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Epidemiological, clinical and microbiological characteristics of patients with biliary tract diseases with positive bile culture in a tertiary hospital

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Abstract

Purpose The prevalence of biliary tract diseases, which are common gastrointestinal disorders, is steadily rising. If it progresses to sepsis or septic shock, it can endanger the patient's life. Therefore, it is crucial to promptly diagnose bacterial infection in individuals suffering from biliary diseases and comprehend the risk factors associated with infection. The objective of this study was to examine the types of bacteria present in the bile of patients with biliary tract diseases, assess any alterations in their susceptibility to antimicrobial agents, and identify the risk factors contributing to the development of infection in these patients.

Patients and methods From June 2019 to November 2022, 317 patients of biliary tract diseases with positive bile culture were included in this hospital-based descriptive analysis. The hospital's computerized medical records were used to collect data on demographic information (including gender, age, and occupation), laboratory, and clinical findings, physical examination results, comorbidities, basic diseases, treatment history, complications, and in-hospital outcomes. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) principles.

Results Of the 317 patients with positive biliary tract diseases, 247 had benign diseases and 70 had malignant diseases. Patients with benign disease experienced a higher prevalence of statistically significant symptoms such as abdominal pain (81.4% vs. 57.1%, $P=0.000$), nausea (31.2% vs. 14.3%, $P=0.005$), vomiting (30.0% vs. 12.9%, $P=0.004$), and chills (10.9% vs. 2.9%, $P=0.039$), while jaundice (12.6% vs. 37.1%, $P=0.000$) was more common in patients with malignant disease. At the species level, *Escherichia coli* (105; 40.5%), *Klebsiella pneumoniae* (41; 15.8%), and *Pseudomonas aeruginosa* (30; 11.6%) were the most commonly found Gram-negative bacterial strains in biliary tract infection. *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were most susceptible to tigecycline, ertapenem and ceftazidime/avibactam, respectively.

Conclusion Gram-negative bacteria are the most commonly isolated biliary bacteria. Clinical doctors should pay attention to patients with malignant diseases with low hemoglobin, high total bilirubin and high alkaline phosphatase. Carbapenems, tigecycline, and minocycline are the recommended antibiotics for *Enterobacteriaceae*. In

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recent years, the proportion of enterococcus has gradually increased, and clinical attention should be paid to enterococcus infection. Linezolid and vancomycin were recommended for the treatment of *Enterococci* infections. Overall, this work can provide reference for clinical diagnosis, treatment and effective interventions.

Keywords Biliary tract diseases, Bile culture, Microbiological characteristics, Epidemiological

Introduction

Biliary diseases are common digestive system disorders and include cholangiocarcinoma, gallstones, gallbladder carcinoma, and gallbladder polyps. Their incidence is gradually increasing in the general population [1]. The biliary tract is usually sterile, and its colonization and/or infection is usually due to changes in bile flow caused by anatomical disruption, changes in intestinal structure, or the use of endovascular devices [2]. Merging biliary tract infection (BTI) is straightforward under the appropriate conditions [1]. It is a common cause of intra-abdominal infections and life-threatening complications, especially in the elderly [3]. Biliary obstruction is the most important cause of biliary tract infection and obstruction in the duct leads to increased bile duct pressure. The increase in pressure allows bacteria to enter the systemic circulation via the hepatic sinus [4]. Hepatocytes synthesize bile, which is subsequently stored and concentrated in the gallbladder. The primary role of this entity is to enhance the assimilation of lipophilic compounds like fat and vitamins, eliminate cholesterol, and maintain the balance of microorganisms in the intestines through its bactericidal properties [5]. Biliary microbiome and duodenal microbiome have relatively high similarity [6]. Bile is typically devoid of microorganisms, although bacterial growth can occur in the bile of certain asymptomatic individuals. This can be attributed to contamination either from the duodenum via upward movement or from blood-borne sources through the portal vein [7]. Local biliary tract infection can progress into advanced disease with sepsis and multiple organ dysfunction syndrome [8]. Biliary tract infection is a common cause of bacteremia and is associated with high mortality [9, 10]. Bile samples have become easily accessible since the introduction of biliary decompression techniques. For these patients, the only feasible treatments are early percutaneous transhepatic biliary drainage (PTBD) and surgery. Endoscopic retrograde cholangiopancreatography (ERCP) is the most effective method for achieving biliary decompression when compared to percutaneous and surgical decompression. Many patients have biliary drainage tubes for various indications [11, 12].

Studies have shown an increased prevalence of hospital-acquired and community-acquired infections, the most common of which is *E. coli*, possibly due to its production of broad-spectrum beta-lactamase (ESBL) [13–15]. In addition, microorganisms exhibit regional and temporal changes. Treatment options include empirical antibiotic or antifungal therapy and subsequent biliary drainage. However, the process of culturing bile requires a significant amount of time. Antibiotic therapy in clinical practice cannot be postponed until the findings of culture are obtained. Hence, it is crucial to have a comprehensive knowledge of prevalent infections and their specific susceptibility patterns in the local area to make appropriate and prompt choices for empirical antibiotic therapy [16, 17].

There is a lack of research regarding the microbiology and antibiotic susceptibility of biliary tract infections in our region. However, this type of epidemiological data can be utilized to provide guidelines for prescribing appropriate antibiotics to patients with biliary tract diseases. It is important to take into account the microbial resistance that is specific to the local area while determining treatment options [4, 8]. Therefore, the purpose of this study was to analyze the types of bile microorganisms in patients with biliary tract diseases, the changes of antimicrobial susceptibility and the risk factors associated with it.

Material and methods

Patients and study design

This descriptive analysis included all patients with biliary tract diseases and positive bile cultures at the First Affiliated Hospital of Anhui Medical University in Hefei, China, between June 2019 and November 2022. The patient had any of the following biliary tract infections or related conditions: gallstones, cholangitis, cholecystitis, common bile duct stones, intrahepatic duct stones, cholangiocarcinoma, choledochal cyst, gallbladder cancer, gallbladder polyps, or biliary stricture. Samples of were taken from 317 individuals who had biliary surgery, percutaneous transhepatic biliary drainage, therapeutic endoscopic retrograde cholangiopancreatography, or other biliary procedures. The bile samples was inoculated on blood Agar and McConkey Agar medium, and the positive strains were analyzed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS; BioMérieux, France). The samples were isolated, cultivated, and inoculated strictly in compliance with the People's Republic of China's Basic technical requirements for clinical microbiological

investigation (WS/T805-2022), which are standards set by the health industry.

A total of 427 pathogens were identified from the bile samples of 317 patients throughout the specified time. The patients were categorized into two groups: one consisting of individuals with benign diseases and the other consisting of individuals with malignant diseases. Patients with malignant diseases are those diagnosed with cholangiocarcinoma, gallbladder cancer, pancreatic cancer, liver cancer, stomach cancer, duodenal cancer and other cancers that compress the biliary tract. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) principles.

Data collection

Data regarding demographic characteristics (including gender, age, and occupation), laboratory, and clinical test results, physical examination findings, presence of other medical comorbidities, basic diseases, previous history, treatment history, complications, and outcomes during hospitalization (such as discharge clinical status and length of stay) were extracted from the electronic medical records of the hospital.

