Clinical comparison of febrile and afebrile patients with pyogenic liver abscess: A two-centre retrospective study

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Abstract

Background: Limited research has been conducted on afebrile pyogenic liver abscess (PLA). This poses a challenge in rapid diagnosis and early tailored care to physicians. In his study, we aimed to compare the clinical characteristics of afebrile and febrile patients with PLA.

Methods: We retrospectively analyzed the data of patients with PLA who were admitted to the emergency departments of two university hospitals between January 2014 and March 2020. Patients were classified into afebrile and febrile groups by using body temperature higher than 38°C as the reference standard. The demographic, clinical, and laboratory characteristics of both groups were compared. The primary outcome was all-cause in-hospital mortality and length of hospital stay. Multivariate analysis was performed to define factors associated with afebrile PLA.

Results: Of the 239 patients included in this study, 51 patients (21.3%) were afebrile and 188 patients (78.7%) were febrile. There were no differences between the abscess characteristics, laboratory manifestations, and disease severity of both groups; however, age and Charlson score differed between the groups ($P = 0.009$ and $P = 0.011$). The all-cause in-hospital mortality rate was much higher in the afebrile PLA group than in the febrile PLA group (9.8% vs. 2.1%, $P = 0.011$). Regarding the length of stay, no significant differences were noted in the febrile PLA group compared with the afebrile PLA group (18.5% vs 17.3%, $P = 0.514$). In multivariate analyses, only age greater than 65 years was significantly associated with afebrile PLA.

Conclusions: Afebrile patients with PLA tend to be older, have higher Charlson scores, and in-hospital mortality rate than those with febrile patients. PLA patients older than 65 years are more likely to present without fever (<38°C) at the time of the emergency visit.

Keywords: Afebrile, clinical characteristics, outcomes, pyogenic liver abscess.

INTRODUCTION

Pyogenic liver abscess (PLA) is a potentially life-threatening disease with increasing incidence worldwide. The results of large population-based retrospective studies in China indicated that the incidence rate of the disease is 5.7-17.6

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per 100,000 population.[1-3] Although PLA is still associated with significant morbidity, mortality, and complications,[4-7] early diagnosis and effective treatment have substantially reduced the sequelae and improved clinical outcomes. Even though clinical symptoms of liver abscess are often non-specific and diagnosis requires a high degree of clinical suspicion, early diagnosis may be especially important in patients attending the emergency department. The classic presentation of PLA is the triad of fever, pain in the upper right quadrant of the abdomen, and jaundice.

However, as fever is the most common clinical manifestation,[8-11] emergency clinicians frequently rely on the presence of fever to initiate an infection workup. Notably, fever is a complex and non-specific host defense response against infection and might be absent in patients with PLA. Afebrile patients with PLA often have atypical clinical manifestations, such as fatigue, lethargy, or confusion, leading to decreased survival and poorer prognosis.[12] Furthermore, these atypical clinical manifestations sometimes make it difficult to promptly diagnose afebrile patients with PLA. The paucity of reported cases in the available literature may also contribute to the difficulties in the timely diagnosis of afebrile PLA. Besides, as to how the clinical manifestations and outcomes of afebrile and febrile patients with PLA differ has not yet been established. In this study, we aimed to compare the differences between the characteristics of afebrile and febrile patients with PLA and identify factors associated with afebrile PLA.

METHODS

Study design and setting
This retrospective observational study was conducted in the emergency department (ED) of Shanghai Jiao Tong University of Medicine affiliated with Renji Hospital and Xinhua Hospital, from January 2014 to March 2020. Both are urban 2250-bed and 2090-bed university tertiary-care hospitals with annual ED visits of more than 290,000 and 240,000, respectively. During the study period, patients in the ED who met the diagnostic criteria for PLA, as defined with the K75.0 diagnosis code in the International Classification of Diseases, 10th revision, were reviewed. The ethics committees of Renji and Xinhua hospitals approved the study protocol. As the study contained a retrospective review of de-identified data, requirements for informed consent were waived.

Study population
The diagnosis of PLA was based upon clinical manifestations, imaging examinations, and microbiological analyses of blood or pus culture results.[13] Diagnosis of

all cases was confirmed by an experienced physician, radiologist, and microbiologist.

