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The impact of preoperative biliary stenting in pancreatic cancer: A case-matched study from the German nationwide pancreatic surgery registry (DGAV StuDoQ|Pancreas)☆

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ABSTRACT

Background/Objective: The impact of preoperative biliary stenting (PBS) before pancreatoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) is controversial.
Methods: Patients undergoing PD with or without PBS for PDAC were identified from the German DGAV-StuDoQ|Pancreas registry. The impact of PBS on perioperative complications was analyzed.
Results: 1133 patients undergoing PD for PDAC were identified from the registry. After matching, 480 PBS patients vs. 480 patients without PBS were analyzed. Postoperative complications Clavien-Dindo classification (CDC) grade IIIa-IVb were higher in PBS patients (PBS 27% vs. no PBS 22%, $p = 0.027$). 320 PBS patients (66%) had no history of jaundice. In these patients, PBS was associated with higher morbidity. In contrast, PBS was not associated with higher complication rates in patients with history of jaundice. Serum bilirubin levels of 15 mg/dl and higher lead to more CDC IIIa-IVb (24% vs. 28%, $p = 0.053$) and higher mortality (3% vs. 7%, $p < 0.001$). PBS in patients with serum bilirubin levels of >15 mg/dl increased CDC IIa-IVb complications (21% vs. 50%, $p = 0.001$), mortality was equivalent.
Conclusion: Most PBS procedures were performed in patients with no history of jaundice and increased morbidity. Serum bilirubin levels >15 mg/dl lead to higher morbidity and mortality. PBS correlated with higher complication rates in these patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive solid tumor associated with early local and systemic dissemination resulting in dismal prognosis [1]. Complete surgical resection remains the only curative option in PDAC patients, and pancreatoduodenectomy (PD) is the standard approach for tumors of the pancreatic head [2]. Prior to PD patients often present with obstructive jaundice as the most common symptom of PDAC [3]. Obstructive jaundice causes various pathophysiological changes and patients may suffer from pruritus and abdominal pain.

☆ The paper is currently not submitted to another journal. An abstract of the data was submitted to the European Pancreasclub and presented in June 2018 as an oral presentation at the 50th annual meeting of the European Pancreasclub (Title "Preoperative biliary stenting is associated with detrimental perioperative morbidity - a prospensity matched analysis of over 900 patients from the German pancreas registry"). The abstract was awarded a travel grant.

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Additionally, jaundice is associated with functional impairment of kidney, heart and liver as well as reduced immunity and dysfunction of gastrointestinal mucosal barriers [4–6]. Preoperative jaundice was furthermore identified as a negative prognostic parameter in patients undergoing pancreatic resections [7]. PBD was initially established as a preoperative option in patients with obstructive jaundice to obtain symptom relief and to counteract pathophysiological jaundice-related changes contributing to postoperative morbidity [4,8,9]. Early case series yielded promising results of reduced postoperative morbidity and mortality in patients undergoing preoperative biliary drainage (PBD) [10–12]. PBD may be performed as percutaneous biliary drainage or as endoscopic preoperative biliary stent placement (PBS). In the 1980s and 1990s PBS was more and more established to reduce preoperative serum bilirubin levels and to potentially improve postoperative outcome. In these years, mortality after PD was still high (10–30%) and postoperative complication rates ranged from 30 to 60% [2,12–14]. Consequently, attempts were made to identify potential risk factors influencing postoperative outcome, and hyperbilirubinemia was found to negatively impact postoperative mortality and morbidity [13]. PBD lead to an improvement of mainly postoperative mortality, and was increasingly used in jaundiced PDAC patients [12,13]. As a major progress in pancreatic surgery, postoperative mortality rates after PD could be radically reduced to less than 5% in experienced centers over the past years. Postoperative morbidity currently ranges from 20 to 50% [2,15]. These improvements are mainly based on advances in perioperative complication management and intensive care standards [16]. In the last years, attempts have been made to further reduce postoperative complication rates after PD.

A growing number of studies and meta-analyses demonstrated detrimental effects of PBD regarding postoperative morbidity [14,17–19]. Infectious complications in particular were found to be associated with PBD [8,20]. Specific PBD-associated complications were pancreatitis or cholangitis as well as post-operative complications such as wound infections contributing to an increase in overall morbidity of PBD patients undergoing PD. On the other hand, several studies and meta-analyses failed to detect a difference in postoperative complications in patients receiving PBD as compared to upfront surgery [21,22].

Posing a major obstacle to clinical guidance, studies regarding the effects of PBD are heterogeneous and rely on small single-center patient cohorts, varying proportions of benign and malignant obstructive jaundice, different PBD techniques, and study designs. Only 3 currently available retrospective studies used matching against potential selection bias [17,23,24].

