Burden of Liver Abscess and Survival Risk Score in Thailand: A Population-Based Study

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Abstract. In Thailand, the burden of liver abscess, a life-threatening infectious disease, has not been thoroughly evaluated. We developed a predictive scoring system to estimate survival of patients with liver abscess using information from the 2008–2013 Nationwide Hospital Admission Data to evaluate the burden of liver abscess in Thailand. All patients with primary diagnosis of pyogenic liver abscess (PLA) and amoebic liver abscess (ALA) were included. Epidemiological data, baseline characteristics, hospital course, and survival were analyzed. Overall, 11,296 admissions comprising 8,423 patients from 844 hospitals across Thailand were eligible for analysis. The mean age was 52 ± 17 years and 66.1% of patients were male. ALA was significantly prevalent in southern and western border regions of Thailand, and PLA occurred nationwide. The highest incidence of liver abscess occurred in the rainy season (June–November, P < 0.01). The median length of hospital stay was 8 days (interquartile range = 4–13 days), and mean direct cost of hospitalization was US$846 ± 1,574. Incidence of ALA decreased over the 5-year study period, whereas PLA incidence increased (P < 0.01). Using multivariable Cox regression methods with stepwise variable selection, we developed a final model with five highly significant baseline parameters associated with increased 60-day mortality: older age, PLA, underlying chronic kidney disease, cirrhosis, and human immunodeficiency virus infection. Range of estimated probability of 60-day survival was 95–16% at cumulative risk score 0–13. This simplified score is practical, and may help clinicians prioritize patients requiring more intensive care.

INTRODUCTION

Liver abscess is a life-threatening infectious disease. The etiology of liver abscess can be majorly classified into pyogenic liver abscess (PLA) and amoebic liver abscess (ALA). Despite current advances in early diagnosis, effective antibiotic treatment, and therapeutic procedure, liver abscess is still one cause of fatal infectious diseases worldwide, especially in developing countries.

Mortality rates have decreased substantially over the past several decades, with recent studies reporting rates of 13–31%.1,2 The mean age of patients with PLA has increased, and the most common cause reported in recent series has shifted to biliary disease.3 Historically, Escherichia coli has been the predominant causative agent, but Klebsiella liver abscess has been reported to be an emerging disease in western countries, such as the United States.4 Klebsiella pneumoniae infection has also emerged as one of the most common causes of PLA in many Asian countries in the past three decades.5 The emerging serotype K1 K. pneumoniae with multilocus sequence type 23 has been strongly associated with the virulence of liver abscess and invasive syndrome.6,7

ALA has not been a topic of focus, but it is a potentially life-threatening complication by infection with the protozoan parasite Entamoeba histolytica.8 ALA is widely distributed throughout the tropics and sub tropics, causing up to 40 million infections annually.9

The extent of liver abscess has remained unclear because of the lack of a population-based study. A recent previous report in Taiwan showed that PLA was endemic and that some factors including diabetes, malignancy, renal disease, and pneumonia were associated with a higher risk for the disease.10 To date, the outcomes in terms of disease burden and national economic impact of liver abscess have not been well studied. There is much knowledge regarding liver abscess in terms of diagnosis, microbiology, and risk factors. However, the burden of disease is unclear, especially in Thailand. This study evaluated the burden of liver abscess in Thailand and developed a simple predictive scoring method to estimate the survival of patients with liver abscess.

MATERIALS AND METHODS

Study design. A community-wide, retrospective cohort, observational study was conducted on the Thailand population. We analyzed liver abscess data from the 2008–2013 Nationwide Hospital Admission Data, National Health Security Office (NHSO), Thailand. All diagnoses were according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10). All patients with a primary diagnosis of PLA (ICD10-K750) and ALA (ICD10-A064) by physicians were included. Epidemiological data, baseline characteristics, hospital course, and survival were analyzed.

In Thailand, hospitals are classified into three levels: primary hospitals are community hospitals for primary health care, secondary hospitals are hospitals for general health care, and tertiary hospitals are referral hospitals for complicated diseases and specialized health care.

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Study population and cohort. The study population comprised community-based data from 851 districts in all 77 provinces in Thailand. A mean of 5.6 million admissions occurred each year from all diseases and indications from 2008 to 2013. Overall, 11,296 admissions were patients with a primary diagnosis of PLA and ALA during the study period. Among all admissions, 8,424 individual patients from 844 hospitals across Thailand were included in this study analysis. Overall long-term survival was based on the national death registry at the date of data extraction.

