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Liver resection for perihilar cholangiocarcinoma: Impact of biliary drainage failure on postoperative outcome. Results of an Italian multicenter study

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ABSTRACT

Background: Preoperative biliary drainage may be essential to reduce the risk of postoperative liver failure after hepatectomy for perihilar cholangiocarcinoma. However, infectious complications related to preoperative biliary drainage may increase the risk of postoperative mortality. The strategy and optimal drainage method continues to be controversial.

Methods: This is a retrospective multicenter study including patients who underwent hepatectomy for perihilar cholangiocarcinoma between 2000 and 2016 at 14 Italian referral hepatobiliary centers. The primary end point was to evaluate independent predictors for postoperative outcome in patients undergoing liver resection for perihilar cholangiocarcinoma after preoperative biliary drainage.

Results: Of the 639 enrolled patients, 441 (69.0%) underwent preoperative biliary drainage. Postoperative mortality was 8.9% (12.5% after right-side hepatectomy versus 5.7% after left-side hepatectomy; $P = .003$). Of the patients, 40.5% underwent preoperative biliary drainage at the first admitting hospital, before evaluation at referral centers. Use of percutaneous preoperative biliary drainage was significantly more frequent at referral centers than at community hospitals where endoscopic preoperative biliary drainage was the most frequent type. The overall failure rate after preoperative biliary drainage was 43.3%, significantly higher at community hospitals than that at referral centers (52.7% *v* 36.9%; $P = .002$). Failure

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of the first preoperative biliary drainage was one of the strongest predictors for postoperative complications after right-side and left-side hepatectomies and for mortality after right-side hepatectomy. Type of preoperative biliary drainage (percutaneous versus endoscopic) was not associated with significantly different risk of mortality.

Conclusion: Failure of preoperative biliary drainage was significantly more frequent at community hospitals and it was an independent predictor for postoperative outcome. Centers' experience in preoperative biliary drainage management is crucial to reduce the risk of failure that is closely associated with postoperative morbidity and mortality.

Introduction

Extended hepatectomy for perihilar cholangiocarcinoma (PHC) remains one of the most demanding surgical procedures in liver surgery.[1,2] Indeed, postoperative mortality and morbidity rates are still reported to be higher than those observed after liver resection for other indications.[3] In Western series postoperative mortality rate ranges between 6.2% and 15%, with postoperative morbidity rate reaching 60%.[4–7] In the majority of these cases, mortality is related to liver failure and biliary sepsis. Indeed, in such patients the risk of liver failure after extended hepatectomy usually demonstrates a close relationship with sepsis that develops in the injured liver by previous jaundice, cholangitis, and malnutrition[4–8].

Preoperative biliary drainage (PBD)[1,2,9,10] and portal vein embolization[11–14] are fundamental strategies, introduced in the past years, to reduce the risk of postoperative liver failure. Patients with PHC usually present with obstructive jaundice.[15] In such cases, PBD is used to reduce jaundice and to improve liver function and its ability to regenerate.[2] However, cholangitis represents the most important complication related to PBD and it has been considered an independent prognostic factor for postoperative mortality[4,8,16,17] Percutaneous transhepatic biliary drainage (PTBD) and endoscopic biliary drainage (EBD) are the two most common procedures available to drain the bile ducts. The optimal drainage method continues to be controversial and remains one of the most debated issues regarding the preoperative management of PHC. Three recent meta-analyses demonstrated that PTBD was associated with a lower risk of cholangitis.[18–20] On the other hand, a recent randomized controlled trial comparing PTBD with EBD was prematurely ended because of the excessively higher mortality in the PTBD group; however, these data should be interpreted with caution because of the small sample size.[21]

The aim of this multicenter study was to assess the current attitude of Italian hepatobiliary surgery referral centers on the use and type of PBD for PHC and to identify the critical issues related to biliary drainage and the operative risk after liver resection. The primary end point was to evaluate independent predictors for postoperative outcome in patients undergoing liver resection for PHC after biliary drainage.

Materials and Methods

Data were collected from 14 Italian hepatobiliary surgery referral centers, members of the Italian Association of Hepato-Biliary-Pancreatic Surgeons, which corresponds to the previous Italian Chapter of the European-African Hepato-Pancreato-Biliary Association. This study included only patients who underwent major hepatectomy combined with resection of the main biliary confluence for histologically proven PHC between January 1, 2000, and December 31, 2016.

