ORIGINAL ARTICLE

Incidence and risk factors for anastomotic bile leakage in hepatic resection with bilioenteric reconstruction – A international multicenter study

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Abstract

Background: Anastomotic leak (AL) after bilioenteric reconstruction (BR) is a feared complication after bile duct resection, especially in combination with liver resection. Literature on surgical outcome is sparse. This study aimed to determine the incidence and risk factors for AL after combined liver and bile duct resection with a focus on operative or endoscopic reinterventions.

Methods: Data from consecutive patients who underwent liver resection and BR between 2004 and 2018 in 11 academic institutions in Europe were collected from prospectively maintained databases.

Results: Within 921 patients, AL rate was 5.4% with a 30d mortality of 9.6%. Pringle maneuver ($p<0.001$),postoperative external biliary ($p=0.007$) and abdominal drainage ($p<0.001$) were risk factors for clinically relevant AL. Preoperative biliary drainage ($p<0.001$) was not associated with a higher rate of AL. AL was more frequent in stented patients (76.5%) compared to PTCD (17.6%) or PTCD+stent (5.9%,$p=0.017$). AL correlated with increased incidence of postoperative liver failure ($p=0.036$), cholangitis, hemorrhage and sepsis (all $p<0.001$).

Conclusion: This multicenter data provides the largest series to date of LR with BR and could help in the management of these patients which are often challenging and hampering the patients' postoperative course negatively.

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Introduction

Bilioenteric reconstruction (BR) is a common surgical procedure performed for a variety of indications. This includes either malignant tumors involving the bile duct or benign biliary tract pathology with malignant potential such as primary sclerosing cholangitis, choledochal cysts, hepatolithiasis or echinococcus disease.

The incidence of clinically relevant biliary anastomotic leak (AL) after BR varies considerably depending on the type of procedure. AL after BR in general ranges between 3% and 43%.[1] Accompanying established risk factors are blood loss, extended operation time, preoperative stenting and postoperative liver dysfunction.

In the context of pancreaticoduodenectomy or pancreatectomy, leak rates of 0–5% have been reported[2–5] whereas after combined bile duct and hepatic resection, e.g. for hilar cholangiocarcinoma, higher AL rates are reported. ALs are often associated with intraabdominal abscesses in up to 30%.[6] AL often leads to re-intervention which has been associated with an adverse impact on patients' outcome and increased add on postoperative morbidity and mortality.[1,7] AL is associated with concomitant complications including hemorrhage, surgical site infection (SSI), cholangitis, sepsis and intraabdominal fluid collection or abscess, resulting in a prolonged hospital stay and recovery after surgery[2,8,9], further affecting time to adjuvant treatments, hence having potential negative impact on oncological outcomes. Furthermore, the estimated number of unreported cases might be high, as most data is of retrospective nature.

Management of biliary AL has changed during the last decade. With advances in radiological interventions and endoscopic techniques, AL at BR site can often be managed with percutaneous or endoscopic drainage. The role of relaparotomy is depending on onset of leakage as well as leakage volume and usually only performed early after the index operation. With advances in radiological techniques, percutaneous transhepatic biliary drainage (PTBD) became a less invasive and attractive option, especially in cases with later complications like strictures. Leaks are clinically challenging to be externally drained by PTBD due to lack of bile duct dilatation.

Literature on surgical outcome for BR in combination with liver resection is sparse. We therefore aimed to determine the incidence and risk factors for clinically relevant biliary AL that require re-intervention after combined liver and bile duct resection in a large multicenter cohort.

Methods

Data collection

Data from consecutive patients who underwent liver resection and BR between 2004 and 2018 in 11 academic institutions (Innsbruck, Milan, Stockholm, Frankfurt, Vienna, Leeds, London, Liverpool, Groningen, Graz, Linz) were collected from prospectively maintained databases. Indications for liver surgery were benign and malignant indications involving the biliary tract. BR was performed either due to the extent of necessary surgery or due to biliary invasion and/or compression of the bile ducts inducing a risk of ischemic lesions. Patients with bile duct injury following cholecystectomy, previous liver or bile duct resection or transplantation were excluded.

