

Effect of Preoperative Biliary Drainage on Complications Following Pancreatoduodenectomy

A Meta-Analysis

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Abstract: Preoperative biliary drainage (PBD) prior to pancreatoduodenectomy (PD) is still controversial; therefore, the aim of this study was to examine the impact of PBD on complications following PD.

A meta-analysis was carried out for all relevant randomized controlled trials (RCTs), prospective and retrospective studies published from inception to March 2015 that compared PBD and non-PBD (immediate surgery) for the development of postoperative complications in PD patients. Pooled odds ratio (OR) and 95% confidence interval (CI) were estimated using fixed-effect analyses, or random-effects analyses if there was statistically significant heterogeneity ($P < 0.05$).

Eight RCTs, 13 prospective studies, 20 retrospective studies, and 3 Chinese local retrospective studies with 6286 patients were included in this study. In a pooled analysis, there were no significant differences between PBD and non-PBD group in the risks of mortality, morbidity, intra-abdominal abscess, sepsis, hemorrhage, pancreatic leakage, and biliary leakage. However, subgroup analysis of RCTs yielded a trend

toward reduced risk of morbidity in PBD group (OR 0.48, CI 0.24 to 0.97; $P = 0.04$). Compared with non-PBD, PBD was associated with significant increase in the risk of infectious complication (OR 1.52, CI 1.07 to 2.17; $P = 0.02$), wound infection (OR 2.09, CI 1.39 to 3.13; $P = 0.0004$), and delayed gastric emptying (DGE) (OR 1.37, CI 1.08 to 1.73; $P = 0.009$).

This meta-analysis suggests that biliary drainage before PD increased postoperative infectious complication, wound infection, and DGE. In light of the results of the study, PBD probably should not be routinely carried out in PD patients.

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Abbreviations: CI = confidence interval, DGE = delayed gastric emptying, IAA = intra-abdominal abscess, OR = odds ratio, PBD = preoperative biliary drainage, PD = pancreatoduodenectomy, RCTs = randomized controlled trials.

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INTRODUCTION

Although the mortality rate for pancreatoduodenectomy (PD) has fallen to approximately 5% in the last 20 years because of improvements in perioperative care and operative management, the morbidity rate remains as high as 40%.¹ Preoperative biliary drainage (PBD) was considered to reduce postoperative complication rate after PD for the first time in 1935 by Whipple et al.² Drainage can be accomplished either externally, by inserting a transhepatic catheter into the biliary tract percutaneously, or internally, by endoscopic retrograde cannulation of the bile duct with insertion of an endoprosthesis. Both techniques are used safely, but the potential benefit of biliary decompression on postoperative morbidity remains controversial.³

Despite effective reducing levels of jaundice, the majority of studies defining the role of PBD for the development of postoperative complications are with conflicting results. Several experimental studies and retrospective case series have suggested that PBD reduced morbidity and mortality after surgery.^{3–5} However, some current studies showed a deleterious effect of PBD on postoperative infectious complications, including wound infection and/or intra-abdominal abscess (IAA).^{6–9} More recently, one randomized controlled trial (RCT) in 2010 has suggested that PBD increased the rate of complications and should not be performed routinely.¹⁰ Nevertheless, PBD has been incorporated into the surgical treatment of cancer of the pancreatic head in many centers.^{11–13} In other words, the safety of routine PBD for obstructive jaundice has not been established. To assess the benefits and harms of PBD versus non-PBD (direct surgery) in patients with obstructive jaundice (irrespective of a benign or malignant cause), 7 meta-analyses^{9,14–19} from 2002 to 2013 have been reported. The previous meta-analyses were mostly focused on postoperative

overall morbidity and mortality, without systematic analysis of various postoperative complications. On the contrary, trials included in these meta-analyses were not comprehensive. The previous meta-analysis in 2013 also concentrated on postoperative morbidity and mortality based on 6 RCTs, and did not include recent nonrandomized studies to analyze postoperative complications in detail, which may no longer be in line with modern surgical practice.

Therefore, this study was to find and update sufficient evidence to support or refute routine PBD for PD patients with obstructive jaundice in clinical practice based on randomized and nonrandomized trials, as well as Chinese local relevant studies, to guide clinicians in their management of these patients.

