RESEARCH ARTICLE

Analysis of risk factors for infection after percutaneous biliary stenting in patients with cholangiocarcinoma and its impact on prognosis

Cheng G, Li XS, Zhang M

Department of Interventional Therapy, Affiliated Hospital of Jiangnan University, Wuxi, China

Abstract

Background: Cholangiocarcinoma (CCA) may invade the bile duct, causing malignant biliary obstruction, which is mainly treated by percutaneous biliary stenting. Biliary tract infection after stenting is a severe and common complication in the early postoperative period. In this study, we investigated the risk factors predisposing to infection after percutaneous biliary stenting in patients with CCA and its effect on prognosis. Our findings might reference early clinical prevention, diagnosis, and treatment.

Methods: We analyzed retrospective data regarding 337 patients who developed CCA and underwent percutaneous biliary stenting from December 2016 to December 2021. We collected the patients' general characteristics and clinical data utilizing a questionnaire regarding general information designed by the investigator. We performed the t-test and chi-square test to investigate the association between the clinical characteristics and postoperative infection and binary logistic regression to analyze the independent risk factors for patients developing postoperative infections. We used the Cox risk regression to determine each factor's effect on patients' survival status.

Results: Seventy-three cases of postoperative infection occurred in total, with an estimated infection rate of 21.7 %. Logistic regression analysis revealed that age [odds ratio (OR) =1.041, p =0.031], presence of combined gallstones (OR =2.200, p =0.030), stent type (OR =2.607, p =0.003), administration of preoperative prophylactic antibiotics (OR =0.473, p =0.042), presence of intraoperative complications of biliary bleeding (OR =2.452, p =0.017), presence of postoperative biliary pneumoperitoneum (OR =2.355, p =0.013), duration of surgery (OR =1.026, p =0.008), preoperative serum albumin (Alb) (OR =0.946, p =0.005), and preoperative hemoglobin (Hb) (OR =0.964, p =0.014) were the independent factors influencing postoperative infection development. The Cox risk regression analysis showed that infection occurrence was an independent factor influencing patients' survival time (OR =1.041, p =0.031).

Conclusion: Biliary tract infection is the most common complication after biliary interventions, and severe infection may even lead to death. Clinical studies should analyze and evaluate patients' clinical characteristics, perioperative indicators, and relevant serological indicators, identify relevant risk factors, and administer prompt treatment to reduce the chance of infection and improve patients' prognosis. HIPPOKRATIA 2023, 27 (2):89-98.

Keywords: Cholangiocarcinoma, CCA, biliary stenting, infection, prognosis, survival

Corresponding author: Gang Cheng, Associate Chief Physician, Department of Interventional Therapy, Affiliated Hospital of Jiangnan University, No. 1000, Hefeng Road, 214122, Wuxi, China, tel: +8613812536167, e-mail: cgtomorrow@163.com

Introduction

Cholangiocarcinoma (CCA) is a highly heterogeneous group of biliary tract malignant tumors that can arise in any location of the biliary tree[1]. It is the second most common liver cancer after hepatocellular carcinoma[2], accounting for 15 % of all primary liver tumors[3]. Its global incidence has been increasing for many years; for example, the incidence of intrahepatic CCA has increased by 109 %, from 0.67 per 100,000 individuals in 2007 to 1.40 per 100,000 individuals in 2016[4]. The incidence of CCA accounts in China for 3.9 % of the total incidence of malignant tumors, and also its rate is increasing every year[5]. Patients with CCA confront dismal prognosis; a European study[6] reported that patients with CCA who underwent surgical resection had the best survival outcome, especially those with negative margins (R0) [median overall survival (mOS) =45.1 months]; in contrast, the mOS was 24.7 months for margin involvement (R1) and 23.3 months for lymph node infiltration. Surgery is the only direct route for treating CCA and one of the leading clinical approaches; for patients in whom tumor excision is not feasible with curative intent, palliative surgery is performed[7].

However, the difficulty in treating biliary tract tumors is not related to the choice of surgical procedure. Biliary tract tumors are often advanced at the time of diagnosis, and malignant obstructive jaundice (MOJ) might have already developed[8]. Patients with biliary obstruction display abnormal liver function, poor nutrient absorption, and low protein levels, which can lead to a range of sequelae[9]. Should the condition worsen, bilirubin could enter the bloodstream, affect multiple organ systems, and threaten the life of the patient[10,11]. Several studies have shown that the incidence of lesions in CCA patients with malignant obstructive jaundice is more than twice that of healthy individuals. Thus, such a condition greatly threatens human life[12,13]. Further studies have found that the three-year survival rate of patients with MOJ is less than 50 %[14,15]. Therefore, the difficulty of accomplishing sufficient bile drainage increases mortality risk[16]. The current consensus regarding treating such patients is to restore the patency of the stenotic segment as soon as possible to preserve the function of the liver and administer oncologic treatment. Commonly used interventions for jaundice include percutaneous hepatic choledochal drainage (PTCD) and the placement of a percutaneous hepatic percutaneous biliary stent (PTIBS). For patients without surgical indications or unwilling to undergo an operation, biliary stenting can alleviate obstruction, improve liver function, enhance quality of life, and prolong survival[17,18]. Nonetheless, biliary stenting can also cause several complications. Among them, early postoperative biliary infection (EBI) is a prevalent and more difficult complication of biliary intervention[19]. Few studies reported the incidence of biliary infection after biliary stenting to range from 14 % to 47 %[20,21]. According to the 2013 Japanese guidelines, the lethality rate of acute cholangitis is 2.7-10 %[22], and thus, the prevention and treatment of biliary tract infections after biliary stenting are essential. We acknowledge that percutaneous biliary stenting in patients with CCA carries a high infection risk, and the risk factors may be associated with complications such as prolonged operative time, stent type, and biliary bleeding. To provide a reference for reducing postoperative complications and improving the quality of life and prognosis, we aimed to assess the risk factors associated with infection development after percutaneous biliary stenting in CCA patients and define its effects on patient prognosis.

