Long-term Outcome of Pyogenic Liver Abscess
Factors Related With Abscess Recurrence

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Background/Aims: Long-term surveillance of pyogenic liver abscess remains unavailable. We thus aimed to identify the recurrence rates of pyogenic liver abscess among various etiologies and pathogens, and to elucidate the factors related with this recurrence.

Methods: Six-hundred and one patients with pyogenic liver abscess were prospectively enrolled to observe abscess recurrence during a mean follow-up period of up to 6.06 years. On the basis of the etiology of the initial abscess, patients were divided into different subgroups as follows: there were 152 (25.3%) patients classified as cryptogenic, 229 (38.1%) with diabetes mellitus, 144 (24%) with underlying biliary tract disease, and 76 (12.6%) with other organic diseases or mixed subgroups.

Results: The cumulative recurrence rates of pyogenic liver abscess were lower in both the cryptogenic (2.0%) and diabetic (4.4%) groups than in the underlying biliary tract disease (23.8%) group (log-rank test, \( P < 0.001 \)). The diabetic group had a higher rate of Klebsiella pneumoniae infection and a lower rate of Escherichia coli infection than the biliary tract group (\( P < 0.001 \)). For patients infected with K. pneumoniae, the recurrence rate of pyogenic liver abscess was as low as that of the diabetes and the cryptogenic groups (\( P > 0.05 \)).

Conclusions: Pyogenic liver abscess is more commonly recurrent in patients with underlying biliary tract disease. Irrespective of diabetic status or cryptogenic etiology, the recurrence of K. pneumoniae-infected liver abscess is low in the long-term.

Key Words: liver abscess, pyogenic, K. pneumoniae, diabetes mellitus, recurrence

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Pyogenic liver abscess is a common intra-abdominal infection that can result in mortality. In the past, Escherichia coli served as the predominant causative agent.\(^1,2\) Besides being susceptible after having complications of intra-abdominal or biliary tract infection, patients with diabetes mellitus are most at risk of getting pyogenic liver abscess.\(^3,4\) The common pathogen associated with diabetes patients with liver abscess has been well validated as Klebsiella pneumoniae.\(^3–6\) Recent reports have disclosed that K. pneumoniae has increased worldwide, surpassing E. coli, and thus has become an emerging infectious pathogen leading to pyogenic liver abscesses.\(^3–6\) Although extrahepatic complications such as endophthalmitis, metastatic abscesses may be fatal, the improvement of control of such pyogenic liver abscess has been achieved by early usage of more powerful antibiotics plus local drainage intervention.\(^3–6\) Therefore, once the liver abscess can be completely controlled for the short-term morbidity and mortality outcome, there still needs to be long-term surveillance to determine the rate of its recurrence and the relevant factors that determine its recurrence.

Besides the commonly reported predisposing risk factors such as diabetes or underlying biliary tract infection, there remain patients, defined as cryptogenic and without such predisposing risk factors, who get pyogenic liver abscess. It is thus interesting to determine whether such cryptogenic liver abscesses have different long-term outcomes and their recurrence rates.

Accordingly, this large-scale study enrolled 601 patients with pyogenic liver abscess, who were followed up for a mean duration of 72.7 months. The study aimed (1) to elucidate the clinical course and recurrence rate of pyogenic liver abscess among various etiologies and infected pathogens, and (2) to determine the possible factors related with the recurrence of pyogenic liver abscess.

MATERIALS AND METHODS

Patient Enrollment and Study Design

The study enrolled patients with liver abscess, treated in a 1238-bed referred center, servicing 750,000 city residents in Southern Taiwan, during the period from June 1988 to March 2004. These patients were defined as having liver abscess by the typical clinical manifestations, image studies with abdominal sonography, or computed tomography. Their demographic characteristics and
associated medical background diseases, especially diabetes mellitus and underlying biliary tract disease, were surveyed. The presence of diabetes mellitus was defined by having an elevated plasma sugar level and glucosylated hemoglobin. The presence of underlying biliary tract disease was defined by an abdominal sonography and/or endoscopic retrograde cholangiopancreatography.

