

Management of bilioenteric anastomosis leakage after major liver resection

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Abstract

Background: Post-hepatectomy bile leakage is a challenging issue that can lead to morbidities and mortality after liver resection. This leakage can occur either from a bilioenteric anastomosis (BEA) or from the transected surface of the liver. This study investigated the incidence, risk factors, and effective management of BEA leakage after major liver resection.

Methods: Bile leakage was diagnosed through drain fluid analysis based on the International Study Group of Liver Surgery definition. Leakage from a BEA was confirmed via fluoroscopy during percutaneous interventions or reoperation. Perioperative data and data on the management of patients with BEA leakage were collected and analysed. Bivariate analysis used Mann–Whitney *U* and χ^2 tests, and binary logistic regression identified risk factors for BEA leakage, with variables having $P < 0.200$ included in multivariable analysis.

Results: Of 2936 patients undergoing hepatectomy between 2008 and 2023, 229 underwent liver resection with BEA. Leakage from the BEA was identified in 44 patients (19.2%). These patients had a higher rate of post-hepatectomy haemorrhage ($P = 0.005$), major complications ($P = 0.001$), BEA stenosis ($P = 0.006$), and mortality ($P = 0.043$). The success rate of the management of BEA leakage was 70% for reoperation and 58% for percutaneous transhepatic cholangiography and drainage (PTCD).

Conclusion: BEA leakage after major liver resection is a severe complication associated with higher morbidity and mortality rates. Surgical treatment appeared to be more successful than PTCD in the early postoperative phase. PTCD proved to be a valuable additional therapy option following reoperation. These conclusions should be taken with caution and need to be confirmed through further prospective studies.

Introduction

Despite technical advances in liver surgery, post-hepatectomy bile leakage (PHBL) remains a common and challenging complication^{1,2}, and is associated with an increased risk of morbidity and mortality^{3,4}. Following liver resection with bilioenteric anastomosis (BEA), leakage can occur from the BEA or from the transected liver surface⁵. These two types of PHBL have different underlying pathophysiology: BEA leakage is influenced by the anastomosis technique, tension, and ischaemia in the anastomotic area⁶, whereas leakage from the transected surface is influenced by the extent of liver resection and the transection technique^{7,8}.

Given their distinct pathophysiology, the postoperative management of these two types of PHBL may differ^{9,10}. Numerous studies have evaluated the risk factors and therapeutic options for PHBL, but most have not distinguished between bile leakage from the BEA and the transected surface. The effective management of BEA leakage remains unclear. The aims of this study were to evaluate the incidence of and associated risk factors for BEA leakage, as well as to evaluate

and compare the different therapies for this type of bile leakage after major liver resection with BEA.

Methods

Study design

Data were extracted from a prospectively maintained hepatectomy database. All patients who underwent liver resection for benign or malignant hepatobiliary disorders between 1 January 2008 and 31 March 2023 in University Hospital of Heidelberg were included. Patients who underwent liver resection without concomitant BEA were excluded. The study was approved by the Ethics Committee of the Medical Faculty of Heidelberg (Approval no. S-754/2018).

Surgical procedures

BEA was performed in accordance with standardized procedures¹¹. An end-to-side anastomosis was created between the retrocolic Roux-en-Y limb and the bile duct using an

Keywords: hepatectomy, bile duct anastomosis, post-hepatectomy complications, post-hepatectomy bile leakage

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interrupted single-layer technique with polydioxanone 5/0 sutures. Multiple intrahepatic bile ducts were either combined by forming a common ostium or separately anastomosed to the jejunal limb. An abdominal surgical drain was placed close to the anastomoses. Transanastomotic stents were not placed routinely. In rare situations in which preoperative percutaneous biliary drainage was performed, the transhepatic tube was briefly left in place during anastomosis.

