Gangrenous cholecystitis: Deceiving ultrasounds, significant delay in surgical consult, and increased postoperative morbidity!

Daniel Dante Yeh, MD, Catrina Cropano, MS, Peter Fagenholz, MD, David R. King, MD, Yuchiao Chang, PhD, Eric N. Klein, MD, Marc DeMoya, MD, Haytham Kaafarani, MD, MPH, *and* **George Velmahos, MD, PhD,** *Boston, Massachusetts*

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BACKGROUND: Gangrenous cholecystitis (GC) is difficult to diagnose preoperatively in the patient with suspected acute cholecystitis. We sought to characterize preoperative risk factors and post-operative complications.

METHODS: Pathology reports of all patients undergoing cholecystectomy for suspected acute cholecystitis from June 2010 to January 2014 and admitted through the emergency department were examined. Patients with GC were compared with those with acute/chronic cholecystitis (AC/CC). Data collected included demographics, preoperative signs and symptoms, radiologic studies, operative details, and clinical outcomes.

RESULTS: Thirty-eight cases of GC were identified and compared with 171 cases of AC/CC. Compared with AC/CC, GC patients were more likely to be older (57 years vs. 41 years, $p < 0.001$), of male sex (63% vs. 31%, $p < 0.001$), hypertensive (47% vs. 22%, $p = 0.002$), hyperlipidemic (29% vs. 14%, $p = 0.026$), and diabetic (24% vs. 8%, $p = 0.006$). GC patients were more likely to have a fever (29% vs. 12%, $p = 0.007$) and less likely to have nausea/vomiting (61% vs. 80%, $p = 0.019$) or an impacted gallstone on ultrasound (US) (8% vs. 26%, $p = 0.017$). Otherwise, there was no significant difference in clinical or US findings. Among GC patients, US findings were absent (8%, n = 3) or minimal (42%, n = 16). Median time from emergency department registration to US (3.3 hours vs. 2.8 hours, $p = 0.28$) was similar, but US to operation was longer (41.2 hours vs. 18.4 hours, $p < 0.001$), conversion to open cholecystectomy was more common (37% vs. 10%, $p < 0.001$), and hospital stay was longer (median, 4 days vs. 2 days, $p < 0.0001$). Delay in surgical consultation occurred in 16% of GC patients compared with 1% of AC patients ($p < 0.001$).

CONCLUSION: Demographic features may be predictive of GC. Absent or minimal US signs occur in 50%, and delay in surgical consultation is common. Postoperative morbidity is greater for patients with GC compared with those with AC/CC. (*J Trauma Acute Care Surg*. 2015;79: 812–816. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic study, level III; therapeutic study, level IV.

KEY WORDS: Gangrenous cholecystitis; surgical consult; ultrasound; acute cholecystitis.

Acute cholecystitis (AC) complicates 1% to 2% of patients with asymptomatic cholelithiasis annually, and more than 500,000 cholecystectomies are performed each year in the United States.[1] In patients presenting with presumed AC, the incidence of gangrenous cholecystitis (GC) is approximately 20%,[2–4] yet the diagnosis is often only made intraoperatively because the clinical presentation is often identical. While AC arises from cystic duct obstruction with inflammation, GC is characterized by full-thickness vascular ischemia and necrosis of the gallbladder, sometimes in the absence of cholelithiasis or cystic duct obstruction. It is thus unclear if GC represents the natural history of untreated AC or if it represents a wholly different disease altogether, as previous studies have documented distinctly different patient populations. While AC complicating cholelithiasis has a middle-aged female predominance, GC seems to affect older male patients with comorbid medical conditions.[3]

In addition to a more frequent need for open conversion, outcomes after cholecystectomy for GC are worse, with a higher rate of intensive care unit admission, longer postoperative stay, and mortality reported as high as 15%.[2–5] It is generally agreed that treatment for known GC is expeditious removal of the gallbladder. As such, previous reports have attempted to identify risk factors for the development of GC,[2,6] as an earlier diagnosis may hasten treatment and improve outcomes. In addition to demographic characteristics such as male sex and diabetes mellitus, we hypothesized that patients presenting with GC would have other clinical features distinctly different from those presenting with AC, which could aid in their preoperative identification. In addition, we sought to examine the sensitivity of ultrasound (US) compared with computed tomography in diagnosing gallbladder inflammation.

