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Original Article

Risk factors, management, and prognosis for liver abscess after radical resection of hilar cholangiocarcinoma

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Abstract: Objectives: Pyogenic liver abscess (PLA) is a rare but potentially lethal infectious complication after radical surgical resection of hilar cholangiocarcinoma (HC), this study is aimed to identify the risk factors, management and prognosis of PLA after curative surgical resection of HC. Methods: Between January 2003 and October 2013, 95 patients who underwent surgical resection of HC at a tertiary center were included in this study. The risk factors pertaining to PLA formation were identified by exact logistic regression. Results: PLA developed in 8 of 95 patients. The median duration of PLA formation following surgical procedure was 145 days (range, 16-295 days) and the most commonly isolated microorganism was Escherichia coli (4/8). Though most patients who developed PLA after surgery were successfully managed with antibiotics and invasive therapy, the overall survival was statistically poorer than those without PLA formation (median, 16.9 *vs.* 34.2 months, *P*=0.048). Univariate analysis revealed that coexisting biliary disorders (37.5% *vs*. 8.0%, *P*=0.036), vascular reconstruction (37.5% *vs*. 9.2%, *P*=0.041) and margin status (62.5% vs. 21.8%, *P*=0.023) were associated with PLA formation, whereas only vascular reconstruction (odds ratio (OR), 10.31; 95% confidence interval (CI), 1.03-142.73; *P*=0.047) and margin status (OR, 8.45; 95% CI, 1.13-109.38; *P*=0.035) were identified as independent risk factors by multivariate analysis. Conclusions: Intraoperative vascular reconstruction and positive margin status pose greater risks for PLA formation after radical resection of HC. For patients with high risk factors, careful follow-up is needed for early detection and management of this infrequent complication.

Keywords: Pyogenic liver abscess, complications, hilar cholangiocarcinoma, surgical treatment

Introduction

Over the past two decades, extensive hepatectomy inclusive of segment I combined with radical biliary resection and lymphadenectomy of the hepatoduodenal ligament have been established as the standard operation for hilar cholangiocarcinoma (HC) [1-6]. Despite improvements in surgical techniques and perioperative management, postoperative morbidity still remains high, ranging from 43% [1] to 69% [5], even in many leading centers [1, 2, 4-6], among which, the postoperative infectious complication is a major problem [5, 7]. Pyogenic liver abscess (PLA) is an uncommon, but potentially lethal infectious complication after surgical resection of HC. However, detailed information about this complication, such as the incidence rate, treatment and outcome, is limited in the current literature [4, 6, 8, 9].

The aim of this retrospective study was to identify the potential risk factors, management and prognosis of PLA in patients who underwent surgical resection of HC based on a prospectively maintained database.

Material and methods

Patients

A retrospective review was done on 98 patients who had received surgical resection with curative intent for HC at the Binzhou Medical College affiliated hospital between January 2003 and October 2013. Data were extracted from a prospectively maintained database, and the study

was approved by the Institutional Review and Privacy Board of the Binzhou Medical College affiliated hospital. Three patients were excluded from this study due to in-hospital mortality caused by liver failure (2/3), and lost follow-up after discharge (1/3). PLA was diagnosed under the following criteria: (i) clinical symptoms of infection (e.g. fever, leukocytosis) and evidence of discrete abscess cavity of the liver from imaging studies (i.e. abdominal ultrasonography and/or computed tomography with contrast enhancement); (ii) positive bacterial blood or abscess culture results [10]. Cytological or pathological examination was performed with aspiration or biopsy of the hepatic lesion to rule out metastasis, and patients with PLA who had not undergone radical resection of HC were excluded from analysis.

Clinical data

Patient demographics, coexisting diseases (diabetes mellitus, biliary disorders, alcoholism, liver cirrhosis, etc.) and all other relative perioperative information (biochemical values, biliary drainage, ASA scores, type of operation, pathological margin status, UICC stage, degree of tumor differentiation, etc.) were collected. Preoperative percutaneous transhepatic biliary drainage (PTBD) or endoscopic naso-biliary drainage (ENBD) was performed to reduce serum bilirubin concentration for patients with obstructive jaundice. In this study, none of the patients had a history of chronic pancreatitis, and none of them had been histologically diagnosed preoperatively. Preoperative portal vein embolization had not been performed for any patient.