Materials and Methods

We included 337 patients with CCA who underwent percutaneous biliary stenting at the Affiliated Hospital of Jiangnan University from December 2016 to December 2021. We defined as inclusion criteria i) age above 18 years, ii) clinical diagnosis of malignant biliary obstruction based on history, symptoms, serum markers [glucoprotein antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA)], imaging studies [ultrasound, computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET)], or pathology, iii) contraindication to surgery or unwillingness to undergo surgery, iv) first treatment with biliary stenting, v) anticipated survival time more than three months, vi) signed informed consent and ability to cooperate and complete the questionnaire, and vii) complete follow-up information in patients' records. We excluded from the study patients i) who could not tolerate interventional procedures, such as those suffering from severe cardiopulmonary insufficiency, coagulation dysfunction [prothrombin time (PT) >13 sec], and massive ascites, ii) who had preoperative biliary tract infection, iii) with anticipated survival time less than three months, iv) who had mental illness or were unable to complete the questionnaire, and vi) for whom we had incomplete follow-up data (Figure 1).

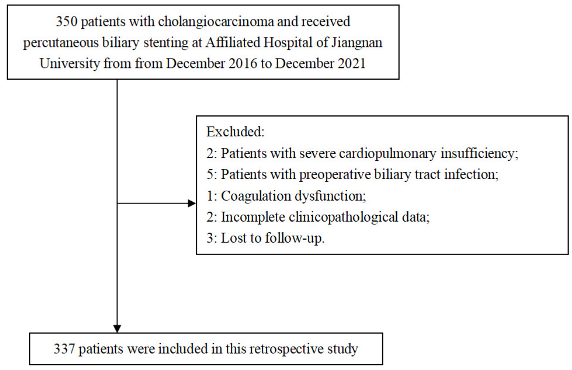

Figure 1: Flow chart showing selection of patient with cholangiocarcinoma who underwent percutaneous biliary stenting from December 2016 to December 2021.

According to previous studies by our group and other researchers, the probability of infection after percutaneous biliary stenting in patients with CCA is 20 %. Therefore, after setting the tolerance error at 3 % and the confidence level at 1-α =0.95, we calculated the sample size to be investigated at 264 patients, utilizing the PASS 15 software (NCSS, LLC, East Kaysville, Utah, USA). Assuming a study population's non-response rate of 10 %, the required sample was estimated at n =264 × 1.1 =290 cases. Accepting a questionnaire's 90 % pass rate, we calculated the total sample size needed at n =290/0.9 =322 cases. Therefore, the designed sampling for this study consisted of 350 cases. Thirteen cases were lost in follow-up, and the final study's sample was 337 cases. The Ethics Committee of the Affiliated Hospital of Jiangnan University approved the study (No. LC2016852), which was conducted according to the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all patients.

Questionnaire acquiring general information

We acquired the general information with a questionnaire that included demographic data [e.g., age, gender, and body mass index (BMI)] and clinical data [TNM stage, comorbidity with diabetes, hypertension, and hyperlipidemia, presence of gallstones, biliary obstruction staging, liver function Child-Pugh classification, stent type, number of stents, prophylactic administration of preoperative antibiotics, complication with intraoperative biliary bleeding, occurrence of postoperative intrahepatic bile duct gas accumulation, operation time, intraoperative blood loss, yellowing control time, hospitalization days, relevant laboratory indicators, and prognostic indicators, such as the Karnofsky performance score (KPS) and the Fact-hep score].

Diagnostic criteria for postoperative biliary tract infection

We defined biliary tract infection as a persistent increase in the leukocyte and neutrophil count, fever (temperature ≥37.3 °C), and positive bile culture within 30 days of biliary stent implantation, possibly accompanied by perihepatic pain or persistent progression of xanthogranuloma and exclusion of preoperative or other organ infection occurrence[23]. The postoperative follow-up time points were 1-14 days and 30 days postoperatively, with an outpatient visit or telephone follow-up by a trained clinician. Patients were considered lost to follow-up if they were out of contact or their follow-up medical information was incomplete. The last follow-up visit was recorded in January 2022. Patients were divided into two groups (i.e., the biliary tract infection group and the non-biliary tract infection group) based on whether they had a concurrent biliary tract infection within one month after surgery.

Type of bile duct obstruction

High biliary obstruction is defined as obstruction of Bismuth type II and above, whereas low biliary obstruction is defined as obstruction of Bismuth type I and below.

Karnofsky performance score

KPS is based on the patient's condition, ability to perform everyday activities, and their degree of self-care[24]. A higher score indicates a more satisfactory health status and greater tolerance to treatment's side effects. The specific scores and their implications are as follows: 100 indicates that a patient is in normal health with no symptoms and signs; 90 indicates that a patient can accomplish everyday activities with minor symptoms and signs; 80 indicates that a patient is barely capable of performing everyday activities with some symptoms or signs; 70 indicates a patient that can take self-care but cannot maintain normal life activities and work; 60 indicates a patient largely able to self-care but requires occasional help; 50 indicates that a patient often needs care; 40 indicates that a patient is unable to self-care and requires support and assistance; 30 indicates that a patient is mainly unable to self-care; 20 indicates a seriously ill patient mandating hospitalization and active, supportive treatment; 10 indicates a critically ill patient and pending death; and 0 indicates a dead patient. We evaluated patients before the operation and ten days postoperative, with the last follow-up being recorded in January 2022.

Functional assessment of cancer therapy using the Hepatobiliary score

The Fact-Hep scale[25] consists of the standard module FACT-G (containing 27 items), which can be utilized for assessing all cancer patients, and the hepatobiliary tumor-specific module (with an additional concern section of 18 items), totaling 45 items. The FACT-G module is divided into several domains, including physical (six items), social (six items), psychological (six items), and functional (seven items) domains. All entries are scored on a five-point scale (0-4), with higher scores indicating a better patient's quality of life. We evaluated patients before the operation and ten days postoperative, with the last follow-up being recorded in January 2022.