Patient demographics such as age, sex, ASA score, underlying liver cirrhosis, cardiac or pulmonary comorbidities, body mass index (kg/m^2), indication and tumor stage were analyzed.

Surgical parameters

Operative parameters such as volume and type of liver resection, open or minimal invasive approach, duration of operation, estimated blood loss (ml), transfusions (ml) and technical factors like Pringle maneuver,[10,11] lymphadenectomy and vascular resection were calculated. Anatomical resections where classified according to the Brisbane 2000 Terminology of Liver Anatomy and Resections.[12]

Outcomes

All outcomes within the dataset are 90-day outcomes. The primary outcome of the study was endoscopic, percutaneous or surgical re-intervention related to biliary AL after combined liver resection and BR. Biliary AL was defined as objective evidence of bile in intra- or postoperatively placed drains and a radiologically or surgically confirmed AL. Indication for re-operation was considered if dehiscence of the BR was suspected early (within 72h) after the index operation or failure of interventional treatment. Endoscopic re-interventions included postoperative placement of biliary stents (endoscopic biliary drainage (EBD)) and percutaneous re-intervention included PTBD. Operative procedures included over-sewing or re-reconstruction of the BR.

Additional outcomes studied included hemorrhage, bile leakage originating from the parenchymal resection margin (according to ISGLS classification[13]), cholangitis, sepsis, jaundice, postoperative liver failure (PHLF, according to ISGLS classification[14]), SSI, overall 30-day/90-day morbidity other than biliary AL and 30-day/90-day mortality. Postoperative variables also included length of hospital stay.

BR-specific variables analyzed included jaundice before surgery, preoperative biliary drainage (PBD, either EBD or PTBD), suture technique for BR, and use of intraoperatively placed external biliary or abdominal drainage. In case of PBD antibiotic treatment was used according to centers standard operating procedures. In case of proofed infection in bile culture preoperative antibiotic treatment was administered. BR was usually performed in an end-to-side cholangio-jejunostomy. BR of the proximal biliary system was performed either as several single anastomoses to the orifices of intrahepatic bile ducts or to the periductal fibrous plate of several joining ducts. In case of multiple duct situations especially in extended left hepatectomies, the same jejunal limb was used for multiple anastomoses or combined as a joint reconstruction according to the surgeons' preference and expertise. A single layer monofilament absorbable suture was used to perform the anastomosis with mucosal apposition, in an interrupted, continuous or mixed fashion. Either an internal – external biliary or an abdominal drain was used based on surgeons' preference.

Statistical analysis

Univariate and multivariate analyses of clinically relevant variables with two-sided Pearson's chi-squared tests for nominal variables and Student's t tests for continuous variables were performed to examine the association of patients' factors, intraoperative parameters and outcomes with AL on BR. A logistic multivariable model was constructed using variables with significance level of p = 0.05 to identify independent predictors for AL on BR. All analyses were performed with IBM SPSS software version26 (SPSS Inc. Chicago, IL) by the Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria.

Results

Association of patient characteristics and biliary anastomotic leakage

In the study period, 921 patients were eligible for inclusion. Median follow-up was 34[9–43] months. Indications for liver resection and BR were perihilar cholangiocarcinoma (CCC; n = 612), hepatocellular carcinoma (HCC; n = 54), intrahepatic cholangiocarcinoma (ICC; n = 53), gallbladder cancer (n = 64), colorectal cancer liver metastases (CRC; n = 38), non-colorectal cancer liver metastases (non-CRC; n = 38), and benign lesions including adenoma, hemangioma, echinococcal disease, focal nodular hyperplasia (FNH; n = 62). Patient characteristics are summarized in Table 1. Baseline parameters, including age, BMI, comorbidities and tumor stage were comparable between both groups. 50 patients (5.4%) underwent re-intervention because of AL of BR (44 surgical, 6 interventional). Univariable analysis revealed male sex (p = 0.048) and perineural infiltration in pathologic examination (p < 0.001) as significantly associated with AL.

