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Research article

The usefulness of preoperative bile cultures for hepatectomy with biliary reconstruction

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ABSTRACT

Background: Infectious complications can cause lethal liver failure after hepatectomy with biliary reconstruction. This study assessed the increased risk for postoperative infectious complications in patients who underwent hepatectomy with biliary reconstruction and explored the possibility of predicting pathogenic microorganisms causing postoperative infectious complications based on preoperative monitoring of bile cultures.

Methods: This study involved 310 patients who received major hepatectomy with or without biliary reconstruction at our institution between January 2010 and December 2019. The relationship between the microorganisms detected through perioperative monitoring of bile culture and those in the postoperative infectious foci was examined.

Results: Forty-nine patients underwent major hepatectomy with biliary reconstruction, and 261 received hepatectomy without biliary reconstruction. The multivariate analysis revealed hepatectomy with biliary reconstruction to be associated with an increased risk of postoperative infectious complications (odds ratio: 22.9, 95% confidence interval: 5.2–164.3) compared to hepatectomy without biliary reconstruction. In the patients with biliary reconstruction, the concordance rates between the microorganisms detected in the postoperative infectious foci and those in preoperative bile cultures were as follows: incisional surgical site infection (44.4%), organ/space surgical site infection (52.9%), bacteremia (47.1%), and pneumonia (16.7%); the concordance rates were high, and the risk of infection increased over time.

Conclusions: Biliary reconstruction is a significant risk factor for postoperative infectious complications, and preoperative bile cultures may aid in prophylactic and therapeutic antimicrobial agent selection.

1. Introduction

Advanced biliary tract cancer often causes biliary stricture and obstructive jaundice, so many such patients develop biliary infections before surgery [1, 2]. Advanced biliary tract cancer often requires highly invasive operations, including extended hepatectomy with biliary reconstruction. Despite recent improvements in surgical techniques and perioperative management, hepatectomy with biliary reconstruction still carries a high rate of complication mortality [3, 4, 5, 6]. In particular, inadequate control of biliary infections can lead to severe postoperative infectious complications and liver failure [7, 8].

Preoperative biliary drainage is often performed for patients with obstructive jaundice [7, 9]. A sample of bile cultures can be obtained in patients with external biliary drains before surgery, enabling surveillance of biliary colonization. If biliary colonization is deemed likely to contribute to postoperative infectious complications, the administration of prophylactic and therapeutic antimicrobial agents based on bile cultures can prevent and help manage postoperative infectious complications, thereby helping to reduce mortality and decrease the duration of hospitalization.

The present study explored the risk of postoperative infectious complications in patients who underwent biliary reconstruction and assessed the possibility of predicting which pathogenic microorganisms might cause postoperative infectious complications based on the preoperative monitoring of bile cultures.

2. Methods

2.1. Patients

This study was a retrospective observational study conducted at a single institution (Kyoto University Hospital, Kyoto, Japan). The study

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protocol was approved by the Ethics Committee of the Graduate School of Medicine, Kyoto University (R1721-1), and performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all study participants. This study involved 310 consecutive patients who underwent major hepatectomy with or without biliary reconstruction at our institution between January 2010 and December 2019. In this study, major hepatectomy was defined as right or left hepatectomy and right or left trisectionectomy.

2.2. Preoperative management

All patients who had preoperative obstructive jaundice underwent preoperative biliary drainage with endoscopic naso-biliary drainage (ENBD), an endoscopic biliary stent (EBS), or percutaneous transhepatic biliary drainage (PTBD). Preoperative bile culture samples were obtained via external drainage at the time of biliary drain placement and during the preoperative period. In patients who had preoperative cholangitis, antimicrobial agents were administrated based on the results of the preoperative biliary cultures. Surgeries were performed only after complete improvement of cholangitis with no fever, a normal white blood cell count and C-reactive protein levels, and no cholangitis flare-ups after completion of antimicrobial therapy. In patients who underwent preoperative biliary drainage, oral replacement of externally drained bile was performed to maintain the intestinal immune function [10]. Percutaneous transhepatic portal vein embolization was performed as needed in order to achieve residual hepatic enlargement.

2.3. Surgical procedure

All surgeries were performed in the absence of any infection, including preoperative cholangitis. The operative procedure was determined based on the location of the tumor diagnosed by preoperative computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and cholangiography. Biliary reconstruction was performed via Roux-en-*Y choledochojejunostomy* in all patients. In hepatopancreatoduodenectomy (HPD), pancreaticojejunostomy or pancreaticogastrojejunostomy, choledochojejunostomy, and gastrojejunostomy were performed in this order. All anastomosed bile ducts were drained externally. Drains were placed at the site of choledochojejunostomy and pancreaticojejunostomy. The wound margins were protected with a surgical ring or gauze to prevent surgical site infection (SSI). Hepatic parenchymal dissection was performed with CUSA EXcel and bipolar cautery equipped with a channel for water dripping. An intermittent Pringle maneuver or selective vascular clamping, if necessary, was applied to reduce the blood inflow of the liver. A jejunostomy tube was surgically placed for nutrition in patients who underwent hepatectomy with biliary reconstruction. Intraperitoneal irrigation and wound irrigation with warm saline were routinely performed.