PATIENTS AND METHODS

Patients and Setting

We performed a retrospective review of a prospectively collected database of all patients undergoing cholecystectomy by the acute care surgery service for presumed AC from July 2010 to January 2014. The preoperative criteria for presumed AC were a clinical constellation of symptoms including right upper quadrant (RUQ) abdominal tenderness, fever, leukocytosis, nausea/vomiting, postprandial symptoms, and Murphy'ls sign combined with a radiologic imaging study (US or computed tomography [CT]) showing features characteristic of acute inflammation such as gallbladder distention, gallbladder wall thickening, pericholecystic fluid, impacted stone at the neck of the gallbladder, and a sonographic Murphy'ls sign. The presence of cholelithiasis was not considered mandatory for the diagnosis of presumed AC. Exclusion criteria included transfer from another hospital or direct hospital admission (i.e., bypassing the emergency department [ED]), previous cholecystostomy tube, and previous endoscopic retrograde cholangiopancreatography with sphincterotomy. Data collected included demographics, clinical and radiographic findings, time elapsed from ED arrival to radiologic study, and time to operation. Operative and pathology reports were also abstracted. The final pathologist'ls impression was used to establish the diagnosis of GC, and the pathologic criteria included focal or diffuse gangrene as well

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From the Division of Trauma, Emergency Surgery, and Surgical Critical Care (D.D.Y., C.C., P.F., D.R.K., E.N.K., M.D., H.K., G.V.), Department of Surgery, and Department of Medicine (Y.C.), Massachusetts General Hospital, Boston, Massachusetts.
This study was presented at the 27th annual meeting of the Panamerican Trauma Society, November 11–14, 2014, in Panama City, Panama.
Address for reprints: Daniel Dante Yeh, MD, Division of Trauma, Emergency Surgery, and Surgical Critical Care, Department of Surgery, Massachusetts General Hospital, 165 Cambridge St #810, Boston, MA 02114; email: Dyeh2@partners.org.

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as abscess or perforation of the gallbladder wall. Clinical outcomes data collected included conversion to open procedure, hospital length of stay (LOS), postoperative hospital LOS, and postoperative complications such as bile leak, bleeding requiring transfusion, surgical site infection, and intra-abdominal abscess. Because of the observational study design, Partners Human Research Committee (institutional review board) waived the requirement to obtain informed consent.

Clinical Management

After clinical evaluation and confirmation with US and/or CT, patients were started on intravenous cefoxitin (in patients with allergies to cephalosporins, appropriate antibiotics were chosen to provide gram-negative and gram-positive organism coverage) and added to the operative schedule for cholecystectomy. In patients with laboratory evidence of choledocholithiasis (elevated direct bilirubin and/or elevated alkaline phosphatase), the laboratory tests were repeated several hours later. If the laboratory values improved, the patient proceeded straight to cholecystectomy. If they remained elevated, the patient underwent preoperative endoscopic retrograde cholangiopancreatography with sphincterotomy or intraoperative cholangiogram according to surgeon preference.

Laparoscopic cholecystectomy was first attempted in the vast majority of patients. Reasons for conversion to open procedure included inability to perform safe dissection of the inflamed gallbladder, inability to completely visualize the biliary anatomy, and hemorrhage with inability to control laparoscopically.

Patients were divided into two groups and then compared based on the final pathologic findings: AC/chronic cholecystitis (CC) and GC. Patient characteristics (age, sex, comorbid conditions, clinical presentation), diagnostic process (radiologic workup, time to surgical consult and operating room [OR]), as well as clinical, US, and CT signs and outcomes (hospital/postoperative LOS, conversion to open) were compared between the two groups. Continuous variables were summarized using medians with interquartile ranges and compared using the Wilcoxon rank-sum test. Categorical variables were summarized using frequencies, and groups were compared using the χ^2 test. To adjust for the imbalance in patient characteristics, a quantile regression model was used to compare the median hospital LOS controlling for age, comorbid condition (diabetes, hypertension, hyperlipidemia), and time from ED to OR.