Association of outcomes and biliary anastomotic leakage

Intraoperative and postoperative characteristics are shown in Table 2. No association between resected volume or type of liver resection and AL was seen. Of all patients who received an anatomical resection, AL most frequently occurred after extended right hepatectomy (36.2%), extended left hepatectomy (27.7%) and left hepatectomy (12.8%). Intraoperative factors such as duration of operation, blood loss and transfusion, vascular resection or lymphadenectomy were not associated with AL. The use of intermittent pedical clamping (Pringle maneuver) revealed to be a protective factor for AL on BR (47.7% vs. 12.0%,

Table 1 Patient characteristics; IQR interquartile range; BMI body mass index; kg kilogram; m meter; mm millimeter, HCC hepatocellular carcinoma, ICC intrahepatic cholangiocarcinoma, CCC perihilar cholangiocarcinoma, CRC colorectal cancer, Non-CRC non-colorectal cancer

	Anastomotic leak (n = 50)	No anastomotic leak (n = 871)	*P* value
Age, median (IQR)	66 (58–73)	67 (56–74)	0.783
Male sex, n (%)	33 (66.0)	450 (57.1)	**0.048**
BMI (kg/m^2) (IQR)	25.1 (23.0–28.1)	24.8 (22.2–27.0)	0.211
ASA			0.223
1/2	33 (66.0)	659 (73.8)	
3/4	17 (34.0)	212 (26.2)	
Previous hepatobiliary surgery, n (%)	9 (18.0)	87 (10.6)	0.103
Cirrhosis, n (%)	9 (18.0)	175 (20.1)	0.719
Cardiac comorbidity, n (%)	14 (28.0)	244 (28.0)	0.988
Pulmonary comorbidity, n (%)	3 (6.0)	77 (8.8)	0.488
Indication for surgery, n (%)			0.123
HCC	2 (4.0)	52 (6.0)	
ICC	7 (14.0)	46 (5.3)	
CCC	26 (52.0)	586 (67.3)	
CRC	3 (6.0)	35 (4.0)	
Non-CRC	3 (6.0)	35 (4.0)	
Gallbladder cancer	4 (8.0)	60 (6.9)	
Benign disease	5 (10.0)	57 (6.5)	
T-stage			0.132
T1	7 (16.3)	65 (8.9)	
T2	20 (46.5)	351 (48.0)	
T3	10 (23.3)	256 (35.0)	
T4	6 (14.0)	60 (8.2)	
Perineural infiltration, n (%)	35 (77.8)	352 (43.5)	**<0.001**

Table 2 Intraoperative characteristics and postoperative results; IQR interquartile range; PVE portal vein embolization; min minutes; ml milliliter; PHLF post hepatectomy liver failure; d days, SSI surgical site infection