Statistical analysis

The statistical analysis was performed using version 25.0 of Statistical Package for the Social Sciences (SPSS). The mean ± standard deviation (SD) of continuous variables, assuming a normal distribution, were used for comparison using the Student's *t*-test. On the other hand, for variables without a normal distribution, medians [interquartile range (IQR)] were used and compared using the Mann–Whitney *U*-test. For categorical variables, the data were presented as n (%) and compared using Fisher's exact test. With a two-tailed *p*-value of less than 0.05, the results were deemed to be statistically significant.

Results

Epidemiological and clinical characteristics

Between June 2019 and November 2022, data was gathered on 317 patients diagnosed with biliary tract disease who had positive bile cultures in the First Affiliated Hospital of Anhui Medical University. Patients were categorized into two groups based on the presence of biliary illnesses: benign disease (247 cases) and malignant disease (70 cases). Out of the 317 bile samples, 247 were obtained from patients diagnosed with non-cancerous conditions like cholecystitis, gallstones, and gallbladder obstruction. The remaining seventy bile samples were taken from individuals who had been given a cancer diagnosis, including pancreatic cancer, liver cancer, cholangiocarcinoma, gastric cancer, duodenal cancer, and gallbladder cancer.

The study revealed that the mean age of patients admitted to the hospital was 62.7 years, with a minimum age of 18 years and a maximum age of 97 years. Furthermore, the mean duration of hospitalization was 19 days. The studied patients had a majority of women, specifically 181 female patients were present in total. The most frequently observed clinical symptoms included abdominal pain, abdominal distension, fever, nausea, vomiting, jaundice, and chills. Patients with benign disease experienced a higher prevalence of statistically significant abdominal pain (81.4% vs. 57.1%, $P=0.000$), nausea (31.2% vs. 14.3%, $P=0.005$), vomiting (30.0% vs. 12.9%, $P=0.004$), and chills (10.9% vs. 2.9%, $P=0.039$). On the other hand, patients with malignant disease had a higher prevalence of jaundice (12.6% vs. 37.1%, $P=0.000$). Patients with chills were often accompanied by fever. The primary complications were diabetes, hypertension, hepatic insufficiency, cerebral infarction, and heart disease. During patient admission, 156 individuals underwent cholecystectomy, 143 and 151 patients had a prior history of biliary surgery and biliary disease, respectively. The two groups exhibited statistical significance in patients with a previous occurrence of biliary disease (52.6% vs. 30.0%, $P=0.001$), a history of biliary surgery (49.8% vs. 28.6%, $P=0.002$), and percutaneous transhepatic cholangio drainage (3.2% vs. 22.9%, $P=0.000$). A total of 95 patients presented multiple bacterial infections. A total of 29 patients were diagnosed with bloodstream infections, out of which 8 patients experienced septic shock and 5 patients had multiple bacterial infections in their bloodstream. There were 21 patients with the same strain of blood infection and bile infection. The bacteria with the highest infection rates in the blood were *Escherichia coli*, with 13 strains, *Klebsiella pneumoniae*, with 6 strains, and *Pseudomonas aeruginosa*, with 3 strains. Only 29 patients with biliary tract disease had bloodstream infection, 21 patients with biliary-tract bloodstream infection, and 5 patients with multi-bacterial infection in blood. There were 8 patients with septic shock due to bloodstream infection. The epidemiological and clinical characteristics of the 317 patients with biliary tract infections are summarized in Table 1.

Microbiological characteristics

As shown in Fig. 1, a total of 427 strains were obtained from 317 clinical bile specimens. Out of the total number of strains, 153 were classified as Gram-positive bacteria, accounting for 35.8% of the total. Similarly, 259 strains were categorized as Gram-negative bacteria, making up 60.7% of the total. Lastly, 15 strains were identified as fungus, representing 3.5% of the total. At the family level, the most common isolated pathogens were *Enterobacteriaceae* (181; 42.4%) and

Table 1 Epidemiological and clinical characteristics in patients with benign disease and malignant disease

	Total (*N* = 317)	Benign disease(*N* = 247)	Malignant disease (*N* = 70)	*P* value
Gender				
Male	136 (42.9)	104 (42.1)	32 (45.7)	0.590
Female	181 (57.1)	143 (57.9)	38 (54.3)	0.590
Median age in years	62.7	62.5	63.1	
Mean hospitalization time (day)	19	18.4	21.9	
Clinical manifestations				
Fever	182 (57.4)	142 (57.5)	40 (57.1)	0.959
Abdominal pain	241 (76.0)	201 (81.4)	40 (57.1)	0.000
Abdominal distension	34 (10.7)	23 (9.3)	11 (15.7)	0.126
Nausea	87 (27.4)	77 (31.2)	10 (14.3)	0.005
Vomiting	83 (26.2)	74 (30.0)	9 (12.9)	0.004
Chills	29 (9.1)	27 (10.9)	2 (2.9)	0.039
Jaundice	57 (18.0)	31 (12.6)	26 (37.1)	0.000
Operation				
Cholecystectomy[a]	156 (49.2)	124 (50.2)	33 (47.1)	0.651
ERCP	41 (12.9)	31 (12.6)	10 (14.3)	0.703
PTCD	24 (7.6)	8 (3.2)	16 (22.9)	0.000
ENBD	16 (5.0)	13 (5.3)	3 (4.3)	0.984
History of biliary tract diseases	151 (47.6)	130 (52.6)	21 (30.0)	0.001
History of biliary tract surgery[b]	143 (45.1)	123 (49.8)	20 (28.6)	0.002
Comorbidities				
Diabetes	34 (10.7)	24 (9.7)	10 (14.3)	0.275
Hypertension	55 (17.4)	42 (17.0)	13 (18.6)	0.760
Hepatic insufficiency	14 (4.4)	11 (4.5)	3 (4.3)	1.000
Cerebral infarction	21 (6.6)	16 (6.5)	5 (7.1)	1.000
Heart disease	13 (4.1)	11 (4.5)	2 (2.9)	0.800
Bacterial infection				
Multi-bacterial infection	95 (30.0)	75 (30.4)	20 (28.6)	0.773
Bloodstream infections	29 (9.1)	22 (8.9)	7 (10.0)	0.779
Septic shock	8 (2.5)	8 (3.2)	0 (0.0)	0.207
Multi-bacterial infection in blood	5 (1.6)	5 (2.0)	0 (0.0)	0.590
biliary-tract bloodstream infection	21 (6.6)	18 (7.3)	3 (4.3)	0.586

Cholecystectomy[a], patient underwent cholecystectomy during admission; History of biliary tract surgery[b], 30 days before

