Impact of Enhanced Recovery After Surgery on Postoperative Recovery for Pancreaticoduodenectomy: Pooled Analysis of Observational Study

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Purpose: To assess the impact of enhanced recovery after surgery (ERAS) protocols in pancreaticoduodenectomy.

Methods: Four databases were searched for studies describing ERAS program in patients undergoing pancreatic surgery published up to May 01, 2018. Primary outcomes were mortality, readmission, reoperation and postoperative complications. Secondary outcomes were the length of stay and cost.

Results: A total of 19 studies met inclusion and exclusion criteria and included 3,387 patients. Meta-analysis showed a decrease in pancreatic fistula (OR = 0.79, 95% CI: 0.67 to 0.95; $I^2 = 0\%$), infection (OR = 0.63, 95% CI: 0.50 to 0.78; $I^2 = 0\%$), especially incision infection (OR = 0.62, 95% CI: 0.42 to 0.91; $I^2 = 0\%$), and pulmonary infection (OR = 0.28, 95% CI: 0.12 to 0.66; $I^2 = 0\%$). Length-of-stay (MD: −3.89 days, 95% CI: −4.98 to −2.81; $I^2 = 78\%$) and cost were also significantly reduced. There was no significant increase in mortality, readmission, reoperation, or delayed gastric emptying.

Conclusion: This analysis revealed that using ERAS protocols in pancreatic resections may help decrease the incidence of pancreatic fistula and infections. Furthermore, ERAS also reduces length of stay and cost of care. This study provides evidence for the benefit of ERAS protocols.

Keywords: pancreaticoduodenectomy, enhanced recovery after surgery, mortality, postoperative complications, delayed gastric emptying

INTRODUCTION

The concept of enhanced recovery after surgery (ERAS) (1–3) was firstly applied in colorectal surgery and is increasingly applied to other surgical fields, such as gastric (4) and orthopedic (5) surgeries. In 2013, guidelines for perioperative care for pancreaticoduodenectomy (PD) were published by the European Society for Clinical Nutrition and Metabolism and the International Association for Surgical Metabolism and Nutrition; these guidelines contain 27 care items and

change to three aspects; preoperation, intraoperation, and postoperation (6). The purpose of these changes was to reduce patients' stress responses and time-to-recovery by close cooperation between surgeons, anesthesiologists, intensive care workers and nurses (7).

At present, pancreaticoduodenectomy is one of the major treatments for malignancies such as pancreatic cancer, periampullary cancer and endocrine neoplasm (8). PD is a technically complex and subtle operation, which has been performed with increasing frequency and decreased mortality rates (9) using ERAS protocols over the past few years. However, morbidity rates have remained high (30–60%) (10). Four meta-analyses confirmed that ERAS can reduce length-of-stay (LOS) and hospital costs; one meta-analysis published in 2013 (11) indicated that the incidence of delayed gastric emptying (DGE) and pancreatic fistula (PF) did not differ significantly between groups, whereas the other three, published in 2015 (12), 2016 (13), and 2018 (14) found that the incidence of DGE was lower in the ERAS groups. In a study from 2015, additional outcome measures were used, and postoperative complication rate and mortality, were reduced in the ERAS groups. Another article published in 2018 (14) mentioned that ERAS has a lower incidence of the mild complications, and abdominal infection. Therefore, ERAS programs in patients undergoing PD have not been completely analyzed, and the use of various outcome measures in different studies increases the difficulty of comparison.

To solve this problem, we need to clarify the real impact of ERAS protocols in this study. The purpose of this meta-analysis was to evaluate the influence of ERAS programs for patients undergoing PD and to provide information for establishing reliable predictions for clinical treatment outcomes.

METHODS

Selection of Studies
Our search used the guidelines of Preferred Reporting Items for Meta-analysis (15). We obtained a list of eligible studies from the following databases: Ovid MEDLINE, OVID EMBase, the Cochrane Library, and ISIWeb of Science, published in English up to May 01, 2018. The search strategy is shown in **Supplemental Method 1**.

Inclusion and Exclusion Criteria
Studies were included in the meta-analysis if the following criteria were met: studies that involved patients undergoing PD, pylorus-preserving pancreatoduodenectomy (PPPD), pancreaticojejunostomy, proximal pancreatic resection, or distal pancreatectomy, approached either with open or minimally invasive surgery; studies that included both an ERAS group and a conventional group, treated by ERAS protocols and conventional care, respectively; studies that reported outcomes such as mortality (in-hospital death, irrespective of duration of stay, or death occurring within 30 days of discharge), reoperation and hospital readmission, various types of fistula such as pancreatic fistula (16) [PF, according to the International Study Group on Pancreatic Fistula (ISGPF), defined as any measurable

amount of drainage fluid, with amylase three times the normal level, on or after postoperative day 3], anastomosis leakage, biliary fistula, chylous fistula, intestinal fistula, different types of infections, DGE (17) (need for nasogastric decompression or vomiting occurring), length of hospital stay (LOS) including the postoperative LOS and total LOS and/or costs. Primary outcome measures were mortality, reoperation, readmission, and postoperative complications; complications mainly cover fistula, infection, and DGE. Other outcomes were seen as secondary outcome. The type of study design was observational study.

Studies meeting any of the following selection criteria were excluded: (1) the language is not English, (2) repetitive studies, (3) unobtainable source literature or original data cannot be obtained from the literature, (4) emergency operations, and (5) total pancreatectomy.

Data Extraction and Quality Assessment
Relative data were extracted by two independent authors (Cao and Huang) with a unified standard. Differences or contradictions between the authors were resolved by discussion or consultation of a third investigator (Gu). The extracted variables include country of author; publication year; study design; the age and gender of patients; follow-up time; operation; LOS; mortality; readmission and complications, including fistula, infection, and DGE. Hospital costs were also extracted from the articles, if possible. Methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS) (18, 19) with eight items. A study can be rewarded a maximum of nine stars, with a maximum of two stars for Comparability and one star for each numbered item within the Selection and Exposure categories. More than six stars indicate a study of high quality.

Assessment of Bias
Identified studies were roughly divided into 2 types, either cohort studies or case-control studies, and were assessed using the NOS with the accompanying coding manual for bias. Two authors (Cao and Huang) were independently responsible for assessment of bias.

Statistical Analysis
Meta-analysis was conducted by using the R Programming Language. Dichotomous variables mainly used odds ratio (OR) for mortality, reoperation, readmission, various fistula, infection, and DGE and 95% confidence intervals (CI) obtained by standard technique (20). Mean difference (MD) and standard deviation were calculated for continuous variables. The results were presented graphically using forest plots. Heterogeneity (21) of the included results was detected by I^2. If $I^2 \geq 40\%$, we chose the random effect model, else we selected the fixed effect model. The I^2 statistics represents the amount of variability in the meta-analysis attributed to study heterogeneity. All analyses were conducted with a significance level of 0.05 (22). To determine the source of heterogeneity, results of fistula, infection, DGE, and LOS were analyzed by subgroup; fistula and infection were classified according to type, DGE was divided according to severity, and LOS was divided into preoperative and total time, which can determine the source of heterogeneity.