	Anastomotic leak (n = 50)	No anastomotic leak (n = 871)	*P* value
Major hepatectomy, n (%)	43 (86.0)	720 (87.1)	0.828
Type of resection, n (%)			0.677
Anatomical	44 (88.0)	795 (91.6)	
Non-anatomical	5 (10.0)	60 (6.9)	
Combined anatomical/non-anatomical	1 (2.0)	13 (1.5)	
Laparoscopic resection, n (%)	0 (0.0)	13 (1.5)	0.384
PVE, n (%)	7 (14.0)	111 (12.7)	0.796
Portal vein thrombosis, n (%)	2 (6.3)	29 (6.9)	0.893
Pringle maneuver, n (%)	6 (12.0)	413 (47.4)	**< 0.001**
Lymphadenectomy, n (%)	37 (74.0)	663 (76.1)	0.733
Vascular reconstruction, n (%)	8 (16.0)	105 (12.1)	0.414
Operative time, min, median (IQR)	424 (314–540)	376 (304–523)	0.528
Blood transfusion, ml, median (IQR)	560 (300–1500)	500 (445–840)	0.330
Intraoperative blood loss, ml, median (IQR)	750 (400–1500)	600 (400–900)	0.161
Hospital stay, days, median (IQR)	34 (23–54)	13 (20 - 23)	**< 0.001**
Morbidity and mortality			
Any other complication, n (%)	42 (84.0)	531 (61.0)	**0.001**
PHLF, n (%)	16 (32.7)	117 (20.0)	**0.036**
Cholangitis, n (%)	14 (28.0)	77 (8.8)	**< 0.001**
Hemorrhage, n (%)	13 (26.5)	38 (6.6)	**< 0.001**
Sepsis, n (%)	20 (40.0)	106 (12.2)	**< 0.001**
Jaundice postoperative, n (%)	14 (31.1)	101 (19.0)	0.051
SSI, n (%)			0.598
Superficial	6 (12.5)	87 (17.6)	
Deep	12 (25.0)	103 (20.9)	
Mortality (<90d), n (%)	10 (20.0)	118 (13.6)	0.204
Mortality (<30d), n (%)	5 (10.0)	84 (9.7)	0.940

$p < 0.001$). Median hospital stay was significantly longer in patients with AL (34 vs. 13 days, $p < 0.001$). Overall morbidity, other than biliary AL, within 90 days was 84.0% (versus 61.0%; $p = 0.001$). AL correlated with increased incidence of PHLF ($p = 0.036$), cholangitis ($p < 0.001$), hemorrhage ($p < 0.001$) and sepsis ($p < 0.001$). Overall, 30-day and 90-day mortality was high for the entire cohort (30d: 9.7%; 90d: 13.9%), but rates did not differ between groups (Table 2).

Association of bilioenteric reconstruction - specific parameters and biliary anastomotic leakage

No significant difference between the suture technique (continuous, single or mixed) of BR was found ($p = 0.264$, Table 3). AL was less frequent in patients without preoperative jaundice (58.6% vs. 22.0, $p < 0.001$) and in patients with PBD (34.0 vs. 59.9%, $p < 0.001$). In contrast, intraoperative placed external biliary drainage (28.0% vs. 14.0%, $p = 0.007$) and abdominal drainage (49.0 vs. 17.6%, $p < 0.001$) were associated with a higher incidence of clinically relevant biliary AL. PBD was indicated in 539 patients. Of those, 42.7% received an EBD, 44.3% were treated with PTBD and 13.0% had both. The rate of biliary AL was higher in patients with EBD (76.5%) compared to PTBD (17.6%) or PTBD and EBD (5.9%, $p = 0.017$, Table 3).

Multivariable logistic regression analysis indicated that PBD ($p = 0.046$) and Pringle maneuver ($p = 0.002$) are preventive for biliary AL, however the use of an abdominal drainage ($p < 0.001$) was an independent predictive factor for biliary AL that required re-intervention (Table 4). In contrast to the univariate analysis, an intraoperative placed external biliary drainage was not an independent factor.

Management of biliary anastomotic leakage

In 44 cases of patients a surgical reintervention was necessary due to biliary anastomotic leakage (88.6%) or an insufficiency of BR

Table 3 Procedural characteristics; PTBD percutaneous transhepatic biliary drainage, EBD endoscopic biliary drainage

