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Original Article

PREDICTORS FOR GANGRENE AND PERFORATION OF GALLBLADDER WALL IN PATIENTS WITH ACUTE CHOLECYSTITIS

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Summary

Perforation of the gallbladder wall leads to a local perivesical abscess or progression to biliary peritonitis. The study aimed to analyse clinical, laboratory, and imaging indicators that have the strongest relationship with the presence of gangrenous cholecystitis and perforation of the wall and to design a predictive scoring system that highlights the risk of developing gangrenous cholecystitis with perforation. We performed a retrospective analysis of a total of 331 patients operated for five years (2016-2020) at the Department of Surgical Diseases" of Medical University - Pleven, with histologically verified chronic cholecystitis (120 patients; 36.4%), acute cholecystitis (100 patients; 30.1%), and destructive cholecystitis (111 patients; 33.5%). The statistical analysis identified nine main factors with the most substantial statistical significance in patients with gangrene and perforation of the gallbladder wall: age >65, male gender, diabetes mellitus, cardiovascular pathology, tachycardia>90 bpm, WBC>14.109, the thickness of gallbladder wall > 4 mm with pericholecystic fluid, ASAT and ALAT > 40 UI, CRP>150 ng/l. The total possible score was 11 points. The positive predictive value of the scale was 96% and identified the cases with micro-perforation and perivesical abbesses among the group with the highest total score.

Keywords: gangrenous cholecystitis, predictors of gangrene and gallbladder wall perforation, score system

Introduction

Acute calculous cholecystitis is a widespread surgical p.athology predominantly seen in older people. The incidence of acute gangrenous cholecystitis ranges from 2% to 29% of all cases of acute cholecystitis. According to the literature, the factors associated with a higher probability of gangrenous inflamed gallbladder wall are advanced age, leukocytosis above 15.10^9, and concomitant coronary artery pathology [1, 2]. Gallbladder perforation in severe acute cholecystitis is a life-threatening

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condition with a mortality rate of 12-16% [3]. Usually, this complication occurs in 2% to 11% of patients with acute cholecystitis. The onset of this complication is marked by deterioration of the patient's condition and severe general intoxication that dominates as a clinical condition over the local abdominal symptoms of the inflamed gallbladder wall. Necrosis in the gallbladder wall manifests with toxicity, tension and cardiovascular signs. Gallbladder wall circulation is compromised due to persistently high intraluminal pressure and concomitant ischemia, which causes wall necrosis. Necrosis, as a manifestation of tissue destruction, is followed by perforation. At first, the perforation is microscopic and may not be detected when observing the macroscopic specimen immediately after cholecystectomy.

Depending on whether the perforations are covered by the greater omentum or another structure surrounding the gallbladder wall, the perforation may be covered or open when the purulent bilious content leaks through the intra-abdominal space. This may lead to biliary peritonitis or the progression of inflammation to hepatobiliary sepsis, both life-threatening conditions [3]. From a total cohort of 11 360 patients diagnosed and verified with gangrenous cholecystitis over a 20-year study period, 30 cases of gallbladder perforation were reported [4]. Only 3% of the perforations were proven preoperatively. A worrying fact is the misdiagnosis of gallbladder perforation preoperatively. The profile of a patient with that complication includes more frequent concomitant cardiovascular pathology (50% vs 29%), a higher frequency of postoperative complications, including septic ones (37% vs 19%), requiring treatment in an intensive care unit (33% vs 9%), have a more extended hospital stay, respectively, and higher costs for hospital treatment (13 vs 8 days) [4]. Early cholecystectomy is recommended within the first 24 hours after hospitalisation to reduce the risk of late diagnosis of bladder perforation when it is not clinically recognised [4].

Our investigation aimed to perform a retrospective analysis of all patients operated on in our department for gangrenous cholecystitis and have histologically proven diagnosis of destructive gangrenous inflammation of the gallbladder wall. We tried to identify statistically significant factors that may preoperatively predict gangrene and perforation of the gallbladder wall. With the results obtained, we aimed to create a scale for predicting these severe complications on admitting patients with acute cholecystitis and thus prevent its progression to further dangerous septic complications.

