ORIGINAL ARTICLE

Preoperative biliary drainage in severely jaundiced patients with pancreatic head cancer: A retrospective cohort study

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Abstract

Background: Guidelines recommend against preoperative biliary drainage (PBD) in patients with pancreatic head cancer if bilirubin levels are <250 μmol/l. However, patients with higher bilirubin levels undergo PBD, despite the lack of supporting evidence. This study aims to evaluate outcomes in patients with a bilirubin level ≥250 and < 250.

Methods: Patients were identified from databases of 3 centers. Outcomes were compared in patients with a bilirubin level ≥250 versus <250 both at the time of diagnosis and directly prior to surgery.

Results: 244 patients were included. PBD was performed in 64% (123/191) with bilirubin <250 at diagnosis and 91% (48/53) with bilirubin ≥250. PBD technical success (83% vs. 81%, p = 0.80) and PBD related complications (33% vs. 29%, p = 0.60) did not differ between these groups.

Analyzing bilirubin levels ≥250 versus <250 directly prior to surgery, no differences in severe post-operative complications and mortality were found.

Conclusions: In patients with a pancreatic head cancer, PBD technical success and complications, and severe postoperative complications did not differ between patients with a bilirubin level ≥250 and < 250. Our study does not support a different approach regarding PBD in patients with severe jaundice.

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Introduction

Whether preoperative biliary drainage (PBD) in jaundiced patients with a tumor of the pancreatic head is beneficial has been debated for decades.

In the past, PBD was advocated due to the results of experimental studies. A causal relation between obstructive jaundice and a pro-inflammatory state with increased levels of endotoxins and cytokines in the systemic circulation was demonstrated, presumably due to an impaired barrier function with subsequent bacterial translocation.[1–6] Clinical outcome regarding abdominal infections, postoperative complications and mortality was better in jaundiced animals undergoing PBD compared to animals with ongoing jaundice.[7,8] Internal biliary drainage has proven to be superior to external drainage, indicating the important effects of bile in the gut lumen.[1,3–5,9,10]

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In contrast to the above-mentioned animal studies, most clinical studies show that direct surgery is superior to PBD followed by surgery. In 2010, van der Gaag et al. published the results of the largest clinical trial on this topic, randomizing patients with obstructive jaundice due to a resectable tumor of the pancreatic head to internal PBD followed by surgery or direct surgery. The overall complication rate in the PBD group was significantly higher due to the 46% PBD related complications. In patients undergoing PBD, no advantage regarding post-operative complications and mortality was found compared to the direct surgery group.[11] Based on this and other studies,[12–15] guidelines recommend against routine PBD in patients with pancreatic head cancer and obstructive jaundice.[16]

However, all these studies except one,[15] excluded patients with a bilirubin level ≥250 μmol/l. Patients with bilirubin levels ≥250 μmol/l currently still undergo PBD in most practices, despite the lack of evidence to support this practice.

We hypothesized that in the patients with bilirubin levels of ≥250 μmol/l, PBD would not be more beneficial compared to patients with a bilirubin < 250. Even more, PBD in general, and endoscopic retrograde cholangiopancreatography (ERCP) in particular might even be associated with more complications in this subset of patients because one might speculate that high bilirubin levels indicate a tighter obstruction. The aim of this study was therefore to compare tumor characteristics, PBD technical success rate and complications, and postoperative complications in patients with pancreatic head cancer and a bilirubin level ≥250 and < 250.

Methods

Design and study population

We performed a retrospective, multicenter cohort study among three hospitals (two regional and one academic: Meander Medical Center, St. Antonius Hospital and University Medical Center Utrecht) in the Netherlands, which are part of the alliance 'Regional Academic Cancer Center Utrecht (RAKU)'. All patients diagnosed with pancreatic head cancer in the presence of cholestasis that were candidates for curative surgery were selected between January 2008 and May 2018. Patients were identified from prospectively compiled databases used for local multidisciplinary meetings including all cases with pancreatic cancer. In all patients, laboratory tests including bilirubin level and a CT scan were performed at diagnosis and all patients were discussed in multidisciplinary oncology meetings specialized in treating pancreatic cancer according to standard procedures following our local and national guidelines.