Bile leak diagnosis and localization

Bile leakage was diagnosed and classified in accordance with the International Study Group of Liver Surgery (ISGLS) definition⁵ during routine analysis of the drain fluid on postoperative days (PODs) 1 and 3. In patients whose drains had been removed, who developed fever, or who showed increased infectious parameters, diagnostic procedures, including ultrasonography and imaging, were performed. If fluid collection was detected, a percutaneous drain was inserted, and bile leakage was diagnosed based on the aforementioned criteria. Confirmation of BEA leakage was obtained either radiologically or during reoperation. In patients with a percutaneous drain for bile collection, a contrast agent was injected through the drain; if contrast was observed in the biliary system, BEA leakage was diagnosed. In patients with percutaneous transhepatic cholangiography and drainage (PTCD), the contrast agent was injected through the PTCD, and leakage outside the biliary system indicated BEA leakage. During ongoing reoperation, BEA leakage was diagnosed intraoperatively. Although a clear distinction between the types of bile leak was made in most patients, some overlap may have occurred.

Bile leak management

First-line therapy

Bile leakage was managed based on the time of detection, its severity, and the patient's condition. In patients with high-flow bile leakage (≥ 100 ml/day with a bile concentration of ≥ 10 mg/dl) diagnosed on or before POD 7, a reoperation was performed. In patients with high-flow bile leakage diagnosed after POD 7, PTCD was performed through both internal drainage into the jejunum and external drainage. Patients with low-flow bile leakage (< 100 ml/day) or with a bile concentration < 10 mg/dl were managed conservatively with a watch-and-wait approach or antibiotic therapy. If the patient's condition did not improve or deteriorated before POD 7, a reoperation was performed; for patients whose condition did not improve or deteriorated after POD 7, a PTCD was performed.

Further therapies

Treatment success was defined as the complete resolution of BEA leakage, as indicated by the cessation of bile flow from the drainage site (either after surgery or PTCD) and improvement in clinical symptoms. In patients treated with PTCD, upsizing of the inserted drain was considered in some and performed until the leakage resolved. If bile leakage remained and/or the patient's condition deteriorated, a reoperation was performed. If reoperation was unsuccessful, PTCD was performed. In the event of a patient's death, the presence of bile leakage at the time of death indicated unsuccessful therapy.

Data collection

Preoperative data included patient demographic data, tumour characteristics, preoperative treatments (preoperative biliary

drainage including endoscopic stents, PTCD, or both) and liver function tests. Intraoperative data included the location and type of liver resection; the type and number of BEAs; intraoperative procedures, such as associating liver partition and portal vein ligation (ALPPS), Pringle manoeuvre, vascular resection, and extensive lymphadenectomy; operative time, and transfusion data. Postoperative data included post-hepatectomy liver failure, post-hepatectomy haemorrhage (both defined according to the ISGLS definitions¹²), major complications (Clavien–Dindo grade $\geq$ III¹³) within 90 days of surgery, duration of intensive care unit (ICU) and hospital stays, biliary stenosis, and 90-day mortality. The management of BEA leaks was also documented.

Statistical analysis

Statistical analyses were conducted using SPSS® version 26 (IBM, Armonk, NY, USA). Continuous variables are expressed as the mean with standard deviation (s.d.) and categorical variables are expressed as frequencies with proportions. Bivariate analysis was conducted using the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. Binary logistic regression was used to determine risk factors for BEA leakage. Variables with $P < 0.200$ in the bivariate analysis were entered into multivariable analysis. $P < 0.050$ was considered statistically significant.

Results

Preoperative data

Of the 2936 patients who underwent liver resection during the study period, 229 (7.8%) underwent major liver resection with BEA (143 (62.4%) male, mean(s.d.) age 63(12.2) years). Of these patients, 44 (19%) had a BEA leak, 9 (20%) of which were grade B leaks and 35 (80%) of which were grade C leak (Table 1). The study flow chart is presented in Fig. S1.

The mean age of patients with BEA leakage was significantly higher than that of patients without BEA leakage ($P = 0.001$), and patients with BEA leakage had a higher prevalence of hypertension than patients without BEA leakage (64% (28 patients) versus 39.5% (73 patients); $P = 0.004$). In addition, tumour diameter was significantly higher in patients without than with BEA leakage ($P = 0.014$). There were no further differences in demographics, tumour characteristics, preoperative treatment, and liver function tests between the BEA leakage and no BEA leakage groups.