On the basis of the related etiologies, these enrolled patients were divided into subgroups according to their diseases as follows: diabetes mellitus, underlying biliary disease, other organic disease, or mixed (defined as having both underlying biliary disease and diabetes mellitus, or having a traceable organic infection in the abdomen other than liver abscesses). Furthermore, patients without diabetes, underlying biliary tract disease, or other organic infections, were classified into the cryptogenic group. We excluded abscess patients whose pathogens came from amebiasis.

Apart from the demographic characteristics and etiologies, all the enrolled patients’ charts were reviewed for the features of the abscess image under sonography or abdominal computed tomography scan, the admission treatment course, and the microbiologic records of the infected pathogens of the liver abscess. Their chart records were reviewed after discharge, once these patients had regularly returned to the outpatient clinics. Otherwise, we prospectively maintained telephone contact to determine the status of recurrence of liver abscess after discharge. Moreover, we invited the patients to return to the clinics at least annually, if possible, to our outpatient clinics, to check on the possible recurrence of liver abscesses during the period between the discharge and follow-up visit. This study project has been approved by the Human Experiment and Ethics Committee of the National Cheng Kung University Hospital, Tainan, Taiwan.

The Recurrence of Liver Abscess After Discharge for the First Episode

Patients’ participation in this study ended when liver abscess recurred, if they died, or were lost to follow-up. The recurrence of liver abscess was defined as having a typical clinical presentation, and new ultrasonographic findings of the abscess recurring after the first episode of abscess had been fully resolved. The duration period between the 2 episodes of liver abscess was then calculated from the admission day of the first event to the admission day of the second event. However, if the patients had recurrent clinical symptoms within 1 month after discharge, and had a similar echolocation as liver abscess (irrespective of abscess size or numbers), such patients were then noted as having a relapse due to incomplete treatment. These patients were not defined as having recurrence of liver abscess.

Accordingly, after being discharged following the first episode of liver abscess, this study defined the recurrence of pyogenic liver abscess based on the following: (1) the chart records showing typical clinical symptoms, sonographic findings, and admission treatment courses in our institute; or (2) the historical review from the return visit to the clinic or the historical review by phone call to those patients who did not return regularly to our hospital.

Statistical Analysis

The Pearson χ² test or the Fisher exact test was used for the qualitative data. The Student t test or 1-way analysis of variance with Bonferroni correction was used for quantitative data as appropriate. All tests were checked in a 2-tailed manner taking a P value < 0.05 as significant. The Kaplan-Meier survival curve and the log-rank test were used to compare the cumulative recurrence rates of the pyogenic liver abscess among the patients with different etiologies, and also among patients infected by different pathogens during the follow-up period.

RESULTS

Demographic Characteristics and the Etiology of the Study Patients

There were 601 patients enrolled in this study who were confirmed to have liver abscess upon admission to our hospital. On the basis of the etiology of the initial abscess, there were 152 (25.3%) patients whose cases were considered cryptogenic, 229 (38.1%) who had diabetes mellitus, 144 (24%) with underlying biliary tract disease, and 76 (12.6%) classified as having other organic diseases or a combination (mixed group). Among these 76 patients, there were 28 patients who had both underlying biliary tract disease and diabetes mellitus.