2.4. Postoperative management

Enteral feeding was initiated on the day after surgery in patients with a jejunostomy tube. In patients with an external biliary drain, replacement of the drained bile juice was performed through the jejunostomy tube. Postoperative symbiotic therapy was administered from the start of oral intake. Routine blood examinations were performed 1, 2, 3, 5, 7, 9, 12, and 14 days after surgery, and additional blood examinations were performed as needed. CT was performed routinely on day 7. Bile was routinely collected from the external drain of the anastomosed bile ducts as a surveillance, and the timing depended on the surgeon. Some bile was collected at the time the patients developed a fever, but most was routinely collected from patients with no fever. Abdominal fluid was routinely collected from the abdominal drains and cultured. Blood culture was performed when a patient developed a fever over 38.0 °C and/or had other infectious sources. Sputum was collected and cultured when a patient developed pneumonia. The abdominal drains were removed as soon as possible in cases with clear drainage fluid in the absence of any microorganisms.

2.5. Selection and administration of antimicrobial agents

Second-generation cephems were routinely used for antimicrobial prophylaxis according to the CDC guideline for Class II/Clean-Contaminated surgical wounds [11] in patients with negative preoperative monitoring of bile culture or those for whom preoperative monitoring of a bile culture had not been performed. If pathogenic microorganisms were detected in the preoperative monitoring of bile cultures, antimicrobial prophylaxis was selected based on the susceptibility of the detected organisms. When multiple organisms were detected, multiple susceptible antimicrobial agents were used.

On the day of surgery, all patients received a single intravenous drip infusion of antibiotics 30 min before surgery [12, 13]. Additional antimicrobial agents were administered to maintain a therapeutic level of the antimicrobial agents in blood and tissue throughout the surgery. Many antimicrobial agents were administered every 3 h, while VCM, new quinolone, and tetracycline were administered every 24 h. Additional antimicrobial prophylaxis was administered until 72–96 h after surgery. Antimicrobial prophylaxis was decreased appropriately depending on the patients' renal function. Additional therapeutic antimicrobial agents were administered based on various culture results when a patient developed signs of infection, such as a fever over 38 °C and an elevated white blood cell count.

2.6. Postoperative infectious complications

All patients were routinely followed for 90 days after surgery, as either inpatients or outpatients. Postoperative complications up to 90 days after surgery were collected from the medical records. Superficial and deep incisional SSI (I–SSI), organ/space SSI (O–SSI), bacteremia, pneumonia, postoperative cholangitis, and catheter-related infections were considered postoperative infectious complications. SSI was defined based on the criteria of the CDC guideline [11]. In brief, SSI was diagnosed when purulent discharge from the wounds or abdominal drains with positive results from cultures was observed within 30 days after surgery. In this study, I–SSI was defined as that involving both superficial incisional SSI, in which only the skin and subcutaneous tissue were infected, and deep incisional SSI, in which the deeper soft tissue (fascia and muscle layer) was infected. O–SSI was also defined when evidence of infection was present during reoperation and/or was shown on radiological studies, including CT. The day when this definition was met was defined as the onset date. I–SSI and O–SSI were routinely noted in the medical records. In addition, all laboratory data were reviewed to prevent any oversights. Bacteremia was defined as an isolate of microorganisms grown in any one of two sets of blood cultures. When the isolated microorganism was identified as a coagulase-negative *Staphylococcus*, the diagnosis of bacteremia required the isolation of the microorganism from both of the blood cultures [14]. The onset date was defined as the date when the blood culture was submitted for examinations. Pneumonia was defined as a characteristic pulmonary infiltrate on a chest radiograph accompanied by leukocytosis with bacterial detection from the sputum. In patients who met this definition, the onset date was defined as the date when the sputum culture was submitted for an examination. Cholangitis was defined when patients had a fever over 38 °C with elevated liver enzyme levels, jaundice (if any), or a white blood cell count of $\geq$10,000 and when other infections were ruled out. The onset date was defined as the date of the fever or when the white blood cell count was increased. Catheter-related infections were defined based on the criteria of the CDC guidelines [15]. In brief, these infections were defined as bacteremia or fungemia in patients with indwelling vascular catheters accompanied by certain clinical signs of infection (e.g. a fever, chills, hypotension, etc.). In addition, catheter-related infections were diagnosed in cases with no apparent cause of bloodstream infection other than the catheter when the same organisms were isolated from both the catheter and peripheral blood culture. The onset date was defined as the date when the catheter culture or peripheral blood culture was submitted for an examination. If a patient had multiple infectious complications, multiple counts were allowed. When the same species of microorganism was detected in the same patient from different infectious foci, multiple counts were allowed. Only one count was allowed when the same microorganism was detected from the same infectious foci. When multiple microorganisms were detected in one culture specimen, all of them were counted.