Intraoperative data

The intraoperative data are presented in Table 2. Extended hepatectomy was more prevalent in patients without BEA leakage, whereas hemihepatectomy was more common in patients with BEA leakage ($P = 0.030$). Patients in the BEA leakage group received significantly more fresh frozen plasma (FFP) than patients without BEA leakage (48% (21 patients) versus 25.9% (48 patients), $P = 0.005$). There were no significant differences in the number and level of BEAs, or in other operative variables between the BEA leakage and no BEA leakage groups.

Postoperative data

Postoperative data are presented in Table 3. Compared with patients without BEA leakage, those with BEA leakage had a higher prevalence of post-hepatectomy haemorrhage (4% (8 patients) versus 15.9% (7 patients); $P = 0.005$) and Clavien–Dindo grade $\geq$ III (29.2% (54) versus 54% (24); $P = 0.001$). In addition,

Table 1 Preoperative baseline characteristics in all patients and in those with and without BEA leakage separately

	All (n = 229)	No BEA leakage (n = 185)	BEA leakage (n = 44)	P*
Demographics				
Age (years), mean(s.d.)	63(12.2)	61.6(12.5)	68.7(8.6)	0.001
Sex				0.391
Male	143 (62.4%)	118 (63.8%)	25 (57%)	
Female	86 (37.6%)	67 (36.2%)	19 (43%)	
BMI (kg/m ²), mean(s.d.)	25.8(5.5)	25.6(4.2)	27(9.1)	0.922
ASA grade ≥III	110 (48%)	86 (46.5%)	24 (54%)	0.575
Diabetes	26 (11.4%)	18 (9.7%)	8 (18%)	0.112
Hypertension	101 (44.1%)	73 (39.5%)	28 (64%)	0.004
Cirrhosis	4 (1.7%)	2 (1.1%)	2 (4%)	0.167
Hepatobiliary malignancy	216 (94.3%)	175 (94.6%)	41 (93%)	0.716
Tumour characteristics				
Tumour maximum diameter (cm), mean(s.d.)	4.3(3.5)	4.5(3.5)	3.4(3.4)	0.014
Cholangiocarcinoma	187 (81.7%)	149 (80.5%)	38 (86%)	0.772
Gall bladder carcinoma	14 (6.1%)	12 (6.5%)	2 (4%)	
Hepatocellular carcinoma	2 (0.9%)	2 (1.1%)	0 (0%)	
Metastatic lesion	12 (5.2%)	11 (5.9%)	1 (2%)	
Other	14 (6.1%)	11 (5.9%)	3 (7%)	
Distant metastasis	26 (11.4%)	23 (12.4%)	3 (7%)	0.291
Vascular infiltration	103 (45%)	86 (46.5%)	17 (37%)	0.357
Preoperative treatment				
Chemoradiotherapy	22 (9.6%)	19 (10.3%)	3 (7%)	0.485
Biliary drainage	107 (46.7%)	90 (48.6%)	17 (39%)	0.232
Liver function test				
AST (U/L), mean(s.d.)	102(173)	105(188)	86(79)	0.593
ALT (U/L), mean(s.d.)	127(204)	133(220)	106(109)	0.467
GGT (IU/L), mean(s.d.)	567(551)	576(567)	530(485)	0.753
Bilirubin total (mg/dl), mean(s.d.)	3.4(4)	3.4(4)	3.4(4.1)	0.992
Bilirubin direct (mg/dl), mean(s.d.)	2.5(3.6)	2.6(3.7)	2(3.3)	0.431

Values are n (%) unless otherwise stated. BEA, bilioenteric anastomosis leakage; BMI, body mass index; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase. *Chi square test was used for categorical variables. Mann-Whitney U test was used for continuous variables.