Liver resections were defined according to the International Hepato-Pancreato-Biliary Association terminology.[22] Resections of three or more segments were classified as major hepatectomies. The extent of bile duct involvement was defined according to the classification by Bismuth and Corlette.[23] Portal vein resection was not systematically performed according to the no-touch technique described by Neuhaus et al.[24] All vascular resections were selectively performed only when the portal vein or the hepatic artery could not be freed from the tumor during dissection of the hepatic pedicle.

The multicenter database included only patients who were selected for liver resection by the single referral center. In this series, patients initially evaluated for liver transplantation were not included. For each patient, the following data were collected: demographic information, use, timing, and type of PBD (ie, PTBD or EBD) as well as use of preoperative portal vein embolization. The indication for doing preoperative portal vein embolization was: future remnant liver volume <35% to 40%.

The first PBD was defined as "drainage before referral" when it was performed at a community hospital before the patient was referred to one of the hepatobiliary surgery referral centers included in this analysis. Community hospitals were defined as public hospitals that serve local populations. In community hospitals there are digestive endoscopy units where endoscopic retrograde cholangiopancreatography may be performed, radiology departments with interventional radiology services, and general surgery units. In community hospitals there are no specialized hepatobiliary surgery units. On the other hand, the first PBD was defined as "drainage at referral centers" when it was first performed at one of the hepatobiliary surgery referral centers included in this analysis. Both types of biliary drainages—endoscopic and percutaneous—were available in all 14 Italian hepatobiliary referral centers. However, the type of PBD was the center's preference.

Failure of the first PBD included the following: occurrence of complications attributable to the procedure, need to perform further multiple procedures (contralateral or ipsilateral), need to conversion from one type of drainage (percutaneous or endoscopic) to the other type. Insufficient PBD was defined as preoperative total bilirubin level >5 mg/dL. Operative details included type of resection and intraoperative blood transfusions requirement. Postoperative mortality was defined as 90-day mortality. Postoperative complications were scored according to the Clavien-Dindo grading system.[25] Major complications were defined as Clavien-Dindo grade ≥3.

For this analysis we collected operative data available from each center for resected patients, from a prospectively collected database. Patients did not undergo additional examinations for this study. Therefore, ethical committee approval was waived.

Primary outcome

The primary end point was to evaluate independent predictors for postoperative outcome (morbidity and mortality) in patients undergoing liver resection for PHC after biliary drainage.

Table I
Characteristics of the 639 patients

Characteristics	Value
Age, y	
Median (range)	67 (29–89)
Sex, n (%)	
Male	393 (61.5)
Female	246 (38.5)
Extent of biliary involvement, number (%)*	
Type 1	20 (3.1)
Type 2	84 (13.15)
Type 3	399 (62.45)
3A	162 (46.1%)
3B	189 (53.9%)
Not available	48
Type 4	136 (21.3)
Preoperative biliary drainage, number (%)	441 (69.0)
Preoperative portal vein embolization before right-side hepatectomy, number (%)	91/303 (30.0)
Type of liver resection, number (%)	
Right-side hepatectomy	303 (47.4)
Right hepatectomy	54
Right hepatectomy with S4	30
Right hepatectomy with S1	135
Right hepatectomy with S4-1	84
Left-side hepatectomy	313 (49.0)
Left hepatectomy	31
Left hepatectomy with S1	266
Left hepatectomy with S5-8-1	16
Mesohepatectomy (S4–5-8)	23 (3.6)
Mesohepatectomy	8
Mesohepatectomy with S1	15
Vascular resection, number (%)	85 (13.3)
Blood transfusions, number (%)	152 (23.8)

* Classification by Bismuth and Corlette.[23]

