












Preoperative biliary drainage in perihilar cholangiocarcinoma: retrospective multicentre analysis

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Abstract

Background: There is no consensus on the use of preoperative biliary drainage for resectable perihilar cholangiocarcinoma. This retrospective cohort study aimed to explore the association of biliary drainage with postoperative mortality and morbidity.

Methods: This retrospective observational cohort study included patients who underwent resection of histologically confirmed perihilar cholangiocarcinoma from the Perihilar Cholangiocarcinoma Collaboration Group database across 27 Western hepatobiliary centres (2000–2022). To correct for baseline differences between patients who did or did not undergo drainage, propensity score weighting was applied. Outcomes were compared using propensity score-weighted regression and multivariable analysis.

Results: Overall, 2067 patients were included, of whom 350 (16.9%) did not undergo biliary drainage. Before propensity score weighting, patients who did not undergo drainage were less likely to have Bismuth III–IV disease (297 (78.9%) versus 1448 (84.3%); $P < 0.001$), had lower median bilirubin levels (12.0 versus 85.5 $\mu\text{mol/l}$; $P < 0.001$), and a higher proportion had left hepatectomies (150 (42.9%) versus 454 (26.4%); $P < 0.001$). After propensity score-weighted regression analysis, patients in the drainage group were more likely to experience major postoperative complications (odds ratio 1.43, 95% confidence interval 1.04 to 1.95; $P = 0.027$) and posthepatectomy liver failure (odds ratio 2.12, 1.25 to 3.58; $P = 0.005$). In multivariable analysis, only posthepatectomy liver failure remained significant (odds ratio 2.13, 1.29 to 3.54; $P = 0.003$).

Conclusion: In this retrospective propensity score weighting analysis, preoperative biliary drainage was associated with a higher incidence of posthepatectomy liver failure in resectable perihilar cholangiocarcinoma. These findings suggest that a subgroup of patients with perihilar cholangiocarcinoma can be operated safely without biliary drainage. The indication for preoperative biliary drainage should be considered on an individual basis.

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Introduction

Perihilar cholangiocarcinoma (pCCA) represents the predominant subtype of biliary tract cancer, emerging at the junction of the hepatic ducts^{1,2}. Radical surgical resection achieves a median overall survival (OS) of 30–45 months^{2,3}. The Nagoya group⁴ has demonstrated a postoperative mortality rate below 2% and Western centres report 90-day mortality rates of 8–18%, with more than half of patients experiencing major postoperative complications⁵. Despite these risks, aggressive surgical management is justified, as palliative systemic therapy offers a median OS of 13 months⁶.

Given these risks, optimal preoperative management is essential². Preoperative biliary drainage (BD) is commonly performed in patients with obstructive jaundice and is considered mandatory before liver hypertrophy-inducing procedures^{4,7}. BD can be achieved via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic BD (PTBD)⁸.

Drainage-induced cholangitis is the most severe complication in pCCA, and frequently necessitates antibiotic treatment and repeated interventions^{9,10}. Preoperative cholangitis is associated with prolonged hospital stay, deterioration of performance status, and reduced resectability, as illustrated by nationwide data showing low surgical rates among patients with pCCA². Before surgery, BD is also associated with a high mortality rate ranging from 11 to 46%^{10,11}; cholangitis is the most common complication and a likely contributor to these outcomes. Preoperative cholangitis can also increase the risk of morbidity and mortality after surgery, predominantly owing to posthepatectomy liver failure (PHLF)^{5,12,13}.

Several retrospective studies^{14–16} have failed to demonstrate a clear improvement in postoperative outcomes with routine BD compared with no drainage, except in selected subgroups¹⁷. This retrospective cohort study aimed to explore the association between preoperative BD and postoperative outcomes in patients with pCCA.

Methods

Study design

Data from the pCCA Collaboration Group were analysed in this retrospective cohort study. Data on patients with histologically confirmed pCCA, who underwent surgical resection in 1 of 27 hepatobiliary centres between 2000 and 2022, were used. All participating European or North American centres are expert centres, with a median yearly volume of six resections during the inclusion period. The data set included information on patient characteristics, disease presentation, biochemical parameters, preoperative management, surgery, and postoperative outcomes. Tumour node metastasis (TNM) staging was done according to the

seventh edition of the Union for International Cancer Control, as the inclusion period preceded the release of the eighth edition.

Ethical approval was not required for this study, as it involved only retrospective analysis of anonymized data. Approval for data use was obtained from the pCCA Collaboration Group.