Table 2 Intraoperative data of patients with and without BEA leakage

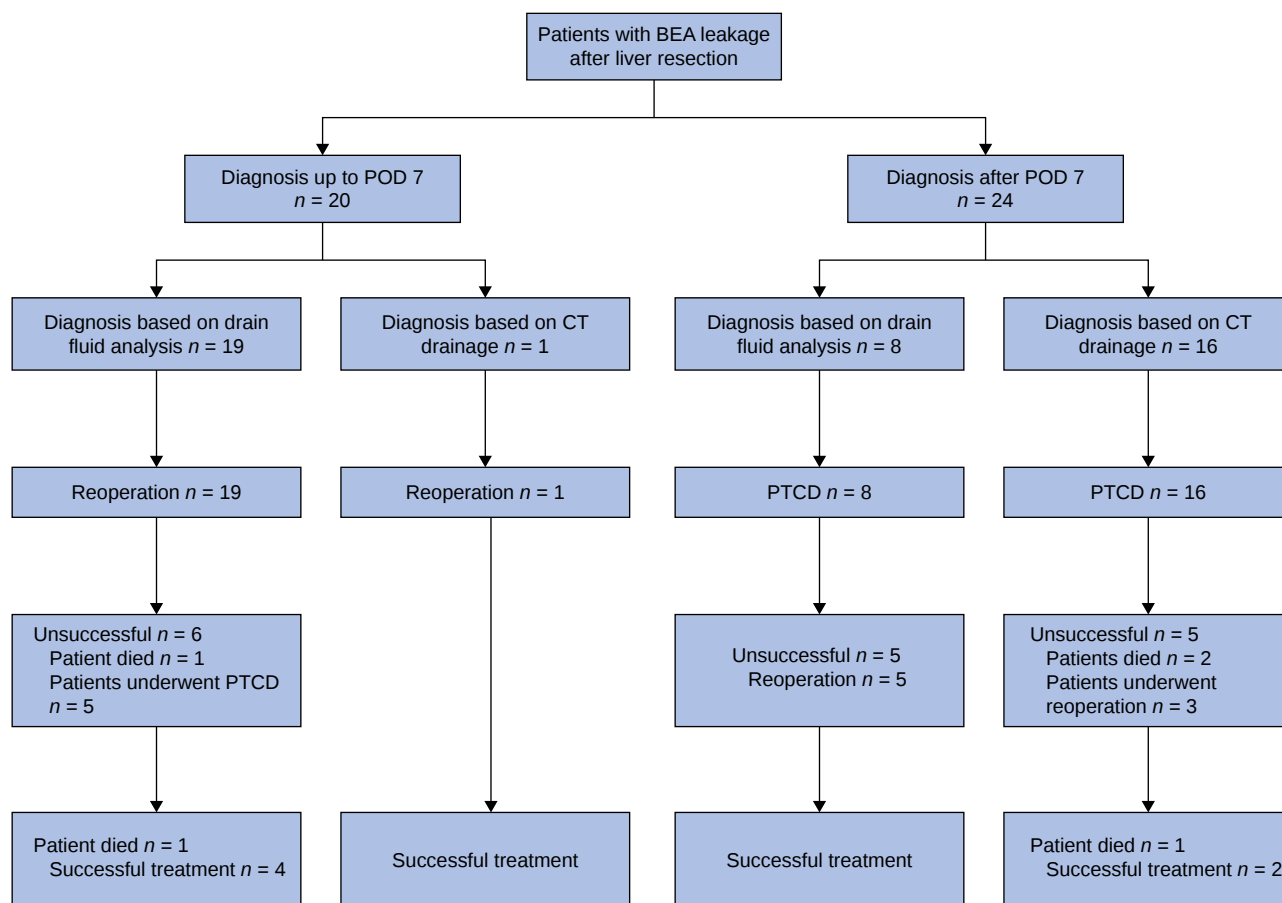
	All (n = 229)	No BEA leakage (n = 185)	BEA leakage (n = 44)	P*
Location of liver resection				
Left hepatectomy	84 (36.7%)	64 (34.6%)	20 (45%)	0.219
Right hepatectomy	145 (63.3%)	121 (65.4%)	24 (54%)	
Type of liver resection				
Extended hepatectomy	117 (51.1%)	101 (54.6%)	16 (36%)	0.030
Hemihepatectomy	112 (48.9%)	84 (45.4%)	28 (64%)	
Type of BEA†				
One large duct	186 (81.2%)	148 (80%)	38 (86%)	0.257
One small duct	11 (4.8%)	11 (5.9%)	0 (0%)	
Two small ducts	22 (9.6%)	17 (9.2%)	5 (11%)	
Three small ducts	5 (2.2%)	4 (2.2%)	1 (2%)	
Four small ducts	1 (0.5%)	1 (0.5%)	0 (0%)	
One large and one small duct	4 (1.7%)	4 (2.2%)	0 (0%)	
No. of anastomoses				
1	197 (86%)	159 (85.9%)	38 (86%)	0.943
>1	32 (14%)	26 (14.1%)	6 (14%)	
Small duct anastomosis	39 (17%)	33 (17.8%)	6 (14%)	0.505
PVE	9 (3.9%)	9 (4.8%)	0 (0%)	0.213
ALPPS	21 (9.2%)	20 (10.8%)	1 (2%)	0.078
Pringle manoeuvre	15 (6.5%)	12 (6.5%)	3 (7%)	0.936
Vascular resection	74 (32.3%)	65 (35.1%)	9 (20%)	0.061
Extensive lymphadenectomy	36 (15.7%)	30 (16.2%)	6 (14%)	0.848
Blood loss (ml), mean(s.d.)	1951(1380)	1964(1395)	1897(1327)	0.750
Operation time (min), mean(s.d.)	362(99)	363(100)	359(96)	0.679
Receiving PC	121 (52.8%)	95 (51.4%)	26 (59%)	0.355
Receiving FFP	69 (30.1%)	48 (25.9%)	21 (47%)	0.005