Kaplan-Meier survival curve

We initiated a one-year postoperative follow-up via telephone, SMS, or outpatient review. During the follow-up, we evaluated the inflammation index, liver and kidney function, and tumor marker test results. Should the patient experience discomfort, we visit the hospital immediately. The follow-up endpoint was death or one year, with the deadline for follow-up defined as December 2022.

Statistical analysis

We performed all statistical analyses utilizing the IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). We expressed continuous variables as mean and standard deviation and categorical variables as frequency and percentage for data that fit a normal distribution. For the measurement data conforming to normal distribution and homogeneous variance, we compared differences between groups with the t-test and chi-square test. We compared differences between the two groups using the Mann-Whitney U test for measurement data that did not conform to normal distribution or uneven variance. We analyzed the factors influencing the occurrence of postoperative infection with binary logistic regression and the independent risk factors affecting survival with Cox regression. Collinearity diagnosis was performed before regression analysis to exclude confounding factors. All groups' differences were considered statistically significant at a p-value of <0.05.

Results

Baseline data

The baseline data are presented in Table 1. We found 73 cases of postoperative infections, with an infection rate of 21.7 %. The results of the t-test and chi-square test showed that age, whether combined with diabetes, hyperlipidemia, gallstones, obstruction staging, stent type, prophylactic preoperative antibiotic use, complication with intraoperative biliary bleeding, and occurrence of postoperative intrahepatic bile duct pneumatosis were significantly different between the infected and non-infected groups ($p < 0.05$).

Perioperative indicators in the two groups

The t-test analysis showed that the patients with infection had longer operative time (98.56 ± 16.92 min vs 91.87 ± 16.75 min, p =0.003) and more significant intraoperative bleeding (59.29 ± 16.32 mL vs 55.25 ± 14.06 mL, p =0.037). The differences in jaundice control time and hospitalization time between the two groups were not significant ($p > 0.05$) (Table 2).

Table 1: Baseline data of patients 337 enrolled patients with cholangiocarcinoma who underwent percutaneous biliary stenting and were divided into two groups depending on whether they developed postoperative infection.

	Infection group	Non-infection group	t / x^2	p
Age (year)	62.81 ± 8.349	60.07 ± 8.808	-2.379	0.018
Gender				
Male	40 (54.8)	129 (48.9)	0.805	0.370
Female	33 (45.2)	135 (51.1)		
BMI (kg/m^2)	19.871 ± 2.7079	19.846 ± 2.6294	-0.071	0.943
TNM staging				
I	2 (2.7)	2 (0.8)	4.575	0.206
II	4 (5.5)	11 (4.2)		
III	5 (6.8)	37 (14.0)		
IV	62 (84.9)	214 (81.1)		
With diabetes or not				
Yes	15 (20.5)	2 0(7.6)	10.340	0.001
No	58 (79.5)	244 (92.4)		
With hypertension or not				
Yes	18 (24.7)	62 (23.5)	0.043	0.835
No	55 (75.3)	202 (76.5)		
With hyperlipidemia or not				
Yes	5 (6.8)	10 (3.8)	9.488	0.002
No	68 (93.2)	254 (96.2)		
With gallstones or not				
Yes	24 (32.9)	41 (15.5)	11.053	0.001
No	49 (67.1)	223 (84.5)		
Obstruction type				
low position	48 (65.8)	213 (80.7)	7.297	0.007
high position	25 (34.2)	51 (19.3)		
Child-Pugh class				
A	6 (8.2)	12 (4.5)		
B	31 (42.5)	106 (40.5)	1.900	0.387
C	36 (49.3)	146 (55.3)		
Stent type				
Percutaneous I^{125} seed-loaded stent	33 (45.2)	66 (25.0)	11.253	0.001
Conventional stent	40 (54.8)	198 (75.0)		
Number of stents				
Single stent	65 (89.0)	242 (91.7)	0.486	0.486
Multiple stents	8 (11.0)	22 (8.3)		
Prophylactic antibiotic use or not				
Yes	15 (20.5)	94 (35.6)	5.926	0.015
No	58 (79.5)	170 (64.4)		
Intraoperative hemobilia or not				
Yes	23 (31.5)	41 (15.5)	9.488	0.002
No	50 (68.5)	223 (84.5)		
Postoperative biliary pneumatosis				
Yes	28 (38.4)	63 (23.9)	6.094	0.014
No	45 (61.6)	201 (76.1)		

Values are reported as number with percentage in brackets or mean ± standard deviation in brackets. t: t-test, x^2: chi-square test, BMI: Body Mass Index, TNM: Tumor Node Metastasis.

Preoperative laboratory indices of patients in the two groups

The t-test analysis showed that patients with infection compared to those without infection, had lower preoperative Alb levels (38.89 ± 8.94 g/L vs 43.48 ± 7.73 g/L, p <0.001), as well as preoperative Hb level (116.30 ± 12.31 g/L vs 120.93 ± 8.83 g/L, p =0.003), and higher preoperative white blood cells (8.97 ± 3.47 ×10^9/L vs 8.03 ± 2.23 ×10^9/L, p =0.032). However, the differences in preoperative levels of C-reactive protein, prothrombin time, and CA19-9 were not significant between the groups (p >0.05) (Table 3).

Comparison of the liver function indices between the groups

The t-test analysis showed that patients with infection compared to those without infection, had in the three days after stenting, higher mean postoperative alanine transaminase (ALT) (113.22 ± 25.50 U/L vs 95.16 ± 17.91 U/L, p <0.001), higher mean alkaline phosphatase (ALP) (159.18 ± 41.05 U/L vs 147.36 ±37.88 U/L, p =0.021), higher mean total bilirubin (TBIL) (195.51 ± 54.42 U/L vs 180.07 ± 58.91 U/L, p =0.045), and higher mean direct bilirubin (DBIL) (111.05 ± 11.40 U/L vs 40.55 ± 6.37 U/L, p <0.001). While the differences in preoperative ALT, aspartate transaminase (AST), ALP, γ-glutamyltransferase (γ-GT), TBIL, DBIL, and post-

Table 2: Perioperative indicators regarding the two cholangiocarcinoma patient's groups (with and without postoperative infection after percutaneous biliary stenting).

