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Gangrenous Cholecystitis: Mortality and Risk Factors

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As a serious complication of cholelithiasis, gangrenous cholecystitis presents greater mortality than noncomplicated cholecystitis. The aim of this study was to specify the risk factors on mortality. 107 consecutive patients who underwent surgery due to gangrenous cholecystitis between January 1997 and October 2011 were investigated retrospectively. The study included 60 (56.1%) females and 47 (43.9%) males, with a mean age of 60.7 ± 16.4 (21–88) years. Cardiovascular diseases were the most frequently accompanying medical issues (24.3%). Thirty-six complications (33.6%) developed in 29 patients, and surgical site infection was proven as the most common. Longer delay time prior to hospital admission, low white blood cell count, presence of diabetes mellitus, higher blood levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin, pericholecystic fluid in abdominal ultrasonography, and conversion from laparoscopic surgery to open surgery were identified as risk factors affecting mortality ($P < 0.001$, $P = 0.001$, $P = 0.044$, $P = 0.005$, $P = 0.049$, $P = 0.009$, $P = 0.022$, $P = 0.011$, and $P = 0.004$, respectively). Longer delay time prior to hospital admission and low white blood cell count were determined as independent risk factors affecting mortality.

Key words: Gangrenous cholecystitis – Cholecystectomy – mortality

Gangrenous cholecystitis (GC) is defined as necrosis and perforation of the gallbladder wall as a result of ischemia following progressive vascular insufficiency.[1,2] GC is a severe complication of cholelithiasis.[3,4] Factors such as male sex, advanced age, delayed surgery, leukocytosis, cardiovascular diseases (CVDs), and diabetes mellitus (DM) increase the likelihood of developing GC.[3,5–8] Compared with uncomplicated acute cholecystitis, GC carries a significantly higher mortality rate, which has been reported to be between 15% and 50%.[3,4] We aimed in this study to specify the risk factors affecting mortality in patients with GC who underwent surgery.

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Materials and Methods

Case files from 107 consecutive patients with the diagnosis of GC who underwent a surgical operation in the Department of General Surgery, Faculty of Medicine, Dicle University, between January 1997 and October 2011 were retrospectively investigated. Age, sex, time of hospital admission, time of surgical operation undertaken, accompanying disease, laboratory findings at the admission [white blood cells (WBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin], findings in abdominal ultrasonography and computed tomography (CT), length of hospital stay, complications, and mortality were recorded for each patient. The group of patients excluded from the study was composed of patients who were operated on after implementation of tube cholecystostomy and medical therapy. The definitive diagnosis of GC was established on patient's physical examination (pain in upper right abdominal quadrant, fever >37°C, positive Murphy's sign, and/or findings indicating peritoneal irritation), laboratory findings (WBC count, ALT, and AST elevations), radiologic findings, and detection of full-thickness necrotic areas along with infiltration by neutrophils and mononuclear cells in histologic sections.[4,9] All cases were operated on within 24 hours of their presentation. A second-generation cephalosporin of 1 mg dosage was injected intravenously before the operation as a regimen for perioperative prophylaxis. Cholecystectomy was undertaken laparoscopically or as open procedure. Subcostal or median incisions were preferred in open cholecystectomy. In patients with extensive adhesions in whom sufficient anatomic exploration could not be performed, conversion to open laparotomy became inevitable owing to technical difficulties. Choledochal exploration and T-tube drainage were undertaken in patients in whom injury to choledoc was detected and in whom perioperative cholangiogram or palpation revealed stone in the choledocus[8] The gallbladder fossa was copiously irrigated with normal saline, followed by insertion of a drain. The diagnosis of sepsis was established according the criteria identified by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM).[10] CVDs and respiratory diseases were defined as ischemic heart disease and/or heart failure and chronic obstructive pulmonary disease and/or asthma, respectively. The patients were subdivided into two groups: group 1 in which no mortality occurred, and group 2 in which mortality occurred. Age >51 years, sex, time period between the onset of symptoms and hospital admission, accompanying diseases (DM, CVD), laboratory findings (WBC: $\leq$ 4000/mm^3, 4001–15,000/mm^3, and >15,000/mm^3); AST $\geq$ 43 U/L; ALT $\geq$ 50 U/L; ALP $\geq$ 200 U/L; and total bilirubin $\geq$ 1.2 mg/dL), and radiologic findings (identification of pericholecystic fluid, the thickness and the anatomic integrity of the gallbladder in all of the patients by ultrasonography (USG), and distension, wall thickening, pericholecystic inflammation, irregular or absent wall, and adjacent hepatic enhancements in 89 patients by CT examination) were evaluated as risk factors affecting mortality.[5,11] USG was used in all our patients, but CT was performed only for 89 patients since the diagnoses of 18 patients were achieved by USG.