Table II
Postoperative results of the 639 patients

Postoperative morbidity, number (%)	396 (62.0)
Grade I–II, number (%)	244 (38.2)
Total number of complications in 244 grade I–II patients, number	287
Biliary leak, number (%)	79/287 (27.5)
Septic complications, number (%)	78/287 (27.2)
Liver failure, number (%)	77/287 (26.8)
Other, number (%)	53/287 (18.5)
Grade III–IV, number (%)	152 (23.8)
Total number of complications in 152 grade III–IV patients, number	210
Biliary leak, number (%)	49/210 (23.3)
Septic complications, number (%)	84/210 (40.0)
Liver failure, number (%)	43/210 (20.5)
Other, number (%)	34/210 (16.2)
Reintervention, number (%)	64 (10.0)
90-day mortality, number (%)	57 (8.9)
After right-side hepatectomy	38/303 (12.5)
After left-side hepatectomy	18/313 (5.7)
After mesohepatectomy	1/23 (4.3)
Cause of mortality, number (%)	
Sepsis	33 (57.9)
Liver failure	14 (24.5)
Hemoperitoneum	3 (5.3)
Other	7 (12.3)

Statistical analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were expressed in numbers and percentages. The χ^2 test was used for comparing categorical variables. Logistic regression analysis was used to determine independent predictors of postoperative complications and of 90-day mortality. A preliminary univariable model was created. All the variables at $P < .2$ were used for constructing the multivariable model. An odds ratio (OR) and 95% confidence intervals (95% confidence interval [CI]) were reported. In all the analyses, a $P < .05$ was considered statistically significant. Analyses were carried out with SPSS 23.0 software (IBM Corp, Armonk, NY, USA).

Results

Between January 1, 2000, and December 31, 2016, a total of 738 patients underwent surgical resection for PHC at 14 Italian hepatobiliary surgery centers. Of these patients, 65 (8.8%) underwent biliary resection alone and 34 (4.6%) had insufficient data. These patients were excluded from this analysis, and the remaining 639 patients were enrolled in the study (Table I). These patients underwent major hepatectomy combined with resection of the main biliary confluence for histologically proven PHC. Right-side hepatectomy was performed in 303 patients (47.4%), left-side hepatectomy in 313 patients (49.0%), and mesohepatectomy (resection of segments 4-5-8) in 23 patients (3.6% [Table I]). Overall, 516 (80.7%) major hepatectomies with caudate lobe resection were performed. Caudate lobe resection was performed more frequently in association with left-side hepatectomy (282/313, 90.1%) than with right-side hepatectomy (219/303, 72.3%; ($P < .001$). When assessing the type of stricture according to Bismuth classification, of the 399 Bismuth type 3 strictures, the side of the neoplastic extent was specified in 351 cases—162 (46.1%) were classified as type 3A and 189 were classified as type 3B (53.9%). Of the 162 strictures classified as type 3A, 95.7% underwent right-side hepatectomy. Of the 189 strictures classified as type 3B, 93.6% underwent left-side hepatectomy. Of the 136 strictures classified as type 4, 54.4% (74 patients) underwent left-side hepatectomy.

Overall, the postoperative 90-day mortality rate was 8.9% (57 patients [Table II]). The mortality rate was significantly higher after right-side than after left-side hepatectomies (38/303, 12.5% vs. 18/313, 5.7%, respectively; $P = .003$). In the 57 patients who died during the postoperative course, the most frequent causes of mortality were septic complications (33, 57.9%) and liver failure (14, 24.5% [Table II]).

Overall, the postoperative morbidity rate was 62.0% (396/639), and the rate of major complications (Clavien-Dindo grade III-IV) was 23.8% (152/639 [Table II]. Morbidity rate after right-side hepatectomy was significantly higher than that after left-side hepatectomy (209/303, 69.0% vs. 172/313, 54.9%, respectively; $P < .001$).

Multivariable logistic regression analysis indicated that independent predictive factors for 90-day mortality were age >70 y, right-side hepatectomy, and intraoperative blood transfusions requirement (Table III).

PBD

PBD was performed in 441 patients (69.0% [Table I]). A PBD was significantly more frequent in patients who underwent right-side hepatectomy than in those who underwent left-side hepatectomy (221/303, 72.9% *v* 199/313, 63.6%, respectively; $P = .01$).