Excluding those with other organic diseases or the mixed group, the differences in demographic characteristics of the patients are compared among the 3 different etiologies of pyogenic liver abscess as shown in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cryptogenic (n = 152)</th>
<th>Diabetes Mellitus (n = 229)</th>
<th>Biliary Disease (n = 144)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>30.9</td>
<td>38.0</td>
<td>54.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age (y)*</td>
<td>55.6</td>
<td>59.1</td>
<td>60.5</td>
<td>0.005</td>
</tr>
<tr>
<td>White counts ≥ 15,000/ cm² (%)</td>
<td>47.3</td>
<td>42.8</td>
<td>45.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Albumin &lt; 3 g/dL (%)</td>
<td>42.9</td>
<td>68.3</td>
<td>61.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine ≥ 1.5 mg/dL (%)</td>
<td>22.4</td>
<td>22.7</td>
<td>20.4</td>
<td>0.88</td>
</tr>
<tr>
<td>Total bilirubin ≥ 5 mg/dL (%)</td>
<td>4.1</td>
<td>4.5</td>
<td>16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALP ≥ 3-fold (%)</td>
<td>14.9</td>
<td>20.7</td>
<td>28.6</td>
<td>0.03</td>
</tr>
<tr>
<td>GGT ≥ 3-fold (%)</td>
<td>40</td>
<td>29.5</td>
<td>39.4</td>
<td>0.27</td>
</tr>
<tr>
<td>Abscess number (%)</td>
<td>83:17</td>
<td>81.6:18.4</td>
<td>78.8:21.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Location of abscess right lobe: left lobe: both lobes</td>
<td>72:22:6</td>
<td>67:21:12</td>
<td>65:25:10</td>
<td>0.44</td>
</tr>
<tr>
<td>Abscess size ≥ 5 cm (%)</td>
<td>68.7</td>
<td>58.9</td>
<td>47.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pearson χ² test.
*One-way ANOVA model.
ALP indicates alkaline phosphatase; GGT, γ-glutamyl transferase.
The patients in the underlying biliary tract disease group had more female patients, and a higher chance of having an elevated serum total bilirubin level $\geq 5$ mg/dL than the cryptogenic and diabetic groups ($P < 0.001$). Also, more patients in the underlying biliary tract disease group had an elevated serum alkaline phosphatase ($\geq 3$-fold) than the other 2 groups ($P = 0.03$).

We further analyzed whether the image features of the abscess differed in size, location, distribution, and number among patients with different etiologies. There were no differences in the numbers of abscesses and the distribution of their locations among the three groups ($P > 0.05$). As compared with the abscess features of the patients in the biliary group, both the diabetic and cryptogenic groups had a higher incidence of larger liver abscess of more than 5 cm in diameter ($P < 0.001$).

Among the 3 study groups, there were similar proportional distributions of patients, receiving either antibiotics only or antibiotics plus drainage (21.1% or 78.9% in the cryptogenic group; 17.5% or 82.5% in the diabetic group; and 27.8% or 72.2% in the biliary tract disease group, $P > 0.05$). Moreover, in both the diabetic and biliary tract disease groups (Table 2), there were no differences in the selection of treatment as antibiotics only or as antibiotics plus drainage between patients with or without recurrence ($P > 0.05$).

The Pathogens of Initial Liver Abscess Among Various Etiologies

In Figure 1, the distributions of the infected pathogens of the first episode of liver abscess among patients with different etiologies are shown. For all 3 etiology groups, K. pneumoniae was the most common pathogen leading to pyogenic liver abscess in our study populations. Moreover, in Figure 1, we see the rates of infection by E. coli were only 2% (3/152) in the cryptogenic group and 5.2% (12/229) in the diabetic group, which were both significantly lower than the 20.8% (30/144) in the biliary group ($P < 0.001$). In contrast, the rates of infection by K. pneumoniae were significantly higher—at 62.5% (95/152) in the cryptogenic group and 76.0% (174/229) in the diabetic group, compared with 30.6% (44/144) for the biliary group ($P < 0.001$).

Follow-up to the Rates of Recurrence of Liver Abscess in the Different Groups

All patients were monitored for the rate of recurrence of pyogenic liver abscess for a mean follow-up period of 6.06 years (range, 0 to 17.8 y). The overall rate of recurrent pyogenic liver abscess was 9.1% (48/525). The recurrent rates were significantly lower in the group, which were both significantly lower than the 20.8% (30/144) in the biliary group ($P < 0.001$). In contrast, the rates of infection by K. pneumoniae were significantly higher—at 62.5% (95/152) in the cryptogenic group and 76.0% (174/229) in the diabetic group, compared with 30.6% (44/144) for the biliary group ($P < 0.001$).