The extent of surgery was categorized as bile duct resection alone (BDR); BDR plus hepatectomy; or combined BDR, hepatectomy and vascular (portal vein and/or hepatic artery) resection and reconstruction [3]. The types of hepatectomy were classified as limited (less than hemihepatectomy), hemihepatectomy or an extended hepatectomy. The bilioenteric reconstruction was conducted by cholangio- or hepaticojejunostomy with a Roux-en-Y jejunal limb. The lymph nodes and resection margin status were determined from the pathology reports. The resection margins were categorized as R_0 (absence of residual tumor), R_1 (positive microscopic margin) and R_2 (macroscopic residual tumor).

When patients were diagnosed with PLA, initial management was individualized based on their clinical manifestations, but included the following treatment plan: (i) broad-spectrum antibiotics were administered intravenously after blood and/or liver abscess samples were taken for cultures and drug susceptibility tests. Then antimicrobials were modified, if necessary, on the basis of clinical presentation as well as the results of culture and susceptibility tests. (ii) All patients were treated with ultrasound guided percutaneous catheter drainage (PCD) or percutaneous needle aspiration (PNA).

Follow-up

Follow-up was terminated either on January 2014 or on the date of death. After discharge, all patients were followed-up in an outpatient setting at least every 3 months during the first year after operation, then every 6 months thereafter. Overall survival was calculated from the time of operation to the date of death. Patients who survived up to the most recent follow-up were treated as censored cases.

Statistical analysis

Comparisons between groups were performed using Student's *t*-test, Mann-Whitney U tests or Fisher's exact test as appropriate. Because of the relatively small and unbalanced data set in this study, multivariate analysis was performed with exact logistic regression [11, 12], incorporating all variables with $P \leq 0.20$ in univariate analysis, to identify independent risk factors for PLA formation. Odds ratios (OR) and 95% confidence intervals (95% CI) were also estimated. Survival was determined by the Kaplan-Meier method and compared with the log-rank test. A two-tailed *P* value of <0.05 was considered significant. SPSS software (version 16.0, SPSS, Chicago, IL) was used for all statistical analysis except the exact logistic regression, which was carried out using Stata software (Version12.0, Stata Corp LP, Texas, USA).

Results

Risk factors for PLA formation

The patients were divided into two groups, a PLA group and a Non-PLA group. The pre-, intra- and postoperative variables are summarized in **Tables 1-3**, respectively. Statistical analyses

Table 1. Demographic, concomitant disease, and laboratory data

Variable	PLA (n=8, %)	Non-PLA (n=87, %)	*P* value
Gender (male/female)	5/3	61/26	0.697
Median age in years (range)	56 (45-69)	59.0 (31-79)	0.470
ASA score†			0.499
1	1 (12.5%)	19 (21.8%)	
2	5 (62.5%)	45 (51.7 %)	
3	2 (25.0%)	23 (26.5%)	
Biliary drainage			0.874
Percutaneous transhepatic bile drainage	5 (62.5%)	61 (70.1%)	
Endoscopic nasobiliary drainage	2 (25%)	9 (10.3%)	
None	1 (12.5%)	17 (19.6%)	
Coexisting diseases‡			
Diabetes mellitus	2 (25.0%)	7 (8.0%)	0.166
Biliary disorders§	3 (37.5%)	7 (8.0%)	0.036
Alcoholism	0	2 (2.3%)	1.000
Liver cirrhosis	1 (12.5%)	5 (5.7%)	0.419
Hypertension	1 (12.5%)	6 (6.9%)	0.471
Chronic obstructive pulmonary disease	0	4 (4.6%)	1.000
Hepatitis B virus	2 (25%)	11 (12.6%)	0.300
Laboratory variables, median (range)			
Albumin (g/L)	36.8 (34.6-44.8)	38.2 (33.8-45.8)	0.589
Total bilirubin on admission (umol/L)	248.0 (67.4-502.2)	270.1 (45.0-523.6)	0.852
Total bilirubin at surgery (umol/L)	30.4 (21.4-87.8)	32.8 (10.4-91.3)	0.627

ASA, American Society of Anesthesiologists. †Patients with an ASA score of 4 or 5 were not operated on. ‡Patients fitting into multiple categories were counted in each category. §Biliary disorders including cholecystolithiasis, choledocholithiasis or hepatolithiasis.

were performed to identify any risk factors for PLA formation.

