Hepatobiliary Scan for Assessing Disease Severity in Patients With Cholelithiasis

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Objective: To evaluate the role of a hepatobiliary scan for predicting the severity of cholecystitis and the difficulty of laparoscopic cholecystectomy.

Design: Prospective study.

Setting: Department of surgery at a tertiary university hospital.

Patients: From July 1, 2004, through June 30, 2007, data from 941 patients who underwent a preoperative hepatobiliary scan before laparoscopic cholecystectomy were prospectively recorded.

Main Outcome Measures: Prediction of the severity of cholecystitis.

Results: The overall predictive value of the gallbladder ejection fraction (GBEF) for predicting acute cholecystitis was 82.9% ($P < .001$), and the sensitivity and specificity of the GBEF at a set point of 30.0% were 92.1% and 61.6%, respectively. The mean (SD) severity of the cholecystitis score and the difficulty in performing laparoscopic cholecystectomy scores in the patients with gallbladder nonvisualization or a GBEF less than 30.0% (2.9 [2.5] and 0.5 [0.9], respectively) were significantly higher than those for the patients with a GBEF of 30.0% or higher (0.5 [1.1] and 0.3 [0.6]; $P < .001$ and $P = .01$, respectively). Moreover, the patients with gallbladder nonvisualization or a GBEF less than 30.0% experienced higher rates of complication after laparoscopic cholecystectomy than did the patients with a GBEF of 30.0% or higher (6.3% vs 2.6%; $P = .006$).

Conclusions: A hepatobiliary scan is useful for predicting the severity of cholecystitis, and a difficult laparoscopic cholecystectomy is predicted for patients with gallbladder nonvisualization or a GBEF less than 30.0%.

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When acute cholecystitis (AC) occurs, a cholecystectomy should be performed as early as possible.¹ A hepatobiliary scan has been used as a helpful diagnostic tool for patients with suspected AC.² Two retrospective studies³,⁴ have indicated that a hepatobiliary scan is more sensitive and accurate than ultrasonography for diagnosing AC because it directly measures the outflow of bile from the gallbladder. However, for those patients with chronic nonspecific symptoms, it is still difficult to decide whether to operate immediately or to wait until the symptoms become more severe. Furthermore, the role of a hepatobiliary scan for patients with chronic cholecystitis (CC) has not been well elucidated. One of the useful diagnostic findings of a hepatobiliary scan is whether the gallbladder can be visualized. Nonvisualization of the gallbladder is a characteristic feature of AC on a hepatobiliary scan, yet there are still no clear data, to our knowledge, regarding whether nonvisualization of the gallbladder will occur even in a patient with CC or a gallbladder polyp.

Besides nonvisualization of the gallbladder, gallbladder emptying, which is quantitatively presented by the gallbladder ejection fraction (GBEF), is another important measurement that can be obtained by a hepatobiliary scan.⁵ If the GBEF is low in a patient with biliary colic, this may be a good indication to consider performing cholecystectomy, especially in the subset of patients in whom acute acalculous cholecystitis is suspected.⁶ However, few reports exist, to our knowledge, regarding the clinical roles of the GBEF in patients with calculous cholecystitis.

Acute cholecystitis is associated with a more difficult operation compared with that for CC.⁷ Therefore, it would be beneficial for patients if we could predict the severity of cholecystitis and the difficulty of per-
forming cholecystectomy ahead of time so that we could perform cholecystectomy before these patients develop the complications of cholecystitis. We prospectively evaluated the role of a hepatobiliary scan for predicting the severity of cholecystitis and the difficulty of performing an operation in patients with benign gallbladder disease.

**STUDY POPULATION AND STUDY DESIGN**

From July 1, 2004, through June 30, 2007, data from 1060 patients who underwent laparoscopic cholecystectomy (LC) for benign gallbladder disease, including chronic calculous cholecystitis, acute calculous cholecystitis, and gallbladder polyps, at Seoul National University Bundang Hospital were prospectively recorded in the gallbladder registry. Each patient provided informed consent for the laparoscopic procedures before surgery, and approval for this prospective study was obtained from the institutional review board at our hospital. The registry includes data regarding the demographic characteristics (32 items), subjective symptoms (14 items), preoperative treatments (23 items), laboratory and radiologic results (31 items), operative findings (60 items), postoperative results (23 items), and histologic results (7 items). For all patients with benign gallbladder disease, ultrasonography and/or computed tomography was used as the initial diagnostic modality.