Statistical Analysis

Statistical analysis was performed using SPSS 15 program (SPSS Inc, Chicago, IL) during the evaluation of study results. Quantitative data were defined as mean ± SD. Mann-Whitney *U* test was used owing to nonhomogenous distribution of the independent variables. Multivariate logistic regression test was used to determine risk factors affecting mortality. P values < 0.05 were accepted to be significant.

Results

Of the 107 patients, 60 (56.1%) were female and 47 (43.9%) were male, with a median age of 60.7 ± 16.4 years (21–88 years). Mean time delay to hospital admission was 21.7 ± 26.9 hours (2–112 hours). Choledochal exploration and T-tube insertion in addition to cholecystectomy were implemented in a total of 12 patients: in 9, stone was detected via cholangiography and palpation in the main bile ducts, and in 3, injury to the choledochus existed. The results from histopathologic examinations in all patients were compatible with GC. Table 1 shows the characteristics and demographics of the patients. A total of 63 accompanying diseases were detected in 44 of the cases; with CVDs ranking first, affecting 26 (24.3%) patients. A total of 36 (33.6%) complications were observed in 29 of the cases, the most common of which was surgical site infection. The accompanying diseases and the complications are shown in Table 2. Of all patients, 88 (88.2%) were assigned to group 1 and 19 (17.8%) to group 2. Upon making a comparison between the patients in whom

Table 1 Patients' demographic and characteristic findings

Age, y (range)	60.7 ± 16.4 (21–88)
Sex, n (%)	
Female	60 (56.1)
Male	47 (43.9)
PSBA, h (range)	21.7 ± 26.9 (2–112)
Clinical symptoms, n (%)	
Upper right quadrant pain	84 (78.5)
Nausea, vomiting	55 (51.4)
Temperature >38°C	45 (42.1)
Physical examination, n (%)	
Murphy's sign or signs of peritoneal irritation	83 (77.6)
Laboratory findings (range)	
WBC, mm^3	15,294.5 ± 6196.8 (2300 −39,400)
AST, U/L	90.9 ± 139.9 (6–1148)
ALT, U/L	83.6 ± 118.7 (6–834)
ALP, U/L	159.6 ± 124.7 (76–576)
Total bilirubin, mg/dL	1.3 ± 0.9 (0.3–7.2)
Abdominal ultrasonography, n (%)	
Wall thickening and edema	107 (100)
Pericholecystic fluid collection	21 (19.6)
CT, n (%)	
Wall thickening and edema	89 (100)
Irregular or absent gallbladder wall	77 (86.5)
Type of surgery, n (%)	
Conventional	44 (41.1)
Laparoscopic	48 (44.9)
Conversion	15 (14)
T-tube application, n (%)	12 (11.2)
Morbidity, n (%)	36 (33.6)
Mortality, n (%)	19 (17.8)
Hospital stay, d (range)	8.0 ± 5.7 (1–28)

PSBA, period of symptoms before admission.