TABLE 2. Comparison of the Characteristics of Diabetic and Biliary Disease Patients With and Without Recurrence of Pyogenic Liver Abscess

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Diabetic Mellitus (n = 229)</th>
<th>Underlying Biliary Disease (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrence (n = 10)</td>
<td>No Recurrence (n = 219)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>20</td>
<td>38.8</td>
</tr>
<tr>
<td>Age (y)*</td>
<td>54.5</td>
<td>59.3</td>
</tr>
<tr>
<td>White counts $\geq 15,000$ cm$^2$ (%)</td>
<td>30</td>
<td>43.3</td>
</tr>
<tr>
<td>Albumin $&lt; 3$ g/dL (%)</td>
<td>50</td>
<td>69.1</td>
</tr>
<tr>
<td>Creatinine $\geq 1.5$ mg/dL (%)</td>
<td>10</td>
<td>23.3</td>
</tr>
<tr>
<td>Total bilirubin $\geq 5$ mg/dL (%)</td>
<td>0</td>
<td>4.7</td>
</tr>
<tr>
<td>ALP $\geq 3$-fold (%)</td>
<td>22.2</td>
<td>20.6</td>
</tr>
<tr>
<td>GGT $\geq 3$-fold (%)</td>
<td>66.7</td>
<td>28.3</td>
</tr>
<tr>
<td>Location of abscess (%) right lobe: left lobe: both lobes</td>
<td>60/40/0</td>
<td>67.6/20.3/12</td>
</tr>
<tr>
<td>Abscess size $\geq 5$ cm (%)</td>
<td>40</td>
<td>59.8</td>
</tr>
<tr>
<td>Abscess number (%) single: multiple</td>
<td>90/10</td>
<td>81.9</td>
</tr>
<tr>
<td>Treatment of abscess (%) Antibiotics only: plus drainage</td>
<td>0/100</td>
<td>18.3/81.7</td>
</tr>
</tbody>
</table>

Pearson $\chi^2$ test.
*Student t test.
ALP indicates alkaline phosphatase; GGT, $\gamma$-glutamyl transferase.
cryptogenic group [2.0% (3/152)] and diabetic group [4.4% (10/229)] than in the biliary group [23.8% (35/144)] (\(P < 0.001\)). The cumulative recurrence of abscess was also recorded with the Kaplan-Meier survival curves (Fig. 2). It revealed that the diabetic and cryptogenic groups had lower rates of recurrence than the biliary group (\(P < 0.001\), by log-rank test). Although the rates of recurrence were significantly different among the various etiologic subgroups, for those for whom the abscess recurred, there was no difference among groups in the mean duration between the first episode and recurrence (cryptogenic group, 3.9 ± 3.3 y; diabetic group, 3.9 ± 3.8 y; and biliary group, 3.2 ± 3.9 y; \(P = 0.27\) by 1-way analysis of variance model with Bonferroni correction). There were no patients in the cryptogenic group, 2 (20%) in the diabetic group, and 15 (42.9%) patients in the biliary group (\(P = 0.27\)) to have recurrent abscess during the first year.

No Significant Demographic Factors Related to Recurrence of Pyogenic Liver Abscess

Whether or not the liver abscess recurred, there were no differences between the diabetic and biliary groups, in age, sex, and laboratory tests (Table 2). Neither were there differences in the abscess image studies regarding the location, size, and number of initial liver abscess (Table 2).