	Anastomotic leak (n = 50)	No anastomotic leak (n = 871)	*P* value
Jaundice preoperative, n (%)	11 (22.0)	510 (58.6)	**<0.001**
Preoperative biliary drainage, n (%)	17 (34.0)	522 (59.9)	**<0.001**
Type of preoperative biliary drainage, n (%)			**0.017**
EBD	13 (76.5)	217 (41.6)	
PTBD	3 (17.6)	236 (45.2)	
PTBD and EBD	1 (5.9)	69 (13.2)	
External biliary drainage, n (%)	14 (28.0)	115 (14.0)	**0.007**
Technique bilioenteric reconstruction, n (%)			0.264
Continuous suture	4 (12.5)	57 (8.1)	
Single knot suture	25 (78.1)	616 (87.5)	
Mixed suture	3 (9.4)	31 (4.4)	
Abdominal drainage, n (%)	24 (49.0)	153 (17.6)	**<0.001**

in combination with hemorrhage (11.4%). Of these 44 patients, perihilar CC patients were affected in more than half of the cases (n = 25, 56.8%), followed by ICC patients (n = 5, 11.4%), gallbladder cancer patients (n = 4, 9.1%) and other indications (HCC n = 2, CRC n = 3, Non CRC n = 2, benign disease n = 3). In median, reintervention was performed on the 9th post-operative day (0–34) after index surgery. Of the 11 patients in whom bleeding occurred in addition to an AL, the biliary leak seemed causative for the erosion of local vessels. AL was fixed by simply over-sewing in 50.0% of cases (n = 22), in 29.5% (n = 13) the BR was taken down and then reconstructed and in 9.1% (n = 4) insertion of an external biliary drainage was added. An additional anastomosis was created in two patients because the initial anastomosis of 2 adjacent small bile ducts was not sufficient. In another two patients, biliary leakage was managed by open insertion of a transanastomotic PTBD.

Subgroup analysis of 612 patients with cholangiocarcinoma

Surgical resection of perihilar CCC is considered high-risk surgery and is associated with one of highest rates of adverse events compared to any other elective cancer surgery. Both, the small liver remnant and biliary drainage make these patients prone to perioperative complications. In order to minimize the heterogeneity of the entire cohort, a subgroup analysis of perihilar CCC was performed. AL occurred in 26 (3.6%) of the 612 CCC patients. Patient characteristics are summarized in Table 5. Compared to the entire collective, this subgroup showed a significantly higher median intraoperative blood loss (1500 vs 600 ml, p = 0.002). Regarding morbidity, AL did not correlate with an increased incidence of PHLF (28.0% vs. 24.6%, p = 0.707).

Table 4 Multivariable logistic regression analysis for identification of risk factors and predictive parameters for anastomotic leakage on bilioenteric anastomosis; OR odds ratio; 95% CI confidence interval

	OR	95% CI	*P* value
External biliary drainage	1.780	0.907–3.494	0.094
Preoperative biliary drainage	0.518	0.272–0.988	**0.046**
Abdominal drainage	3.132	1.708–5.742	**<0.001**
Pringle maneuver	0.237	0.096–0.586	**0.002**

In terms of BR-specific parameters, PBD was preoperatively indicated in 425 patients. AL was less frequent in patients with PBD (38.5% vs. 70.8%, p < 0.001, Table 6), the type of PBD had no influence on the rate of AL (Table 6). Multivariable logistic regression analysis indicated same results as for the entire cohort, PBD (p = 0.049), Pringle maneuver (p = 0.010) and the use of abdominal drainage (p < 0.001) were independent predictive factors for biliary AL, respectively (Table 7).

Discussion

This study aimed to identify risk factors for prediction of post-operative AL and surgical morbidity in patients undergoing liver resection with BR in a very large cohort of patients. The incidence of clinically relevant bile leaks after BR varies considerably depending on the type of procedure with rates of 2.2%–10%.[1,8,9,15] Especially in case of concomitant liver resection literature is sparse with only single center experiences and small patient numbers. The few reported leak rates (mainly in perihilar cholangiocarcinoma) range from 3.6% to 50%[9,16] with a reported 30d-mortality of 6.5%, which seems rather low.[1,9] The rate of AL with necessity for re-intervention in our cohort was 5.4% (biliary AL not requiring an intervention were excluded), resulting in a prolonged hospital stay (34 vs. 13 days) and a 30d-mortality of nearly 10%.