Cholestasis was defined as a total bilirubin level ≥40 μmol/l. Patients were eligible for curative resection if the tumor was (borderline) resectable according to the Dutch Pancreatic Cancer Group (DPCG) 2012 criteria. The following exclusion criteria were applied for this study: recent ERCP or percutaneous transhepatic cholangiography (PTC) before diagnosis, pancreatic tumor diagnosed during surgery and PBD performed in a referring hospital with missing relevant PBD related data. This study is not subject to the Medical Research Involving Human Subjects Act (WMO).

Data collection

Medical records of the selected patients were reviewed in the three hospitals, and the relevant study data were collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application designed to support data capture for research.[18] The following baseline parameters were collected: age, sex, American Society of Anesthesiologist (ASA) classification, clinical TNM classification, tumor resectability and bilirubin level at diagnosis. Tumors were staged according to the eighth edition of the TNM cancer staging manual of the American Joint Committee on Cancer.[19] If TNM and/or resectability were unclear based on the CT scan report and the multidisciplinary meeting, the CT scan was revised by an expert radiologist (T.L.B. and M. v.L). The following PBD related data were collected: bilirubin level prior to PBD, type of procedure, achievement of successful biliary drainage (endoscopic endpoint), stent type, PBD related complications and mortality. PBD complications were graded as mild, moderate or severe according to the international consensus definition.[20] The following surgery related data were collected: timing of surgery in relation to date of diagnosis and date of PBD, reasons (if any) for refraining from surgery, bilirubin level prior to surgery, type of surgery and surgery related complications and mortality. Post-operative complications were defined according to the International Study Group of Pancreatic Surgery (ISGPS).[21–25] ISGPS grade A complications were not listed since there are no clinical consequences. Electrolyte imbalances, glucose metabolism disorders and hypertension were also not registered as postoperative complications if the clinical impact was insignificant. All post-operative complications were graded according to the Clavien-Dindo classification of surgical complications.[26] At last, final histology data were collected.

Evaluation of outcomes

The primary endpoints of this study were PBD technical success and complications compared between patients with a bilirubin level ≥250 μmol/l versus <250 μmol/l *measured at diagnosis*, and severe surgery related complications and mortality compared between patients with a bilirubin level ≥250 μmol/l versus <250 μmol/l *measured prior to surgery*. Severe surgery related complications and mortality in patients with a bilirubin level ≥250 μmol/l versus <250 μmol/l *measured at diagnosis* were included in the supplementary material. A severe postoperative complication was defined as Clavien-Dindo III or higher (complications requiring surgical, endoscopic or radiological intervention). The bilirubin level at diagnosis was used to reflect the moment of clinical decision making. The preoperative bilirubin levels were used to evaluate the actual effect of the

bilirubin level on surgical outcomes. This is of importance as the bilirubin level changes during the time frame between diagnosis, PBD and surgery; it may increase quickly due to the natural disease course and is expected to decrease following PBD.[27] Secondary endpoints were postoperative histology, predictors of PBD related complications and predictors of severe postoperative complications.

Statistical analysis

Continuous variables were expressed as mean (±standard deviation; used in normally distributed variables) or median (interquartile range) and comparisons were made using the Student's T test and the Kruskal Wallis test, respectively. The Chi-Squared test was used to compare categorical variables. Independent predictors of PBD complications and severe postoperative complications were identified using multivariable logistic regression analyses and were expressed as odds ratios. A p-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using IBM SPSS Statistics Version 25. If applicable, the numbers of missing values were reported and a complete case analysis was performed if values were missing at random.

Results

Patient characteristics

A total of 244 patients with cancer of the pancreatic head and cholestasis were included in this study, of which 53 (22%) with a total bilirubin level ≥250 and 191 (78%) with a level <250 at diagnosis (Fig. 1). Relatively more men than women presented with a bilirubin level ≥250 (66% vs. 49%, p = 0.03). No other differences in baseline characteristics including radiological tumor stage were found at baseline (Table 1).

