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Original Article

The value of preoperative biliary drainage in hilar cholangiocarcinoma: a systematic review and meta analysis of 10 years' literatures

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Abstract: Background: Preoperative biliary drainage (PBD) is widely used for the recovery of liver function before hilar cholangiocarcinoma (HC) surgery. However, the application of PBD is still under debate nowadays. Methods: Studies using PBD in patients with HC were included in this study. Online search was conducted using Pubmed and Cochrane Library. Meta-analysis was run to combine the data for PBD-related complication, post-operative complication, mortality, hospital stay, R0 rate and survival. R0 resection was defined as radical resection with pathologically clear margin. The therapeutic efficacy of PBD was represented on the potentially decreased incidence of post-operative morbidity and mortality, increased R0 rate and longer survival. So these observational points were used to analyze the therapeutic efficacy. Results: Nineteen studies with 2047 patients were selected and reviewed. PBD-related complications occurred in 25.6% patients. The odds ratio (OR) for morbidity in PBD group versus no PBD group was 1.51 (95% CI: 0.94-2.43). In jaundiced patients, the OR for mortality was 0.70 (95% CI: 0.33-1.45). The PBD group showed slightly longer hospital stay after surgery but without significance (mean difference: 4.53, 95% CI: -3.19-12.25). There is no difference between the two groups regarding R0 rate (OR 0.58, 95% CI: 0.30-1.13) and survival (HR 0.94, 95% CI: 0.66-1.34). Conclusions: PBD didn't change the incidence of post-operative complications, post-operative hospital stay, R0 rate and survival. In jaundiced patients, PBD may decrease the post-operative mortality. The OR for mortality was 0.70 in jaundiced patients. We divided studies into 2 groups based on the study quality when we measured the difference of mortality in 2 groups. The OR smaller than 1 in jaundiced patients (studies of higher quality) may suggest the beneficial effect of PBD. Based on these results and clinical experiences reported in the recent studies, PBD may be necessary to improve the clinical outcome in some jaundiced HC patients.

Keywords: Preoperative biliary drainage, hilar cholangiocarcinoma, post-operative morbidity, mortality

Background

Hilar cholangiocarcinoma (HC) is a bile duct carcinoma involving the hilar region of the liver. The prognosis is poor. The incidence of the disease is increasing world wide. Radical resection is the only possible treatment for cure. However, HC often causes obstructive jaundice, which then impairs liver function. Since liver is important for coagulation and metabolism, jaundiced patients are facing a higher rate of post-operative morbidity and mortality. Moreover, major hepatic resection is often necessary for the treatment of HC, thus the preservation of liver function is more important than other malignancies causing jaundice.

Preoperative biliary drainage (PBD) is designed to decrease the bilirubin level and to recover the liver function. The ultimate purpose is to decrease the post-operative morbidity and mortality. PBD is also used to treat acute cholangitis, for cholangioscopy, to prevent cholangitis after diagnostic endoscopic retrograde cholangiopancreatography (ERCP), and to increase the resectability of the lesion [1-3]. Biliary dilatation secondary to obstruction may compress the portal vein, leading to ischemia and necrosis of the remnant liver and suppressing regeneration. Some authors believe PBD is a solution to recover the portal flow [4]. Currently, PBD is achieved by percutaneous transhepatic biliary drainage (PTBD), endoscopic retrograde biliary drainage (ERBD), endoscopic naso-biliary drainage (ENBD) and operation.

In 2002, Sewnath et al. published a meta-analysis on the efficacy of PBD for tumors causing obstructive jaundice [5]. This meta-analysis showed that PBD carried no benefit for obstructively jaundiced surgical candidates and increased the overall complication rate. Therefore, the authors suggested PBD should not be performed routinely. Recently, another systemic review by Moole et al. found that patients undergoing PBD had less major adverse effects than the "direct surgery" group [6]. Both these studies were focused on the effect of PBD on obstructive jaundice, regardless of the level of an obstruction. In 2011, Liu et al. reviewed 11 studies with 711 HC patients and showed the overall complication rate and postoperative infectious complication rate were adversely affected by PBD treatment [7]. However, the improved techniques of biliary drainage was expected to provide more safety and efficiency in the past decades, thus an update of the systemic review on this topic is required.

Methods

Criteria for considering studies for this review

Both RCT and retrospective studies investigating hospitalized patients undergoing surgery for hilar carcinoma are considered appropriate for this review. No restriction on the bilirubin level was set. Primary outcomes include PBD-related complication, post-operative mortality, post-operative complication and post-operative infectious complication. Secondary outcomes include R0 rate, post-surgery hospital stay and survival.

Search methods for identification of studies

Online search was conducted using Pubmed and Cochrane Library. The words used for search included two parts: 1) hilar cholangiocarcinoma, parahilar cholangiocarcinoma, Klatskin tumor, or proximal bile duct carcinoma; 2) preoperative biliary drainage/decompression, percutaneous transhepatic biliary drainage, endoscopic retrograde biliary drainage, endoscopic naso-biliary drainage, or stent. We searched part 1 firstly, and then part 2. Only studies related were selected for further selection. Duplicated studies found were skipped.

Selection of studies

There are three types of included studies. 1) RCT focused on the effect of PBD on HC treatment. 2) Retrospective studies focused on the effect of PBD on HC treatment. 3) Surgical experience. Only experiences containing accessible data related to the effect of PBD on HC treatment were included.

