Close Relation Between Cirrhosis and Gallstones

Cross-sectional and Longitudinal Survey

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Background: Increased gallstone prevalence and incidence in cirrhosis have already been reported in different series, including a limited number of patients with cirrhosis.

Objective: To evaluate the frequency of gallstones and related risk factors in a large series of patients with cirrhosis.

Patients and Methods: The cross-sectional study involved 1010 patients with cirrhosis related to alcohol abuse, chronic viral infection, or miscellaneous causes (42%, 48%, and 10%, respectively) in Child class A, B, or C (48%, 36%, and 16%, respectively). In the longitudinal study gallstone development was monitored ultrasonographically in 618 patients free of gallstones at enrollment.

Results: The overall prevalence of gallstone(s) was 29.5% and increased significantly with age without differences according to sex or cause of cirrhosis. Multiple logistic regression analysis showed that only Child classes B and C were significantly related to a higher risk of gallstone (odds ratio, 1.63 for class C vs class A and 1.91 for class B vs class A; \( P = .001 \)). During a mean ± SD follow-up of 50 months ± 9 months, 141 (22.8%) of 618 patients developed gallstone(s), with an estimated cumulative probability of 6.5%, 18.6%, 28.2%, and 40.9% at 2, 4, 6, and 8 years, respectively. Multivariate analysis showed that Child class (hazard ratio, 2.8 for class C vs class A and 1.8 for class B vs class A; \( P = .002 \) and \( P = .001 \), respectively) and high–body mass index (hazard ratio, 1.31; \( P = .04 \)) carried a significantly greater risk of gallstone formation.

Conclusion: Cirrhosis per se represents a major risk factor for gallstones whose prevalence and incidence were far higher than those reported in a general population from the same area.

Arch Intern Med. 1999;159:49-52
PATIENTS AND METHODS

Four different referral hospitals in the industrialized area 100 km around Milan, Italy, were involved in the study, which was approved by the local ethics committee. Data from the different centers were assumed to be homogeneous as the equipment, investigational procedures, and data collection were standardized.

The cross-sectional part of the study was performed on 1010 consecutive patients with cirrhosis recruited from January 1988 to December 1995. There were 645 men (64%) and 365 women (36%) aged 26 to 87 years (mean ± SD age, 60 ± 12 years). The presence of cirrhosis was confirmed by histological liver findings in 721 patients (71%) according to accepted criteria. The remaining 289 (29%) had a contraindication to liver biopsy (prolonged prothrombin time and/or low platelet count) or refused the procedure; in these cases diagnosis was based on clinical and biochemical data and direct (coarse hepatic echopattern, irregular margins, caudate lobe–right lobe ratio >0.65) and indirect (signs of portal hypertension such as splenomegaly, increased portal diameter, and/or portal collaterals, and/or ascites) ultrasonographic signs. Cirrhosis was considered alcohol related in 421 subjects (42%) who reported a daily consumption of more than 100 g for the previous 10 years; and virus related in 480 (48%) of whom 110 were chronic carriers of hepatitis B surface antigen (HBsAg). 260 were positive for antibody to hepatitis C virus (anti-HCV), and 104 had no other cause of chronic liver disease (anti-HCV tests were not performed on the last subgroup who were studied before 1990, and stored serum samples were not available). The other 109 patients had cirrhosis attributable to miscellaneous causes, including genetic hemochromatosis in 81 cases. Characteristics of the study population are given in Table 1. Cholelithiasis was diagnosed in the presence of 1 or more of the following ultrasonographic findings: (1) 1 or more echogenic, distally shadowing, possible movable structures within the gallbladder; (2) 1 or more echogenic movable but not shadowing structures within the gallbladder; and (3) echogenic structures with constant shadowing in the region of the gallbladder fossa, with little or no visualization of the gallbladder. After an overnight fast all patients underwent liver ultrasonographic scan performed with a 3.5-MHz transducer (BK Medical, Gentofte, Denmark; Hitachi EUB26, Uchi Kanda, Japan). Patients with a history of cholecystectomy had a score of cirrhosis, but no diagnosis of cirrhosis were also included. All ultrasonographic examinations were performed by 3 of us (M.F., F.F., and L.B.) with specific training and experience in ultrasonography.

Six hundred eighteen patients without GS at enrollment (62% of the whole series) agreed to participate in the longitudinal part of the study and underwent liver ultrasonographic scans at 6-month intervals to investigate GS development. This group consisted of 404 men and 214 women aged 34 to 82 years (mean ± SD age, 60 ± 9 years). Liver cirrhosis was related to alcohol abuse in 278 patients (45%), chronic viral infection in 249 (40%, including 46 chronic carriers of HBsAg and 203 positive for anti-HCV), and miscellaneous causes in the remaining 91 (15%). Severity of cirrhosis was graded according to the time-honored and validated Child-Pugh classification that takes into account 5 factors (presence or absence of ascites and hepatic encephalopathy; nutritional status; reduced plasma albumin concentration; prolonged prothrombin time, compared with controls). Each factor has a score that increases from 1 to 3 according to the degree of derangement, with an overall score of 5 to 15; a total score of less than 6 places the patient in class A, a score of 7 to 9 in class B, and a score of 10 to 15 in class C. According to Child-Pugh classification at enrollment 371 patients (60%) were in Child class A, 193 (31%) in class B, and 54 (9%) in class C. The minimum duration of follow-up was 6 months.