Primary endpoints

PBD related outcomes; analysis based on bilirubin level at diagnosis

PBD was attempted in 48 of the 53 (91%) patients with a bilirubin level ≥250 and in 123 of the 191 (64%) patients with a bilirubin level <250 at diagnosis (Table 2). The median interval between diagnosis and the first PBD procedure was significantly shorter in patients with a bilirubin ≥250 compared to patients with a bilirubin <250 (6 vs. 9 days, respectively; p < 0.01). In both groups, PBD was primarily performed by means of an ERCP and the most common indication was hyperbilirubinemia. No differences in technical success at the first attempt were found

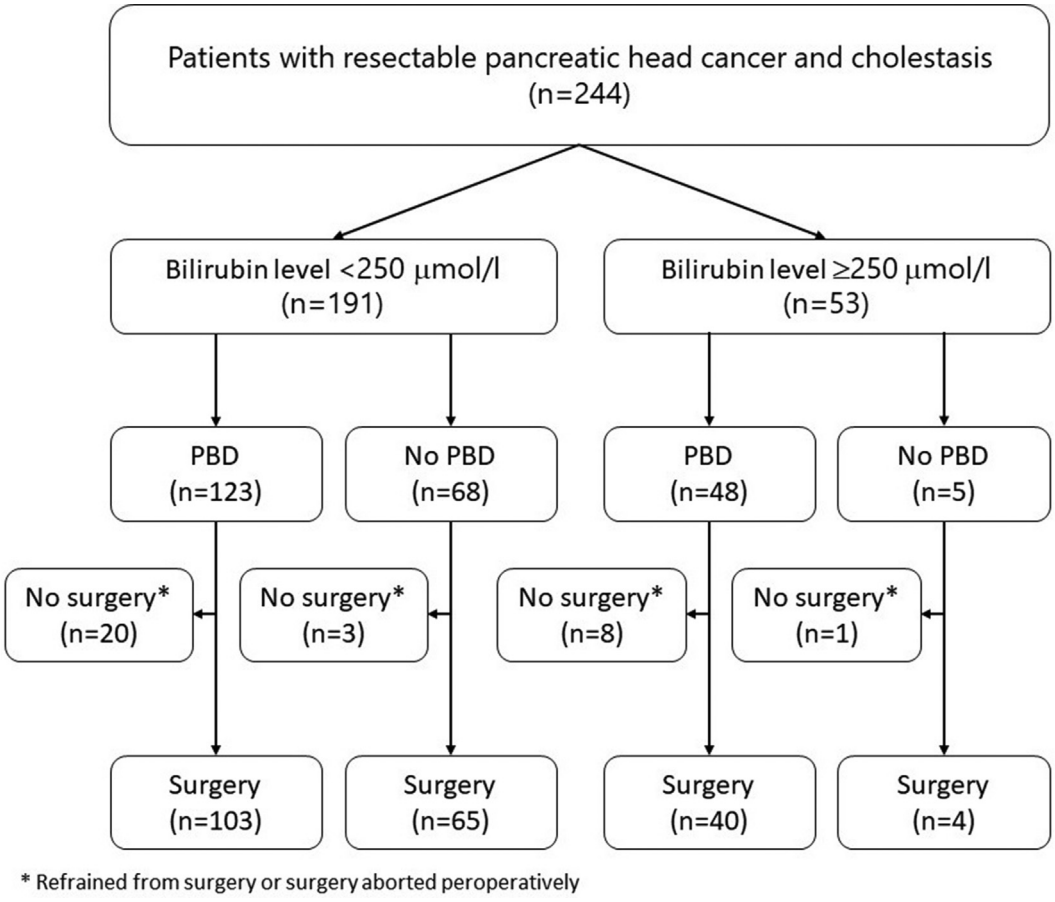

Figure 1 Flowchart (The displayed bilirubin levels are measured at diagnosis)