Patients

All patients who underwent hepatectomy with histologically confirmed pCCA before surgery or on histopathological examination of the resected specimen were considered eligible for inclusion. Patients were excluded if they underwent isolated bile duct resection or liver transplantation, or if they had missing data for the primary endpoint or preoperative BD status. Patients were grouped according to whether they underwent preoperative BD.

Outcomes

The primary endpoint was 90-day postoperative mortality, defined as any death occurring within 90 days following surgery. Secondary outcomes included major postoperative complications, classified as \geq grade III according to the Clavien–Dindo scale¹⁸, PHLF, postoperative bile leak, and postoperative bleeding, each defined by International Study Group of Liver Surgery criteria^{19–21}. Grade B and C were considered clinically relevant for the latter three outcomes. Duration of operation and estimated intraoperative blood loss were considered.

Analysis

To ensure equivalence between the two groups, propensity score weighting (PSW) was employed. PSW requires a complete data set and, because some weighting and secondary outcome variables had missing data, imputation was done with the mice package in R (R Foundation for Statistical Computing, Vienna, Austria)²². Propensity scores were calculated using a generalized linear model. The decision to use weighting instead of matching was made to retain the full data set, as matching would have necessitated the exclusion of considerable numbers of patients, potentially introducing bias. It is important to recognize that PSW produces a weighted pseudopopulation rather than a cohort of individual patients, which adds complexity to interpretation of the findings. Variables for the propensity score model were selected using a two-step approach: initial identification based on baseline differences, followed by selection of clinically relevant confounders suitable for PSW. The twang package²³ in R was used for calculation.

Statistical analysis

Categorical variables are presented as absolute numbers with percentages, and continuous variables as mean or

