ISSN 1669-9106 MEDICINA (Buenos Aires) 0000: 00: 00-00

Original article

# TIME AND DEPARTMENTS OF CONSULTATION AFFECTING PYOGENIC LIVER ABSCESS DIAGNOSIS

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**Received:** 12-III-2025
**Accepted:** Accepted: 18-VIII-2025

## Abstract

**Introduction:** This article surveys the time from symptom onset to consultation and diagnosis of pyogenic (bacterial) liver abscess patients, depicts first specialized outpatient visit and hospitalization departments, and analyzes influencing factors to aid early diagnosis.

**Materials and methods:** Patients diagnosed with pyogenic liver abscess from 2013 to 2023 were studied through retrospective medical record review.

**Results:** 191 patients (63.9% male, age 64.8 ± 13.8 years) were included. Patients with pyogenic liver abscess may present with respiratory (33%), neurological (32%), urinary (17%), and cardiovascular (10%) manifestations. Median time from symptom onset to initial medical consultation, initial consultation to diagnosis, and symptom onset to diagnosis were 2 days (IQR 1, 4), 4 days (IQR 2, 7), and 7 days (IQR 4, 11), respectively; 16% of patients initially sought specialized outpatient visit in endocrinology, neurology, cardiology, nephrology, and pulmonology departments. Of these, 83% were hospitalized with varied initial diagnoses including diabetes, cerebral infarction, acute coronary syndrome, pneumonia, and acute pyelonephritis. Factors influencing the time to consultation and diagnosis included high fever (Tmax>39°C), emaciation, nausea, differences in initial hospitalization and diagnostic departments, low albumin (<30g/L), and thrombocytopenia.

**Discussion:** The non-specific and sometimes misleading symptoms of pyogenic liver abscess leads patients to seek care in inappropriate specialized outpatient departments, resulting in erroneous preliminary diagnoses by physicians and consequently delaying the correct diagnosis. Clinicians should conduct thorough and careful inquiries and physical examinations, choose appropriate and effective diagnostic modalities, and make accurate diagnoses as early as possible.

**Key words:** pyogenic liver abscess, consultation and referral, admission department, diagnostic tests, early diagnosis, clinical decision making

## Resumen

*Tiempo de consulta y departamentos que afectan el diagnóstico de absceso hepático piógeno*

**Introducción:** Este artículo analiza el tiempo de consulta y diagnóstico en pacientes con absceso hepático piogénico (bacteriano), describe la primera consulta y departamento de hospitalización, y analiza factores para el diagnóstico precoz.

**Materiales y métodos:** Se efectuó una revisión retrospectiva de historias clínicas de pacientes diagnosticados entre 2013 y 2023.

**Resultados:** Se incluyeron 191 pacientes (63,9% varones, edad 64,8 ± 13,8 años). Presentaron manifestaciones respiratorias (33%), neurológicas (32%), urinarias (17%) y cardiovasculares (10%). La mediana del tiempo desde

síntomas a primera consulta, a diagnóstico y desde síntomas a diagnóstico fue de 2 (RIC 1, 4), 4 (RIC 2, 7) y 7 días (RIC 4, 11) respectivamente. El 16% consultó inicialmente en especialidades como endocrinología. El 83% fue hospitalizado con diagnósticos iniciales erróneos. Factores influyentes fueron fiebre alta, emaciación, náuseas, diferencias en hospitalización y diagnóstico inicial, baja albúmina y trombocitopenia.

**Discusión:** Los síntomas inespecíficos llevan a consultas inadecuadas y diagnósticos erróneos, retrasando el correcto. Los clínicos deben examinar exhaustivamente, elegir buenas modalidades de diagnóstico, y efectuar el diagnóstico precozmente

**Palabras clave:** absceso hepático piogénico, consulta y remisión, departamento de admisión, pruebas diagnósticas, diagnóstico precoz, toma de decisiones clínicas

## KEY POINTS
### Current knowledge

- The incidence of pyogenic liver abscess (PLA) is rising. Timely diagnosis and treatment can improve prognosis.
- There's currently no research on influencing factors of PLA diagnostic time.

### Contribution of the article to current knowledge

- Inappropriate departments for initial specialized outpatient visit, along with high fever, emaciation, hypoproteinemia, and thrombocytopenia, can affect the diagnostic time of pyogenic liver abscess.
- Clinicians should conduct thorough and careful inquiries and physical examinations, choose appropriate and effective diagnostic modalities, and make accurate diagnoses as early as possible.

Liver abscess is a focal suppurative hepatic pathology characterized by the infiltration of pathogens via the biliary tract, hepatic artery, portal vein, and direct extension from adjacent inflammatory sites. Notably, common etiological agents encompass bacteria, fungi, and amoebae, with pyogenic (bacterial) liver abscess (PLA) constituting approximately 80% of reported cases[1]. Epidemiological studies revealed an incidence of PLA ranging from (1.1-5.7)/100 000 persons in mainland China, (1.0-4.1)/100 000 persons in European and American countries, and notably elevated rates ranging from (12-18)/100 000 persons in certain Asian nations[2-6]. Disparities in incidence rates are intricately linked to underlying patient comorbidities, geographical variations, and disparities in medical infrastructure. Contemporary trends suggest a rising incidence of PLA, attributed to the increasing prevalence of diabetes mellitus (DM), malignancies, organ transplantation, immunosuppressive therapies, and hepatobiliary invasive procedures[5, 7-10]. Thus, PLA remains a condition with significant mortality if not promptly diagnosed and treated.