We excluded patients with any of the following criteria:
(1) History of immunological disease;
(2) Treatment with immunosuppressive medications within the previous 3 months;
(3) Transfer from other medical facilities (including prior antibiotic use);
(4) Age under 18 years old;
(5) Patients who took drugs that could affect body temperature; and
(6) Missing body temperature data [Figure 1]. Following inclusion, patients were classified into febrile (≥ 38°C) and afebrile (<38°C) groups according to the body temperature criteria of the Systemic Inflammatory Response Syndrome (SIRS) score,[14,15] using the core temperature assessed at the time of presentation at the emergency department.

Data collection
All data were obtained from patients' electronic and physical medical records. Anonymous patient data were collected by two trained observers using a pre-specified case report form. The following data were collected: demographic data and medical information such as coexisting diseases, signs and symptoms, primary etiology, underlying conditions, laboratory results, imaging findings, medications administered, drainage used, and clinical outcomes. The collated information also included the patients' initial temperatures and maximum temperatures during the course of their ED visits. The severity of illness was evaluated during the first 24-hours after admission, using the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring systems. Data that were not available, such as data on PaO2, were considered a zero score.
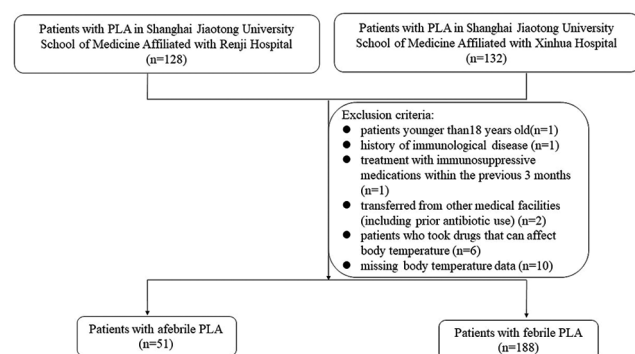

Figure 1: Flow chart

Definitions

For 24-hours prior to and following the emergency admission (a period of 48 hours) was used to judge whether the patient had symptoms of fever. Information on the patients' body temperatures before admission was obtained from self-reports, and the temperatures after admission were extracted from electronic medical and nursing records. Core body temperatures (oesophageal, bladder, or rectal), if recorded, were preferentially assessed to determine group assignment. If only peripheral temperatures were measured during this period, core temperatures were estimated by adding 0.5°C to the documented peripheral temperatures.[14]

The primary outcome measurements included all-cause in-hospital mortality and length of hospital stay. Secondary outcomes were complications including sepsis, elevated troponin, pleural effusion, and endophthalmitis. The length of hospital stay was defined as the number of days from the time of emergency admission to the time of hospital discharge. Mortality was defined as all-cause death during hospitalization. The definition of sepsis used in this study was based on the Sepsis-3 definition.[15] Elevated troponin was defined as a troponin level beyond the upper limit of the normal range. The definition of pleural effusion was based on clinical signs and radiology examination. Endophthalmitis was defined as an infection inside the eye involving the vitreous and/or aqueous humor and diagnosed by a physician and ophthalmologist.

Statistical analysis

Continuous variables are presented as means and standard deviations, whereas categorical variables are presented as frequencies and percentages. For univariate analysis, the comparison between categorical variables was done using the Chi-square test or Fisher's exact test. The Mann–Whitney U test was used for analyzing continuous variables as they were not normally distributed. A multiple logistic regression analysis was conducted to determine the risk factors for afebrile PLA. The variables were chosen from the available literature, based on experience, and form factors with $P < 0.02$ in the univariate analysis, which included age, C-reactive protein (CRP) level, number of abscesses, size of the abscess, and sepsis. In the multivariable logistic regression analyses, age at the time of diagnosis was categorized as 18-64 years or more than 65 years. CRP level was categorized as less or more than 150 mg/L,[16] the number of abscesses was categorized as single or multiple, and size of the abscess was categorized as less or more than 5 cm.[8] Point estimates were presented as adjusted odds ratios with 95% confidence intervals (CI). All analyses were performed using SPSS (IBM SPSS Statistics 25) and considered significant for $P < 0.05$.