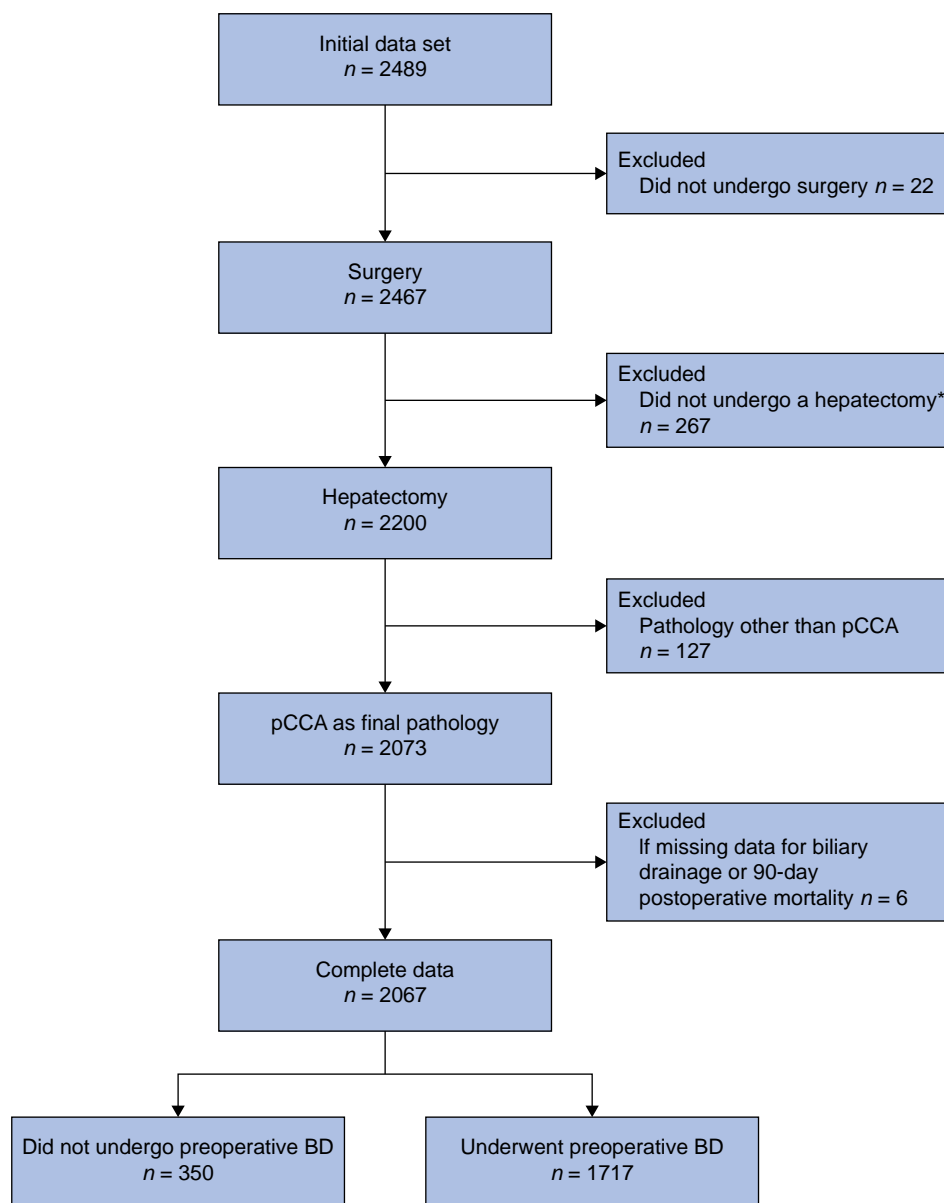


Fig. 1 Flow chart showing patient selection from the pCCA Collaboration Group database

*Patients undergoing isolated bile duct resection or liver transplant. pCCA, perihilar cholangiocarcinoma; BD, biliary drainage.

median (range), depending on normality assessment based on the Shapiro–Wilk test. Differences between the two groups were tested using Pearson’s χ^2 test and the Mann–Whitney U test, as appropriate. $P \leq 0.050$ was considered statistically significant. Statistical analyses were undertaken using SPSS® version 28 (IBM, Armonk, NY, USA), R version 3.5.3, and RStudio® version 1.1.463 (RStudio, Boston, MA, USA). Tables and figures were generated using Microsoft® Excel® (Microsoft, Redmond, WA, USA) and Miro (Miro, San Francisco, CA, USA) respectively.

Results

Patients and baseline characteristics

Following patient selection (Fig. 1), the final data set included information from 2067 patients, of whom 350 (16.9%) did not undergo preoperative BD. Among the group that had drainage,

490 patients (28.6%) underwent percutaneous PTBD, 933 (54.3%) had ERCP, and 294 (17.1%) underwent both. Table 1 shows baseline characteristics for both groups.

Prior to applying PSW, undrained patients less frequently presented with bilirubin levels exceeding 150 $\mu\text{mol/L}$ (8.8 mg/dL, 23 vs 403, $P < 0.001$) and had a lower prevalence of preoperative cholangitis (12 vs. 432, $P < 0.001$). The undrained group had less advanced disease stages (Bismuth III–IV 297 vs. 1448, $P = 0.015$) and underwent PVE less often (30 vs. 380, $P < 0.001$). Undrained patients more frequently underwent left hemihepatectomies (150 vs. 454, $P < 0.001$). Portal reconstruction was less frequent in undrained patients (75 vs. 694, $P < 0.001$).

Following PSW, the proportion of undrained patients with bilirubin levels exceeding 150 $\mu\text{mol/L}$ (8.8 mg/dL) at initial presentation was similar between the groups (21.9% vs. 20.6%, $P = 0.75$). When assessed as a continuous variable, bilirubin at presentation showed an SMD of 0.18 after weighting (Fig. S1).