Enterococcusceae (134; 31.4%). At the species level, *Escherichia coli* (105; 40.5%), *Klebsiella pneumoniae* (41; 15.8%), *Pseudomonas aeruginosa* (30; 11.6%), and *Enterobacter cloacae* (14; 5.4%), were the most commonly found Gram-negative bacterial strains. Similarly, *Enterococcus faecium* (51; 33.3%), *Enterococcus faecalis* (48; 31.4%), *Enterococcus casseliflavus* (18; 11.8%), and *Enterococcus gallinarum* (9; 5.9%). were the most frequently found strains of Gram-positive bacteria. Out of the 15 fungi identified, the majority (60%) were *Candida albicans*, while the remaining 6 were identified as *Candida tropicalis* (13.3%), *Candida krusei* (6.7%), *Candida parapsilosis* (13.3%), and *Candida metapsilosis* (6.7%). In the current study, *Escherichia coli* (26.4%), *Enterococcus faecium* (12.8%), *Enterococcus faecalis* (11.0%), *Klebsiella pneumoniae* (10.1%) and *Pseudomonas aeruginosa* (7.7%) were the most frequently found bacteria in the bile cultures of patients with benign diseases. *Escherichia coli* (17.8%), *Enterococcus faecalis* (12.2%), *Enterococcus faecium* (8.9%), *Klebsiella pneumonia*e (7.8%), and *Pseudomonas aeruginosa* (4.4%) were the most common bacteria found in the bile of patients with malignant diseases. No significant difference occurred between the two groups. Among the *Enterobacteriaceae* isolates, 61 of them were found to have microorganisms that produce extended-spectrum β-lactamase (ESBL). Out of all the isolates, there were a total of 20

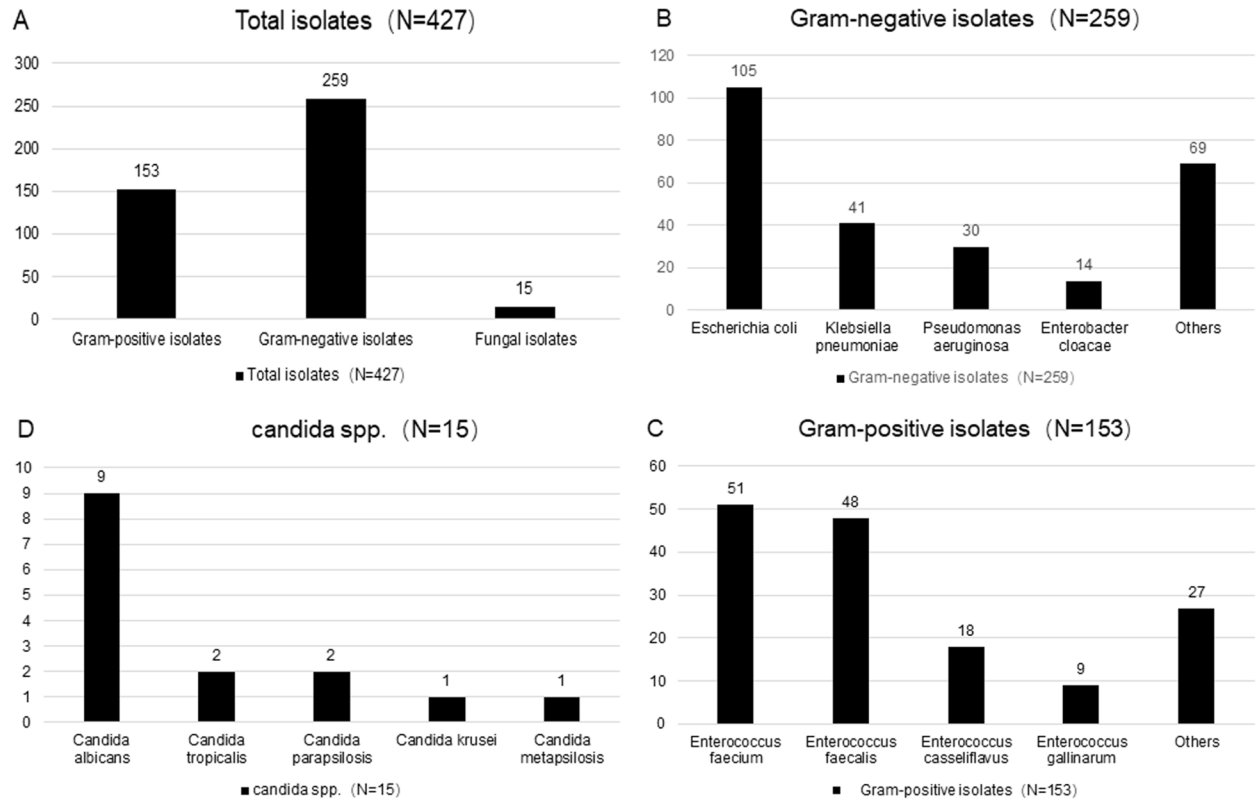

Fig. 1 Microbiological distribution. The number of bacteria and fungal isolated from bile samples. **A** Total; **B** Gram-negative isolates; **C** Gram-positive isolates; **D** Candida spp

Gram-negative bacilli that were resistant to carbapenem. One isolate was methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant (VRE) was detected in 17 *Enterococcus* isolates. Table 2 demonstrates that there was no statistically significant difference in the prevalence of multi-drug resistance bacteria between the two groups.

Table 2 Organisms and multidrug resistant isolates from benign disease and malignant disease

	Total (*N* = 427)	Isolates from patients with benign diseases (*N* = 337)	Isolates from patients with malignant diseases (*N* = 90)	*P* value
Organisms				
Escherichia coli	105 (24.6)	89 (26.4)	16 (17.8)	0.091
Klebsiella pneumoniae	41 (9.6)	34 (10.1)	7 (7.8)	0.509
Pseudomonas aeruginosa	30 (7.0)	26 (7.7)	4 (4.4)	0.281
Enterococcus faecium	51 (11.9)	43 (12.8)	8 (8.9)	0.314
Enterococcus faecalis	48 (11.2)	37 (11.0)	11 (12.2)	0.740
Enterococcus casseliflavus	18 (4.2)	15 (4.5)	3 (3.3)	0.862
Multidrug resistant organisms				
ESBL	61 (14.3)	49 (14.5)	12 (13.3)	0.771
MRSA	1 (0.2)	0 (0.0)	1 (1.1)	0.478
CRE	20 (4.7)	18 (5.3)	2 (2.2)	0.335
VRE	17 (4.0)	13 (3.9)	4 (4.4)	1.000

ESBL Extended-spectrum β-lactamase, *MRSA* Methicillin-resistant Staphylococcus aureus, *CRE* Carbapenem-resistant Enterobacteriaceae, *VRE* Vancomycin resistant Enterococcus

Laboratory findings

White blood cell (WBC) counts, platelet count, total bilirubin (TBIL), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) levels were elevated in patients with malignant diseases compared to those with benign diseases. Conversely, the levels of hemoglobin (Hb), serum creatinine and C-reactive protein (CRP) were lower in patients with malignant diseases. Hb ($P=0.000$), TBIL ($P=0.000$) and ALP ($P=0.006$) were statistically significant. However, there was no significant difference in the results of other laboratory tests between benign and malignant diseases ($P>0.05$; Table 3).