FIGURE 1 | Meta-Analyses (PRISMA) flow diagram depicting the process of identification and inclusion of selected studies.
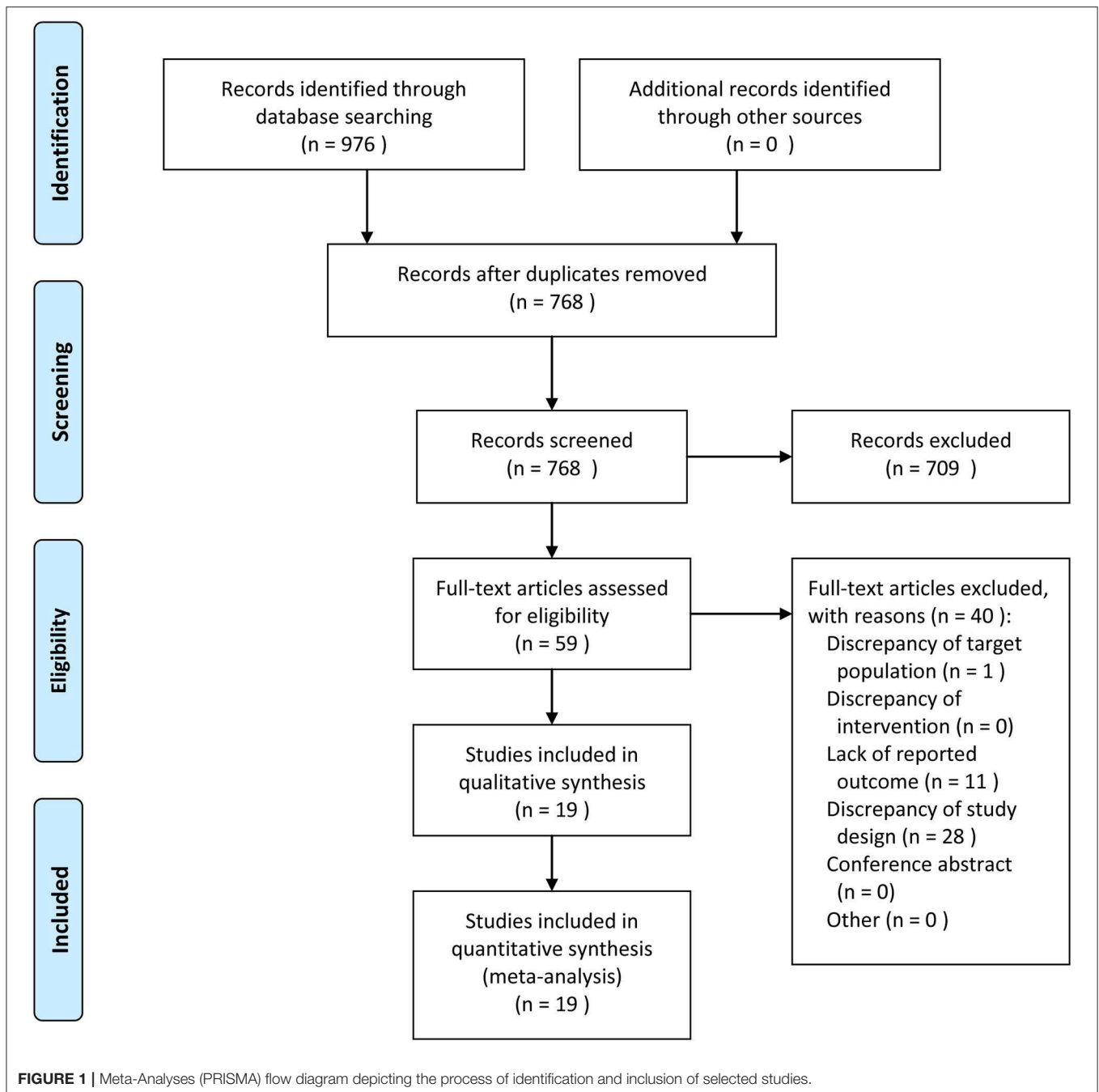
RESULTS

Literature Identification

The flow of study identification and inclusion is shown in **Figure 1**. The initial search resulted in 976 abstracts. After removing 208 duplicate studies, 768 potentially relevant studies were selected on the basis of the abstract. Then, 709 studies were further excluded on the basis of the abstract, and the full texts of the remaining 59 articles were assessed for eligibility. An additional 40 articles (**Supplemental Table 1**) were excluded. Finally, 19 articles were included in this study.

Study Characteristics

The characteristics of the 19 included articles, which comprised 7 cohort studies (8, 23–28) and 12 case-control studies (7, 29–39), are shown in **Table 1**, which totally contains 3387 patients. Thirteen studies (8, 23, 26, 28–34, 37–39) included patients undergoing PD, one study (35) included patients undergoing distal pancreatectomy (DP), one study (25) included patients undergoing proximal pancreatic resection, one study (36) included patients undergoing laparoscopic pancreatoduodenectomy (LDP), and three studies (7, 24, 27) included patients undergoing two forms of pancreatectomy.

TABLE 1 | Study characteristics.

References	Study design	Group	Age (years)	Male/female	Operations	Follow-up time (months)	Sample size	Country
Balzano et al. (23)	Cohort study	ERAS	64.3 ± 13.75	155/97	PD	36	252	England
		CPC	62.9 ± 14.5	148/104	PD	48	252	
French et al. (25)	Cohort study	ERAS	53.8 ± 11.6	NA	PPR	18	9	England
		CPC	66.2 ± 10.3	NA	PPR	18	49	
Abu Hilal et al. (29)	Case-control	ERAS	68.5 ± 5.58	10/10	PD	15	20	England
		CPC	68.92 ± 11.97	10/14	PD	15	24	
Nikfarjam et al. (33)	Case-control	ERAS	65.5 ± 9	13/7	PD	88	20	Australia
		CPC	55 ± 16.5	12/9	PD	88	21	
Braga et al. (31)	Case-control	ERAS	69 ± 2.17	66/49	PD	26	115	Italy
		CPC	69 ± 2.17	66/49	PD	33	115	
Coolsen et al. (7)	Case-control	ERAS	67 ± 11	44/42	PD/PPPD	24	86	Netherlands
		CPC	62 ± 13	58/39	PD/PPPD	120	97	
Kobayashi et al. (32)	Case-control	ERAS	67.5 ± 10.7	61/39	PD	36	100	Japan
		CPC	65.4 ± 10.8	62/28	PD	48	90	
Pillai et al. (8)	Cohort study	ERAS	44.2 ± 15.9	9/11	PD	8	20	India
		CPC	47.6 ± 12.0	10/10	PD	NA	20	
Williamsson et al. (38)	Case-control	ERAS	69 ± 16.25	31/19	PD	NA	50	Sweden
		CPC	67 ± 14	26/24	PD	36	50	
Richardson et al. (36)	Case-control	ERAS	63.41 ± 12.68	9/13	LDP	19	22	England
		CPC	56.81 ± 22.22	20/24	LDP	48	44	
Shao et al. (27)	Cohort study	ERAS	56.96 ± 11.50	194/131	PD/PPPD	24	325	China
		CPC	57.05 ± 12.30	184/126	PD/PPPD	24	310	
Zouros et al. (39)	Case-control	ERAS	65.9 ± 10.5	46/29	PD	48	75	Greece
		CPC	63.9 ± 11.6	34/16	PD	48	50	
Shah et al. (37)	Case-control	ERAS	61.9 ± 9.1	84/58	PD	50	142	India
		CPC	59.1 ± 10.4	30/16	PD	28	46	
Partelli et al. (34)	Case-control	ERAS	77.75 ± 1.75	14/8	PD	NA	22	Italy
		CPC	78 ± 1.75	33/33	PD	NA	66	
Bai et al. (30)	Case-control	ERAS	58 ± 13	69/55	PD	15	124	China
		CPC	57 ± 12	37/26	PD	9	63	
Dai et al. (24)	Cohort study	ERAS	58.5 ± 12.75	34/34	PD/PPPD	28	68	China
		CPC	58.2 ± 11.5	51/47	PD/PPPD	28	98	
van der Kolk et al. (28)	Cohort study	ERAS	64.59 ± 12.04	56/39	PD	24	95	Netherlands
		CPC	65.29 ± 10.67	35/13	PD	36	52	
Pecorelli et al. (35)	Case-control	ERAS	62.4 ± 13.4	49/51	DP	48	100	Italy
		CPC	60.4 ± 13.8	44/56	DP	48	100	
Kagedan et al. (26)	Cohort study	ERAS	65 ± 13.51	74/47	PD	12	121	Canada
		CPC	65.85 ± 12.10	31/43	PD	18	74	

ERAS, Enhanced Recovery after Surgery; CPC, conventional perioperative care; PD, Pancreaticoduodenectomy; PPR, proximal pancreatic resection; PPPD, pylorus-preserving pancreatoduodenectomy; DP, Distal pancreatoduodenectomy. Values of Age are mean ± SD.

ERAS Characteristics

Characteristics of these studies are shown in **Table 2**. The most common ERAS interventions in the studies were preoperative counseling, antimicrobial prophylaxis and skin preparation, epidural analgesia, postoperative artificial nutrition, and early and scheduled mobilization. That was followed by anti-thrombotic prophylaxis, postoperative nausea and vomiting (PONV) and avoiding hypothermia. However, none of the

studies reported on perioperative biliary drainage, preoperative smoking, wound catheters or transversus abdominis plane block, alcohol consumption, or somatostatin analogs.

Quality Assessment of Included Studies

Cohort and case-control studies were both evaluated for bias based on the New-castle-Ottawa Scale (**Supplemental Tables 2**, **3**). Among cohort studies, six studies received more than six stars,

TABLE 2 | ERAS characteristics.