The postoperative morbidity rate was significantly higher in patients who underwent PBD than that in patients resected without PBD (289/441, 65.5% *v* 107/198, 54.0%, respectively; $P = .006$). The mortality rate was similar between patients resected after PBD and patients resected without PBD (14/198, 7.1% *v* 43/441, 9.7%, respectively; $P = .271$). The first biliary drainage was unilateral in 355 patients (80.5%) and bilateral in 86 patients (19.5%). Postoperative morbidity and mortality rates were similar between patients who underwent unilateral PBD and patients who underwent

Table III
Univariable and multivariable logistic regression analysis for the identification of risk factors associated with 90-day mortality

Variables	Univariable analysis *P*	Multivariable analysis OR (95% CI)	*P*
Age (y) >70	<.001	2.354 (1.233–4.492)	.009
Male sex	.987		
Bismuth stricture type 3-4	.518		
Preoperative biliary drainage	.274		
Preoperative portal vein embolization	.456		
Right-side hepatectomy	.003	1.971 (1.007–3.856)	.048
Vascular resection	.012		
Intraoperative blood transfusions	.016	2.034 (1.065–3.885)	.031

bilateral PBD (65.9% and 9.6% *v* 63.9% and 10.5%, respectively; $P = .731$ and $P = .803$).

Among the 441 patients who underwent PBD, specific data about the timing and the type of the first biliary drainage were available for 365 patients. The indication for PBD in such patients was a planned right-side hepatectomy in 190 patients (52.0%). In the remaining 175 patients in whom a left-side hepatectomy was planned, indications for PBD were as follows: jaundice with total bilirubin level ≥10 mg/dL in 76 patients (20.8%), presence of comorbidities (American Society of Anesthesiologists score 2–3) in 28 patients (7.7%), age ≥70 y in 25 patients (6.9%), concomitant chronic hepatitis in 4 patients (1.1%); unavailable data for 42 patients (11.5%). First PBD was performed by PTBD in 203 patients (55.6%) and by EBD in 162 patients (44.4%).

The overall rate of failure after first PBD was 43.3% (156/365). Causes of failure were septic complications in 67 patients (42.4%), need of multiple procedures or conversion from one type of drainage to the other type in 68 patients (43.0%), pancreatitis in 16 patients (10.1%), and hemobilia in 7 patients (4.5%).

Failure rate after EBD was 47.5% (77/162). Of these patients, 67.5% (52/77) underwent PTBD. A second endoscopic procedure was performed in the remaining patients (25/77, 32.5%). Failure rate after PTBD was 38.9% (79/203). A total of 57 patients (57/79, 72.1%) required a second PTBD.

The overall rate of failure after PTBD was not significantly different from that after EBD (79/203, 38.9% *v* 77/162, 47.5%, respectively; $P = .098$). Overall, multiple drainage procedures were necessary in 40.0% of patients (146/365), and both procedures (EBD and PTBD) were eventually performed in 20.3% of patients (74/365).

Biliary drainage before referral versus biliary drainage at referral centers

PBD was performed at community hospitals in 148 patients (40.5%) before beginning evaluation at referral hepatobiliary centers. In these patients, EBD was more frequently used than PTBD (89/148, 60.1% *v* 59/148, 39.9%, respectively; $P < .001$ [Table IV]). On the contrary, for 217 patients who were first drained at referral centers, PTBD was more frequently used than EBD (144/217, 66.4% *v* 73/217, 33.6%, respectively; $P < .001$ [Table IV]).

Of those who underwent PBD at community hospitals, unilateral biliary drainage was performed in 124 patients (83.8%), and bilateral drainage was performed in 24 patients (16.2%). In patients who were first drained at referral centers, biliary drainage of the future remnant liver was performed in 180 patients (82.9%), and bilateral drainage was performed in 37 patients (17.1%).

The mean interval time from biliary drainage to surgery was 36 ± 35 days and it was significantly longer for patients first drained at community hospitals than that for patients first drained at referral centers (44 ± 37 days *v* 31 ± 32 days, respectively; $P = .003$).

Patients who underwent EBD before referral needed additional percutaneous biliary drainages in 47.2% of cases (42/89). On the contrary, in patients who underwent EBD at referral centers, the need of additional PTBD occurred in 13.7% of patients (10/73) ($P < .001$).

Overall, rate of failure after the first PBD was significantly higher when performed at community hospitals than when performed at referral hepatobiliary centers (77/148, 52.0% vs 79/217, 36.4%, respectively; $P = .003$ [Table IV]). Of the 77 patients with PBD failure at community hospitals, 32 (41.5%) presented at referral centers with cholangitis.

A total of 75 patients (20.5%) underwent liver resection with insufficient biliary drainage (total bilirubin level >5 mg/dL). The rate of patients with preoperative insufficient biliary drainage was significantly higher in patients undergoing left-side hepatectomy than that in patients undergoing right-side hepatectomy (44/175, 25.1% *v* 31/190, 16.3%, respectively; $P = .037$).