Table 1 Baseline characteristics

Characteristics	Bilirubin <250 N = 191	Bilirubin ≥250 N = 53	P-value
Male gender, N (%)	94 (49)	35 (66)	0.03
Age, years ± SD[a]	66 ± 11	69 ± 7	0.08
Total bilirubin at diagnosis, μmol/l[a]	132 (91–185)	316 (278–379)	<0.01
ASA classification, N (%)			
I	42 (22)	6 (11)	0.10
II	111 (58)	39 (74)	
III	38 (20)	8 (15)	
Radiological T-stage at diagnosis, N (%)			
Tx	11 (6)	2 (4)	0.67
T1	33 (17)	8 (15)	
T2	109 (57)	36 (68)	
T3	30 (16)	6 (11)	
T4	8 (4)	1 (2)	
Radiological lymph node involvement, N (%)	54 (28)	17 (32)	0.59

[a] Age is expressed as mean (±SD) and bilirubin levels are expressed as median (IQR).

between patients with bilirubin ≥250 versus <250 (83% vs. 81%, p = 0.80). The overall PBD related complication rate was not significantly different between patients with a bilirubin level ≥250 and < 250 (29% vs. 33%, p = 0.60). The severity of complications was graded as mild in the majority of patients in both groups, however, 3 patients died because of PBD related complications; 1 patient with a bilirubin >250 due to cholangitis and 2 patients with a bilirubin level <250 due to post-ERCP pancreatitis (see Table 2).

Surgery related endpoints; analysis based on bilirubin level directly prior to surgery

In total, 212 of the 244 patients (87%) underwent surgical resection. The bilirubin level directly prior to surgery was reported in 152 patients: 25 patients had a bilirubin ≥250 and in 127 patients the bilirubin level was <250 (Table 3). As expected, significantly more patients in the <250 group had undergone successful biliary drainage prior to surgery compared to the ≥250 group (79% and 8%, respectively; p < 0.001). A total of 32 patients did not complete surgery due to PBD related complications (n = 4), poor performance status (n = 10), disease progression (n = 3), death prior to surgery (n = 2) or because surgery was aborted peroperatively due to distant metastasis or locally advanced disease (n = 13). None of the reasons for not completing surgery was significantly different between patients with a bilirubin level ≥250 and < 250 and between patients who did or did not undergo PBD.

The number of severe postoperative complications in patients with a bilirubin ≥250 directly prior to surgery was lower than in patients with a bilirubin <250, but this failed to reach statistical significance (16 vs. 35%, p = 0.06). The severity of postoperative complications did not differ significantly between the <250 and the ≥250 group (35% and 16%, respectively; p = 0.06), nor did the in-hospital postoperative mortality (6% and 8%, respectively; p = 0.75). When analyzing surgery related endpoints based on the bilirubin level *at diagnosis* the complication rate was similar between patients with a bilirubin ≥250 μmol/l and <250 μmol/l (supplementary material).

Secondary endpoints

Postoperative histology

Postoperative histological diagnosis, T-stage, the presence of lymph node metastases and the proportion of complete (R0) resections were not significantly different between patients with a bilirubin ≥250 at diagnosis and patients with a bilirubin <250 (Table 4). In both groups, most of the tumors were classified as T3 and metastasized to the local lymph nodes.

Bilirubin level as a predictor of PBD- and severe postoperative complications

Multivariate logistic regression analyses were performed to identify independent predictors of PBD related complications (Table 5) and severe postoperative complications (Table 6), including bilirubin level at diagnosis as a continuous variable. Bilirubin level was no independent predictor for PBD complications (OR 1.00 per 1 μmol/l, 95% CI 1.00–1.00), nor for severe postoperative complications (OR 1.00 per 1 μmol/l, 95% CI 1.00–1.01). Also, no significant association between severe postoperative complications and PBD was found (OR 0.78, 95% CI 0.40–1.53).