The strength of this study lies in the currently largest number of cases (921 patients) of liver resection with BR in the literature, which was collected in 11 European high-volume HBP- centers

Table 5 CCC subgroup analysis: intraoperative characteristics and postoperative results; IQR interquartile range; PVE portal vein embolization; min minutes; ml milliliter; PHLF post hepatectomy liver failure; d days, SSI surgical site infection

	Anastomotic leak (n = 26)	**No anastomotic leak (n = 586)**	***P* value**
Perineural infiltration, n (%)	20 (87.0)	239 (44.9)	**< 0.001**
Major hepatectomy, n (%)	25 (96.2)	515 (94.8)	0.767
Type of resection, n (%)			0.478
Anatomical	24 (92.3)	544 (93.2)	
Non-anatomical	1 (3.8)	33 (5.7)	
Combined anatomical/non-anatomical	1 (3.8)	7 (1.2)	
Laparoscopic resection, n (%)	0 (0.0)	13 (2.2)	0.443
PVE, n (%)	5 (19.2)	71 (12.1)	0.282
Portal vein thrombosis, n (%)	0 (0.0)	17 (8.2)	0.283
Pringle maneuver, n (%)	3 (11.5)	332 (56.7)	**< 0.001**
Lymphadenectomy, n (%)	19 (73.1)	464 (79.2)	0.455
Vascular reconstruction, n (%)	5 (19.2)	76 (13.0)	0.359
Operative time, min, median (IQR)	510 (470–680)	425 (330–552)	0.598
Blood transfusion, ml, median (IQR)	250 (0–375)	0 (0–250)	0.060
Intraoperative blood loss, ml, median (IQR)	1500 (800–1765)	600 (377–800)	**0.002**
Hospital stay, days, median (IQR)	39 (7–168)	13 (4–127)	**< 0.001**
Morbidity and mortality			
Any other complication, n (%)	23 (88.5)	333 (56.8)	**0.001**
PHLF, n (%)	7 (28.0)	83 (24.6)	0.707
Cholangitis, n (%)	6 (23.1)	52 (8.9)	**0.016**
Hemorrhage, n (%)	7 (28.0)	23 (7.1)	**< 0.001**
Sepsis, n (%)	10 (38.5)	66 (11.3)	**< 0.001**
Jaundice postoperative, n (%)	5 (21.7)	70 (25.1)	0.721
SSI, n (%)			0.225
Superficial	5 (20.8)	59 (21.3)	
Deep	2 (8.3)	63 (22.7)	
Mortality (<90d), n (%)	4 (28.6)	87 (24.1)	0.702
Mortality (<30d), n (%)	3 (21.4)	69 (19.1)	0.829

and thus provides an insight in real clinical life in Europe on the management of these challenging patients.

In order to improve the rate of AL and morbidity, we initially focused on the factors that can be potentially changed in patients' management. Management starts preoperatively, in case of a jaundiced patient, a very common clinical scenario. Should PBD routinely be performed before resection in cholestatic livers? This is an ongoing debate between hepatobiliary surgeons around the world. On one hand, major hepatectomy is associated with a high risk of PHLF.[17] Therefore, many surgeons prefer PBD to obtain biliary decompression of the future liver remnant (FLR) to improve the regenerative capacity after hepatectomy.[18,19] On the other hand, some authors demonstrated, that PBD carries a risk of septic complications and cholangitis.[20,21] Chamberlain et al. analyzed patients with hilar cholangiocarcinoma and reported that infectious complications associated with PBD greatly overweigh any potential advantage and therefore advise no routine use before surgery.[22] Jarnagin et al. found a strong correlation of bacterial colonization of bile with preoperatively placed biliary stents and significantly increased risk of death and morbidity.[6] Keeping in mind that most of these studies analyzed only perihilar CCC patients usually suffering high morbidity, our data of a mixed cohort demonstrated that AL was less frequent in patients after PBD compared to those without (34.0% vs. 59.9%, $p < 0.001$). Same results were found for the CCC subgroup (38.5% vs. 70.8%, $p < 0.001$).