Univariate analysis indicated that the incidence of biliary tract disease in the PLA group was significantly higher than that in the Non-PLA group (3/8 [37.5%] *vs*. 7/87 [8.0%], *P*=0.036). There was no statistical difference between the two groups for diabetes mellitus (2/8 [25.0%] *vs*. 7/87 [8.0%], *P*=0.166) although it was more frequently found in the PLA group (**Table 1**). Regarding the intra- and postoperative parameters, the frequency of combined vascular reconstruction in the PLA group was significantly higher compared with the Non-PLA group (3/8 [37.5%] *vs*. 8/87 [9.2%], *P*=0.041) (**Table 2**). Pathologic analysis showed that no patient had a macroscopically positive margin (R_2). The incidence of R_1 resection was significantly greater in the PLA group than that in the Non-PLA group, (5/8 [62.5%] *vs*. 19/87 [21.8%], *P*=0.023) (**Table 2**). There were no significant differences between the two groups regarding other variables.

Coexisting biliary disorders, diabetes mellitus, intraoperative vascular reconstruction and margin status were further selected for exact logistic regression analyses for *P* values ≤0.20 in the univariate analysis. Only the vascular reconstruction (OR, 10.31; 95% CI, 1.03-142.73; *P*=0.047) and margin status (OR, 8.45; 95% CI, 1.13-109.38; *P*=0.035) were independent risk factors for development of PLA.

Microbiological findings, treatment and outcome

There were 8 (8.4%) patients who had developed hepatic abscess after operation. The clinical profiles of each patient and features of the PLA are listed in **Table 4**. The median formation time of PLA after surgical resection was 145 days (range, 16-295 days). Blood cultures were obtained in 6 patients, and were positive in 4 cases. The pus or purulent material cultures were obtained in all cases, and were positive in 7 patients. Among the eight patients, 6 had a monomicrobial infection. The other 2 patients

Table 2. Intraoperative and postoperative variables

Variable	PLA (n=8, %)	Non-PLA (n=87, %)	*P* value
Type of surgery			0.341
BDR	2 (25%)	21 (24.1%)	
BDR+hepatectomy	3 (37.5%)	58 (66.7%)	
BDR+hepatectomy+vascular resection	3 (37.5%)	8 (9.2%)	
Type of liver resection			0.876
Limited hepatectomy	3 (37.5%)	24 (27.6%)	
Hemihepatectomy	2 (25%)	37 (42.5%)	
Extended hepatectomy	1 (12.5%)	5 (5.8%)	
None	2 (25%)	21 (24.1%)	
Vascular reconstruction			0.041
Venous	2 (25%)	6 (6. 9%)	
Arterial	0	1 (1.2%)	
Both	1 (12.5%)	1 (1.2%)	
None	5 (62.5%)	79 (90.7%)	
Duration of obstruction (day)†	64 (8-120)	58 (4-212)	0.511
Length of postoperative antibiotic administration (day)†	3 (2-5)	3 (2-7)	0.422
Number of lymph nodes harvested†	5 (1-9)	4 (1-14)	0.757
Operative time (minute)†	380 (255-520)	340 (215-545)	0.396
Blood loss at surgery (ml)†	675 (320-1250)	550 (260-1600)	0.367
Intraoperative RBC transfusion performed	4 (50%)	30 (34.5%)	0.451
Margin status			0.023
R_0	3 (37.5%)	68 (78.2%)	
R_1	5 (62.5%)	19 (21.8%)	
Histologic differentiation			0.870
Well	4 (50.0%)	38 (43.68%)	
Moderate	3 (37.5%)	43 (49.43%)	
Poor	1 (12.5%)	6 (6.89%)	
UICC stage (7th edition)			0.459
I, II	2	39	
III, IV	6	48	

BDR, bile duct resection; R_0, absence of residual tumor; R_1, positive microscopic margin; †Median (range).

