Prognostic factors for the development of gangrenous cholecystitis

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Abstract

Background: The operative morbidity and mortality for patients with gangrenous cholecystitis (GC) remains high. Our objective was to identify preoperative prognostic factors for GC in order to distinguish this subset of patients with acute cholecystitis (AC).

Methods: From 1/98 to 11/01 the medical records of patients who presented with the diagnosis of AC were reviewed. Univariate and multivariate analysis were performed on this retrospective data.

Results: Of 113 patients with acute cholecystitis, 45 (39.8\%) had histologically confirmed gangrenous cholecystitis. Nine variables were identified that were associated with GC by univariate analysis: age \(\geq 51\) years, African-American race, white blood cell count \(\geq 15,000\), diabetes, pericholecystic fluid, asparate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lipase. Two variables were identified by multivariate analysis: diabetes, and white blood cell count.

Conclusions: Our data suggest that patients with a history of diabetes and white blood cell count \(\geq 15,000\) to be at an increased risk for having GC upon presentation and they should have urgent surgical intervention. © 2003 Excerpta Medica, Inc. All rights reserved.

Keywords: Gangrenous cholecystitis; Prognostic factors; Multivariate logistic regression

More than 500,000 cholecystectomies are performed annually in the United States. While a majority of the procedures are performed electively or semi electively, a small percentage of patients require emergent intervention for full thickness necrosis of the gallbladder wall. Gangrenous cholecystitis is an advanced form of acute cholecystitis. The incidence of gangrenous cholecystitis varies from 2\% to 29.6\% of all cases of acute cholecystitis and is associated with significantly greater morbidity and mortality [1]. While recent reports have focused on the safety and efficacy of laparoscopic removal of the gangrenous gallbladder, the preoperative diagnosis remains elusive. Teefy et al [2] reported 48\% of patients with histologically proven gangrenous cholecystitis had little or no evidence to suggest this disease process preoperatively. Previous reports have identified advanced age, history of coronary artery disease, and leukocytosis to be associated with an increased risk for gangrenous cholecystitis [1,3,4]. Unfortunately, many of these studies were of a small sample size thus limiting the ability to identify preoperative prognostic factors. Our objective was to identify preoperative prognostic factors for gangrenous cholecystitis in order to distinguish the subset of patients with acute cholecystitis that require emergent intervention.

Methods

With approval of the Baylor College of Medicine Institutional Review Board, the records of all patients who underwent cholecystectomy for acute cholecystitis between January 1998 and November 2001 at the Houston Veterans Affairs Medical Center, a 420-bed tertiary care hospital serving Southeast Texas, were evaluated retrospectively. The preoperative diagnosis of acute cholecystitis was established by the presence of right upper quadrant pain, leukocytosis, fever, and ultrasonographic evidence of cholelithiasis, gallbladder wall thickening or pericholecystic fluid. The criteria for operation was determined by the surgeon. Two groups of patients were established, acute cholecystitis and...
gangrenous cholecystitis, based on histological evaluation of the surgical specimen. For each patient, the medical record was analyzed for 21 variables: demographics (age, sex, race), preexisting comorbidities (diabetes mellitus, coronary artery disease, hyperlipidemia), preoperative signs and symptoms (right upper quadrant abdominal pain, nausea, diarrhea, fever); initial laboratory values (leukocyte count, blood urea nitrogen, creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, alkaline phosphatase [ALP], bilirubin, amylase, lipase), and preoperative imaging (ultrasonography). In the basic analysis, the mean and standard deviation for continuous variables and the frequency and proportion for categorical variables were calculated on the entire data set.

Univariate analysis for the histological diagnosis, the dependent variable in this study, was performed with chi-square testing. The P value, odds ratio (OR), and 95% confidence interval (CI) were determined for each variable. The variables with a P value of 0.1 or less were selected for further multivariate analysis. Multivariate analysis was performed with logistic regression analysis to determine those variables independently predictive of gangrenous cholecystitis.