Values are n (%) unless otherwise stated. †Large duct presented left main hepatic duct, right main hepatic duct, or common bile duct. BEA, bilioenteric anastomosis leakage; PVE, portal vein embolization; ALPPS, associating liver partition with portal vein ligation for staged hepatectomy; s.d., standard deviation; PC, packed cells; FFP, fresh frozen plasma. *Chi square test was used for categorical variables. Mann-Whitney U test was used for continuous variables.

Table 3 Postoperative data in all patients and those with and without BEA leakage separately

	All (n = 229)	No BEA leakage (n = 185)	BEA leakage (n = 44)	P*
PHLF	42 (18.3%)	33 (17.8%)	9 (20%)	0.687
PHH	15 (6.6%)	8 (4.3%)	7 (16%)	0.005
Clavien–Dindo grade ≥III	78 (34.1%)	54 (29.2%)	24 (54%)	0.001
Length of ICU stay (days), mean(s.d.)	13.7(18.1)	11.7(15.9)	21.8(23.9)	0.001
Length of hospital stay (days), mean(s.d.)	37.7(24.8)	34.3(22)	52.2(30.4)	<0.001
Biliary stenosis	13 (5.7%)	6 (3.2%)	7 (16%)	0.006
Mortality	37 (16.1%)	25 (13.5%)	12 (27%)	0.043

Values are n (%) unless otherwise stated. BEA, bilioenteric anastomosis leakage; PHLF, post-hepatectomy liver failure; PHH, post-hepatectomy haemorrhage; ICU, intensive care unit; s.d., standard deviation. *Chi square test was used for categorical variables. Mann-Whitney U test was used for continuous variables.

**Fig. 1** Flow chart of BEA leakage treatment

BEA, bilioenteric anastomosis leakage; POD, postoperative day; CT, computed tomography; PTCD, percutaneous transhepatic cholangiography and drainage.

patients with BEA leakage had longer ICU ($P = 0.002$) and hospital ($P < 0.001$) stays and a higher incidence of biliary stenosis (16% (7) versus 3.2% (6); $P = 0.006$) and mortality (27% (12) versus 13.5% (25); $P = 0.043$) than patients without BEA leakage.

In the multivariable model, receiving FFP was the only factor influencing BEA leakage (odds ratio 3.99; 95% confidence interval 1.63 to 9.80; $P = 0.003$). The results of the multivariable regression model are presented in [Table S1](#).

Management of bile leakage

Of the 44 patients with BEA leakage, 28 underwent one-stage treatment and 16 underwent two-stage treatment. Thirty-nine of these patients (89%) were successfully treated, but the treatment success in the remaining five patients was unclear because they died before their treatment could be evaluated.