Statistical analysis. All statistical analyses were performed using SPSS version 13 software (SPSS Inc., Chicago, IL). The mean ± standard deviation was used to describe continuous variables where a percentage was used for categorical data. Temporal trends were assessed by the incidence rate ratio (IRR) derived from regression analysis. Continuous variables were compared between groups using an independent t test or one-way analysis of variance. Categorical variables were compared between groups using the χ² or Fisher’s exact test. Multiple logistic regression analysis was used to identify factors influencing mortality rate. The odds ratio (OR) and 95% confidence interval (CI) of each factor are presented. P values < 0.05 were considered statistically significant. For survival analysis, Kaplan–Meier survival curves between different groups were compared using the log-rank test. Cox regression models were used to identify risk factors associated with inhospital mortality caused by liver abscess. The strength of the association was represented with liver abscess, N (%) 30 days 725 (8.6) 20 (4.46) 705 (8.54) < 0.01 90 days 1,335 (15.85) 34 (7.59) 1,301 (16.31) < 0.01 1 year 2,003 (23.78) 55 (12.28) 1,948 (24.42) < 0.01 3 years 2,451 (29.1) 69 (15.4) 2,382 (29.87) < 0.01 5 years 2,609 (30.97) 71 (15.84) 2,538 (31.82) < 0.01

Study population characteristics. Overall, 7,975 patients had a primary diagnosis of PLA, whereas 448 patients had a primary diagnosis of ALA. The mean age was 52 ± 17 years and 66.1% of patients were male. The median length of hospital stay was 8 days, and mean cost of hospitalization was 846 ± 1,574 USD. The overall inhospital mortality rate was 2.8%. Long-term all-cause mortality after hospitalization with liver abscess was increased by time. The long-term overall mortality rate was very high, up to 15% in ALA and 30% in PLA (Table 1). Overall long-term survival was significantly higher among patients with ALA compared with PLA (HR = 0.54; 95% CI = 0.42–0.68; P < 0.001) (Figure 1).
Overall cases of liver abscess were geographically distributed nationwide (Figure 2A). However, after we classified the type of liver abscess into ALA (Figure 2B) and PLA (Figure 2C), ALA was shown to be predominant in some southern and western border regions of Thailand. Most patients with PLA were from the northeastern part of the country (40.1%), different from the patients with ALA who were mostly from the south (42.4%). ALA had a significantly high prevalence in Narathiwat Province, a southern border region (16.7% of total cases).

Incidence of ALA decreased over the 5-year study period, whereas the incidence of PLA increased ($P < 0.01$). Inhospital mortality did not significantly change ($P = 0.68$), but the cost of treatment gradually increased over the 5-year period ($P < 0.01$) (Table 2).

The 5-year mean and 95% CI of liver abscess incidence classified by month was analyzed. The highest incidence of liver abscess occurred in the rainy season (between June and November, IRR = 1.11; 95% CI = 1.07–1.16; $P < 0.01$) (Figure 3).

The etiology of PLA was determined from documents in 1,029 cases (12.9%). The most common identified pathogen causing PLA was *Burkholderia pseudomallei* (56.5%), followed by *K. pneumonia* (22.2%), *E. coli* (10%), *Staphylococcus* spp. (4.1%), *Pseudomonas aeruginosa* (2.5%), and *Salmonella* spp. (2.3%). Of these, *E. coli*, *K. pneumonia*, and *P. aeruginosa* posed statistically significant increased risk of inhospital mortality (HR = 3.55; 95% CI = 1.82–6.94; $P < 0.001$, HR = 2.11; 95% CI = 1.20–3.69; $P < 0.01$, and HR = 4.48; 95% CI = 1.42–14.15; $P = 0.01$, respectively). Various inhospital complications were significantly associated with inhospital mortality including congestive heart failure, acute kidney injury, septic shock, requiring a ventilator, and hemodialysis (Table 3).

**Survival risk scoring system.** Using multivariable Cox regression methods with stepwise baseline variable selection, we derived the final model with five highly significant baseline parameters associated with increased 60-day mortality: age, etiology of liver abscess, underlying chronic kidney disease, cirrhosis, and human immunodeficiency virus (HIV) infection. HIV infection was found to be one of the most significant comorbidities associated with increased inhospital mortality (HR = 6.15; 95% CI = 4.58–8.27; $P < 0.001$). In contrast, ALA was found to be associated with a significantly reduced risk of inhospital mortality (HR = 0.52; 95% CI = 0.40–0.66; $P < 0.01$). HRs were converted into an easy-to-use integer risk score (0–13) to identify the risk of 60-day mortality (Table 4).