Table 1 Baseline characteristics before and after PSW

	Before PSW			After PSW		
	No drainage (n = 350)	Drainage (n = 1717)	P	No drainage (n = 2051.18)*	Drainage (n = 2067.83)*	P
Age (years), median (i.q.r.)†	68 (58–75)	65 (57–72)	<0.001§	64 (55–73)	65 (57–72)	0.623§
Sex†						0.836
Female	144 (41.1%)	714 (41.6)	0.926	(40.7%)	(41.5%)	
Male	206 (58.9%)	1003 (58.4%)		(59.3%)	(58.5%)	
BMI (kg/m ²), median (i.q.r.)	26.0 (23.4–29.1)	25.0 (22.6–28.2)	<0.001§	26.0 (23.0–29.07)	25.0 (22.8–28.3)	0.149§
ASA grade III + IV†	163 (46.6%)	626 (36.5%)	<0.001	(43.0%)	(38.4%)	0.213
Bilirubin at presentation > 150 µmol/l or 8.8 mg/dl†	23 (7%)	403 (23.5%)	<0.001	(21.9%)	(20.6%)	0.752
Bilirubin at presentation (µmol/l), median (i.q.r.)	12.0 (7.0–37.6)	85.5 (19.0–198.9)	<0.001§	17.0 (8.6–153.9)	73.0 (18.0–75.0)	<0.001§
Bilirubin at presentation (mg/dl), median (i.q.r.)	0.7 (0.41–2.2)	5.0 (1.11–11.6)		1.0 (0.5–9)	4.3 (1.1–4.4)	
Preoperative bilirubin (µmol/l), median (i.q.r.)	12.0 (7.0–38.5)	21.0 (9.0–43.0)	<0.001§	15.0 (8.0–63.0)	20.5 (8.6–41.6)	0.855§
Preoperative bilirubin (mg/dl), median (i.q.r.)	0.7 (0.41–2.25)	1.23 (0.53–2.51)		0.88 (0.47–3.68)	1.20 (0.5–2.43)	
Primary sclerosing cholangitis	9 (3%)	46 (3%)	0.643	(4%)	(3%)	0.795
CA19-9 at presentation or preoperative value (units/ml), median (i.q.r.)	126 (37–377)	149 (41–516)	0.976§	120 (30–397)	145 (40–497)	0.428§
Preoperative cholangitis	12 (3%)	432 (25.2%)	<0.001	(4%)	(24.6%)	<0.001
Bismuth–Corlette classification III + IV†	297 (78.9%)	1448 (84.3%)	0.015	(84.7%)	(83.4%)	0.591
Tumour category T3 + T4 (7th edition)	127 (36.2%)	614 (35.8%)	<0.001	(38.8%)	(35.4%)	0.343
Node category N1 + N2 (7th edition)	146 (41.7%)	745 (40.4%)	0.496	(45.5%)	(42.7%)	0.604
Metastasis category M1(7th edition)	11 (3%)	76 (4%)	0.303	(5%)	(5%)	0.992
Differentiation grade moderate–well	237 (67.7%)	1173 (68.3%)	0.070	(29.6%)	(31.5%)	0.547
Perineural invasion	217 (62.0%)	240 (14.0%)	0.015	(79.5%)	(77.5%)	0.488
Preoperative biliary drainage			<0.001			<0.001
None	350 (100%)	0 (0)		(100%)	(0%)	
PTBD	0 (0)	490 (28.6%)		0 (0)	(28.9%)	
ERCP	0 (0)	933 (54.3%)		0 (0)	(54.8%)	
Both	0 (0)	294 (17.1%)		0 (0)	(16.3%)	
Portal vein embolization†	30 (9%)	380 (22.1%)	<0.001	(17.1%)	(19.8%)	0.480
Type of hepatectomy†			<0.001			0.993
Left hemihepatectomy	150 (42.9%)	454 (26.4%)		(29.8%)	(29.2%)	
Left extended hemihepatectomy	57 (17%)	291 (17.0%)		(17.1%)	(16.8%)	
Right hemihepatectomy	64 (18%)	294 (17.1%)		(17.9%)	(17.3%)	
Right extended hemihepatectomy	66 (19%)	618 (36.0%)		(32.3%)	(33.1%)	
Segment IV/V	12 (3%)	42 (3%)		(2%)	(3%)	
Central or mesohepatectomy	1 (<1%)	18 (1%)		(0.6%)	(1%)	
Segment I resected	238 (68.0%)	1022 (59.5%)	0.140	(72.8%)	(75.1%)	0.529
Pancreatoduodenectomy	5 (1%)	29 (2%)	0.892	(2%)	(1.75%)	0.918
Portal vein reconstruction†	75 (21%)	604 (40.4%)	<0.001	(35.9%)	(37.2%)	0.728
Hepatic artery reconstruction†	11 (3%)	71 (4%)	0.075	(6.2%)	(4%)	0.207

Values are n (%) unless otherwise stated. *Value in the weighted population after propensity score weighting (PSW) reflects the sum of patient weights rather than the actual number of individual patients. †Variables used for PSW. i.q.r., Interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; CA, carbohydrate antigen; PTBD, percutaneous transhepatic biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography. ‡Pearson's χ^2 test, except §Mann-Whitney U test.

Advanced disease stage was also equivalent (Bismuth III-IV: 84.7% vs. 83.4%, $P = 0.59$), as well as the proportions of left hepatectomies and right extended hemi-hepatectomies (29.8% vs. 29.2% and 32.3% vs. 33.1%, resp.; $P = 0.99$). No differences were noted in percentages of PVE procedure ($P = 0.48$) or PV reconstruction ($P = 0.73$). Preoperative cholangitis was not used to determine the propensity score weights, and its incidence remained lower in the undrained group after PSW (4.42% vs 24.64%, $P < 0.001$).