2.7. Concordance between microorganisms isolated from postoperative infectious foci and those isolated from perioperative bile cultures

The relationship between the microorganisms detected in the perioperative bile culture and the pathogenic microorganisms detected in the postoperative foci of infection was examined. Concordance was defined when there was at least one match between microorganisms isolated from postoperative infectious foci and microorganisms isolated from preoperative bile cultures or postoperative bile cultures before the onset of postoperative infectious complications. When specimens were collected more than once from postoperative infectious foci, concordance was defined if the microorganisms matched at least once. Over the course of the postoperative period, the number of patients who showed "concordance" was cumulatively added up. By dividing this number by the total number of patients who experienced each postoperative infectious complication, the cumulative concordance rates were then calculated.

2.8. Statistical analyses

Continuous data were expressed as median and range and analyzed using the Wilcoxon rank sum test. Categorical data were analyzed using Fisher's exact test. A multivariate analysis was performed using logistic regression models: clinical parameters with P values of <0.01 were entered into a logistic regression analysis to identify independent risk factors for postoperative infectious complications. A P value of <0.05 was considered statistically significant. The R statistical software program, version 3.6.0, was used for all statistical analyses.

3. Results

3.1. Patient characteristics

Between 2010 and 2019, a total of 310 patients who underwent major hepatectomy were enrolled in the study. Two-hundred and sixty-one patients received major hepatectomy (lobectomy or more) without biliary reconstruction (control group), and 49 patients underwent hepatectomy with extrahepatic bile duct resection, biliary reconstruction, and preoperative biliary drainage (study group).

The characteristics of each group are summarized in Table 1. In the study group, most of the patients had extrahepatic bile duct cancer (n = 47, 95.9%), while in the control group, 126 (48.3%), 97 (37.2%), and 35 (13.4%) patients had hepatocellular carcinoma, metastatic liver cancer, and intrahepatic cholangiocarcinoma, respectively; there were no cases of extrahepatic bile duct cancer. Eleven patients (22.4%) in the study group underwent HPD, and none in the control group underwent HPD. In the study group, lymph node dissection was performed in all patients, and none underwent laparoscopic surgery. Both hepatic artery and portal vein reconstruction were performed in 8 patients (16.3%) in the study group but in none in the control group. Inferior vena cava (IVC) resection was not performed in the study group but was performed in 13 patients (5%) in the control group. The patients in the study group had a significantly longer operative time ($P < 0.001$), greater operative blood loss ($P < 0.001$), and more frequent blood transfusions ($P < 0.001$) than those in the control group. The most common prophylactic antimicrobial in the study group was oxacephem (n = 26, 53.1%), followed by cephalosporin (n = 11, 22.4%). The median duration of antimicrobial prophylaxis was four days.

Table 1. Patient characteristics.

