Pyogenic liver abscess in non-liver cancer patients and liver cancer patients treated with TACE: Etiological characteristics, treatment, and outcome analysis

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Abstract
Clinical, laboratory, and microbiological features, clinical outcomes, and pyogenic liver abscess (PLA) prognosis evaluation in non-liver cancer (Non-LC) and liver cancer patients treated with transarterial chemoembolization (TACE, LC-TACE). Clinical data of 48 consecutive PLA patients from January 2016 to December 2020 were retrospectively analyzed. Mortality between two PLA patient groups were compared, and mortality risk factors were evaluated. A total of 48 PLA patients (31 males and 17 females) from January 2016 to December 2020 met the study’s inclusion criteria. There were 32 and 16 patients in the Non-LC and LC-TACE groups, respectively. Positive pus culture rate in the Non-LC group was 87.5% and positive pus culture rate in LC-TACE group was 81.3%. In the Non-LC group, 28 patients improved after treatment, 1 patient did not improve, and 3 patients died during hospitalization, with a 9.4% mortality rate. In the LC-TACE group, nine patients improved after treatment, three patients did not improve, and four patients died during hospitalization, with a 25% mortality rate. PLA of the Non-LC group and the LC-TACE group were different in terms of pathogenic bacteria and cure time, and so on. A more comprehensive treatment should be considered for PLA after TACE.

KEYWORDS
liver cancer, pathogenic bacteria, pyogenic liver abscess, transarterial chemoembolization

1 | INTRODUCTION
Pyogenic liver abscess (PLA) is an intrahepatic infection that accounts for about 80% of all liver abscesses and is caused by supplicative bacteria that invade the liver. This is commonly seen in malnourished and immunocompromised patients.\textsuperscript{1,2} Abscess occurs when normal liver clearance mechanisms are overwhelmed or when the system fails. Aplastic cholangitis and appendicitis are recognized PLA causes, while the PLA frequency caused by cholangitis and/or appendicitis have decreased dramatically with effective imaging tools use and early administration of appropriate antibiotics.\textsuperscript{3} A recent study\textsuperscript{4} indicated that PLA incidence has more than tripled in the past 35 years, suggesting other reasons for the increase.
Transarterial chemoembolization (TACE) has become a popular unresectable liver cancer treatment and has been considered as an effective treatment modality. It can target multiple liver cancer lesions in a single treatment and repeatedly used in the same patient. There are some life-threatening side effects after TACE, including liver abscesses. Similar to post-embolization syndrome, the most common complication after TACE, PLA also presents with fever and right upper quadrant pain. However, unlike post-embolization syndrome, PLA requires aggressive interventions, such as appropriate antibiotics and percutaneous catheter drainage. Therefore, PLA caused by TACE in liver cancer patients should be monitored closely.

TACE can lead to PLA formation, which may be caused by many factors: (1) bacterial infection superimposed upon embolization and necrosis; (2) intraoperative aseptic practice non-adherence; (3) immunosuppression on patients undergoing chemotherapy; (4) diabetic patients. No study has analyzed and compared the clinical characteristics and causative pathogenic characteristics of PLA in non-liver cancer patients and liver cancer patients treated with TACE, although many studies have reported the incidence, risk factors, and treatment methods of PLA after TACE.

Hence, a retrospective study of PLA patients was conducted, including comparing the demographic characteristics, symptoms, clinical manifestations, laboratory and microbial pathogenic bacteria, clinical outcomes, and PLA patients’ mortality (non-liver cancer and TACE treatment groups) between two groups. Meanwhile, factors related to the mortality were also analyzed.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and the institutional review board of the local hospital (UHCT-IEC-SOP-023-04-01) gave their approval.

All PLA patients’ medical and microbiological records from January 2016 to December 2020 was retrospectively analyzed. A total of 48 patients who met the following criteria were included in our study: (1) PLA patients confirmed by percutaneous drainage or percutaneous aspiration; (2) imaging demonstrated liquefied abscess cavity without rupture; (3) laboratory tests such as leukocytes, neutrophils and other indicators significantly increased; (4) no other extra-hepatic abdominal abscesses were found. Exclusion criteria were: (1) incomplete clinical information; (2) amoebic liver abscess or infected liver cyst; (3) general infection; (4) Severe mental disorders are not compatible with treatment.