References	Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
																				Enhanced recovery after surgery/Conventional perioperative care interventions							
Balzano et al. (23)	ERAS	√								√	√	√	√		√					√						√	√
	CPC									√	√	√	√		√												
French et al. (25)	ERAS																										
	CPC																										
Abu Hilal et al. (29)	ERAS				√						√				√		√			√						√	√
	CPC				√						√	√			√		√			√							
Nikfarjam et al. (33)	ERAS	√			√			√		√	√		√		√			√	√	√					√	√	√
	CPC							√		√	√															√	√
Braga et al. (31)	ERAS	√			√	√	√	√	√	√	√	√			√		√		√	√						√	√
	CPC	√			√	√		√		√	√	√					√		√	√						√	√
Coolsen et al. (7)	ERAS	√			√				√											√							
	CPC																										
Kobayashi et al. (32)	ERAS	√			√		√	√			√	√			√					√						√	√
	CPC							√			√	√			√												
Pillai et al. (8)	ERAS	√								√		√	√		√			√	√							√	√
	CPC									√		√						√								√	
Williamsson et al. (38)	ERAS	√			√					√	√		√		√				√	√	√				√	√	√
	CPC	√						√			√		√		√												
Richardson et al. (36)	ERAS							√											√		√		√			√	√
	CPC				√																					√	
Shao et al. (27)	ERAS											√														√	
	CPC										√																
Zouros et al. (39)	ERAS	√					√	√	√	√	√	√	√				√			√			√		√	√	√
	CPC																										
Shah et al. (37)	ERAS	√								√	√		√										√			√	√
	CPC																										
Partelli et al. (34)	ERAS	√					√		√	√	√	√					√	√		√		√				√	√
	CPC								√	√	√		√				√	√									√
Bai et al. (30)	ERAS	√					√			√	√	√			√								√				
	CPC	√									√		√		√												
Dai et al. (24)	ERAS	√					√			√	√						√			√			√			√	√
	CPC	√									√	√					√						√				
van der Kolk et al. (28)	ERAS	√			√					√	√	√					√	√	√								√
	CPC	√			√					√	√	√					√										√
Pecorelli et al. (35)	ERAS	√					√		√	√	√	√			√		√	√		√			√			√	√
	CPC	√								√	√	√					√	√								√	
Kagedan et al. (26)	ERAS	√			√							√						√	√	√						√	√
	CPC																										

ERAS, Enhanced Recovery after Surgery; CPC, conventional perioperative care; Items of Enhanced Recovery After Surgery/Fast-Track Surgery Interventions: 1 = Preoperative counseling, 2 = Perioperative biliary drainage, 3 = Preoperative smoking and alcohol consumption, 4 = Preoperative nutrition, 5 = Perioperative oral immunonutrition (IN), 6 = Oral bowel preparation, 7 = Preoperative fasting and preoperative treatment with carbohydrates, 8 = Preanaesthetic medication, 9 = Anti-thrombotic prophylaxis, 10 = Antimicrobial prophylaxis and skin preparation, 11 = Epidural analgesia, 12 = Intravenous analgesia Some evidence, 13 = Wound catheters and transversus abdominis plane block, 14 = Postoperative nausea and vomiting (PONV), 15 = Incision, 16 = Avoiding hypothermia, 17 = Postoperative glycaemic control, 18 = Nasogastric intubation, 19 = Fluid balance, 20 = Perianastomotic drain, 21 = Somatostatin analogs, 22 = Urinary drainage, 23 = Delayed gastric emptying, 24 = Stimulation of bowel movement, 25 = Postoperative artificial nutrition, 26 = Early and scheduled mobilization.

while the remaining study (25) received six stars. Among case-control studies, most articles obtained at least six stars, and only two articles received fewer than six stars. Therefore, most of the studies considered for this meta-analysis were of high quality.

Primary Outcome Measures

Fistula

Our results illustrate the incidence of complications comparing a multimodal ERAS protocol to conventional care. ERAS is associated with a decreased incidence of PF [**Figure 2**; number of comparisons reporting outcome ($n = 16$; OR = 0.79; 95% CI: 0.67–0.95; P for heterogeneity = 0.50, $I^2 = 0\%$)]. However, subgroup analysis of studies for other fistulas showed that the ERAS group did not differ significantly from the control group in the incidence of anastomosis leakage ($n = 1$; OR = 0.96; 95% CI: 0.31–2.99; heterogeneity is not applicable), biliary fistula ($n = 7$; OR = 1.16; 95% CI: 0.69 to 1.97; P for heterogeneity = 0.45, $I^2 = 0\%$), chylous fistula ($n = 3$; OR = 0.91; 95% CI: 0.56 to 1.46; P for heterogeneity = 0.37, $I^2 = 0\%$) and intestinal fistula ($n = 1$; OR = 0.50; 95% CI: 0.03 to 8.19; heterogeneity is not applicable). Sensitive analysis of the quality of the article was performed after removing two articles with less than six stars, and the conclusion is the same as before ($n = 14$; OR = 0.84; 95% CI: 0.72 to 0.98; P for heterogeneity = 0.51, $I^2 = 0\%$).

Infection

Compared to the control group, the incidence of infection (**Figure 3**; OR = 0.63; 95% CI: 0.50 to 0.78) was lower in the ERAS group. Different types of infections were mentioned in the studies, and the data for each infection are different. ERAS was associated with a lower incidence of incision infection ($n = 9$; OR = 0.62; 95% CI: 0.42 to 0.91) and pulmonary infection ($n = 4$; OR = 0.28; 95% CI: 0.12 to 0.66), but there were no significant differences in abdominal infection ($n = 3$; OR = 0.72; 95% CI: 0.52 to 1.00) and urinary infection ($n = 3$; OR = 0.46; 95% CI: 0.14 to 1.49) between the experimental group and the control group. No heterogeneity was found in this subgroup analysis ($I^2 = 0\%$, $P = 0.86$).

Sensitive analysis of the quality of the article was performed after removing two articles with less than six stars, and the conclusion is the same as before ($n = 14$; OR = 0.84; 95% CI: 0.72 to 0.98; P for heterogeneity = 0.51, $I^2 = 0\%$).

Delayed Gastric Emptying

Differences in the rates of DGE (**Figure 4**) were not consistently reduced in the ERAS group. There was also no significant difference between the control group and the experimental group in different grades of DGE. Five studies (7, 8, 24, 38, 39) reported DGE grade A (OR = 0.54; 95% CI: 0.18 to 1.67; $I^2 = 76\%$, $p < 0.01$), grade B (OR = 0.67; 95% CI: 0.37 to 1.20; $I^2 = 0\%$, $p = 0.45$), and grade C (OR = 0.66; 95% CI: 0.35 to 1.24; $I^2 = 33\%$, $p = 0.20$). There was moderate heterogeneity in this subgroup analysis ($I^2 = 46\%$, $p = 0.03$) using the random effects model.

Mortality

Sixteen studies (7, 8, 23–25, 28–32, 34–39) reported mortality as the primary outcome (**Figure 5**). The OR for mortality was 0.96

(95% CI: 0.59 to 1.55). Compared with the control group, the risk of mortality in the ERAS group was not significantly different. The heterogeneity determination of these studies using the fixed effect model was $I^2 = 0\%$, $P = 0.99$; therefore, no heterogeneity was found. After eliminating two articles with less than six stars in their quality scores, the result is as follows: OR = 0.94; 95% CI: 0.58 to 1.55; P for heterogeneity = 0.97, $I^2 = 0\%$.

Readmission

The primary outcome measure readmission (**Figure 6**) was also used in 16 studies (7, 23, 24, 26–37, 39). No significant difference from the control group was found when evaluating the combination of all included studies (OR = 1.02; 95% CI: 0.80 to 1.28). No heterogeneity ($I^2 = 0\%$, P for heterogeneity = 0.86) using the fixed effect model was detected. After eliminating two articles with less than six stars in their quality scores, the result is as follows: OR = 1.03, 95% CI: 0.82 to 1.31; P for heterogeneity = 0.85, $I^2 = 0\%$.

Reoperation

Reoperation data were shown in 8 studies (7, 23, 24, 28–31, 39). We found no evidence that reoperation (**Figure 7**) performed significantly differently between the two groups in the fixed effect model (OR = 0.82; 95% CI: 0.55 to 1.21). No heterogeneity ($I^2 = 0$; $p = 0.80$) was detected.

Secondary Outcome Measures

All studies reported the secondary outcome: LOS (MD = −3.89; 95% CI: −4.98 to −2.81; $I^2 = 78\%$, $p < 0.01$; **Figure 8**). Meta-analysis including 1,087 patients showed that patients in the ERAS group had a shorter postoperative LOS than those in the conventional group (MD = −4.60 days; 95% CI: −5.85 to −3.36), although a moderate degree of heterogeneity was observed ($I^2 = 55\%$, $P = 0.02$). Ten studies (7, 24–26, 28, 31, 34, 35, 37, 39) provided the data total LOS. The estimated mean for the meta-analysis of these studies was −3.12 days (95% CI: −4.81 to −1.42), indicating a significant reduction in the mean of total LOS for the ERAS patients compared with the conventional group. The statistical results of I^2 (83%) showed highly heterogeneous research results in forest plots. Hospitalization costs (**Figure 9**) were reported by five studies and statistical analysis showed that ERAS protocols significantly reduced costs. Only one of the articles showed a lower cost in the control group. Pancreatic surgery can cost up to tens of thousands of dollars and costs at least several thousand dollars.