RESULTS

Demographic and clinical characteristics

During the 6-year study period, 260 consecutive patients of PLA were reviewed and 239 eligible patients were finally analyzed, 51 (21.3%) of whom were afebrile [Table 1]. Patients with afebrile were older than those with febrile (68.0 years vs. 62.5 years, $P = 0.009$). Sex ratios were not different between the two groups. Underlying comorbid conditions, such as diabetes mellitus, hepatobiliary benign disease, malignancy, abdominal surgery history, were also not different between the afebrile and febrile cases. However, the Charlson score was significantly higher in the afebrile PLA than in the febrile group (3.0 vs 1.0, $P = 0.003$). Furthermore, the abscess characteristics, laboratory manifestations, SOFA scores, and APACHE II scores were similar in both groups.

Clinical outcomes

The overall mortality rate of PLA in this study was 3.8% (9/239). Four patients died of severe general sepsis or septic shock, three died of multiple organ failure, one died of inadequate antibiotic coverage, and one died of a severe hypertonic hyperglycaemic syndrome. Furthermore, all-cause in-hospital mortality was higher in the afebrile group than in the febrile group (9.8% vs. 2.1%, $P = 0.011$). Not surprisingly, deceased patients were older than surviving patients (79.1 years vs. 63.1 years, $P = 0.002$). When comparing the afebrile group with the febrile group, we found no difference in terms of length of hospital stay (18.5 days vs. 17.3 days, $P = 0.541$) [Table 1]. Besides, complications including sepsis, pleural effusion, elevated troponin, and endophthalmitis were similar between the groups [Table 1].

Microbiological characteristics

Thirty-five (68.6%) specimen samples from the afebrile PLA group and 112 (59.6%) from the febrile PLA group were submitted for culture. The rates of detection of isolated microorganisms in the afebrile and febrile groups were 37.1% and 42.9% ($P = 0.742$), respectively. The overall predominant causal microorganism was *Klebsiella pneumoniae* (n = 50, 82.0%). Streptococcus spp., *Escherichia coli*, Enterobacter spp., ranking from second to fourth were all detected in 3 cases. The distribution of the isolated microorganisms was comparable in both groups [Table 2].

Multivariate logistic regression analysis for predicting afebrile pyogenic liver abscess

Univariate analysis identified five factors that were potentially associated with afebrile PLA. These were:

Table 1: Differences Between the Baseline Characteristics and Outcomes of Patients with Afebrile and Febrile Pyogenic Liver Abscess

	Afebrile PLA (*n*=51)	Febrile PLA (*n*=188)	*P*
Age (ys), mean (SD)	68.0 (13.1)	62.5 (13.2)	0.009
Elderly patients (age ≥65 ys), *n* (%)	32 (62.8%)	75 (39.9%)	0.004
Gender, *n* (%)			0.485
Male	31 (60.8%)	104 (55.3%)	
Female	20 (39.2%)	84 (44.7%)	
Coexisting diseases, *n* (%)			
Diabetes mellitus	29 (56.9%)	96 (51.1%)	0.462
Underlying malignancy	4 (7.8%)	15 (8.0%)	0.975
Abdominal surgery history	8 (15.7%)	35 (18.6%)	0.629
Charlson Score, median (IQR)	3.00 (1.0-6.0)	1.00 (0.0-4.0)	0.003
Body Temperature max (°C)	37.7 (0.4)	39.4 (0.7)	<0.001
Abscess location, *n* (%)			0.625
Right lobe	40 (78.4%)	140 (74.5%)	
Left lobe	8 (15.7%)	40 (21.3%)	
Both lobes	3 (5.9%)	8 (4.3%)	
Abscess number, *n* (%)			0.061
Solitary abscess	39 (78.0%)	166 (88.3%)	
Multiple abscess	11 (22.0%)	22 (11.7%)	
Abscess size (cm), mean (SD)	6.3 (2.9)	5.9 (2.6)	0.331
Laboratory findings, mean (SD)/median (IQR)			
Leucocytes count (×10⁹/L)	11.6 (5.1)	10.8 (4.8)	0.280
C-reactive protein (mg/L)	118.3 (56.3)	105.3 (65.5)	0.293
Procalcitonin (ng/ml)	0.3 (0.2-2.5)	0.5 (0.2-7.3)	0.241
Lactate (mmol/L)	2.0 (1.8-2.4)	2.0 (1.5-2.5)	0.442
Alanine transaminase (U/L)	29.5 (24.2-33.7)	31.3 (26.5-40.0)	0.699
Albumin (g/L)	29.7 (24.3-34.4)	30.8 (26.0-36.1)	0.552
SOFA scores, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.808
APACHE II scores, median (IQR)	8.0 (6.0-20.0)	8.50 (6.0-19.0)	0.650
Sepsis, *n* (%)	14 (27.5%)	53 (28.2%)	0.917
Pleural effusion, *n* (%)	2 (9.5%)	13 (14.8%)	0.530
Elevated Troponin, *n* (%)	0 (0.0%)	5 (5.7%)	NA
Endophthalmitis, *n* (%)	0 (0.0%)	2 (2.3%)	NA
In-hospital mortality, *n* (%)	5 (9.8%)	4 (2.1%)	0.011
Length of hospitalization (days), mean (SD)	18.5 (9.7)	17.3 (11.7)	0.514