Drug susceptibility results

Antibiotic susceptibilities for Gram-negative bacilli are shown in Table 4. The susceptibility of the most common isolates to antibiotics was analyzed in this study. The resistance rates of isolated *E. coli* to cefazolin, ampicillin and piperacillin were 47/64 (73.4%), 47/64 (73.4%) and 47/64 (73.4%), respectively. Tigecycline exhibited the highest level of activity against *E. coli* (100.0%). This was followed by ertapenem at 97.8%, imipenem at 96.2%, amikacin at 95.2%, and meropenem at 94.7%. Ampicillin resistance was observed in 95% of *Klebsiella pneumoniae* strains. Ertapenem was active against 100% of *Klebsiella pneumoniae* isolates, and tigecycline was active against 97% of the isolates. *Pseudomonas aeruginosa* showed 100.0% susceptibility to ceftazidime/avibactam and 89.7% while it showed 100.0% susceptibility to amikacin. Ampicillin, cefoxitin, cefuroxime and cefazolin resistance were observed in 100.0%, 100.0%, 100.0% and 92.3% of the *Enterobacter cloacae* isolates, respectively. *Enterobacter cloacae* exhibited 100.0% susceptibility to tigecycline, minocycline, tobramycin and amikacin.

The antimicrobial susceptibilities of the Gram-positive organisms obtained from bile cultures are displayed in Table 5. For *Enterococcus faecium*, the most active antibiotic was tigecycline (41/41), followed by linezolid (49/50), vancomycin and quinupristin/dalfopristin (37/41). The prevalence of *Enterococcus faecalis* strains resistant to quinupristin/dalfopristin was 91.2% (31/34). Tigecycline and vancomycin exhibited efficacy activity all *Enterococcus faecalis* isolates. The resistance rate of *Enterococcus casseliflavus* to vancomycin was 87.5%, and its susceptibility to ampicillin and tigecycline was 100.0%. Furthermore, *Enterococcus gallinarum* exhibited 100.0% susceptibility to tigecycline, linezolid, ampicillin, penicillin and high concentration of streptomycin.

Discussion

Biliary tract diseases often cause biliary tract infections, and biliary tract infections are associated with high morbidity and mortality [1, 18]. However, the process of analyzing bile culture requires a significant amount of time, and there is a scarcity of information available regarding the bacteria present in the biliary system in this specific area. The objective of this study was to examine the

Table 3 Laboratory results of patients with benign disease and malignant disease

	Benign diseases ($N=247$)	Malignant diseases ($N=70$)	*P* value
WBC counts ($\times 10^9$/L)	7.1 (5.0–10.0)	7.6 (5.4–12.4)	0.230
Hb (g/L)	114.0 (100.0–125.0)	102.1 ± 17.4	0.000
PLT counts ($\times 10^9$ platelets/L)	189.0 (140.0–252.0)	221.8 ± 93.8	0.071
ALB (g/L)	37.4 ± 5.7	35.9 ± 5.0	0.051
TBIL (μmol/L)	19.1 (12.2–40.2)	38.5 (14.6–100.3)	0.000
ALT (U/L)	35.0 (21.0–81.0)	36 (24.0–77.3)	0.654
AST (U/L)	28.0 (18.0–58.0)	37.5 (22.0–68.3)	0.062
ALP (U/L)	134.0 (90.0–229.0)	190.5 (117.8–308.3)	0.006
GGT (U/L)	133.0 (48.0–288.0)	159.5 (69.3–392.3)	0.131
TBA (μmol/L)	5.1 (2.5–11.1)	5.2 (2.9–15.6)	0.379
UREA (mmol/L)	4.9 (3.6–6.3)	4.8 (3.6–5.8)	0.747
CRE (μmol/L)	56.0 (46.0–70.0)	50.5 (38.0–72.3)	0.080
CRP (mg/L)	68.8 (19.9–129.3)	40.1 (9.4–115.7)	0.252
Glu (mmol/L)	5.6 (5.0–6.5)	5.6 (5.0–7.0)	0.546

Data are expressed as number (%), X ± SD, or M (IQR). *P*-value: benign diseases versus malignant diseases

WBC White blood cell, *Hb* Hemoglobin, *PLT* Platelet, *ALB* Albumin, *TBIL* Total bilirubin, *ALT* aspartate aminotransferase, *AST* Aspartate aminotransferase, *ALP* Alkaline phosphatase, *GGT* γ-glutamyl transpeptidase, *TBA* Total bile acid, *CRE* Creatinine, *CRP* C-reactive protein, *Glu* Glucose. *WBC* (3.5–9.5) × 10^9/L, *Hb* male (130–175) g/L and female (115–150) g/L, *PLT* (125–350) × 109 g/L, *ALB* (40.0–55.0) g/L, *TBIL* (0.0–23.0) μmol/L, *ALT* Male (9–50) U/L and female (7–40) U/L, *AST* male (15–40) U/L and female (13–35) U/L; ALP, male (45–125) U/L female (35–100) U/L, GGT, male (10–60) U/L and female (7–45) U/L; TBA, (0.0–10.0) μmol/L; UREA, male (3.10–8.00) mmol/L and female (2.60–7.50) mmol/L; CRE, male (57.0–97.0) μmol/L and female (41.0–73.0) μmol/L; CRP, (0.00–10.00) mg/L; Glu, (3.92–6.16) mmol/L

Table 4 Antimicrobial susceptibilities of isolated Gram-negative bacilli from bile cultures