The aim of this study was to perform a nation-wide registry analysis to determine the effect of endoscopic preoperative biliary stenting (PBS) on postoperative complication rates and mortality in PDAC patients undergoing PD. Furthermore, current clinical practice in Germany and the effect of PBS in the subgroups of patients with and without a history of jaundice as well as patients presenting with different levels of serum hyperbilirubinemia were evaluated.

Methods

Registry characteristics, patient cohort, treatment groups and case matching

Anonymized data was extracted from the German DGAV StuDoQ|Pancreas registry [25]. The German pancreatic surgery registry (StuDoQ Pancreas) was developed by the German Society for General and Visceral Surgery (DGAV) in 2013. The registry is designed as a prospectively maintained multicenter database with web-based data entry. Observed units are patients undergoing pancreatic surgery in the participating institutions. The registry underwent systematic assessment of registry quality and met the criteria of a high-quality registry [25]. On the basis of current routine administrative data of the registry, 10–20% of all pancreatic resections in Germany are documented in the StuDoQ|Pancreas registry. Participation in the registry has become mandatory since 2017 for institutions that aim to meet certification standards of the German Society of General and Visceral Surgery, so the number of entries is growing constantly. 20% coverage of the national case load can be regarded as representative as also the National Inpatient Sample of the US covers 20% of all hospital admissions [25,26].

Patients undergoing pancreatoduodenectomy (PD) for histologically proven PDAC from 2014 to 2016 were identified. Patients were grouped according to preoperative endoscopic retrograde biliary stenting (PBS) or upfront surgery. Patients signed informed consent for their anonymized data to be entered to the registry. The indication for PBS was determined according to the standards of the participating centers or its referring partners and not specified by the DGAV-StuDoQ|Pancreas registry. In evaluating PBS treatment one has to consider that the current German guidelines for PDAC do not recommend routine PBS [27]. To obtain comparable treatment groups, 1:1 propensity score matching was performed based on baseline parameters found to differ significantly between patients with versus without PBS. Propensity score matching was conducted using the MatchIt package of the R Software [28].

Baseline data

Preoperative baseline parameters included age, sex, body mass index (BMI), American Society of Anesthesiologists Score (ASA Score), performance status, co-morbidities (cerebrovascular events, COPD and diabetes mellitus), medication (corticosteroid medication and immunosuppressive medication), history of jaundice and serum bilirubin levels. History of jaundice was defined as the clinical presentation of icterus at time of PDAC diagnosis or in the time period from diagnosis to resection. Age and BMI were dichotomized according to the median. Surgical baseline parameters were operation procedure (pylorus preserving PD (PPPD) vs. classical Whipple), mesentericoportal vein resection and pancreatic texture. Pancreatic texture was categorized as hard or soft.

Outcome definitions

Perioperative morbidity parameters were preoperative cholangio-sepsis, postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), post pancreatectomy hemorrhage (PPH), intra-abdominal abscess, surgical site infection (SSI), hepaticojejunostomy leakage, leakage of the gastro-enteric anastomosis, burst abdomen with fascial dehiscence, postoperative pulmonary embolism, postoperative pneumonia, postoperative stroke, 30-days-readmission, intensive-care-unit stay (ICU), overall hospital stay (OHS) and 30 days-mortality. POPF, DGE and PPH were defined according to the ISGPS definition criteria [29–31]. Overall postoperative complication rates were assessed according to the Clavien-Dindo-Classification (CDC) [32]. Grade I includes any deviation from the normal postoperative course without the need of surgical, endoscopic and radiological interventions. Drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes as well as wound infections opened at the bedside are included in grade I. Grade II comprises patients requiring pharmacological treatment with drugs other than such allowed for grade I as well as blood transfusions and total parenteral nutrition. Grade III requires surgical, endoscopic or radiological intervention under general anesthesia (grade IIIb) or without general anesthesia (grade IIIa). Grade

IV includes life-threatening complications requiring intensive care management with single organ failure (IVa) or multi-organ failure (IVb). Grade V means death of the patient and is equivalent to in-hospital mortality. CDC was dichotomized as grade 0-II versus grade IIIa-IVb. CDC grade V was analyzed separately. POPF, DGE and PPH were dichotomized as non/grade A versus grade B/C. All postoperative complications as well as postoperative mortality 30 days postoperatively is mandatory in the registry. For patients who had a prolonged stay of more than 30 days, documentation of all in-house morbidity and mortality was performed for the registry.