	Infection group	Non-infection group	t	p
Operative time	98.56 ± 16.92	91.87 ± 16.75	-3.015	0.003
Intraoperative blood loss	59.29 ± 16.32	55.25 ± 14.06	-2.097	0.037
Jaundice control time	6.29 ± 1.93	5.91 ± 1.99	-1.428	0.154
Hospital days	8.90 ± 2.27	8.66 ± 2.23	-0.840	0.402

Values are reported as mean ± standard deviation. t: t-test.

Table 3: Preoperative laboratory indices of the two cholangiocarcinoma patient's groups (with and without postoperative infection after percutaneous biliary stenting).

	Alb (g/L)	CRP (mg/L)	Hb (g/L)	PT (s)	CA19-9 (U/ml)	WBC ($\times 10^9$/L)
Infection group	38.89 ± 8.94	16.52 ± 1.52	116.30 ± 12.31	12.43 ± 0.81	334.50 ± 27.15	8.97 ± 3.47
Non-infection group	43.48 ± 7.73	16.29 ± 1.47	120.93 ± 8.83	12.50 ± 0.82	333.78 ± 26.09	8.03 ± 2.23
t	3.990	-1.205	3.009	0.687	-0.204	-2.183
p	0.000	0.229	0.003	0.492	0.838	0.032

Values are reported as mean ± standard deviation. t: t-test, Alb: Albumin, CRP: C-reactive protein, Hb: Hemoglobin, PT: Prothrombin time, CA19-9: Carbohydrate antigen 19-9, WBC: White blood cells.

Table 4: Comparison of the liver function indexes between the two cholangiocarcinoma patient's groups (with and without postoperative infection after percutaneous biliary stenting).

	Infection group	Non-infection group	t / x^2	p
Pre-stenting				
ALT(U/L)	182.84 ± 33.45	179.96 ± 33.98	-0.645	0.520
AST(U/L)	134.85 ± 28.33	138.23 ± 27.20	0.931	0.353
ALP(U/L)	235.60 ± 32.83	237.79 ± 34.14	0.489	0.625
γ-GT(U/L)	294.45 ± 63.92	307.06 ± 60.02	1.567	0.118
TBIL(U/L)	304.58 ± 58.90	318.41 ± 57.46	1.810	0.071
DBIL(U/L)	111.05 ± 11.40	110.41 ± 12.04	-0.408	0.683
Three days after stenting				
ALT(U/L)	113.22 ± 25.50	95.16 ± 17.91	-5.677	0.000
AST(U/L)	78.34 ± 15.56	79.01 ± 16.47	0.312	0.755
ALP(U/L)	159.18 ± 41.05	147.36 ± 37.88	-2.316	0.021
γ-GT(U/L)	183.43 ± 44.84	177.35 ± 41.27	-1.093	0.275
TBIL(U/L)	195.51 ± 54.42	180.07 ± 58.91	-2.014	0.045
DBIL(U/L)	44.16 ± 5.91	40.55 ± 6.37	-4.360	0.000

Values are reported as number with percentage in brackets or mean ± standard deviation in brackets. t: t-test, x2: chi-square test, ALT: alanine transaminase; AST, aspartate transaminase, ALP: alkaline phosphatase, γ-GT: γ-glutamyl transpeptadase, TBIL: total bilirubin, DBIL: direct bilirubin.

operative AST and γ-GT were not significant (p >0.05) (Table 4).

Prognosis assessment of patients in the two groups

The chi-square and t-test analysis showed that 50 cases (68.5 %) in the infected group had recurrent biliary obstruction within six months, and 23 cases (31.5 %) in the non-infected group had the above symptoms. Compared to those without infection, the patients with infection had lower mean stent patency time (7.77 ± 2.69 months vs 8.66 ± 2.30 months, p =0.001). In the ten days after stenting, it had a lower mean postoperative KPS score (57.15 ± 8.07 vs 69.71 ± 9.26, p =0.039) and a higher mean postoperative Fact-hep score (120.03 ± 12.45 vs 117.00 ± 10.76, p =0.040). The differences in the preoperative KPS score and preoperative Fact-hep score were not significant (p >0.05) (Table 5).

Risk factors of infection analyzed by binary logistic regression models

The results of the binary logistic regression analysis showed that age [odds ratio (OR) =1.041, 95 % confidence interval (CI): 1.004~1.080, p =0.031), presence of gallstones (OR =2.200, 95 % CI: 1.079~4.485, p =0.030), stent type (OR =2.607, 95 % CI: 1.373~4.950, p =0.003), use of prophylactic antibiotic (OR =0.473, 95 % CI: 0.229~0.974, p =0.042), intraoperative biliary bleeding (OR =2.452, 95 % CI: 1.173~5.124, p =0.017), postoperative biliary pneumatosis (OR =2.355, 95 % CI: 1.196~4.640, p =0.013), operative time (OR =1.026, 95 % CI: 1.007~1.045, p =0.008), Alb (OR =0.946, 95 % CI: 0.910~0.984, p =0.005), Hb (OR =0.964, 95 % CI: 0.936~0.992, p =0.014) were independent risk factors for the infection (Table 6, Figure 2).

Survival-related prognostic factor analysis for all patients

The results of the Cox risk regression analysis showed that infection (OR =2.240, 95 % CI: 1.098~4.568, p =0.027), combination with diabetes mellitus (OR =9.115, 95 % CI: 3.988~20.831, p =0.000), high Child-Pugh

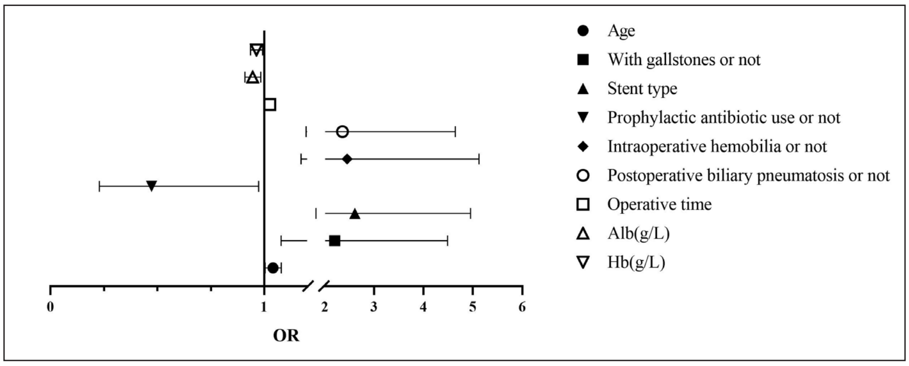

Figure 2: Risk factors of infection analyzed by binary logistic regression.
Alb: albumin, Hb: Hemoglobin.