SD: standard deviation; IQR: interquartile range; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; NA: not applicable

age ≥65 years, abscess number, abscess size ≥5 cm, CRP ≥150 mg/L, and the development of sepsis. In multivariate analysis, only age ≥65 years (OR = 2.12, 95% CI: 1.03-4.49, $P = 0.045$) was identified as an independent predictor of afebrile PLA [Table 3].

Univariate and multivariate analysis for prognosis

Univariate analysis of risk factors for prognosis showed that elderly age, underlying malignancy, and afebrile patients were related to higher mortality. Further, the association of underlying malignancy with mortality remained significant in the multivariate analysis (OR = 9.12, 95% CI: 1.09-76.41, $P = 0.042$). Afebrile patients were related to higher mortality in the univariate analysis, however, its P value (OR = 5.57, 95% CI: 0.88-35.12, $P = 0.068$) did not reach a statistical significance in the multivariate analysis [Supplementary appendix Table S1].

DISCUSSION

In this study, we compared the differences between the characteristics of afebrile and febrile patients with PLA

and identified factors associated with afebrile PLA. Since studies on the epidemiology, outcome, and predictors of afebrile PLA are rare, the present study helps to address the issue of scarcity of studies on afebrile PLA.

More than one-fifth of the patients (51/239, 21.3%) in this study were afebrile; this finding is roughly consistent with

Table 2: Comparison of the Microbiological Features of Patients with Afebrile and Febrile Pyogenic Liver Abscess

Microbiological features	Afebrile PLA (*n*=51)	Febrile PLA (*n*=188)	*P*
Positive	13 (25.5%)	48 (25.5%)	0.742
Klebsiella pneumoniae	9 (69.2%)	41 (85.4%)	0.178
Streptococcus spp.	1 (7.7%)	2 (4.9%)	0.519
Staphylococcus spp.	NA	2 (4.9%)	NA
Pseudomonas aeruginosa	NA	2 (4.9%)	NA
Escherichia coli	1 (7.7%)	2 (4.9%)	0.519
Enterococcus spp.	1 (7.7%)	1 (2.4%)	0.389
Enterobacter spp.	1 (7.7%)	2 (4.9%)	0.519
Negative	22 (43.1%)	64 (34.0%)	0.587
Unavailable	16 (31.4%)	76 (40.4%)	0.239

NA: not applicable

Table 3: Multivariate Logistic Regression Analysis of the Risk Factors that Predict Afebrile Pyogenic Liver Abscess

Variables	OR	95%CI	*P*
Age ≥65 ys (yes vs. no)	2.12	1.03-4.49	0.045
Abscess number (single or multiple)	2.36	0.81-6.87	0.112
Abscess size ≥5 cm (yes vs. no)	1.63	0.68-3.94	0.277
CRP ≥150 mg/L (yes vs. no)	1.34	0.54-3.30	0.525
Sepsis (yes vs. no)	0.79	0.32-1.93	0.599

OR: odds ratio; CI: confidence interval

those in previous reports.[2,8,17,18] We found that the afebrile patients were older and had higher Charlson comorbidity index scores than the febrile patients. There were significant differences between febrile and afebrile patients regarding abscess characteristics, laboratory manifestations, the severity of disease, and microbiological data.