The diagnosis of typical PLA is straightforward following typical clinical presentation, laboratory investigations, and imaging evaluation. The typical clinical manifestations of PLA include fever and abdominal discomfort, with other common symptoms such as nausea, vomiting, and anorexia. Abdominal discomforts are typically localized to the right upper quadrant, including pain, guarding, liver tenderness, and rebound tenderness. Approximately half of the patients with PLA may have hepatomegaly, right upper quadrant tenderness, or jaundice[11]. However, due to factors such as prior antibiotic use, weakened responses in elderly patients, deep-seated abscesses not involving the liver capsule, lower virulence of bacteria, as well as overshadowing by other abdominal pathologies, atypical PLA are more common in clinical practice[1]. Moreover, the department where patients initially seek specialized outpatient consultation can also influence the diagnosis time of PLA. Physicians in departments specializing in liver and liver-related infectious diseases, such as the Department of Infectious Diseases, Gastroenterology, and Hepatobiliary Surgery, are well-versed in diagnosing PLA. Conversely, specialists in other systemic disease departments, including the Departments of Endocrinology, Neurology, Cardiology, Respiratory Medicine, and Nephrology, have limited knowledge of PLA. When faced with patients presenting with unexplained fever accompanied by abdominal discomfort, it is challenging for them to consider PLA as a potential diagnosis. This difficulty is exacerbated when patients' symptoms are predominantly non-specific, such as dizziness, chest tightness, and cough. In such cases, these specialists tend

to focus on diseases within their own specialties. For instance, elderly patients may initially present with symptoms such as dizziness and limb weakness, leading them to seek outpatient consultation in the neurology department, where they may be misdiagnosed with acute cerebral infarction or cerebral ischemia. In addition, some patients may present with fatigue and emaciation, along with elevated blood glucose levels, leading to the mistaken assumption that these symptoms are solely due to DM potentially overlooking the presence of a PLA and resulting in delayed diagnosis. These atypical presentations, resembling many other systemic diseases, contribute to delays in accurate diagnosis[12-18].

There are many publications on PLA, but most focus on pathogens and treatment. No articles have been found regarding the timing of the diagnosis of PLA and its influencing factors. The purpose of this article is to survey the time from symptom onset to initial medical consultation and diagnosis in patients with PLA, depict the departments of first specialized outpatient visit and hospitalization, and analyze the factors affecting consultation and diagnosis time, ultimately providing recommendations for clinicians to facilitate early diagnosis.

## Materials and methods

### *Patients and methods*

Patients diagnosed with PLA and admitted to the Nanjing First Hospital over a ten-year period (2013-2023) were included in the study. The diagnosis of PLA is based on the following criteria: symptoms such as fever and abdominal discomfort; presence or absence of tenderness in the liver area during physical examination; laboratory results indicating bacterial infectious diseases, such as elevation of white blood cells and inflammatory markers; computed tomography (CT) scans showing low-density lesions or ultrasound indicating hypoechoic areas in the liver; blood cultures identifying bacteria, or aspiration of fluid from the lesion with subsequent microscopic examination or culture confirming pus or bacteria; pathological examination from the aspiration or surgery showing infiltration of inflammatory cells; and clinical improvement and reduction or disappearance of the lesion after antibacterial treatment[1].

The symptoms, physical signs, and laboratory test results of these patients, as well as the time intervals from symptom onset to initial medical consultation, from initial medical consultation to diagnosis, and from symptom onset to diagnosis were recorded. As the departments for a patient's first specialized outpatient visit, first hospitalization, and final correct diagnosis of PLA may vary, we also recorded these departments. The first visit of a symptomatic outpatient to specialized departments may include departments related to the liver and its infections, such as the Department of Infectious Diseases, the Department of Gastroenterology, and the Department of Hepatobiliary Surgery. Other departments involved not related to the liver and its infections, such as the Departments of Endocrinology, Neurology, Cardiology, Respiratory Medicine, and Nephrology. We analyze whether there is an impact on the diagnosis time of PLA when the department of a patient's first specialized outpatient visit is a non-liver or liver-infection-related department. In addition, if the hospital or department where a patient was first hospitalized failed to make a clear diagnosis and referred the patient to a higher-level hospital or specialty, this inevitably affected the patient's diagnosis time. Patients whose department of first hospitalization was inconsistent with the department that finally made the correct diagnosis were also recorded and analyzed for their impact on the diagnosis time.

Typical symptoms of the disease include fever (with peak body temperature), shiver, nausea, abdominal distension/pain, anorexia, fatigue, and emaciation. Atypical symptoms, which occur in the absence of typical symptoms, involve manifestations from other systems such as respiratory (cough, nasal congestion, rhinorrhea, sore throat, chest tightness, and dyspnea), neurological (dizziness, headache, altered consciousness, and limb numbness), urinary (frequency, urgency, dysuria, and urinary retention), and cardiovascular (chest pain and palpitations). The main physical sign is tenderness in the liver area.

The onset date of symptoms refers to the first day on which the patient begins to experience symptoms. The consultation date is defined as the day when the patient first visits a medical institution (including private clinics, community hospitals, and general hospitals that offer professional medical services). The diagnosis date is the day when the patient is clearly diagnosed with PLA according to the aforementioned criteria. We divided patients' timeline from symptom onset to diagnosis into three periods: First, the time from symptom onset to initial medical consultation spans from the onset date

to the consultation date (time 1). Second, the time from initial medical consultation to diagnosis refers to the duration between the consultation date and the diagnosis date (time 2). Finally, the time from symptom onset to diagnosis is the entire period from the onset date to the diagnosis date (time 3).

The study protocol was approved by the Ethics Committee of Nanjing First Hospital, Nanjing Medical University with the waiver of informed consent.