The probability of surviving 60 days after admission was estimated by weighted score ($P_{\text{surviving 60 days}} = 1 - 1/(1 + 20.80 \times \exp[-0.36 \times \text{score}])$. The range of estimated probability of 60-day survival was 95–16% over the cumulative risk score of 0–13 (Figure 4). The scoring system was

**Table 2**

<table>
<thead>
<tr>
<th>Years</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALA cases</td>
<td>133</td>
<td>110</td>
<td>114</td>
<td>109</td>
<td>109</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>PLA cases</td>
<td>2,105</td>
<td>2,011</td>
<td>2,011</td>
<td>2,136</td>
<td>2,230</td>
<td>2,239</td>
</tr>
<tr>
<td>Hospitalization cost, mean ± SD (USD)</td>
<td>799 ± 1,701</td>
<td>855 ± 1,546</td>
<td>853 ± 1,504</td>
<td>967 ± 1,837</td>
<td>883 ± 1,490</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>Inhospital mortality</td>
<td>2.5%</td>
<td>2.73%</td>
<td>2.98%</td>
<td>2.95%</td>
<td>2.73%</td>
<td>0.68</td>
</tr>
</tbody>
</table>

ALA = amoebic liver abscess; PLA = pyogenic liver abscess; SD = standard deviation; USD = U.S. dollar.
validated with different populations with significant accuracy of the expected number of survivals compared with observed data for any given score ($\chi^2 = 3.4138; P = 0.9980$). The goodness of fit of this scoring system ($R^2$) was then assessed among subgroups from different hospital levels, that is, primary, secondary, and tertiary. The $R^2$ for primary, secondary, and tertiary patient data was 78.3%, 94.8%, and 96.3%, respectively. This demonstrated that the scoring system accurately predicted the probability of survival in all levels of hospitals with the highest accuracy in tertiary level hospitals (Figure 5).

**DISCUSSION**

Between 2008 and 2013, 8,423 patients had an inpatient primary diagnosis of liver abscess across Thailand. Our data show that liver abscess is still a problem and a significant cause of morbidity and mortality. Inhospital mortality was 2.8%, but the long-term all-cause of mortality was much higher (1-year mortality of 23.78%). This might be explained by complications directly associated with liver abscess or comorbidity in patients with liver abscess. Interestingly, we discovered that the characteristics of patients with ALA and PLA were different. ALA patients were younger than those with PLA. In addition, almost 80% of amoebic cases were male. This might be explained by differences in occupation and environmental exposure. It has also been reported that testosterone influences susceptibility to ALA in a mouse model of the disease.11

Our data demonstrate different geographic distributions of endemic liver abscess. It is known that the northeastern part of Thailand has a very high incidence of *B. pseudomallei*.12 Presentation of hepatic abscess and/or splenic involvement is

### Table 3

Significant risk factors (identified organisms and inhospital complications) associated with inhospital mortality in patients hospitalized with liver abscess

<table>
<thead>
<tr>
<th>Identified organisms</th>
<th>Hazard ratio</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Burkholderia pseudomallei</em></td>
<td>0.472</td>
<td>0.233</td>
<td>0.958</td>
<td>0.038</td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
<td>2.512</td>
<td>1.470</td>
<td>4.293</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>3.382</td>
<td>1.691</td>
<td>6.762</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>4.404</td>
<td>1.319</td>
<td>14.704</td>
<td>0.016</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>0.418</td>
<td>0.197</td>
<td>0.889</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Inhospital complications

| Congestive heart failure | 6.491 | 3.826 | 11.010 | < 0.01 |
| Acute kidney injury | 12,897 | 9,961 | 16,698 | < 0.01 |
| Septic shock | 15,558 | 10,635 | 22,759 | < 0.01 |
| Required ventilator | 24,091 | 17,961 | 32,313 | < 0.01 |
| Required hemodialysis | 29,815 | 16,374 | 54,288 | < 0.01 |

CI = confidence interval.

### Table 4

Predictive parameters, adjusted hazard ratio, simplified risk score, and estimated probability of 60-day survival from cumulative risk score*.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adjusted hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
<th>Score (total = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 years</td>
<td>1.00</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–60 years</td>
<td>2.07</td>
<td>1.79–2.38</td>
<td>&lt; 0.001</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>4.86</td>
<td>4.23–5.58</td>
<td>&lt; 0.001</td>
<td>4</td>
</tr>
<tr>
<td>Chronic kidney diseases</td>
<td>1.76</td>
<td>1.51–2.06</td>
<td>&lt; 0.001</td>
<td>0.75</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.20</td>
<td>1.86–2.60</td>
<td>&lt; 0.001</td>
<td>1.25</td>
</tr>
<tr>
<td>Pyogenic liver abscess</td>
<td>1.94</td>
<td>1.51–2.49</td>
<td>&lt; 0.001</td>
<td>1</td>
</tr>
<tr>
<td>HIV infection</td>
<td>6.15</td>
<td>4.58–8.27</td>
<td>&lt; 0.001</td>
<td>5</td>
</tr>
</tbody>
</table>

*Estimated probability of 60-day survival from cumulative risk score (score: probability of 60-day survival [%]: score = 0–2: 91–95%; score = 3–5: 77–88%; score = 6–8: 54–71%; score = 9–11: 28–45%; and score = 12–13: 16–22%.