	Study (n = 49)	Control (n = 261)	*P*-value
Age (years), median (range)	67 (33–48)	68 (20–90)	0.714
Sex	Male: 34	Male: 190	0.606
	Female: 15	Female: 71	
Total bilirubin (mg/dL), median (range)	1.1 (0.4–41.8)	0.7 (0.3–3.4)	**<0.001**
Diagnosis, *n* (%)			**<0.001**
Hepatocellular carcinoma	0	126 (48.3)	
Intrahepatic cholangiocarcinoma	0	35 (13.4)	
Extrahepatic bile duct cancer	47 (95.9)	0 (0.0)	
Metastatic liver cancer	0	97 (37.2)	
Others	2 (4.1)	3 (1.1)	
Preoperative monitoring of bile culture	46 (93.9)	0 (0.0)	**<0.001**
Operative procedure, *n* (%)			**<0.001**
Right hemi hepatectomy	19 (38.8)	136 (52.1)	
Right trisectionectomy	4 (8.2)	9 (3.4)	
Left hemi hepatectomy	8 (16.3)	107 (41.0)	
Left trisectionectomy	7 (14.3)	9 (3.4)	
Hepatopancreatoduodenectomy	11 (22.4)	0 (0.0)	
Lymph node dissection	49 (100)	35 (13.4)	**<0.001**
Laparoscopic surgery	0 (0.0)	38 (14.6)	**0.001**
Both portal vein and hepatic artery resection	8 (16.3)	0 (0.0)	**<0.001**
IVC resection	0 (0.0)	13 (5.0)	0.234
Operative time (min), median (range)	682 (552–2660)	429 (206–975)	**<0.001**
Operative blood loss (g), median (range)	1500 (360–5810)	705 (0–11980)	**<0.001**
Blood transfusion, *n* (%)	27 (55.1)	61 (23.4)	**<0.001**
Antimicrobial prophylaxis, *n* (%)			**<0.001**
Oxacephem	26 (53.1)	0 (0.0)	
Second generation	26 (53.1)	253 (96.9)	
Cephalosporin	11 (22.4)	0 (0.0)	
First generation	0 (0.0)	0 (0.0)	
Second generation	0 (0.0)	0 (0.0)	
Third generation	7 (14.3)	2 (0.77)	
Fourth generation	4 (8.2)	0 (0.0)	
β-Lactam	4 (8.2)	3 (1.15)	
β-Lactam/β-Lactamase inhibitor	5 (10.2)	3 (1.15)	
Cephalosporin Third/β-Lactamase	3 (6.1)	0 (0.0)	
Carbapenem	4 (8.2)	1 (3.8)	
Tetracycline	1 (2.0)	0 (0.0)	
Combination regimen	5 (10.2)	1 (3.8)	
Postoperative infectious complication, *n* (%)	34 (69.4)	26 (10.0)	**<0.001**
SSI	25 (51.0)	19 (7.3)	**<0.001**
Superficial and deep incisional SSI	11 (22.4)	7 (2.7)	**<0.001**
Organ/space SSI	22 (44.9)	15 (5.7)	**<0.001**
Bacteremia	19 (38.8)	7 (2.7)	**<0.001**
Pneumonia	7 (14.3)	4 (1.5)	**<0.001**
Other infectious complication	9 (18.4)	6 (2.3)	**<0.001**
Cholangitis	7 (14.3)	4 (1.5)	**<0.001**
Catheter-related bloodstream infection	2 (4.1)	1 (0.4)	0.066
Clavien grade of infectious complication ≥3a	22 (44.9)	19 (7.3)	**<0.001**

IVC: inferior vena cava, SSI: surgical site infection.

3.2. Postoperative infectious complications

The postoperative infectious complications that occurred within 90 days are summarized in Table 1. Postoperative infectious complications were observed in 34 patients (69.4%) in the study group and 26 (10%) in the control group, with a significant difference ($P < 0.001$). In the study group, I–SSI was observed in 11 patients (22.4%), O–SSI in 22 patients (44.9%), bacteremia in 19 patients (38.8%), pneumonia in 7 patients (14.3%), and postoperative cholangitis in 7 patients (14.3%). Each complication occurred more frequently than in the control group with a significant difference ($P < 0.001$). There was no significant difference in the frequency of catheter-related bloodstream infections between the two groups. Severe infectious complications, namely those with Clavien-Dindo grade of ≥3a, occurred more frequently in the study group (n = 22, 44.9%) than in the control group (n = 19, 7.3%) with a significant difference ($P < 0.001$). The mortality in the study group (n = 5, 10.2%) was also higher than that in the control group (n = 4, 1.5%) with a significant difference ($P < 0.004$).

3.3. Risk factors for postoperative infectious complications

To identify possible risk factors for postoperative infectious complications, the 10 clinical variables were subjected to univariate analyses, which indicated that a high value of preoperative total bilirubin (≥2 mg/dL), the presence of biliary reconstruction, the presence of lymph node dissection, the presence of both portal vein and hepatic artery reconstruction, the presence of blood transfusion, and a long operation duration (≥720 min) were significant for postoperative infectious complications. A multivariate analysis revealed that hepatectomy with biliary reconstruction was an independent risk factor for postoperative infectious complications (odds ratio [OR] = 22.9, 95% confidence interval [CI]: 5.23–164.34, $P < 0.001$) (Table 2).

3.4. Microorganisms isolated from postoperative infectious foci

The microorganisms isolated from postoperative infectious foci are summarized in Table 3. In the study group, one of the most commonly isolated microorganisms was *Enterococcus* spp. in I–SSI and O–SSI, and *Staphylococcus* spp. in bacteremia and pneumonia. *Enterobacter* spp., *Klebsiella* spp., *Pseudomonas* spp. and *Stenotrophomonas* spp. which were all Gram-negative rods, were isolated in all infection types. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Candida* spp. were isolated in all infection types, and extended-spectrum β-lactamase (ESBL)-producing *Klebsiella* was isolated in O–SSI and pneumonia. In the control group, *Staphylococcus* spp. and *Enterococcus* spp. were commonly isolated, similar to the study group, and MRSA was isolated in all infection types.