Relation Between Infected Pathogens and the Recurrent Rate of Liver Abscess

As the distributions of the infected pathogens were significantly different between the biliary and diabetic groups, we tested whether different recurrent rates of abscess related to the different infected pathogens within each group. Among the diabetics, 12 were infected with \(E. coli\) initially, but none had recurrence of abscess. In Figure 3A, we can see that among the diabetic group initially infected with \(K. pneumoniae\), the cumulative recurrence rate only nonsignificantly increased to 5.7% (10/174) (\(P = 0.45\)). In Figure 3B, for the biliary group, there were similar cumulative recurrent rates of abscess between patients infected initially by \(E. coli\) or \(K. pneumoniae\) [26.7% (8/30) vs. 29.5% (13/44), \(P = 0.93\)]. Compared with the recurrent patients in the diabetic group who were almost all related to \(K. pneumoniae\) abscess infection (not even statistically significantly), 14 (40%) of 35 recurrences in the biliary group were from “others or no-growth” of initially infected abscesses. Moreover, this heterogeneity of primary infecting

FIGURE 2. The Kaplan-Meier estimator analyzed the cumulative proportions of the patients free from liver abscess recurrence during the 18-year follow-up in the different etiologies, including cryptogenic factors, diabetes mellitus, and underlying biliary disease. The difference of the cumulative proportions free from liver abscess recurrence was significant between the cryptogenic and the biliary groups (log-rank test, \(P < 0.001\)), and between the diabetes and biliary groups (log-rank test, \(P < 0.001\)), but not significant between the cryptogenic and diabetes groups (log-rank test, \(P = 0.16\)).

FIGURE 3. A, The Kaplan-Meier curve disclosed that the cumulative recurrence of liver abscess was not different between the patients infected initially by \(E. coli\) or \(K. pneumoniae\) in the diabetic subgroup (log-rank test, \(P = 0.45\)). B, The Kaplan-Meier curve disclosed that the cumulative recurrence of liver abscess was not different between the patients infected initially with \(E. coli\) or \(K. pneumoniae\) in the underlying biliary tract disease subgroup (log-rank test, \(P = 0.93\)).
pathogens was reported in the biliary group also for pathogens of recurrent abscesses.

**Comparison of Pathogens Between the Initial and the Recurrent Liver Abscess**

Focusing on those patients whose liver abscess recurred, we further compared the infected pathogens between the first episode and the recurrent abscess (Table 3). Eighty percent of the diabetic patients initially infected by *K. pneumoniae* were infected by *K. pneumoniae* again when their abscess recurred. In contrast, patients in the biliary group had more diverse infected pathogens in the recurrent abscess. The same species of the infected pathogens between the first episode and the recurrent abscess existed only in 23.1% of *K. pneumoniae* abscesses, and 12.5% of *E. coli* abscesses in the biliary group.

**DISCUSSION**

Among this large-scale surveillance of patients with pyogenic liver abscess, the first 3 major possible etiologies were disclosed as cryptogenic, diabetic, and biliary in origin. This finding supports previous studies to confirm that pyogenic liver abscess is commonly of cryptogenic origin.2–8

In Table 1, our study shows that patients with pyogenic liver abscess in the biliary group had a predominantly female distribution, older mean age, small-sized abscess, hypoalbuminemia (<3 g/dL), and elevated alkaline phosphatase (≥3-fold) on the first episode admission, as compared with patients in the diabetic and cryptogenic groups (*P* < 0.05). Moreover, as shown in Figure 1, the distribution of the infected pathogens in the biliary group were also significantly different (*P* < 0.001). On the basis of evidently different clinical features in the biochemistry, echo images of liver abscess size, and the distributions of the infected pathogens, we supposed that there should exist a difference in the pathophysiological consequences or even the recurrence rates among these groups.

In Figure 2, we see a dramatically higher rate of abscess recurrence in the biliary group compared with the other 2 (*P* < 0.001). Moreover, during the follow-up period, the overall rates of recurrence were significantly lower in the cryptogenic group [2.0% (3/152)] and diabetic group [4.4% (10/229)] than in the biliary subgroup [23.8% (35/144)] (*P* < 0.001). Therefore, patients with underlying biliary disease are more prone to have recurrence of liver abscess than those with diabetes or of cryptogenic origin.