Studies should contain accessible data on at least 1 of the 7 outcomes below: 1) PBD-related complication; 2) Post-operative complication; 3) Post-operative infectious complication; 4) Post-operative mortality; 5) Post-operative hospital stay; 6) The rate R0 resection (defined as radical resection with pathologically clear margin) in patients underwent surgical treatment; 7) Survival.

In several studies, a few patients with other malignancies involving the hilum region than HC were also included [8-10]. They are gallbladder cancer, intra-hepatic cholangiocarcinoma and colorectal metastasis. However, the numbers of these patients are small [8-10], while the outcomes are similar with HC patients, so the studies were also included in this meta-analysis.

Data extraction and management

Only published data was extracted. A pre-designed form querying basic information, surgical information and accessible outcome information was filled for each study. These completed forms were then checked by another author.

Data synthesis and assessment of heterogeneity

Data of basic information is synthesized by equations given in Cochrane Handbook 5.1.0. Data represented as median and IQR or range were transformed into mean ± SD also by equations in the book. Continuity data are reported as "mean ± SD" in this review. Both M-H fixed and M-H random effects models were adopted for meta-analysis. Under fixed effects model, the chi-square test for the homogeneity test statistic Q, and the heterogeneity measure I^2

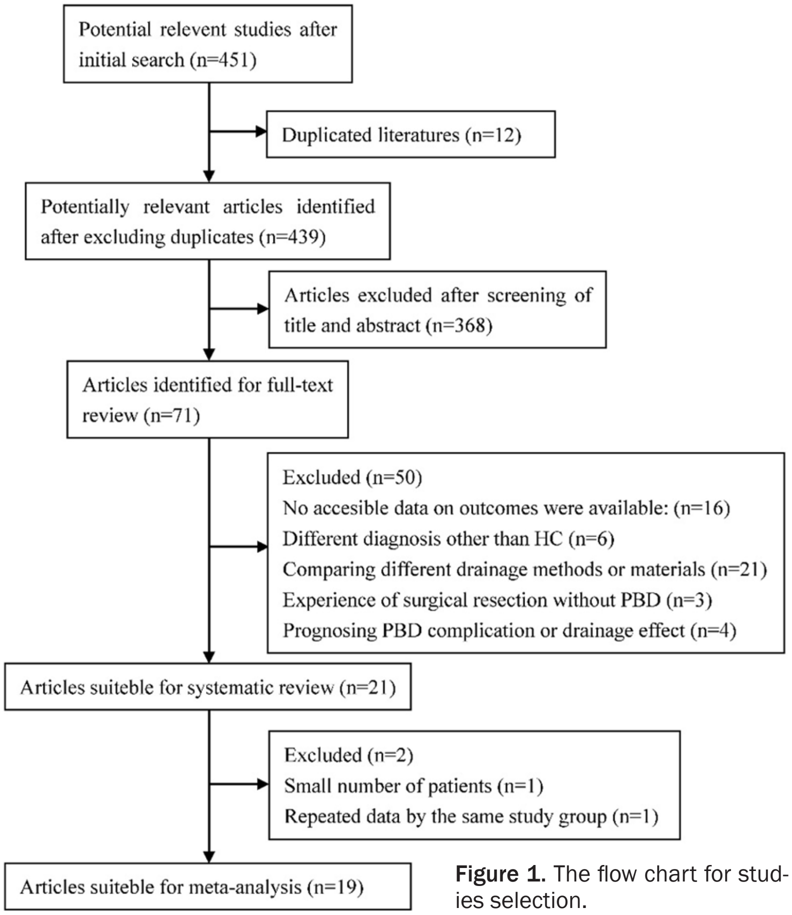

Figure 1. The flow chart for studies selection.

were calculated by Revman. Fixed effects model was accepted when $P < 0.10$ and $I^2 < 25\%$. Otherwise, Random effects model was considered. Dichotomous data, survival data and continuous data are presented as odds ratio (OR), hazard ratio (HR) and weighted mean difference (WMD) with the corresponding 95% confidence interval (CI) respectively. Funnel plots were constructed to evaluate potential publication bias.

Results

Description of studies

The flow chart for studies selection is shown in **Figure 1**. A total of 19 retrospective studies on 2178 patients with perihilar malignancy undergoing surgery were included. They were conducted in Belgium, China, Egypt, France, Italy Japan, Korea, Netherlands and USA (**Table 1**). In 16 studies, all the perihilar malignancies were diagnosed as HC. In only 4 studies, all included patients were jaundiced [9, 11-13]. Seven studies mainly focused on the effect of PBD on HC treatment [9-15], while the other 12 were published surgical experiences where PBD was analyzed as a factor to influence the outcome. In at least 9 studies, only patients undergoing hepatectomy were included. Most HC patients were Bismuth-Corlette Type III (60.0%). At least 1382 patients were jaundiced, and 1434 patients were drainaged. 2135 operations including 1787 hepatectomies were operated, and at least 249 caudate lobes were resected.

PTBD is the most common procedure as PBD (58.6%, **Table 2**). The mean duration of PBD before surgery is 30.8 ± 27.3 d. Patients in PBD group underwent portal vein embolization (PVE) more frequently than no PBD group. Since PVE may cause procedure-related complication, improve liver function and thus affect surgical outcomes, the different frequency may affect the comparison. There are more jaundiced patients in the PBD group (97.2% vs. 42.6%), as we shall see in the discussion, this leads to a bias in our results. The quality of each study was evaluated based on the extent of selection bias. Study with lower selection bias was considered as of higher quality.