Twenty-seven patients (61%) were diagnosed with BEA leakage based on drain fluid analysis and clinical symptoms. Nineteen of these patients were diagnosed on or before POD 7 and underwent reoperation, which had a success rate of 70%. Reoperation failed in six patients; one of these patients died before the BEA leakage could be resolved and the remaining five underwent PTCD. PTCD was successful in four of the five patients, but one patient died before the BEA leakage could be resolved. Of the 27 patients with BEA leakage, 8 were diagnosed after POD 7 and underwent PTCD, which failed in 5 patients. These five patients were subsequently treated successfully through reoperation.

Seventeen patients (39%) were diagnosed with BEA leakage through postoperative imaging. One patient was diagnosed before POD 7 and was successfully treated with reoperation; 16 were diagnosed after POD 7 and underwent PTCD, which failed

Table 4 Postoperative management and outcomes of bilioenteric anastomosis leakage

	Number of patients	Reoperation	PTCD	P*
Successful first-stage treatment	28	14 of 20 (70%)	14 of 24 (58%)	0.517
Bile leak-related mortality after first-stage treatment	3	1 of 18 (5%)	2 of 24 (8%)	0.999
Successful second-stage treatment	11	7 of 8 (88%)	4 of 5 (80%)	0.999
Bile leak-related mortality after second-stage treatment	2	1 of 8 (12%)	1 of 5 (20%)	0.999
Length of hospital stay in successfully treated patients (days), mean(s.d.)	39	42.4(35.4)	55.9(24.9)	0.244

Values are n (%) unless otherwise stated. The denominators in the Reoperation and PTCD columns indicate the number of patients in each group who reached the relevant treatment stage. PTCD, percutaneous transhepatic cholangiography and drainage; s.d., standard deviation. *Chi square test was used for categorical variables. Mann-Whitney U test was used for continuous variables.

in 5 patients. Two of these patients died before the BEA leakage could be resolved and three underwent reoperation. Of the three who underwent reoperation, two were successfully treated and the other died before the BEA leakage could be resolved. The treatment flow chart is presented in [Fig. 1](#).

The overall first-stage treatment success rate was 70% (14 of 20) for reoperation and 58% (14 of 24) for PTCD ($P=0.517$). Of those patients who died following first-stage treatment before BEA leakage could be resolved, one underwent reoperation and two underwent PTCD ($P=0.999$). The overall second-stage treatment success rate was 88% (7 of 8) for reoperation and 80% (4 of 5) for PTCD ($P=0.999$). Of those patients who died after second-stage treatment before BEA leakage could be resolved, one had received reoperation and the other had received PTCD ($P=0.999$). There were no complications related to PTCD in the cohort. The mean hospital length of stay was not significantly shorter for patients who were successfully treated by reoperation than by PTCD (42.4(35.4) versus 55.9(24.9) days; $P=0.244$). Postoperative management and treatment outcomes are presented in [Table 4](#).

Discussion

This study is the largest single-centre study on BEA leakage after liver resection to date. Of 229 patients undergoing liver resection with BEA, anastomotic leakage was reported in 44 (19.2%), and this leakage was related to a higher rate of postoperative complications, longer ICU and hospital stays, and a higher mortality rate. Surgical therapy showed higher success rates than PTCD (70 versus 58%, respectively; not significant).

Liver resection with BEA was rare (only 8% of all liver resections), but the rate of anastomotic leakage was high. This may be because all patients underwent major or extended liver resections. These statistics align with findings from previous studies^{14–16}, with reported BEA leakage rates ranging from 10 to 21%. A reason for this high rate of anastomosis failure may be the compromised synthetic function of the small liver remnant influencing tissue healing¹⁷. This could explain why BEA leakage rates following pancreas surgery were considerably lower (2.9%) in a previous study³ from the same centre. Another reason could be the technical challenges associated with the anastomosis of smaller bile ducts (segmental ducts)¹⁸. Alternatively, deeper preparation and radical resection of the liver hilum could compromise the blood supply to the bile ducts¹⁹.

Multivariable analysis identified receiving FFP as the only risk factor for BEA leakage. This finding is possibly a confounding factor, and a relationship is difficult to establish. FFP is often administered to correct coagulopathy, which may reflect underlying liver dysfunction or significant intraoperative blood loss, both of which are associated with higher postoperative complication rates, including bile leakage²⁰. Patients needing

FFP typically undergo more extensive liver resections¹⁰. Another explanation may be infusion-related oedema of the intestines²¹.