In line with that finding AL developed more frequently in patients with preoperative jaundice (58.6 vs. 22.0% $p < 0.001$). Hence, we assume that the rate of AL is higher if preoperative cholestasis exists and that PBD has a protective effect.

The next clinical question we analyzed is which PBD method is the better approach for postoperative outcome after liver

Table 6 CCC subgroup analysis: procedural characteristics; PTBD percutaneous transhepatic biliary drainage, EBD endoscopic biliary drainage

	Anastomotic leak (n = 26)	No anastomotic leak (n = 586)	*P* value
Jaundice preoperative, n (%)	7 (26.9)	411 (70.1)	**<0.001**
Preoperative biliary drainage, n (%)	10 (38.5)	415 (70.8)	**<0.001**
Type of preoperative biliary drainage, n (%)			0.106
EBD	7 (70.0)	156 (37.6)	
PTBD	2 (20.0)	207 (49.9)	
PTBD and EBD	1 (10.0)	52 (12.5)	
External biliary drainage, n (%)	10 (38.5)	68 (12.6)	**<0.001**
Technique bilioenteric reconstruction, n (%)			0.288
Continuous suture	2 (14.3)	25 (5.4)	
Single knot suture	11 (78.6)	421 (90.7)	
Mixed suture	1 (7.7)	18 (3.9)	
Abdominal drainage, n (%)	15 (57.7)	93 (15.9)	**<0.001**

resection with BR. In our cohort significantly more AL occurred after EBD or combined PTBD and EBD. Many academic surgeons have dealt with this topic. However, the influence of the respective PBD method on AL was not properly examined. It was demonstrated that PTBD was associated with a lower risk of cholangitis.[23–25] Rassam et al. had better results with EBD due to an increase in portal vein thrombosis or seeding metastasis following PTBD.[19] A Dutch randomized controlled trial comparing percutaneous and endoscopic biliary treatment methods was discontinued because of the high mortality rate after PTBD.[26] In general, we have conflicting results and no clear-cut recommendations can be drawn, however, in our study the risk for AL was significantly lower after PTBD for the entire cohort. No superior method could be detected in CCC patients.

The question of postoperative external biliary drainage has also been discussed widely in the literature. In our cohort, significantly more AL occurred when an external biliary drainage was placed. Olthof et al. showed that a postoperative external bile drain was an independent risk factor for development of clinically relevant PHLF in patients who underwent major liver resection for perihilar cholangiocarcinoma, no other risk factors for postoperative biliary leakage could be identified.[27] Suzuki et al. analyzed the effect of postoperative biliary drains on hepaticojejunostomy in different procedures with a reported leak rate of 15.2%. Risk of AL was associated with concomitant hepatic resection and the presence of a trans-anastomotic stents.[28] Whether external biliary drains make sense remains unclear, even if the majority of low-quality studies showed no benefit.

Operative site drains have been routinely inserted during liver resection for many decades. This question has been challenged in the past years, some randomized controlled trials have suggested that drains are unnecessary.[29–31] A recent meta-analysis by Dezfouli et al., which included five non-randomized (N = 4809) and three randomized controlled trials (N = 241), favored the no-drain group due to significantly more complications in the drain group.[32] One has to keep in mind that these studies reported on liver resection without BR and no conclusions from that high level evidence can be drawn for our cohort of patients.

Another interesting finding of this study was that intermittent pedical clamping reduced re-intervention after AL (12.0% vs. 47.4%, $p < 0.001$). This effect was also found in the CCC subgroup (11.5% vs. 56.7%, $p < 0.001$), but was not significant in all other patients (data not shown). Clinically relevant literature on that topic is scarce, however Jansen-Winkeln et al. demonstrated in a rat model that hepatic pedicle clamping had a detrimental effect on anastomotic healing and increased anastomotic complications,[33] the opposite of what we have seen in the human setting. Heizmann et al. evaluated in a randomized controlled trial the protective potential of ischemic preconditioning with regard to ischemic-related morbidity and mortality of patients after liver resection.[34] In addition to other protective effects, ischemic preconditioning reduced the rate of biliary complications significantly (10% vs. 19%, $p = 0.04$).