Discussion

This is one of the very few studies focusing on patients with cancer of the pancreatic head with severe cholestasis (bilirubin level ≥250 μmol/l) in order to evaluate the rationale for a different approach regarding PBD in these patients compared to patients with a lower bilirubin level. Patient and tumor characteristics (both clinical and pathological staging) and the number of complete (R0) resections did not differ between patients with a bilirubin level at diagnosis ≥250 and < 250. No significant differences in PBD technical success and complication rates were found between patients with a bilirubin level at diagnosis ≥250 and < 250. In addition, a higher bilirubin level at diagnosis was not an independent predictor for PBD complications, nor for severe postoperative complications. Finally, when analyzing the bilirubin level measured directly prior to surgery, postoperative complications were not increased in patients with a bilirubin ≥250 compared to patients with lower bilirubin levels.

Few retrospective studies have been published including patients with pancreatic head cancer and a bilirubin level

Table 2 PBD related outcomes; analysis based on bilirubin level *at diagnosis*

Characteristics	Bilirubin <250 N = 123	Bilirubin ≥250 N = 48	P-value
Bilirubin level at diagnosis (μmol/l)[a]	152 (103–193)	317 (283–380)	<0.01
Interval between diagnosis and PBD (days)[a]	9 (4–16)	6 (1–12)	<0.01
Interval between PBD and surgery (days)[a]	28 (19–45)	34 (23–46)	0.16
Indication first PBD procedure, N (%)			
High bilirubin level	93 (76)	42 (88)	0.09
Pruritus	36 (29)	12 (25)	0.58
Cholangitis	6 (5)	2 (4)	0.84
Improvement of nutritional status	4 (3)	–	0.21
Other	4 (3)	1 (2)	0.68
PBD method, N (%)			
Primary ERCP	115 (93)	46 (96)	0.76
Primary PTC	1 (1)	–	
ERCP followed by PTC	7 (6)	2 (4)	
Cumulative PBD success rate, N (%)			
At first attempt	102 (83)	39 (81)	0.80
After two attempts	115 (94)	45 (94)	0.95
After three attempts or more	117 (95)	47 (98)	0.41
PBD related complications, N (%)			
Any	41 (33)	14 (29)	0.60
Pancreatitis	15 (12)	3 (6)	0.26
Cholangitis	15 (12)	7 (15)	0.68
Stent occlusion (without cholangitis)	9 (7)	4 (8)	0.82
Perforation	1 (1)	0 (0)	0.53
Cardiopulmonary complications	1 (1)	1 (2)	0.49
Other	1 (1)	–	0.53
Severity of PBD related complications, N (%)			
Mild	26 (21)	11 (23)	0.49
Moderate	11 (9)	1 (2)	
Severe	2 (2)	1 (2)	
Death	2 (2)	1 (2)	
Re-ERCP/PTC after drainage was initially achieved, N (%)	28 (23)	13 (27)	0.55

[a] Time intervals and bilirubin levels are expressed as median (IQR).

>250 μmol/l. The study by Arkadopoulos et al. focused specifically on patients with a high bilirubin level (>255 μmol/l) at the time of surgery and found a significantly lower postoperative complication rate in the 'direct surgery group' compared to the group of patients undergoing PBD.[15] Bolm et al. included a subgroup analysis in patients with a high bilirubin level (>255 μmol/l) and found that preoperative biliary stenting significantly increased the postoperative complication rate.[28] Another study worth mentioning is by Roberts et al. The authors found that direct surgery led to significantly more patients proceeding to resection compared to PBD followed by surgery. This was despite a median bilirubin level of 306 μmol/l at the time of surgery in the 'direct surgery group'.[29]

On the contrary, in the study by Shen et al., including 200 patients with a bilirubin level >250 μmol/l undergoing pancreaticoduodenectomy, overall postoperative complications were lower in the PBD group compared to the direct surgery group.[30] Possible explanations for this difference might be the high proportion of patients (49.7%) in their study who have undergone a PTC instead of an ERCP and the relatively low number of PBD-related complications.