	Escherichia coli (*n* = 105) (%)		Klebsiella pneumoniae (*n* = 41) (%)		Pseudomonas aeruginosa (*n* = 30) (%)		Enterobacter cloacae (*n* = 14) (%)	
	R	S	R	S	R	S	R	S
Ceftazidime	39/104 (37.5)	64/104 (61.5)	14/41 (34.1)	27/41 (65.9)	11/29 (37.9)	13/29 (44.8)	5/14 (35.7)	8/14 (57.1)
Amikacin	3/105 (2.9)	100/105 (95.2)	3/41 (7.3)	38/41 (92.7)	1/29 (3.4)	26/29 (89.7)	0/14 (0.0)	14/14 (100.0)
Aztreonam	53/103 (51.5)	48/103 (46.6)	15/40 (37.5)	25/40 (62.5)	6/23 (26.1)	10/23 (43.5)	5/14 (35.7)	8/14 (57.1)
Cefotetan	8/93 (8.6)	82/93 (88.2)	10/38 (26.3)	28/38 (73.7)	-	-	7/8 (87.5)	1/8 (12.5)
Cefazolin	47/64 (73.4)	17/64 (26.6)	12/23 (52.2)	11/23 (47.8)	21/21 (100.0)	0/21 (0.0)	12/13 (92.3)	1/13 (7.7)
Cefepime	38/105 (36.2)	59/105 (56.2)	11/41 (26.8)	30/41 (73.2)	6/30 (20.0)	15/30 (50.0)	2/14 (14.3)	12/14 (85.7)
Ceftriaxone	60/103 (58.3)	43/103 (41.7)	11/41 (26.8)	26/41 (63.4)	-	-	7/14 (50.0)	7/14 (50.0)
Ciprofloxacin	67/103 (65.0)	31/103 (30.1)	20/40 (50.0)	18/40 (45.0)	8/29 (27.6)	17/29 (58.6)	4/14 (28.6)	10/14 (71.4)
Gentamycin	36/101 (35.6)	64/101 (63.4)	12/40 (30.0)	27/40 (67.5)	2/27 (7.4)	22/27 (81.5)	2/14 (14.3)	12/14 (85.7)
Ertapenem	1/89 (1.1)	87/89 (97.8)	0/32 (0.0)	32/32 (100.0)	-	-	1/11 (9.1)	9/11 (81.8)
Imipenem	3/105 (2.9)	101/105 (96.2)	7/41 (17.1)	33/41 (80.5)	13/30 (43.3)	12/30 (40.0)	2/14 (14.3)	12/14 (85.7)
Levofloxacin	61/105 (58.1)	26/105 (24.8)	15/41 (36.6)	16/41 (39.0)	7/30 (23.3)	20/30 (66.7)	3/14 (21.4)	10/14 (71.4)
Piperacillin/ tazobactam	12/105 (11.4)	84/105 (80.0)	11/41 (26.8)	29/41 (70.7)	4/26 (15.4)	15/26 (57.7)	3/14 (21.4)	11/14 (78.6)
Tobramycin	18/104 (17.3)	71/104 (68.3)	6/40 (15.0)	30/40 (75.0)	3/30 (10.0)	26/30 (86.7)	0/14 (0.0)	14/14 (100.0)
Co-trimoxazole	40/105 (38.1)	65/105 (61.9)	9/41 (22.0)	32/41 (78.0)	-	-	2/14 (14.3)	12/14 (85.7)
Piperacillin	48/70 (68.6)	21/70 (30.0)	14/32 (43.8)	11/32 (34.4)	3/22 (13.6)	16/22 (72.7)	2/7 (28.6)	4/7 (57.1)
Cefuroxime	49/76 (64.5)	20/76 (26.3)	14/35 (40.0)	16/35 (45.7)	-	-	5/5 (100.0)	0/5 (0.0)
Cefotaxime	47/74 (63.5)	27/74 (36.5)	12/34 (35.3)	21/34 (61.8)	-	-	4/6 (66.7)	2/6 (33.3)
Cefmetazole	12/70 (17.1)	57/70 (81.4)	8/30 (26.7)	22/30 (73.3)	-	-	1/2 (50.0)	1/2 (50.0)
Meropenem	4/76 (5.3)	72/76 (94.7)	7/34 (20.6)	27/34 (79.4)	7/27 (25.9)	16/27 (59.3)	1/11 (9.1)	10/11 (90.9)
Cefoperazone/ sulbactam	21/72 (29.2)	45/72 (62.5)	7/32 (21.9)	24/32 (75.0)	4/24 (16.7)	14/24 (58.3)	0/7 (0.0)	5/7 (71.4)
Minocycline	4/69 (5.8)	63/69 (91.3)	5/31 (16.1)	25/31 (80.6)	-	-	0/7 (0.0)	7/7 (100.0)
Tigecycline	0/77 (0.0)	77/77 (100.0)	0/33 (0.0)	32/33 (97.0)	-	-	0/12 (0.0)	12/12 (100.0)
Ampicillin/ sulbactam	56/101 (55.4)	34/101 (33.7)	19/40 (47.5)	15/40 (37.5)	-	-	3/5 (60.0)	1/5 (20.0)
Ampicillin	73/101 (72.3)	21/101 (20.8)	38/40 (95.0)	1/40 (2.5)	-	-	5/5 (100.0)	0/5 (0.0)
Fosfomycin	-	-	-	-	2/12 (16.7)	9/12 (75.0)	-	-
Ceftolozane/tazobactam	-	-	-	-	0/13 (0.0)	13/13 (100.0)	-	-
Cefoxitin	-	-	-	-	-	-	5/5 (100.0)	0/5 (0.0)

R Resistant, *S* Susceptible

pathogenic pathogens of positive bile cultures and characterize their patterns of drug resistance.

The proportion of women (57.1%) in the current study was slightly higher compared to males, which is consistent with the results of other studies [19, 20]. Studies have shown that preoperative ERCP and advanced age are important risk factors for positive bile culture [21]. In this study, the patients had a higher average age (M = 62.7). The elderly population may have comorbidities compromised immune systems. Several academics have discovered that there is a high prevalence of positive bile culture in the aged population [1]. Additionally, patients who experience fever also have a significant chance of testing positive for bile culture [1]. The most common clinical symptoms of biliary diseases are reported to be abdominal pain, fever, and jaundice [1, 3]. However, abdominal pain ($P = 0.000$), nausea ($P = 0.005$), vomiting ($P = 0.004$), chills ($P = 0.039$) and jaundice ($P = 0.000$) were statistically significant according to univariate analysis. Jaundice occurred more in patients with malignant diseases and other symptoms occurred more in patients with benign diseases.

According to the research of Ozturk-Engin et al., the increase of ALP, CRP, total bilirubin and WBC count is an important predictor of positive bile culture [4]. The univariate analysis showed that decreased Hb, increased TBIL and ALP were risk factors for patients with malignant diseases. The levels of ALP and TBIL in the malignant biliary tract group were higher, which was consistent with the results of Li et al. [22]. However, the CRP level in individuals with benign diseases exceeded that of patients with malignant conditions. Many individuals with benign diseases may experience a sudden and severe onset of symptoms.

Table 5 Antimicrobial susceptibilities of isolated Gram-positive bacilli from bile cultures

	Enterococcus faecium (*n* = 51) (%)		Enterococcus faecalis (*n* = 48) (%)		Enterococcus casseliflavus (*n* = 18) (%)		Enterococcus gallinarum (*n* = 9) (%)	
	R	S	R	S	R	S	R	S
Quinupristin/dalfopristin	1/41 (2.4)	37/41 (90.2)	31/34 (91.2)	1/34 (2.9)	11/14 (78.6)	2/14 (14.3)	4/6 (66.7)	2/6 (33.3)
Ciprofloxacin	25/51 (49.0)	21/51 (41.2)	3/48 (6.3)	43/48 (89.6)	1/18 (5.6)	16/18 (88.9)	0/9 (0.0)	8/9 (88.9)
High concentration of gentamicin (200 μg)	13/50 (26.0)	37/50 (74.0)	8/44 (18.2)	36/44 (81.8)	1/17 (5.9)	16/17 (94.1)	1/8 (12.5)	7/8 (87.5)
Levofloxacin	22/50 (44.0)	21/50 (42.0)	3/48 (6.3)	45/48 (93.7)	0/18 (0.0)	15/18 (83.3)	0/9 (0.0)	8/9 (88.9)
Tigecycline	0/41 (0.0)	41/41 (100.0)	0/33 (0.0)	33/33 (100.0)	0/14 (0.0)	14/14 (100.0)	0/6 (0.0)	6/6 (100.0)
Tetracycline	11/51 (21.6)	39/51 (76.5)	17/47 (36.2)	30/47 (63.8)	4/18 (22.2)	14/18 (77.8)	3/9 (33.3)	6/9 (66.7)
Linezolid	0/50 (0.0)	49/50 (98.0)	0/42 (0.0)	38/42 (90.5)	0/16 (0.0)	15/16 (93.8)	0/9 (0.0)	9/9 (100.0)
High concentration of streptomycin	19/49 (38.8)	30/49 (61.2)	8/43 (18.6)	35/43 (81.4)	1/17 (5.9)	16/17 (94.1)	0/8 (0.0)	8/8 (100.0)
Ampicillin	23/51 (45.1)	28/51 (54.9)	1/48 (2.1)	47/48 (97.9)	0/18 (0.0)	18/18 (100.0)	0/9 (0.0)	9/9 (100.0)
Erythromycin	39/50 (78.0)	6/50 (12.0)	19/47 (40.4)	12/47 (25.5)	3/18 (16.7)	6/18 (33.3)	1/9 (11.1)	6/9 (66.7)
Penicillin	24/51 (47.1)	27/51 (52.9)	1/48 (2.1)	47/48 (97.9)	1/18 (5.6)	17/18 (94.4)	0/9 (0.0)	9/9 (100.0)
Vancomycin	0/51 (0.0)	50/51 (98.0)	0/48 (0.0)	48/48 (100.0)	14/16 (87.5)	2/16 (12.5)	6/9 (66.7)	0/9 (0.0)