PBD-related complications

Ten studies were pooled to estimate the incidence of PBD-related complications. They occurred in 25.5% patients. The most common one is cholangitis (19.0%). Pancreatitis were reported to occur in 3.2% patients, and peritonitis occurred in 0.9% patients. Bleeding was common and occurred in 5.6% patients. No PBD-related death was reported.

Post-operative morbidity

Eleven studies including 1263 participants were pooled to compare the incidence of post-

Table 1. Basic information of the included studies

Author	Publishing Time	Country	Covering years	Study design	Number of patients	Age	Male	Jaundiced	PBD	Type of drainage	Study quality	Hepatectomy	Reference
Dinant	2006	Netherlands	1988-01~2003-01	Retrospective	99	60 ± 10.1	61 (61.6%)	67 (67.7%)	85 (85.9%)	PTBD and ERBD	Low	38 (38.4%)	[22]
Sano	2006	Japan	2000-01~2004-12	Retrospective	102 (perihilar colangiocarcinoma)	65.5 ± 11	71 (69.6%)	60 (58.8%)	65 (63.7%)	PTBD and ERBD	Low	102 (100%)	[8]
Ferrero	2009	Italy	1989-01~2006-06	Retrospective	60 (carcinoma involving proximal bile duct)	64.8 ± 11.3	32 (53.3%)	60 (100%)	30 (50.0%)	PTBD and ERBD	High	60 (100%)	[9]
Sakata	2009	Japan	1988-01~2005-03	Retrospective	81	68 ± 11.8	52 (64.2%)	63 (77.8%)	71 (87.7%)	PTBD and ERBD	Low	81 (100%)	[16]
Hirano	2010	Japan	2001-01~2008-12	Retrospective	146	68.5 ± 10.5	115 (78.8%)	118 (80.8%)	131 (89.7%)	PTBD and ENBD	Low	128 (87.7%)	[1]
Ercolani	2010	Italy	1989-11~2007-12	Retrospective	51	62.6 ± 8.9	32 (62.7%)	44 (86.3%)	44 (86.3%)	PTBD and ERBD	Low	51 (100%)	[23]
El-Hanafy	2010	Egypt	1995-01~2007-01	Retrospective	100	51.7 ± 11.5	64 (64.0%)	Unknown	46 (46.0%)	PTBD and ERBD	Low	Unknown	[14]
Grandadam	2010	France	1997-01~2007-06	Retrospective	38	Unknown	Unknown	24 (63.2%)	12 (31.6%)	PTBD	Low	38 (100%)	[17]
Rocha	2010	USA	2001-01~2008-12	Retrospective	60	64	36 (60%)	Unknown	38 (63.3%)	Unknown	Low	57 (95%)	[24]
Regimbeau	2011	France	2008-01~2008-12	Retrospective	56	63 ± 11	40 (71.4%)	47 (83.9%)	38 (67.9%)	PTBD and ERBD	Low	39 (69.6%)	[25]
Cho	2012	Korea	2000-01~2009-12	Retrospective	105	63 ± 13	67 (63.8%)	84 (80%)	84 (80.0%)	Mainly PTBD	Low	79 (75.2%)	[3]
Nuzzo	2012	Italy	1992-01~2007-12	Retrospective	299	Unknown	Unknown	299 (100%)	252 (84.3%)	PTBD and ENBD	High	299 (100%)	[11]
Farges	2013	France & Belgium	1997~2008	Retrospective	366	62 ± 11	234 (63.9%)	259 (70.8%)	180 (49.2%)	PTBD and ERBD	High	366 (100%)	[15]
Xiong	2013	China	2002-12~2012-01	Retrospective	78	58.8 ± 11.1	49 (62.8%)	78 (100%)	32 (41.0%)	PTBD, ENBD and surgery	High	78 (100%)	[12]
Ratti	2013	Italy	2004-01~2012-05	Retrospective	94	59 ± 11.5	44 (46.8%)	55 (58.5%)	55 (58.5%)	PTBD and ERBD	Low	80 (85.1%)	[26]
Yu	2013	China	1993-01~2010-12	Retrospective	116	55.7 ± 8.0	81 (69.8%)	116 (100%)	56 (48.3%)	PTBD	High	Unknown	[13]
Furusawa	2014	Japan	1990-01~2012-12	Retrospective	144	69.5 ± 11.2	42 (29.2%)	Unknown	122 (84.7%)	PTBD and ERBD	Low	143 (99.3%)	[27]
Yan	2014	China	1998-01~2007-12	Retrospective	131	58 ± 8.8	75 (57.3%)	92 (70.2%)	64 (48.9%)	PTBD and ERBD	Low	96 (73.3%)	[28]
Ito	2016	Japan	2010-01~2014-03	Retrospective	52 (Hilar malignancy)	59.5 ± 10.6	25 (48.1%)	Unknown	29 (55.8%)	PTBD, ERBD and ENBD	Low	52 (100%)	[10]
Total	19 studies	9 countries	1988-01~2014-03	19 retrospective studies	2178	62.0 ± 10.8	1120 (60.8%)	1382 (80.5%)	1434 (65.8%)	PTBD, ERBD, ENBD and surgery		1787 (82.0%)	

PBD, preoperative biliary drainage, *PTBD*, percutaneous transhepatic biliary drainage, *ERBD*, endoscopic retrograde biliary drainage, *ENBD*, endoscopic naso-biliary drainage. Study quality was evaluated based on the extent of selection bias.