DISCUSSION

Progress in surgical techniques, improvements in equipment, technology, anesthesia, and perioperative care have contributed significantly to reducing the mortality after pancreatoduodenectomy; in most high-volume centers, the mortality rate is <5% (9). While reducing mortality, the emphasis now is on strengthening rehabilitation and reducing complications (8). Complications are a major reason for longer LOS. Previous studies have shown that reducing complications can reduce LOS. Some controversies

Study	Experimental Events	Total	Control Events	Total	Odds Ratio	OR	95%−CI	Weight (fixed)	Weight (random)
anastomosis leakage									
Coolsen 2014	6	86	7	97		0.97	[0.33; 2.90]	1.8%	2.0%
Fixed effect model		86		97		0.96	[0.31; 2.99]	1.8%	−−
Random effects model						0.96	[0.31; 2.99]	−−	2.0%
Heterogeneity: not applicable									
biliary fistula									
Braga 2014	10	115	6	115		1.68	[0.61; 4.62]	1.6%	2.3%
Kobayashi 2014	4	100	2	90		1.65	[0.34; 7.96]	0.7%	1.0%
Zhuo 2015	4	325	5	310		0.78	[0.22; 2.73]	1.5%	1.5%
Zouros 2016	2	75	4	50		0.35	[0.07; 1.72]	1.4%	0.9%
Shah 2016	3	142	2	46		0.45	[0.09; 2.34]	1.0%	0.9%
Partelli 2016	6	22	9	66		2.38	[0.76; 7.44]	1.0%	1.8%
Xue 2016	4	124	2	63		0.92	[0.19; 4.44]	0.9%	1.0%
Fixed effect model		903		740		1.16	[0.69; 1.97]	8.2%	−−
Random effects model						1.18	[0.69; 2.01]	−−	9.4%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.45$									
chylous fistula									
Zhuo 2015	15	325	13	310		1.10	[0.52; 2.32]	3.7%	4.3%
Partelli 2016	0	22	9	66		0.13	[0.01; 2.41]	1.3%	0.3%
Xue 2016	35	124	18	63		0.98	[0.50; 1.90]	4.9%	5.4%
Fixed effect model		471		439		0.91	[0.56; 1.46]	9.9%	−−
Random effects model						0.97	[0.59; 1.58]	−−	10.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.37$									
intestinal fistula									
Xue 2016	1	124	1	63		0.51	[0.05; 4.97]	0.5%	0.5%
Fixed effect model		124		63		0.50	[0.03; 8.19]	0.5%	−−
Random effects model						0.50	[0.03; 8.19]	−−	0.5%
Heterogeneity: not applicable									
pancreatic fistula									
Balzano 2008	60	252	65	252		0.90	[0.60; 1.35]	13.9%	14.7%
Abu 2013	4	20	4	24		1.24	[0.29; 5.34]	0.9%	1.1%
Braga 2014	30	115	36	115		0.78	[0.44; 1.37]	7.5%	7.4%
Coolsen 2014	11	86	12	97		1.04	[0.44; 2.46]	2.8%	3.2%
Kobayashi 2014	9	100	25	90		0.27	[0.12; 0.60]	6.8%	3.6%
Pillai 2014	11	20	10	20		1.21	[0.36; 4.07]	1.3%	1.6%
Williamsson 2015	11	50	14	50		0.73	[0.30; 1.79]	3.1%	3.0%
Richardson 2015	3	22	8	44		0.77	[0.20; 3.01]	1.4%	1.3%
Zhuo 2015	53	325	56	310		0.88	[0.59; 1.33]	13.4%	14.2%
Zouros 2016	11	75	11	50		0.61	[0.25; 1.52]	3.2%	2.9%
Shah 2016	7	142	6	46		0.34	[0.11; 1.04]	2.6%	2.0%
Partelli 2016	4	22	21	66		0.51	[0.16; 1.63]	2.5%	1.8%
Xue 2016	39	124	18	63		1.14	[0.59; 2.20]	4.7%	5.5%
Jun 2017	28	68	44	98		0.86	[0.46; 1.60]	6.0%	6.2%
van 2017	12	95	5	52		1.29	[0.45; 3.75]	1.7%	2.1%
Pecorelli 2017	56	100	64	100		0.72	[0.41; 1.26]	7.9%	7.5%
Fixed effect model		1616		1477		0.79	[0.67; 0.95]	79.6%	−−
Random effects model						0.80	[0.67; 0.95]	−−	78.1%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.50$									
Fixed effect model		3200		2816		0.84	[0.72; 0.97]	100.0%	−−
Random effects model						0.84	[0.72; 0.99]	−−	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$									

0.01 0.1 1 10 100

FIGURE 2 | Forest plots demonstrating fistula of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

Study	Experimental		Control		Odds Ratio	OR	95%−CI	Weight (fixed)	Weight (random)
	Events	Total	Events	Total					
abdominal infection									
Balzano 2008	93	252	106	252		0.81	[0.56; 1.15]	35.3%	42.0%
Xueli Bai 2016	10	124	9	63		0.53	[0.21; 1.34]	6.1%	6.1%
Juntao Dai 2017	2	68	10	98		0.32	[0.08; 1.31]	4.4%	2.7%
Fixed effect model		444		413		0.72	[0.52; 1.00]	45.7%	−−
Random effects model						0.68	[0.44; 1.06]	−−	50.8%
Heterogeneity: I^2 = 15%, τ^2 = 0.0362, p = 0.31									
incision infection									
Braga 2014	7	115	12	115		0.57	[0.22; 1.47]	6.1%	6.0%
Kobayashi 2014	14	100	26	90		0.41	[0.20; 0.84]	12.6%	10.4%
C Williamsson 2015	8	50	11	50		0.69	[0.26; 1.84]	5.0%	5.5%
Richardson 2015	1	22	1	44		2.02	[0.20; 20.62]	0.5%	1.0%
Zhuo Shao 2015	1	325	2	310		0.57	[0.07; 4.34]	1.3%	1.3%
Zouros 2016	4	75	4	50		0.65	[0.17; 2.53]	2.7%	2.9%
J Shah 2016	10	142	3	46		0.98	[0.28; 3.46]	2.6%	3.4%
Juntao Dai 2017	4	68	9	98		0.66	[0.20; 2.11]	3.8%	3.9%
Pecorelli 2017	5	100	4	100		1.24	[0.34; 4.43]	2.2%	3.3%
Fixed effect model		997		903		0.62	[0.42; 0.91]	36.9%	−−
Random effects model						0.62	[0.42; 0.91]	−−	37.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86									
pulmonary infection									
Kobayashi 2014	1	100	2	90		0.53	[0.07; 4.12]	1.4%	1.3%
Zouros 2016	0	75	3	50		0.09	[0.00; 1.78]	2.2%	0.6%
Xueli Bai 2016	3	124	2	63		0.71	[0.14; 3.70]	1.7%	2.0%
Juntao Dai 2017	2	68	16	98		0.19	[0.05; 0.74]	6.9%	2.9%
Fixed effect model		367		301		0.28	[0.12; 0.66]	12.1%	−−
Random effects model						0.32	[0.13; 0.77]	−−	6.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.48									
urinary infection									
Braga 2014	1	115	2	115		0.59	[0.08; 4.58]	1.3%	1.3%
J Shah 2016	2	142	1	46		0.54	[0.07; 4.20]	1.2%	1.3%
Pecorelli 2017	2	100	5	100		0.44	[0.10; 2.02]	2.8%	2.3%
Fixed effect model		357		261		0.46	[0.14; 1.49]	5.3%	−−
Random effects model						0.47	[0.14; 1.53]	−−	4.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94									
Fixed effect model		**2165**		**1878**		**0.63**	**[0.50; 0.78]**	**100.0%**	**−−**
Random effects model						**0.64**	**[0.51; 0.81]**	**−−**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86									

0.01   0.1   1   10   100

FIGURE 3 | Forest plots demonstrating infection of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

regarding decreasing complications such as pancreatic fistula, infection and DGE using ERAS protocols after PD still persists.