R Resistant, *S* Susceptible

History of biliary tract disease ($P=0.001$) and history of biliary tract surgery ($P=0.002$) were also risk factors for patients with benign diseases. A prior history of biliary system surgery raises the risk of a positive bile culture. This can occur due to the introduction of bacteria during surgery or increased chance of bacteria entering the bile duct from the intestine, which may be caused by medical intervention [23]. Postoperative positive bile culture can result from the anatomical connection between the duodenum and biliary tract, sphincter resection, and infection of the ascending bile duct. Biliary drainage enables bacteria and food particles to enter the biliary tree, potentially causing contamination of the bile [21, 24]. Moreover, percutaneous transhepatic cholangial drainage (PTCD) was a risk factor for malignant patients in this study. In this paper, percutaneous drainage accounts for a large proportion of patients with malignant diseases. This may be due to the long course and treatment of patients with malignant biliary diseases, which leads to frequent percutaneous drainage. Literature shows that foreign bodies in biliary tract are usually related to biofilm formation, which leads to persistent and recurrent bacterial infection, and bacterial infection cannot be eradicated without removing prosthesis [25, 26]. The use of medical devices improves the treatment of many diseases and ultimately improves the quality of life of patients. Device-associated nosocomial infections, however, are usually associated with biofilm formation [27–30]. Bacteria within the biofilm are highly resistant to antimicrobials, thus becoming a major cause of persistent and chronic infections [31]. Hypertension (17.4%) was the most common complication, followed by diabetes (10.7%), cerebral infarction (6.6%), liver dysfunction (4.4%) and heart disease (4.1%). The literature is consistent with the obtained results that hypertension and diabetes are the most common underlying diseases [4].

Multiple bacterial infections were found in bile cultures from 30% of patients. Research has indicated that over 40% of patients experience several bacterial infections, whereas other studies have suggested that less than 20% of patients are affected by multiple bacterial infections [32–35]. In the current study, patients with multiple bacterial infections were less likely than those infected with a single bacterial type, which is also consistent with the results of a study [1]. Multiple infections may be caused by postoperative intestinal contamination, low immunity, and nosocomial infections. In the present research, the most infected bacteria in the blood were *Escherichia coli*, with a total of 13 strains. There was only one strain of *Enterococcus faecalis* involved. It has been reported that most of the biliary diseases caused by bloodstream infection are Gram-negative bacilli, and most of them are *Escherichia coli* [9, 36, 37]. The original definition of bacteremia caused by biliary tract infection involved the same organism identified from bile fluid and blood samples [9]. It was found that 9.1% of patients with biliary tract disease had bacteremia, and biliary tract infection was considered a common cause of bacteremia [38]. A total of 8 patients developed septic shock after bacteremia. Severe biliary tract infection of the biliary system can cause the liver's immunological barrier to weaken, resulting in sepsis and septic shock [39]. Most patients

with biliary tract diseases have catheter-related operations, and the source of bacteremia may be catheter-related bloodstream infection caused by peripheral central catheter insertion [40]. A study has shown that biliary-tract bloodstream infection (BT-BSI) is a common infectious complication in cancer patients and may cause high mortality [10]. It is the second most common cause of sepsis in the elderly [36, 41]. However, in this investigation, there were only 3 cases of biliary-tract bloodstream infection in tumor patients. And only one person died of septicemia, and the same bacteria were isolated from blood and bile. Patients with biliary tract infections need rapid antibiotic therapy for specific pathogens to improve septicemia. Moreover, inappropriate empiric antibiotic therapy was an independent factor associated with mortality [36, 42].

This study also examined bile samples collected during the past three years. Gram-negative bacteria comprised for 60.7% of the total, Gram-positive bacteria accounted for 35.8%, and fungi made up 3.5%. *Escherichia coli* was the predominant Gram-negative bacterium, with *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* being next most prevalent. *Enterococcus faecium* and *Enterococcus faecalis* were the predominant Gram-positive bacteria. The primary Gram-negative organisms documented in earlier literature included *Escherichia coli*, *Acinetobacter baumannii* complex, *Klebsiella pneumoniae* and *Enterobacter cloacae* [43]. A study by Mukaiya et al. reported that Gram-negative aerobic bacteria are most commonly isolated from patients with biliary tract infections [44]. The bacteria often isolated from bile samples were *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus*, which aligns with the current results [33, 45, 46]. The most common possible reason is that *Escherichia coli* is more resistant to bile than Gram-positive microorganisms and is often colonized in the gallbladder, becoming a major cause of biliary tract infection [47]. In recent years, the proportion of *Enterococcus* is also slowly increased [48, 49]. Currently, the empirical therapy of BTI mostly focuses on *Enterobacter*. However, it is crucial to acknowledge that *Enterococcus* is also a significant pathogen in such infections and should not be disregarded. Therefore, it is essential to give due consideration to the treatment of *Enterococcus* infections. *Enterococcus* is often identified as the cause of bacterial cholangitis [23]. Compared with the previously published data, the prevalence of *Pseudomonas aeruginosa* isolates (7.0%) in the present study was comparable to that of the other regions [18, 50]. The literature indicates that the occurrence of anaerobic bacteria is very common, and the current findings did not occur in anaerobic bacteria [51]. It was previously reported that *Candida* species accounted for 28.5% of the culture [48]. However, no statistical difference occurred in strains between the two studied groups.

Within a community, the susceptibility of the most common Gram-negative bacteria to ciprofloxacin has significantly diminished, rendering it unsuitable as an empirical antibiotic treatment for suspected acute cholangitis [48]. In many areas, the same Gram-negative bacteria have increased resistance to this common antibiotic [52, 53]. In the present study, the resistance rate of *Escherichia coli* to ciprofloxacin was 65.0%, and the resistance rate of *Klebsiella pneumoniae* was 50.0%. A study have shown that Gram-negative bacilli are less susceptible to ceftriaxone, quinolones, and ampicillin, and the obtained results are consistent with it [1]. In this study, carbapenem antibiotics (ertapenem, imipenem, meropenem) have high activity against the most common *Enterobacteriaceae*. In South Korea, the medical system continued to use carbapenems, such as imipenem, meropenem and ertapenem, as a second-line therapy option [54]. Prior studies have indicated that stents are commonly inserted to prevent the occurrence of jaundice. However, this practice can potentially result in the colonization of the biliary tract by bacteria and mergence of strains that are resistant to antibiotics [55]. In this research, amikacin was an effective antibiotic for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterobacter cloacae*. Tigecycline and minocycline were effective antibiotics for *Enterobacteriaceae*. Within the group of Gram-positive bacteria, the *Enterococcus* bacteria exhibited a higher level of susceptibility to linezolid and tigecycline. Additionally, *E. faecalis* and *E. faecium* were also highly susceptible to vancomycin. For *Enterobacteriaceae*, the use of carbapenems, tigecycline, and minocycline was recommended. Linezolid and vancomycin were used for *Enterococci*.