Ethics and statistics

Ethical approval was obtained from the Ethics Committee of the University of Lübeck. The data was extracted from the registry by anonymized export. Statistical analysis was performed with IBM SPSS Version 22 (SPSS Inc, Chicago, IL) and R software [33]. Continuous and categorical variables were expressed as median/range and absolute/relative frequencies, respectively. Cross-tabulation analyses were performed to compare PBS and upfront surgery group as well as different subgroups of hyperbilirubinemia using two-sided Student t-test and Chi-squared test. The significance level was set to $p < 0.05$. If statistically significant differences in baseline parameters were detected for PBS vs. upfront surgery patients, prospensity score based matching was performed for these parameters.

Missing data analysis and imputation

Descriptive missing data analysis with percentage missing data per variable and per case as well as missing data patterns was performed. Assuming missing at random process, multiple imputation for missing data using the chained equations method was implemented with the R package mice [34].

Results

Patient cohort and case matching

A total of 1133 patients undergoing PD for histologically proven PDAC from 2014 to 2016 at 52 institutions participating in the nationwide DGAV StuDoQ|Pancreas registry were identified. Patients undergoing preoperative endoscopic biliary stenting (PBS) were identified for analysis. 480 patients received PBS prior to surgery and 754 patients underwent upfront surgery. For details of the study flow chart, see Fig. 1. Regarding baseline parameters, significant differences in history of jaundice and pancreatic texture were noted between both groups. After propensity-score matching for these two parameters, 480 PBS patients versus 480 patients with upfront surgery were included in the study. Mean serum bilirubin in non-PBS patients (4,19 mg/dl) was lower as compared to unstented patients (5,45 mg/dl). As this can be interpreted as a treatment effect, no matching for serum bilirubin was performed.

Baseline parameters (Table 1)

Preoperative and surgical baseline parameters were well-balanced in the matched dataset (Table 1). Median age in all patients after matching was 69 years, ranging from 31 to 88 years. 56% of the patients were male. After prospensity score-based matching, 50% had an ASA score of I-II. 6% of the patients needed partial or full care. Regarding co-morbidities, 5% of the patients reported a history of cerebrovascular events, 5% had COPD, and 30% suffered from diabetes mellitus. 2% of the patients took corticosteroid medication and 1% took other immunosuppressive medication prior to surgery. 32% of the patients presented with a history of jaundice. Concerning surgical parameters, 62% of the patients underwent a pylorus-preserving pancreatoduodenectomy and 38% had a Whipple procedure. 16% of the patients received a portal vein resection. Pancreatic texture was assessed as soft in 50% of the patients after matching.

Perioperative morbidity total cohort (Table 2)

Preoperative cholangio-sepsis was more frequent in PBS patients as compared to patients not receiving PBS (PBS 6% vs. no PBS 2%, $p < 0.001$). Regarding postoperative morbidity, the rate of clinically relevant grade B/C POPF was higher in patients undergoing PBS (PBS 11% vs. no PBS 7%, $p = 0.013$). Rates of clinically relevant grade B/C PPH (PBS 8% vs. no PBS 7%, $p = 1.000$) and grade B/C DGE (PBS 10% vs. no PBS 9%, $p = 0.740$) were not different between the treatment groups.

While incidence of intra-abdominal abscess was comparable between patients with and without PBS (PBS 4% vs. no PBS 4%, $p = 1.000$), surgical site infections (SSI) were more frequent in PBS patients (PBS 18% vs. no PBS 8%, $p < 0.001$) and burst abdomen including fascial dehiscence occurred more often (PBS 4% vs. no PBS 1%, $p = 0.013$). There was no difference for the incidence of postoperative hepaticojejunostomy leakage (PBS 3% vs. no PBS 4%, $p = 0.398$) or leakage of the gastro-enteric anastomosis (PBS 2% vs. no PBS 1%, $p = 0.773$).

Rates of postoperative pneumonia (PBS 9% vs. no PBS 7%, $p = 0.408$) and postoperative stroke were comparable in patients with and without PBS (PBS 1% vs. no PBS 1%, $p = 1.000$).

Rates of postoperative complications classified as CDC grade IIIa-IVb were higher in PBS patients (PBS 27% vs. no PBS 22%, $p = 0.027$). Mortality (Clavien Dindo Grade V) were not different in both groups (PBS 3% vs. no PBS 3%, $p = 1.000$).

Median intensive care unit stay was 4.94 days in the PBS group and 4.81 days in patients with upfront surgery ($p = 0.865$). Length of overall hospital stay was comparable in both groups (PBS median 16 vs. no PBS median 16, $p = 0.269$). 30-days-readmission rates were 8% in the PBS group and 6% in patients without PBS ($p = 0.297$).