Table 2. Clinical characteristics of patients underwent surgery with or without PBD

	PBD group	No PBD group	Included studies	References
Patients number	1434 (65.8%)	744 (34.2%)		
Age	59.0 ± 9.9	58.4 ± 10.9	6	[9, 10, 12-15]
Gender			6	[9, 10, 12-15]
Male	243 (65.1%)	242 (60.7%)		
Female	130 (34.9%)	157 (39.3%)		
Type of drainage			15	[3, 8-10, 12-17, 22, 23, 25-27]
PTBD	556 (58.6%)			
ERBD	286 (30.1%)			
ENBD	30 (3.2%)			
Operatively	6 (0.6%)			
Multiple methods	44 (4.6%)			
Duration of PBD (d)	30.8 ± 27.3		7	[9, 12, 13, 15-17, 26]
Jaundiced patients	866 (93.9%)	313 (60.9%)	11	[1, 8, 9, 11-13, 15-17, 25, 26]
Total bilirubin at admission (umol/L)	252.5 ± 116.4	275.3 ± 151.9	10	[1, 9, 10, 12-15, 17, 25, 26]
Total bilirubin before surgery (umol/L)	78.2 ± 102.7	270.5 ± 52.2	9	[1, 9, 10, 12, 13, 15, 17, 25, 26]
PVE	174 (49.3%)	42 (16.8%)	9	[8-10, 12, 13, 17, 25-27]
Surgery				
Hepatectomy	837 (98.9%)	426 (99.8%)	10	[1, 8-12, 15-17, 23]
Curative (R0 + R1)	715 (95.0%)	389 (93.7%)	9	[3, 8, 9, 11, 13, 15, 17, 23, 24]
Palliative	38 (5.0%)	26 (6.3%)		

PBD, preoperative biliary drainage, *PTBD*, percutaneous transhepatic biliary drainage, *ERBD*, endoscopic retrograde biliary drainage, *ENBD*, endoscopic naso-biliary drainage, *PVE*, portal vein embolization.

operative complication between two groups (**Figure 2A**). The post-operative complications include infectious morbidity (pancreatitis, cholangitis, peritonitis, abdominal abscess, surgical site infection pneumonia and sepsis) and non-infectious morbidity (bleeding, anastomosis leakage, and hepatic insufficiency). Visually, the ORs were found to be larger in the first 5 years, then 2 subgroups were established. As shown in **Figure 2A**, 6 studies in the first 5 years and 5 studies in the next 5 years were subgrouped. In the first 5 years, the pooled results suggested that PBD increases morbidity (57.4% vs. 35.9%, OR 2.67, 95% CI: 1.71-4.16). While in the second 5 years, the difference between these two groups became smaller (61.3% vs. 60.8%, OR 0.86, 95% CI: 0.52-1.42). When these subgroups were combined, the OR was not statistically significant (OR 1.51, 95% CI: 0.94-2.43). No publication bias was found by observing the funnel plot (**Figure 2C**). Five studies [9, 12, 13, 16, 17] including 344 participants were combined to compare the incidence of post-operative infectious complication (**Figure 2B**) [9, 12, 13, 16, 17]. 43.5% patients in the PBD group and 29.8% in the non-PBD group suffered from infectious complications, but the difference was not significant (OR 0.95, 95% CI: 0.30-3.02).

Post-operative mortality

Nine studies including 1172 patients were combined (**Figure 3**). Chi-square test for the homogeneity test statistic Q showed $P > 0.10$, so the random effects model was accepted. In the first 4 studies, only jaundiced patients were included, the combined estimate showed a tendency of PBD to decrease mortality (OR 0.70, CI 0.33-1.45). When all the 9 studies (no restriction of the patients on jaundice) were pooled together, the difference of mortality rates between the two groups was still not significant (OR 0.94, CI 0.54-1.63). However, the definitions of mortality differed among these studies. In the study by Sakata et al., only deaths occurred in hospital were included [16]. In the study by Nuzzo et al., the mortality rate was adjusted for blood transfusion and resection extent, which were considered to affect the mortality by multivariate analysis in their study [11]. Sano et al. experienced zero mortality in