A large number of data in this meta-analysis showed that ERAS and conventional groups did not significantly differ in the rates of mortality, reoperation, and readmission indicating that earlier discharge after implementation of the ERAS protocol did not affect patient morbidity (24). Most of the readmissions were due to complications, and slightly longer hospital stays can be greatly reduced (37). The results of this study suggest that the number of complications, such as PF and infection, can be safely decreased using ERAS protocols, especially with regard to incision and pulmonary infections. Reducing blood loss during surgery can reduce postoperative complications, especially suppurative infections (40). Because of the electronic laparoscopy used in some surgeries, the incision is smaller, the amount of bleeding is correspondingly reduced, and the chance of incision infection is greatly reduced. The reduction of pulmonary infection may be caused by early mobilization (41) and early removal of nasogastric tubes (42). In most surgeries,
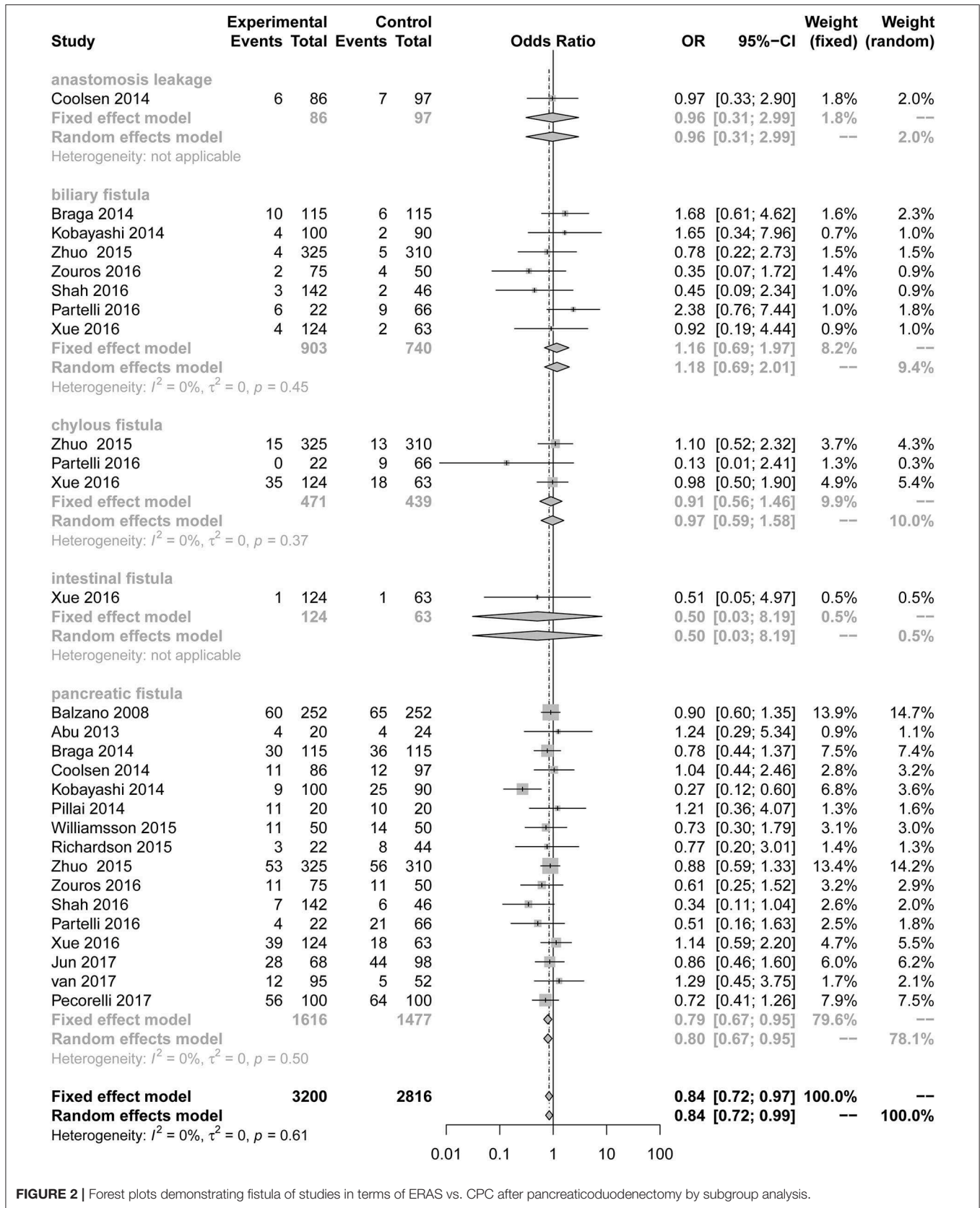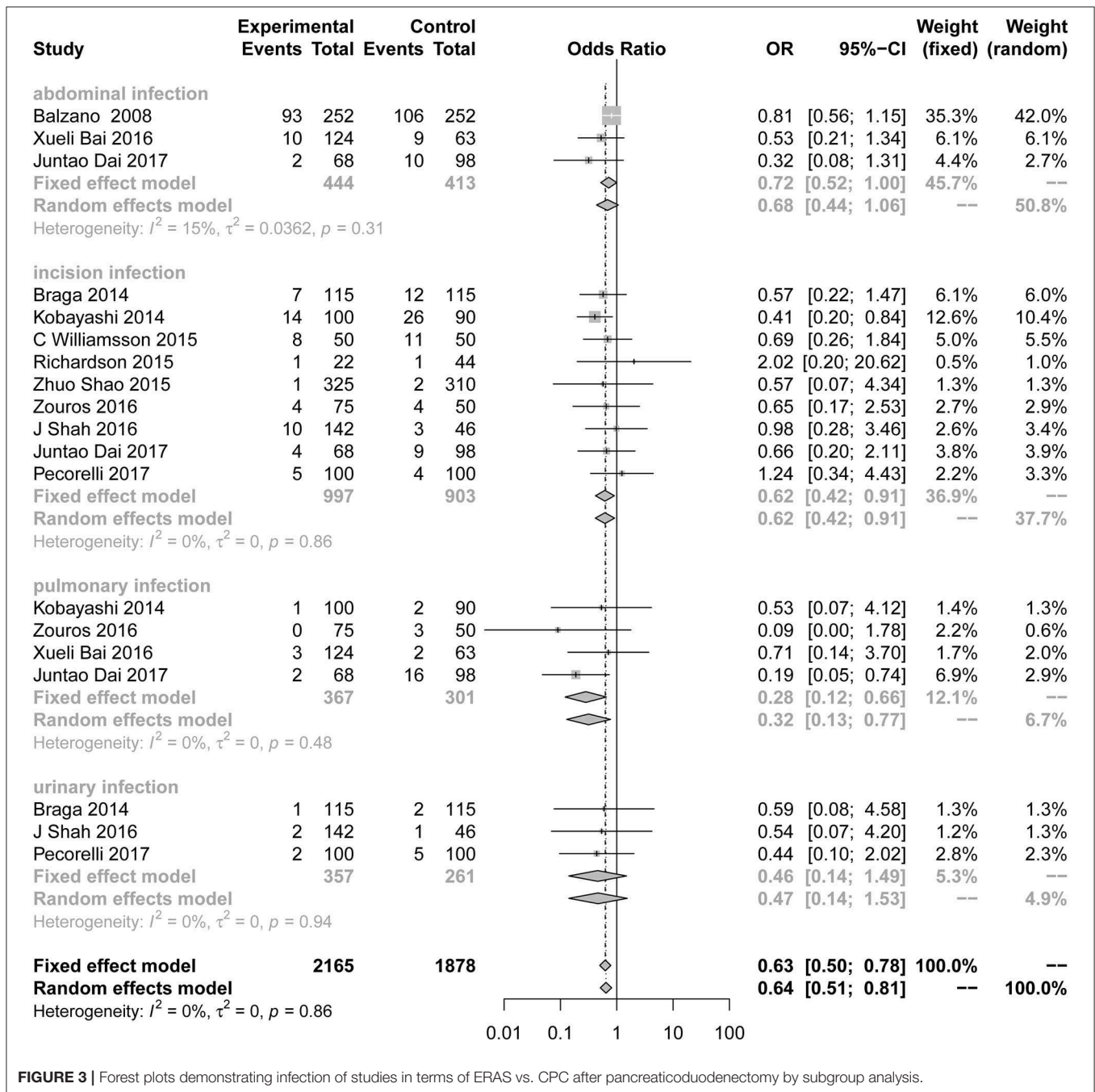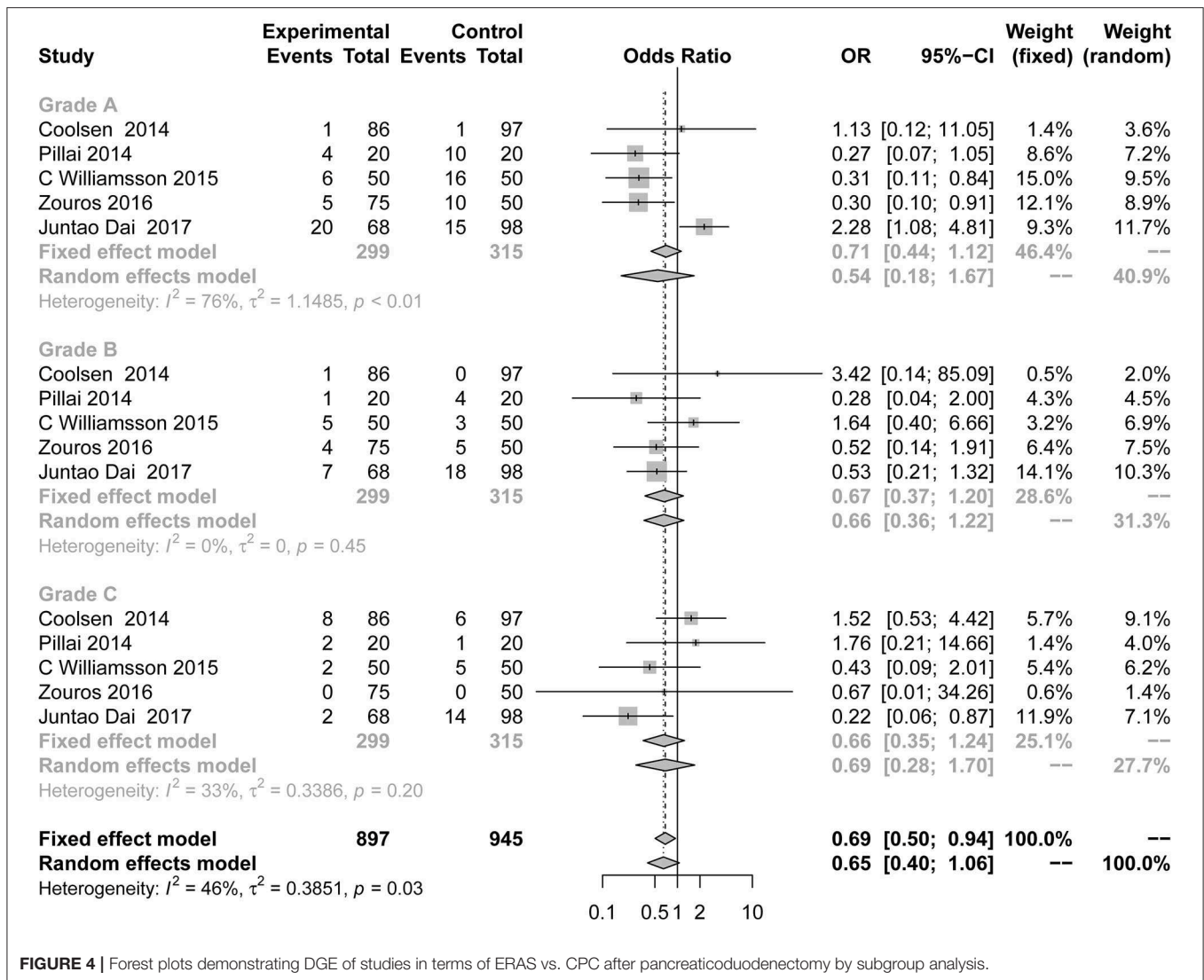
FIGURE 4 | Forest plots demonstrating DGE of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