Results

During the study period, a total of 113 patients were identified that underwent a cholecystectomy with the preoperative diagnosis of acute cholecystitis. All specimens demonstrated microscopic evidence of acute cholecystitis. Of these, 45 (39.8%) patients had histological evidence of gangrenous cholecystitis. The demographic data for each study group are shown in Table 1. Univariate analysis performed using chi-square testing identified nine variables with P values less than 0.1, the selection criteria for multivariate analysis: age (OR = 3.5, P = 0.04), African-American race (OR = 2.1, P = 0.08), white blood cell count ([WBC] OR = 4.4, P = 0.002), diabetes mellitus (OR = 2.84, P = 0.001), pericholecystic fluid (OR = 8.5, P = 0.056), AST (OR = 0.32, P = 0.01), ALT (OR = 0.25, P = 0.002), ALP (OR = 0.15, P = 0.015), and lipase (OR = 0.31, P = 0.06; Table 2). In the multivariate analysis, AST was removed because ALT and AST were highly correlated (Spearman correlation coefficient = 0.767) and the P value of ALT was lower than that of AST.

The results of multivariate logistic regression analysis using selected variables are shown in Table 3. Two variables—history of diabetes mellitus and WBC ≥15,000 K/mm³ positively correlated with the presence of gangrenous cholecystitis.

Comments

Acute cholecystitis is the most common complication of cholelithiasis occurring in approximately 1% to 2% of asymptomatic patients annually [5]. The primary etiology of acute cholecystitis is obstruction of the cystic duct secondary to an impacted stone. In approximately 80% of patients, the impacted stone dislodges allowing for initial conservative nonoperative management [3]. However, in approximately 2% to 30% of patients, the disease process progresses to gallbladder wall necrosis or gangrenous cholecystitis. The etiology of gangrenous cholecystitis is pri-

Table 1
Demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cut off</th>
<th>Acute cholecystis (n = 68)</th>
<th>Gangrenous cholecystitis (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥51 years</td>
<td>74.1% 90.9%</td>
<td>63.8% 45%</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>89.7% 97.7%</td>
<td>Female 22.4% 20.0%</td>
</tr>
<tr>
<td>Race</td>
<td>African American</td>
<td>13.8% 35%</td>
<td>Caucasian 63.8% 45%</td>
</tr>
</tbody>
</table>

Table 2
Univariate analysis (n = 113)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cut off</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥51 years</td>
<td>3.5 (1.07–11.40)</td>
<td>0.0386</td>
</tr>
<tr>
<td>Race</td>
<td>African American</td>
<td>2.03 (0.91–4.52)</td>
<td>0.0829</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>≥15 K/cmm</td>
<td>4.38 (1.75–10.97)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Present</td>
<td>2.84 (1.26–6.40)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Pericholecystic fluid</td>
<td>Present</td>
<td>8.5 (0.95–76.94)</td>
<td>0.0559</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>≥50 U/L</td>
<td>0.247 (0.1–0.59)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>≥43 U/L</td>
<td>0.318 (0.13–0.76)</td>
<td>0.0097</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>≥200 U/L</td>
<td>0.147 (0.03–0.69)</td>
<td>0.0148</td>
</tr>
<tr>
<td>Lipase</td>
<td>≥200 U/L</td>
<td>0.308 (0.09–1.07)</td>
<td>0.0636</td>
</tr>
</tbody>
</table>

P ≤ 0.1.

CI = confidence interval.

Table 3
Multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2.70 (1.02–7.16)</td>
<td>0.045</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>≥15 K/cmm</td>
<td>5.56 (1.97–15.7)</td>
</tr>
<tr>
<td>Alkaline aminotransferase</td>
<td>≥50 U/L</td>
<td>0.36 (0.14–0.93)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0.13 (0.02–78)</td>
<td>0.026</td>
</tr>
<tr>
<td>Pericholecystic fluid</td>
<td>13.3 (0.58–304)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

P ≤ 0.05.

CI = confidence interval.
branes leading to an intense epithelial injury. As a result of the epithelial injury, phospholipases are released that degrade adjacent cell membranes leading to an intense inflammatory reaction [7]. It is the combination of gallbladder wall tension and the intense inflammatory reaction that results in either local or global gallbladder wall ischemia [8].

