Risk Factors for Acute Cholecystitis and a Complicated Clinical Course in Patients With Symptomatic Cholelithiasis

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Background: We prospectively evaluated the risk factors for acute cholecystitis (AC).

Design: Prospective study.

Setting: Department of surgery at a university hospital.

Patients: From July 2004 through December 2007, the data of 1059 patients who underwent laparoscopic cholecystectomy for symptomatic gallstones were prospectively recorded. The relationships between the clinical outcomes and the patients' demographic factors and comorbidities were analyzed by performing multivariate analyses.

Main Outcome Measures: Risk factors for AC and operative outcome.

Results: The diagnoses of the 1059 patients who underwent laparoscopic cholecystectomy were chronic cholecystitis (n=704 [66.5%]) and AC (n=355; [33.5%]). An age older than 60 years (odds ratio [OR], 1.955; 95% confidence interval [CI], 1.441-2.652), male sex (OR, 1.769; 95% CI, 1.346-2.325), the presence of cardiovascular disease (OR, 1.826; 95% CI, 1.325-2.517), the presence of diabetes mellitus (OR, 1.802; 95% CI, 1.153-2.816), and a history of cerebrovascular accident (ischemic stroke or cerebral hemorrhage) (OR, 8.107; 95% CI, 2.650-24.804) were identified as independent risk factors for AC after multivariate analysis. Approximately 85% of the patients with a history of cerebrovascular accident presented with AC ($P<.001$), 54.5% of whom experienced complicated AC ($P<.001$). Acute cholecystitis was associated with greater operative difficulty and more postoperative morbidity than chronic cholecystitis.

Conclusion: For the patients with risk factors for AC, early cholecystectomy is recommended before the disease progresses to AC.

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THE NECESSITY OF PERFORMING cholecystectomy for the patients with gallbladder stones usually depends on whether symptoms are present. If the patient complains of recurrent attack of biliary colic, then operative treatment should be considered. Some of these patients may complain of mild symptoms, such as indigestion or intermittent abdominal discomfort, while others may present with a severe form of gallbladder inflammation, such as acute cholecystitis (AC),[1,2] which requires urgent intervention.[3-8] In the case of AC, the systemic symptoms and signs are more severe than those seen in patients with chronic cholecystitis (CC), with an increased morbidity. If AC develops in the patients with preexisting comorbidities, then it may lead to more profound illness.[9]

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Laparoscopic cholecystectomy (LC) has rapidly become the treatment of choice for symptomatic gallstones.[10-14] However, LC is still considered as a challenging procedure for AC because a high incidence of common bile duct injuries has been reported in several series.[15,16] Aside from the risk of intraoperative organ injury, the postoperative morbidity is also higher for the patients with AC.[17-20] It would be beneficial for the patients if physicians could predict the severity of cholecystitis ahead of time and thus perform cholecystectomy before they develop AC. Therefore, determining the risk factors for developing AC may help to select the group of patients who are prone to the severe form of cholecystitis.

At present, the well-known risk factors for developing AC are old age[21] and comorbidities such as diabetes.[22] We previously reported that male sex was identified as a risk factor for AC, and cholecystitis tends to be more severe in men,[19] although the cause of the higher proportion of cases of severe cholecystitis in men is still un-

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Table 1. Univariate Prediction for the Development of Acute Cholecystitis

Variable	CC (n=704)	AC (n=355)	*P* Value
Age, mean (SD), y	49.6 (14.3)	57.9 (17.0)	<.001
Sex, No.			<.001
Male	293	198	
Female	411	157	
ASA score 3-4, No. (%)	26 (3.7)	41 (11.5)	<.001
Cardiovascular disease, No. (%)[a]	149 (21.2)	153 (43.1)	<.001
Cerebrovascular accident, No. (%)[b]	4 (0.6)	22 (6.2)	<.001
Diabetes mellitus, No. (%)[c]	46 (6.5)	57 (16.1)	<.001
Respiratory disease, No. (%)[d]	40 (5.7)	33 (9.3)	.03
Chronic liver disease, No. (%)[e]	34 (4.8)	14 (3.9)	.51
Previous upper abdomen operation, No. (%)[f]	9 (1.3)	18 (5.1)	<.001

Abbreviations: AC, acute cholecystitis; ASA, American Society of Anesthesiologists; CC, chronic cholecystitis.