With approximately 30%, our overall PBD-related complication rate turned out to be lower compared to the 46% reported by van der Gaag et al. in a large clinical trial randomizing patients with cancer of the pancreatic head between PBD and direct surgery.[11] In this study, patients with a bilirubin level

Table 3 Surgery related endpoints; analysis based on bilirubin level *directly prior to surgery*

Variables	Bilirubin <250 N = 127	Bilirubin ≥250 N = 25	P-value
PBD was attempted prior to surgery, N (%)	101 (80)	6 (24)	**<0.001**
PBD was successful (drainage achieved), N (%)	99 (79)	2 (8)	**<0.001**
Interval between bilirubin measurement and surgery[a]	7 (2–21)	5 (2–8)	0.02
Severe postoperative complications, N (%)[b]			
Any	45 (35)	4 (16)	0.06
Pancreaticojejunostomy leakage	7 (6)	–	0.23
Chyle leakage	9 (7)	–	0.17
Delayed gastric emptying (total)	13 (10)	–	0.09
Hemorrhage after pancreatectomy	12 (9)	2 (8)	0.82
Biliary leakage	2 (2)	–	0.53
Gastrojejunostomy or duodenojejunostomy leakage	6 (5)	1 (4)	0.87
Intra-abdominal abscess	15 (12)	–	0.07
Intra-abdominal infection (other than abscess)	8 (6)	–	0.20
Wound infection	7 (13)	–	0.23
Portal-vein thrombosis	4 (3)	–	0.37
Hepatic artery thrombosis	2 (2)	–	0.53
Cardiac complication	6 (5)	1 (4)	0.87
Pneumonia	10 (18)	1 (4)	0.49
Pulmonary embolism	1 (1)	–	0.66
Other	9 (7)	1 (4)	0.57
Severity of surgery related complications, N (%)			
CD III	26 (21)	2 (8)	0.14
CD IV	12 9)	–	
CD V/death	7 (6)	2 (8)	
In-hospital mortality, N (%)	8 (6)	2 (8)	0.75

Bold represents P ≤ 0.05.
[a] Median number of days (IQR).
[b] Severe postoperative complications were defined as Clavien-Dindo (CD) classification III or higher.[26]

>250 μmol/l at diagnosis or >300 μmol/l at the time of surgery were excluded. This difference might be explained by the fact that only plastic stents were used in the van der Gaag trial. Also, our cohort is of more recent date, and quality probably improved after the earlier studies. In our study, PBD led to adequate drainage on the first attempt in 82% of the patients and this did not differ significantly between patients with a bilirubin level ≥250 or <250. This technical success rate is largely comparable to the 75% found by van der Gaag et al. and the 80–85% reported by Kapral et al. in a large nationwide prospective study from Austria including a diverse group of patients.[11,31] This indicates that PBD is not technically more difficult in patients with pancreatic head cancer and severe cholestasis. Although most of the PBD-related complications in our study were classified as mild, three patients died, and one patient refrained from surgery because of PBD complications; this indicates serious PBD related morbidity. Nowadays, the use of metal stents is preferred in PBD over plastic stents as metal stents lead to significantly less PBD-related complications.[32] In our study the use of metal stents was equal between patients with a bilirubin level at diagnosis ≥250 and < 250 (40% vs. 36%, p = 0.66). The relative low number of metal stents used in our study is inherent to the era that we have studied.

Analyzing severe post-surgical complication rates based on the bilirubin level *directly prior to surgery*, to evaluate the actual effect of the degree of cholestasis on postoperative outcomes, no significant differences in mortality or severe postoperative complications were found between patients with a bilirubin level ≥250 versus <250. In fact, there was a trend towards fewer complications in the ≥250 group in this analysis in (16% and 35%; p = 0.06). These numbers a somewhat lower than in the study from Van der Gaag et al., as they reported an overall postoperative complication rate of 42%. The difference with our study could be explained by the fact that we only

Table 4 Postoperative histology; analysis based on bilirubin level *at diagnosis*