Table 2 Comorbidities and complications in patients

Associated diseases, n (%)	
CVH	26 (24.3)
DM	21 (19.6)
Respiratory diseases	7 (6.5)
Other diseases	5 (4.7)
Kidney failure	4 (3.7)
Complications, n (%)	
Wound infections	12 (33.3)
Pulmonary complications	7 (19.5)
Intra-abdominal abscess	6 (16.7)
Evisceration	5 (13.9)
Trocar area infection	3 (8.3)
Bile fistula	3 (8.3)

CVH, cardiovascular disease.

mortality occurred (group 2) and those in whom mortality did not occur (group 1), significant difference was detected with regard to time to hospital admission, presence of DM, results of WBC count, AST, ALT, ALP and total bilirubin, detection of pericholecystic fluid collection in USG, wall thickening, pericholecystic inflammation, irregular or absent wall and adjacent hepatic enhancements on CT examination, and conversion from laparoscopic operation to open surgery (Table 3). Delayed admission to hospital and low WBC count were found to be independent risk factors affecting mortality (Table 4).

Discussion

Acute cholecystitis develops in 1% to 2% of patients with asymptomatic cholelithiasis each year.[12] Conservative treatment comprising intravenous fluid resuscitation and antibiotic therapy proves effective in 80% of patients with acute cholecystitis.[13] As one of the severe complications of acute cholecystitis, GC develops in 2% to 20% of the cases with acute cholecystitis.[5,6,14] Epithelial injury by increasing gallbladder wall tension owing to vascular insufficiency arising secondary to persistent obstruction of the cystic duct gives way to the development of GC, which follows a quite rapid course.[5] The phospholipases released from cell membranes of damaged epithelium initiate heavy inflammatory reaction.[1,2,5,15] Inflammation and ischemia of the gallbladder wall show progressive worsening as a result of deteriorating venous insufficiency with age, thereby giving rise to more necrosis and perforation.[7,16,17] Although 73.8% of the cases in our study were aged 51 years and older, age did not influence mortality.

The risk of developing GC is higher in males compared with females.[3,6] However, the fact that the incidence of cholelithiasis is higher in females than in males led to a relative abundance of female cases over males in our study. Furthermore, mortality occurred in 15% of female patients and in 21.1% of male patients in our study, which didn't reach the level of significance.

Making the diagnosis of GC is quite challenging in the preoperative period. Nonspecific physical examination and laboratory findings along with absence of the classic clinical symptoms and signs pointing out acute cholecystitis in the elderly may give rise both to missed diagnosis and to delayed implementation of treatment.[5,18] Contini *et al*[8] reported that delayed admission was an important criterion in the development of GC. Eldar *et al*[17] reported worsening macroscopic alterations in the case of hospital admissions later than 48 hours. While the total mean time delay to hospital admission of our patients was 21 hours, it was 54 hours in those in whom mortality occurred. We believe that factors such as older age and

Table 3 The differences between the mortality and nonmortality groups in patients with gangrenous cholecystitis

Parameters	Group 1 n (%)	Group 2 n (%)	*P*
Age, y			
≤50	26 (92.9)	2 (7.1)	NS
≥51	62 (78.5)	17 (21.5)	
Sex			
Female	51 (85.0)	9 (15.0)	NS
Male	37 (78.7)	10 (21.3)	
PSBA, h (range)	14.7 ± 16.6 (2–72)	54.1 ± 99.9 (36–112)	< 0.001
WBC			
<4000/mm^3	3 (42.9)	4 (57.1)	0.001
4000–15,000/mm^3	27 (71.1)	11 (28.9)	
>15,000/mm^3	56 (93.3)	4 (6.7)	
AST			
<50 U/L	54 (91.5)	5 (8.5)	0.005
>50 U/L	34 (70.8)	14 (29.2)	
ALT			
<44 U/L	45 (90.0)	5 (10.0)	0.049
>44 U/L	43 (75.4)	14 (24.6)	
ALP			
>200 U/L	82 (86.3)	13 (13.7)	0.009
<200 U/L	6 (50.0)	6 (50.0)	
Total bilirubin			
>1.2 g/dL	44 (91.7)	4 (8.3)	0.022
<1.2 g/dL	44 (74.6)	15 (25.6)	
DM			
+	74 (86.0)	12 (14.0)	0.044
−	14 (66.7)	7 (33.3)	
CVH			
+	67 (82.7)	14 (17.3)	NS
−	21 (80.8)	5 (19.2)	
Pericholecystic fluid collection by USG			
+	13 (61.9)	8 (38.1)	0.011
−	75 (87.2)	11 (12.8)	
CT findings			
+	60 (77.9)	17 (22.1)	NS
−	11 (91.7)	1 (8.3)	
Surgery			
Conventional	42 (95.5)	2 (4.5)	0.004
Laparoscopic	37 (77.1)	11 (22.9)	
Conversion	9 (60.0)	6 (40.0)	