Table 3. Postoperative complications except for PLA

Variable†	PLA (n=8, %)	Non-PLA (n=87, %)	*P* value
Bile leakage from liver stump	1 (12.5%)	6 (6.9%)	0.471
Wound infection	1 (12.5%)	3 (3.4%)	0.301
Intra-abdominal abscess	0 (0)	2 (2.3%)	1.000
Anastomotic leak of hepaticojejunostomy	0 (0)	3 (3.4%)	1.000
Intra-abdominal hemorrhage	0 (0)	1 (1.15%)	1.000
Delayed gastric emptying	1 (12.5%)	5 (5.7%)	0.419
Pleural effusion requiring thoracentesis	2 (25.0%)	12 (13.8%)	0.335
Gastrointestinal bleeding	0 (0)	2 (2.3%)	1.000
Stricture of reconstructed portal vein	0 (0)	1 (1.15%)	1.000
Pneumonia	0 (0)	5 (5.7%)	1.000
Cholangitis	2 (12.5%)	14 (16.1%)	0.618

†Patients fitting into multiple categories were counted in each category.

were infected with two species of bacteria. The most commonly isolated pathogen was Escherichia coli (4/8). Multidrug-resistant (≥3 of the antibiotic classes) bacteria were detected in two patients, both of whom were infected with extended spectrum beta-lactamase-producing *Escherichia coli* (cases 5 and 6). These cases were treated under strict isolation precautions.

Except parenteral antibiotics and ultrasound guided PCD or PNA, none of these patients

Table 4. Characteristics of patients with PLA Formation after surgical resection of HC

Case number	Age/ Sex	Coexisting diseases	Margin status	Time to PLA formation (days)	Microbiology features	Intervention treatment	Drainage duration (days)	Survival period (months)
1	62/M	Hypertension; HBV	R_1	204	Escherichia coli	PCD	114†	10.6
2	47/F	Diabetes mellitus	R_1	71	K. pneumoniae	PCD	25	3.2‡
3	69/M	Hepatolithiasis; Hypertension	R_1	135	Escherichia coli§	PCD	41	30
4	45/M	None	R_0	27	Escherichia coli	PCD	28	13.5
5	57/F	Calculous cholecystitis	R_0	154	K. pneumoniae; Bacteroidesfragilis	PCD	353†	16.9
6	55/M	HBV	R_1	295	K. pneumoniae; Proteus mirabilis	PNA	0	42 (Alive)
7	66/F	Diabetes mellitus	R_0	16	Escherichia coli§	PCD	36	26.3
8	49/M	Calculous cholecystitis	R_1	257	Enterobacter cloacae	PCD	24	18.7

M, male; F, female; PCD, percutaneous catheter drainage; PNA, percutaneous needle aspiration; R_0, absence of residual tumor; R_1, positive microscopic margin; HBV, hepatitis B virus; K. pneumoniae, Klebsiella pneumoniae. †The patient required permanent drainage due to non-healing biliary fistula. ‡The patient died of metastatic lung infection secondary to PLA. §Multi-drug-resistant bacteria.

required any surgical interventions. Finally, 7 patients recovered and were discharged after PLA was well controlled. The other patient (case 2) died of metastatic lung infection secondary to PLA. In addition, 2 patients required permanent drainage due to a non-healing biliary fistula resulting from a communication between the liver abscess and the biliary tree.

Overall survival

As shown in **Figure 1**, the overall survival of patients who developed liver abscess after surgery was significantly shorter than those without abscess formation (median: 16.9 *vs*. 34.2 months, *P*=0.048).