Of the 365 analyzed patients having had biliary drainage, the 90-day postoperative mortality rate was 7.9% (29/365). The most frequent cause of mortality in this group was septic complications (18/29; 62.1%). Of the 18 patients who died as a result of septic complications, failure of first PBD occurred in 61.1% (11 patients). This rate of failure was higher than that observed in the other 11 patients who died as a result of other causes (45.4%). However, this difference did not reach a statistical significance because of the small number of observations.

In patients having had biliary drainage, the impact of the following factors on postoperative morbidity and mortality was analyzed: age, sex, type of biliary stricture (Bismuth classification), type of first biliary drainage, occurrence of failure of biliary drainage, interval time from biliary drainage to surgery, preoperative insufficient biliary drainage, preoperative portal vein embolization, vascular resection, and intraoperative blood transfusion. These factors were analyzed in two subgroups of patients according to the side of the hepatectomy.

When assessing patients who had biliary drainage and had undergone right-side hepatectomy, at multivariable logistic regression analysis, independent predictive factors for postoperative complications were as follows: intraoperative blood transfusions (OR = 2.938; 95% CI = 1.231–7.011; $P = .015$) and failure of the first biliary drainage (OR = 2.188; 95% CI = 1.035–4.627; $P = .040$). Independent predictive factors for 90-day mortality were failure of the first biliary drainage and age >70 y (Table V).

When assessing patients who had biliary drainage and had undergone left-side hepatectomy, independent predictive factors for postoperative complications were as follows: intraoperative blood transfusions (OR = 2.998; 95% CI = 1.288–6.983; $P = .011$) and failure of the first biliary drainage (OR = 2.106; 95% CI = 1.032–4.299; $P = .041$). Age >70 y was the only predictor for mortality (Table V).

Table IV
Management and type of first preoperative biliary drainage

Characteristics, number (%)	First biliary drainage before referral (148 patients)	First biliary drainage at referral centers (217 patients)	*P*
PTBD	59 (39.9)	144 (66.4)	<.001
EBD	89 (60.1)	73 (33.6)	
Failure	77 (52.0)	79 (36.4)	.003

PTBD, percutaneous transhepatic biliary drainage; *EBD*, endoscopic biliary drainage.

Discussion

Biliary drainage before hepatectomy for PHC remains debated regarding drainage timing, choice of drainage technique, and the site of the drainage. This multicenter study provides a snapshot of real clinical life in Italy on the management of jaundiced patients with PHC and offers the possibility to focus on factors that negatively affect the immediate results of 639 resected patients.

Major hepatectomy for PHC in jaundiced patients is associated with a high risk of postoperative mortality and morbidity attributable to liver failure[9,26] PBD is commonly used in most centers to obtain biliary decompression of the future remnant liver and to improve liver regeneration after a major hepatectomy[1,2] However, biliary drainage is associated with a risk of cholangitis and postoperative septic complications that may significantly increase postoperative mortality in patients undergoing extensive surgical procedures on injured livers[8,27] For these reasons, the perioperative management of patients undergoing surgery for PHC is challenging, and the postoperative mortality has been reported to be significantly higher than that reported for other indications[3,28] In Western series postoperative mortality rate ranges between 6.2% and 15% with postoperative morbidity rate reaching 60%.[4–7] In this study, the overall 90-day mortality rate of 8.9% was similar to the results reported in a majority of published studies[4–7,29–31] and much lower than that reported in a previous multicenter Italian study in which the mortality rate was 10.1% in patients resected between 1992 and 2007.[15]

Because of the high risk of septic complications related to biliary drainage, most authors agree that PBD should be selectively performed[1,2,9] In a recent multicenter study, Farges et al[32] demonstrated that PBD significantly reduced mortality after right-side hepatectomy. In contrast, after left-side hepatectomy, the PBD was significantly associated with increased mortality attributable to septic complications, suggesting that in patients with adequate future remnant liver volume, the risk of sepsis-related mortality after drainage may not justify the biliary decompression.[32] In a similar single-center study, Kennedy et al[33] demonstrated that PBD improved outcomes for patients with small future remnant liver volume (<30%) where the postoperative mortality rate was 0% in patients having had biliary drainage compared with 33% in patients having had no biliary drainage. On the other hand, in patients with future remnant liver volume >30%, postoperative mortality rate was 9% in patients who underwent PBD, compared with 0% for those who did not.[32] In other words, PBD may improve the outcomes for patients with small future remnant liver, but may also be detrimental to those with future remnant liver volumes >30%. Our study demonstrated that postoperative mortality rate was similar between patients resected after PBD and patients resected without PBD (7.1% *v* 9.7%, respectively; $P = .271$), confirming that in selected patients, liver resection for PHC could be performed safely also without PBD.