### *Statistical analysis*

Continuous variables were presented as mean±standard deviation (SD), while median and interquartile range (IQR) were reported for non-normally distributed parameters. Categorical variables were depicted as numbers and percentages. The independent sample t-test or Mann-Whitney U test was performed for continuous variables, and the Chi-square test or Fisher's exact test was used for categorical variables. A two-sided p-value of less than 5% was deemed statistically significant.

Outcome measures were: time from symptom onset to initial medical consultation, initial medical consultation to diagnosis, and symptom onset to diagnosis, which were dichotomized taking the upper quartile of the time interval as reference. Multivariate stepwise logistic regression analyses were employed to identify factors influencing the occurrence of the three mentioned outcome variables. Variables with p-values less than 0.05 in univariate analysis were included in multivariate analysis. Additionally, variance inflation factor analysis was conducted to assess multicollinearity. Statistical analyses were performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Software Inc., La Jolla, California, USA).

## Results

### *Clinical characteristics*

A total of 191 patients were included in the study. Of them, 63.9% (122/191) were male. The common comorbidities were diabetes, biliary tract diseases, which including biliary tract infection, gallstone, bile duct calculus, cholecystectomy, and cholecystolithotomy, as well as malignant tumors (Table 1). The most common symptom was fever (99.0%, 189/191), with 61.8% (118/191) of patients experiencing a temperature peak of 39°C or higher ($T_{max}$≥39°C). The 32.5% (62/191) of patients presented with respiratory manifestations such as cough, nasal congestion, rhinorrhea, sore throat, chest tightness, and dyspnea; 31.9% (61/191) exhibited neurological manifestations, including dizziness, headache, altered consciousness, and limb numbness. Furthermore, 17.3% (33/191) of individuals experienced urinary system manifestations such as frequency, urgency, dysuria, and urinary retention. Moreover, two individuals reported chest pain, while four individuals presented with palpitations (Fig. 1). Among them, 6 patients had mixed infections, including *Escherichia coli* and *Streptococcus* in 2 cases, *Escherichia coli* and *Bacteroides fragilis* in 2 cases, *Escherichia coli* and *Enterococcus faecalis* in 1 case, and *Klebsiella pneumoniae* and *Clostridium perfringens* in 1 case (Table 2). Among these patients, no deaths occurred.

### *Time from symptom onset to initial medical consultation, time from initial medical consultation to diagnosis, time from symptom onset to diagnosis*

The median time for patients to reach their initial medical consultation was 2 days (IQR 1, 4), with 72.0% (134/186) of them seeking care within three days and 87.6% (163/186) within one week. Four individuals presented for medical consultation one month after the onset of symptoms, comprising three males and one female. One patient presented only with anorexia and neglected medical consultation. Three others had fever, which resolved after self-medication with antipyretics and antibiotics, thus they did not seek hospital care. The median diagnosis time from initial presentation was 4 days (IQR 2, 7), with 44.9% (84/187) diagnosed within three days, 76.5% (143/187) within one week, and 93.6% (175/187) within two weeks. Part of the remaining patients were initially hospitalized elsewhere without a conclusive diagnosis before being transferred to our institution. Additionally, one patient with pancreatic cancer and liver metastasis was initially admitted to the oncology department. Although his symptoms ameliorated following anti-infective therapy, fever recurred post-discharge. Subsequent CT scans indicated the possibility of a liver abscess, necessitating antibiotic therapy and percutaneous transhepatic drainage for disease control.

**Table 1** | Epidemiological characteristics of 191 patients, underlying diseases, and initial specialized outpatient visit to departments

| Variables | Percentage % |
|---|---|
| Male | 63.9 (122/191) |
| Age (years) | 64.8 (±13.8) |
| DM | 61.3 (117/191) |
| Biliary diseases | 44.0 (84/191) |
| Neoplasia | 8.4* (16/191) |
| Gastric cancer | 12.5 (2/16) |
| Duodenal cancer | 6.25 (1/16) |
| Colon cancer | 6.25 (1/16) |
| Rectal cancer | 12.5 (2/16) |
| Pancreatic cancer | 18.8 (3/16) |
| Renal cancer | 12.5 (2/16) |
| Breast cancer | 25.0 (4/16) |
| Cervical cancer | 6.25 (1/16) |
| Endometrial cancer | 6.25 (1/16) |
| Departments | 15.7 (30/191)† |
| Endocrinology | 40.0 (12/30) |
| Neurology | 20.0 (6/30) |
| Cardiology | 13.3 (4/30) |
| Nephrology | 6.7 (2/30) |
| Respiratory medicine | 20.0 (6/30) |

