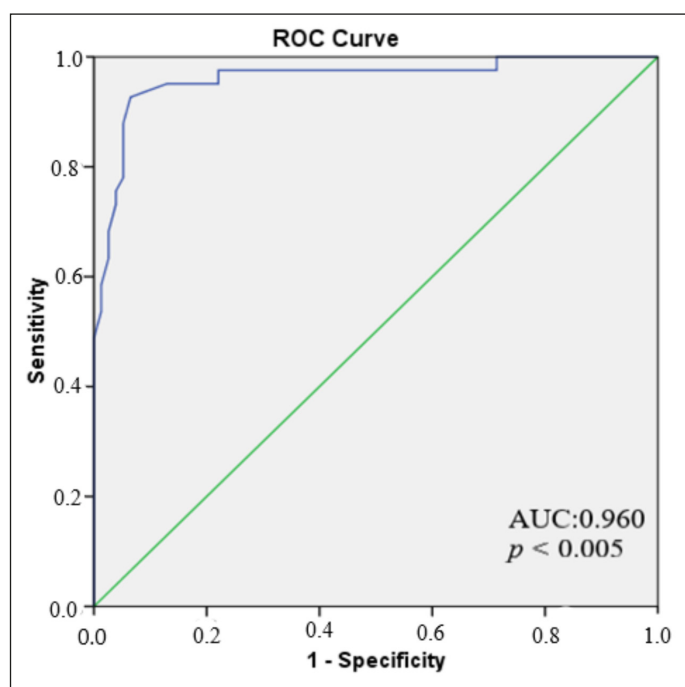
The timing of performing a cholecystectomy is still debated. Early studies<sup>11</sup> have reported

that early LC for AC is associated with a higher conversion rate, more complications, and longer surgery times. Today, with the advancement of laparoscopic techniques, recovery time has been shortened after early LC, and no significant difference is found in terms of procedural time, morbidity, or mortality<sup>12,13</sup>. As a result of the studies<sup>14,15</sup> conducted in order to determine the timing of early laparoscopic cholecystectomy, early laparoscopic cholecystectomy has been recommended for patients having symptoms for less than 72 hours. If the patient has symptoms for more than 72 hours, LC is recommended to be performed 4-6 weeks after medical treatment with antibiotics<sup>16</sup>. However, regardless of the duration of symptoms, majority of surgeons<sup>17,18</sup> still plan medical treatment for A. cholecystitis and prefer to perform delayed laparoscopic cholecystectomy. In 23% of the patients followed-up with medical treatment, the white blood cell count increases due to the increase in gallbladder distension, and the treatment is unsuccessful, and emergency laparoscopic cholecystectomy is performed. In our study, emergency laparoscopic cholecystectomy was performed in 34 (28.8%) of 118 patients.

Today, the Tokyo guideline<sup>2</sup> is a guide used to diagnose and determine the severity of AC. According to the guideline, diagnostic criteria for AC include physical examination findings, laboratory results such as C-reactive protein (CRP) and white blood cell levels (WBC), and radiological evaluation. However, in studies<sup>19,20</sup> conducted on patients who underwent emergency surgery for gangrenous cholecystitis and acute perforated

**Table II.** Laboratory data and hospitalization period of the patients.

	Group 1 (n=77)	Group 2 (n=41)	p-value
Fibrinogen (mg/dl)	$298.3 \pm 111.7$	$637.73 \pm 124.5$	<b>&lt;0.001</b>
White Blood Cell	$12.9 \pm 5.3$	$14.8 \pm 4.7$	0.056
Hospitalization period (day)	$4.1 \pm 3.9$	$4.85 \pm 3.2$	0.073



**Figure 1.** ROC curve and area under the curve analysis of serum fibrinogen level.

cholecystitis, no statistical difference was found in terms of white blood cell count. In our study as well, no statistical difference was found in terms of white blood cell count in correlation with these studies ( $p=0.056$ ).

Fibrinogen is an acute phase reactant. The serum fibrinogen level is usually increased in any acute inflammatory condition and tissue necrosis and is therefore expected to increase in acute cholecystitis as well. Fibrinogen levels increase proportionally in injured tissues secondary to depletion of coagulation factor VII by activation of the extrinsic pathway of tissue factor presented by monocytes and neutrophils after stimulation by inflammatory cytokines<sup>7</sup>. There are no studies regarding the determination of fibrinogen level in cases of AC.

In studies<sup>21-23</sup> conducted on patients with acute appendicitis, it was determined that fibrinogen level could be used in diagnosis of acute appendicitis, differential diagnosis, and also in differentiating whether or not there is a complication (perforation). In our study, plasma fibrinogen level was found to be higher when compared with normal limits in patients with A. cholecystitis. In addition, fibrinogen level was statistically significantly higher in patients with acute cholecystitis who underwent surgery (Group 2) as compared to our patients in Group 1. As a result of increased gallbladder wall tension and intense inflammatory reaction, ischemia developed on the gallbladder

wall due to the deterioration of the blood supply to the gallbladder wall. We think that fibrinogen levels might have been elevated due to tissue necrosis (complicated cholecystitis) that occurs as a result of the progression of this ischemia.

Heterogeneity in the treatment of patients with acute cholecystitis makes it difficult for the surgeon to decide the appropriate treatment. Delay in diagnosis and treatment may cause complications such as gangrene and perforation that increase mortality and morbidity. This is especially true for patients who are not healed with medical treatment and who need to be operated on urgent basis<sup>24-26</sup>.

### **Limitations**

There are also some limitations in our study. First, medical treatment was planned for all patients, regardless of the onset of symptoms. Second, during hospitalization of the patients, fibrinogen level was checked only once.

### **Conclusions**

As a result of our study, we concluded that when the data obtained are evaluated, it should be kept in mind that despite medical treatment, there is an urgent need for an operation in patients with AC, and in patients with high plasma fibrinogen level (cut-off) at first admission.



### Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

### Ethics Approval

This study was reviewed and approved by the Ethics Committee of the Harran University Faculty of Medicine (approval No.: 13.07.2017- 07).

### Informed Consent

Informed consent was not required due to the retrospective nature of the study.

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### Authors' Contributions

Osman Bardakçı: Manuscript editing. İbrahim Burak Bahçecioğlu: Statistical analysis and preparation. Faik Tatlı: Quality control of data and algorithms. Abdullah Özgönül: Manuscript review. Muhammet Emin Güldür: Study concepts and design. Ali Uzunköy: Study concepts and design.

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### Data Availability

The data supporting this article is available from the corresponding author on reasonable request.

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