Materials and Methods

We performed a retrospective analysis of all patients surgically treated for acute cholecystitis from 2016 to 2020 at the Department of Surgical Diseases, Medical University Pleven. We collected data from the clinical records of the patients who underwent surgery for acute or chronic cholecystitis and the histological reports of all specimens collected intraoperatively. Patient information was obtained from the University hospital database- Gamma Code Master®. The data was analysed and presented with non-destructive and destructive forms. All cases with mechanical jaundice due to choledocholithiasis, cholangiocarcinoma, and carcinoma of the head of the pancreas were excluded from the analysis.

The Medical University Ethics Commission approved the investigation and is part of a University Scientific Project No D3/2013.

Statistical analysis was performed with IBM- SPSS version 26 for Windows. Then we performed univariate, multivariate, and regressive analyses, a chi-square test, a U-test of all patients, and laboratory and imaging variables related to histologically confirmed gangrenous cholecystitis with perforation. A p-value less than 0.05 was accepted as statistically significant. After univariate analysis verifying all the nine factors that had strong relationships with cases of gangrenous destructive cholecystitis, we used them in multivariate logistic regression analysis to calculate the final score in points. We gave 1 point for factors with the smallest value of the regression coefficient (strength of association), 1.5 points for factors that reached a regression coefficient of 1.0, and 2 points for factors with a regression coefficient which reached 2.0. The total possible result was 11 points. The risk patients were divided into three groups: a low-risk group with a total score of 0-3 points, a

moderate-risk group with 4-7 points, and a high-risk group with 8-11 points. We compared our results with data in the literature.

Results

From 2016 to 2020, 799 patients with cholelithiasis and cholecystitis were admitted to the Clinic of Surgery, Dr Georgi Stranski University Hospital. Of these, 468 patients (58.5%) were treated for gallbladder inflammation conservatively, and 331 (41.5%) underwent surgery. The average age of the patients was 64.4 ±10.2 years (age range 21-94). After histological verification of the type of gallbladder wall inflammation, we divided the patients into three groups: group 1 - 120 patients with chronic and chronic exacerbated cholecystitis (35 males and 85 females, average age 63.3±9.3; group 2 – 100 patients with acute cholecystitis (44 males and 56 females, average age 64.7±8.4), and group 3 – 111 patients with gangrenous cholecystitis and perforation of the gallbladder wall (63 males and 48 females, average age 70.3±6.9) The demographic characteristics of the patients of each histology group and their clinical, laboratory and imaging results are presented in **Table 1.**

After univariate analysis of the patient's profile data, we identified nine factors with a strong relation to the presence of gangrenous inflammation and perforation of the gallbladder wall:

1. age > 65 years ($p< 0.001$); 2. male gender ($p<0.001$); 3. comorbidities – diabetes mellitus ($p< 0.003$); 4. concomitant cardiovascular pathology – ischemia, previous myocardial infarction, chronic ischemic heart disease ($p< 0.05$); 5. tachycardia with a heart rate of more than 90 beats per minute ($p<0.05$); 6. C-reactive protein levels more than 150 ng/l; ($p<0.05$); 7. leukocytosis with more than 14.10 ^{3}cells/µl white blood cells ($p<0.05$), 8. elevated ASAT and ALAT more than the normal upper limit of 40 UI ($p<0.05$); and 9. ultrasonography data for gallbladder wall thicker than 4 mm with a perivesical fluid collection. ($p<0.05$). We found that the complaints of nausea, vomiting, and high fever had no significant relation to the group with gangrenous cholecystitis patients, so we excluded these factors for further statistical analyses. We used these nine factors for multivariate logistic regression analysis, and we calculated regression coefficients for each factor because of their independent statistically significant association with gallbladder wall gangrene and perforation. We gave 1 point to the lowest regression coefficient (0.65 for ASAT and ALAT>40 UI). According to their relative proportion to the lowest regression coefficient, the other variables were assigned a score as a common denominator (Table 2).