METHODS

Search Strategy

Electronic databases including PubMed/MEDLINE, EMBASE Databases, Web of Science, the Cochrane library, Wanfang Data, CNKI database, and scholar.google.com were searched by using the keyword “preoperative biliary drainage” and “obstructive jaundice.” All the articles were published before March 2015. Reference lists of identified studies were scrutinized to reveal additional sources. This study was subject to approval by the Research Ethics Committee of Sun Yat-Sen Memorial Hospital.

Criteria for Study Selection

Studies were considered for inclusion based upon the following criteria: patients underwent PD with obstructive jaundice; studies with PBD and non-PBD groups; and studies with postoperative mortality and incidence of complications assessed. The main exclusion criteria were as follows: studies not in English or Chinese language; studies with unretrievable or unclear data; studies that were reviews, comments, or replies, and meta-analyses; studies that used duplicated data; and studies that contained <10 patients in either intervention arm.

Data Extraction

Data was extracted independently by 2 investigators. Discrepancies were resolved by consensus or a third author adjudication. The following data were abstracted from each study: study group, year, number of included patients, postoperative mortality, incidence of postoperative complication, infectious complication, wound infection, IAA, sepsis, delayed gastric emptying (DGE), pancreatic leakage, biliary leakage, and hemorrhage.

Statistical Analysis

We conducted this meta-analysis in line with the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.²⁰ Treatment effects of the measures are represented as the odds ratio (OR) with 95% confidence interval (CI) for binary variables. The Mantel–Haenszel method was used to combine the OR for the outcomes of interest. The presence of heterogeneity across trials was assessed using a standard χ^2 test with the level of significance set at $P < 0.05$ and also evaluated via I^2 statistic with the level of significance set at $I^2 > 30\%$. If heterogeneity was present, a random-effects model was used for meta-analysis. If heterogeneity was not present, the fixed-effect model was applied instead. Furthermore, stratified analysis was conducted based on the study design. The OR, its 95% CI, and heterogeneity of either subgroup were calculated respectively. The subgroup differences were assessed and a

$P < 0.05$ was considered representative of statistical significance. In addition, we conducted sensitivity analyses between RCTs, prospective studies, and retrospective studies. Public bias was assessed by visual inspection of a funnel plot. All statistical analyses were performed with the Review Manager Version 5.2 (Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

Study Selection

A total of 372 studies were retrieved from PubMed/MEDLINE, EMBASE Databases, Web of Science, the Cochrane library, Wanfang Data, CNKI database, and scholar.google.com. After the duplicates were identified and excluded, 270 studies were left. Then, we also excluded the articles not written in English or Chinese, reviews comments, or replies, and meta-analyses, leaving 100 studies that were found to be relevant were closely reviewed. At last a total of 44 studies were included and analyzed (Figure 1), including 8 RCTs,^{10,21–27} 13 prospective studies,^{6,12,13,28–37} 20 retrospective studies,^{8,38–56} and 3 Chinese local retrospective studies^{57–59} with 6286 patients. Among 8 RCTs, only 1 RCT in 2010 detected specifically the incidence of different postoperative complications. The results of meta-analyses are summarized in Table 1. Two reviewers achieved complete consensus in applying the eligibility criteria.

Mortality

Twenty-nine trials, including 8 RCTs, reported the incidence of postoperative overall mortality. In a pooled analysis of all studies, there was no significant difference between the PBD and non-PBD groups for mortality. In general, it occurred in 99 patients (5.22%, 99/1898) in the PBD group and 95