As there were similar clinical features, echo images, and distributions of infected pathogens between the cryptogenic and diabetic groups (Table 1 and Fig. 1), this may account for their similar recurrence rates during the long-term follow-up. We wished to determine why the biliary group had a higher recurrence and whether any different presentations of clinical features or pathogen could be related to this higher rate. Therefore, we further investigated whether there were any specific clinical or echo-image features that were significantly different between the patients with and without recurrence of abscess (Table 2). However, we found no significant univariate factors related with the recurrence of abscess in all the 3 groups. This implies that the significantly different distributions of pathogens between the diabetic and biliary groups (Fig. 1) might possibly account for the different recurrence rates of liver abscess.

It can easily be concluded that the high recurrent rate of liver abscess in patients with underlying biliary disease should be in part due to the anatomic obstruction or fistula formation between the biliary and bowel tract. Therefore, there will be a higher rate of enteric bacteria moving retrograde via the biliary tract into the liver tissue for colonization. The infected pathogens may be as diverse as *K. pneumonia*, *E. coli*, and even mixed in flora for the first episode of abscess. Moreover, patients in the biliary subgroup had more diverse-infected pathogens of the recurrent abscess. The same species of the infected pathogens between the first episode and the recurrent abscess existed only in 23.1% of *K. pneumoniae* abscesses, and 12.5% of *E. coli* abscesses in the biliary group (Table 3). This finding was dramatically different from the diabetic group, of which *K. pneumonia* was the dominant pathogen with a rate of 80% repeat infection. Therefore, apart from the preexistent anatomic change in the biliary group, we further tested whether there were different recurrence rates of liver abscess between *E. coli* and *K. pneumonia* infection in the biliary group.

As shown in Figure 3B, we found a similar recurrence of liver abscess between the patients infected by these 2 pathogens. These data suggested that in patients with underlying biliary tract disease, the effect of the initial pathogen may not determine the long-term recurrence outcome. Alternatively, the host factor as with biliary tract disease is enough to predispose a higher recurrence rate of liver abscess.

Nevertheless, in the diabetic group, there was no recurrence of liver abscess if the patients were infected by *E. coli* during their first episode. Moreover, the rate of recurrence only nonsignificantly increased to 5.7% (*P* = 0.45), although all recurrences of liver abscess were due to *K. pneumonia* infection. These data are very

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**TABLE 3. The Infected Pathogens of the First Episode and the Recurrence of Liver Abscess in the Diabetic and Underlying Biliary Tract Disease Groups**

<table>
<thead>
<tr>
<th>First Episode Pathogens</th>
<th>K. pneumoniae</th>
<th>E. coli</th>
<th>Others or No-growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>8 (80)</td>
<td>0</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Underlying biliary tract disease</td>
<td>3 (23.1)</td>
<td>1 (7.7)</td>
<td>9 (69.2)</td>
</tr>
</tbody>
</table>

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important as it shows how such a critical infection could become so silent during the long-term follow-up. The reason why the recurrence rate of the diabetic group was so low is unclear. It could be because of control of the diabetes or even from acquiring immunity to the infecting pathogen. Further study would be welcome to determine whether there exists such a possible acquisition of immunity to the most commonly infecting pathogen, *K. pneumoniae*.

Although the recurrence rate of liver abscess in diabetic patients was low, most recurrence of abscess was due to *K. pneumoniae* rather than *E. coli*. This may be because of either impaired immunity of the diabetic patients or the existence of other *K. pneumoniae* with specifically different virulence.

In conclusion, the presence of underlying biliary disease seems to predispose patients to a higher recurrence rate of pyogenic liver abscess. Although *K. pneumoniae* is the most common pathogen leading to pyogenic liver abscess in diabetic patients, its recurrence was limited in the long-term.

REFERENCES