A hepatobiliary scan could not be performed in 81 patients because there was insufficient time to perform the scan before the operation, and the scan failed in 38 patients because of intolerance to the contents of a standard high-fat meal ingested per the prescan study protocol. Finally, 941 patients who underwent LC were enrolled in this study. After the patients had fasted overnight, hepatobiliary scintigraphy was performed using an intravenous bolus infusion of technetium Tc 99m mebrofenin at a dose of 15 mCi. If no radioactivity could be detected in the gallbladder area at 4 hours after the infusion, the patient was classified as having nonvisualization of the gallbladder, and the scintigraphic recording was stopped. For the patients with detectable radioactivity corresponding to the gallbladder area, the infusion of the radioactive marker and the scintigraphic recordings continued. Then, the patients ingested a standard high-fat meal consisting of an omelet and a glass of water, and scintigraphic recordings continued. The overall difficulty score was calculated as the sum of the scores for each step, with a possible range of 0 to 4.

**DEFINITION OF AC, SEVERITY SCORE OF CHOLECYSTISITIS, AND OPERATION DIFFICULTY SCORE**

As previously described,10,11 AC was defined when the patient had 2 or more of the following clinical and operative findings. The 4 clinical factors are a temperature higher than 37.5°C, a leukocyte count greater than 10,000/µL (to convert to ×10⁹/L, multiply by 0.001), right upper abdominal pain with tenderness, and continuous symptoms that lasted longer than 48 hours despite medical treatment. The operative findings (4 factors) included a gallbladder wall thickness greater than 4 mm, severe adhesion to an adjacent organ, distortion of the biliary anatomy, and gross inflammation of the gallbladder serosa. The severity of AC was graded as present (score of 1) or absent (score of 0) for the clinical and operative findings. The total severity score (range, 0-8) was generated by summing the scores for the clinical and operative findings. Acute cholecystitis was considered to be complicated if complications such as hydrops, empyema, and pericholecystic abscess or gangrenous developed. The diagnosis of hydrops or empyema of the gallbladder was based on the content of the clear fluid or pus in the gallbladder. Gangrenous cholecystitis was diagnosed if there was a gangrenous patch on the gallbladder wall during surgery that was later confirmed by the pathologic examination.

The technical difficulties were assessed using the previously described method. Briefly, the operation difficulty score was assessed as present (score of 1) or absent (score of 0) for each of the operative steps: (1) dissection of adhesions from the gallbladder; (2) dissection of the triangle formed by the common bile duct (CBD), 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.

**STATISTICAL ANALYSIS**

The continuous, normally distributed variables are presented as mean (SD), and nonparametric variables are expressed as median (range). The continuous parameters for each group were compared by independent sample t tests, and categorical parameters were compared using the χ² test. The Pearson correlation coefficient was used to determine the correlations among the continuous, normally distributed variables. Three groups were compared using analysis of variance, and the Tukey test was used as a post hoc test if a significant difference was found.

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 the fixed factors and the covariates. Binary logistic regression analysis was used to assess the relative influences of variables on the categorical data. The sensitivity and specificity of our predictive model were estimated by a receiver operating characteristic (ROC) curve analysis, and the overall diagnostic performances of the different tests were compared using the areas under the ROC curve. All analyses were performed using SPSS statistical software for Windows (release 11.0; SPSS Inc, Chicago, Illinois), and differences were considered significant at P < .05.

**RESULTS**

**PREOPERATIVE CLINICAL DATA AND DIAGNOSIS**

The diagnoses of the 941 patients who underwent a preoperative hepatobiliary scan before LC included polyp (n = 103; 11.0%), CC (n = 624; 66.3%), and AC (n = 214; 22.7%). Among the patients with AC, complicated AC developed in 137 patients, who comprised 14.6% of the entire study population.
RATE OF GALLBLADDER NONVISUALIZATION ACCORDING TO DIAGNOSIS

Of the 941 patients, nonvisualization of the gallbladder 4 hours after the injection of tracer occurred in 350 patients (37.2%). In all 103 patients with gallbladder polyps, the gallbladder was visualized within 4 hours after the injection of tracer. However, nonvisualization of the gallbladder was observed in 165 of the 624 patients with CC (26.4%) and in 185 of the 214 patients with AC (86.4%). The rate of nonvisualization of the gallbladder was significantly different among the 3 groups with different diagnoses (P < .001; Figure 1). In the 214 patients with AC, the gallbladder was not visualized in most of the patients with complicated AC (92.7%) compared with the patients with uncomplicated AC (75.3%; P < .001).