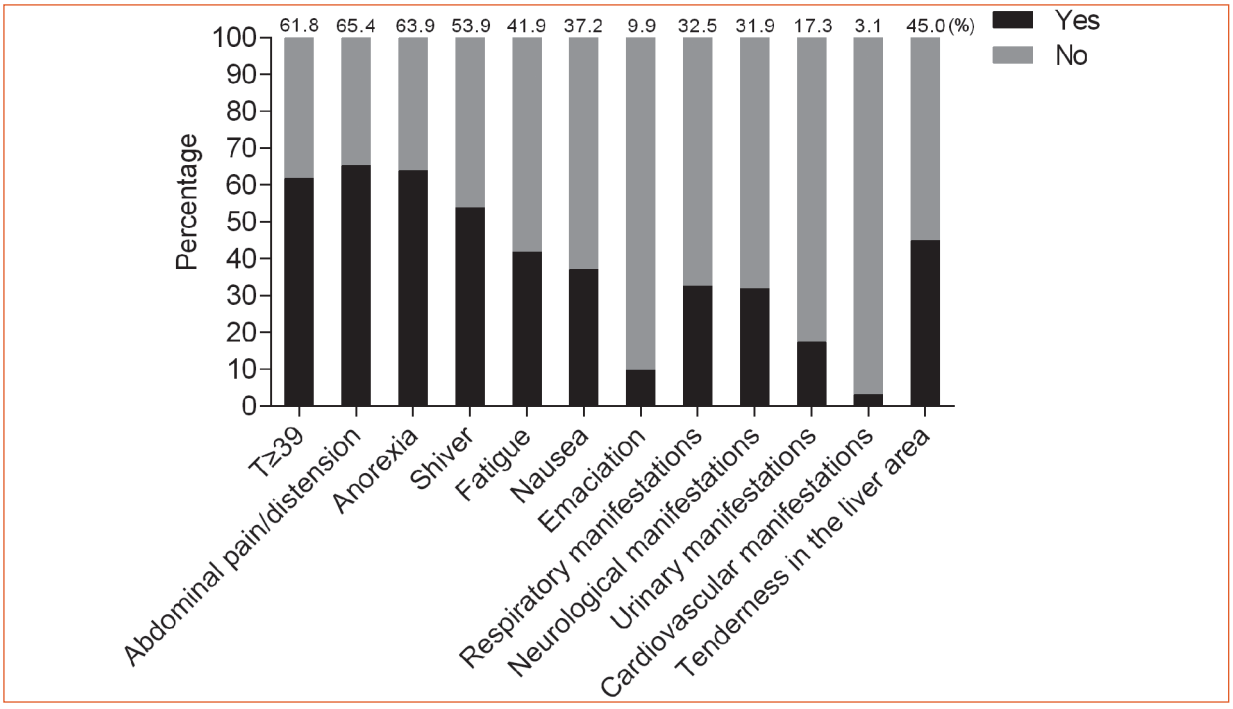
*DM: diabetes mellitus*
*One of the patients suffered from both pancreatic cancer and colon cancer.
†Among the 191 patients, 30 initially went to outpatient departments for other-system diseases like endocrinology, neurology, cardiology, nephrology, and respiratory departments. The rest visited outpatient departments related to liver and its infections, such as infectious diseases, gastroenterology, and hepatobiliary surgery departments.
Continuous variables are presented as mean±standard deviation (SD) or median and interquartile range (IQR) and categorical variables as numbers and percentages.

Another patient admitted to endocrinology with thirst, anorexia, and asthenia had multiple liver and lung lesions, suggestive of potential malignancy and metastasis. A liver biopsy was conducted in oncology for diagnosis. The two examples illustrate the challenge of distinguishing between primary and metastatic malignant liver tumors and liver abscess. The median time from symptom onset to diagnosis was 7 days (IQR 4, 11), with 14.1% (27/191) diagnosed within three days, 54.5% (104/191) within one week, and 90.1% (172/191) within three weeks. Many patients had undergone antibiotic therapy and achieved clinical remission, but experienced disease relapse after treatment cessation due to incorrect diagnosis, inappropriate antibiotics chosen, ineffective drainage, or an inadequate course of treatment (Fig. 2).

### *Department of first specialized outpatient visit and hospital admission*

Thirty patients (15.7%, 30/191) presented to the outpatient departments of endocrinology, neurology, cardiology, nephrology, and respiratory medicine due to atypical symptoms and unawareness of fever. Among them, twelve patients (6.3%) initially had an outpatient visit to endocrinologists, exhibiting symptoms such as polydipsia, polyuria, weight loss, anorexia, and fatigue, accompanied by significantly elevated blood glucose levels. Nine of these patients were admitted for inpatient care, with three having no prior history of diabetes. Additionally, six patients (3.1%) sought consultation with neurologists because of symptoms like dizziness, bradykinesia, gait disturbances, and even alterations in consciousness. All six were admitted,

**Figure 1** | Percentage of different symptoms and signs in 191 cases




*T≥39: peak temperature≥39°C; Respiratory manifestations included cough, nasal congestion, rhinorrhea, sore throat, chest tightness, and dyspnea; Neurological manifestations included dizziness, headache, altered consciousness, and limb numbness; Urinary manifestations included frequency, urgency, dysuria, and urinary retention; Cardiovascular manifestations included chest pain and palpitations*

and four were diagnosed with posterior circulation ischemia, one with cognitive impairment, and the remaining one with cerebral infarction. Four patients presented at the cardiovascular outpatient department, complaining of chest tightness and pain. Two of them were admitted; one showed elevated myocardial enzymes suggestive of acute coronary syndrome, while the other experienced repeated paroxysmal palpitations and chest tightness, raising the possibility of arrhythmia or coronary artery disease. Six patients with fever, cough, and sputum indicating a potential pulmonary infection were admitted to the hospital after an initial outpatient consultation at the respiratory department. Furthermore, two patients with fever, urinary irritation, proteinuria and renal insufficiency were considered with acute pyelonephritis and diabetic nephropathy at the nephrology outpatient and then admitted for in-hospital treatment.

### *Factors affecting time to initial medical consultation and diagnosis*

Univariate analysis showed that age, high fever ($T_{max}$≥39°C), emaciation, nausea, shiver, albumin level below 30 g/L, platelet count less than $125\times10^9$/L, neutrophil ratio, and procalcitonin level greater than 5 μg/L were factors influencing the diagnosis time (Supplementary Tables). Multivariate analysis revealed that high fever and emaciation were related to the timing of initial medical consultation. Patients with a peak temperature of 39°C or higher tend to consult earlier, while those with emaciation have a delayed first consultation compared to those without weight loss. In terms of the time from initial medical consultation to diagnosis, patients with nausea were more likely to be diagnosed earlier.