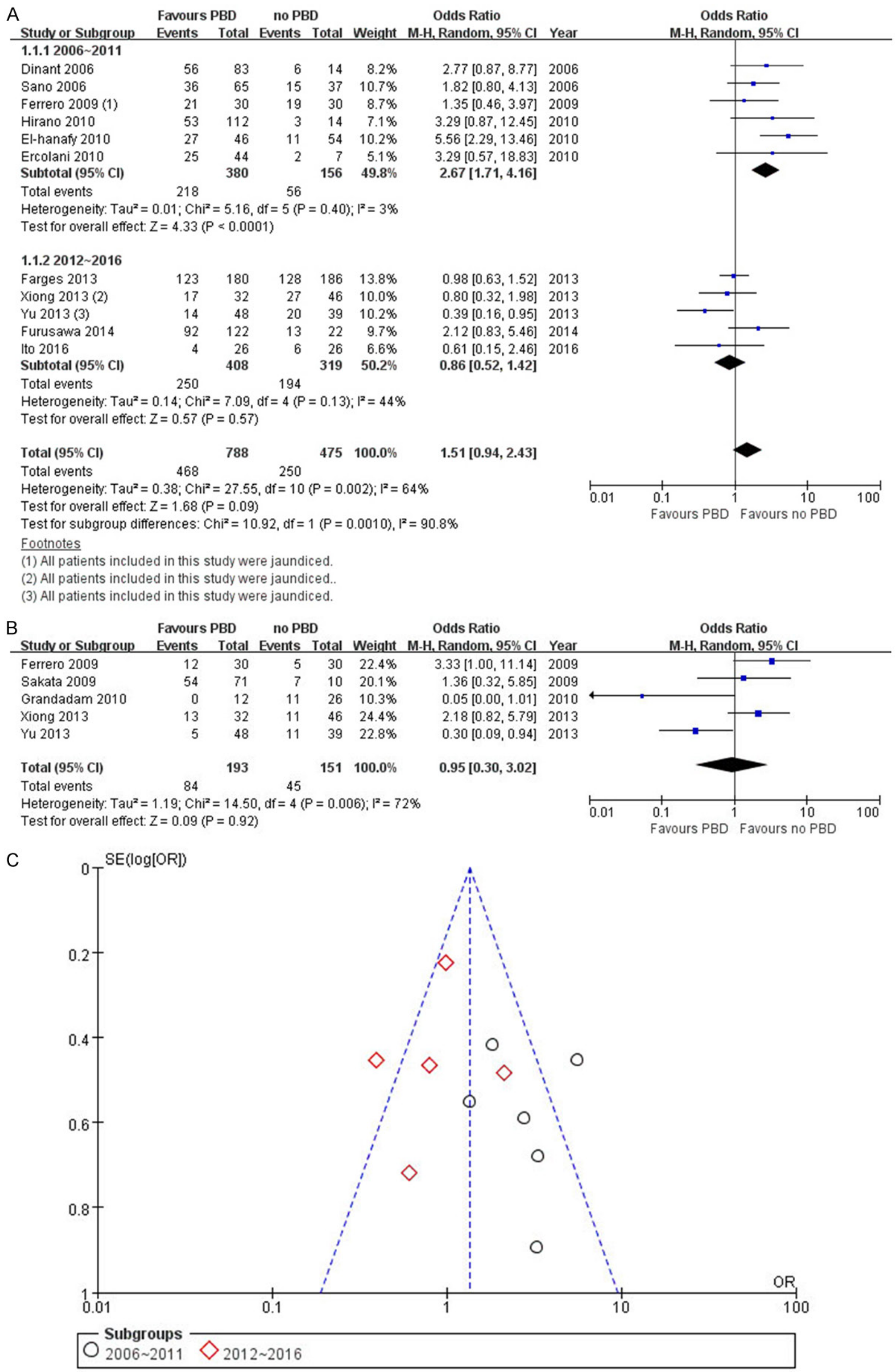
A
Favours PBD
no PBD
Odds Ratio
Odds Ratio
Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year
M-H, Random, 95% CI
1.1.1 2006~2011
Dinant 2006 | 56 | 83 | 6 | 14 | 8.2% | 2.77 [0.87, 8.77] | 2006
Sano 2006 | 36 | 65 | 15 | 37 | 10.7% | 1.82 [0.80, 4.13] | 2006
Ferrero 2009 (1) | 21 | 30 | 19 | 30 | 8.7% | 1.35 [0.46, 3.97] | 2009
Hirano 2010 | 53 | 112 | 3 | 14 | 7.1% | 3.29 [0.87, 12.45] | 2010
El-hanafy 2010 | 27 | 46 | 11 | 54 | 10.2% | 5.56 [2.29, 13.46] | 2010
Ercolani 2010 | 25 | 44 | 2 | 7 | 5.1% | 3.29 [0.57, 18.83] | 2010
Subtotal (95% CI) | 380 | 156 | 49.8% | 2.67 [1.71, 4.16]
Total events | 218 | 56
Heterogeneity: Tau² = 0.01; Chi² = 5.16, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 4.33 (P < 0.0001)
1.1.2 2012~2016
Farges 2013 | 123 | 180 | 128 | 186 | 13.8% | 0.98 [0.63, 1.52] | 2013
Xiong 2013 (2) | 17 | 32 | 27 | 46 | 10.0% | 0.80 [0.32, 1.98] | 2013
Yu 2013 (3) | 14 | 48 | 20 | 39 | 10.2% | 0.39 [0.16, 0.95] | 2013
Furusawa 2014 | 92 | 122 | 13 | 22 | 9.7% | 2.12 [0.83, 5.46] | 2014
Ito 2016 | 4 | 26 | 6 | 26 | 6.6% | 0.61 [0.15, 2.46] | 2016
Subtotal (95% CI) | 408 | 319 | 50.2% | 0.86 [0.52, 1.42]
Total events | 250 | 194
Heterogeneity: Tau² = 0.14; Chi² = 7.09, df = 4 (P = 0.13); I² = 44%
Test for overall effect: Z = 0.57 (P = 0.57)
Total (95% CI) | 788 | 475 | 100.0% | 1.51 [0.94, 2.43]
Total events | 468 | 250
Heterogeneity: Tau² = 0.38; Chi² = 27.55, df = 10 (P = 0.002); I² = 64%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Chi² = 10.92, df = 1 (P = 0.0010), I² = 90.8%
0.01 0.1 1 10 100
Favours PBD Favours no PBD
Footnotes
(1) All patients included in this study were jaundiced.
(2) All patients included in this study were jaundiced..
(3) All patients included in this study were jaundiced.
B
Favours PBD
no PBD
Odds Ratio
Odds Ratio
Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year
M-H, Random, 95% CI
Ferrero 2009 | 12 | 30 | 5 | 30 | 22.4% | 3.33 [1.00, 11.14] | 2009
Sakata 2009 | 54 | 71 | 7 | 10 | 20.1% | 1.36 [0.32, 5.85] | 2009
Grandadam 2010 | 0 | 12 | 11 | 26 | 10.3% | 0.05 [0.00, 1.01] | 2010
Xiong 2013 | 13 | 32 | 11 | 46 | 24.4% | 2.18 [0.82, 5.79] | 2013
Yu 2013 | 5 | 48 | 11 | 39 | 22.8% | 0.30 [0.09, 0.94] | 2013
Total (95% CI) | 193 | 151 | 100.0% | 0.95 [0.30, 3.02]
Total events | 84 | 45
Heterogeneity: Tau² = 1.19; Chi² = 14.50, df = 4 (P = 0.006); I² = 72%
Test for overall effect: Z = 0.09 (P = 0.92)
0.01 0.1 1 10 100
Favours PBD Favours no PBD
C
SE(log[OR])
0
0.2
0.4
0.6
0.8
1
OR
0.01 0.1 1 10 100
Subgroups
2006~2011
2012~2016