Gangrenous cholecystitis is a severe form of acute cholecystitis and is defined histologically as full thickness necrosis of the gallbladder wall in association with an intense leukocytic infiltration. The disease process is associated with significantly greater morbidity and mortality when compared with uncomplicated acute cholecystitis [9]. Due to increased morbidity and mortality several authors have advocated emergent cholecystectomy for gangrenous cholecystitis [10]. Unfortunately, the preoperative diagnosis of gangrenous cholecystitis is difficult and often only entertained after deterioration of a patient suspected of having simple or uncomplicated cholecystitis. Several authors have attempted to identify the subgroup of patients with gangrenous cholecystitis by examining preoperative risk factors [4,10]. However since gangrenous cholecystitis occurs with an overall incidence of 1% to 3% of all cases of cholecystic disease, the ability to consistently identify preoperative risk factors is often limited by small sample size [6]. In our retrospective review of 113 cases of acute cholecystitis, 45 patients (39.8%) were found to have histologically proven gangrenous cholecystitis. Based on the univariate analysis from our study, nine variables were found to be associated with gangrenous cholecystitis: age 51 years or older, African-American race, history of diabetes mellitus, WBC >15,000, AST ≥43 U/L, ALT ≥50 U/L, ALP ≥200 U/L, lipase ≥200 U/L, and pericholecystic fluid on ultrasonography.

Gangrenous cholecystitis has traditionally been considered a disease of the elderly [9]. Multiple studies have identified advanced age as a preoperative risk factor for gangrenous cholecystitis [3,4]. Consistent with these previous reports, our results demonstrate that persons greater than age 51 were at greater risk for gangrenous cholecystitis by univariate analysis. This is an important clinical finding since calculous disease of the gallbladder is the most common indication for intraabdominal surgery in the elderly [11]. Furthermore, the diagnosis of acute biliary tract disease is often difficult in the elderly due to the infrequent classic clinical presentation. Morrow et al [11] reported that the degree of abdominal pain in elderly patients (aged more than 60 years) with acute biliary tract disease did not correlate with their degree of sepsis. Additionally, of their patients treated with nonoperative conservative medical management, 97.4% failed. Based on these results and previous reports, one should consider and exclude acute biliary tract disease in any septic elderly patient due to the high risk of gangrenous cholecystitis and failure of medical management.

While the risks of postoperative complications after cholecystectomy in patients with diabetes is well established [12-14], the association of diabetes and preoperative risk of gangrenous cholecystitis is controversial. Several investigators have demonstrated no correlation between diabetes and gangrenous cholecystitis while others have found a direct correlation [1,4,15]. In our series we found diabetes to be a strong preoperative risk factor for the presence of gangrenous cholecystitis by univariate and multivariate analysis. Although uncertain, one possible explanation for this association is the advanced atherosclerotic disease accompanying diabetes. Because gangrenous cholecystitis is secondary to vascular compromise, several investigators have suggested that cystic artery atherosclerosis or microvascular disease may predispose a diabetic patient to gangrenous transformation [1,4]. Other investigators refute this potential explanation due to the finding of proinflammatory agents increasing gallbladder wall vascularity in the presence of acute and gangrenous cholecystitis [16,17]. The preoperative diagnosis of diabetes in association with acute biliary tract disease appears to increase the incidence of gangrenous transformation and postoperative complications.

As previously mentioned the preoperative diagnosis of gangrenous cholecystitis remains elusive. Habib et al [18] were able to preoperatively identify gangrenous cholecys-
titis in only 7.5% of their patients despite the use of clinical, laboratory and image findings. One explanation for the inability to diagnosis gangrenous cholecystitis preoperatively is the nonspecific laboratory findings. The only preoperative laboratory value consistently found to be associated with gangrenous cholecystitis is a leukocyte count above 15,000 WBC/mL as supported by this study. Further evidence supports the direct correlation between the degree of leukocytosis and the incidence of gangrenous cholecystitis. Merriam et al. found gangrenous cholecystitis in 58% of patients with leukocyte counts greater than 17,000 WBC/mL compared with 83% of patients with leukocyte counts greater than 20,000 WBC/mL [4]. The elevated leukocytosis appears to be related to the intense inflammatory reaction associated with gangrenous cholecystitis and not to bacterial invasion. Only 50% to 63% of bile cultures from gangrenous cholecystitis specimens yield an identifiable pathogen [6,9,18,19].