PLA patients meeting the inclusion criteria for this study were divided into two groups: patients with liver cancer receiving TACE (LC-TACE group) and patients without liver cancer (Non-LC group). Among them, there were 16 patients (mean age 58.4 ± 12.6 years, 41–78 years) in the LC-TACE group and 32 patients (mean age 55.7 ± 13.9 years, 29–78 years) in the Non-LC group.

2.2 | Treatments

All patients were given an intravenous empirical broad-spectrum antibiotic drip until the availability of pus culture sensitivity report after PLA diagnosis. Ornidazole, meropenem, cefoperazone sodium, and sulbactam sodium are the commonly used antibiotics in our center. Invasive procedures such as percutaneous catheter drainage (PCD) were also one of the first treatment options to be considered in addition to intravenous antibiotics. In general, a ≥3 cm abscess characterized by cystic appearance should be considered a drainage indication. PCD was performed under full aseptic precaution. The 21G Chiba needle was punctured into the abscess cavity under ultrasound guidance after local anesthesia. Pus was sucked out with a syringe. Pus color and properties were observed and was sent for culture and sensitivity analysis. As much pus as possible was drained. A 10-F multipurpose drainage catheter was then placed into the abscess cavity and a drainage bag was attached (Figures 1 and 2). Drainage volume was measured daily and the catheter flushed with normal saline regularly to prevent clogging.

2.3 | Microbiologic sample collection and cultivation

PLA patients’ blood and pus were extracted for microbial cultures and all samples were cultured under aerobic and anaerobic conditions. Blood samples from patients were collected under the following conditions: (1) body temperature >38°C or <36°C; (2) patient with chills; (3) leukocyte count >10 × 10⁹/L or <4 × 10⁹/L.

2.4 | Clinical data and definitions of outcomes

Demographic characteristics, etiological factors, co-existing conditions, abscess number and location, laboratory examination, diagnosis and treatment methods, treatment response, and PLA patients’ mortality were analyzed. The “cure” criteria were: (1) normal body temperature for at least 3 days; (2) normal routine blood and inflammatory indexes; (3) <5 ml of drainage of fluid per day. Meanwhile, the drainage catheter removal time was defined as the cure time. “Uncured” was defined as no significant improvement or further clinical symptom deterioration after treatment or two abnormal items in laboratory examination or imaging results despite improvement in symptoms.

2.5 | Statistical analysis

SPSS software (version 24.0; IBM, Armonk, NY) was used for analyses. Quantitative data were represented by mean ± standard deviation and discrete variables were represented by proportion. The t-test, chi-square test, and ANOVA test were used to compare quantitative or discrete variables between the groups. Factors associated
FIGURE 1  A 65-year-old male with type 2 diabetes was admitted with high fever, abdominal pain, and malignant vomiting with a maximum temperature of 39.6°C. The CT scan showed a 7.6 cm diameter hypodense shadow with gas in the left lateral lobe of the liver (A). The abscess was treated with antibiotics and drained (B). Three months after treatment, CT showed the absence of low-density shadows (C).

FIGURE 2  A 30-year-old male HCC patient developed high fever, chill, and abdominal pain 3 days after TACE, with a maximum body temperature of 39.4°C. The CT scan indicated a large low-density shadow in the right lobe of the liver (A). The abscess was actively drained while antibiotic treatment was given (B). The CT scan 1 week after drainage demonstrated that the drainage tube was in good position (C).
with mortality were analyzed using binary logistic regression analysis. The p < 0.05 (two-tailed) was considered statistically significant.

3 | RESULTS

3.1 | Study population and patient characteristics

A total of 48 PLA patients from January 2016 to December 2020, including 31 males and 17 females, were included in this study after excluding patients who did not meet the inclusion criteria. There were 32 and 16 patients in the Non-LC and LC-TACE groups, respectively (Table 1). In the Non-LC group, 17 patients had diabetes, while only one in the LC-TACE group had diabetes, showing a statistically significant difference between the two groups (p = 0.002). There was no statistically significant difference between the two groups (p > 0.05), although the maximum body temperature (39.0°C ± 0.8°C vs. 38.8°C ± 1°C) and maximum abscess diameter (7.6 ± 3.8 vs. 7.3 ± 2.6 cm) of patients in the LC-TACE group were higher than those in the Non-TACE group. Most of the PLA in both groups were located in the right lobe of the liver and most of the PLA were single abscess. Fever and chills were the most common symptom in both groups, followed by abdominal pain. Shock was experienced by two patients in the Non-LC group and three patients in the LC-TACE group.