Figure 2. Meta-analysis of the effect of preoperative biliary drainage (PBD) on post-operative morbidity. A. Forest plot of odds ratios (ORs) for post-operative morbidity. The post-operative morbidity includes infectious morbidity (pancreatitis, cholangitis, peritonitis, abdominal abscess, surgical site infection pneumonia and sepsis) and non-infectious morbidity (bleeding, anastomosis leakage, and hepatic insufficiency). B. Forest plot of odds ratios for post-operative infectious complication. C. Funnel plot of ORs corresponding to post-operative morbidity. It is constructed for publication bias assessment. The standard error is for the log odds ratio. The vertical dashed line is plotted at the fixed effect estimate and the oblique dashed lines indicate the extremes of the pseudo 95% confidence intervals.

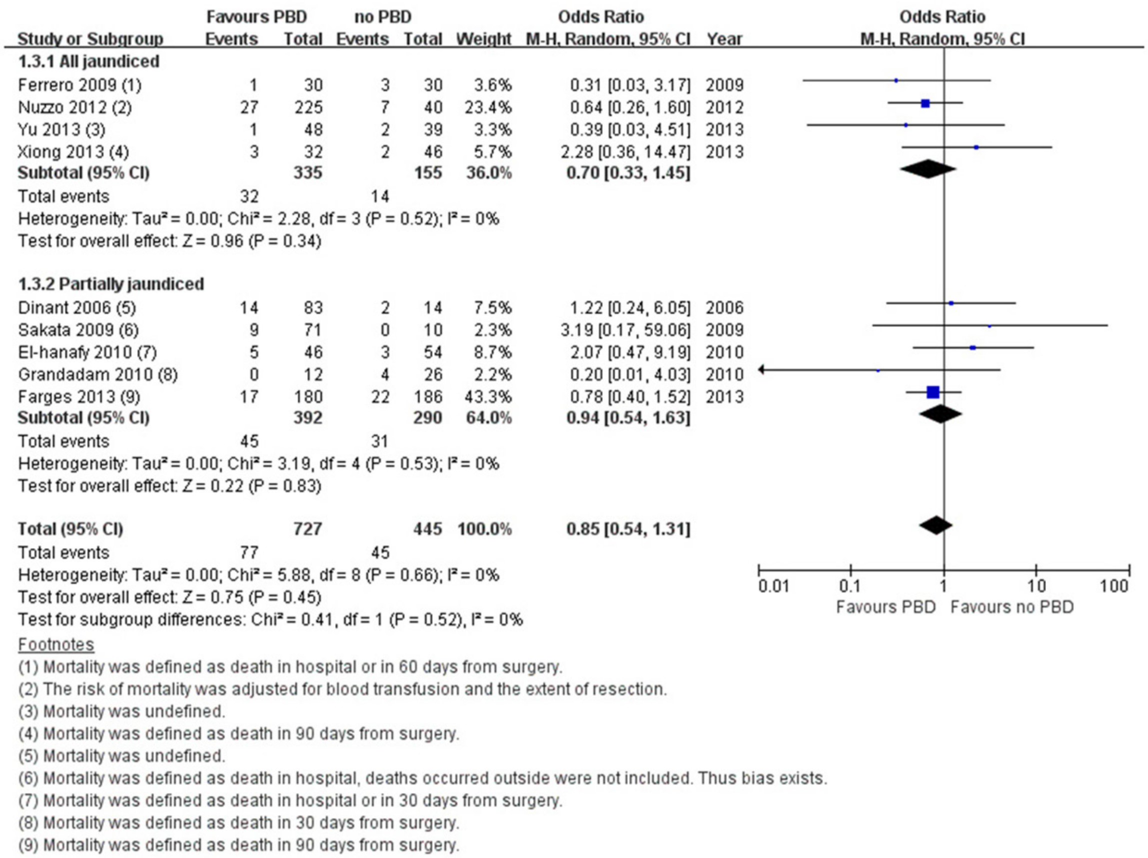

Figure 3. Meta-analysis of the effect of preoperative biliary drainage (PBD) and on post-operative mortality. Forest plot of odds ratios for post-operative mortality.

their facility, but this study was unable to be included [18].