Table 5: Prognosis assessment in patients in the two cholangiocarcinoma patient's groups (with and without postoperative infection after percutaneous biliary stenting).

	Drainage time	Restenosis within 6 months	KPS score		FACT-Hep score	
			Pre-stenting	Ten days after stenting	Pre-stenting	Ten days after stenting
Infection group	7.77 ± 2.69	50 (68.5)	57.15 ± 8.07	67.25 ± 7.90	100.78 ± 11.53	120.03 ± 12.45
Non-infection group	8.66 ± 2.30	23 (31.5)	55.31 ± 8.34	69.71 ± 9.26	99.32 ± 10.44	117.00 ± 10.76
t / x^2	2.576	5.705	-1.683	2.076	-1.035	-2.057
p	0.011	0.017	0.093	0.039	0.301	0.040

Values are reported as number with percentage in brackets or mean ± standard deviation in brackets. t: t-test, x2: chi-square test, KPS: Karnofsky performance score, FACT-Hep: Functional Assessment of Cancer Therapy-Hepatobiliary.

Table 6: Risk factors of infection analyzed by binary logistic regression models.

	B	SE	Wald	p	OR	95 % CI	
						Upper	Lower
Age	0.040	0.019	4.635	0.031	1.041	1.080	1.004
With gallstones or not	0.788	0.363	4.705	0.030	2.200	4.485	1.079
Obstruction type	0.450	0.360	1.563	0.211	1.569	3.179	0.744
Stent type	0.958	0.327	8.577	0.003	2.607	4.950	1.373
Prophylactic antibiotic use or not	-0.749	0.369	4.121	0.042	0.473	0.974	0.229
Intraoperative hemobilia or not	0.897	0.376	5.684	0.017	2.452	5.124	1.173
Postoperative biliary pneumatosis or not	0.857	0.346	6.133	0.013	2.355	4.640	1.196
Operative time	0.026	0.010	7.079	0.008	1.026	1.045	1.007
Intraoperative blood loss	0.011	0.011	1.106	0.293	1.011	1.033	0.990
Alb (g/L)	-0.055	0.020	7.826	0.005	0.946	0.984	0.910
Hb (g/L)	-0.037	0.015	6.093	0.014	0.964	0.992	0.936
WBC ($\times 10^9$/L)	0.099	0.057	3.000	0.083	1.104	1.235	0.987

Alb: albumin, Hb: Hemoglobin, WBC: White blood cells, SE: standard error, OR: odds ratio, CI: confidence interval.

class (OR =4.300, 95 % CI: 2.139~8.645, p =0.000), obstruction staging (OR =0.440, 95 % CI: 0.207~0.937, p =0.033), and use of prophylactic antibiotic (OR =0.470, 95 % CI: 0.233~0.948, p =0.035) were independent risk factors for poor prognosis (Table 7, Figure 3, Figure 4). 25

Discussion

Complicated biliary tract infection after percutaneous transhepatic biliary stenting is a common postoperative complication in patients with malignant obstruction of the biliary tract and can be life-threatening in severe cases. Therefore, identifying the risk factors affecting postoperative infection and early intervention are necessary for improving patients' prognosis.

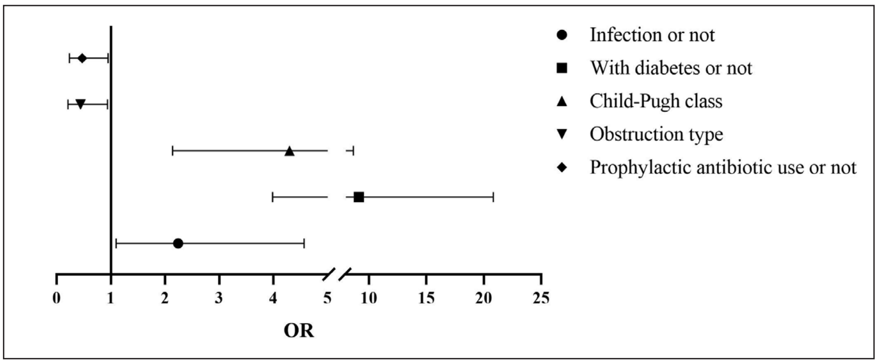

Figure 3: Survival-related prognostic factors in Cox risk regression analysis.

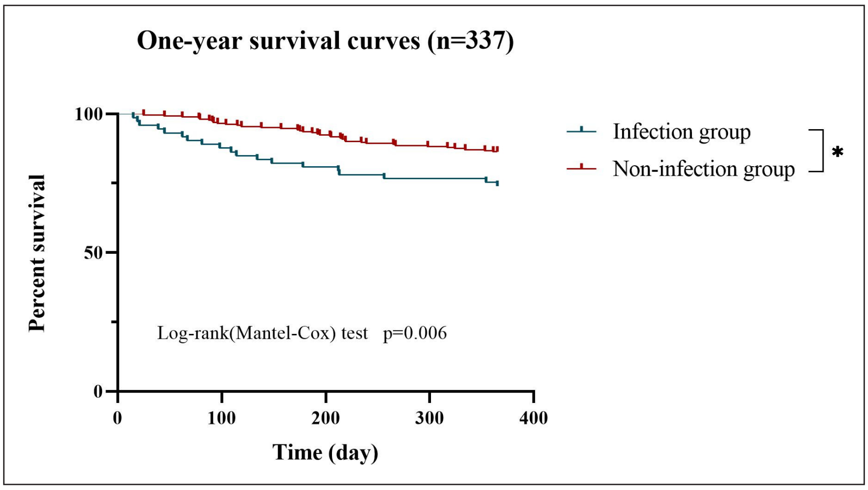

Figure 4: Kaplan-Meier survival curve between cholangiocarcinoma patient's groups with and without postoperative infection (infection and non-infected groups).

