Increased risk and case fatality rate of pyogenic liver abscess in patients with liver cirrhosis: a nationwide study in Denmark

I Mølle, A M Thulstrup, H Vilstrup, H T Sørensen

Abstract

Background—Patients with liver cirrhosis are at increased risk of serious bacterial infections carrying a high case fatality rate. Case reports have suggested an association between liver cirrhosis and pyogenic liver abscess.

Aims—To estimate the risk and case fatality rate of pyogenic liver abscess in Danish patients with liver cirrhosis compared with the background population.

Methods—Identification of all patients with liver cirrhosis and pyogenic liver abscess over a 17 year period in the National Registry of Patients. Information on death was obtained from the Danish Central Person Registry.

Results—We identified 22 764 patients with liver cirrhosis and 665 patients with pyogenic liver abscess, of whom 21 were cirrhotics and 644 were non-cirrhotics. The crude incidence rate of liver abscess in cirrhotics was 23.3 (95% CI 14.4–35.6) per 100 000 person years. The age adjusted risk of liver abscess was increased 15-fold in patients with cirrhosis compared with the background population. The 30 day case fatality rates in patients with liver abscess and cirrhosis were 38.5% (13.9–68.4) in alcoholic cirrhosis and 62.5% (24.5–91.5) in non-alcoholic cirrhosis compared with 26.9% (23.5–30.5) in liver abscess patients from the background population. After adjustment for sex, age, and comorbidity, the relative risk of death was increased more than fourfold in alcoholic cirrhosis and non-alcoholic cirrhosis compared with the background population.

Conclusions—Liver cirrhosis is a strong risk factor for pyogenic liver abscess associated with a poor prognosis.

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Keywords: bacterial infections; complications; epidemiology; liver abscess; liver cirrhosis; mortality

Pyogenic liver abscesses are rare in industrialised countries,1–3 and the incidence has been estimated at 1.1 per 100 000 person years in a Danish regional study.4 Biliary disease, malignancy, bacterial infection in other intra-abdominal organs, and bacteraemia are factors associated with the occurrence of liver abscess, but the disease is often cryptogenic.2–5 However, an association between pyogenic liver abscess and liver cirrhosis has been suggested in case reports, and most often in patients with iron overload.6–8 In a few case series of patients with pyogenic liver abscesses, the prevalence of liver cirrhosis was 0.9–13%,2,3,7 and the prevalence of chronic alcoholism was more than 10% in other studies.4,8

To determine if liver cirrhosis is a risk factor for liver abscess, we estimated the incidence rate and 30 day case fatality rate of pyogenic liver abscess in a nationwide cohort of patients with liver cirrhosis referring to the entire Danish population.

Methods

STUDY POPULATION AND DATA SOURCES

Denmark has approximately 5.2 million inhabitants. Admission, stay, and treatment in Danish public hospitals are free. Records on hospital admissions have been computerised since 1977 in the Danish National Registry of Patients (NRP), and 99.9% of all discharges from somatic departments in the entire country are recorded here.14 Each admission record includes the CPR number (see below), date of admission, date of discharge, and up to 20 discharge diagnoses.

Every Danish citizen has been recorded in the Central Person Registry (CPR) since 1968, using a personal identification number (CPR number) for each citizen. The CPR number is assigned at birth or immigration, and includes date of birth and an additional number carrying a code for sex.

The study was based on record linkage between two nationwide population based cohorts from the NRP. The first cohort included patients with liver cirrhosis and the second patients with pyogenic liver abscess. Diagnosis codes according to the Danish version of the International Classification for Diseases, 8th edition (ICD-8), were used for primary identification in the NRP.15 Dates of death or emigration were obtained in the CPR.

IDENTIFICATION OF PATIENTS WITH LIVER CIRRHOSIS

The inclusion criterion for this study cohort was at least one discharge with a diagnosis of liver cirrhosis: alcoholic cirrhosis (ICD-8=571.09), primary biliary cirrhosis (571.90),

Abbreviations used in this paper: CPR, Danish Central Person Registry; CPR number, personal identification number; NRP, Danish National Registry of Patients; ICD-8, International Classification of Diseases, 8th edition; IR, incidence rate; IRR, incidence rate ratio; SIR, age standardised incidence ratio.
Table 1 Characteristics of patients with liver cirrhosis in the National Registry of Patients in Denmark, 1977–93