ROC CURVE ANALYSIS OF THE GBEF AND DETERMINATION OF THE CUTOFF VALUE

The mean GBEF was higher in the patients with gallbladder polyps (62.1% [19.7%]) than in the patients with CC (54.9% [25.5%]; P = .002). The mean GBEF in the patients with AC with gallbladder visualization (37.7% [30.5%]) was significantly lower than that for the patients with CC (P = .007) or polyps (P = .005; Figure 2). The overall predictive value of the GBEF for predicting AC, as determined by its areas under the ROC curve, was 82.9% (P < .001; 95% confidence interval, 0.80-0.86), and the sensitivity and specificity of the GBEF at a set point of 30.0% on the scan were 92.1% and 61.6%, respectively. When the GBEF was at a set point of 30.0%, the sensitivity and specificity of the test were highest.

PREDICTING THE SEVERITY OF CHOLECYSTITIS AND THE DIFFICULTY OF THE OPERATION BY THE HEPATOBILIARY SCAN

The mean severity score of cholecystitis (range, 0-3) according to the clinical findings was 0.2 (0.6) in the patients with a GBEF of 30.0% or higher and 1.3 (1.4) in the patients with gallbladder nonvisualization or a GBEF less than 30.0% (P < .001). The mean severity score of the operative findings (range, 0-4) was 0.3 (0.7) in the patients with a GBEF of 30.0% or higher and 1.7 (1.5) in the patients with a GBEF less than 30.0% (P < .001). Accordingly, the total severity score (range, 0-8) for the patients with a GBEF of 30.0% or higher (0.5 [1.1]) was significantly lower than that for the patients with gallbladder nonvisualization or a GBEF less than 30.0% (2.9 [2.5]; P < .001).

The mean score of the operation difficulty for the patients with gallbladder nonvisualization or a GBEF less than 30.0% (0.5 [0.9]) was significantly higher than that for the patients with a GBEF of 30.0% or higher (0.3 [0.6]; P = .01). Moreover, for the patients with gallbladder visualization (n = 591), there was negative linear correlation between the GBEF and the score of the operation difficulty (r = 0.234; P < .001).

OPERATIVE OUTCOMES AFTER LC ACCORDING TO THE SCAN RESULTS

After 941 consecutive LCs, 1 conversion (0.11%) and 40 complications (4.3%) occurred. One conversion occurred due to duodenal injury in a patient with gallbladder nonvisualization who had a history of surgery for peptic ulcer perforation. The mean operation time and blood loss in the patients with gallbladder nonvisualization or a GBEF less than 30.0% (56.7 [36.0] minutes and 72.3 [81.9] mL, respectively) were significantly higher than those in the patients with a GBEF of 30.0% or higher (38.6 [25.8] minutes and 24.6 [33.7] mL; P < .001 for each). Moreover, the patients with gallbladder nonvisualization or a GBEF less than 30.0% experienced a higher rate of complications after LC than did those patients with a GBEF of 30.0% or higher (6.3% vs 2.6%, respectively; P = .006; Table), and they especially displayed a fluid collection in the gallbladder bed (P = .001), bile leakage (P = .04), or missed CBD stone (P = .004). All 3 bile duct injuries occurred in the patients with gallbladder nonvisualization or a GBEF less than 30.0%. One patient experienced complete transection of CBD during LC, which was repaired with laparoscopic end-to-end choledochotomy. Right hepatic duct injuries occurred in 1 patient due to an aberrant low-lying duct, which was repaired.

Table

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>GBEF, %</th>
<th>Polyps</th>
<th>CC</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder nonvisualization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>0%</td>
<td>26.4%</td>
<td>86.4%</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>0%</td>
<td>26.4%</td>
<td>86.4%</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>0%</td>
<td>26.4%</td>
<td>86.4%</td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>0%</td>
<td>26.4%</td>
<td>86.4%</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>0%</td>
<td>26.4%</td>
<td>86.4%</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
<td>26.4%</td>
<td>86.4%</td>
<td></td>
</tr>
</tbody>
</table>
with intracorporeal suture of the injured site without any postoperative sequelae. A CBD injury was detected postoperatively in 1 patient, so open Roux-en-Y hepaticojejunostomy was performed on postoperative day 7.