This study has several limitations as well. Due to the nature of this study being a hospital-based descriptive study, there is a possibility that certain data may have been lost, missing, or inaccurately recorded. Moreover, the presence of geographical and regional variations in microbial frequency and antibiotic resistance patterns, this may restrict the generalizability of the results obtained in this study. One additional constraint of this research was the inability to do sequencing analysis due to its exorbitant cost, and the descriptive analysis was unable to gather raw bile samples.

Conclusion

Gram-negative bacteria are frequently found in the biliary system. Risk factors such as jaundice and PTCD operation may have an impact on patients with malignant diseases. Clinical doctors should pay attention to patients with malignant diseases with low hemoglobin,

high total bilirubin and high alkaline phosphatase. For *Enterobacteriaceae*, the use of carbapenems, tigecycline, and minocycline was recommended. In recent years, the proportion of *Enterococcus* has gradually increased, and clinical attention should be paid to enterococcus infection. Linezolid and vancomycin were used for *Enterococci*. This study has initially established the pattern of drug susceptibility of bile microorganisms for clinical reference in this specific geographic area.

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Authors' contributions
Tingting Liu wrote the main manuscript text and Ling Tang prepared Fig. 1. Ying Huang, Tingting Li and Bo Wang did Formal analysis. Yajuan Li and Yuanhong Xu supervised the project. Moyan Li collected and analyzed supplementary information of the manuscript. All authors reviewed the manuscript.

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Availability of data and materials
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the First Affiliated Hospital of Anhui Medical University.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University in accordance with the Declaration of Helsinki (ethical approval number: Quick-PJ 2023–11-54). Formal consent is waived for this type of study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Gu X, Zhang M, Zhao Y, Huang G. Clinical and microbiological characteristics of patients with biliary disease. World J Gastroenterol. 2020;26(14):1638–46.
2. Navaneethan U, Jayanthi V, Mohan P. Pathogenesis of cholangitis in obstructive jaundice-revisited. Minerva Gastroenterol Dietol. 2011;57(1):97–104.
3. Zhao C, Liu S, Bai X, Song J, Fan Q, Chen J. A retrospective study on bile culture and antibiotic susceptibility patterns of patients with biliary tract infections. Evid Based Complement Alternat Med. 2022;2022:1–11.
4. Ozturk-Engin D, Agalar C, Cag Y, Can FK, Balkan II, Karabay O, et al. Microorganisms isolated from the bile of the patients who have undergone cholecystectomy and their antibiotic resistance pattern: multicenter prospective study. Int Microbiol. 2022;25(4):759–67.
5. Arteta AA, Carvajal-Restrepo H, Sanchez-Jimenez MM, Diaz-Rodriguez S, Cardona-Castro N. Gallbladder microbiota variability in Colombian gallstones patients. J Infect Dev Ctries. 2017;11(3):255–60.
6. Grigor Eva IN, Romanova TI. Gallstone Disease and Microbiome. Microorganisms. 2020;8(6):835.
7. Sokal A, Sauvanet A, Fantin B, de Lastours V. Acute cholangitis: diagnosis and management. J Visc Surg. 2019;156(6):515–25.
8. Salvador VBDG, Lozada MCH, Consunji RJ. Microbiology and antibiotic susceptibility of organisms in bile cultures from patients with and without cholangitis at an asian academic medical center. Surg Infect (Larchmt). 2011;12(2):105–11.
9. Jo IH, Kim Y, Chung WC, Kim J, Kim S, Lim ES, et al. Microbiology and risk factors for gram-positive Cocci bacteremia in biliary infections. Hepatobiliary Pancreat Dis Int. 2020;19(5):461–6.
10. Grafia I, Chumbita M, Segui E, Cardozo C, Laguna JC, Garcia DHM, et al. Epidemiology and risk factors for recurrence in biliary source bloodstream infection episodes in oncological patients. Microbiol Spectr. 2023;11(5):e214223.
11. Park JW, Lee JK, Lee KT, Lee KH, Sung YK, Kang C. How to interpret the bile culture results of patients with biliary tract infections. Clin Res Hepatol Gastroenterol. 2014;38(3):300–9.
12. Ramchandani M, Pal P, Reddy DN. Endoscopic management of acute cholangitis as a result of common bile duct stones. Dig Endosc. 2017;29:78–87.
13. Kwon JS, Han J, Kim TW, Oh J, Kwon HH, Jung JT, et al. Changes in causative pathogens of acute cholangitis and their antimicrobial susceptibility over a period of 6 years. Korean J Gastroenterol. 2014;63(5):299.
14. Rodríguez-Baño J, Alcalá JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum β-Lactamase–Producing Escherichia coli. Arch Intern Med. 2008;168(17):1897–902.
15. Weber A, Schneider J, Wagenpfeil S, Winkle P, Riedel J, Wantia N, et al. Spectrum of pathogens in acute cholangitis in patients with and without biliary endoprosthesis. J Infect. 2013;67(2):111–21.
16. Voigtländer T, Leuchs E, Vonberg R, Solbach P, Manns MP, Suerbaum S, et al. Microbiological analysis of bile and its impact in critically ill patients with secondary sclerosing cholangitis. J Infect. 2015;70(5):483–90.
17. Kwon W, Jang JY, Kim EC, Park JW, Han IW, Kang MJ, et al. Changing trend in bile microbiology and antibiotic susceptibilities: over 12 years of experience. Infection. 2013;41(1):93–102.
18. Ehrenstein BP, Salamon L, Linde HJ, Messmann H, Scholmerich J, Gluck T. Clinical determinants for the recovery of fungal and mezlocillin-resistant pathogens from bile specimens. Clin Infect Dis. 2002;34(7):902–8.
19. Darkahi B, Sandblom G, Liljeholm H, Videhult P, Melhus A, Rasmussen IC. Biliary microflora in patients undergoing cholecystectomy. Surg Infect (Larchmt). 2014;15(3):262–5.
20. Katyal A, Bala K, Bansal A, Chaudhary U. Clinico-microbiological analysis of bactibilia isolates in patients of cholecystectomy. Int J Res Med Sci. 2017;5(9):4030–5.
21. Mahafzah AM, Daradkeh SS. Profile and predictors of bile infection in patients undergoing laparoscopic cholecystectomy. Saudi Med J. 2009;30(8):1044–8.
22. Li L, Zhu C, Huang H. Clinical epidemiology and outcomes of biliary tract infections caused by Klebsiella pneumoniae. Ann Transl Med. 2019;7(14):304.
23. Zigmond E, Zecher BF, Bartels A, Ziv-Baran T, Rösch T, Schachschal G, et al. Bile Duct Colonization With Enterococcus sp. Associates with disease progression in primary Sclerosing cholangitis. Clin Gastroenterol Hepatol. 2023;21(5):1223–32.
24. De Pastena M, Paiella S, Marchegiani G, Malleo G, Ciprani D, Gasparini C, et al. Postoperative infections represent a major determinant of outcome after pancreaticoduodenectomy: Results from a high-volume center. Surgery. 2017;162(4):792–801.
25. Caldara M, Belgiovine C, Secchi E, Rusconi R. Environmental, Microbiological, and Immunological Features of Bacterial Biofilms Associated with Implanted Medical Devices. Clin Microbiol Rev. 2022;35(2):e22120.
26. van den Hazel SJ, Speelman P, Tytgat GN, Dankert J, van Leeuwen DJ. Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. Clin Infect Dis. 1994;19(2):279–86.
27. Stewart PS, Bjarnsholt T. Risk factors for chronic biofilm-related infection associated with implanted medical devices. Clin Microbiol Infect. 2020;26(8):1034–8.