Postoperative outcomes

Postoperative morbidity and mortality are shown in Table 2. Before PSW, the 90-day postoperative mortality rate was lower in the undrained group compared to the drained group (33 vs. 240, $P = 0.027$), as well as major postoperative complications (Clavien-Dindo \geq III, 126 vs. 880, $P < 0.001$). The undrained group also had

lower incidences of PHLF (26 vs. 285, $P = 0.002$) and postoperative bleeding (22 vs. 195, $P = 0.006$). no differences were observed in postoperative biliary leaks ($P = 0.084$).

After PSW, the difference in 90-day mortality rate between the groups became non-significant (9.8% vs. 13.7%, $P = 0.11$). the undrained group continued to show a lower incidence of major postoperative complications (41.5% vs 50.3%, $P = 0.027$) and of PHLF (7.7% vs 15.5%, $P = 0.004$). There was no difference in postoperative biliary leaks ($P = 0.21$) or bleeding ($P = 0.15$).

Propensity score-weighted regression (PSWR) and multivariable analysis

The results of the PSWR analysis are shown in Table 3. Patients who underwent BD did not have a significantly higher chance of death within 90 days of surgery (odds ratio (OR) 1.46, 95% confidence interval 0.92 to 2.34; $P = 0.112$), but they had a higher

Table 2 Postoperative outcomes before and after PSW

	Before PSW			After PSW		
	No drainage (n = 350)	Drainage (n = 1717)	P†	No drainage (n = 2051.18)*	Drainage (n = 2067.83)*	P†
90-day postoperative mortality	33 (9%)	240 (14.0%)	0.027	(9.8%)	(13.7%)	0.110
Major postoperative complication (Clavien–Dindo ≥ III)	126 (36.0%)	880 (51.3%)	<0.001	(41.5%)	(50.3%)	0.027
PHLF grade B + C#	26 (7%)	285 (16.6%)	0.002	(8.2%)	(15.9%)	0.004
Postoperative bile leak grade B + C#	57 (16.3%)	352 (20.5%)	0.084	(15.9%)	(20.3%)	0.208
Postoperative bleeding grade B + C#	22 (6%)	195 (11.4%)	0.006	(7.4%)	(10.9%)	0.150
Operative blood loss (ml), median (i.q.r.)	700 (400–1175)	840 (500–1600)	<0.001‡	700 (500–1400)	800 (500–1530)	0.094‡
Duration of operation (min), median (i.q.r.)	420 (311.5–5010)	430 (353–525)	0.003‡	420 (324–505)	428 (352–525)	0.042‡

Values are n (%) unless otherwise stated. *Value in the weighted population after propensity score weighting (PSW) reflects the sum of patient weights rather than the actual number of individual patients. #As defined by International Study Group of Liver Surgery. PSW, propensity score weighting; PHLF, posthepatectomy liver failure; i.q.r., interquartile range. †Pearson's χ^2 test, except ‡Mann–Whitney U test.

Table 3 PSWR and multivariable analysis comparing effect of drainage versus no drainage on primary and secondary outcomes

	Adjusted odds ratio¶	P
PSWR*		
90-day postoperative mortality	1.46 (0.92, 2.34)	0.112
Major postoperative complication (Clavien–Dindo ≥ III)‡	1.43 (1.04, 1.95)	0.027
PHLF grade B + C‡§	2.12 (1.25, 3.58)	0.005
Postoperative bile leak grade B + C‡§	1.35 (0.85, 2.15)	0.209
Postoperative bleeding grade B + C‡§	1.54 (0.85, 2.77)	0.152
Multivariable analysis†		
PHLF grade B + C‡§	2.13 (1.29, 3.54)	0.003
Major postoperative complication (Clavien–Dindo ≥ III)‡	1.21 (0.85, 1.73)	0.291

Values in parentheses are 95% confidence intervals. *Survey-weighted logistic models; †for significant outcomes after propensity score-weighted regression (PSWR). ‡Imputed variables. §As defined by the International Study Group of Liver Surgery. ¶Analysis adjusted for age (> 65 years), sex (female), body mass index (> 30 kg/m²), American Society of Anesthesiologists grade (I–II versus III–IV), primary sclerosing cholangitis, bilirubin at presentation (threshold 150 μ mol/l or 8.8 mg/dl), preoperative cholangitis, carbohydrate antigen 19-9 levels (> 100 units/ml), type of hepatectomy (major versus minor), resection of segment I, pancreatoduodenectomy, portal venous embolization, portal venous reconstruction, hepatic artery reconstruction, Bismuth–Corlette classification (I–II versus III–IV), and preoperative biliary drainage. For full univariable and multivariable analyses please refer to [Table S1](#). PHLF, posthepatectomy liver failure.