the nasogastric tube was removed 1 day after placement to monitor hemorrhage in all types of anastomosis. Prolonged placement of the nasogastric tube can lead to fever, pneumonia and atelectasis (37). The reduction in these complications is desirable because they are the most common complications in patients undergoing PD and constitute the dominant reasons for prolonged LOS and high hospital costs (43). Other types of fistula after operation have been investigated in this meta-analysis, such as anastomotic fistula, biliary fistula, chylous fistula and intestinal fistula. Perhaps owing to the small sample size, no statistical significance could be found. One study suggested early post-operative feeding may improve gastric emptying and peristalsis in the intestine, thereby reducing DGE (44). A subgroup analysis of DGE showed no significant correlation with DGE grade, independent of utilization of the ERAS program. This finding indicated that heterogeneity of DGE was mainly derived from grade A, but such a result did not indicate a limitation of ERAS.

Regarding secondary outcome measures, ERAS programs are associated with shorter LOS, both in the postoperative LOS and total LOS. From a patient perspective, the reduction in postoperative LOS is associated with reduced DGE rates and an earlier return to normal nutrition and enteric function, as well as lower levels of pain and a quicker return to preoperative levels of mobility, resulting in an overall improvement in the postoperative experience. One of the determining factors is the healthcare system depending on different cultural and economic environments. The variable may contribute to the higher heterogeneity observed in our analysis, which was different when analyzing only studies from western centers or Asian countries (13). Some of the reduced LOS is not just improvement of the hospital medical equipment, but includes the patients without the complications (39). The use of laparoscopic technique can make time shorter during operations (27). This result is consistent with a meta-analysis of pancreaticoduodenectomy showing a reduction in the LOS with 4 days (13). Hospitalization costs
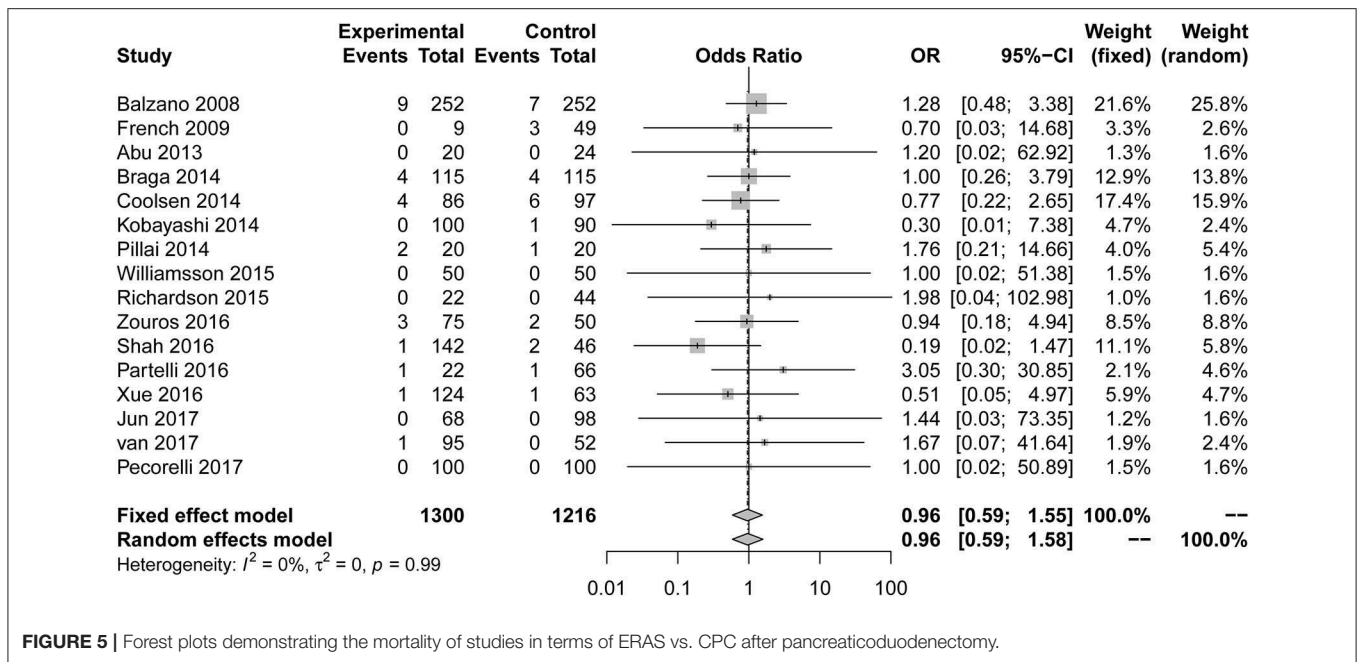
Study	Experimental Events	Total	Control Events	Total	Odds Ratio	OR	95%–CI	Weight (fixed)	Weight (random)
Balzano 2008	9	252	7	252		1.28	[0.48; 3.38]	21.6%	25.8%
French 2009	0	9	3	49		0.70	[0.03; 14.68]	3.3%	2.6%
Abu 2013	0	20	0	24		1.20	[0.02; 62.92]	1.3%	1.6%
Braga 2014	4	115	4	115		1.00	[0.26; 3.79]	12.9%	13.8%
Coolsen 2014	4	86	6	97		0.77	[0.22; 2.65]	17.4%	15.9%
Kobayashi 2014	0	100	1	90		0.30	[0.01; 7.38]	4.7%	2.4%
Pillai 2014	2	20	1	20		1.76	[0.21; 14.66]	4.0%	5.4%
Williamsson 2015	0	50	0	50		1.00	[0.02; 51.38]	1.5%	1.6%
Richardson 2015	0	22	0	44		1.98	[0.04; 102.98]	1.0%	1.6%
Zouros 2016	3	75	2	50		0.94	[0.18; 4.94]	8.5%	8.8%
Shah 2016	1	142	2	46		0.19	[0.02; 1.47]	11.1%	5.8%
Partelli 2016	1	22	1	66		3.05	[0.30; 30.85]	2.1%	4.6%
Xue 2016	1	124	1	63		0.51	[0.05; 4.97]	5.9%	4.7%
Jun 2017	0	68	0	98		1.44	[0.03; 73.35]	1.2%	1.6%
van 2017	1	95	0	52		1.67	[0.07; 41.64]	1.9%	2.4%
Pecorelli 2017	0	100	0	100		1.00	[0.02; 50.89]	1.5%	1.6%
Fixed effect model		**1300**		**1216**		0.96	[0.59; 1.55]	100.0%	––
Random effects model						0.96	[0.59; 1.58]	––	100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$

0.01 0.1 1 10 100

FIGURE 5 | Forest plots demonstrating the mortality of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy.