### Table. Operative Outcomes After Laparoscopic Cholecystectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonvisualization or GBEF</th>
<th>GBEF ≥30.0%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion, No. of patients</td>
<td>1</td>
<td>0</td>
<td>.19</td>
</tr>
<tr>
<td>Operation time, mean (SD), min</td>
<td>56.7 (36.0)</td>
<td>38.6 (25.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood loss, mean (SD), mL</td>
<td>72.3 (81.9)</td>
<td>24.6 (33.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complications, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid collection</td>
<td>8 (1.7)</td>
<td>1 (0.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Bile leakage</td>
<td>7 (1.5)</td>
<td>1 (0.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Bile duct injury</td>
<td>3 (0.6)</td>
<td>0</td>
<td>.99</td>
</tr>
<tr>
<td>Missed CBD stone</td>
<td>5 (0.1)</td>
<td>0</td>
<td>.004</td>
</tr>
<tr>
<td>Othera</td>
<td>7 (1.5)</td>
<td>10 (2.2)</td>
<td>.80</td>
</tr>
<tr>
<td>Total</td>
<td>30 (6.3)</td>
<td>12 (2.6)</td>
<td>.006</td>
</tr>
</tbody>
</table>

Abbreviations: CBD, common bile duct; GBEF, gallbladder ejection fraction.

a Included bowel injury, bleeding, wound infection, ileus, voiding difficulty, ascites, subcutaneous emphysema, and transient hypotension.

Although LC had already gained wide acceptance for treating symptomatic cholelithiasis,12-16 the standard treatment for AC still has not been determined, to our knowledge. Laparoscopic cholecystectomy for AC has a relatively higher incidence of bile duct injury17,18 and a higher rate of conversion to open cholecystectomy19,20 than that for CC, so some surgeons prefer to perform open cholecystectomy for the patients with AC as a first-line treatment.21 Urgent cholecystectomy is recommended for the patients with AC on the basis of the reported randomized clinical trials22-26 and a meta-analysis,27 and early cholecystectomy has been proved to reduce the total hospital stay.

There may be a subgroup of patients with CC for whom the operation would be as difficult as that for patients with AC.28 Yet it is difficult to select the subgroup of CC patients with characteristics that are similar to those of patients with AC. Hepatobiliary scanning has been used as a valuable tool for diagnosing AC. Nonvisualization of the gallbladder is one of the most distinct clinical findings on a hepatobiliary scan. In this study, the GBEF can also be useful to detect the patients with severe cholecystitis. Our results showed that the mean GBEF in the patients with AC was significantly lower than that for the patients with CC or polyps. In addition, the overall predictive value of a GBEF less than 30.0% on a hepatobiliary scan for diagnosing AC was 82.9%. The rate of gallbladder nonvisualization in the patients with complicated AC was higher than that for the patients with uncomplicated AC (92.7% vs 75.3%; P < .001). In the previous prospective studies, higher conversion rates and higher morbidity rates have been reported when gangrenous cholecystitis or empyema of the gallbladder was approached by laparoscopic procedure.20-22 These facts show the need for accurate, real-time methods to preoperatively diagnose and accurately predict the severity of cholecystitis.33 This study showed that the severity score and operation difficulty were higher in patients with gallbladder nonvisualization or a GBEF less than 30.0% than those values in patients with a GBEF of 30.0% or higher on a hepatobiliary scan. Moreover, the patients with gallbladder nonvisualization or a GBEF less than 30.0% more frequently experienced complications after LC. To our knowledge, this is the first report on predicting the severity of cholecystitis and the surgical outcomes with use of a hepatobiliary scan.

Hepatobiliary scanning is known to be a sensitive test for diagnosing AC. Nonvisualization of the gallbladder on the scan occurred in 185 of the 214 patients with AC (86.4%), whereas nonvisualization of the gallbladder was also observed in 165 of the 624 patients with CC (26.4%). That nonvisualization of the gallbladder can occur in patients with CC is, to our knowledge, a novel finding. It is believed that most cases of AC result from obstruction of the cystic duct by gallstones or by biliary sludge that has become impacted at the neck of the gallbladder. However, cystic duct obstruction is not essential for the diagnosis of AC because there is still controversy regarding the definition of AC. If partial obstruction or intermittent obstruction of the cystic duct exists, visualization of the gallbladder by a hepatobiliary scan is possible. In addition, it is possible that CC progresses to AC or vice versa as time passes. Nonvisualization of the gallbladder may occur due to the chronic inflammation of the gallbladder in patients with CC. If patients with CC have a lower GBEF or nonvisualization of the gallbladder on hepatobiliary scanning, a difficult operation can also be anticipated despite the CC diagnosis. A hepatobiliary scan may be helpful to predict the severity of cholecystitis and the degree of operative difficulty in some patients; however, it may be unnecessary in some patients and may have the untoward effect of increasing health care costs. In addition, some of the criteria for scoring the severity of cholecystitis and difficulty are subjective.