Discussion

Many studies have described an increasing incidence of PLA during the past decades. Several studies attributed the increased incidence to the bilioenteric anastomosis caused during aggressive management of hepatobiliary or pancreatic disease [13, 14]. However, few studies have focused exclusively on PLA formation following surgical management of HC.

In the current study, 8 of 95 patients developed PLA after surgical resection of HC, demonstrating that the incidence of PLA was about 8.4%, which is comparable to the previous reports [6, 13, 14]. Among the coexisting diseases, our study showed that biliary disorders were closely associated with the occurrence of PLA by univariate analysis. Many investigations have established that biliary tract-related diseases are now the most common etiology of PLA [8, 10, 15]. However, the current subsequent multivariate analysis found that biliary tract-related diseases were not an independent risk factor for development of PLA. Furthermore, contrary to the previous studies [10, 12, 15], we also failed to show that diabetes mellitus is the contributing factor to PLA formation. The conflicting findings might be due to different patient populations between the current and previous studies. In addition, the relatively small sample size might also have contributed to bias in the current study.

According to multivariate analyses, vascular reconstruction was an independent risk factor for PLA formation after surgical resection of HC. Locally advanced HC often involves the hepatic artery and/or portal vein. Therefore, in such cases curative surgical resection usually requires combined vascular resection and reconstruction, which may result in ischemic damage to the remnant liver after hepatectomy [1-3, 6, 9, 16, 17]. Furthermore, the biliary tree is primarily supplied by peribiliary capillary plexus which can be damaged during lymphadenectomy of the hepatoduodenal ligament resulting in necrosis of the intrahepatic bile duct [18]. As a result, the combination of hepatic ischemic damage, translocation of gut-derived bacteria, and bile duct injury provide a plausible explanation for the appearance of PLA within 3 months after surgery, but not in patients who developed PLA more than 3 months after the surgical procedure [13, 14].

In order to decrease ischemic liver damage, many studies emphasized that simultaneous interruption of the hepatic artery and portal vein should be avoided during surgical procedure [1, 6, 16, 17]. The portal vein ought to be

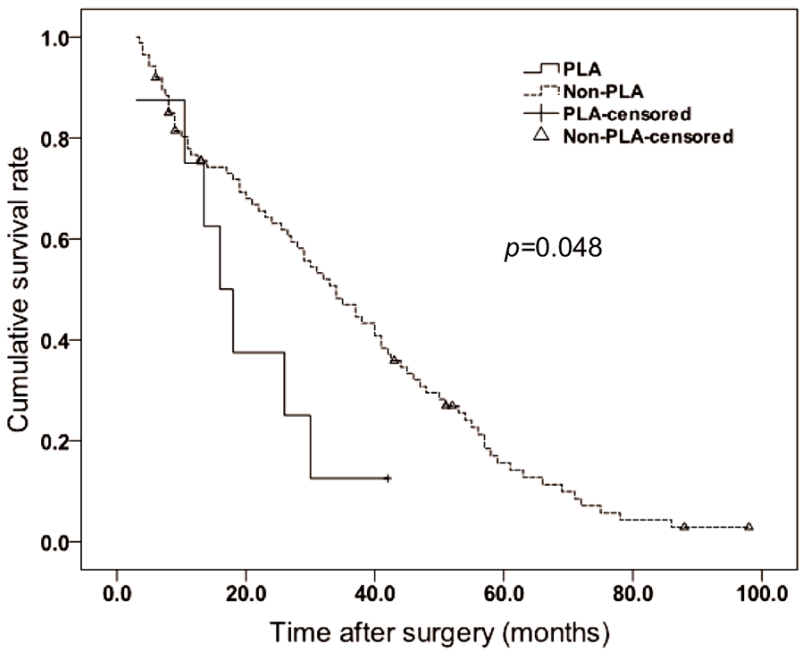

Figure 1. Kaplan-Meier curves for overall survival in PLA and Non-PLA group (median: 16.9 *vs*. 34.2 months, *P*=0.048).

resected first and reconstructed before hepatic artery resection [16]. De Santibanes et al. [17] reported that maintaining a sustained and effective arterial blood supply to the remnant liver during portal vein reconstruction could decrease the ischemic time and limit ischemic injury of the biliary tree.