Multivariable analysis

Regarding anastomotic leakage, PBS was an independent risk factor of POPF (OR 1.461, 95%CI 1.20−1.78, $p < 0.001$) among known other factors like soft pancreatic texture (OR 2.869, 95%CI 0.38−0.56, $p = 0.001$), preoperative corticosteroid medication (OR 0.228, 95%CI 0.05−0.97, $p = 0.045$) and reduced performance status (OR 2.272, 95%CI 1.63−3.16, $p < 0.001$).

With respect to infectious complications, PBS qualified as independent risk factor of SSI (OR 2.224, 95%CI 1.85−2.68, $p < 0.001$), further independent risk factors being reduced performance status (OR 1.783, 95%CI 1.30−2.45, $p < 0.001$), hepaticojejunostomy leakage (OR 1.893, 95%CI 1.27−2.83, $p = 0.002$), POPF (OR 3.006, 95%CI 2.38−43.80, $p < 0.001$) and PPH (OR 2.258, 95%CI 1.72−2.96, $p < 0.001$).

Subgroup analysis of patients with history of jaundice (Table 3).

Of 480 patients receiving PBS, 160 patients (33%) had a history of jaundice. These 160 patients were compared to patients with a history of jaundice and no PBS ($n = 148$). Both groups were well-balanced regarding baseline parameters, so no matching had to be performed. For the incidence of perioperative complications, there was no difference between patients with and without PBS. ICU stay was prolonged by one day in patients without PBS (PBS 2

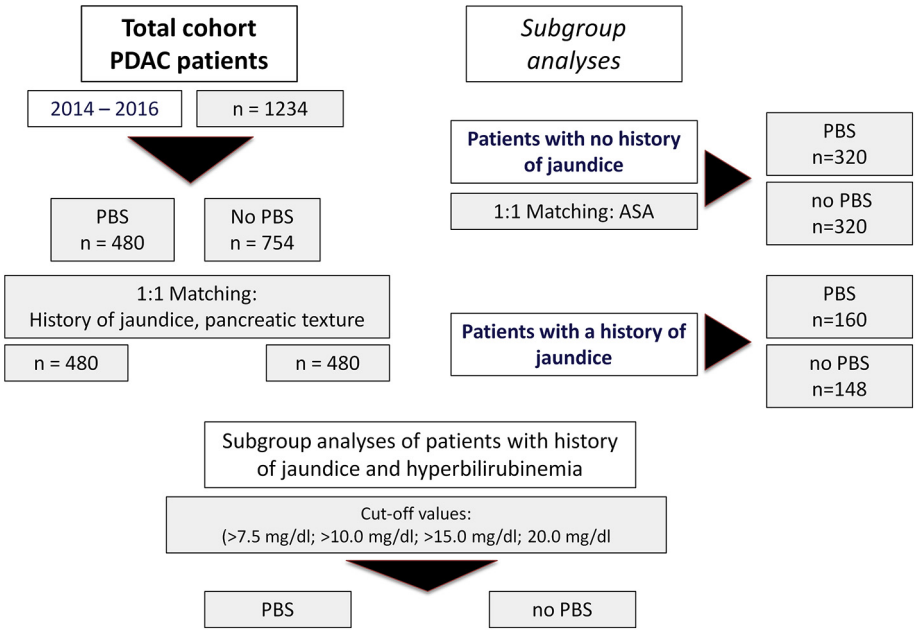

Fig. 1. Study flow chart and subgroup analyses.
PBS: preoperative biliary stenting; ASA score: American Society of Anesthesiologists Score.

Table 1
Baseline parameters.