TABLE 1. Demographics

	AC/CC (n = 171)	GC (n = 38)	*p*
Age, y	41 (31–58)	57 (43–73)	<0.001
Male sex	31%	63%	<0.001
Diabetes mellitus	8%	24%	0.006
Hypertension	22%	47%	0.002
Hyperlipidemia	14%	29%	0.026
Steroids/chemotherapy	0%	8%	<0.001
Male diabetic	6%	18%	0.01
ED to US, h	2.8 (1.8–4.2)	3.3 (1.8–5.8)	0.28
US to OR, h	18.4 (11.6–30.7)	41.2 (17.4–57.0)	<0.001
ED to OR, h	22.1 (16.2–35.1)	45.5 (18.9–63.3)	<0.001
CT scan	24%	42%	0.023
Surgical consultation > 24-h delay	1%	16%	<0.001

TABLE 2. Clinical and Radiographic Signs of Cholecystitis

	AC/CC (n = 171)	GC (n = 38)	*p*
Clinical signs			
Nausea/vomiting	80%	61%	0.019
Postprandial symptoms	43%	29%	0.15
RUQ tenderness	92%	89%	0.64
Murphy'ls sign	58%	61%	0.68
Fever	12%	29%	0.007
White blood cell count > 11	54%	68%	0.10
US signs			
Cholelithiasis	92%	89%	0.64
Gallbladder thickening > 3 mm	46%	58%	0.19
Pericholecystic fluid	27%	29%	0.80
Sonographic Murphy'ls sign	43%	45%	0.87
Gallbladder distention	23%	32%	0.29
Incarcerated gallstone	26%	8%	0.017
CT signs (among those who had CT performed)	(n = 41)	(n = 16)	
Gallbladder thickening	59%	44%	0.31
Pericholecystic fluid	41%	63%	0.15
Gallbladder distention	44%	75%	0.035
Fat stranding	37%	75%	0.009

RESULTS

Thirty-eight cases of GC were identified and compared with 171 cases of AC/CC. Compared with AC/CC patients, GC patients were more likely to be older (57 years vs. 41 years, $p < 0.001$), of male sex (63% vs. 31%, $p = <0.001$), hypertensive (47% vs. 22%, $p = 0.002$), hyperlipidemic (29% vs. 14%, $p = 0.026$), diabetic (24% vs. 8%, $p = 0.006$), and male diabetic (18% vs. 6%, $p = 0.01$) (Table 1). Delay in surgical consultation (>24 hours from ED arrival) was more common in patients with GC than those with AC/CC (16% vs. 1%, $p < 0.001$).

In the preoperative workup, GC patients were more likely to have a fever (29% vs. 12%, $p = 0.007$), less likely to have nausea/vomiting (61% vs. 80%, $p = 0.019$), and less likely to have an impacted gallstone on US (8% vs. 26%, $p = 0.017$). Otherwise, there were no significant differences in history and physical examination findings or US findings (Table 2). Among GC patients, US findings were absent (n = 3) or minimal (only one finding, n = 16) in 50%, whereas CT scan, when performed,

TABLE 3. Outcomes

	AC/CC (n = 171)	GC (n = 38)	*p*
Hospital LOS, d	2 (2–3)	4 (3–6)	<0.001
Postoperative LOS, d	1 (1–2)	3 (2–4)	<0.001
Conversion to open	17 (10%)	14 (37%)	<0.001
Postoperative bile leak	1 (1%)	2 (5%)	0.086
Bleeding	1 (1%)	0 (0%)	1.0
Surgical site infection	3 (2%)	3 (8%)	0.075
Intra-abdominal abscess	1 (1%)	0 (0%)	1.00

had absent or minimal findings in only 13%. When CT was performed, patients with GC were more likely to have fat stranding (75% vs. 37%, $p = 0.009$) and gallbladder distention (75% vs. 44%, $p = 0.035$) when compared with patients with simple AC. Time from ED registration to US was similar (3.3 hours vs. 2.8 hours, $p = 0.28$), but time from US to operation was longer (41.2 hours vs. 18.4 hours, $p < 0.001$), conversion to open cholecystectomy was more common (37% vs. 10%, $p < 0.001$), and hospital stay was longer (4 days vs. 2 days, $p < 0.001$) (Table 3). Follow-up was complete in 33 (87%) of 38 patients in the GC group and 150 (88%) of 171 patients in the AC/CC group. After adjusting for age, comorbid conditions (diabetes, hypertension, hyperlipidemia), and time from ED to OR using a quantile regression model, the hospital stay remained significantly longer among GC patients ($p = 0.017$).