3.2 | Microbiologic identifications and laboratory examinations

The positive pus culture rate was 87.5% in the Non-LC group and 81.3% in the LC-TACE group. There was no significant statistical difference between the two groups (p = 0.563; Table 2). In the Non-LC group, among the 28 positive cases, 50% of the pathogens were Klebsiella pneumoniae, followed by Viridans streptococcus, Escherichia coli, and Pseudomonas aeruginosa; while in the LC-TACE group, among the 13 positive cases, the most common pathogens were...
E. coli, followed by Staphylococcus aureus, V. streptococcus, and Proteus mirabilis, and only one case with K. pneumonia. The differences were statistically significant between the two groups (p = 0.009).

Detailed antibiotic regimens for the two groups are provided in Tables S1 and S2.

Compared with the LC-TACE group, patients in the Non-LC group had higher inflammatory biomarkers, including leukocytes (13.5 ± 6.8 G/L vs. 11.5 ± 6.8 G/L, p = 0.4), neutrophils (11.7 ± 6.7 G/L vs. 10.2 ± 6.8 G/L, p = 0.509), C-reactive protein (142.7 ± 76.6 mg/L vs. 121.6 ± 56.7 mg/L, p = 0.388), and procalcitonin (20.1 ± 28.8 μg/L vs. 6.4 ± 7.4 μg/L, p = 0.102), but there was no statistically significant difference between the two groups. After treatment of PLA, C-reactive protein (Non-LC group 89.4 ± 64.1 mg/L vs. 80.3 ± 41.5 mg/L, p = 0.644) and procalcitonin (Non-LC group 7.9 ± 21.1 μg/L vs. 2.3 ± 3.5 μg/L, p = 0.352) were significantly decreased in both groups, and there was no significant difference between the two groups. Meanwhile, alanine transaminase (ALT, 65.4 ± 47.6 U/L vs. 48.7 ± 35.7 U/L, p = 0.275) and aspartate aminotransferase (AST, 55.7 ± 50.0 U/L vs. 47.9 ± 23.4 U/L, p = 0.601) in the Non-LC group were higher than those in the LC-TACE group, while albumin (28.2 ± 5.1 g/L vs. 29.6 ± 3.5 g/L, p = 0.334) and total bilirubin (22.3 ± 17.0 μmol/L vs. 24.4 ± 14.8 μmol/L, p = 0.717) were lower than those in the LC-TACE group, and there was no significant difference in liver function between the two groups. Although PLA patients had elevated inflammatory biomarkers and abnormal liver function, the mean renal function including blood urea nitrogen and creatinine were normal in both groups (Table 3).

### 3.3 Treatment outcomes and risk factors for mortality

All patients were treated with intravenous sensitive antibiotics while receiving PCD. Of the patients in the Non-LC group, 62.5% (20/32) received combined antibiotic treatment, that is, third-generation cephalosporins or carbapenems combined with fluoroquinolones and metronidazole, and only 12 patients received single antibiotic treatment. Of the patients in the LC-TACE group, 62.5% (10/16) were treated with combination antibiotics and 6 patients were treated with single antibiotic.