In this study, the diabetes mellitus prevalence in the infected group was significantly higher (20.5 %) than in the non-infected group (7.6 %), and concomitant diabetes mellitus was an independent risk factor for the postoperative complications of biliary tract infection. The possible mechanism might be: First, insulin has a direct anti-inflammatory effect and can reduce inflammatory factors, such as tumor necrosis factor alpha (TNF-a), at the transcriptional level[26]. Second, diabetic patients have weakened defense mechanisms and a lower ability to respond to microbial invasion, including the chemotaxis and phagocytosis of leukocytes, as well as a reduction in the neutralization of chemical toxins, serum modulators, bactericidal effects, and cellular immunity. Third, the body of diabetic patients has high blood glucose levels, which promote the growth of certain bacterial colonies in the biliary tract. Fourth, diabetic patients are prone to gallbladder stones and infections due to nerve dysfunction, a decrease in gallbladder contraction function, and bile stasis. Additionally, due to long-term abnormal nutritional metabolism, the ratio of cholesterol and bile salts in the body experiences an imbalance, causing gallstones and infection[27]. Therefore, in patients with combined diabetes mellitus, blood glucose fluctuations should be dynamically monitored throughout the perioperative period, adjusting the dosage of hypoglycemic drugs or insulin accordingly to minimize the risk of developing postoperative infection due to high blood glucose.

Avaliani et al reported stone bile duct obstruction as an independent risk factor for biliary tract infection[28]. When stones in the gallbladder or bile duct enter the biliary stent with the flow of bile and block the biliary stent, which in turn obstructs bile drainage and bile sludge, the sludge acts as a good medium for bacterial growth that increases the risk of biliary tract infection after biliary stent implantation significantly. We found 65 cases of combined gallstones, including 24 cases (32.9 %) in the infected group and 41 cases (15.5 %) in the non-infected group. The regression analysis revealed that combined gallstones were an independent risk factor for postoperative complications of biliary tract infection. Therefore, proper drainage after surgery needs to be ensured for patients with preoperative combined gallstones. When stones are found to block the stent, the stones in the bile duct should be treated promptly to avoid the development or worsening of postoperative infection.

We also found that the type of stent was an independent risk factor for postoperative complications of biliary tract infection. The incidence of postoperative complications of biliary tract infection after percutaneous biliary

Table 7: Survival-related prognostic factors in Cox risk regression analysis for all patients.

	B	SE	Wald	P	OR	95 % CI	
						Upper	Lower
Infection or not	0.806	0.364	4.921	0.027	2.240	4.568	1.098
Age	-0.006	0.019	0.096	0.756	0.994	1.032	0.957
Gender	0.006	0.308	0.000	0.985	1.006	1.839	0.550
BMI	0.047	0.066	0.507	0.477	1.048	1.191	0.921
With diabetes or not	2.210	0.422	27.459	0.000	9.115	20.831	3.988
With hypertension or not	0.180	0.394	0.209	0.647	1.197	2.590	0.553
With hyperlipidemia or not	0.112	0.513	0.048	0.827	1.119	3.059	0.409
With gallstones or not	-0.106	0.393	0.072	0.788	0.900	1.945	0.416
Child-Pugh class	1.459	0.356	16.755	0.000	4.300	8.645	2.139
TNM staging	0.785	0.852	0.850	0.357	2.193	11.636	0.413
Obstruction type	-0.821	0.386	4.533	0.033	0.440	0.937	0.207
Stent type	0.230	0.307	0.564	0.452	1.259	2.297	0.690
Number of stents	0.164	0.432	0.145	0.704	1.178	2.746	0.506
Prophylactic antibiotic use or not	-0.756	0.358	4.447	0.035	0.470	0.948	0.233
Intraoperative hemobilia or not	-0.296	0.401	0.545	0.460	0.744	1.632	0.339
Postoperative biliary pneumatosis or not	-0.017	0.374	0.002	0.963	0.983	2.045	0.472
Operative time	0.008	0.009	0.847	0.357	1.009	1.027	0.990
Intraoperative blood loss	0.005	0.011	0.254	0.614	1.005	1.027	0.985
Jaundice control time	-0.060	0.103	0.336	0.562	0.942	1.153	0.769
Hospital days	-0.082	0.086	0.910	0.340	0.921	1.091	0.778

BMI: Body Mass, TNM: Tumor Node Metastasis, SE: standard error, OR: odds ratio, CI: confidence interval.

^{125}I particle stenting was higher than that recorded after ordinary bare stenting; the infection rate increased with the number of implanted ^{125}I particle stents. An et al[29] suggested that in a healthy state, the human biliary system acts as a barrier against adverse external agents, and interventional treatment may damage the normal protective barrier and decrease the resistance of the biliary system to infection. Additionally, after the internal irradiation of biliary tract malignancy and some nearby normal biliary tract tissues, the secondary tissue cell necrosis might increase bile and related necrosis factors in the blood, further inducing biliary tract infection[30]. However, Hasimu et al[31] suggested that ^{125}I particle strip biliary cavity irradiation therapy facilitates improvements in the body's immune function, although the mechanism of action is unclear. The effects of ^{125}I particle stent on immunity and its mechanism of action are still controversial and need to be clarified through further studies.

The duration of surgery is also an independent risk factor for biliary tract infection after stent implantation, and according to Haridas[32], the risk of infection increases as the duration of surgery increases. The exposure of tissue to air increases as the operative time increases. If the air in the operating room is not disinfected thoroughly, the chance of infection in patients increases. The ^{125}I-particle stent implantation procedure is more complex than a standard bare stent, with more unpredictable intraoperative conditions and a longer average operative time. These factors also increase the incidence of infection to some extent.