Post-operative hospital stay, R0 rate and survival

To study post-operative hospital stay, 3 studies including 238 participants were combined. The PBD group showed slightly longer hospital stay after surgery but without significance (MD 4.53, 95% CI: -3.19-12.25, **Figure 4A**). To study R0 rate, 3 studies including 243 participants were combined. In the patients undergoing curative operation, 64.0% in the PBD group and 67.1% in the non-PBD group achieved R0 resection. There is no difference between the two groups (OR 0.58, 95% CI: 0.30-1.13, **Figure 4B**). To study survival, 4 studies including 430 participants were combined by inverse variance (IV) method. There is no difference between the two groups (HR 0.94, 95% CI: 0.66-1.34, **Figure 4C**). El-Hanafy et al. found a non-significant beneficial effect of PBD, but only mean ± SD (22.6 ± 17 vs. 19.7 ± 16.6 months, not HR) was provided, thus it is unable to be pooled [14]. Grandadam et al. showed after pre-operative optimization (either PBD or PVE), the survival of HC patients after major hepatectomy improved, but still without statistical significance (P = 0.09) [17]. Since the optimization also included PVE without PBD, their data were not incorporated either.

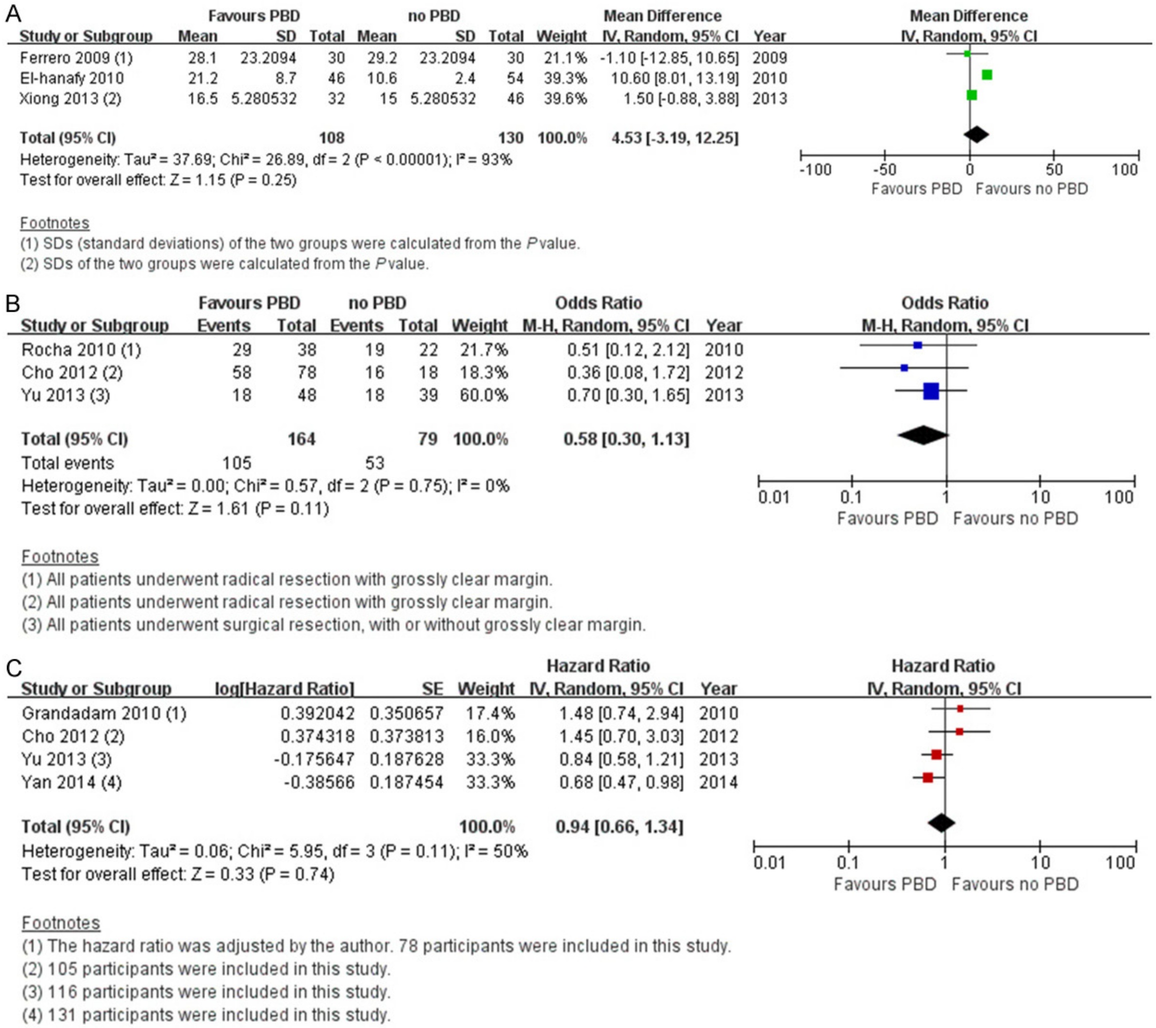

Figure 4. Meta-analysis of the effect of preoperative biliary drainage on post-operative hospital stay, R0 rate and survival. A. Forest plot of mean differences for post-operative hospital stay. B. Forest plot of odds ratios for R0 rate. C. Forest plot of hazard ratios for post-operative survival.