Body mass index (BMI), which is a measure of weight in kilograms divided by the square of the height in meters was calculated. The HBsAg was sought by radioimmunoassay (Abbott Laboratories, Chicago, Ill) and anti-HCV by enzyme-linked immunosorbent assay with confirmation by radioimmunoblot assay (Ortho Diagnostic System, Milan) in positive cases.

RESULTS

CROSS-SECTIONAL STUDY

The overall prevalence of GS was 298 (29.5%) of 1010 cases, including 237 patients (23.4%) with actual stones seen on ultrasonographic liver scan and 61 (6.1%) who reported a previous cholecystectomy that was confirmed by absence of the gallbladder at ultrasonography. As shown in Table 2, which reports the results of univariate analysis, GS prevalence increased with age from 14% in patients younger than 40 years to 39%, without differences related to sex or cause of cirrhosis. Gallstones were significantly more frequent in patients in both Child classes B (odds ratio, 1.63) and C (odds ratio, 1.91)
A recent large nationwide epidemiological study aimed at estimating the overall prevalence of GSs (ie, actual GSs or previous cholecystectomy) in Italy involved 29,684 subjects who agreed to participate and were highly representative of the entire population of 46,139 subjects (64.3%). Gallstone disease was diagnosed in a significantly higher proportion of women than men (2603/13,774 [18.8%] vs 1512/15,910 [9.5%]) and the GS frequency rose significantly with age in both sexes. The overall prevalence of GSs in patients with cirrhosis of different causes was significantly higher than that observed in patients in Child class A (56/193 [29%] and 23/54 [43%] vs 62/371 [16.7%], respectively; $P = .001$). The cumulative probability of GS development according to observation period was 6.5%, 18.6%, 28.2%, and 40.9% at 2, 4, 6, and 8 years of follow-up, respectively (Table 3). With multivariate analysis the only variables identified as independent predictors of GS development were severity of liver disease at enrollment, with a significantly higher probability of GS formation for patients in Child class C vs class A (hazard ratio, 2.8; $P = .001$) and Child class B vs class A (hazard ratio, 1.8; $P < .002$), and high BMI (hazard ratio, 1.31, $P = .04$).

### Table 3. Estimated Cumulative Probability of Developing Gallstone(s) (GS) During Follow-up in 618 Consecutive Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Duration of Follow-up, y</th>
<th>Variable</th>
<th>Patients at risk, No.</th>
<th>Cumulative probability of GS development, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0  2  4  6  8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>618 558 331 192 129</td>
</tr>
</tbody>
</table>

### Table 1. Sex, Age, Cause of Cirrhosis, and Child Class at Enrollment in 1010 Consecutive Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Patients With GS, No. (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>645</td>
<td>181 (28)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>365</td>
<td>117 (32)</td>
<td>1.22</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>50</td>
<td>7 (14)</td>
<td>1.00</td>
</tr>
<tr>
<td>40-49</td>
<td>126</td>
<td>36 (29)</td>
<td>1.50</td>
</tr>
<tr>
<td>50-59</td>
<td>300</td>
<td>75 (25)</td>
<td>1.23</td>
</tr>
<tr>
<td>60-69</td>
<td>334</td>
<td>102* (30)</td>
<td>1.58</td>
</tr>
<tr>
<td>≥70</td>
<td>200</td>
<td>79* (39)</td>
<td>2.11</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>421</td>
<td>137 (32)</td>
<td>1.00</td>
</tr>
<tr>
<td>Viral</td>
<td>480</td>
<td>123 (25)</td>
<td>0.60</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>109</td>
<td>26 (24)</td>
<td>1.04</td>
</tr>
<tr>
<td>Child class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>489</td>
<td>117 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>B</td>
<td>364</td>
<td>123† (28)</td>
<td>1.63</td>
</tr>
<tr>
<td>C</td>
<td>157</td>
<td>58† (37)</td>
<td>1.91</td>
</tr>
</tbody>
</table>

*$P = .02$ vs the younger than 40 years age group.
†$P = .001$ vs class A.