Under normal circumstances, the biliary system lacks gases, and medical factors mainly cause intrahepatic bile duct pneumatosis. Surgery can cause impairments in the function of the sphincter of Oddi, retrograde entry of gas and bacteria from the intestine into the bile duct, gas production by gas-producing bacteria leading to biliary pneumatosis[33], and an increase in the chance of developing biliary tract infection. We found 91 cases of biliary pneumatosis, including 28 cases (38.4 %) in the infected group and 63 cases (28.9 %) in the non-infected group. The results of the univariate analysis showed that postoperative biliary pneumatosis was an independent risk factor for postoperative complications of biliary tract infection. Therefore, attending physicians should pay attention to the occurrence of bile duct pneumatosis during postoperative imaging review, and the presence of bile duct pneumatosis should be promptly treated by flushing the bile duct and applying antibiotics quickly to avoid or alleviate biliary tract infection.

The current study's results indicated that the absence of preoperative prophylactic antibiotics, preoperative Hb, and preoperative Alb were risk factors for biliary tract infection after percutaneous biliary stenting. Preoperative prophylactic antibiotics might be administered to prevent infection. For the target of prophylactic antibiotics, the American Society of Gastrointestinal Endoscopy[34] recommends prophylactic anti-infection treatment in patients with a history of liver transplantation or biliary obstruction but recommends not administering routine prophylactic anti-infection therapy before endoscopic retrograde cholangiopancreatography (ERCP) for general patients; whereas, the European Society of Gastrointestinal Endoscopy[35] recommends that prophylactic antibiotics might be administered to patients with biliary drainage insufficiency and severely compromised immune function. Patients requiring choledochoscopy in ERCP should be administered antibiotic prophylaxis before ERCP and continued postoperatively. The preoperative Hb levels were correlated with immunity and the body's nutritional status; lower levels of Alb and Hb were associated with the body's lower resistance to foreign adverse factors and a higher risk of infection after the invasion of biliary pathogenic microorganisms. These findings suggested that the postoperative indices and signs of patients with low preoperative Hb and Alb levels should be monitored closely to effectively reduce the risk of biliary tract infection after treatment.

The factors potentially affecting patients' prognosis based on the results of Cox risk regression screening included whether biliary tract infection occurred after surgery, whether diabetes mellitus was combined, the preoperative Child-Pugh score, whether antibiotics were administered prophylactically, and the type of obstruction. The liver function based on Child-Pugh grade and the biliary obstruction type were not found to be independent risk factors for postoperative biliary tract infection but reflected patients' condition and correlated with prognosis. The complex pathophysiological mechanism of biliary obstruction caused by CCA may lead to rapid deterioration and progression of the disease course, which often has a poor survival prognosis. Monitoring multiple factors that might contribute to postoperative infections and decreasing the incidence of postoperative infection can help improve the prognosis of patients with CCA who undergo percutaneous biliary stenting.

This study initially identified the risk factors and prognostic effect of biliary tract infection after percutaneous biliary stenting in CCA patients. Our findings provided a theoretical basis for effectively preventing and treating biliary tract infection risk after treatment. Nevertheless, many factors are associated with biliary tract infection after percutaneous biliary stenting, and more randomized controlled studies involving many participants are needed to investigate the critical risk factors further.

The study suffered some limitations as it was retrospective, and the data were collected over a long time, even though the study indicators were obtained from the data collected in the same hospital. Thus, laboratory tests and treatment methods might influence the data collected in different periods differently. Also, the study's sample size was small, and the risk factors included in the indicator analysis were limited.

Conclusion

Biliary tract infection is the most common complication after biliary interventions, and severe infection may even lead to death. Clinical studies should analyze and evaluate patients' clinical characteristics, perioperative indicators, and relevant serological indicators, identify relevant risk factors, and administer prompt treatment to reduce the chance of infection and improve patients' prognosis.

Conflict of interest

The authors have no conflicts of interest to declare.