Table 1. Characteristics of patients, operated on for gallbladder inflammation, 2016-2020.

	Chronic and exacerbated cholecystitis n= 120	Acute cholecystitis n=100	Gangrenous / perforative cholecystitis n= 111
Gender			
Male	35	44	63 ($p<0.001$)
Female	85	56	48
Age (Mean)	63.3years	65.5 years	70.3 years ($p< 0.001$)
Diabetes mellitus	26	43	73 ($p< 0.003$)
Cardiovascular pathology	33	46	67 ($p< 0.05$)
Right upper quadrant pain	78	87	108
Temperature-mean (°C)	36.8	37.3	37. 5
Nausea	48	55	61
Vomiting	34	49	52
Murphy positive sign	61	67	71
Tachycardia (>90 bpm)	14	22	74 ($p<0.05$)
Leukocytosis (Mean) (x10^3 cells/µl)	10±1.4	11.5± 1.5	16.6±1.6($p<0.05$)
ASAT/ALAT > 40 UI	37	53	85 ($p<0.05$)

Table 2. Score system for evaluating the risk of gangrene and perforation of gallbladder wall in patients with acute cholecystitis.

Variable	p-value	Regressive coefficient	Points
Age > 65	< .0001	2.01	2
Male	.0015	1.05	1.5
Diabetes mellitus	.0016	0.97	1.5
Cardiovascular pathology	.003	0.75	1
Leukocytosis > 14. x 10^3 cells/µl)	.002	0.85	1
CRP> 150 ng/l	.002	0.85	1
Tachycardia> 90b/min	.003	0.75	1
Wall thickness and perivesical effusion	.002	0.85	1
ASAT and ALAT >40 UI	.004	0.65	1
Total possible score			11

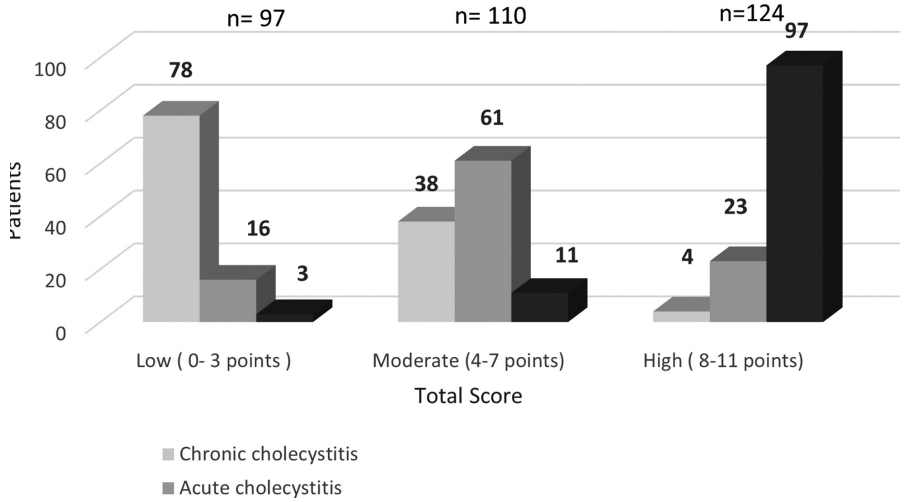

Figure 1. Distribution of the patients according to final total score and histological type of gallbladder wall inflammation.

The maximum total score was calculated as 11 points. We calculated the score for all patients from groups 1, 2 and 3 in our investigation, and we put two cut-off scores to divide the patients at low, moderate, and high-risk for gangrene with perforation of the gallbladder wall. Patients with a total score of up to 3 points were accepted to be at low risk for gangrene of gallbladder or perforation; those with a total score of 4 to 8 points – to be at moderate risk, and the ones with a total score of more than 9 points – at high risk and suspected for gangrene with perforation, requiring urgent surgery (Figure 1).