[a] History of hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or isolated systolic hypertension), arrhythmia, angina pectoris, or myocardial infarction.

[b] History of a cerebrovascular accident (ischemic stroke or cerebral hemorrhage) with minor or no residual or transient ischemic attacks or chronic cognitive deficit.

[c] Fasting plasma glucose concentration of 126 mg/dL or higher or plasma glucose concentration of 200 mg/dL or higher for 2 hours during an oral glucose tolerance test (to convert glucose to millimoles per liter, multiply by 0.0555).

[d] History of pulmonary tuberculosis and chronic obstructive pulmonary disease.

[e] Chronic viral hepatitis, cirrhosis, portal hypertension, or a history of variceal bleeding.

[f] Gastrectomy or peptic ulcer operation.

known. There are also a few reports that have shown that cardiovascular disease is associated with severe AC.[23,24] Given these facts, we prospectively evaluated the risk factors for developing AC and determined the impact of demographic factors and comorbidities to distinguish the subset of patients who are vulnerable to the severe form of cholecystitis.

METHODS

STUDY POPULATION AND THE DEFINITIONS USED

From July 2004 to December 2007, the data of 1059 patients who underwent LC for symptomatic gallstones in Seoul National University Bundang Hospital, Seongnam, Korea, was prospectively recorded. Patients with acalculous cholecystitis were excluded. Laparoscopic cholecystectomy was performed as a first-line treatment for all the patients with cholecystitis. The operation was performed by the same surgical team using the standard 3- or 4-port technique. Laparoscopic cholecystectomy was electively performed in the patients with CC, and LC was performed as soon as possible for the patients with AC during their initial hospital admission. For patients with cholecystitis that is associated with organ or system dysfunction, a percutaneous cholecystostomy tube was inserted as an alternative to operating on high-risk patients and thereby converting their operation to an elective procedure.

As previously described,[18,19] AC was defined when the patient had 2 or more of the following clinical and operative findings. The clinical factors (4 factors) consist of fever with a body temperature higher than 37.5°C, leukocytosis, right upper abdominal pain with tenderness, and continuous symptoms for more than 48-hour duration despite medical treatment. The operative findings (4 factors) included a gallbladder wall thickness of greater than 4 mm, severe adhesion to an adjacent organ, distortion of the biliary anatomy, and gross inflammation of the gallbladder serosa. Complicated cholecystitis was defined if hydrops, empyema, pericholecystic abscess, or gangrene developed.[18,19,25]

Table 2. Multivariate Analysis for the Development of Acute Cholecystitis

Category[a]	Adjusted OR (95% CI)	*P* Value
Age >60 y	1.955 (1.441-2.652)	<.001
Male sex	1.769 (1.346-2.325)	<.001
Cardiovascular disease, present	1.826 (1.325-2.517)	<.001
Diabetes mellitus, present	1.802 (1.153-2.816)	.01
CVA, present	8.107 (2.650-24.804)	<.001

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident (ischemic stroke or cerebral hemorrhage); OR, odds ratio.

[a] See Table 1 for definitions.

Technical difficulties were assessed according to a previously described method.[25] Briefly, the operative difficulty was assessed as present (score of 1) or absent (score of 0) for each of the following 4 operative steps: (1) dissection of adhesions from the gallbladder, (2) dissection of the triangle formed by the common bile duct, cystic duct and liver (Calot triangle), (3) dissection of the gallbladder bed, and (4) extraction of the gallbladder from the abdominal cavity. The overall difficulty score was calculated as the sum of the scores for each step, with a possible range of 0 to 4. The operative time was defined as the time from insertion of the Veress needle to closure of the trocar insertion sites.