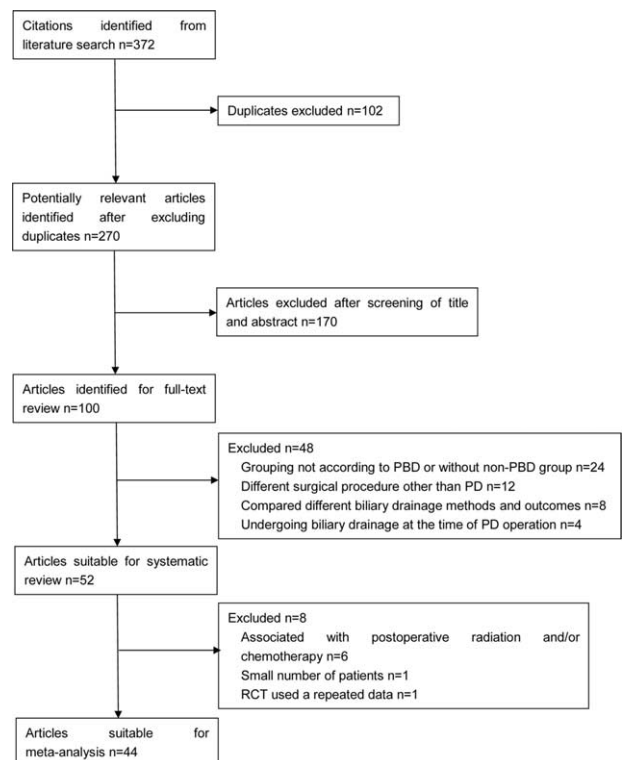


FIGURE 1. Flow chart showing literature search strategies.

TABLE 1. Summary of Pooled Odds Ratios in the Meta-Analysis

Outcome	No. of Studies	Positive Proportion		Test for Association		
		PBD	Non-PBD	Pooled Odds Ratio	Z	P
Mortality	29	99/1898	95/1848	1.03 (0.76, 1.38)	0.17	0.86
Morbidity	33	1176/2417	1029/2178	0.99 (0.81, 1.22)	0.07	0.94
Infectious complication	15	381/1132	280/1120	1.52 (1.07, 2.17)	2.35	0.02
Wound infection	19	264/1676	145/1548	2.09 (1.39, 3.13)	3.57	0.0004
IAA	13	106/1243	90/1005	0.96 (0.57, 1.64)	0.14	0.89
Sepsis	7	50/496	36/513	1.70 (0.75, 3.85)	1.27	0.20
DGE	17	193/1353	167/1436	1.37 (1.08, 1.73)	2.60	0.009
Pancreatic leakage	24	225/1929	228/2076	1.07 (0.80, 1.44)	0.45	0.65
Biliary leakage	14	37/1185	56/1283	0.76 (0.50, 1.17)	1.23	0.22
Hemorrhage	19	123/1534	155/1716	0.88 (0.68, 1.14)	0.98	0.33

DGE = delayed gastric emptying, IAA = intra-abdominal abscess, PBD = preoperative biliary drainage.