However, when the department of initial hospitalization differed from the department of diagnosis, the time to diagnosis was

**Table 2** | Major laboratory findings, diagnostic modalities, and pathogenic microorganisms (N:191)

| Variables | Percentage % |
|---|---|
| WBC ($\times 10^9$/L) | 13.5 (±5.7) |
| Neutrophil ratio (%) | 84.8 (±8.8) |
| ALT elevation | 55.0 (105/191) |
| Albumin<30g/L | 56.0 (107/191) |
| Procalcitonin >5ug/L | 50.8 (97/191) |
| Platelet <125×$10^9$/L | 35.1 (67/191) |
| D-dimer≥5mg/L | 29.8 (57/191) |
| Creatinine elevation | 24.6 (47/191) |
| Different departments | 9.4 (18/191) |
| Diagnostic modalities | |
| B-ultrasound | 28.8 (55/191) |
| CT | 68.1 (130/191) |
| MRI | 1.6 (3/191) |
| Biopsy | 1.0 (2/191) |
| Surgery | 0.5 (1/191) |
| Pathogenic microorganisms | 54.5 (104/191) |
| *Klebsiella pneumoniae* | 84.6 (88/104) |
| *Escherichia coli* | 7.7 (8/104) |
| *Streptococcus* | 3.8 (4/104) |
| *Staphylococcus* | 3.8 (4/104) |
| *Enterococcus* | 1.9 (2/104) |
| *Salmonella* | 1.0 (1/104) |
| *Bacteroides fragilis* | 1.9 (2/104) |
| *Clostridium perfringens* | 1.0 (1/104) |
| Mixed | 5.8 (6/104) |
| Sample types | 54.5 (104/191) |
| Blood | 39.4 (41/104) |
| Pus | 35.6 (37/104) |
| Both | 25.0 (26/104) |

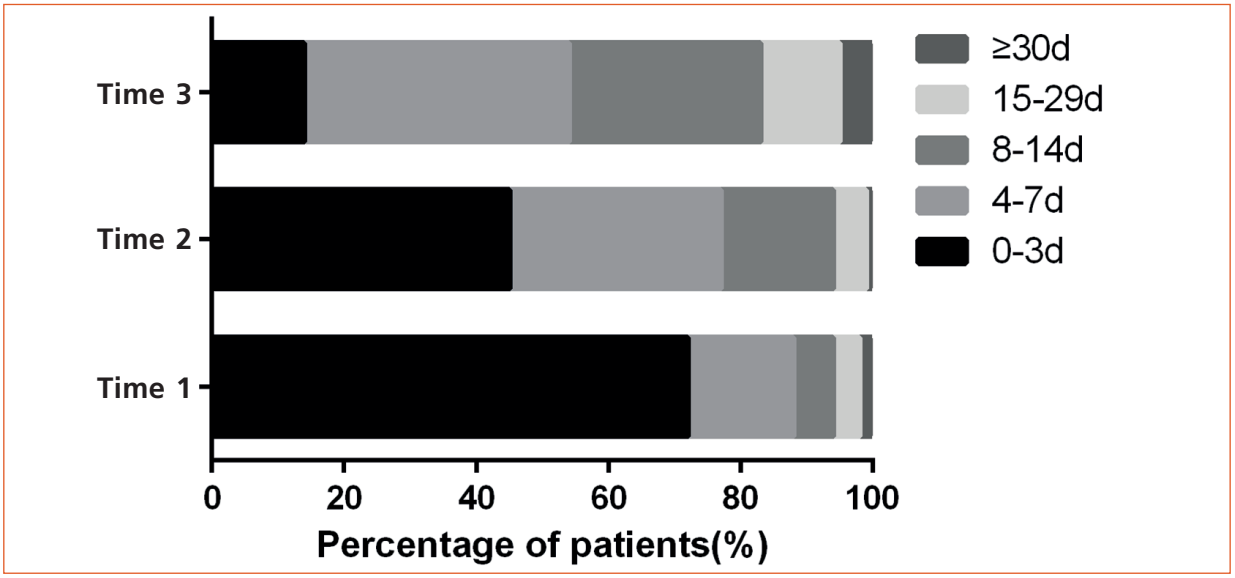
*WBC: white blood cell; ALT: alanine transaminase; Different departments: the department of first hospitalization was different from the department of final diagnosis; CT: computed tomography; MRI: magnetic resonance imaging;*
Continuous variables are presented as mean±standard deviation (SD) or median and interquartile range (IQR) and categorical variables as numbers and percentages.

significantly prolonged. In the process from symptom onset to diagnosis, factors such as $T_{max}$≥39°C, emaciation, hypoproteinemia (<30 g/L), thrombocytopenia, and a difference between departments of first hospitalization and diagnosis would all affect the time to diagnosis. Specifically, patients with $T_{max}$≥39°C and those with thrombocytopenia experienced a significantly shorter time to clear diagnosis, while emaciation, hypoproteinemia, and the department difference between initial hospitalization and diagnosis lead to a significantly prolonged diagnosis time (Table 3).