More detailed information about the patients with delayed surgical consultation (>24 hours from ED registration) are displayed in Table 4. The patients were overwhelmingly male, were of older age, and were admitted to a medical service or to an ED observation unit. All but one patient (Case 6) had imaging study evidence of cholecystitis; however, the ED discharge diagnosis did not specifically mention cholecystitis in the differential diagnosis in any patient.

DISCUSSION

In this study, patients presenting with GC were more commonly older, male, and diabetic when compared with those with simple AC/CC. In addition, those with GC more commonly had hypertension and hyperlipidemia and were more commonly on immunosuppressive medications such as steroids or chemotherapy. The only distinguishing preoperative clinical characteristics were fever (which was present in almost one third of patients with GC) and nausea/vomiting, which was significantly less common in patients with GC. Typical sonographic features of acute gallbladder inflammation were absent or minimal in half of patients with GC. However, CT scan, when performed, was highly sensitive for gallbladder inflammation. While time from ED arrival to US was not significantly different between those with AC and GC, delay to surgical consultation was common in the latter group and may have contributed to a delay in diagnosis and treatment. The outcomes after cholecystectomy were worse in the gangrenous cohort, with a higher rate of conversion to open cholecystectomy and longer postoperative stay. It is currently unknown whether earlier treatment of GC is associated with improved outcomes. However, hospital LOS would likely be improved with early surgical consultation, as there was little delay to operation once the diagnosis of GC was suspected, except in cases of high perioperative risk requiring preoperative optimization, such as unstable angina or active coronary ischemia.

When reviewing the patients for whom surgical consultation was delayed by more than 24 hours from ED registration, it is interesting to note that they were overwhelmingly male, were of older age, and had alternate diagnoses listed as the main ED discharge diagnosis, despite imaging evidence of AC in all but one patient. These patients were admitted to medical teams or placed in an observation unit, and the surgical team was later consulted when the clinical condition failed to improve. In two patients (Cases 4 and 6), coronary ischemia was significant early in the hospital course and was likely responsible for significant delays to operative intervention (212 hours and 121 hours, respectively). Because we were unable to interview the ED physician during the ED workup, we cannot say with absolute confidence that they were unaware of the possibility of GC as the etiology of the symptoms. However, none of the patients was intentionally admitted for preoperative optimization before surgical consultation, and the term *cholecystitis* did not appear on the ED discharge note. The common theme that emerges is that of an older male patient with vague chest or abdominal symptoms who has US or CT evidence of AC; however, the diagnosis is not seriously entertained until after a significant time delay. Therefore, in this particular scenario, early surgical consultation in the ED is recommended. From Table 4, it is apparent that patients were taken promptly to the operating room, within 1 day to 2 days of surgical consultation, with the exception of the case where the patient required preoperative optimization for unstable angina.

The difficulty of preoperative diagnosis of GC has been well documented. Merriam et al.[3] reported that while there were no distinguishing clinical features between GC and AC in the history and physical examination, risk factors for GC were older males (age > 50 years), white blood cell count greater than 17, and a history of cardiovascular disease. In a study of 295 patients with AC, Borzellino et al.[2] reported that fever, gallbladder distension, and gallbladder wall edema were predictive of GC. Similar to other series, we report a higher rate of GC in older men as compared with other patient, confirming that patients with GC comprise a unique demographic population.[3,5]

Fagan et al.[6] reported that in multivariate analysis, diabetes mellitus and leukocytosis greater than 15,000 were identified as a risk factor for GC. In a subsequent study from the same group,

TABLE 4. Delayed Surgical Consults

Case	Age	Sex	ED Discharge Diagnosis	No. US Signs of Cholecystitis	No. CT Signs of Cholecystitis	ED to US, h	ED to CT, h	ED to OR, h	Consult to OR, d
1	33	Male	Community-acquired pneumonia	3	3	34	33	68	1
2	81	Male	Diarrhea with dehydration	3	3	61	25	87	2
3	73	Male	Epigastric pain	1	N/A	6	N/A	80	2
4	76	Male	Unstable angina	0	2	43	53	212	6
5	74	Female	Abdominal pain	1	3	7	4	43	1
6	59	Male	STEMI	0	0	50	14	121	1

N/A, not applicable; STEMI, ST segment elevation myocardial infarction.