<table>
<thead>
<tr>
<th></th>
<th>Alcoholic cirrhosis</th>
<th>Non-alcoholic cirrhosis</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>No of patients</td>
<td>10 001</td>
<td>3 874</td>
<td>4 224</td>
</tr>
<tr>
<td>Cases with liver abscess</td>
<td>9.3</td>
<td>5.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Mean age at entry (y)</td>
<td>53.7</td>
<td>53.7</td>
<td>61.4</td>
</tr>
<tr>
<td>Mean follow up (y)</td>
<td>4.1</td>
<td>4.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Person years at risk</td>
<td>40 635</td>
<td>17 683</td>
<td>12 667</td>
</tr>
<tr>
<td>IR per 100 000 years</td>
<td>22.2</td>
<td>22.6</td>
<td>23.7</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(10.1–42.0)</td>
<td>(6.2–57.9)</td>
<td>(4.9–69.2)</td>
</tr>
</tbody>
</table>

IR, incidence rate.

For each type of cirrhosis and sex, the incidence rate ratio (IRR) of liver abscess in the cirrhosis cohort was estimated by dividing the IR in the alcoholic cirrhosis subcohort by the IR in the non-alcoholic subcohort. The standardised incidence rate (SIR) of liver abscess was based on the age specific IR values in the cirrhosis cohort and in the background population, using 20 year age groups in sex specific strata.

The relative risk (odds ratio) of 30 day case fatality in patients with liver abscess and liver cirrhosis adjusted for sex, age, and comorbidity was estimated using logistic regression models. The cohort was subdivided according to age: less than 55 years (the reference category) and older than 55 years. The comorbidity index was estimated as described by Charlson and colleagues. Liver diseases were not scored, and only discharge diagnoses registered at the same admission for pyogenic liver abscess were scored.

Results

The cirrhosis cohort comprised 22 764 individuals (table 1). In both subcohorts there was a shorter mean follow up period for men, and there was a considerably larger proportion of alcoholic men than women in the cohort. Sixty one percent of all patients with cirrhosis were alcoholics, and in these patients cirrhosis was diagnosed on average 8–10 years earlier than non-alcoholics, according to their age (table 1).

The liver abscess cohort comprised 665 individuals, of whom 21 also had a diagnosis of liver cirrhosis.

The overall IR of pyogenic liver abscess in the cirrhosis cohort was 23.3 (14.6–35.6) per 100 000 person years (table 1). The overall IR of liver abscess in the background population (cirrhosis cohort not included) was 1.0 (0.9–1.1).

The increased risk of liver abscess in cirrhotics compared with the background population is shown in table 2. The overall age SIR was 15.4 (9.6–23.6). The SIRs of liver abscess in patients with alcoholic and non-alcoholic liver cirrhosis were 15.5 (8.2–26.5) and 15.7 (6.8–30.9) respectively, compared with the background population. However, the magnitude of the estimates changed according to age as the incidence rate ratios of liver abscess (IRR) in alcoholic cirrhotics and non-alcoholic cirrhotics differed significantly in the two age groups: 3.3 (0.5–143.1) versus 0.4 (0.1–1.6) in cirrhotics younger and older than 55 years, respectively. Thus the SIRs in the two cirrhosis groups (table 2) should be related to the background population and not to each other. The first year after the diagnosis of liver cirrhosis was associated with the highest SIR for pyogenic liver abscess (36.4) but during the...
Table 2  Observed and expected numbers and age standardised incidence rates of liver abscess in 22 764 patients with liver cirrhosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cirrhotics</td>
<td>21</td>
<td>1.4</td>
<td>15.4</td>
<td>9.6–23.6</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>13</td>
<td>0.8</td>
<td>15.5</td>
<td>8.2–26.5</td>
</tr>
<tr>
<td>Non-alcoholic cirrhosis</td>
<td>8</td>
<td>0.5</td>
<td>15.7</td>
<td>6.8–30.9</td>
</tr>
<tr>
<td>Men</td>
<td>9</td>
<td>0.5</td>
<td>18.0</td>
<td>8.2–34.2</td>
</tr>
<tr>
<td>First year after cirrhosis</td>
<td>12</td>
<td>0.9</td>
<td>14.0</td>
<td>7.2–24.4</td>
</tr>
<tr>
<td>Subsequent follow up period</td>
<td>13</td>
<td>1.1</td>
<td>11.8</td>
<td>6.3–20.2</td>
</tr>
</tbody>
</table>

1Age standardised incidence rate.
2Reference to the sex specific strata in the background population, cirrhosis cohort excluded.
3Reference to the background population, cirrhosis patients excluded.