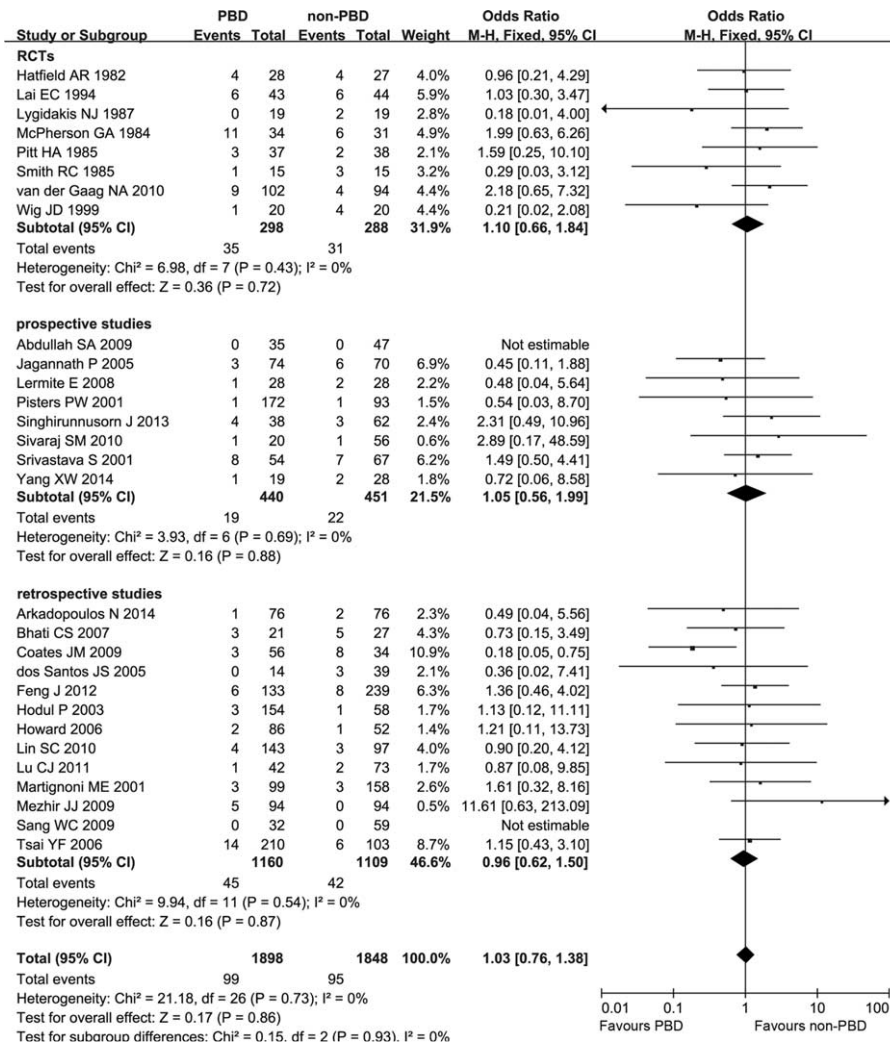


FIGURE 2. Meta-analysis of postoperative mortality with PBD versus non-PBD. A Mantel-Haenszel method was used for meta-analysis. Odds ratios are shown with 95% CI. CI = confidence interval, PBD = preoperative biliary drainage.

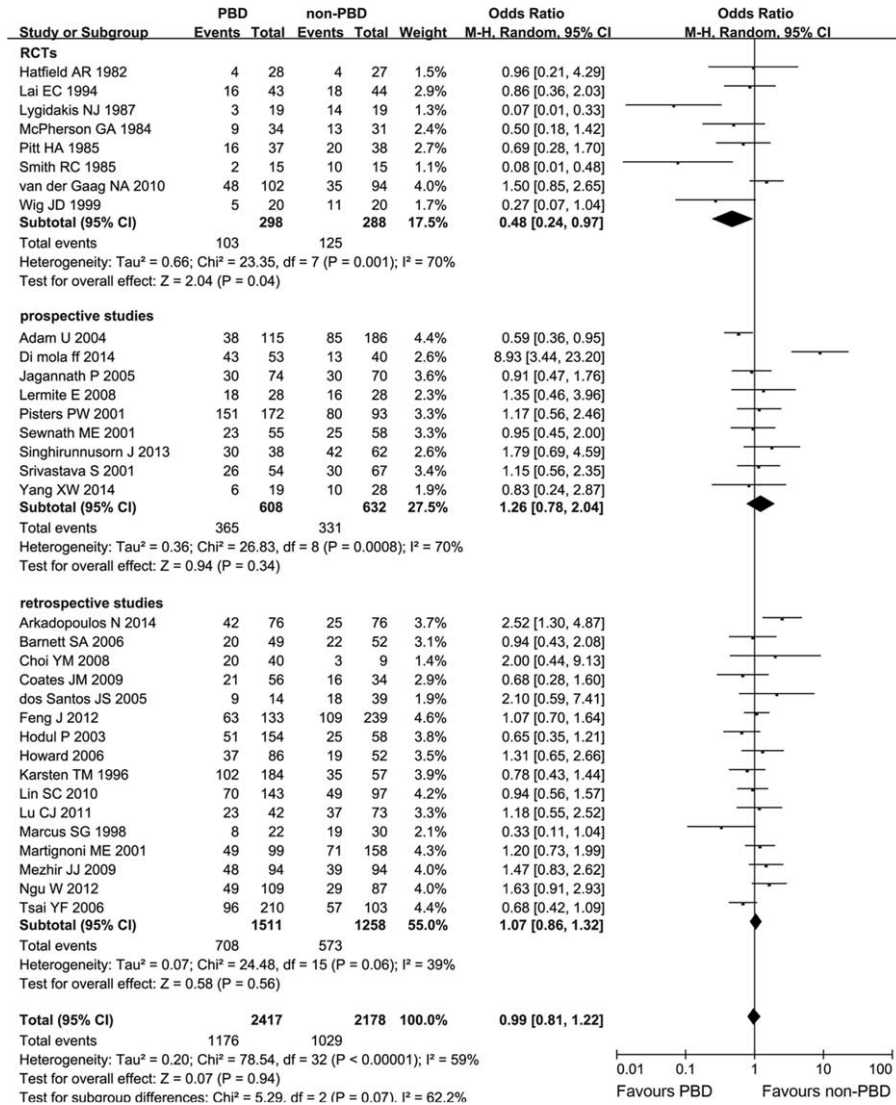


FIGURE 3. Meta-analysis of postoperative morbidity with PBD versus non-PBD. A Mantel–Haenszel method was used for meta-analysis. Odds ratios are shown with 95% CI. CI = confidence interval, PBD = preoperative biliary drainage.