Study	Experimental Events	Total	Control Events	Total	Odds Ratio	OR	95%–CI	Weight (fixed)	Weight (random)
Balzano 2008	18	252	16	252		1.13	[0.57; 2.25]	10.9%	12.0%
Abu 2013	1	20	2	24		0.69	[0.08; 5.73]	1.5%	1.3%
Nikfarjam 2013	3	20	0	21		8.60	[0.42; 177.93]	0.3%	0.6%
Braga 2014	14	115	12	115		1.18	[0.53; 2.64]	7.8%	8.8%
Coolsen 2014	11	86	14	97		0.88	[0.38; 2.02]	8.4%	8.2%
Kobayashi 2014	2	100	2	90		0.90	[0.15; 5.31]	1.8%	1.8%
Richardson 2015	2	22	8	44		0.52	[0.12; 2.37]	3.6%	2.5%
Zhuo 2015	43	325	44	310		0.92	[0.59; 1.45]	28.1%	28.0%
Zouros 2016	5	75	3	50		1.06	[0.26; 4.25]	2.8%	2.9%
Shah 2016	16	142	3	46		1.62	[0.49; 5.40]	3.3%	3.9%
Partelli 2016	3	22	11	66		0.87	[0.24; 3.19]	3.5%	3.3%
Xue 2016	11	124	2	63		2.49	[0.61; 10.13]	2.1%	2.9%
Jun 2017	0	68	6	98		0.10	[0.01; 1.88]	3.8%	0.7%
Van 2017	12	95	9	52		0.69	[0.27; 1.72]	7.6%	6.7%
Pecorelli 2017	12	100	8	100		1.54	[0.61; 3.85]	5.3%	6.7%
Kagedan 2017	20	121	12	74		1.01	[0.47; 2.18]	9.2%	9.6%
Fixed effect model		**1687**		**1502**		1.02	[0.80; 1.28]	100.0%	––
Random effects model						1.02	[0.80; 1.29]	––	100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$
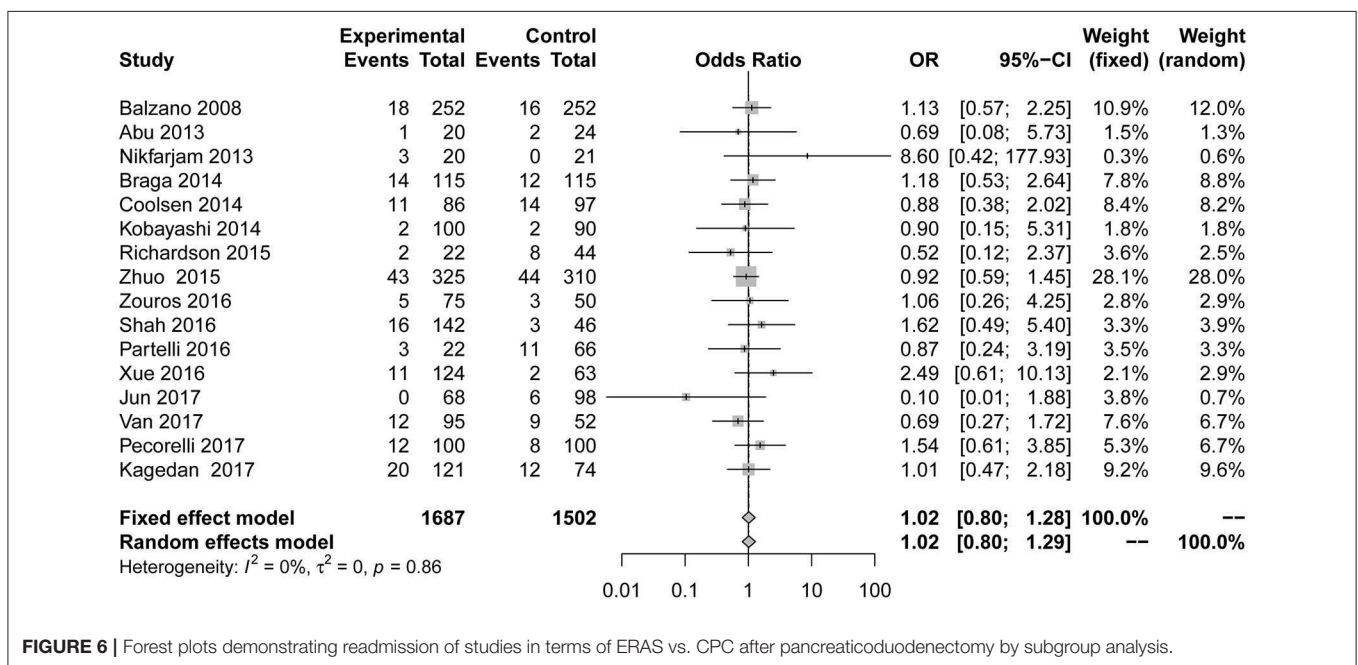
0.01 0.1 1 10 100

FIGURE 6 | Forest plots demonstrating readmission of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

were lower in the experimental group than in the control group, independent of the country in which the treatment was received. Fewer complications and LOS correspondingly lead to fewer costs. Sometimes it is undeniable that doctors don't have a uniform level of expertise, and less experienced doctors need more tests to help diagnosis and patients spend more. One of the articles found that the most important economic effect associated with ERAS was the cost reduction in laboratory investigations, medical imaging, pharmaceuticals and patient food (26). There is no denying that laparoscopic surgery, or the use of robotic

surgery, can have varying degrees of impact on the cost and recovery time of surgery. In this study, there was only one case of laparoscopic surgery and no robotic surgery.

Compared with the meta-analyses published in 2016 (13) and 2018 (14), we found consistency in LOS, rates of readmission, reoperation, and mortality. However, PF rates were lower for the ERAS group in our study. Additionally, incision infection and pulmonary infection rates were reduced in the ERAS group. DGE rates did not differ between the two groups in our study. According to the guideline for pylorus-preserving PDs, it has
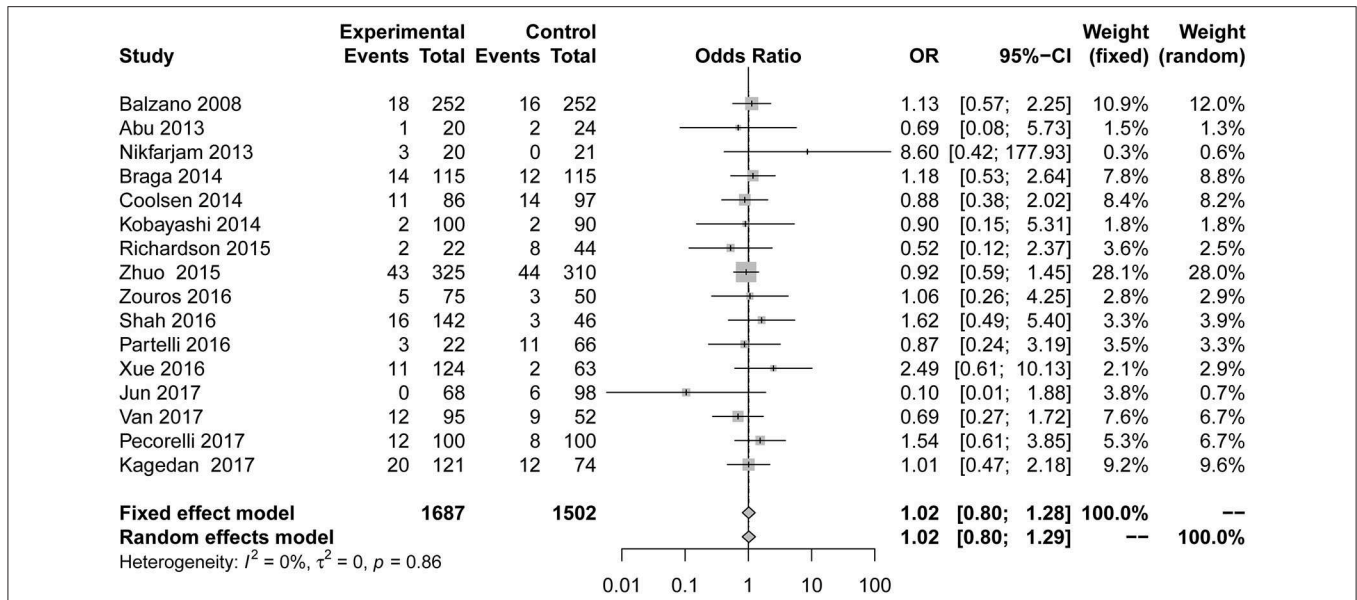
Study	Experimental Events	Total	Control Events	Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Balzano 2008	18	252	16	252		1.13	[0.57; 2.25]	10.9%	12.0%
Abu 2013	1	20	2	24		0.69	[0.08; 5.73]	1.5%	1.3%
Nikfarjam 2013	3	20	0	21		8.60	[0.42; 177.93]	0.3%	0.6%
Braga 2014	14	115	12	115		1.18	[0.53; 2.64]	7.8%	8.8%
Coolsen 2014	11	86	14	97		0.88	[0.38; 2.02]	8.4%	8.2%
Kobayashi 2014	2	100	2	90		0.90	[0.15; 5.31]	1.8%	1.8%
Richardson 2015	2	22	8	44		0.52	[0.12; 2.37]	3.6%	2.5%
Zhuo 2015	43	325	44	310		0.92	[0.59; 1.45]	28.1%	28.0%
Zouros 2016	5	75	3	50		1.06	[0.26; 4.25]	2.8%	2.9%
Shah 2016	16	142	3	46		1.62	[0.49; 5.40]	3.3%	3.9%
Partelli 2016	3	22	11	66		0.87	[0.24; 3.19]	3.5%	3.3%
Xue 2016	11	124	2	63		2.49	[0.61; 10.13]	2.1%	2.9%
Jun 2017	0	68	6	98		0.10	[0.01; 1.88]	3.8%	0.7%
Van 2017	12	95	9	52		0.69	[0.27; 1.72]	7.6%	6.7%
Pecorelli 2017	12	100	8	100		1.54	[0.61; 3.85]	5.3%	6.7%
Kagedan 2017	20	121	12	74		1.01	[0.47; 2.18]	9.2%	9.6%
Fixed effect model		**1687**		**1502**		1.02	[0.80; 1.28]	100.0%	--
Random effects model						1.02	[0.80; 1.29]	--	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$									