LONGITUDINAL STUDY

The mean ± SD duration of follow-up was 50 ± 9 months (range, 6-163 months) and 21 patients were lost to follow-up after 12 to 63 months. During the observation period GS developed in 141 (23.8%) of 618 enrolled patients with cirrhosis, 90 (22.3%) of 404 men and 51 (22.3%) of 214 women, without significant difference between the 2 sexes. No differences in GS development were detected when we considered age, cause of cirrhosis, and the relationship between sex and age. The frequency of newly diagnosed GSs in patients in Child classes B and C was significantly higher than that observed in patients in Child class A (56/193 [29%] and 23/54 [43%] vs 62/371 [16.7%], respectively; $P = .001$). The cumulative probability of GS development according to observation period was 6.5%, 18.6%, 28.2%, and 40.9% at 2, 4, 6, and 8 years of follow-up, respectively (Table 3). With multivariate analysis the only variables identified as independent predictors of GS development were severity of liver disease at enrollment, with a significantly higher probability of GS formation for patients in Child class C vs class A (hazard ratio, 2.8; $P = .001$) and Child class B vs class A (hazard ratio, 1.8; $P < .002$), and high BMI (hazard ratio, 1.31, $P = .04$).

### Comment

A recent large nationwide epidemiological study aimed at estimating the overall prevalence of GSs (ie, actual GSs or previous cholecystectomy) in Italy involved 29,684 subjects who agreed to participate and were highly representative of the entire population of 46,139 subjects (64.3%). Gallstone disease was diagnosed in a significantly higher proportion of women than men (2603/13,774 [18.8%] vs 1512/15,910 [9.5%]) and the GS frequency rose significantly with age in both sexes. The overall prevalence of GS disease in our patients with cirrhosis of different causes was significantly higher than in the above-mentioned general population (298/1010 [29.8%] vs 4115/29,684 [13.9%]; $\chi^2 = 192.8, P = .001$), confirming previous findings in comparable but more limited series.\(^7,12\) Our data also confirm that GSs are more prevalent in female patients with cirrhosis. However, the difference was not significant (32% vs 28% in men); moreover, GS prevalence was 3 and 1.5 times higher, respectively, in male and female patients with cirrhosis than in sex-matched controls. This indicates that despite the higher absolute frequency of GS in female patients with cirrhosis observed in this study and in other series,\(^8,12\) the risk of cholelithiasis in male patients with cirrhosis is much higher than in the general population. Another factor that has only little effect on GS prevalence in patients with cirrhosis is age. In fact, unlike findings in the general population, a statistically significant increase in GS prevalence was observed only for the highest age groups (odds ratio, 2.11 for patients aged >70 years and 1.58 for those aged 60-69 years; $P < .02$ compared with those aged <40 years). Thus, an interesting point emerging from our study is that factors such as sex and age, closely associated with GS in the general population, are far less important in patients with cirrhosis. In these patients the main factor affecting GS prevalence was severity of liver disease.
as shown by Child class, which was statistically signifi-
cantly also with multivariate analysis. In fact, patients in Child
class B or C had a significantly higher prevalence of GSs
compared with those in class A. This could merely reflect
the duration of underlying chronic liver disease but could
also be a consequence of reduced hepatic synthesis and
transport of bile salts and nonconjugated bilirubin34 and
of high estrogen levels,34 both frequently reported in end-
stage liver disease. A further explanation for the increased
prevalence of GSs in advanced liver disease has recently
been suggested by ultrasonographic studies35 that demon-
strated both reduced gallbladder contraction in response
to a meal in patients with cirrhosis and a progressive wors-
ening of gallbladder inertia with progressive liver failure
and a possible consequent increase in estrogen levels. Fi-

nally, our prevalence study revealed a rate of previous cho-
lecystectomy for symptomatic GSs that was comparable with
the rate previously reported in a similar population.9,10,12

Prospective large series25,26 focused on general popu-
lations in Italy found that the annual rate of GS formation
in subjects free of GSs at enrollment was about 0.5%. Of 618
patients with cirrhosis without GSs at entry in this study
and followed up for a mean period of about 5 years, 22.8%
developed GSs, ie, an estimated annual rate of 5%, with a
10-fold increase in GS incidence compared with that in the
general population. The GS incidence was independent of
sex and age of patients, whereas, as observed in the cross-
sectional part of this study, a 2- to 3-fold increase in GS
formation was observed in patients with cirrhosis in Child
class B or C compared with class A. Thus, our findings
strongly support the concept that severity of underlying liver
disease, in most cases reflecting its duration, represents an
independent risk factor for GS formation in patients with
cirrhosis. Overall, our results indicate that in patients with
cirrhosis the probability of developing GSs is increased per
se. In fact, sex and age, which in the general population
represent well-known risk factors for GSs, were not sig-
nificantly related to GS in our patients with cirrhosis. Even
though BMI correlated significantly with GS formation, the
hazard ratio (1.31) was much lower than that observed in
the general population for GS development in patients with
a high BMI.

Accepted for publication May 12, 1998.

This study was supported in part by Associazione Amici
Gastroenterologia del Padiglione Granelli, Milan, Italy.
Presented as a poster at the Convention of the Ameri-
can Association for the Study of the Liver, Chicago, Ill,
November 1997.

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