Although the sensitivity of transabdominal ultrasonography to detect gallbladder stones is reported to be 95%, it is not as sensitive for diagnosing AC.34 In the absence of jaundice, a hepatobiliary scan is known to be a more sensitive test than ultrasonography for confirming AC.5 Ultrasonography is operator dependent with respect to the technical and interpretative components. In contrast, the hepatobiliary scan can be interpreted without difficulty by any independent observer, so it is not subject to interobserver variability.5 One of the drawbacks of the hepatobiliary scan is that it requires specialized equipment and personnel to perform and may not be available at all institutions. Furthermore, it is time-consuming, and several hours may be needed to make the final diagnosis in patients who require delayed scans to check for slow emptying. It is usually not applicable at nighttime in most centers. Patients with an elevated bilirubin level may not be eligible for this type of study because of interference from the cholestasis with the procedure.35

In this study, 137 of 214 patients with AC had complicated cholecystitis. This relatively high proportion of complicated cholecystitis may have occurred because...
our institution is a tertiary referral university hospital and the data were prospectively recorded. In addition, during the study period approximately 300 patients did not undergo cholecystectomy after a hepatobiliary scan. Usually, these patients had nonspecific mild pain with favorable ejection fraction. Most of these patients are in favorable health, but several patients eventually underwent cholecystectomy. For the outcome of patients who underwent a hepatobiliary scan but no cholecystectomy, long-term follow-up and further study are needed.

Based on the preoperative findings of a hepatobiliary scan, surgeons can plan the surgical technique and schedule the operation accordingly. This is especially important for the surgical trainees who are learning to perform LC. The most frequent technical complication of LC is bile duct injury. This complication usually occurs during difficult surgical procedures, and the less experienced the surgeon, the higher the risk of bile duct injury. The incidence of bile duct injury has now decreased compared with the earlier series, but it is still associated with significant morbidity and mortality. For patients with gallbladder nonvisualization or a GBEF less than 30.0% who are undergoing LC, an experienced surgeon should perform the LC or open cholecystectomy should be considered as the first-line treatment.

In conclusion, our prospective study shows that a hepatobiliary scan is useful for predicting the severity of cholecystitis in patients with symptomatic cholecystitis. This study was supported by grant 03-2005-002 from the Seoul National University Bundang Hospital Research Fund.

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Author Contributions: Drs Cho, Han, Yoon, Lee, and Hwang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Han and Yoon. Acquisition of data: Ahn, Lee, and Hwang. Analysis and interpretation of data: Cho. Drafting of the manuscript: Cho, Ahn, and Lee. Critical revision of the manuscript for important intellectual content: Cho, Han, Yoon, and Hwang. Statistical analysis: Cho and Ahn. Obtained funding: Han. Administrative, technical, and material support: Lee and Hwang. Study supervision: Han and Yoon.

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REFERENCES

Assessing Disease Severity in Patients With Cholelithiasis

The HIDA Way

Chao and colleagues advocate the use of hepatobiliary imaging to predict the severity of cholecystitis and the difficulty of performing a laparoscopic cholecystectomy. In a large retrospective study that includes more than 1000 patients who underwent laparoscopic cholecystectomy for benign gallbladder disease, they found that a gallbladder ejection fraction (GBEF) less than 30.0% is a predictor of the difficulty of the operation. Therefore, they recommend that a hepatobiliary scan (HIDA) be performed before a cholecystectomy to predict the difficulty of the operation and to be able to plan accordingly. Their data may be skewed because they included, in the group of patients who had an ejection fraction of 30.0% or greater, patients with gallbladder polyps, a group that had the easiest operations and the fewest complications. In addition, they do not mention the number of patients who had a hepatobiliary scan and did not undergo a laparoscopic cholecystectomy.

Surgeons are constantly looking for ways to predict the severity and difficulty of an operation. With gallbladder disease, the difficulty of the operation often can be predicted based on clinical parameters and other laboratory values. For example, as in the patient who had had a recent episode of gallstone pancreatitis, this is usually a more difficult operation. However, in these patients, the hepatobiliary scan may have a high ejection fraction if the patient already passed the gallstone.

Therefore, I believe using the hepatobiliary scan to predict the severity of cholecystitis and the difficulty of the operation is marginally useful. In addition, it is costly and can delay the operation. In most institutions, a hepatobiliary scan is not available at night and on weekends, and consequently a clinical decision has to be made based on clinical information without the use of a hepatobiliary scan.

The authors should be congratulated on introducing a new paradigm to consider in gallbladder surgery. However, I believe it will have limited usefulness in determining which patients should undergo laparoscopic cholecystectomy.

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