However, the all-cause in-hospital mortality rate in the afebrile PLA group was more than 4-fold higher than that in the febrile PLA group. Furthermore, elderly age was associated with the development of afebrile PLA. In a survey from Korea, the percentage of patients with febrile PLA in the elderly group was significantly lower than that in the non-elderly group,[17] a finding which is similar to that of the present study. Besides, a retrospective cohort study of bloodstream isolates from 994 adults showed that elderly persons (age ≥65 years) are associated with afebrile bacteremia.[19] The reason behind this finding may be that infection is easily masked by the high number of underlying diseases associated with elderly age. Furthermore, the findings of Drewry's study suggested that the absence of fever is associated with monocyte dysfunction in early sepsis, as well as worse clinical outcomes.[20]

Previous studies described afebrile bacteremia as a unique manifestation of geriatric or immunocompromised patients.[21,22] We clarified that older age and higher Charlson comorbidity index are the comorbid conditions that are most associated with afebrile PLA. This might offer clinicians a clue for early recognition and treatment of afebrile patients. Tian's study indicated that more patients with PLA and DM had temperatures >38.5°C than patients with PLA but without DM.[2] Yo *et al*.,[19] reported that more patients with high Charlson comorbidity index tend to have afebrile bacteremia, which has a 2–3 fold higher probability of accompanying organ failures, than febrile patients.

In the present study, the microbiological yield from the sample culture was 41.5%, which is lower than that of other studies.[8,11,17,23] This difference could be explained by the fact that the rates of positive blood and pus cultures in the studies are discrepant. In the present study, although

most patients underwent blood culture examination, a considerable number of patients did not undergo any culture examination. *K. pneumoniae* was the most isolated aerobe in both groups. Notably, the rate of isolation of *K. pneumoniae* has been reported to be increasing worldwide.[24-26] The distributions of bacteria isolated from blood cultures were similar between the groups in the present study. However, Yo *et al*.,[19] found that *Escherichia coli* is associated with more cases of febrile bacteremia and is seen more often in patients with diabetes or urinary tract infection.

The overall mortality rate in our study was lower than in previous studies.[7,18,27] The low mortality rate may be associated with early antibiotics administration, intervention with radiology-guided percutaneous techniques, and the low rate of underlying malignancy. The deceased in the present study mainly died of old age, severe general sepsis, septic shock, and subsequent multiple organ failure. The prognosis of the patients in the afebrile PLA group was worse than that of the patients in the febrile PLA group, with all-cause in-hospital mortality reaching 9.80% in our series. Previous studies have shown that the absence of fever is associated with higher morbidity, organ failures, and mortality in patients with sepsis and bacteremia.[19,20] It may be possible that organ failures are associated with the compromised immune system, as fever itself is a marker of a sound immune response. Afebrile patients were related to higher mortality in the univariate analysis, however, its *P* value did not reach a statistical significance in the multivariate analysis.

Several limitations to this study should be acknowledged. The measurement of body temperature was not standardized, and information on patients' temperatures prior to emergency admission was collected from patients' self-reports, which might present reporting bias. But our results would hardly be affected because the time frame was only 24 hours. Although this may have added a small amount of heterogeneity in the measurement of temperature, it reflects real-world practice. Additionally, inter-institutional differences and differences in the quality of management by physicians may have confounded our study results. Finally, the relationship between afebrile PLA and mortality was not assessed because of the limited sample of the deceased in this study. We aim to collate more quality cases and analyze the risk factors that affect the prognosis of afebrile PLA.

CONCLUSIONS

In conclusion, a considerable proportion of patients with PLA are afebrile and have a higher mortality rate than

febrile patients with PLA. Elderly patients and those with a higher Charlson comorbidity index are prone to afebrile PLA. In the future, prospective multicentre studies with large samples will be required to provide more high-quality research evidence to validate the findings of the present study.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Appendix Table S1: The Univariate and Multivariate Analysis for Mortality

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95%CI	P	OR	95%CI	P
Age ≥65 yrs (yes vs. no)	1.14	1.05-1.24	0.002	1.10	1.00-1.21	0.051
Charlson score >4 (yes vs. no)	1.33	0.94-1.89	0.109	1.41	0.88-2.27	0.150
Abscess size >5 cm (yes vs. no)	1.23	0.96-1.56	0.102	1.24	0.93-1.65	0.143
Underlying malignancy (yes vs. no)	6.69	1.53-29.26	0.012	9.12	1.09-76.41	0.042
Afebrile (yes vs. no)	5.00	1.29-19.36	0.020	5.57	0.88-35.12	0.068

OR: odds ratio; CI: confidence interval