patients (5.14%, 95/1848) in the non-PBD group (OR 1.03, CI 0.76 to 1.38; $P = 0.86$). Subgroup analysis by study design, RCTs (OR 1.10, CI 0.66 to 1.84; $P = 0.72$), prospective studies (OR 1.05, CI 0.56 to 1.99; $P = 0.88$), and retrospective studies (OR 0.96, CI 0.62 to 1.50; $P = 0.87$), yielded similar results (Figure 2). There was no significant heterogeneity for all studies ($I^2 = 0\%$, $P = 0.73$). The heterogeneity remains no significance for RCTs ($I^2 = 0\%$, $P = 0.43$), prospective studies ($I^2 = 0\%$, $P = 0.69$), and retrospective studies ($I^2 = 0\%$, $P = 0.54$). No subgroup difference between RCTs, prospective studies, and retrospective studies was observed ($P = 0.93$).

Morbidity

Thirty-three trials, including 8 RCTs, compared PBD with non-PBD and reported the incidence of postoperative complications. Overall, there was no statistically significant difference in morbidity rate between patients who had PBD compared with those who did not (1176/2417, 48.66% vs 1029/2178, 47.25%, respectively; OR 0.99, CI 0.81 to 1.22; $P = 0.94$). Subgroup

analysis by study design, RCTs yielded a trend toward reduced risk of morbidity in PBD group (OR 0.48, CI 0.24 to 0.97; $P = 0.04$), whereas prospective studies (OR 1.26, CI 0.78 to 2.04; $P = 0.34$) and retrospective studies (OR 1.07, CI 0.86 to 1.32; $P = 0.56$) did not yield similar results. There was significant heterogeneity for all studies ($I^2 = 59\%$, $P < 0.00001$). The heterogeneity remains significant for RCTs ($I^2 = 70\%$, $P = 0.001$), prospective studies ($I^2 = 70\%$, $P = 0.0008$), and retrospective studies ($I^2 = 39\%$, $P = 0.06$) (Figure 3). No subgroup difference between RCTs, prospective studies, and retrospective studies was observed ($P = 0.07$). And no obvious publication bias was found (Figure S1, <http://links.lww.com/MD/A340>).

Postoperative Infectious Complication

Fifteen trials with 2252 patients provided available data about the frequency of postoperative infectious complication. And no RCT was included. Heterogeneity between studies was assessed ($I^2 = 65\%$, $P = 0.0002$), and a random-effects model was applied. The weighted mean clinically relevant

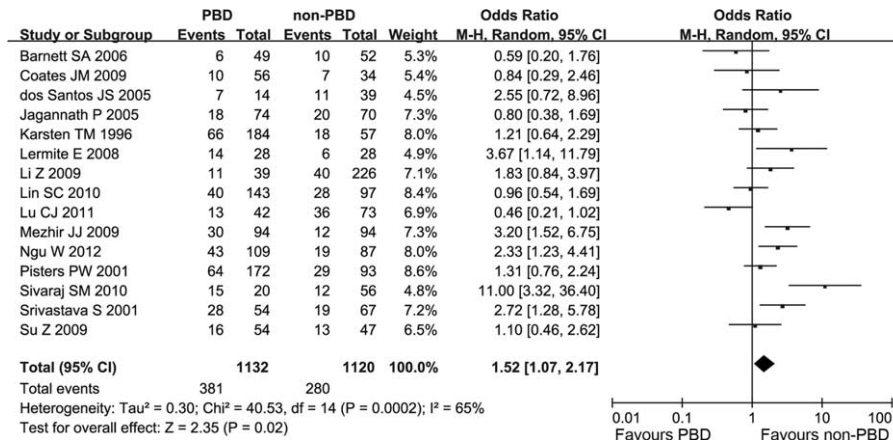


FIGURE 4. Meta-analysis of postoperative infectious complication with PBD versus non-PBD. A Mantel–Haenszel method was used for meta-analysis. Odds ratios are shown with 95% CI. CI = confidence interval, PBD = preoperative biliary drainage.

postoperative infection rate in the PBD group was 33.66% and that in the non-PBD group was 25%. A statistically significant difference was observed between the 2 groups in this meta-analysis (OR 1.52, CI 1.07 to 2.17; *P* = 0.02) (Figure 4).