NS, nonsignificant.

poor awareness about diseases play a pivotal role in delayed admissions. Delayed admissions culminate in the development of peritonitis and impaired general condition in the affected patients. The results obtained from our study demonstrate that delayed admission was a crucial criterion regarding mortality.

It has been proposed that pathologies of the cystic artery emerging from atherosclerosis or microvascular diseases might lead to vascular insufficiency, therefore predisposing factors such as DM and CVD could be regarded as risk factors in development of GC.[5,19–21] However, in contrast to the former proposal, some other studies identify no direct relationship between development of GC and DM.[3–7] In our study, 24.3% of cases had CVD and 19.6% had DM. Presence of DM was found to influence mortality.

A high degree of leukocytosis has been documented to be correlated with the infection severity in the gallbladder wall.[22] Fagan *et al*[5] and Aydın *et al*[6] reported that WBC count >15,000/mm^3 predicted development of GC, whereas it was 17,000/mm^3 in the study by Merriam *et al*.[3] The number of WBCs in the patients with GC in our study was detected to be high, yet the WBC count was found to be significantly lower in the patients with GC in whom mortality occurred. Girgin *et al*[23] reported that a high WBC count put forth as a predictive factor in the development of

Table 4 Multivariate logistic regression analysis of predicting factors for mortality of gangrenous cholecystitis

Factors	Odds ratio	CI 95%	*P*
PSBA, h	1.046	1.015–1.078	0.004
DM	0.410	0.058–2.913	NS
CVH	2.230	0.320–15.542	NS
WBC			
>15,000/mm^3	1	–	NS
4000–15,000/mm^3	5.529	0.224–136.288	NS
<4000/mm^3	17.38	1.71–176.34	0.008
Total bilirubin	0.991	0.895–1.097	NS
ALP	1.003	0.996–1.008	NS
Pericholecystic fluid collection by USG	0.341	0.053–2.207	NS
CT findings	0.087	0.004–1.761	NS

CI, confidence interval.

GC decreased as sepsis developed, which might herald an increase in mortality rate. The presence of low WBC count and its negative correlation with the mortality rate in our study prompt us to consider that sepsis leads to mortality.

Elevation in serum liver enzymes indicates hepatocyte necrosis. GC-related inflammatory alterations in the gallbladder bed induce elevation liver enzymes.[5,24] Accordingly, bilirubin levels elevate in the serum via edema and inflammation in the bile ducts and direct impingement of the hydropic gallbladder on the choledoc duct (Mirizzi syndrome).[25] Polymorphonuclear leukocyte infiltration along with focal hepatic parenchymal necrosis was observed in biopsy specimens obtained from the GC patients with elevated enzymes.[26] It was reported in our study that AST, ALT, ALP, and total bilirubin levels were elevated in the all of the patients; moreover, further elevations in the former markers were found in the cases in whom mortality occurred. This situation can be ascribed to the likelihood that elevation in the level of serum enzymes and bilirubin may point to deterioration of the gangrenous pathology in the gallbladder.