likelihood of major complications (Clavien–Dindo ≥ III: OR 1.43, 1.04 to 1.95; $P=0.027$). This group also had a higher likelihood of clinically relevant PHLF (OR 2.12, 1.25 to 3.58; $P=0.005$). Although patients who underwent drainage had higher odds of clinically relevant bile leaks (OR 1.35, 0.85 to 2.15; $P=0.209$) and postoperative bleeding (OR 1.54, 0.85 to 2.77; $P=0.152$), these differences were not statistically significant.

Because major postoperative complications and clinically relevant PHLF remained more prevalent after PSWR in the group that underwent drainage, univariable and multivariable analyses were conducted ([Table S1](#)). For major postoperative complications, the isolated effect of preoperative BD was non-significant (OR 1.21, 0.85 to 1.73; $P=0.291$). For clinically relevant PHLF, the isolated effect of preoperative BD remained significant, with an OR similar to that observed in the PSWR (OR 2.13, 1.29 to 3.54; $P=0.003$).

Discussion

Randomized clinical trials comparing upfront surgical resection with and without preoperative BD in patients with pCCA have not been conducted. Most research on this topic is retrospective and relies on techniques such as PSW to ensure comparability between groups²⁴. In the present study, before applying PSW, there were large differences in baseline characteristics and postoperative outcomes between groups of patients with pCCA who did or did not undergo BD (disease stage, bilirubin levels, preoperative cholangitis, PVE, portal vein reconstruction). Higher rates of preoperative cholangitis in the drained group remained after PSW, as it was intentionally excluded from the PSW model. This decision was made because cholangitis is usually a consequence of BD rather than an indication for it, and the data set did not distinguish between cholangitis at presentation and that developing after drainage. As such, it can act as a mediator and including it in the model would not have been appropriate.

In terms of outcomes, before PSW, postoperative morbidity and mortality rates were higher in the drained group. Ninety-day postoperative mortality, major postoperative complications, PHLF, and bleeding were more common among patients who underwent BD. Expect for PHLF, they became non-significant after PSW(R) and multivariable analysis, suggesting that the variations in outcomes were due to baseline differences rather than related to BD. PHLF rates remained significantly lower in the undrained group, highlighting the potential link between BD and an increased risk of PHLF.

However, an alternative interpretation should be considered. The group without drainage had markedly lower bilirubin levels at baseline, reflecting less severe cholestasis. The lower PHLF rates may therefore also relate to this more favourable physiological status rather than to the absence of drainage itself. This is consistent with expert practice, whereby surgery is undertaken only once the bilirubin level is below 35 μ mol/l (2 mg/dl)⁴. In addition, multivariable analysis of a PSW cohort may also suffer from residual confounding.

The baseline characteristics and outcomes of this full cohort align with those described in a benchmark study²⁵, suggesting that the present findings are clinically applicable. These results showed some variation from those reported by Farges et al.¹⁷ in terms of Bismuth–Corlette classification and portal vein reconstruction, whereas both studies identified differences in

cholangitis, jaundice, bilirubin levels, and hepatectomy type. These additional findings may be attributed to the larger sample size in the present study, allowing more detailed detection of differences.

A recent study by Sarkhampee *et al.*²⁴ showed similar baseline differences between drained and undrained patients with pCCA, but they reported substantially higher bilirubin levels at presentation and before surgery for both drained and undrained groups compared with values in the present study. That study reported higher rates of postoperative morbidity and mortality in the undrained group. It could be argued that, despite matching, the difference in bilirubin levels before surgery, which remained raised in both groups, most notably in patients without drainage, may have had a negative impact on outcomes among those who did not undergo BD.

The primary rationale for preoperative BD is to restore bile flow, and consequentially reduce hepatic and serum accumulation of cholephiles such as bilirubin, which serve as a marker of biliary obstruction and cholestasis. Several experimental studies^{26,27} have reported improved liver regeneration when the enterohepatic circulation is restored before hepatectomy. Clinically, a raised bilirubin level has been linked to a higher risk of postoperative complications, including PHLF^{28–31}. Drainage-related complications, such as cholangitis, also increase postoperative morbidity and mortality among patients with pCCA⁹. Cholangitis can also weaken patients, both before and after surgery, and prolong the time from diagnosis to surgery compared with upfront resection^{10,12,13,32}.