Postoperative Wound Infection

Nineteen trials with 3224 patients comparing PBD with non-PBD showed that PBD had a significantly higher incidence of postoperative wound infection than non-PBD (15.75% vs 9.37%). Only 1 RCT was included. Heterogeneity was observed in this meta-analysis (*I*² = 60%, *P* = 0.0005). In a random-effects model, the difference was statistically significant, and the combined OR was 2.09 (CI 1.39 to 3.13; *P* = 0.0004) (Figure 5).

Postoperative Sepsis and Intra-Abdominal Abscess

Seven trials reported the incidence of postoperative sepsis. In general, it occurred in 50 patients (10.08%, 50/496) in the PBD group and 36 patients (7.02%, 36/513) in the non-PBD

group. Although there was a trend favoring the non-PBD group, no statistically significant difference was observed between the 2 groups in the meta-analysis (OR 1.70, CI 0.75 to 3.85; *P* = 0.20) (Figure S2, <http://links.lww.com/MD/A340>). Thirteen studies investigated the incidence of postoperative IAA, and only 1 RCT was included. Taking all the data together, the PBD group was associated with a minor trend toward a reduced risk of IAA (OR 0.96, CI 0.57 to 1.64; *P* = 0.89), although the difference was not statistically significant (Figure S3, <http://links.lww.com/MD/A340>).

Incidence of Postoperative DGE

The meta-analysis of 17 studies with 2789 patients comparing PBD with non-PBD showed that the PBD group had a significantly higher incidence of DGE than the non-PBD group (14.26% vs 11.63%). One RCT was included, and subgroup analysis in line with the study design was not carried out. Heterogeneity between studies was assessed (*I*² = 0%, *P* = 0.74). In a fixed-effect model, there was a significant between-group difference, and the combined OR was 1.37 (CI 1.08 to 1.73; *P* = 0.009) (Figure 6).

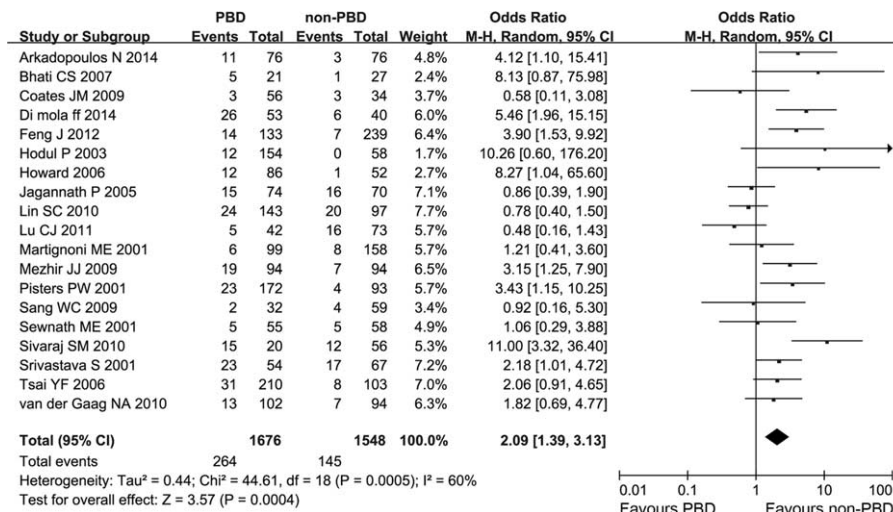


FIGURE 5. Meta-analysis of postoperative wound infection with PBD versus non-PBD. A Mantel–Haenszel method was used for meta-analysis. Odds ratios are shown with 95% CI. CI = confidence interval, PBD = preoperative biliary drainage.