According to our data, the positive predictive value of that score is when it identifies most cases with acute and gangrenous inflammation in the group of patients with the highest score. In the high-risk group (total calculated score points 9 and more), we had 97 patients with acute phlegmonous cholecystitis with histologically improved micro-perforation of the mucosal layer and 23 patients with microscopically and macroscopically confirmed destructive gangrenous cholecystitis. All the patients placed in the third group based on their highest scores were 124. The sensitivity of the predictive scoring identified 120 patients with micro-perforation or with manifest destruction of the gallbladder wall, amounting to 96% of these 124 patients. We found a relatively low percentage (19%)) of the cases in the low-risk group (total score of 5 points), only 3 cases with acute cholecystitis, and another 16 patients with destructive cholecystitis in a low-risk group that included 97 patients. The mean hospital stay for each group was calculated for the three groups: the low-risk group – 5±1.3 days, the moderate-risk group – 7±1.7 days, and the high-risk group

– 9±2.3 days. The patients from high- risk group required treatment in ICU, with a mean stay of 3±1.5 days, and those from the low-risk group did not need treatment in the ICU.

Discussion

The incidence of gangrenous cholecystitis varies between 2% and 29% of all cases with acute gallbladder inflammation and may lead to severe morbidity and mortality among surgically treated patients [5]. The progression of gangrenous cholecystitis to perforation and biliary peritonitis is a common complication with a high risk for hepatobiliary sepsis. Penetrations with masked perforation of the gallbladder wall may present as pericholecystic abscesses. The amount of pus in these abscesses is between 30-350 ml [6]. The most common location of abscesses in acute cholecystitis is: perivesical - most often around the fundus of the bladder or the neck of the bladder and, less often, on the medial surface of the bladder; retrovesical – between the bladder and the hepatic bed; intrahepatic; subdiaphragmatic, subhepatic, parietal, in the small veil, with breakthrough to the pleural cavity or fistulation to the abdominal wall. Usually, wall necrosis occurs within 3 to 5 days of the onset of complaints, which should be considered when timing operative treatment. Only 9 % of all cases with gangrenous cholecystitis perforations of the wall are recognised preoperatively, and the early misdiagnosis is related to severe intraoperative complications such as bile duct injuries, severe haemorrhage, and conversion to open surgery [7]. The early recognition of gangrenous cholecystitis in patients with acute inflammation and the risk for perforation factors are important for a better outcome. Factors such as marked leukocytosis with a white blood count over 17.10^3 cells, patient age over 50 years and a history of concomitant cardiovascular disease have been accepted as significant in predicting wall perforation [8]. A 14-year study (1997-2011) focused on patients operated on for acute cholecystitis, a gangrenous form was histologically proven in 107 patients. The factors found to contribute to the shift of inflammatory changes in the bladder wall to necrosis were male gender and advanced age. However, other clinical conditions - concomitant diseases such as diabetes mellitus and cardiovascular diseases, causing vascular ischemia in the bladder wall were found to be independent risk factors for perforation [9]. Our results correspond with those in the literature. In another study on patients with gangrenous cholecystitis, the conclusion was that male gender, diabetes mellitus, and leukocytosis of more than $14.9.10^3$ cells were risk factors for necrotic changes in the gallbladder wall [10, 11]. In our study, as prognostic factors for the development of gangrenous cholecystitis are recognised, nine different clinical and laboratory factors that are with high impact on predicting gangrenous cholecystitis. Very often, gangrenous cholecystitis affects the elderly population. Our results strongly correspond with the literature data: age over 50 is risky for developing a destructive form of the inflammatory process [12]. In our study, age >65 proved a risk factor. Such patients commonly have comorbidities that imply high perioperative risk. A current score system for recognising gangrenous cholecystitis in patients with chronic or acute gallbladder inflammation was first described in 2010 [13]. The authors offered this system as an opportunity to preoperatively screen for patients with acute non-destructive and destructive cholecystitis, respectively those who were to undergo planned and emergency surgical intervention based on clinical, laboratory, and imaging parameters. It included five factors: age over 45, male gender, WBC>13.10^3 cells, heart rate>90 bpm, and gallbladder wall thickness on echography more than 4,5 mm. The cut-off point was a score of 4.5, which may predict the cases with gangrene of the gallbladder. The percentage of recognised gangrenous cholecystitis in the high probability group was high (87%). Another research described an equation with a positive predictive value for gallbladder wall perforation in 71% [14]. In our research, the positive predictive value of our score system was 96%. We combined nine predictive factors that significantly correspond to acute and gangrenous inflammation and clinical presentation for a systemic inflammatory response to perforation of the inflamed gallbladder wall. A more up-to-date scale was also adopted by the 2018 Tokyo Guideline Consensus expert panel for diagnosing and treating severe forms of acute cholecystitis, including its septic forms. It was presented in 2015.