3.5. Microorganisms isolated from perioperative bile cultures

The microorganisms isolated from perioperative bile cultures are summarized in Supplementary Table 1. Microorganisms were detected in 41 (89.1%) of the 46 patients who underwent preoperative monitoring of bile cultures. *Enterococcus* spp. was the microorganism most commonly isolated from bile cultures during the perioperative period. The microorganism detection rates of the bile cultures are shown in Figure 1. The proportion of *Enterococcus* spp. in the postoperative bile microbiota tended to increase gradually after surgery. MRSA and Candida were isolated from the bile cultures in both the preoperative and postoperative periods. However, ESBL-producing *Klebsiella* was not isolated from the bile cultures during the perioperative period. The concordance rate between the microorganisms detected in the preoperative bile cultures and those detected in the postoperative bile cultures was 65.9% (27/41). The number of patients with no microorganisms detected in the bile was 17 (43.6%) during the period from postoperative day (POD) 0 to POD 5. However, it decreased to 4 (12.1%) during the period from POD 6 to POD 10 and fell to 0 from POD 11 onward.

3.6. Concordance between microorganisms isolated from postoperative infectious foci and those isolated from perioperative bile cultures

The concordance rates between the microorganisms detected in the postoperative infectious foci and those in perioperative bile cultures were 6/9 (66.7%) for I–OSSI, 18/20 (90.0%) for O–SSI, 15/19 (78.9%) for bacteremia, and 7/7 (100%) for pneumonia. The concordance rates between the microorganisms detected in the postoperative infectious foci and those in the postoperative bile cultures were 6/8 (75.0%) for I–SSI, 16/18 (88.9%) for O–SSI, 13/17 (76.5%) for bacteremia, and 6/6 (100%) for pneumonia. In addition, the concordance rates between the microorganisms detected in the postoperative infectious foci and those in the preoperative monitoring of bile cultures were 4/9 (44.4%) for I–SSI, 9/17 (52.9%) for O–SSI, 8/17 (47.1%) for bacteremia, and 1/6 (16.7%) for pneumonia (Table 4). Therefore, the results of preoperative bile cultures were useful for predicting the microorganisms responsible for postoperative infectious complications. The cumulative concordance rates between the microorganisms isolated from postoperative infectious foci and those from the postoperative bile cultures are shown in Figure 2. The cumulative concordance rates showed a time-dependent increase in all types of infectious complications.

3.7. The onset of postoperative infectious complications

The median onset of I–SSI, O–SSI, bacteremia, pneumonia, postoperative cholangitis, and catheter-related bloodstream infections was at POD 8, POD 10, POD 22, POD 27, POD 9, and POD 50, respectively (Figure 3a). The cumulative numbers of patients who had postoperative infectious complications are shown in Figure 3b. This value showed a time-dependent increase.

4. Discussion

Hepatectomy with biliary reconstruction has been reported to carry a high risk of postoperative infectious complications. Although the frequency of SSIs in hepatectomy without biliary reconstruction has been

Table 2. Univariate and multivariate analyses for postoperative infectious complications.

Variable	Univariate analysis	Multivariate analysis				
	P-value	B	S.E.	Wald	*P*-value	Odds ratio (95% CI)
Age, years (<70 vs. ≥70)	0.772					
Sex (Male vs. Female)	0.472					
Total bilirubin, mg/dL (<2 vs. ≥2)	**<0.001**	0.455	0.703	0.419	0.517	1.58 (0.41–6.61)
Biliary reconstruction (yes vs. no)	**<0.001**	3.132	0.843	13.796	**<0.001**	22.9 (5.23–164.34)
Lymph node dissection (yes vs. no)	**<0.001**	-0.596	0.764	0.607	0.436	0.55 (0.09–2.01)
Laparoscopic surgery (yes vs. no)	0.077					
Both portal vein and hepatic artery resection (yes vs. no)	**0.001**	0.243	0.927	0.069	0.794	1.27 (0.23–10.09)
IVC resection (yes vs. no)	0.080					
Blood transfusion, % (yes vs. no)	**<0.001**	0.633	0.368	2.953	0.086	1.88 (0.90–3.85)
Operative time, min (<720 vs. ≥720)	**<0.001**	0.339	0.534	0.403	0.526	1.40 (0.48–3.91)

IVC: inferior vena cava, CI: confidence interval, B: beta coefficient, S.E.: standard error, Wald: wald statistic.

Table 3. Microorganisms isolated from postoperative infectious foci.