STATISTICAL ANALYSIS

The continuous, normally distributed variables are presented as mean (SD), and discontinuous variables are expressed as median (range). The continuous parameters in each group were compared by independent sample *t* tests, and categorical parameters were compared using the χ^2 test. The independent effects of the normally distributed variables were assessed by multiple linear regression analysis. A stepwise approach was used to remove the nonsignificant variables and to determine the most parsimonious model, which included both fixed factors and covariates. The maximum proportion of missing values was 5%. No substantial difference was found when separate analyses were performed, first by excluding the subjects with missing values and then by conservatively replacing the missing values with their corresponding sample means. All the statistical analyses were performed using SPSS 11.0 for Windows (release 11.0; SPSS Inc, Chicago, Illinois), and differences were considered significant at $P<.05$.

RESULTS

There were 491 men (46.4%) and 568 women (53.6%), with a mean (SD) age of 52.4 (15.8) years (range, 9-91 years). The diagnoses given for the 1059 patients who underwent LC included CC (n=704 [66.5%]) and AC (n=355 [33.5%]). Complicated AC developed in 178 patients, and this group composed 16.8% of the entire study population. Complicated AC included empyema (n=104), hydrops (n=39), gangrenous AC (n=22), perforation (n=7), pericholecystic abscess (n=4), and fistula formation (n=2).

The preoperative characteristics of the patients according to the diagnosis are summarized in **Table 1**. Re-

Table 3. Comparison of Surgical Outcomes Between Patients With Chronic and Acute Cholecystitis

Outcome	CC (n=704)	AC (n=355)	*P* Value
Operation time, mean (SD), min	40.3 (26.3)	60.5 (39.0)	<.001
Blood loss, mean (SD), mL	26.2 (33.2)	85.8 (83.9)	<.001
Difficulty score, median (range)	0 (0-4)	2 (0-4)	<.001
Complication, No. (%)	26 (3.7)	34 (9.6)	<.001
Conversion to open surgery, No. (%)	0	2 (0.6)	.046

Abbreviations: AC, acute cholecystitis; CC, chronic cholecystitis.

sults from univariate analysis showed that 8 variables were associated with an increased risk of developing AC. **Table 2** lists the candidate predictors in the final logistic regression model with their odds ratios (ORs), 95% confidence intervals (CIs), and corresponding adjusted *P* values. American Society of Anesthesiologists score, presence of respiratory disease or chronic liver disease, and history of a previous upper abdominal operation were not significant after multivariate analysis.

For patients with AC, the mean operation time was longer ($P<.001$) and the mean blood loss during LC was greater ($P<.001$) (**Table 3**). The cholecystectomies were more difficult in patients with AC than in those with CC ($P<.001$). The complication rate was also higher for the patients with AC than for those patients with CC ($P<.001$), and 2 patients with AC experienced a conversion to open surgery during LC because of bowel injury ($P=.046$).

Compared with the patients without a history of cerebrovascular accident (CVA) (ischemic stroke or cerebral hemorrhage), 84.6% of the patients with a history of CVA presented with AC ($P<.001$) (**Table 4**). Of the 26 patients with a history of CVA, 12 (46.2%) experienced complicated AC ($P<.001$). Preoperative percutaneous cholecystostomy was more frequently required in patients with a history of CVA than in those without a history of CVA ($P<.001$). The patients with a history of CVA were older than 60 years ($P<.001$), had a longer mean operative time ($P=.006$), and underwent a more difficult operation ($P<.001$) compared with those without history of CVA. The complication rate after LC for the patients with a history of CVA (19.2%) was also higher than for those patients without a history of CVA (5.3%) ($P=.003$).