	Baseline Parameters						
	Total		**No PBS (n = 480)**		**PBS (n = 480)**		*p-value*
	n/median	%/range	n/median	%/range	n/median	%/range	
Age	69	20–88	69	33–88	69	31–88	
<median 69	504	53	261	54	243	51	
>median 69	456	47	219	46	237	49	0.272
Sex							
male	540	56	269	56	271	56	
female	420	44	211	44	209	44	0.948
BMI	25	13–57	25	12–57	25	15–45	
<median 25.0	538	56	274	57	264	54	
>median 25.0	422	44	206	43	216	46	0.446
ASA							
I/II	480	50	240	50	240	50	
III/IV	480	50	240	50	240	50	1.000
Need of Care							
no	906	94	455	95	451	94	
partial/full	54	6	25	5	29	6	0.675
Co-morbidities							
Cerebrovasc. events	48	5	24	5	25	5	0.765
COPD	47	5	28	6	23	5	0.557
Diabetes mellitus	288	30	134	28	153	32	0.251
Corticosteroid med.	19	2	7	2	5	1	0.593
Immunosupp. med.	10	1	4	1	6	2	0.550
History of jaundice	308	32	148	31	160	33	0.447
Serum bilirubin level (mg/dl)	2.1	0–43	5.8	0–40	4.2	0–43	**0.001**
Operation technique							
PPPD	593	62	294	61	299	62	
Whipple	367	38	186	39	181	38	0.786
PVR	154	16	79	16	80	16	0.858
Pancreatic texture							
hard	480	50	240	50	240	50	
soft	480	50	240	50	240	50	1.000
Main pancreatic duct diameter							
<3 mm	459	48	227	47	232	48	
>3 mm	501	52	253	53	248	52	0.798
Neoadj.therapy	199	8	99	4	100	4	1.000

PBS: preoperative biliary stenting; BMI: body mass index; ASA: American Society of Anesthesiologists' Score; corticosteroid med.: corticosteroid medication; immunosupp. med.: immunosuppressive medication; PPPD: pylorus-preserving pancreatoduodenectomy; PVR: portal vein resection.

Table 2
Perioperative morbidity total cohort.

Perioperative Morbidity						
		No PBS		PBS		*p-value*
		n/median	%/range	n/median	%/range	
Preoperative cholangiosepsis	no	472	98	452	94	**0.001**
	yes	8	2	28	6	
POPF	no/A	448	93	425	89	
	B/C	32	7	55	11	**0.013**
DGE	no/A	437	91	433	90	
	B/C	43	9	47	10	0.740
PPH	no/A	444	93	443	92	
	B/C	36	7	37	8	1.000
Intra-abdominal abscess		19	4	18	4	1.000
SSI		38	8	85	18	< **0.001**
HJ leakage		21	4	15	3	0.398
GE leakage		5	1	7	2	0.773
Burst abdomen		6	1	19	4	**0.013**
CD Classification	0-II	362	74	336	69	
	IIIa-IVb	104	22	131	27	**0.027**
CD Classification	V	14	3	13	3	1.000
Pneumonia		35	7	43	9	0.408
Stroke		2	1	2	1	1.000
30 days readmission rate		27	6	36	8	0.297
ICU stay		3	0–78	3	0–70	0.865
OHS		16	1–132	16	1–116	0.269

PBS: preoperative biliary stenting; POPF: postoperative pancreatic fistula; DGE: delayed gastric emptying; PPH: postoperative pancreatic hemorrhage; SSI: surgical site infection; HJ hepaticojejunostomy; GE gastroenteric anastomosis; CD Classification: Clavien-Dindo Classification; ICU: intensive care unit stay; OHS: overall hospital stay.

Table 3
Subgroup analysis of patients with history of jaundice.

Perioperative Morbidity						
		No PBS		PBS		*p-value*
		n/median	%/range	n/median	%/range	
Preoperative cholangiosepsis	no	145	98	151	94	0.182
	yes	3	2	9	6	
POPF	no/A	134	91	142	89	
	B/C	14	9	18	11	0.743
DGE	no/A	131	89	144	90	
	B/C	17	11	16	10	0.813
PPH	no/A	133	90	143	89	
	B/C	15	10	17	11	1.000
Intra-abdominal abscess		8	5	2	1	0.083
SSI		12	8	21	13	0.216
HJ leakage		4	3	7	4	0.629
GE leakage		0	0	2	1	0.513
Burst abdomen		2	1	4	2	0.752
CD Classification	0-II	102	69	109	68	
	IIIa-IVb	41	28	46	29	0.938
CD Classification	V	5	3	5	3	1.000
Stroke		1	1	1	1	1.000
30 days readmission rate		9	6	9	6	1.000
ICU stay		3	0–68	2	0–40	**0.001**
OHS		15	1–84	16	2–116	0.454

PBS: preoperative biliary stenting; POPF: postoperative pancreatic fistula; DGE: delayed gastric emptying; PPH: postoperative pancreatic hemorrhage; SSI: surgical site infection; HJ hepaticojejunostomy; GE gastroenteric anastomosis; CD Classification: Clavien-Dindo Classification; ICU: intensive care unit stay; OHS: overall hospital stay.

days vs. no PBS 3 days, $p = 0.001$).

Subgroup analysis of patients with no history of jaundice (Table 4).