Currently, the policy in most Western centers is to selectively drain the future remnant liver when its volume is less than 40% to 50%[1,2,9] A similar policy was adopted at Italian referral hepatobiliary centers. Indeed, in our study, among the 217 patients who were first drained at referral centers, biliary drainage of the future remnant liver was performed in 180 patients (82.9%).

Our study confirmed that right-side hepatectomy was the most demanding and risky procedure. The multivariable logistic regression analysis of the overall series of patients indicated that right-side hepatectomy was one of the strongest predictor for 90-day mortality together with age >70 years and with an intraoperative blood transfusion requirement. Indeed, postoperative mortality after right-side hepatectomy was significantly higher than that after left-side hepatectomy (12.5% *v* 5.7%, respectively; $P = .003$). It should be highlighted that, among the patients who died during the postoperative course, the most frequent cause of mortality was septic complications (57.9%). Liver failure–related mortality occurred in 24.5% of patients who died within 90 days after surgery. Although an accurate preoperative selection of patients at referral centers may reduce the risk of liver failure, these results could mean that, sepsis-related mortality is remains a crucial topic among patients undergoing major hepatectomy for PHC. Because septic complications are mainly related to biliary drainage complications; overall management of biliary drainage has a crucial role as risk factor for postoperative mortality.

The optimal drainage method continues to be debated. Three recent meta-analyses have demonstrated that PTBD was associated with a lower risk of cholangitis.[18–20] On the other hand, some Western centers consider the EBD as the reference method because PTBD might be complicated by portal vein thrombosis or seeding metastasis that may compromise the resectability of the tumor.[2] The potential risk of seeding metastasis associated with PTBD remains controversial[34,35] In a recent multicenter study of 240 resected patients for PHC, oncologic outcomes including disease-specific survival and recurrence-free survival, were similar among patients who underwent PTBD versus EBD, with no difference in tumor recurrence location.[35] To overcome the risk of seeding, endoscopic nasobiliary drainage has been proposed in Japan[10,36] However, this type of drainage is not generally performed in Western centers because it is usually not well tolerated by patients and it may easily dislocate, requiring the patient to undergo additional drainage procedures. Finally, a recent randomized controlled trial comparing PTBD with EBD was done at four academic centers in the Netherlands but it was prematurely ended because of the significantly higher mortality rate in the PTBD group.[21] In this study, 54 patients were randomized and postoperative mortality in the PTBD group was significantly higher than that in the EBD group (41% *v* 11%, respectively; $P = .03$).[21] However, as highlighted by the authors, these data should be interpreted with caution because of the small sample size of the analysis. Therefore, currently the choice between percutaneous or endoscopic drainage seems for the most part to be based on the single center expertise and choice.

In our study a specific analysis of the preferred type of PBD at Italian referral centers was performed. First, it should be highlighted that jaundiced patients with PHC often received a biliary drainage at the first admitting hospital and, therefore, they had often already biliary drainage before a proper hepatobiliary surgical evaluation at referral centers. This could represent an important bias in most meta-analyses because the reported approaches are

Table V
Univariable and multivariable logistic regression analysis for the identification of risk factors associated with 90-day mortality in patients having had biliary drainage