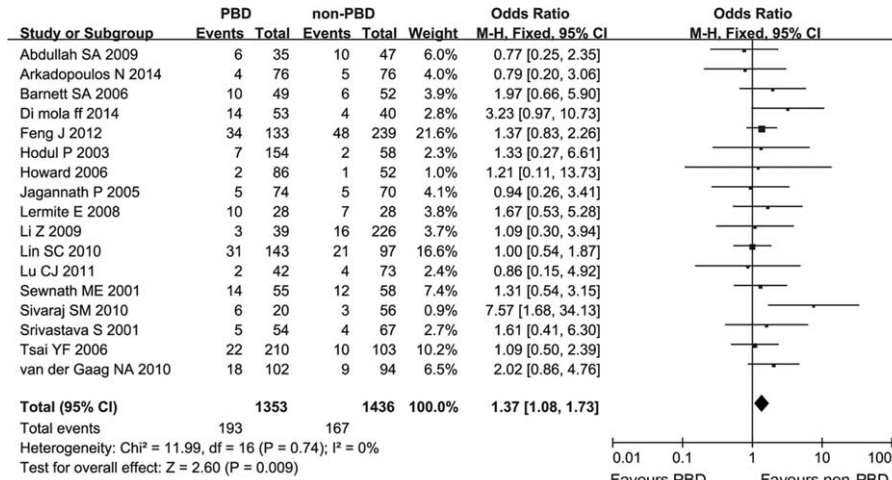


FIGURE 6. Meta-analysis of postoperative delayed gastric emptying with PBD versus non-PBD. A Mantel–Haenszel method was used for meta-analysis. Odds ratios are shown with 95% CI. CI = confidence interval, PBD = preoperative biliary drainage.

Pancreatic Leakage, Biliary Leakage, and Hemorrhage

Twenty-four studies provided data on PBD versus non-PBD for the incidence of postoperative pancreatic leakage. There was a moderate level of heterogeneity ($I^2 = 41\%$, $P = 0.02$). In the random-effects model, there was no statistically significant difference between these 2 groups (OR 1.07, CI 0.80 to 1.44; $P = 0.65$) (Figure S4, <http://links.lww.com/MD/A340>). The incidence of postoperative biliary leakage was reported in 14 studies. Rate of postoperative biliary leakage was not significantly different in PBD and non-PBD groups (3.12% vs 4.36%; OR 0.76, CI 0.50 to 1.17; $P = 0.22$) (Figure S5, <http://links.lww.com/MD/A340>). The incidence of postoperative hemorrhage was reported in 19 studies. Overall, there was no statistically significant difference in the risk of postoperative hemorrhage between patients who had PBD compared to those who did not (8.02% vs 9.03%; OR 0.88, CI 0.68 to 1.14; $P = 0.33$) (Figure S6, <http://links.lww.com/MD/A340>).

Sensitivity Analyses

As prospective and retrospective studies were pooled with the RCTs in the analysis of mortality and morbidity, sensitivity analysis to subtotal the plots by RCTs versus prospective studies versus retrospective studies was conducted, and no significant differences of OR between RCTs, and prospective and retrospective studies were detected (all $P > 0.05$; Figures 2 and 3).

DISCUSSION

PBD is generally performed for patients having jaundice with pancreatic head malignancy. Despite theoretical advantages, such as cholangitis, PBD remains controversial because it has not only failed to show a clinical benefit but also suggested an adverse impact on perioperative outcome. The major findings of this study were as follows: first, overall, PBD resulted in a significant increase in the risk of postoperative infectious complication, wound infection, and DGE compared with non-PBD. Second, in general, there were no between-group differences in terms of the risk of postoperative mortality, morbidity, IAA, sepsis, pancreatic leakage, biliary leakage, and hemorrhage. PBD was demonstrated to increase postoperative

infectious complications in the previous studies,^{31,38,44,60} which is consistent with our findings. Wound infection after surgery was defined as a culture-positive collection that resulted in a hospital stay of >2 weeks or as wound sepsis that required secondary suturing or refashioning. In the present study, the incidence of postoperative wound infection was significantly different in patients with or without PBD, and PBD probably increases the rates of postoperative wound infection by about 6%, which is consistent with other reports.^{8,12,13,27,30,34,36,39,44,51,57,60,61} DGE was defined as the need for nasogastric tube drainage for ≥ 7 days postoperatively or the need for reinsertion after removal. As demonstrated in our study, the incidence of postoperative DGE was increased in patients with PBD compared with those with immediate surgery. The underlying mechanism of DGE is still unclear, but many authors suggest that the local inflammation induced by the leaked pancreatic enzymes may play an important role.^{62,63}