Several limitations of this study should be acknowledged. The multicentre design means that all treatment decisions were made according to local protocols and expertise, inherently introducing variation in the indication, bilirubin cut-off value, and technique for BD, use of liver hypertrophy-inducing procedures, perioperative antibiotic regimens, and operative strategies. The present data set included only patients who underwent surgery for pCCA and does not account for those who became inoperable owing to complications from BD. Although the data set was comprehensive, certain confounders may not have been accounted for, as it does not include all potentially relevant variables. Insufficient data on future liver remnant volume prevented any adjustments to account for its effect on PHLF. Missing data were addressed through imputation, which, although not without potential bias, is preferable to limiting the analysis to patients with complete data. The latter results in less statistical power and a higher likelihood of biased results. Although most variables had only single-digit percentages of missing data, bilirubin level at presentation had approximately 30% missing data. As such, the impact of imputation was more substantial, which in turn may have affected the robustness and generalizability of the weighting and introduced residual confounding. Although PSW is an artificial method for achieving equivalence, data interpretation should be approached with caution because of severe baseline differences between the two groups. The different sample size of undrained cohort after and before PSW, (350 versus 2000) indicated a substantial weighting to achieve balance, and it underscored the artificial nature of the comparability and limits the external validity of the results. As no universal bilirubin threshold exists, any cut-off applied in PSW is inherently arbitrary. Dichotomizing the bilirubin level led to residual confounding as shown in the Love plot (Fig. S1). As such, bilirubin level at presentation showed no difference between groups after PSW when analysed as a dichotomized

variable, but it remained significantly different when assessed as a continuous variable.

This analysis has not demonstrated that direct surgery is equivalent to preoperative BD followed by surgery, yet it has indicated that some patients may undergo upfront resection without clear evidence of worse outcomes despite the different biases. Other potential advantages of upfront surgical resection, although speculative, include a reduced need for preoperative procedures and a shorter time to surgery. At present, real-world data do not support these assumptions. Preventing non-operability owing to drainage-related cholangitis may also be a consideration, but this cannot be confirmed from the present analysis.

Interpretation should be cautious because of the use of PSW and inherent differences between the groups with and without drainage; nevertheless, surgery without preoperative BD may be feasible in carefully selected patients, such as those without cholangitis, with bilirubin levels below a defined threshold (for example < 200 µmol/l), preserved performance status, an adequate future liver remnant (for example > 40%), and adequate renal function. Although the present findings do not argue against preoperative BD in patients with clear indications, the potential additional risk associated with routine drainage supports a more selective approach and underscores the need for prospective studies to guide clinical decision-making.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at [BJS Open](https://doi.org/10.1007/s00135-022-01000-0) online.

Data availability

The data underlying this article were provided by the pCCA Collaboration Group permission. Data will be shared on request to the corresponding author with permission of the pCCA Collaboration Group.

References

- Soares KC, Kamel I, Cosgrove DP, Herman JM, Pawlik TM. Hilar cholangiocarcinoma: diagnosis, treatment options, and management. *Hepatobiliary Surg Nutr* 2014;**3**:18
- van Keulen AM, Franssen S, van der Geest LG, de Boer MT, Coenraad M, van Driel LM et al. Nationwide treatment and outcomes of perihilar cholangiocarcinoma. *Liver Int* 2021;**41**:1945–1953
- Qurashi M, Vithayathil M, Khan SA. Epidemiology of cholangiocarcinoma. *Eur J Surg Oncol* 2025;**51**:107064
- Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann Surg* 2013;**258**:129–140
- van Keulen AM, Buettner S, Erdmann JI, Pratschke J, Ratti F, Jarnagin WR et al. Multivariable prediction model for both 90-day mortality and long-term survival for individual patients with perihilar cholangiocarcinoma: does the predicted survival justify the surgical risk? *Br J Surg* 2023;**110**:599–605
- Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evid* 2022;**1**:EVIDoA2200015
- Ellis RJ, Soares KC, Jarnagin WR. Preoperative management of perihilar cholangiocarcinoma. *Cancers (Basel)* 2022;**14**:2119
- Kim KM, Park JW, Lee JK, Lee KH, Lee KT, Shim SG. A comparison of preoperative biliary drainage methods for perihilar cholangiocarcinoma: endoscopic versus percutaneous transhepatic biliary drainage. *Gut Liver* 2015;**9**:791
- Bednarsch J, Czigan Z, Heij LR, Luedde T, van Dam R, Lang SA et al. Bacterial bile duct colonization in perihilar cholangiocarcinoma and its clinical significance. *Sci Rep* 2021;**11**:2926
- van Keulen AM, Gaspersz MP, van Vugt JL, Roos E, Olthof PB, Coelen RJ et al. Success, complication, and mortality rates of initial biliary drainage in patients with unresectable perihilar cholangiocarcinoma. *Surgery* 2022;**172**:1606–1613
- Coelen RJ, Roos E, Wiggers JK, Besselink MG, Buis CI, Busch OR et al. Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2018;**3**:681–690
- Sakata J, Shirai Y, Tsuchiya Y, Wakai T, Nomura T, Hatakeyama K. Preoperative cholangitis independently increases in-hospital mortality after combined major hepatic and bile duct resection for hilar cholangiocarcinoma. *Langenbecks Arch Surg* 2009;**394**:1065–1072
- Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, Nagino M. The adverse effects of preoperative cholangitis on the outcome of portal vein embolization and subsequent major hepatectomies. *Surgery* 2014;**156**:1190–1196
- Mehrabi A, Khajeh E, Ghamarnejad O, Nikdad M, Chang DH, Büchler MW et al. Meta-analysis of the efficacy of preoperative