	I–SSI		O–SSI		Bacteremia		Pneumonia	
	Study (n = 10)	Control (n = 4)	Study (n = 20)	Control (n = 13)	Study (n = 19)	Control (n = 6)	Study (n = 7)	Control (n = 4)
Total number of isolated microorganisms	20	4	57	19	34	6	15	7
Gram-positive bacteria, *n* (%)								
Enterococcus species	6 (30.0)	0 (0.0)	11 (19.3)	5 (26.3)	3 (8.8)	2 (33.3)	0 (0.0)	0 (0.0)
Staphylococcus species	3 (15.0)	4 (100)	9 (15.8)	6 (31.6)	5 (14.7)	3 (50.0)	4 (26.7)	1 (14.3)
MRSA	3 (15.0)	1 (25.0)	4 (7.0)	3 (15.8)	3 (8.8)	1 (16.7)	4 (26.7)	1 (14.3)
Bacillus species	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Others	0 (0.0)	0 (0.0)	2 (3.5)	1 (5.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Gram-negative bacteria								
Acinetobacter species	0 (0.0)	0 (0.0)	2 (3.5)	1 (5.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Enterobacter species	3 (15.0)	0 (0.0)	4 (7.0)	1 (5.3)	4 (11.8)	0 (0.0)	2 (13.3)	2 (28.6)
Klebsiella species	2 (10.0)	0 (0.0)	3 (5.3)	1 (5.3)	3 (8.8)	0 (0.0)	1 (6.7)	0 (0.0)
Klebsiella pneumoniae ESBL	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Pseudomonas species	2 (10.0)	0 (0.0)	4 (7.0)	1 (5.3)	1 (2.9)	0 (0.0)	2 (13.3)	2 (28.6)
Stenotrophomonas species	1 (5.0)	0 (0.0)	4 (7.0)	0 (0.0)	2 (5.9)	0 (0.0)	5 (33.3)	1 (14.3)
Serratia species	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Escherichia species	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Citrobacter species	0 (0.0)	0 (0.0)	3 (5.3)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Rhizobium species	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Others	2 (10.0)	0 (0.0)	5 (8.8)	0 (0.0)	4 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Candida species	1 (5.0)	0 (0.0)	7 (12.3)	2 (10.5)	6 (17.6)	0 (0.0)	1 (6.7)	1 (14.3)

I–SSI: incisional surgical site infection, O–SSI: organ/space surgical site infection, MRSA: methicillin-resistant *Staphylococcus aureus*, ESBL: extended-spectrum β-lactamase.

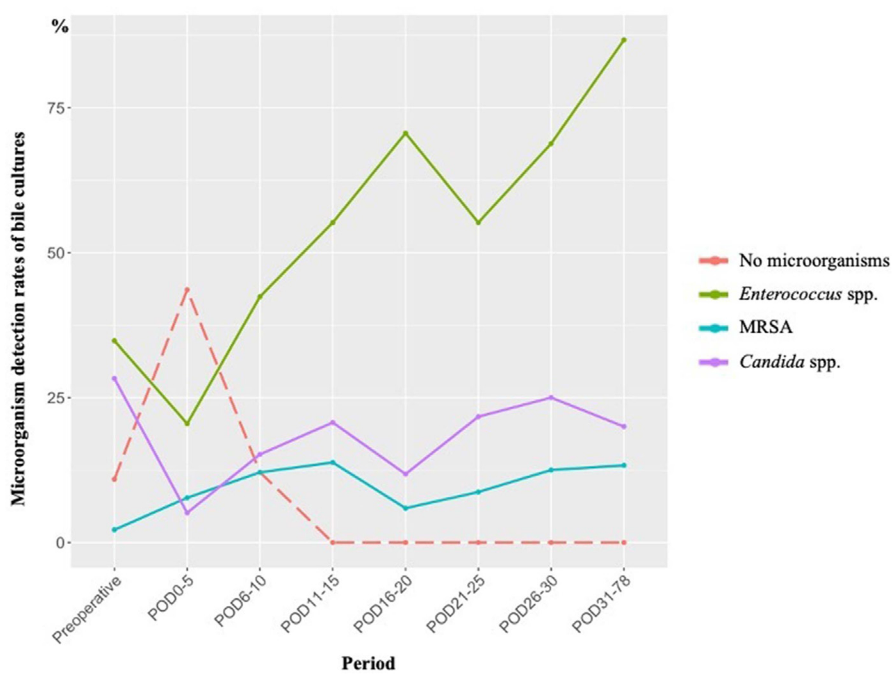

Figure 1. Microorganism detection rates of perioperative bile cultures in the study group.

reported to be approximately 10% [16, 17, 18, 19], the frequency of SSIs in hepatectomy with biliary reconstruction was 29%–75% [8, 17, 20, 21]. However, there have been no reports directly comparing patients with and without biliary reconstruction. The multivariate analysis in this study revealed that hepatectomy with biliary reconstruction (OR: 22.9, 95% CI: 5.23–164.34) was more likely to result in postoperative infectious complications than major liver resection without biliary reconstruction. As biliary infections can lead to serious complications, such as postoperative liver failure, controlling biliary infections might help reduce the mortality risk after hepatectomy with biliary reconstruction.

We speculated that preoperative biliary colonization might induce postoperative infectious complications after hepatectomy with biliary reconstruction. In patients with obstructive jaundice, biliary drainage is

Table 4. Concordance rate between the microorganisms detected in the postoperative infectious foci and those in the perioperative monitoring of bile cultures in the study group.