In the Non-LC group, 28 patients improved after treatment, 1 patient did not improve, and 3 patients died during hospitalization, with a mortality rate of 9.4%. In the LC-TACE group, 9 cases improved after treatment, 3 cases did not improve, and 4 cases died during hospitalization, with a mortality rate of 25%. The 2-week, 1-month, and 3-month cumulative mortality rates in Non-LC group were 3.1%, 9.4%, and 9.4%, respectively. In addition, the 2-week, 1-month, and 3-month cumulative mortality rates in the LC group were 12.5%, 12.5%, and 12.5%, respectively. There were no significant differences in 2-week, 1-month, 3-month and overall mortality between the two groups (p = 0.547, 0.311, 0.311, and 0.068, respectively). Univariate analysis (Table 4) demonstrated that leukocyte count (HR, 1.223; 95% CI: 1.040, 1.439, p = 0.015), neutrophils count (HR, 1.220; 95% CI: 1.041, 1.431, p = 0.014), and total bilirubin (HR, 1.042; 95%CI: 0.993, 1.093, p = 0.095) were associated with mortality. However, when these three factors were included in the multivariate analysis (Table 5), there was no independent prognostic factor associated with mortality. In addition, the results of univariate and multivariate analyses of mortality in two groups were shown in Tables S3–S6. The cure time of the Non-LC group was 37.4 ± 23.1 days (6–90 days), while that of the LC-TACE group was 91.5 ± 49.7 days (19–180 days), with a statistically significant difference between the two groups (p < 0.001).
This is the first large population-based retrospective study to investigate the clinical and microbiological PLA patients' characteristics in the Non-TACE and LC-TACE groups, as well as risk factor evaluation that may affect PLA patients' mortality. Currently, many studies\textsuperscript{17,18,19} have only reported the clinical and microbiological PLA patients' characteristics after TACE. However, this study comprehensively compared the differences between the Non-LC group and the LC-TACE group, providing a new perspective on the mortality, clinical, and epidemiological PLA characteristics.

In this study, the average patient age in both groups was greater than 55 years old. Most PLA patients in the two groups in this study were middle-aged and elderly similar to other studies,\textsuperscript{15,17} which suggested that PLA could be considered as a geriatric disease. A series of reports\textsuperscript{17–19} have all confirmed the relationship between diabetes and PLA, which may be able to explain that 53.1% of the patients in the Non-LC group had diabetes, while only one patient (6.3%) in the TACE group had diabetes. This indicates there are significant differences between the two groups in terms of comorbidities. In this study, the most common patient symptoms in the two groups were fever and chills, followed by abdominal pain, which is consistent with other studies. The most common PLA patients' symptoms in the two groups were fever and chills, followed by abdominal pain, which was basically consistent with previous studies.\textsuperscript{20,21}

TACE can improve survival in liver cancer patients by combining targeted chemotherapy with ischemic necrosis caused by arterial embolization.\textsuperscript{22} However, PLA is a serious postoperative complication, which deserves our attention. It is reported that the mortality rate of PLA patients after TACE ranged from 13.3% to 50%, in this study, the mortality rate of patients in the LC-TACE group was 25%, which was consistent with previous report.\textsuperscript{23} The mortality rate of patients in the LC-TACE group was significantly higher than that in the Non-LC group. Unlike other studies,\textsuperscript{1} multivariate analysis in this study revealed that no risk factors were associated with mortality. Meanwhile, the cure time of patients in the LC-TACE group was also significantly longer than that in the Non-LC group, which may be due to the following reasons:\textsuperscript{7,24,25} (1) Both tumor and TACE can lead to immunodeficiency in patients in the LC-TACE group, which can lead to patient death and prolonged treatment time, meanwhile, the hepatic ischemia and hypoxia induced by TACE provide a good environment for the growth of bacteria; (2) Some patients with fever after TACE were mistaken for postembolism syndrome, and dexamethasone was routinely applied, which accelerated the progress of the PLA; (3) Patients are unable to receive antitumor therapy during the treatment of PLA, leading to the progression of liver cancer, which hastens the patient's death. At the same time, the embolization leads to capillary blockage, and antibiotics cannot reach the abscess cavity. This may also explain the higher mean body temperature and more shock cases in the LC-TACE group. Therefore, we should attach great importance to the PLA after TACE and actively conduct abscess drainage.