Consistent with previous studies, abnormal AST and ALT values were not found to be predictive of gangrenous cholecystitis. Elevated liver serum enzyme levels indicate hepatocyte necrosis. Theoretically, this is consistent with pathological changes within the gallbladder fossa associated with gangrenous cholecystitis. Zufarov et al [20] studied hepatic biopsies from patients with cholelithiasis complicated by gangrenous cholecystitis. Focal areas of hepatic parenchyma necrosis were observed in association with polymorphonuclear leukocytes infiltration. Cholescinti-
graphic imaging supports further evidence of direct extension of the inflammatory process resulting in hepatic parenchyma injury [21]. The rim sign seen on cholescintigraphic imaging is secondary to hepatic dysfunction manifested by the inability to excrete radiotracer normally. As the disease process progresses, the hepatocytes adjacent to the gallbladder further deteriorate resulting in severe biliary stasis and inability to excrete and concentrate the radiotracer. This severe hepatocyte dysfunction/necrosis is seen as an enlarged photon deficient area (enlarged gallbladder fossa) on cholescintigraphic imaging. Our study, however, by univariate and multivariate analysis demonstrated a negative correlation between gangrenous cholecystitis and increasing serum AST and ALT levels. This paradox between liver enzyme elevation and gangrenous cholecystitis may be related to study bias or small sample size.

In addition to clinical and laboratory evaluation, ultrasonography is a useful tool to identify individuals with complications of their biliary tract disease. The sensitivity of ultrasonography in detecting acute inflammation of the gallbladder has been reported to be 90% to 95% [1]. Unfortunately, the sensitivity of ultrasonography in diagnosing gangrenous cholecystitis is uncertain. Previous reports have suggested straited thickening of the gallbladder wall, presence of intraluminal echoes, and absence of a sonographic Murphy’s sign as evidence of gangrenous cholecystitis [22]. The presence of pericholecystitic fluid, as demonstrated in this study, as sonographic evidence of gangrenous cholecystitis has been suggested in previous studies but the sensitivity and specificity are unknown. Teefy et al [2] demonstrated the type of pericholecystitic fluid collection correlated with the presence of gangrenous cholecystitis. Pericholecystitic fluid collections were classified as type I, II, or III based on the short axis measurement of fluid collection and the fluid composition (sonolucent versus complex). Type II and III complex fluid collections, as defined as short axis measurements greater than 2 cm or totally encompassing the gallbladder respectively, were more commonly associated with gangrenous cholecystitis than type I fluid collections. Investigators examining computed tomography imaging in gangrenous cholecystitis have confirmed pericholecystitic fluid collections as predictive in the diagnosis of gangrenous cholecystitis [23]. In contrast to gallbladder wall thickening, which does not correlate with the severity of cholecystitis, the presence of pericholecystitic fluid should be considered predictive of an advanced state of cholecystitis [1].

Gangrenous cholecystitis is an advanced form of acute cholecystitis that is not uncommon among patients presenting with acute cholecystic disease. The treatment of choice is emergent operative intervention but is often delayed owing to the difficulty of establishing the diagnosis. In this retrospective review of 113 patients presenting with acute cholecystitis, 45 patients (39.8%) were found to have gangrenous transformation. Univariate analysis determined age greater than 51 years, African-American race, history of diabetes, leukocytosis, nonelevated serum pancreatic and liver enzymes, and the presence of pericholecystic fluid as prognostic factors for patients at increased risk for having gangrenous cholecystitis. The incidence of gangrenous cholecystitis in our study, which is higher than most previous reported series, does not appear to be due to surgical delay. Patient and physician delay in the initiation of treatment has been previously demonstrated to impact the incidence of gangrenous cholecystitis [24]. Although not a factor investigated in this study, surgical delay does not appear to be responsible for the high incidence of gangrenous cholecystitis found in this study as the data utilized for analysis was at initial surgical evaluation. As recently demonstrated in a meta analysis of acute cholecystitis, no one variable appears to confirm or exclude a disease process [25]. However, patients presenting with acute cholecystic disease and the risk factors identified in this study should be considered for emergent operative intervention due to the high risk of gangrenous transformation. The authors recognize this study is limited by its retrospective nature and, although one of the largest series of gangrenous cholecystitis, by its small sample size. The variables identified in this study need to be prospectively validated in a predictive model of gangrenous cholecystitis.

References