The experts pointed out its advantages over the generally accepted consensus recommendations of the Tokyo Guideline 2018 (TG-2018), emphasising the individualised approach when deciding on therapeutic or surgical treatment of the patients [1, 14]. The expert consultants emphasised factors contributing to future multiple organ failure against the background of severe cholecystitis, dividing them into two main groups: 1. factors related to the patient and 2. factors related to the disease. The first group of factors (patient-dependent) included sex, age, body mass index (BMI), and anaesthetic risk, according to the American Society of Anesthesiologists score (ASA). Factors associated with the disease included a history of previous biliary colic, C-reactive protein (CRP) values, and gall bladder wall thickening on ultrasonography. The maximum score was 9 points. A total score of 0-3 points corresponded to mild cholecystitis – Grade I, a total score of 4 to 6 points determined a moderate risk – Grade II, and a total score of 7 to 9 pointed to severe cholecystitis with a tendency to generalise the inflammatory process, i.e. Grade III according to the classification of Tokyo Guideline-2018. The scale aimed at preoperative assessment and recognition of early manifestations of severe cholecystitis, accompanied by organ dysfunction – Grade III. The risk profile of patient-dependent factors was male sex, age over 65, and an ASA Score >2 points, correlating to the severity of clinical parameters in these patients, i.e. relationship between the severity of patient-related parameters and the severity of clinical parameters [15]. Patients with a total score of ≤7 points with severe cholecystitis complicated by organ dysfunction had prolonged operative time due to the severe inflammation of the gallbladder wall, and 25.9% of them required ICU treatment, i.e. every fourth patient with severe cholecystitis, and mortality almost twice as high compared to patients with moderate cholecystitis – 3.7% vs 1.9% [15]. Our results correspond to the conclusions of that study. However, we did not recognise the ASA score as significant for the patients with gangrenous cholecystitis because most patients included in our study had preoperative high ASA scores higher than 5-6 points. Regarding the C-reactive protein as a factor of severe inflammation, some studies have used it as a strong predictor for gangrenous cholecystitis, with a value higher than 200 ng/dl having a 50% positive predictive value, a specificity of 87.9%, and 100% sensitivity [16]. Our research concluded that a value of CRP higher than 150 ng/dl might be used on a complex scale to predict gangrene and perforation of the gallbladder wall. We assume that this factor strongly corresponds to possible septic complications in the abdominal cavity due to gallbladder inflammation.

Conclusion

The predictive scales for some common surgical diseases, such as acute appendicitis and acute pancreatitis, support the diagnosis and help emergency surgeons to recognize the disease in early stage. The suggested scales for gangrenous cholecystitis help to improve the preoperative diagnosis, before the onset of perforation. Therefore, our score system may be helpful because it is based on complex evaluation of clinical, vital, laboratory, and imaging tests. It may help surgeons in decision-making for early operation in emergency cases.

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