| TABLE 4 | Univariate analysis of prognostic factors for mortality of PLA patients in two groups |
| Variables | HR (95% CI) | p value |
|----------------|-------------------------------|----------|
| Age (y) | 1.017 (0.942, 1.098) | 0.663 |
| Gender | | |
| Female | 1 | |
| Male | 0.333 (0.048, 2.297) | 0.265 |
| Abscess location | | |
| Bilobar involvement | 1 | |
| Right lobe | 0.087 (0.004, 1.981) | 0.126 |
| Left lobe | 0.222 (0.009, 5.275) | 0.352 |
| Number of abscess | | |
| >1 | 1 | |
| 1 | — | 0.999 |
| Maximal abscess diameter (cm) | 1.093 (0.798, 1.498) | 0.580 |
| Body temperature, °C | 0.825 (0.297, 2.291) | 0.712 |
| Pus culture | | |
| No bacteria | 1 | |
| Positive growth | 0.552 (0.049, 6.254) | 0.631 |
| WBCc (X109/L) | 1.223 (1.040, 1.439) | 0.015 |
| Neutrophil count (X109/L) | 1.220 (1.041, 1.431) | 0.014 |
| ALT (IU/L) | 0.996 (0.972, 1.019) | 0.715 |
| AST (IU/L) | 0.992 (0.961, 1.023) | 0.590 |
| Prothrombin time, INR | 1.506 (0.830, 2.734) | 0.178 |
| Total bilirubin (µmol/L) | 1.042 (0.993, 1.093) | 0.095 |
| BUN (mmol/L) | 1.133 (0.917, 1.399) | 0.247 |
| Cr (µmol/L) | 1.019 (0.993, 1.046) | 0.154 |
| CRP (mg/L) | 0.985 (0.966, 1.003) | 0.109 |
| ALP (U/L) | 0.998 (0.991, 1.006) | 0.665 |
| PCT (µg/L) | 0.978 (0.915, 1.046) | 0.519 |
| Albumin (g/dl) | 0.867 (0.692, 1.086) | 0.213 |

| Group | | |
|----------------|-------------------------------|----------|
| LC-TACE | 1 | |
| Non-LC | 0.290 (0.042, 2.011) | 0.210 |

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CI confidence interval; Cr, creatinine; CRP, cross-reacting protein; HR, hazard ratio; LC-TACE, liver cancer receiving TACE; Non-LC, non liver cancer; PCT, procalcitonin; PLA, pyogenic liver abscess; WBCc, white blood cell count.

| TABLE 5 | Multivariate analysis of prognostic factors for mortality of PLA patients in two groups |
| Variables | HR (95% CI) | p value |
|----------------|-------------------------------|----------|
| WBCc (X109/L) | 2.098 (0.298, 14.757) | 0.457 |
| Neutrophil count (X109/L) | 0.585 (0.086, 3.982) | 0.584 |
| Total bilirubin (µmol/L) | 1.042 (0.984, 1.104) | 0.161 |

Abbreviations: CI confidence interval; HR, hazard ratio; PLA, pyogenic liver abscess; WBCc, white blood cell count.
In this study, the inflammatory biomarkers (leukocyte, neutrophils, C-reactive protein, and procalcitonin) in the Non-LC group were higher than those in the LC-TACE group, suggesting that tumor itself may hinder the rise of inflammatory biomarkers. In addition, C-reactive protein and procalcitonin were significantly reduced in both groups after treatment without statistical difference, indicating that there was no significant difference in overall outcomes between the two groups using similar treatment regimens. Therefore, the bacterial etiology of liver abscesses may be different between the two groups, but the treatment of PLA is not substantially different in nature. Furthermore, AST, ALT and albumin in the Non-LC group were worse than those in the LC-TACE group, which indicated that PLA had a great influence on the liver function of patients.

It is reported that the prevalence of PLA caused by *K. pneumoniae* is on the rise worldwide. In this study, the PLA of 50% of patients in the Non-LC group was caused by *K. pneumoniae*, while only 1 case in the LC-TACE group was caused by *K. pneumoniae*. Different from the Non-LC group, the most common pathogen of pus culture in the LC-TACE group was *E. coli* (30.8%), which was consistent with the often encountered bacterium of PLA after TACE reported by other studies. This indicates that the pathogenic bacteria of PLA after TACE are different from those of PLA in Non-liver cancer patients.

This study has its limitations. This was a single-center retrospective study with inherent flaws and a limited sample size. Therefore, it is necessary to conduct a multi-center large-sample study to evaluate the clinical characteristics, microbiological characteristics and treatment outcomes of the two groups of patients.

### 5 | CONCLUSIONS

PLA treatment should be more comprehensive due to factors such as liver cancer and TACE for PLA patients after TACE, and we should attach great importance to the PLA after TACE and actively conduct abscess drainage.

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### CONFLICT OF INTEREST

All authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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