## Discussion

Pyogenic liver abscess is easily diagnosed by experienced physicians but poses challenges for non-specialists due to non-specific symptoms, especially when sepsis affects multiple systems. Our findings show 99% of PLA patients have fever, followed by abdominal pain/distension (65.4%), anorexia (63.9%), shiver (53.9%), and fatigue (41.9%). This is similar to the data published by Tongji University in Wuhan, China. They analyzed the data of 208 patients with PLA from 2015 to 2023. Among these patients, the proportions of patients presenting with fe-

**Figure 2** | Time from symptom onset to initial medical consultation, from initial medical consultation to diagnosis, and from symptom onset to diagnosis (N: 191)




*d: days*
*Time 1: time from symptom onset to initial medical consultation; Time 2: time from initial medical consultation to diagnosis; Time 3: time from symptom onset to diagnosis*

**Table 3** | Multivariate analysis of factors influencing time from symptom onset to initial medical consultation and diagnosis

| | | | | |
|---|---|---|---|---|
| Time 1-time from symptom onset to initial medical consultation | | | | |
| Variables | ≤4d (n=147) | >4d (n=39) | OR (95%CI) | p-values |
| Tmax≥39 °C, n (%) | 97 (66.9) | 16 (41.0) | 0.344 (0.164, 0.720) | 0.005 |
| Emaciation, n (%) | 10 (6.8) | 8 (20.5) | 3.491 (1.230, 9.909) | 0.019 |
| Time 2-time from initial medical consultation to diagnosis | | | | |
| Variables | ≤7d (n=143) | >7d(n=44) | OR (95%CI) | p-values |
| Nausea, n (%) | 60 (42.0) | 11 (25.0) | 0.382 (0.148, 0.991) | 0.048 |
| Different departments, n (%) | 8 (5.6) | 10 (22.7) | 7.393 (2.249, 24.305) | 0.001 |
| Time 3-time from symptom onset to diagnosis | | | | |
| Variables | ≤11d (n=146) | >11d (n=45) | OR (95%CI) | p-values |
| Tmax≥39°C, n (%) | 96 (66.7) | 21 (46.7) | 0.424 (0.196, 0.917) | 0.029 |
| Emaciation, n (%) | 9 (6.2) | 10 (22.2) | 3.277 (1.069, 10.042) | 0.038 |
| Albumin<30g/L, n (%) | 69 (48.3) | 32 (72.7) | 3.136 (1.345, 7.312) | 0.008 |
| Platelet<125×10$^9$/L, n (%) | 59 (40.4) | 8 (17.8) | 0.276 (0.109, 0.701) | 0.007 |
| Different departments, n (%) | 10 (6.8) | 8 (17.8) | 5.693 (1.680, 19.293) | 0.005 |

*Tmax≥39 °C: Peak temperature≥39; OR: odds ratio; CI: confidence interval*

Different departments: the department of first hospitalization was different from the department where patients were finally diagnosed

Continuous variables are presented as mean±standard deviation (SD) or median and interquartile range (IQR) and categorical variables as numbers and percentages

ver, chills, anorexia, and abdominal symptoms were 94.2%, 43.8%, 52.4%, and 50.0% respectively. In our study, over 30% present with respiratory and neurological symptoms, complicating patient care and misleading diagnosis. This is also similar to the data from their study, in which 35.1% of the patients have symptoms involving other organ systems[12]. Although the

atypical symptoms led to a relatively longer diagnostic time, the median time from symptom onset to diagnosis and from the first medical consultation to diagnosis was 7 (4, 11) and 4 (2, 7) days respectively, both of which were shorter than the median diagnostic time of 9 (4, 15) days for pediatric PLA. This may be because pediatric PLA are more commonly seen in patients with underlying diseases such as malignant hematological diseases and primary immunodeficiency diseases. These patients are more likely to have extrahepatic organ involvement and are thus more difficult to diagnose[19].

In our study, among the 191 patients, only 30 initially went to outpatient departments for other-system diseases such as endocrinology, neurology, cardiology, nephrology, and respiratory departments for symptoms like weakness, dizziness, chest tightness and pain, frequent urination, urgency, and cough. The remaining patients visited outpatient departments related to liver and its infections, such as infectious diseases, gastroenterology, and hepatobiliary surgery departments. Of the 30 patients, 25 were hospitalized with initial diagnoses including diabetes, cerebral infarction, acute coronary syndrome, pneumonia, and acute pyelonephritis. Factors influencing the time to initial consultation and diagnosis included high fever ($T_{max}$≥39°C), emaciation, nausea, differences in hospitalization and diagnostic departments, low albumin (<30g/L), and thrombocytopenia.

As Foo et al. found, a neutrophil ratio greater than 70% was a significant predictor of mortality[20]. The neutrophil-to-lymphocyte ratio was positively correlated with poor outcomes in PLA[21-23]. A study involving 298 patients with PLA showed that the age in the deceased group was significantly higher than that of the surviving group[24]. Simultaneously, studies had shown that compared to patients with normal platelet counts, those with decreased platelet counts in *Klebsiella pneumoniae* liver abscess had a threefold increase in mortality[25]. These factors are consistent with those influencing the diagnostic time in univariate analysis in our study. This means that these factors, which can lead to an extended diagnostic time, will ultimately result in poor prognosis, although there were no death cases in our study cohort. In consequence, for elderly patients and those with a significantly elevated neutrophil ratio or decreased platelet counts, early hospital admission, clear diagnosis, and effective interventions can reduce the occurrence of adverse outcomes. Additionally, diabetes, malignancy, as well as elevated procalcitonin and creatinine were all associated with adverse prognosis[24, 26-28]. Gallstone-related diseases can precipitate PLA. The incidence rate ranged from 11% to 37% in Southeast Asia, second only to cryptogenic liver abscess, and was on the rise[29-31].