Infection foci	Preoperative Bile	Postoperative Bile
I–SSI	4/9 (44.4%)	6/8 (75.0%)
O–SSI	9/17 (52.9%)	16/18 (88.9%)
Bacteremia	8/17 (47.1%)	13/17 (76.5%)
Pneumonia	1/6 (16.7%)	6/6 (100%)

I–SSI: incisional surgical site infection, O–SSI: organ/space surgical site infection.

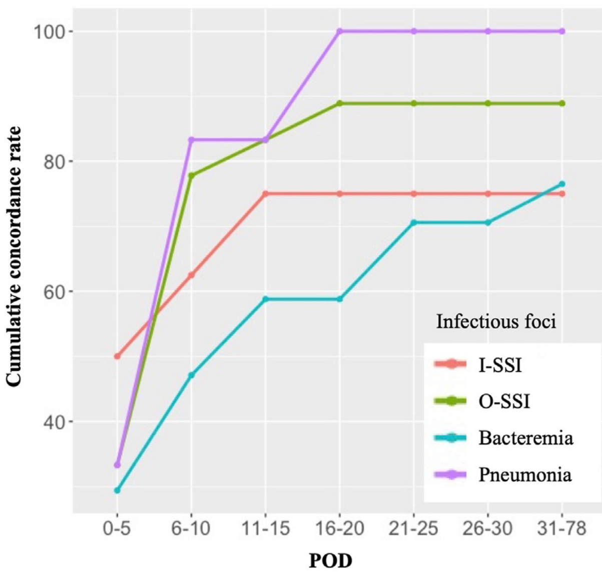

Figure 2. Cumulative concordance rates between the microorganisms isolated from postoperative infectious foci and those from postoperative bile cultures in the study group.

often performed [7, 9]. However, according to a previous study, approximately 75% of patients with preoperative biliary drainage had biliary colonization or infection with microorganisms at the time of surgery [2], and bile infection and preoperative cholangitis were indicated to be risk factors for postoperative infectious complications and increased hospital mortality [2, 8, 22]. In the present study, bacterial colonization in the drained bile was detected in 89.1% of the patients who had undergone preoperative biliary drainage. Because of the high concordance rate between the microorganisms detected in perioperative bile cultures and those detected in postoperative infectious foci, biliary colonization may be responsible for the development of postoperative infectious complications. In the present study, the concordance rate throughout the whole perioperative period was exceedingly high, ranging from 66.7% to 100% for each infectious focus, which was similar to the concordance rates reported in previous studies (range: 22%–88%) [2, 23, 24]. The concordance rate for the preoperative period was also high, ranging from 16.7% to 52.9%. These findings suggested that microorganisms in the bile may be disseminated into the abdominal cavity during surgery. The microorganisms found in preoperative bile cultures strongly matched not only those detected as sources of SSIs but also those detected in remote infectious foci, including pneumonia. These results suggest that the microorganisms causing postoperative infectious complications originated from those that had infiltrated the bile. Therefore, detecting such microorganisms via preoperative monitoring of bile cultures may facilitate the selection of appropriate antimicrobial prophylaxis and therapeutic antimicrobial agents [2, 22, 25, 26, 27].

According to the high concordance rate with preoperative bile cultures, antimicrobial prophylaxis against the microorganisms detected in preoperative bile cultures should be administered first. Since the concordance rates with preoperative bile cultures is not 100% and the cumulative concordance rates with postoperative bile cultures showed a time-dependent increase, postoperative monitoring of bile cultures should also be confirmed to select therapeutic antimicrobial agents. Cultures from postoperative infectious foci should be promptly investigated, and therapeutic antimicrobial agents should be changed if uncovered species are detected.

In this study, the mortality rate of the study group was high at 10.2% (five patients). However, most procedures were considered difficult: HPD (n = 2); left trisectionectomy (n = 2); and right hemi-hepatectomy with biliary reconstruction (n = 1). In addition, four occurred between 2010 and 2011. Since 2012, the mortality has been low (only one patient). This is possibly because the procedures had not been established and patient selection criteria were less stringent than they are today. Furthermore, several previous studies reported mortality rates after hepatectomy with