Nguyen et al.[7] used their predictive factors to develop and validate a predictive equation. Although this equation proved to be very accurate (96% negative predictive value with a cutoff value of $p = 0.72$), it is too unwieldy for routine clinical practice:

$$P = e^{(0.7116 + 0.9944 \times DM + 1.7157 \times WBC - 1.0319 \times ALT \times 2.0518 \times ALP + 2.7078\ PCF)} / (1 + e^{[-0.7116 + 0.9944 \times DM + 1.7157 \times WBC - 1.0319 \times ALT - 2.0518 \times ALP + 2.7078 \times PCF]}).$$

Previously, at our institution, we have reported that in patients presenting with abdominal pain and other features suggestive of cholecystitis, absence of a sonographic Murphy'ls sign actually increases the likelihood of GC.[8] In that study, only 33% of patients with GC had a sonographic Murphy'ls sign, and less than 50% had a clinical Murphy'ls sign. In our study, we report higher rates of positive sonographic and clinical Murphy'ls sign of 45% and 61%, respectively. Despite this, the sensitivity of this sign is too poor to rely on as a distinguishing feature of AC or GC.

CT is becoming increasingly used in cases of diagnostic uncertainty. Findings on CT such as intraluminal or intramural gas, irregular or absent gallbladder wall, and gallbladder abscess are strongly suggestive of the diagnosis of GC. Other authors have reported an overall accuracy of CT for GC at 86.7%.[9] In our series, CT scan, when obtained, was highly sensitive in detecting evidence of gallbladder inflammation. For older male patients with RUQ pain who do not fit the classic clinical picture of AC, CT may be the preferred radiologic workup in the ED to rapidly diagnose GC.

Our study has several limitations. First, we relied on the final pathologic diagnosis as our criterion standard. The pathologists did not routinely adhere to a uniform scale, and thus, there may be interrater differences in the definitions of GC. Second, it is possible that in the time from clinical examination and US to operation, the inflammation could have progressed from AC to GC. However, this natural progression has not been adequately proven. Unfortunately, we did not record the specific reason for the delay in consultation or delay in operation. Third, the sample size is relatively small, making a Type 2 statistical error possible. Fourth, we did not record transaminase levels in our database. However, in our clinical practice, the decision to proceed with cholecystectomy is rarely influenced by the degree of transaminitis, unless the patient has fulminant hepatic failure. None of the patients in this series had clinical evidence of hepatic failure. Therefore, it is unlikely that the transaminase levels were strongly influential in the delay to operation seen in the GC group. Finally, this study was conducted at a single urban academic tertiary hospital, and the results may not be generalized to other settings. Despite these limitations, we believe that our results are useful to both surgeons and emergency medicine providers evaluating such patients. For patients presenting with RUQ pain who happen to be older men with comorbid medical conditions, the diagnosis of GC should be seriously considered, and we suggest initial CT scan, as our results demonstrate that CT is more sensitive than US to confirm the diagnosis. Prompt surgical consultation and earlier treatment may lead to improved outcomes, such as conversion to open cholecystectomy or postoperative morbidity. While this remains to be confirmed by prospective studies, earlier diagnosis will likely shorten ED LOS and hospital LOS by decreasing the preoperative hospitalization period.

CONCLUSION

Preoperative signs and symptoms cannot distinguish GC from AC/CC, although demographic features may be predictive. Emergency physicians and surgeons should be aware that absent or minimal US signs of cholecystitis occur in 50% of patients with confirmed GC and that significant delay in surgical consultation is common. Because of its higher sensitivity, CT may confirm the diagnosis in patients with suggestive clinical findings but without significant US findings.

AUTHORSHIP

D.D.Y. and C.C. contributed in the study concept and design. D.D.Y. and C.C. performed the data collection. D.D.Y., P.F., D.R.K., Y.C., E.N.K., M.D., H.K., and G.V. performed the data interpretation. D.D.Y., C.C., P.F., D.R.K., Y.C., E.N.K., M.D., H.K., and G.V. contributed in the manuscript writing, editing, and finalizing.

DISCLOSURE

The authors declare no conflicts of interest.

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