28. Adlhart C, Verran J, Azevedo NF, Olmez H, Keinanen-Toivola MM, Gouveia I, et al. Surface modifications for antimicrobial effects in the healthcare setting: a critical overview. J Hosp Infect. 2018;99(3):239–49.
29. Arciola CR, Campoccia D, Montanaro L. Implant infections: adhesion, biofilm formation and immune evasion. Nat Rev Microbiol. 2018;16(7):397–409.
30. Percival SL, Suleman L, Vuotto C, Donelli G. Healthcare-associated infections, medical devices and biofilms: risk, tolerance and control. J Med Microbiol. 2015;64(4):323–34.
31. de la Fuente-Nunez C, Reffuveille F, Fernandez L, Hancock RE. Bacterial biofilm development as a multicellular adaptation: antibiotic resistance and new therapeutic strategies. Curr Opin Microbiol. 2013;16(5):580–9.
32. Granel-Villach L, Gil-Fortuño M, Fortea-Sanchis C, Gamón-Giner RL, Martínez-Ramos D, Escrig-Sos VJ. Factores que influyen en la microbiología del líquido biliar en los pacientes colecistectomizados. Rev Gastroenterol Mex. 2020;85(3):257–63.
33. Yun SP, Seo H. Clinical aspects of bile culture in patients undergoing laparoscopic cholecystectomy. Medicine (Baltimore). 2018;97(26):e11234.
34. Capoor MR, Nair D, Rajni, Khanna G, Krishna SV, Chintamani MS, et al. Microflora of bile aspirates in patients with acute cholecystitis with or without cholelithiasis: a tropical experience. Braz J Infect Dis. 2008;12(3):222–5.
35. Chao CM, Lai CC, Tang HJ, Ko WC, Hsueh PR. Biliary tract infections caused by Aeromonas species. Eur J Clin Microbiol Infect Dis. 2013;32(2):245–51.
36. Ortega M, Marco F, Soriano A, Almela M, Martinez JA, Lopez J, et al. Epidemiology and prognostic determinants of bacteraemic biliary tract infection. J Antimicrob Chemother. 2012;67(6):1508–13.
37. Melzer M, Toner R, Lacey S, Bettany E, Rait G. Biliary tract infection and bacteraemia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J. 2007;83(986):773–6.
38. Thabit AK. Antibiotics in the biliary tract: a review of the pharmacokinetics and clinical outcomes of antibiotics penetrating the bile and gallbladder wall. Pharmacotherapy. 2020;40(7):672–91.
39. Hu L, Chai Y, Xi R, Zhu H, Wang Y, Ren F, et al. Pathophysiologic Characterization of a Novel Rabbit Model of Biliary Tract Infection-Derived Sepsis. Sci Rep. 2019;9(1):11947.
40. Ropero-Luis G. Staphylococcus epidermidis catheter-related bloodstream infection leading to acute acalculous cholecystitis and septic shock. Br J Hosp Med (Lond). 2022;83(10):1–3.
41. Sung YK, Lee JK, Lee KH, Lee KT, Kang CI. The clinical epidemiology and outcomes of bacteremic biliary tract infections caused by antimicrobial-resistant pathogens. Am J Gastroenterol. 2012;107(3):473–83.
42. Zhao S, Wu Y, Dai Z, Chen Y, Zhou X, Zhao J. Risk factors for antibiotic resistance and mortality in patients with bloodstream infection of Escherichia coli. Eur J Clin Microbiol Infect Dis. 2022;41(5):713–21.
43. Karpel E, Madej A, Buldak L, Dulawa-Buldak A, Nowakowska-Dulawa E, Labuzek K, et al. Bile bacterial flora and its in vitro resistance pattern in patients with acute cholangitis resulting from choledocholithiasis. Scand J Gastroenterol. 2011;46(7–8):925–30.
44. Mukaiya M, Hirata K, Katsuramaki T, Kihara C, Kimura Y, Yamaguchi K, et al. Isolated bacteria and susceptibilities to antimicrobial agents in biliary infections. Hepatogastroenterology. 2005;52(63):686–90.
45. Gomi H, Solomkin JS, Schlossberg D, Okamoto K, Takada T, Strasberg SM, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25(1):3–16.
46. Kim SB, Gu MG, Kim KH, Kim TN. Long-term outcomes of acute acalculous cholecystitis treated by non-surgical management. Medicine (Baltimore). 2020;99(7):e19057.
47. Suh S, Choi YS, Choi S, Do JH, Oh H, Kim HJ, et al. Antibiotic selection based on microbiology and resistance profiles of bile from gallbladder of patients with acute cholecystitis. Sci Rep. 2021;11(1):2969.
48. Gromski MA, Gutta A, Lehman GA, Tong Y, Fogel EL, Watkins JL, et al. Microbiology of bile aspirates obtained at ERCP in patients with suspected acute cholangitis. Endoscopy. 2022;54(11):1045–52.
49. Zhao J, Wang Q, Zhang J. Changes in microbial profiles and antibiotic resistance patterns in patients with biliary tract infection over a six-year period. Surg Infect (Larchmt). 2019;20(6):480–5.
50. Leung JW, Ling TK, Chan RC, Cheung SW, Lai CW, Sung JJ, et al. Antibiotics, biliary sepsis, and bile duct stones. Gastrointest Endosc. 1994;40(6):716–21.
51. Strohäker J, Wiegand L, Beltzer C, Königsrainer A, Ladurner R, Meier A. Clinical presentation and incidence of anaerobic bacteria in surgically treated biliary tract infections and cholecystitis. Antibiotics. 2021;10(1):71.
52. Voiosu TA, Bengus A, Haidar A, Rimbas M, Zlate A, Balanescu P, et al. Antibiotic prophylaxis prior to elective ERCP does not alter cholangitis rates or shorten hospital stay: results of an observational prospective study of 138 consecutive ERCPS. Maedica (Bucur). 2014;9(4):328–32.
53. Kaya M. Microbial profile and antibiotic sensitivity pattern in bile cultures from endoscopic retrograde cholangiography patients. World J Gastroenterol. 2012;18(27):3585.
54. Jang DK, Kim J, Park WB, Yi SY, Lee JK, Yoon WJ. Increasing burden of biliary tract infection caused by extended-spectrum beta-lactamase-producing organisms in Korea: a nationwide population-based study. J Gastroenterol Hepatol. 2019;35(1):56–64.
55. Scheufele F, Aichinger L, Jager C, Demir IE, Schorn S, Sargut M, et al. Effect of preoperative biliary drainage on bacterial flora in bile of patients with periampullary cancer. Br J Surg. 2017;104(2):e182–8.

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