Table 4. Comparisons Between Patients With or Without a History of CVA

Variable	No CVA (n=1033)	With CVA (n=26)	*P* Value
AC, No. (%)	333 (32.2)	22 (84.6)	<.001
Complicated AC, No. (%)	166 (16.1)	12 (46.2)	<.001
Age, mean (SD), y	52.1 (15.7)	63.2 (15.1)	<.001
Sex, No.			.98
Male	479	14	
Female	554	12	
Preoperative percutaneous cholecystostomy, No. (%)	71 (6.9)	8 (30.8)	<.001
Operation time, mean (SD), min	46.5 (32.1)	65.8 (39.8)	.006
Blood loss, mean (SD), mL	46.8 (63.2)	71.1 (68.1)	.07
Difficulty score, median (range)	0 (0-4)	3 (0-4)	<.001
Complication, No. (%)	55 (5.3)	5 (19.2)	.003
Conversion to open surgery, No. (%)	2 (0.2)	0	.82

Abbreviations: AC, acute cholecystitis; CVA, cerebrovascular accident (ischemic stroke or cerebral hemorrhage).

COMMENT

Cholecystitis is a syndrome that encompasses a continuum of clinicopathologic states.[2] One end of this continuum is CC, with intermittent attacks of pain (biliary colic). The other end is AC, for which abdominal pain lasts longer and is accompanied by fever, leukocytosis, or cholestasis. As we have shown in this study, AC is associated with a higher grade of operative difficulty and postoperative morbidity. Therefore, considering the many adverse influences on the patients and the postoperative outcomes, it is desirable to select the subgroup of patients who are more prone to develop AC. Furthermore, for the patients at high risk of developing AC, it is better to operate before AC develops. For example, early cholecystectomy is recommended for patients with diabetes, based on the high incidence of postoperative complications and the increased mortality rates among diabetic patients with AC.[26]

In the present study, 5 factors were found to be risk factors for AC on multivariate analysis. There are 3 comorbidities, including diabetes, history of cardiovascular disease, and history of CVA, and 2 demographic factors, including age older than 60 years and male sex.

Diabetes is a well-known risk factor for AC. Acute cholecystitis seems to develop more frequently in patients with diabetes than in those without diabetes, and such patients are more likely to have complications of AC when it occurs.[22] There are a few reports that showed that comorbid cardiovascular disease is associated with a severe form of cholecystitis, although its cause is still unknown. In the present study, diabetes and history of cardiovascular disease were found to be independent risk factors for AC, as was expected.

In our series, a history of CVA such as ischemic stroke or cerebral hemorrhage was the most significant independent risk factor for developing AC. In the patients with a history of CVA, the adjusted OR for developing AC was 8.107. It is very interesting that there is a high OR between a history of CVA and AC. There is a possibility that physicians may choose to operate on the patients who have severe symptoms of AC, while they recommend just a wait-and-see approach for those patients with only mild pain, when considering the related operative risk. However, this selection difference for the patients with a history of CVA was not observed for the patients with respiratory disease or chronic liver disease. Even when considering this possibility of a selection bias, the significant OR implies that a history of CVA is an important risk factor for AC. To our knowledge, a history of CVA has not been previously reported as a risk factor for AC. More-

over, our results showed that approximately 85% of the patients with a history of CVA presented with AC, and 46% of these patients experienced complicated AC. Performing cholecystectomies in the patients with a history of CVA was more difficult, and these patients showed more frequent postoperative complications compared with patients without a history of CVA.

Old age is a well-known demographic risk factor for AC, and it is also associated with other comorbidities such as cardiovascular disease, diabetes, and CVA. Male sex is also another independent demographic risk factor for AC. We previously reported that male sex was shown to be a predictive factor for more severe AC.[19] Differences between the sexes may influence symptomatic cholelithiasis in a multifactorial way (ie, from psychologic, behavioral, and anatomic aspects). Women seek medical advice more often than men at the time of symptom onset, which may be owing to men having heavier daily schedules. Moreover, it is more likely that male patients will wait to undergo surgery until the disease is at a more advanced stage.[23,27-29] Furthermore, differences between the sexes in their dietary habits and anatomy, such as the body fat percentage and the size of the peritoneal cavity, can have an effect on the clinical presentation of symptomatic cholelithiasis.[18,28] However, the cause of the higher prevalence of AC in men is still not known.[30] We have previously proposed that the difference of the body mass index is associated with the severity of cholecystitis, especially in men.[18]