The majority ($n = 320$, 66%) of a total of 480 patients undergoing PBS had no history of jaundice. These 320 patients were matched to 320 patients with no history of jaundice not receiving PBS. 1:1 matching was performed based on ASA score as there were significant differences in the distribution of ASA score between both groups. Preoperative cholangio-sepsis was more frequent in PBS patients (PBS 6% vs. no PBS 2%, $p < 0.001$) and PBS patients had a higher rate of grade B/C POPF (PBS 18% vs. no PBS 12%, $p = 0.053$). Also the incidence of SSI (PBS 20% vs. no PBS 11%, $p = 0.001$) and burst abdomen including fascial dehiscence (PBS 5% vs. no PBS 1%, $p = 0.009$) was more frequent in the PBS group. Leakage of the hepaticojejunostomy anastomosis was less frequent in PBS patients (PBS 2% vs. no PBS 7%, $p = 0.010$). There was a trend for higher rates of postoperative complications CDC grade IIIa-IVb (PBS 33% vs. no PBS 26%, $p = 0.083$). In PBS patients, ICU stay was prolonged by one day (PBS 3 days vs. no PBS 2 days, $p = 0.036$). For other postoperative complications, there was no difference between the groups.

Table 4
Subgroup analysis of patients with no history of jaundice.

Perioperative Morbidity						
		No PBS		PBS		*p-value*
		n/median	%/range	n/median	%/range	
Preoperative cholangiosepsis	no	318	99	301	94	**<0.001**
	yes	2	1	19	6	
POPF	no/A	566	92	283	88	
	B/C	46	8	37	12	**0.053**
DGE	no/A	294	92	289	90	
	B/C	26	8	31	10	0.579
PPH	no/A	298	93	300	94	
	B/C	22	7	20	6	0.873
Intra-abdominal abscess		14	4	16	5	0.852
SSI		34	11	64	20	**0.001**
HJ leakage		23	7	8	2	**0.010**
GE leakage		1	0	5	2	0.218
Burst abdomen		3	1	15	5	**0.009**
CD Classification	0-II	227	71	207	65	
	IIIa-IVb	84	26	105	33	**0.083**
CD Classification	V	9	3	8	2	1.000
Pneumonia		20	6	29	9	0.234
Stroke		1	0	1	0	1.000
30 days readmission rate		21	7	27	8	0.453
ICU stay		2	0–65	3	0–70	**0.036**
OHS		16	1–84	16	1–101	0.160

PBS: preoperative biliary stenting; POPF: postoperative pancreatic fistula; DGE: delayed gastric emptying; PPH: postoperative pancreatic hemorrhage; SSI: surgical site infection; HJ hepaticojejunostomy; GE gastroenteric anastomosis; CD Classification: Clavien-Dindo Classification; ICU: intensive care unit stay; OHS: overall hospital stay.

Subgroup analysis of patients with elevated serum bilirubin levels and the effect of PBS (Table 5).

To evaluate the effect of serum bilirubin levels on postoperative morbidity and mortality we defined serum bilirubin cut-off levels of 7.5 mg/dl, 10.0 mg/dl, 15.0 mg/dl and 20.0 mg/dl. A serum bilirubin level of >7.5 mg/dl was not associated with higher CDC grade IIIa-IVb complications (24% vs. 25%, $p = 0.329$) and mortality (CDC grade V) (3% vs. 4%, $p = 326$) as compared to patients with serum bilirubin <7.5 mg/dl. In patients with serum bilirubin levels of >10 mg/dl, CDC grade IIIa-IVb complications (24% vs. 26%, $p = 0.271$) were comparable to patients with serum bilirubin <10 mg/dl and there was a trend for higher mortality (CDC grade V) (3% vs. 5%, $p = 0.097$). Patients with a serum bilirubin level of 15 mg/dl and higher were more likely to develop CDC grade IIIa-IVb complications (24% vs. 28%, $p = 0.053$) and mortality (CDC grade V) was increased (3% vs. 7%, $p < 0.001$) as compared to patients with serum bilirubin levels <15 mg/dl. This effect was even more pronounced in patients presenting with serum bilirubin levels of 20 mg/dl and higher (CDC grade IIIa-IVb 24% vs. 31%, $p = 0.041$; CDC grade V 3% vs. 17%, $p < 0.001$) showing higher postoperative complication and postoperative mortality rates as compared to patients with serum bilirubin <20 mg/dl.