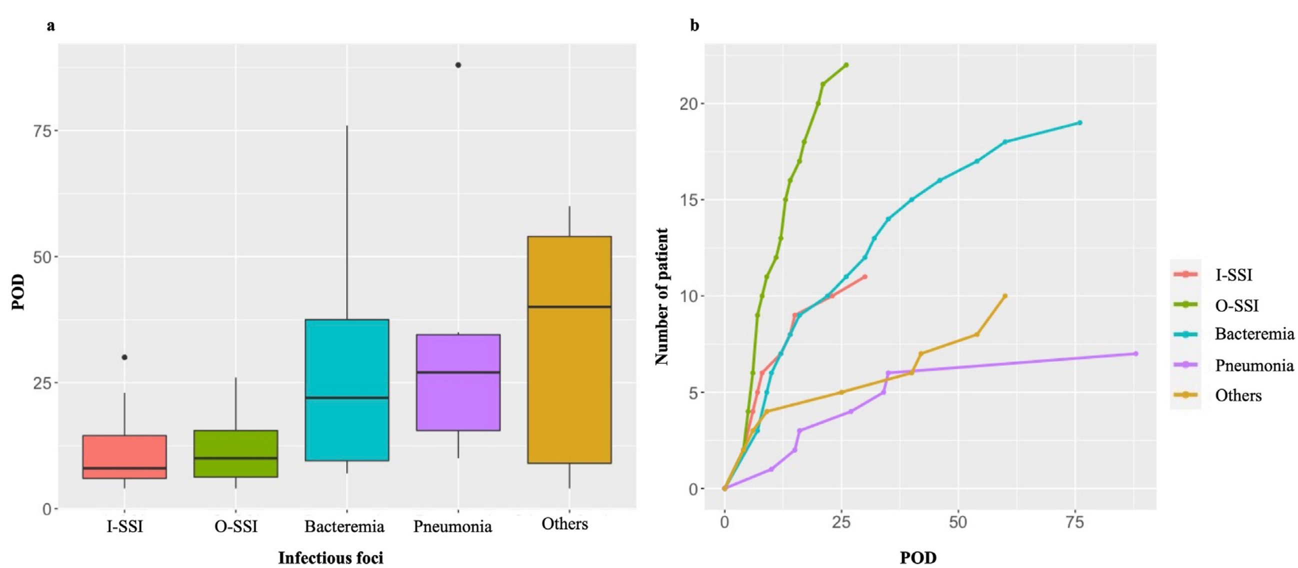

Figure 3. In the study group, the median onset of I–SSI, O–SSI, bacteremia, and pneumonia was at POD 8 (4–30), POD 10 [4-26], POD 22 (7–76), POD 27 (10–88), POD 9 (4–54), and POD 50 (40–60), respectively (a). The ranges are shown in parentheses. The cumulative number of patients with postoperative infectious complications (b).

biliary reconstruction of >10% [3, 6, 7, 8], which is comparable to this study. The incidence of SSI was also relatively high (51% in the study group). However, in a previous study on patients who underwent hepato-pancreato-biliary cancer surgery with biliary reconstruction, the incidence of SSI was 71% (44/62 patients) in patients treated with antimicrobial prophylaxis not based on preoperative bile cultures [28], and similarly, the incidence was 75% (61/78 patients) in another paper on patients who underwent major hepatectomy with biliary reconstruction [8]. Bundled perioperative care, including prophylactic antimicrobial agent selection based on preoperative bile cultures and appropriate nutritional support might contribute to the improvement of postoperative infectious complications.

Enterococcus spp., which were natural and acquired multiple-drug-resistant (MDR) bacteria, were one of the most common microorganisms detected in the postoperative bile cultures. In this study, the isolation rate of *Enterococcus* from the postoperative bile cultures tended to increase progressively with the passage of postoperative days. These results suggested that microorganisms infiltrated the aseptic bile as time passed and were likely derived from the intestinal microbiota (e.g., *Enterococcus* spp.). In addition, the cumulative number of patients with postoperative infectious complications increased linearly over time, with no obvious point of increase. In a previous study, the mortality of patients with postoperative infectious complications caused by MDR pathogens was higher than that in patients with postoperative infectious complications caused by non-MDR pathogens [21]. A randomized controlled trial that selected antimicrobial prophylaxis based on preoperative bile cultures reported that two-day administration of antimicrobial prophylaxis after surgery was sufficient for managing patients undergoing hepatectomy with extrahepatic bile duct resection [29]. Therefore, to minimize the emergence of MDR pathogens, antimicrobial agents should not be administrated indiscriminately for a long time.

To our knowledge, this is the first report to describe the detailed transition of microorganisms isolated from bile. Several limitations associated with the present study warrant mention. First, because this study was not a prospective study, the antimicrobial agent selection policy differed among patients. Second, the number of cases was small. Third, this study was performed at a single institution. Fourth, because bacterial identification was performed by classical bacteriological methods, without bacterial genome sequencing, whether or not the preoperative and postoperative microorganisms were identical was unclear. These limitations might weaken our discussion, so further studies to confirm our findings are necessary.

In conclusion, biliary reconstruction is a significant risk factor associated with postoperative infectious complications. Prophylactic and therapeutic antimicrobial agent selection based on preoperative bile cultures might contribute to the improvement of postoperative infectious complications. Periodic bile cultures are therefore recommended, even after surgery.

Declarations

Author contribution statement

Kenta Makino: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Takamichi Ishii: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Tomoaki Yoh, Satoshi Ogiso, Ken Fukumitsu, Satoru Seo, Kojiro Taura: Analyzed and interpreted the data.

Etsuro Hatano: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

The authors do not have permission to share data.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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