The inflammation and thickening of the gallbladder wall can be seen by USG in 90% to 95% of patients with GC.[7] However, thickening of the wall and presence of pericholecystic fluid collection do not always indicate development of GC, but instead progression of the inflammation.[7] Fagan *et al*[5] reported that detection of pericholecystic fluid by USG predicted development of GC. In our study, edema and thickening of the gallbladder were documented via USG in all of the patients, whereas pericholecystic fluid collection was detected in 19.6% of the patients. Detection of pericholecystic fluid collection was found to be significant with regard to mortality.

Bennett *et al*[11] reported that air in the gallbladder wall or lumen, irregular or absent gallbladder wall, intraluminal membranes, pericholecystic abscess, and lack of gallbladder wall enhancement are specific CT findings of acute cholecystitis complicated by gangrene. In our study, typical CT findings were present in 86.5% of the patients, but it was found to be insignificant over mortality.

Today, cholecystectomy undertaken through laparoscopic methods has become more and more widespread in the treatment of GC. The conversion rates, albeit reported to be 30% to 50% in previous studies,[27,28] have recently dropped to 8.7%.[7] No increase but a decrease in mortality and morbidity rates was reported with the implementation of laparoscopic cholecystectomy for GC.[7,16] In our study, conversion from laparoscopic surgery to open surgery occurred in 14% of the patients. In addition, conversion to open surgery was dictated by difficulties in dissection due to adhesions, insufficient anatomic exploration, complications like bleeding and injury to bile ducts, and technical difficulties. Mortality was higher in cases in which conversion to open surgery occurred, which might be ascribed to the fact that laparoscopic cholecystectomy was undertaken in selected patients with less-severe inflammatory status.

Stones are detected in choledoc duct in 21% of patients with acute cholecystitis. The former ratio was determined to be 13% in patients with GC. Moreover, stones were identified preoperatively in 50% of the patients.[29] As for our study, we detected choledochal stones in 8.4% of the patients. Since surgery under emergency conditions was undertaken in the patients with GC, no endoscopic retrograde cholangiopancreatography (ERCP) was performed. It was for this reason that choledochal exploration plus T-tube insertion was performed in the cases in which stones were detected intraoperatively in the choledoc duct. Now that T-tube implementation has been found not to effect mortality, we don't see any disadvantage with a simultaneous implementation of choledochal exploration, if needed, in patients with GC.

ERCP helps to diagnose and, when combined with endoscopic sphincterotomy and/or biliary stenting, to manage ERCP postcholecystectomy residual choledochal stones and postoperative biliary complications such as bile duct injuries with bile leakage or stricture.[30]

Mortality and morbidity rate imposed by this disease is quite high compared with noncomplicated acute cholecystitis. Habib *et al*[18] and Fry *et al*[15] reported mortality rates of 50% and 40%, respectively, whereas our study documented that the morbidity rate was 29%, and the mortality rate was 17.8%. Despite high morbidity and mortality following surgery, emergency surgery should not be avoided considering the likelihood that delayed surgery may be associated with even higher levels of mortality and morbidity.[5,31,32]

Nguyen *et al*[31] and Fagan *et al*[5] determined that DM, WBC $\geq$ 15,000 mm^3, ALT $\geq$ 50 U/L, AST $\geq$ 43 U/L, ALP $\geq$ 200 U/L, older age (>51 years), and detection of pericholecystic fluid via USG are independent risk factors predicting development of GC, whereas our study found delayed admission to the hospital and low WBC count to be independent risk factors affecting mortality.

Conclusion

GC is a disease state that necessitates emergency treatment because of its high mortality rate. The presence of DM as accompanying disease, high levels of ALT, AST, ALP, and total bilirubin, detection of pericholecystic fluid in USG, and conversion from laparoscopic surgery to open surgery for technical reasons were observed significantly more frequently in the cases in which mortality occurred. Delayed admission to the hospital and low WBC count were found to be independent risk factors affecting mortality.

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