In our case study, a patient with a PLA was initially mistaken for having primary hepatic malignancy, which led to multiple referrals across departments and imposed significant psychological, economic, and temporal burdens on the patient. Distinguishing atypical PLA from liver tumors poses certain challenges, especially in the early stages when liquefaction has not yet occurred[32]. Differential diagnosis can be approached from the following aspects: firstly, patients with liver cancer often have a history of chronic hepatitis or cirrhosis, and tumor markers are frequently elevated[33]. Additionally, as the abscess matures, typical imaging features gradually manifest; therefore, patients highly suspected of having a liver abscess should undergo timely repeat imaging[34]. Finally, most patients with liver abscess respond effectively to antimicrobial therapy, whereas fever resulting from central necrosis in liver cancer often does not respond to antimicrobial treatment.

Numerous examples demonstrate that the absence of typical abdominal pain does not exclude the possibility of PLA. Some patients may present only with fever at the onset of the disease. Moreover, hypervirulent *Klebsiella pneumoniae* infection-induced PLA often accompanies extrahepatic dissemination infections, such as endophthalmitis, brain abscess, pulmonary abscess, endocarditis, soft tissue abscess, splenic abscess, and renal abscess[35-37]. When invasive syndrome occurs, patients may manifest corresponding clinical symptoms in the respective systems. Therefore, in febrile patients, if the infectious focus is not clearly identified after thorough history-taking, and physical examination, or other systemic symptoms may appear, the possibility of PLA should be considered, and prompt imaging modalities, if necessary, serial

imaging studies, should be conducted to aid in diagnosis. Simultaneously, primary care clinicians should enhance their awareness of PLA and broaden their differential diagnostic approaches to minimize misdiagnoses and missed diagnoses.

To the best of our knowledge, this is the first study to comprehensively investigate the impact of clinical manifestations, time and department of initial medical consultation on the diagnostic time of patients with PLA. Nonetheless, this study is not without limitations. Firstly, there are other factors that can influence the diagnostic time, such as abscess size, location, and others. However, we specifically analyzed how factors including patients' symptoms, physical signs, and laboratory test results influence the diagnostic duration of PLA. These are the only available data for the first-attending physician during the initial encounter, and our primary focus is on how the attending physician, prior to the definitive diagnosis, rapidly identifies and performs appropriate imaging examinations based on the patient's medical history, presenting symptoms, physical signs, and laboratory test results to confirm the diagnosis. On the other hand, this is a single-center retrospective study with a limited sample size, which may introduce selection bias. Furthermore, the analysis was based on patient data spanning the last decade. While this timeframe offers valuable insights, conducting a stratified analysis across different time periods could provide further clarity. However, this would necessitate a larger dataset.

In conclusion, the non-specific and sometimes misleading symptoms of pyogenic liver abscess leads patients to seek care in inappropriate outpatient departments, resulting in erroneous preliminary diagnoses by physicians and consequently delaying the correct diagnosis. Clinicians should conduct thorough and careful inquiries and physical examinations, choose appropriate and effective diagnostic modalities, and make accurate diagnoses as early as possible.

**Acknowledgments:** We thank all the participants for their time and effort.

**Conflict of interest:** None to declare

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## Supplementary tables
## Univariate analysis of factors influencing the time of first visit and diagnosis

**Table S1** | Time 1 - time from symptom onset to initial medical consultation

| Variables | ≤4d (n=147) | >4d (n=39) | p-value |
|---|---|---|---|
| Male | 89 (60.5) | 29 (74.4) | 0.111 |
| Age (years) | 65.33 (+/-14.37) | 63.46 (+/-11.84) | 0.455 |
| DM | 85 (57.8) | 28 (71.8) | 0.112 |
| Hepatobiliary diseases | 60 (40.8) | 22 (56.4) | 0.081 |
| Neoplasia | 14 (9.5) | 2 (5.1) | 0.583 |
| Tmax≥39°C | 97 (66.9) | 16 (41.0) | **0.003** |
| Abdominal pain/distension | 97 (66.0) | 26 (66.7) | 0.936 |
| Anorexia | 90 (61.2) | 27 (69.2) | 0.357 |
| Shiver | 85 (57.8) | 16 (41.0) | 0.061 |
| Fatigue | 54 (36.7) | 21 (53.8) | 0.053 |
| Nausea | 55 (37.4) | 15 (38.5) | 0.905 |
| Emaciation | 10 (6.8) | 8 (20.5) | **0.023** |
| Respiratory manifestations | 46 (31.3) | 14 (35.9) | 0.584 |
| Neurological manifestations | 46 (31.3) | 14 (35.9) | 0.584 |
| Urinary manifestations | 27 (18.4) | 6 (15.4) | 0.665 |
| Cardiovascular manifestations | 3 (2.0) | 3 (7.7) | 0.205 |
| Local tenderness | 68 (46.3) | 17 (43.6) | 0.766 |
| WBC ($\times 10^9$/L) | 13.0 | 11.77 | 0.082 |
| (median, IQR) | (10.15, 16.76) | (9.25,14.32) | |
| Neutrophil ratio (%) | 87.80 | 85.25 | 0.065 |
| (median, IQR) | (80.1,91.8) | (79.9,87.6) | |
| ALT elevation | 80 (54.4) | 25 (64.1) | 0.278 |
| Albumin<30g/L | 68 (46.9) | 28 (75.7) | **0.002** |
| Procalcitonin >5ug/L | 61 (48.4) | 11 (40.7) | 0.469 |
| Platelet <125×$10^9$/L | 62 (42.2) | 5 (12.8) | **0.001** |
| D-dime≥5mg/L | 43 (33.3) | 8 (23.5) | 0.273 |
| Creatinine elevation | 37 (25.2) | 10 (25.6) | 0.952 |
| Different departments | 14 (9.5) | 4 (10.3) | 1.0 |

*DM: diabetes mellitus; Tmax≥39°C: Peak temperature≥39°C; WBC: white blood cell; ALT: alanine transaminase; Different departments: the department of first hospitalization was different from the department of final diagnosis*