Coronary artery disease, such as myocardial infarction, and peripheral vascular disease, such as Buerger disease or atherosclerosis, are more frequent in men. Therefore, we can hypothesize that the high prevalence of AC in men may result from the high probability of vascular disease in the cystic artery. Obstruction of the cystic artery is an important factor in the pathophysiologic mechanisms of the severe form of cholecystitis. The vulnerability for severe cholecystitis in patients with cardiovascular disease and diabetes may result from the synergistic pathophysiologic interaction on the acute inflammatory response in the gallbladder wall and the preexisting microvascular atherosclerotic disease. The pathologic progression from acute inflammation to gangrene involves vascular compromise and gallbladder wall ischemia, which eventually result in gallbladder wall necrosis and perforation.[24]

The 5 aforementioned risk factors are closely related with other factors. Old age is frequently accompanied by cardiovascular disease or CVA. In patients with diabetes, there is high probability of cardiovascular disease or CVA, peripheral vascular disease, and AC as well. Men are also known to have a greater prevalence of cardiovascular disease, CVA, peripheral vascular disease, and AC.[31] All of these risk factors may be associated with vulnerability for vascular pathologic abnormalities. However, further study is necessary to confirm the relationship between AC and the vascular disease process.

In conclusion, male sex, age older than 60 years, diabetes, a history of cardiovascular disease, and a history of CVA increase the probability of developing AC in patients with symptomatic gallstones. Therefore, performing early cholecystectomy is recommended in patients with symptomatic cholelithiasis and these adverse risk factors.

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INVITED CRITIQUE

Posing Lesser Risks Against Those That Are Greater

In their article, Cho et al attempt to define the clinical factors that represent risks for the development of AC among patients with symptomatic cholelithiasis. They correctly point out that cholecystectomy in the acute setting is not only more technically challenging but is also associated with a higher incidence of common bile duct injury and postoperative morbidity in general. The authors postulate that if such risks could be identified in advance, then timely intervention with cholecystectomy could circumvent a complicated clinical course. One certainly can only agree with these commendable goals and find the number of patients studied to be impressive. Nevertheless, there may be minor conceptual or procedural issues that somewhat weaken the authors' conclusions.

The first issue relates to the nature of a prospective study and the authority it normally confers. Although the data were acquired prospectively in the study by Cho et al, there were no clinical decision points determined in advance. Once acquired, the data were analyzed in an otherwise entirely retrospective manner. Although possibly only a semantic issue, by some definitions this is actually a retrospective study and perhaps an issue for consideration when determining overall impact.

The second but more important concern is related to the manner in which patients clinically presented in this study. The authors' goal was to identify the risks for developing acute disease among the larger group of those with chronic symptomatic disease. Yet patients presented in 1 of only 2 categories, either with acute or chronic disease. Laparoscopic cholecystectomy was performed in all patients with, by design, no observed symptoms evolving from a chronic to an acute state. Since there was no apparent documentation of each patient's history of symptoms, the implied assumption was that acute symptoms are in all cases preceded by those that are chronic. Indeed, any clinical value to the risks identified by the authors must be predicated on this supposition. This is unfortunately not always true, and obviously, in the absence of symptoms, identified risks become valueless. To be accurate, this study is more about the presence of AC than its development.

Despite any minor criticisms, Cho et al are to be commended on a thoughtful analysis of an impressive volume of clinical activity. No one would dispute the authors' conclusions that cholecystectomy for acute disease is associated with higher morbidity. It is also unlikely that anyone would take issue with the long-established fact that diabetes presents a risk for increased complications. The presence of significant cardiovascular disease, a history of CVA, and more advanced age are factors that certainly make intuitive sense. Along with male sex, this study now brings these factors into focus as significant risks for considering early operative intervention when chronic symptoms are present. Although the authors have not defined an appealing group for elective surgery, one must pose the lesser risks against those that are greater.

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