CI = confidence interval; HIV = human immunodeficiency virus.
a common clinical manifestation of melioidosis. Therefore, this might be associated with the highest distribution of PLA in these areas. However, a causative organism was not defined for a significant proportion of PLA. This limitation might be explained by the use of diagnostic protocols from individual hospitals in Thailand and/or the reporting system in the national data collection process. This indicates the need for improvement in defining specific etiologies of PLA in the Thailand public health system. However, after we classified the type of liver abscess into ALA and PLA, ALA was shown to be predominant in some southern and western border regions of Thailand. This could be owing to personal hygiene or virulence factors of *E. histolytica*. Only 5–10% of those infected with *E. histolytica* developed symptomatic disease, and further analysis of the population structure of *E. histolytica* isolates in highly endemic areas is necessary.

We do not have data regarding the environment of endemic and virulence factors of *E. histolytica* in Thailand. Investigation of the reasons why ALA occurs in that area might lead to disease control and prevention.

The seasonal incidence of liver abscess has been scanty reported. One previous study showed that ALA had the highest incidence during the peak rainy season (April–July). Consistent with this result, in the present study, the highest incidence of liver abscess occurred in the rainy season. The seasonal prevalence of human intestinal parasites including *E. histolytica* was reported. In Thailand, the agriculture season starts at the same time as the rainy season. Thus, the rainy season will increase the risk of occupational exposure to infections such as melioidosis.

Among cases with determined organisms of liver abscess, *B. pseudomallei* was the most frequently reported. This might be due to endemic melioidosis, which is the major cause of community-acquired septicemia in northeast Thailand, and due to a high index of clinical suspicion among physicians in areas of endemic disease. The incidence of PLA from *K. pneumonia* has surpassed that of *E. coli*. This finding was consistent with emerging strains of *Klebsiella* spp. and reports that *K. pneumonia* is the dominant pathogen for liver abscesses in several Asian countries. However, there were some limitations of our retrospective data because less than 20% of cases had a defined causative organism. Thus, for the remaining ~80% of cases, the causative organism remains unknown. The specific etiology of liver abscess also affected the inhospital mortality. We found that *E. coli*, *Klebsiella* spp., and *Pseudomonas* spp. increased the risk of inhospital death compared with melioidosis, and that amoebiasis showed a lower risk of inhospital death.

The burden associated with liver abscess remains a public health problem in Thailand, with an overall inhospital mortality rate of 2.8%. The direct cost of hospitalization was estimated to be 10 million USD. The overall length of stay, hospital cost, and inhospital mortality were higher in patients with PLA than ALA. Liver abscess had almost twice the burden in terms of cost and length of hospital stay than overall admissions. However, overall inhospital mortality from liver abscess did not differ from overall mortality of admitted cases (mortality rate of 2.7%).

After we analyzed the trend, we found that the cost of hospitalization had significantly increased yearly, but the inhospital mortality did not significantly change. However, pyogenic cases seemed to increase. In contrast, amoebic cases seemed to decrease yearly, which might be explained by increased urbanization and improved sanitation and personal hygiene in this region.

There are some previous reports of clinical or laboratory predictors for treatment outcome failure; however, most predictors used data from a single institution.

This study developed a simple survival risk score using five baseline independent predictors associated with mortality from liver abscess in Thailand. Those parameters were age, chronic kidney disease, cirrhosis, HIV infection, and etiology of liver abscess. Such parameters can easily be observed and used as a bedside tool to predict survival of patients. This scoring system has been validated with a validating group and demonstrated accurate survival prediction in all levels of hospitals. This study was limited to the Thailand population. Although this is one of the strengths of the study, its use needs to be validated in other populations to further develop the risk scoring system.

In conclusion, liver abscess remains a public health problem in Thailand necessitating a lengthy hospital stay, high
cost of admission, and high long-term overall mortality rate. The geography and season both have an impact on the incidence of liver abscesses in Thailand. Various factors affecting patient survival include the etiology of liver abscess, baseline characteristics, comorbidities, and complications during admission. The scoring system that we developed is simple and practical, and may help clinicians with intensive care patient prioritization and case management in hospital settings.

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