**Table S 2** | Time 2- time from initial medical consultation to diagnosis

| Variables | ≤7d (n=143) | >7d (n=44) | p-value |
|---|---|---|---|
| Male | 93 (65.0) | 25 (56.8) | 0.323 |
| Age (years) | 66.38 (+/-13.136) | 60.32 (+/-15.152) | **0.011** |
| DM | 89 (62.2) | 26 (59.1) | 0.708 |
| Hepatobiliary diseases | 61 (42.7) | 21 (47.7) | 0.553 |
| Neoplasia | 9 (6.3) | 7 (15.9) | 0.092 |
| Tmax≥39°C | 89 (63.1) | 26 (59.1) | 0.999 |
| Abdominal pain/distension | 98 (68.5) | 26 (59.1) | 0.247 |
| Anorexia | 85 (59.4) | 33 (75.0) | 0.061 |
| Shiver | 79 (55.2) | 24 (54.5) | 0.935 |
| Fatigue | 59 (41.3) | 17 (38.6) | 0.757 |
| Nausea | 60 (42.0) | 11 (25.0) | **0.043** |
| Emaciation | 11 (7.7) | 6 (13.6) | 0.368 |
| Respiratory manifestations | 44 (30.8) | 16 (36.4) | 0.487 |
| Neurological manifestations | 48 (33.6) | 12 (27.3) | 0.434 |
| Urinary manifestations | 30 (21.0) | 3 (6.8) | **0.031** |
| Cardiovascular manifestations | 6 (4.2) | 0 | 0.372 |
| Local tenderness | 65 (45.5) | 21 (47.7) | 0.791 |
| WBC ($\times 10^9$/L) | 12.48 | 13.47 | 0.728 |
| (median, IQR) | (10.14, 15.72) | (9.55, 16.81) | |
| Neutrophil ratio (%) | 87.6 | 83.95 | **0.045** |
| (median, IQR) | (81.30, 91.80) | (76.93, 90.10) | |
| ALT elevation | 83 (58.0) | 22 (50.0) | 0.347 |
| Albumin<30g/L | 75 (53.6) | 22 (51.2) | 0.782 |
| Procalcitonin >5ug/L | 60 (51.3) | 12 (32.4) | **0.045** |
| Platelet <125×$10^9$/L | 53 (37.1) | 14 (31.8) | 0.526 |
| D-dimer≥5mg/L | 38 (30.6) | 13 (32.5) | 0.826 |
| Creatinine elevation | 37 (25.9) | 11 (25.0) | 0.908 |
| Different departments | 8 (5.6) | 10 (22.7) | **0.002** |

*DM: diabetes mellitus; Tmax≥39°C: Peak temperature≥39°C; WBC: white blood cell; ALT: alanine transaminase; Different departments: the department of first hospitalization was different from the department of final diagnosis*

**Table S 3** | Time 3 - time from symptom onset to diagnosis

| Variables | ≤11d (n=146) | >11d (n=45) | p-value |
|---|---|---|---|
| Male | 94 (64.4) | 28 (62.2) | 0.792 |
| Age (years) | 65.54 (+/-13.91) | 62.40 (+/-13.20) | 0.182 |
| DM | 89 (61.0) | 28 (62.2) | 0.879 |
| Hepatobiliary diseases | 60 (41.1) | 24 (53.3) | 0.148 |
| Neoplasia | 9 (6.2) | 7 (15.6) | 0.093 |
| Tmax≥39°C | 96 (66.7) | 21 (46.7) | **0.016** |
| Abdominal pain/distension | 99 (67.8) | 26 (57.8) | 0.216 |
| Anorexia | 86 (58.9) | 36 (80.0) | **0.010** |
| Shiver | 86 (58.9) | 17 (37.8) | **0.013** |
| Fatigue | 56 (38.4) | 24 (53.3) | 0.075 |
| Nausea | 56 (38.4) | 15 (33.3) | 0.542 |
| Emaciation | 9 (6.2) | 10 (22.2) | **0.004** |
| Respiratory manifestations | 43 (29.5) | 19 (42.2) | 0.110 |
| Neurological manifestations | 45 (30.8) | 16 (35.6) | 0.552 |
| Urinary manifestations | 28 (19.2) | 5 (11.1) | 0.211 |
| Cardiovascular manifestations | 4 (2.7) | 2 (4.4) | 0.933 |
| Local tenderness | 64 (43.8) | 22 (48.9) | 0.551 |
| WBC ($\times 10^9$/L) | 12.59 | 12.93 | 0.770 |
| (median, IQR) | (10.20, 16.25) | (9.27, 15.90) | |
| Neutrophil ratio (%) | 87.65 | 83.45 | **0.020** |
| (median, IQR) | (81.37, 91.85) | (78.50, 88.72) | |
| ALT elevation | 84 (57.5) | 21 (46.7) | 0.200 |
| Albumin<30g/L | 69 (48.3) | 32 (72.7) | **0.004** |
| Procalcitonin >5ug/L | 60 (49.2) | 12 (36.4) | 0.190 |
| Platelet < $125\times 10^9$/L | 59 (40.4) | 8 (17.8) | **0.005** |
| D-dimer≥5mg/L | 40 (31.5) | 12 (29.3) | 0.788 |
| Creatinine elevation | 35 (24.0) | 13 (28.9) | 0.506 |
| Different departments | 10 (6.8) | 8 (17.8) | 0.057 |

*DM: diabetes mellitus; Tmax≥39°C: Peak temperature≥39°C; WBC: white blood cell; ALT: alanine transaminase; Different departments: the department of first hospitalization was different from the department of final diagnosis*