Variables	Univariable analysis *P*	Multivariable analysis OR (95% CI)	*P*
Right-side hepatectomies			
Age (y) >70	.014	3.001 (1.220–7.383)	.017
Male sex	.971		
ASA score ≥2	.570		
Bismuth stricture type 3–4	.940		
First biliary drainage (PTBD versus EBD)	.771		
Failure after first biliary drainage	.036	2.690 (1.037–6.975)	.042
Interval time from biliary drainage to surgery >30 days	.856		
Preoperative insufficient biliary drainage (total bilirubin level >5 mg/dL)	.818		
Preoperative portal vein embolization	.785		
Vascular resection	.085		
Intraoperative blood transfusions	.633		
Left-side hepatectomies			
Age (y) >70	.037	12.890 (1.399–118.734)	.024
Male sex	.593		
ASA score ≥2	.704		
Bismuth stricture type 3–4	.100		
First biliary drainage (PTBD *v* EBD)	.698		
Failure after first biliary drainage	.325		
Interval time from biliary drainage to surgery >30 days	.939		
Preoperative insufficient biliary drainage (total bilirubin level >5 mg/dL)	.081		
Vascular resection	.998		
Intraoperative blood transfusions	.761		

ASA, American Society of Anesthesiologists; *PTBD*, percutaneous transhepatic biliary drainage; *EBD*, endoscopic biliary drainage.

highly variable according to the centers' experience with different drainage-related complications.

Unique to our study is the specific analysis on the timing and the type of PBD and the failure rate after biliary drainage. During the study period, 40.5% of patients had their first biliary drainage at the first admitting hospital before evaluation began at referral hepatobiliary surgery centers. In the assessment of the overall series of the first preoperative biliary drainage, PTBD was not significantly used more frequently than EBD (55.6% *v* 44.4%). However, when assessing the type of first biliary drainage according to the centers' experience, it was interesting to note that the choice of biliary drainage method significantly differed between community hospitals and referral centers. Indeed, the preferred method of drainage was EBD (60.1%) in patients initially managed at community hospitals. On the other hand, when patients were first managed at referral hepatobiliary centers, the preferred method of drainage was PTBD (66.4%). It could be argued that more frequent availability of endoscopists in the national territory resulted in a higher rate of EBD outside of referral centers. On the contrary, in referral centers the percutaneous technique is preferred.

The most important results demonstrated the rate of failure of biliary drainage. The overall rate of biliary drainage failure was 43.3% and this rate was not significantly different according to the type of drainage (38.9% after PTBD *v* 47.5% after EBD; $P = .098$). However, after dividing patients between those having had biliary drainage before referral and those having had biliary drainage at referral centers, the rate of failure of biliary drainage was significantly higher at community hospitals than at referral hepatobiliary centers (52.7% *v* 36.9%, respectively; $P = .002$). This means that the choice of biliary drainage of the patient outside of referral centers, before hepatobiliary surgical evaluation, was often related to worse biliary drainage outcome.

Complications related to biliary drainage, such as cholangitis and a need for multiple procedures attributable to incomplete biliary drainage, may increase the risk of postoperative mortality[4,8,16,17,27]. In our study, we analyzed the impact of failure of the first PBD on postoperative results according to the extent of liver resection. Failure of the first PBD was one of the strongest predictors for postoperative complications both in patients undergoing right-side hepatectomy and in patients undergoing left-side hepatectomy. When assessing patients having had biliary drainage and having undergone the riskiest procedure (right-side hepatectomy), at multivariable logistic regression analysis, failure of PBD was one of the strongest predictors for both postoperative morbidity and mortality. Of note, the type of first PBD (PTBD *v* EBD) was not associated with significantly different risk of mortality. According to these results, our study demonstrated that mortality after right-side hepatectomy was significantly higher in patients who experienced biliary drainage failure with consequent need of additional drainage attempts for treating complications. Such patients more had biliary drainage performed at community hospitals. In other words, based on these results, before referral to a hepatobiliary surgery center, biliary drainage should be avoided with a jaundiced patient who has PHC, especially patients who need a high-risk procedure such as a right-side hepatectomy. Therefore, initiating the management of these patients at referral hepatobiliary surgery centers appears to be associated with better perioperative outcomes.

The present study has some limitations. Indeed, it was a retrospective study and was not an intent-to-treat analysis. The multicenter database included only patients who were selected for surgery and who eventually underwent liver resection for PHC. For this reason, the number of patients who were excluded from liver resection because of septic complications related to PBD was not available.

In conclusion, our study demonstrated that biliary drainage failure was significantly more frequent at community hospitals and was an independent predictor for 90-day mortality after right-side hepatectomy. According to our results, the experience of the center that first manages a jaundiced patient with PHC is crucial to reducing the risk of infectious complications of biliary drainage and the related postoperative mortality.

Conflict of interest/Disclosure

The authors have no related conflicts of interest to declare.

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