Furthermore, we evaluated the effect of PBS on postoperative complications in patients with a history of jaundice and elevated serum bilirubin levels applying the same cut-off values. In patients with a serum bilirubin level >7.5 mg/dl, 87 patients underwent PBS while 50 patients had upfront surgery. CDC grade IIIa-IVb complications were more frequent in PBS patients (26% vs. 33%, $p = 0.043$) as compared to patients with upfront surgery in this subgroup with serum bilirubin <7.5 mg/dl. In patients with a serum bilirubin level of >10 mg/dl, PBS was performed in 39 patients, and 66 patients underwent upfront surgery. The rate of CDC grade IIIa-IVb complications was higher in PBS patients (25% vs. 36%, $p = 0.006$) as compared to patients with upfront surgery. A total of 45 patients had serum bilirubin levels of >15 mg/dl, PBS was performed in 14 patients and 31 underwent upfront surgery. In these patients, CDC grade IIIa-IVb complications were more frequent for PBS patients (21% vs. 50%, $p = 0.001$) as compared to patients with upfront surgery, see Table 5. In patients with serum bilirubin levels of >20 mg/dl, 13 patients underwent upfront surgery while 4 patients received PBS. There was a trend for higher CDC grade IIIa-IVb complications (14% vs 38%, $p = 0.069$). Mortality was comparable in patients undergoing PBS versus upfront surgery for all serum bilirubin cut-off levels.

Discussion

The aim of this study was to perform a nation-wide registry

Table 5
Subgroup analysis of PBS in patients with history of jaundice and serum bilirubin >15.0 mg/dl.

Total n 45		no PBS	PBS	*p-value*
		31	14	
		%/mean	%/mean	
Preoperative cholangiosepsis	yes	4	5	0.731
POPF	B/C	15	21	0.268
DGE	B/C	16	27	**0.059**
PPH	B/C	10	40	**0.001**
Intra-abdominal abscess		8	0	**0.011**
SSI		14	20	0.253
HJ leakage		5	8	0.387
GE leakage		0	10	**0.001**
Burst abdomen		1	0	1.000
CD Classification	0-II	79	50	
	IIIa-IV	21	50	**0.001**
CD Classification	V	12	8	0.377
Pneumonia		6	14	**0.057**
Stroke		0	0	
30 days readmission rate		3	7	**0.053**
ICU stay		4	7	0.758

PBS: preoperative biliary stenting; POPF: postoperative pancreatic fistula; DGE: delayed gastric emptying; PPH: postoperative pancreatic hemorrhage; SSI: surgical site infection; HJ hepaticojejunostomy; GE gastroenteric anastomosis; CD Classification: Clavien-Dindo Classification; ICU: intensive care unit stay.

analysis evaluating the effects of preoperative biliary stenting (PBS) on perioperative complications and to present a large PDAC patient cohort with propensity score based matching to address this issue. PBS was associated with an increase in perioperative complications. Surprisingly only 33% of stented patients had reported a history of jaundice. In patients with jaundice, no difference in postoperative complications was observed comparing PBS and non-PBS patients. However, the majority of PBS patients never presented with jaundice, and PBS was associated with higher complication rates in these patients. Serum bilirubin levels of more than 15 mg/dl were associated with an increase in postoperative morbidity and mortality. However, in patients with elevated serum bilirubin of more than 15 mg/dl, PBS did not improve postoperative outcome, but was associated with higher postoperative morbidity as compared to undergoing upfront surgery.

Jaundice is the most common symptom of PDAC and 75% of symptomatic patients present with jaundice [35]. Several recent studies demonstrated elevated preoperative serum bilirubin levels being associated with higher postoperative morbidity and even mortality [36–38]. The actual cut-off serum bilirubin level is currently debated ranging from 7.5 mg/dl to 17.6 mg/dl. Dolejs et al. recently conducted an analysis of the American NSQIP registry focusing on the effect of hyperbilirubinemia in patients undergoing pancreatoduodenectomy [36]. The study disclosed that modest degrees of bilirubinemia (up to > 10 mg/dl) did not affect postoperative morbidity or mortality. The authors concluded that preoperative biliary drainage should be reserved for patients with severe hyperbilirubinemia. De Pastena et al. identified serum bilirubin levels of 7.5 mg/dl (128 μmol/l) as a trigger for postoperative complications [37]. Sauvanet et al. found increased early postoperative morbidity and reduced long-term overall survival in patients presenting with serum bilirubin levels of more than 300 μmol/l (16.4 mg/dl) [38]. However, despite this rationale for PBS no data exist to determine whether PBD in patients with elevated serum bilirubin actually leads to a reduction of postoperative complications and morbidity.

The findings of this registry study propose an increase in postoperative morbidity and in-hospital mortality in patients with serum bilirubin levels higher than 15 mg/dl. However, PBS did not seem to improve postoperative outcome, but was associated with an increased rate of postoperative complications. Even in the large cohort of this registry study, only 45 patients had serum bilirubin levels of >15 mg/dl preoperatively. Consequently, the patient population with pronounced hyperbilirubinemia is small, and not even in these patients, convincing benefit of PBS could not be demonstrated.