References

1. Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020; 17: 557-588.
2. Elvevi A, Laffusa A, Scaravaglio M, Rossi RE, Longarini R, Stagno AM, et al. Clinical treatment of cholangiocarcinoma: an updated comprehensive review. Ann Hepatol. 2022; 27: 100737.
3. Mauro E, Ferrer-Fàbrega J, Sauri T, Soler A, Cobo A, Burrel M, et al. New Challenges in the Management of Cholangiocarcinoma: The Role of Liver Transplantation, Locoregional Therapies, and Systemic Therapy. Cancers (Basel). 2023; 15: 1244.
4. Yao J, Liang X, Liu Y, Li S, Zheng M. Trends in Incidence and Prognostic Factors of Two Subtypes of Primary Liver Cancers: A Surveillance, Epidemiology, and End Results-Based Population Study. Cancer Control. 2022; 29: 10732748211051548.
5. Luo J, Shao GL, Yao HX, Zheng JP, Zhang ZW, Cao F, et al. The efficacy and safety of biliary stenting alone versus stenting combined with iodine-125 seed strand implantation for the treatment of cholangiocarcinoma with malignant obstructive jaundice: a prospective, nonrandomized, controlled clinical study. Ann Palliat Med. 2022; 11: 2422-2431.
6. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen HJ, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol. 2022; 76: 1109-1121.
7. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023; 34: 127-140.
8. Barkay O, Mosler P, Schmitt CM, Lehman GA, Frakes JT, Johanson JF, et al. Effect of endoscopic stenting of malignant bile duct obstruction on quality of life. J Clin Gastroenterol. 2013; 47: 526-531.
9. Huang P, Zhang H, Zhang XF, Lv W, Lou S. Comparison of Endoscopic Ultrasonography Guided Biliary Drainage and Percutaneous Transhepatic Biliary Drainage in the Management of Malignant Obstructive Jaundice After Failed ERCP. Surg Laparosc Endosc Percutan Tech. 2017; 27: e127-e131.
10. Sharaiha RZ, Khan MA, Kamal F, Tyberg A, Tombazzi CR, Ali B, et al. Efficacy and safety of EUS-guided biliary drainage in comparison with percutaneous biliary drainage when ERCP fails: a systematic review and meta-analysis. Gastrointest Endosc. 2017; 85: 904-914.
11. Xia N, Gong J, Lu J, Chen ZJ, Zhang LY, Wang ZM. Percutaneous intraductal radiofrequency ablation for treatment of biliary stent occlusion: A preliminary result. World J Gastroenterol. 2017; 23: 1851-1856.
12. Li J, Liu Y, Wang B, Sun X, Meng X. Malignant melanoma of the esophagus complicated with poorly differentiated mucinous adenocarcinoma of the stomach: A case report. Medicine (Baltimore). 2019; 98: e14783.
13. Cui W, Wang Y, Fan W, Lu M, Zhang Y, Yao W, et al. Comparison of intraluminal radiofrequency ablation and stents vs. stents alone in the management of malignant biliary obstruction. Int J Hyperthermia. 2017; 33: 853-861.
14. Skipworth JR, Olde Damink SW, Imber C, Bridgewater J, Pereira SP, Malagó M. Review article: surgical, neo-adjuvant and adjuvant management strategies in biliary tract cancer. Aliment Pharmacol Ther. 2011; 34: 1063-1078.
15. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59: 225-249.
16. Kurniawan J, Hasan I, Gani RA, Simadibrata M. Mortality-related Factors in Patients with Malignant Obstructive Jaundice. Acta Med Indones. 2016; 48: 282-288.
17. Crosara Teixeira M, Mak MP, Marques DF, Capareli F, Carnevale FC, Moreira AM, et al. Percutaneous transhepatic biliary drainage in patients with advanced solid malignancies: prognostic factors and clinical outcomes. J Gastrointest Cancer. 2013; 44: 398-403.
18. Meller MT, Arts GR, Dean JR. Outcomes in percutaneous stenting of non-hepato-biliary/pancreatic malignant jaundice. Eur J Cancer Care (Engl). 2010; 19: 664-668.
19. Royo-Cebrecos C, Gudiol C, García J, Tubau F, Laporte J, Ar-

danuy C, et al. Characteristics, aetiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours: A prospective cohort study. J Infect. 2017; 74: 172-178.
20. Sarkodie BD, Botwe BO, Brakohiapa EKK. Percutaneous transhepatic biliary stent placement in the palliative management of malignant obstructive jaundice: initial experience in a tertiary center in Ghana. Pan Afr Med J. 2020; 37: 96.
21. Bill JG, Mullady DK. Stenting for Benign and Malignant Biliary Strictures. Gastrointest Endosc Clin N Am. 2019; 29: 215-235.
22. Kimura Y, Takada T, Strasberg SM, Pitt HA, Gouma DJ, Garden OJ, et al. TG13 current terminology, etiology, and epidemiology of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013; 20: 8-23.
23. Zimmer V, Glanemann M, Lammert F. Acute and Chronic Inflammation of the Biliary System. Viszeralmedizin. 2015; 31: 153-154.
24. Yin R, Xu S, Gong Y, Zhu J, Zhu H, Tao Y, et al. The risk factors of biliary fistula after radical resection of perihilar cholangiocarcinoma in elderly patients and its influence on prognosis: a retrospective cohort study. J Gastrointest Oncol. 2023; 14: 390-404.
25. Summart U, Sangruangake M, T Teinprasert S, Chaplik N, Srisuwan P. Validation of the Thai Version of the Memorial Symptom Assessment Scaled - Short Form Among Cholangiocarcinoma Patients. Asian Pac J Cancer Prev. 2022; 23: 3851-3857.
26. Li Y, Xiao Y, Gao W, Pan J, Zhao Q, Zhang Z. Gymnemic acid alleviates inflammation and insulin resistance via PPARδ- and NFκB-mediated pathways in db/db mice. Food Funct. 2019; 10: 5853-5862.
27. Xu X, Ling Q, He ZL, Gao F, Zheng SS. Post-transplant diabetes mellitus in liver transplantation: Hangzhou experience. Hepatobiliary Pancreat Dis Int. 2008; 7: 465-470.
28. Avaliani M, Chigogidze N, Nechipai A, Dolgushin B. Magnetic compression biliary-enteric anastomosis for palliation of obstructive jaundice: initial clinical results. J Vasc Interv Radiol. 2009; 20: 614-623.
29. An J, Dong Y, Niu H, Li Y, Han X, Zou Z, et al. Comparative Study on Nosocomial Biliary Tract Infection Rate Between Biliary Stent Loaded with Radioactive 125 I Seeds and Conventional Biliary Stent in the Treatment of Distal Malignant Biliary Obstruction. Surg Laparosc Endosc Percutan Tech. 2022; 32: 724-729.
30. Patel S, Tuite CM, Mondschein JI, Soulen MC. Effectiveness of an aggressive antibiotic regimen for chemoembolization in patients with previous biliary intervention. J Vasc Interv Radiol. 2006; 17: 1931-1934.
31. Hasimu A, Gu JP, Ji WZ, Zhang HX, Zhu DW, Ren WX. Comparative Study of Percutaneous Transhepatic Biliary Stent Placement with or without Iodine-125 Seeds for Treating Patients with Malignant Biliary Obstruction. J Vasc Interv Radiol. 2017; 28: 583-593.
32. Haridas M, Malangoni MA. Predictive factors for surgical site infection in general surgery. Surgery. 2008; 144: 496-501; discussion 501-503.
33. Okan İ, Tali S, Özsoy Z, Deniz Ç, Acu B, Yenidoğan E, et al. The development of pneumobilia after blunt trauma. Ulus Cerrahi Derg. 2015; 32: 224-225.
34. ASGE Standards of Practice Committee; Chandrasekhara V, Khashab MA, Muthusamy VR, Acosta RD, Agrawal D, et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017; 85: 32-47.
35. Dumonceau JM, Kapral C, Aabakken L, Papanikolaou IS, Tringali A, Vanbiervliet G, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2020; 52: 127-149.