Variables	Bilirubin <250 N = 168	Bilirubin ≥250 N = 44	P-value
Final histological diagnosis, N (%)			
Pancreatic cancer	129 (77)	30 (68)	0.26
Cholangiocarcinoma	18 (11)	11 25)	
Papillary carcinoma	8 (5)	2 (5)	
GIST[a]	1 (1)	–	
NET[b]	2 (1)	–	
Benign disease	5 (3)	–	
Unknown	5 (3)	1 (2)	
T-stage, N (%)[c]			
1	7 (5)	–	0.17
2	22 (14)	3 (8)	
3	116 (75)	32 (80)	
4	9 (6)	5 (12)	
Lymph node metastases, N (%)[d]	126 (81)	35 (88)	0.36
Complete resection (R0), N (%)[d]	86 (55)	23 (59)	0.67

[a] GIST: gastrointestinal stromal tumor.
[b] NET: neuroendocrine tumor.
[c] 18 cases were excluded due to missing data (N = 13) or benign disease (N = 5).
[d] 17 cases were excluded due to missing data (N = 12) or benign disease (N = 5).

Table 5 Predictors of PBD related complications (any complication)

Variables	OR (95% CI)	P-value
Gender		
Female	Reference	–
Male	0.92 (0.46–1.83)	0.82
Age[a]	0.95 (0.91–1.00)	**0.03**
ASA classification		
I	Reference	–
II	1.31 (0.49–3.51)	0.59
III	2.23 (0.62–8.00)	0.22
Radiological T-stage		
T1 & T2	Reference	–
T3 & T4	0.95 (0.39–2.31)	0.91
Tx	0.50 (0.10–2.52)	0.40
Bilirubin level at diagnosis[b]	1.00 (1.00–1.00)	0.62
Stent type		
Plastic	Reference	–
Metal	0.91 (0.42–1.95)	0.80
No stent	0.17 (0.02–1.95)	0.16
Unknown	1.39 (0.34–5.72)	0.65
Drainage achieved at first attempt		
No	Reference	–
Yes	0.47 (0.16–1.36)	0.16

Bold represents $P \leq 0.05$.
[a] Odds ratio per year.
[b] Odds ratio per 1 μmol/l.

included severe complications defined as Clavien-Dindo III or higher.

For the sake of completeness, we also analyzed post-surgical complications rates between patients with a bilirubin level ≥250 and < 250 *at diagnosis*, which reflects the moment of decision making (supplementary material). Beside post-surgical hemorrhage, which occurred slightly more in patients with a bilirubin level ≥250 at diagnosis (15% vs. 5%; p = 0.04), post-operative complication rates were comparable between the two groups. Nevertheless, in-hospital mortality was higher among patients with a bilirubin level ≥250 compared to patients with a bilirubin <250 at diagnosis (15% and 1%, respectively; p < 0.01). However, the results of our study do not imply that performing surgery on patients with severe cholestasis increases the risk of mortality because increased mortality is not seen in patients with a bilirubin level ≥250 *directly prior to surgery*. Jaundice at the moment of presentation is already known to be an independent risk factor for mortality and this suggests that patients with severe cholestasis may be in a worse condition compared to patients with a milder degree of cholestasis (e.g., due to anorexia or delayed care seeking).[33–35] The overall postoperative mortality in all patients was 5% in our study, which is in accordance with previous literature reporting on post-pancreatectomy mortality rates in high-volume centers.[36] As a result of continuous improvement of perioperative care post-pancreatectomy mortality have decreased to <1% within the RAKU alliance over the last years.

Apparently, pancreatic surgery in patients with severe cholestasis is not associated with an increased complication risk compared to patients with lower bilirubin levels. Based on our study, there are no arguments that support the hesitation regarding operating in severely jaundiced patients.