66% of patients receiving PBS in this registry study had never presented with jaundice. The German S3 guideline for PDAC, an evidence-based guideline established by a multidisciplinary panel of experts in the field of pancreatic cancer treatment, recommends PBS only in case of cholangitis or for jaundiced patients with locally advanced tumors undergoing neoadjuvant therapy [27]. Cholangitis without jaundice is very rare and less than 5% of PDAC patients in the study cohort received neoadjuvant therapy. Consequently, the majority of PBS procedures were seemingly not performed in accordance to national guidelines. Different aspects may have contributed to this observation.

Due to a known volume-outcome correlation, Germany has experienced efforts to centralize pancreatic surgery in the last years [39,40]. Consequently, patients are often diagnosed in peripheral hospitals before being referred to a high volume center specialized in pancreatic surgery. It may be hypothesized that patients received PBS at referring hospitals in the course of diagnostics before the final diagnosis of pancreatic cancer was established.

As an additional effect, a low expertise in the treatment of pancreatic cancer in smaller hospitals may have contributed to a high rate of patients receiving PBS without having a history of jaundice.

The consequences of PBS in patients without history of jaundice seem to be mainly negative. Most likely as a complication of PBS, the rates of preoperative cholangio-sepsis were higher in stented patients. PBS is associated with major procedure-related morbidity, and results in a complication rate of about 5% or higher at experienced centers [41]. Additionally, PBS has shown to generate an inflammatory reaction and micro traumata of the bile duct [22,41,42]. Post-PBS complications may require re-interventions and supportive care hindering early surgery. Mezhir et al. report a PBD-complication-related delay of PD by 4 weeks in 17.8% of the patients [19]. A delay of surgical resection becomes particularly relevant in patients presenting with malignant disease. As another obstacle, restoration of hepatic function, immune function and recovery of bile duct epithelium require at least 4–6 weeks after PBS even if bilirubin levels decreased to normal [3].

The registry study disclosed PBS-associated higher postoperative complications grade IIIa-IVb defined according to Clavien-Dindo classification particularly in patients with no history of jaundice. Several retrospective series and randomized-controlled trials detected a similar PBD-related increase in postoperative morbidity [8,17,19,43–45], however, so far nationwide observations including current practice patterns are lacking.

Postoperative wound infections and consequent burst abdomen were increased in PBS patients as compared to patients undergoing upfront surgery. Several studies could also confirm a higher incidence of postoperative wound infections [20,44,45]. Povoski et al. reported a 58% incidence of positive bile culture after biliary drainage procedures, and 87% of patients with postoperative wound infections having intraoperative bactibilia [43]. The authors demonstrated 69% of bile cultures being predictive of microorganisms cultured from wound infections. As the bile duct is transected in the course of resection, a potential contamination of the peritoneal cavity and the surgical wound occurs giving way to infectious complications [41].

The registry study showed a higher incidence of POPF following PBS as compared to upfront surgery. Due to matching, pancreatic texture as the most important risk factor of POPF was well-balanced between both groups and can be excluded as a potential bias [15]. Two larger cohort and two smaller retrospective series also confirmed a higher rate of POPF in patients undergoing preoperative biliary drainage [17,41,46,47]. As a cause, Sohn et al. speculated that PBS may lead to a partial obstruction of the pancreatic duct [41]. On the other hand, pancreatic ductal system and juice might be bacterially colonized in the same way as shown for the biliary tree [48,49].

As a potential limitation, the study was only focused on PDAC patients undergoing PBS. On the other hand, the analysis was therefore based on a more homogeneous patient cohort as compared to other studies. Additionally, the effect of PBS on perioperative complications in PDAC is especially relevant as a potential morbidity-related delay of surgery is more adverse in PDAC as compared to other slowly progressing periampullary malignancies or even benign disease.

In summary, PBS in resectable PDAC patients who had never presented with jaundice is frequently performed despite of evidence or guidelines and seems to result in increased perioperative morbidity. Serum bilirubin levels of more than 15 mg/dl were found to be associated with more CDC complications grade IIIa to IVb as well as higher in-hospital mortality. A convincing beneficial effect of PBS could not be inferred from the data. In consequence, only neoadjuvant therapy or cholangitis are clear indications for PBS. Future studies should strive to define a benefit of PBS in severely

jaundiced patients. Efforts should be made to spread this paradigm and to raise awareness of PBS-related morbidity.

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