Table 3  The risk of 30 day case fatality in patients with liver abscess in Denmark

<table>
<thead>
<tr>
<th></th>
<th>No of cases</th>
<th>Crude odds ratio</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background population</td>
<td>173/644</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>5/13</td>
<td>1.7</td>
<td>4.3</td>
<td>1.2–15.2</td>
</tr>
<tr>
<td>Non-alcoholic cirrhosis</td>
<td>5/8</td>
<td>4.5</td>
<td>4.8</td>
<td>1.0–22.4</td>
</tr>
<tr>
<td>Comorbidity index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 score</td>
<td>97/475</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>1 score</td>
<td>27/87</td>
<td>1.8</td>
<td>1.4</td>
<td>0.8–2.4</td>
</tr>
<tr>
<td>2 score</td>
<td>38/71</td>
<td>4.5</td>
<td>3.9</td>
<td>2.3–6.8</td>
</tr>
<tr>
<td>&gt;2 score</td>
<td>21/32</td>
<td>7.4</td>
<td>8.7</td>
<td>3.9–19.7</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20 &lt;55 yrs</td>
<td>21/191</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>≥55 yrs</td>
<td>162/474</td>
<td>4.2</td>
<td>3.9</td>
<td>2.3–6.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>76/367</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Women</td>
<td>107/298</td>
<td>2.1</td>
<td>2.0</td>
<td>1.3–2.9</td>
</tr>
</tbody>
</table>

1Data from the entire Danish population without cirrhosis cohort.

Discussion
In this nationwide population based study, we found a considerably increased risk of pyogenic liver abscess in patients with liver cirrhosis compared with the background population. We also found that liver abscess associated with cirrhosis increased the risk of dying within 30 days after admission more than fourfold compared with other patients with liver abscess.

Our registry based study design has strengths and limitations. The uniformly structured Danish health care system and the NRP enabled us to conduct a large population based study with a complete follow up. Our registry based estimate of the incidence rate of liver abscess in the background population is in close agreement with earlier findings in a Danish regional study in which several data collection methods were used.

Misclassification of discharge diagnosis codes, a well known methodological problem in registry based research, is probably less than 12%. Any non-differential misclassification would tend to underestimate the association found in this study. Our data lack clinical details on patients. Increased hospitalisation and extensive diagnostic efforts in cirrhotics could partly explain the association and is probably responsible in part for the high risk of pyogenic liver abscess found during the first year after diagnosis of liver cirrhosis (table 2). However, given the magnitude of the association and the lack of compensatory effect in the prognosis, the association between liver cirrhosis and pyogenic liver abscess found in the present study cannot be explained solely in terms of this bias.

Patients with liver cirrhosis have reduced transhepatic blood flow, increased portal pressure, and often ascites, which may compromise immune defences and increase intestinal permeability to bacteria. The macrophage function is impaired, and Kupffer cells are therefore probably less protective; the functions of neutrophilic leucocytes and the complement system are often impaired in liver cirrhosis. Furthermore, in the cirrhosis cohort there was a mean follow up time of only four years, undoubtedly due to a high mortality rate, which indicates that many cirrhotics were diagnosed late in the disease course where immunodysfunction is prominent. These relations may explain the increased risk of liver abscess in cirrhosis.

After stratification for age, the risk of pyogenic liver abscess in the alcoholic and non-alcoholic cirrhosis subcohorts varied over strata, which did not allow us to compare the risks for liver abscess in the two subcohorts. But we did find a substantially increased age adjusted risk of pyogenic liver abscess in both subcohorts compared with the background population. Therefore, the aetiology of liver cirrhosis is probably not a crucial factor for the increased risk of pyogenic liver abscess in cirrhosis. Cirrhosis itself seems to be an important risk factor for pyogenic liver abscess but nevertheless immunosuppression caused by alcohol is probably another important risk factor.

The short term prognosis in the liver abscess cohort was considerably worse in cirrhotics than in other patients, and we conclude that liver cirrhosis is a strong risk factor for liver abscess associated with a poor prognosis. This is probably due to impaired immune defences and structural changes in the cirrhotic liver.

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