Furthermore, Czigany et al. investigated the effects of intestinal remote ischemic preconditioning on ischemia-reperfusion injury and gut barrier integrity in a rat model of total hepatic

Table 7 CCC subgroup analysis: multivariable logistic regression analysis for identification of risk factors and predictive parameters for anastomotic leakage on bilioenteric anastomosis; OR odds ratio; 95% CI confidence interval

	OR	95% CI	*P* value
External biliary drainage	2.311	0.952–5.611	0.064
Preoperative biliary drainage	0.417	0.175–0.998	**0.049**
Abdominal drainage	4.171	1.778–9.785	**<0.001**
Pringle maneuver	0.185	0.051–0.668	**0.010**

ischemia.[35] Remote ischemic preconditioning resulted in a remote hepatocellular damage but also in a reduction of local damage of the intestinal barrier induced by severe congestion and functional ischemia. However, while encouraging results for ischemic preconditioning in hepatic resection,[36,37] like Pringle Maneuver, have been reported, a general benefit on BR following liver surgery has not been documented.

AL is considered a major postoperative complication after liver resection leading to prolonged hospital stay and increased morbidity.[38,39] In line with previous reports, we had an overall morbidity besides AL of 84% compared to 61% in patients without AL.

Among patients undergoing major liver resection with bile duct reconstruction for perihilar CCC, Sano et al. reported a complication rate of 57%, while Xiong et al. noted a rate of 33%.[40,41] However, these studies analyzed morbidity in general and therefore the definition of 'complications' makes comparisons difficult. Interestingly, in our data AL was significantly associated with other complications such as PHLF, cholangitis, hemorrhage and sepsis. Other studies reported similar results.[42,43] However, all significant variables were postoperative measures of complications and might have been rather the consequence of the AL than explanatory predictors. Nevertheless, when planning a complex resection with BR, the increased risk of these consecutive complications should be considered. Furthermore, it is crucial to give patients better information about all risks of surgery during informed consenting.

Univariate analysis also revealed a significantly higher AL rate in patients suffering perineural infiltration (77.8% vs. 43.5%, $p < 0.001$). We excluded this data from multivariable analysis because benign indications were included in the entire cohort. The perineural invasion effect was also found in the subgroup analysis of CCC subjects (87.0% vs. 44.9%, $p < 0.001$) and remained not significant in non-CCC cancer patients (data not shown). No reports on that topic exist in current literature. Perineural invasion is reported in around 85–88% of hilar CCC patients.[44] Reportedly, MMP-9 secretion is significantly enhanced in cholangiocarcinoma cells that invade nerve tissue.[45] Current literature in colorectal surgery shows some relation between MMP-9 activity and colorectal AL.[46] However, at this point this potential influence on biliary anastomotic healing remains speculative.

Like most other perioperative outcome studies, this analysis has some limitations. Indeed, it was a retrospective study and was not an intent-to-treat analysis. This retrospective and multicenter study comprises a broad heterogenous cohort of patients with various tumor entities treated by a broad range of surgical procedures, hence there is a significant risk of selection and reporting bias. A subgroup analysis was carried out of the largest group (perihilar CCC) to minimize the influence of the heterogenous cohort.

In conclusion, AL following liver resection with BR often requires surgical and endoscopical reinterventions with a high rate of postoperative complications, prolonged hospitalization and mortality. Independent factors associated with AL were absence of PBD in jaundiced patients, preoperative EBD, postoperative external biliary drainage, and abdominal drainage. Prospective studies would be desirable to further confirm these findings. Our data can further guide surgeons and patients during informed consenting planning such a challenging resection.

Conflict of interest

None to declare.

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