A positive resection margin of the bile duct (R_1 resection) was another independent risk factor for development of PLA after surgical treatment of HC. It is well known that tumor residual surgical margin can result in localregional neoplasm recurrence during follow-up [19, 20]. With the tumor recurrence at the biliary-intestinal anastomotic site and progression along the bile duct wall, the anastomosis and the biliary duct could become stenosed or even be obstructed by the tumor. This could lead to progressive cholestasis and proximal bile ducts dilation [21]. In addition, it has been shown that after bile duct anastomosis to the jejunum, the risk of retrograde enteric bacterial contamination of the bile duct was likely to increase to more than 84% [22]. Consequently, bacterial contamination of the bile duct combined with the cholestasis caused by malignant biliary strictures or anastomotic stenosis contributes to PLA formation. This finding is consistent with previous reports [8, 10, 15] and may be the pathophysiological mechanism for development of PLA three months after the operation.

In the current study, culture analysis indicated that the *Escherichia coli*, apparently derived from the intestinal flora, was the most commonly isolated pathogen. This is consistent with findings from previous studies [10, 13, 14]. As for the two patients whose cultures grew multidrug resistant (MDR) microorganisms, one of them (case 3) had multiple episodes of acute cholangitis, and had had repeated administered of similar antibacterial agents before hospital admission. The other (case 7) was an older patient (66 years) with concomitant diabetes mellitus. This is not surprising since both increased age and diabetes mellitus are demonstrated as the risk factors for antibiotic resistance [23].

With respect to the patient (case 2) who died of metastatic lung infection, we found that the patient had a Klebsiella pneumoniae liver abscess and diabetes mellitus. Both of these were identified as potential risk factors for developing metastatic infections from PLA [12]. Despite resolution of septic symptoms and gradual obliteration of the abscess cavity, there were 2 patients who suffered from permanent biliary drainage until death due to tumor progression (case 1 and case 5). In these 2 patients, the biliary-intestinal anastomosis might have been obstructed by a local recurrence of HC. This could have prevented complete healing of a fistula between the liver abscess and intrahepatic bile ducts [10, 24]. Sugiyama *et al.* [24] also noted that 5 patients with choledochojejunostomy obstruction due to malignant tumor recurrence developed non-healing biliary fistula following PCD treatment of liver abscess.

In the current series, the overall survival of patients who developed PLA after surgical

resection of HC was significantly shorter than that of patients without PLA formation (**Figure 1**). One of the reasons for this might be that the rate of R_1 resection, a significant negative predictive factor for patient survival [1, 3, 6, 9], was statistically higher in the PLA group compared to the Non-PLA group. Although the hepatic abscess and the possible ensuing biliary fistula were not the direct causes of death in the current study, they no doubt accelerated the deterioration of the patient. A few cases died of secondary infection rather than the cancer (case 2) (**Table 4**).

This study is limited by its retrospective nature, and the small number of patients all from a single institution, and is a hospital-based study. However, the fact that PLA is an infrequent complication after surgical treatment of HC makes it difficult to collect a large sample from a single institution or in a limited research period. Moreover, our sample size is unbalanced. Therefore, we performed the exact conditional inference instead of conventional logistic regression to identify the potential prognostic factors, which could make the conclusions more credible [11, 12]. In addition, much of the data (e.g., physical examination, laboratory findings) were retrieved retrospectively from a prospectively maintained database. The intrinsic limitations within the database (e.g., incomplete blood transfusion data) and varying definitions of postoperative complications are additional limitations. Therefore, the results should be interpreted with caution, and further multicenter studies should be conducted to confirm our findings.

In conclusion, the intraoperative vascular reconstruction and positive margin status pose high risks for PLA formation after surgical resection of HC. Though PLA can be effectively treated with antibiotics and image-guided PCD or PNA, it carries a negative impact on patient overall survival. Therefore, in patients with these risk factors, careful follow-up is required for early detection and management of this infrequent post-surgical complication.

Disclosure of conflict of interest

None.

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