Patients with BEA leakage had a higher rate of major complications, had longer ICU and hospital stays, and had a higher rate of mortality than patients without BEA leakage. Patients with BEA leakage had significantly more BEA stenosis. This finding is in accordance with previously published data^{22,23}. In the present cohort, ALPPS was more commonly used in the study centre during the study period, although it is acknowledged that some authors prefer portal vein embolization, a topic that remains controversial in the literature^{24–27}.

Different treatment approaches for BEA leaks were evaluated. Currently there is limited evidence and no accepted guidelines on optimal therapy, and the standard of care varies between surgeons and centres²⁸. A problem is that existing studies have not differentiated between BEA leakage and leakage from the transected surface. The present study focused on BEA leakage. BEA leakage was categorized into early and late occurrences using a 7-day cut-off, based on clinical experience. This approach was primarily influenced by the risks of peritonitis, sepsis, and abdominal adhesions, which significantly increase the risk of subsequent operations after 1 week. It should be acknowledged that bias may be present, because the timing of leakage could be influenced by different pathophysiological mechanisms. The reported treatment strategy focused on the timing of the intervention rather than the timing of leakage occurrence. Patients diagnosed with BEA leakage before POD 7 underwent surgery, and those diagnosed after POD 7 underwent therapy with PTCD. Surgical therapy had higher success rates and was associated with a shorter hospital stay. Surgery may have been more effective because early BEA leakage is often caused by technical or ischaemic issues, which are less likely to respond to conservative management. In patients in whom reoperation was unsuccessful, PTCD as a second therapy showed promising success rates of 80%, possibly because the underlying issues contributing to the anastomotic leak were resolved during the reoperation. Therefore, PTCD after reoperation may be an effective additional management strategy.

This study has several limitations. As a retrospective analysis, it is subject to selection and chronological biases. The study was limited by missing data regarding patients' nutritional status, the type of perioperative treatment for cholangitis, pre-existing biliary drainage in some patients, intraoperative lymphadenectomy, bile duct diameter, and remnant liver volume. In addition, some overlap may be present when considering the type of bile leak. Nevertheless, this retrospective analysis provides valuable insights to inform future studies. Due to the retrospective nature of the study, it was not possible to conduct an analysis based on the exact cause of anastomotic breakdown, and this should be addressed in future prospective studies. Instead, outcomes of bile leakage therapy were reported in different groups of patients, categorized

by the diagnostic method used (fluid analysis of surgical drains versus interventional techniques) and the timing of diagnosis. It was observed that, regardless of the timing, reoperation had higher success rates. However, conclusions should be drawn with caution, because the reported success rates are based on the timing of bile leakage diagnosis rather than the underlying pathophysiology. In addition, although this study represents the largest single-centre analysis in this field, its statistical power was limited. This limitation may have influenced the findings related to bile duct size and its effect on leakage risk. Finally, it was not possible to determine the exact cause of death in the studied patients. In most cases, mortality was attributed to a combination of bile leakage and liver failure, which led to septic complications.

In conclusion, BEA leakage after major liver resection remains a major challenge, with a high incidence of major complications, prolonged ICU and hospital stays, and a higher mortality rate. Surgical treatment appeared to be more successful than PTCD in the early postoperative phase. However, PTCD proved to be a valuable additional therapy option following reoperation. These conclusions should be taken with caution and need to be confirmed through further prospective studies.

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Author contributions

Sepehr Abbasi Dezfouli (Conceptualization), Elmira Heidenreich (Data curation, Writing—original draft), Mohammadamin Shahrabaf (Formal analysis, Writing—original draft), Elias Khajeh (Writing—review & editing), De-Hua Chang (Writing—review & editing), Miriam Klauss (Writing—review & editing), Markus Mieth (Writing—review & editing), Martin Loos (Writing—review & editing), Markus Büchler (Conceptualization), and Arianeb Mehrabi (Conceptualization, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

Data availability

The data relevant to this study are available from the corresponding author upon request.

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