- biliary drainage in patients undergoing liver resection for perihilar cholangiocarcinoma. *Eur J Radiol* 2020;**125**:108897
15. Liu F, Li Y, Wei Y, Li B. Preoperative biliary drainage before resection for hilar cholangiocarcinoma: whether or not? A systematic review. *Dig Dis Sci* 2011;**56**:663–672
 16. Mansour JC, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015;**17**:691–699
 17. Farges O, Regimbeau J, Fuks D, Le Treut Y, Cherqui D, Bachellier P et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 2013;**100**:274–283
 18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–213
 19. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 2011;**149**:680–688
 20. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011;**149**:713–724
 21. Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford)* 2011;**13**:528–535
 22. Van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011;**45**:1–67
 23. Ridgeway G, McCaffrey DF, Morral AR, Cefalu M, Burgette LF, Pane JD et al. *Toolkit for Weighting and Analysis of Nonequivalent Groups: A Tutorial for the R TWANG Package*. Santa Monica: Rand, 2022
 24. Sarkhampee P, Junrungsee S, Tantraworasin A, Sirichindakul P, Ouransatien W, Chansitthichok S et al. Effects of preoperative biliary drainage on the outcomes of surgical treatment in cholangiocarcinoma: a propensity score matching analysis. *Clin Surg Oncol* 2024;**3**:100046
 25. Mueller M, Breuer E, Mizuno T, Bartsch F, Ratti F, Benzing C et al. Perihilar cholangiocarcinoma—novel benchmark values for surgical and oncological outcomes from 24 expert centers. *Ann Surg* 2021;**274**:780–788
 26. Saiki S, Chijiwa K, Komura M, Yamaguchi K, Kuroki S, Tanaka M. Preoperative internal biliary drainage is superior to external biliary drainage in liver regeneration and function after hepatectomy in obstructive jaundiced rats. *Ann Surg* 1999;**230**:655
 27. van Golen RF, Olthof PB, Lionarons DA, Reiniers MJ, Alles LK, Uz Z et al. FXR agonist obeticholic acid induces liver growth but exacerbates biliary injury in rats with obstructive cholestasis. *Sci Rep* 2018;**8**:16529
 28. Nakanishi Y, Tsuchikawa T, Okamura K, Nakamura T, Tamoto E, Noji T et al. Risk factors for a high Comprehensive Complication Index score after major hepatectomy for biliary cancer: a study of 229 patients at a single institution. *HPB (Oxford)* 2016;**18**:735–741
 29. Nanashima A, Abo T, Hamasaki K, Wakata K, Kunizaki M, Tou K et al. Predictors of intraoperative blood loss in patients undergoing hepatectomy. *Surg Today* 2013;**43**:485–493
 30. Xiong JJ, Nunes QM, Huang W, Pathak S, Wei AL, Tan CL et al. Preoperative biliary drainage in patients with hilar cholangiocarcinoma undergoing major hepatectomy. *World J Gastroenterol* 2013;**19**:8731
 31. Su CH, Tsay SH, Wu CC, Shyr YM, King KL, Lee CH et al. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. *Ann Surg* 1996;**223**:384–394
 32. El-Hanafy E. Pre-operative biliary drainage in hilar cholangiocarcinoma, benefits and risks, single center experience. *Hepatogastroenterology* 2010;**57**:414–419