However, 8 of the studies used in the meta-analysis were RCTs, and only 1 RCT in 2010 specifically detected the incidence of different postoperative complications. In order to define whether PBD was associated with increased specific postoperative complications, prospective and retrospective studies were included. Therefore, this must be considered as a weakness in this study. Second, RCTs were pooled with the prospective and retrospective studies in the analyses of mortality and morbidity. We conducted a sensitivity analysis to examine the effects of RCTs, and prospective and retrospective studies. There was no significant difference of OR between RCTs, and prospective and retrospective studies (Figures 2 and 3). So even for compiled retrospective studies, the same conclusion could be drawn. However, there was heterogeneity in the analysis of morbidity, and RCTs yielded a reduced risk of morbidity in PBD group, which is in conflict with the prospective and retrospective studies (Figure 3). This result may be because of the lack of accurate definition and classification of morbidity in the included trials. In addition, mainly because of different study design, RCTs have ruled out many confounding factors, which are different from prospective and retrospective studies. The results were not adjusted for the presence of confounding, which potentially led to biased estimates. Therefore, further studies were required to clarify this issue.

It is unclear what factors in PBD affect the incidence of postoperative complications after PD. The short duration of PBD might be the reason for its failure to benefit severely jaundiced patients in several studies. The optimal duration of biliary drainage before surgery has not been established. Even if the bilirubin level has decreased to normal levels, normal major synthetic and clearance functions of the liver, as well as mucosal intestinal barrier functions will be fully restored only after at least 4 to 6 weeks according to animal studies.^{3,64} However, whether this nearly complete restoration of liver function can be transformed into better clinical outcome after surgery has not been studied. In fact, in clinical practice, surgery is not usually delayed more than a few weeks except for patients with cholangitis, requiring extensive preoperative assessment (such as liver biopsy) or neoadjuvant treatments. In addition, prolonged PBD causes extensive inflammatory reaction in the bile duct wall leading to difficulties in the subsequent operations, increases the risk of stent-related complications, increases the chance of bacterial colonization of the biliary tree, and delays the definitive surgery.⁶⁵ It is possible that there may be an optimal duration of biliary drainage before surgery, wherein PBD may help reduce morbidity and mortality in those patients who are deeply jaundiced without increasing biliary drainage-related complication. More large-sized comparative studies are needed to answer this question.

Second, there may be a threshold of bilirubin wherein PBD helps to reduce morbidity and mortality of patients with jaundice,¹⁶ or the effect of PBD on postoperative morbidity and mortality may be associated with different bilirubin levels. In this study, such a subgroup analysis was not performed because of the data representation that was not sufficient. Therefore, subsequent studies should focus on the relationship between pre-drainage bilirubin level and patient's prognosis.

Third, another issue is the selection of internal or external drainage in PBD. Different drainage methods may affect the incidence of postoperative complications after PD. Kitahata et al⁶⁶ retrospectively reviewed a prospectively maintained database to assess the associations between biliary drainage-related complications and postoperative complications after PD between internal drainage and external drainage. Compared with external drainage, preoperative internal biliary drainage may increase the risk of postoperative complications. However, there are some drawbacks in external drainage, such as the drainage tube may be shifted or pulled out by patients, discomfort or esthetic issues because of the existence of nasopharynx tube in endoscopic nasobiliary drainage, and the invasiveness or seeding risk in percutaneous transhepatic biliary drainage. In addition, another problem is which kind of stents should be used in internal drainage, plastic or metallic stents. A few studies suggested that in patients awaiting PD, metallic stents have more advantages over plastic stents as for preoperative internal biliary drainage.⁶⁷⁻⁶⁹ Additional studies are required to figure out internal or external drainage, and specific approach for drainage is the optimum method for PBD.

To conclude, the present study suggests that PBD would not benefit patients and additionally it would increase postoperative infectious complications. PBD for PD patients with obstructive jaundice probably should not be routinely carried out. For those patients who can do immediate surgery, obstructive jaundice should not be the contraindication of PD, and immediate surgery is still the first choice. Moreover, PBD should not be performed only for the reason of preoperative biliary decompression, so as to delay surgery. However, a large multicenter RCT of PBD versus immediate surgery for PD

patients with obstructive jaundice is required to confirm the present study results and find out the reasons for the occurrence of postoperative complications in PBD.

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