One of the strengths of our study is that it is one of the very few clinical studies focusing on the role of PBD in severely jaundiced patients, in comparison to patients with lower bilirubin levels. The study is based on a complete dataset with availability of postoperative histology. Furthermore, this is the first study including separate analyses based on the bilirubin level directly prior to PBD and surgery to evaluate the actual effect of the bilirubin level on procedural outcomes. This is of importance as the bilirubin level changes during the time frame between diagnosis, PBD and surgery.[27]

There are also some limitations we need to address. Most ideally, surgery related outcomes would have been compared in patients with a bilirubin level ≥250 μmol/l undergoing PBD versus those not undergoing PBD. As PBD is still performed routinely in patients with pancreatic head cancer and severe cholestasis, only four patients with a bilirubin level ≥250 μmol/l did not undergo PBD. Therefore, a reliable direct comparison

Table 6 Predictors of severe surgery related complications (Clavien-Dindo III or higher)

Variables	OR (95% CI)	P-value
Gender		
Female	Reference	–
Male	1.41 (0.78–2.56)	0.26
Age[a]	1.00 (0.96–1.04)	0.95
ASA classification		
I	Reference	–
II	0.61 (0.28–1.37)	0.23
III	1.13 (0.41–3.13)	0.81
Bilirubin level at diagnosis[b]	1.00 (1.00–1.01)	0.30
Radiological T-stage		
T1 & T2	Reference	–
T3 & T4	0.65 (0.30–1.43)	0.29
Tx	0.51 (0.10–2.58)	0.41
PBD was performed surgery		
No	Reference	–
Yes	0.79 (0.41–1.53)	0.48

[a] Odds ratio per year.
[b] Odds ratio per 1 μmol/l.

between these groups was not possible. Also, the retrospective design of the study results in confounding biases, missing data and heterogeneity in the intervals between diagnosis and PBD and surgery. It is also important to mention that the landscape for pancreatic head cancer is constantly changing and therefore current practice is not all that similar to that from the studied timeframe. For example, much of the procedures have been centralized nowadays to improve outcomes. Also, we did not address the role of CA 19-9 as it was somewhat outside the scope of our study and interpreting CA 19-9 levels in patients with cholestasis remains complex. Nevertheless CA 19-9 is expected to be more and more important in predicting response to therapy and in selecting patients who may benefit from neoadjuvant therapy and PBD in the future.[37]

Although our retrospective data with very few patients with bilirubin levels ≥250 μmol/l not undergoing PBD should be interpreted with caution, our findings suggest that there is no rationale for a different approach regarding PBD in patients with bilirubin levels ≥250 μmol/l compared to patients with a lower bilirubin level. There are several arguments that support this recommendation. Firstly, PBD and surgery related complication rates are comparable between patients with a bilirubin level ≥250 and < 250 μmol/l at diagnosis. Additionally, high bilirubin levels at the time of surgery do not increase the complication risk and bilirubin level is no independent predictor of PBD and post-operative complications. This suggests that patients presenting with high bilirubin levels are not necessarily more prone for developing surgery related complications. Secondly, PBD procedures in patients with suspected cancer of the pancreatic head result in significant morbidity and mortality of approximately 30% and 2%, respectively. Keeping this in mind, the post-operative benefits of PBD need to be significant in order to compensate for this. Thirdly, tumor characteristics (both clinical and pathological staging) do not differ between patients with a bilirubin level ≥250 and < 250 μmol/l.

All these arguments indicate that patients with pancreatic head cancer and cholestasis with a bilirubin ≥250 μmol/l are comparable to patients with a lower bilirubin level and that there is no evidence supporting a different approach regarding PBD in patients with severe cholestasis. Therefore, we recommend that PBD should no longer be performed based on a high bilirubin level alone. We do acknowledge that there are still indications for PBD, for example cholangitis, refractory pruritus and in the setting of neoadjuvant therapy, which is subject of extensive research and increasingly applied in clinical practice. There is also increasing attention for the role of PBD in the setting of prehabilitation, where nutritional status and symptoms like pruritus and sleep deprivation are probably of more importance in the decision making than the bilirubin level alone. Whether a specific subgroup of patients with pancreatic head cancer and cholestasis might benefit from PBD needs to be further evaluated.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.05.1345.