Discussion

In the last 10 years, almost all of published surgical experiences in hilar cholangiocarcinoma treatment described the application of PBD. Along with PVE, PBD has become an important composition in pre-operative optimization. In some Japanese and Korean centers, the rate of PBD in HC patients is high (> 95% in our review) while many Chinese centers (including us) adopted a more conservative attitude. This review compared PBD group with no PBD (direct surgery) group regarding postoperative morbidity, mortality, hospital stay, R0 rate and survival. The current available data didn't support a significant change in all those aspects. The procedure-related complication remains high in the setting of HC (25.6%). However, the reported post-operative morbidity associated with PBD in the last 5 years was evidently improved. Moreover, PBD might reduce the post-operative mortality in jaundiced patients.

The major drawback of this review is the lack of uniformity between selected studies, which may lead to potential biases. First, different indications were adopted by the authors. 14 studies adopted obstructive jaundice as their indication, but the delineation of the jaundice was quite different (**Table 3**). The strength to carry out their established indications also differed. In at least 3 studies, some patients who met the corresponding indication were not drainage.

Table 3. Indications for pre-operative drainage adopted by studies

Indications	Studies	Reference
Jaundice	14	[1, 8, 10-14, 16, 17, 23, 25-28]
Bilirubin > 2 mg/dl	3	[1, 3, 27]
Bilirubin > 3 mg/dl	4	[8, 10, 14, 16]
Others	3	[12, 13, 23]
Unknown	4	[17, 25, 26, 28]
Long-time jaundice	1	[12]
For FLR drainage	3	[1, 8, 16]
Cholangitis	7	[1, 3, 8, 9, 12, 16, 25]
Malnutrition	2	[9, 12]
For cholangioscopy	1	[1]
Physician's discretion	2	[10, 15]
Unknown	3	[11, 14, 24]

FLR, future liver remnant.

Second, different future liver remnant (FLR) policies were executed by the researchers. Eight authors stated that they preferred the drainage of FLR, while Grandadam avoided the drainage of the FLR to prevent cholangitis. Kennedy et al. recommended drainage of the FLR when it < 30% of the total liver volume, according to MSKCC's experience [19]. Farges et al. suggested PBD before right hepatectomy, in which FLR < 30% were more frequently met [15]. However, when FLR > 30% or left hepatectomy was performed, PBD increased morbidity and mortality.

Third, different ways for biliary drainage were used by each study. Some authors preferred endoscopic drainage (Hirano, Ito), while some preferred PTBD (Ferrero, Grandadam, Ratti, Sano). Endoscopic stenting is technically difficult for hilar malignancy, 58.6% of patients received PTBD in our review. However, PTBD was reported to be associated with more serious complications such as vascular injury and cancer dissemination [20]. The heterogeneity in approach selection propensity and technique expertise might have affected the outcomes.

Fourth, patients' condition is not uniformed in these two groups. 97.2% of patients receiving PBD are jaundiced, while only 46.2% of patients undergoing direct surgery are jaundiced. In the studies that all patients were jaundiced, the results may reflect the true function of PBD. When we pool these four studies (Ferrero, Nuzzo, Yu, Xiong), PBD exhibits a tendency to decrease the mortality (OR 0.70, CI 0.33-1.45) and morbidity (OR 0.71, CI 0.36-1.43). However, only Yu et al. claimed that the grouping of these jaundiced patients was randomized [13]. Ferrero et al. drained patients who have cholangitis and malnutrition, Xiong et al. drained patients with long-time jaundice (> 4 weeks), cholangitis or malnutrition, while the indication for PBD was undefined by Nuzzo et al [9, 11, 12]. In the studies that only part of patients were jaundiced, but most (> 90%) of these jaundiced patients underwent PBD, the results can be biased by the effect of jaundice. That was the case in Sano, Sakata, Hirano, Ercolani, Cho, Ratti and Furusawa's studies. Indeed, when we pooled four studies by Sano, Hirano, Ercolani and Furusawa where the complication outcome was available, the pooled OR became significant: 2.22 (1.30 to 3.79). Anyway, we cannot conclude that PBD increase surgical complication by this result.

In clinical practice, when PBD is not performed as routine, patient undergoing PBD often have a worse condition. Thus, the pooled estimates may be biased and under-estimate the importance and benefits of PBD. Randomized trials may solve the problem, but it is poorly operable and has ethical problems. Therefore, when we are trying to access the value of PBD from clinical data, adjustments for the pre-operative condition (bilirubin level, jaundice time, albumin level, liver function) by multivariate analysis or using a propensity score are necessary [21]. In our review, only Nuzzo et al. adjusted their results [11].

Last, the endpoint for the PBD also differed. In 6 studies, surgeons' controlled all the total bilirubin levels to be below 5 mg/dl. In 13 studies, the median bilirubin levels were below 5 mg/dl. Consequently, the duration of PBD varied between studies (30.8 ± 27.3 day). We reran the meta-analysis in these two levels, but no major differences were found. Therefore, we haven't found any evidence to support the existence of a "right" endpoint to terminate PBD and start an operation.

Conclusions

The incidence of PBD-related complication is high in the setting of HC. However, post-operative morbidity associated with PBD in the last 5 years was evidently improved. Moreover, PBD might reduce the post-operative mortality in jaundiced patients. Based on the results from meta-analysis and the latest published literatures, we suggest that PBD should be considered in these following conditions: 1. FLR < 30%, often in planned extended right hepatectomy; 2. Long-time jaundice and high bilirubinemia; 3. Malnutrition. Still, we are calling for further studies to seek out the proper cut-offs of the jaundice time and bilirubin level to be adopted as "golden standards" to apply PBD.

Disclosure of conflict of interest

None.

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