0.01   0.1   1   10   100

FIGURE 7 | Forest plots demonstrating reoperation of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.
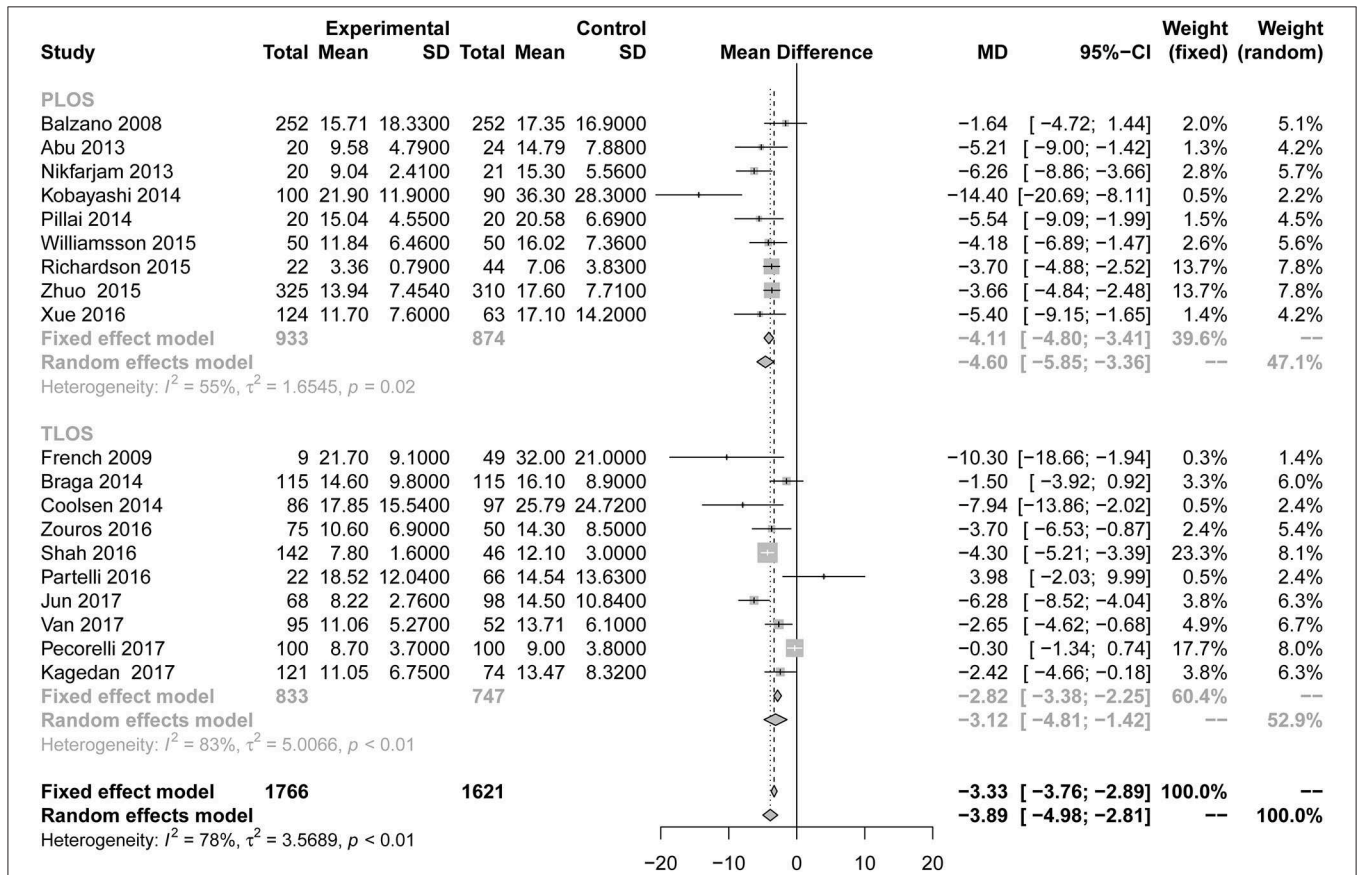
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	Mean Difference	MD	95%-CI	Weight (fixed)	Weight (random)
PLOS											
Balzano 2008	252	15.71	18.3300	252	17.35	16.9000		−1.64	[−4.72; 1.44]	2.0%	5.1%
Abu 2013	20	9.58	4.7900	24	14.79	7.8800		−5.21	[−9.00; −1.42]	1.3%	4.2%
Nikfarjam 2013	20	9.04	2.4100	21	15.30	5.5600		−6.26	[−8.86; −3.66]	2.8%	5.7%
Kobayashi 2014	100	21.90	11.9000	90	36.30	28.3000		−14.40	[−20.69; −8.11]	0.5%	2.2%
Pillai 2014	20	15.04	4.5500	20	20.58	6.6900		−5.54	[−9.09; −1.99]	1.5%	4.5%
Williamsson 2015	50	11.84	6.4600	50	16.02	7.3600		−4.18	[−6.89; −1.47]	2.6%	5.6%
Richardson 2015	22	3.36	0.7900	44	7.06	3.8300		−3.70	[−4.88; −2.52]	13.7%	7.8%
Zhuo 2015	325	13.94	7.4540	310	17.60	7.7100		−3.66	[−4.84; −2.48]	13.7%	7.8%
Xue 2016	124	11.70	7.6000	63	17.10	14.2000		−5.40	[−9.15; −1.65]	1.4%	4.2%
Fixed effect model	933			874				−4.11	[−4.80; −3.41]	39.6%	--
Random effects model								−4.60	[−5.85; −3.36]	--	47.1%
Heterogeneity: $I^2 = 55\%$, $\tau^2 = 1.6545$, $p = 0.02$											
TLOS											
French 2009	9	21.70	9.1000	49	32.00	21.0000		−10.30	[−18.66; −1.94]	0.3%	1.4%
Braga 2014	115	14.60	9.8000	115	16.10	8.9000		−1.50	[−3.92; 0.92]	3.3%	6.0%
Coolsen 2014	86	17.85	15.5400	97	25.79	24.7200		−7.94	[−13.86; −2.02]	0.5%	2.4%
Zouros 2016	75	10.60	6.9000	50	14.30	8.5000		−3.70	[−6.53; −0.87]	2.4%	5.4%
Shah 2016	142	7.80	1.6000	46	12.10	3.0000		−4.30	[−5.21; −3.39]	23.3%	8.1%
Partelli 2016	22	18.52	12.0400	66	14.54	13.6300		3.98	[−2.03; 9.99]	0.5%	2.4%
Jun 2017	68	8.22	2.7600	98	14.50	10.8400		−6.28	[−8.52; −4.04]	3.8%	6.3%
Van 2017	95	11.06	5.2700	52	13.71	6.1000		−2.65	[−4.62; −0.68]	4.9%	6.7%
Pecorelli 2017	100	8.70	3.7000	100	9.00	3.8000		−0.30	[−1.34; 0.74]	17.7%	8.0%
Kagedan 2017	121	11.05	6.7500	74	13.47	8.3200		−2.42	[−4.66; −0.18]	3.8%	6.3%
Fixed effect model	833			747				−2.82	[−3.38; −2.25]	60.4%	--
Random effects model								−3.12	[−4.81; −1.42]	--	52.9%
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 5.0066$, $p < 0.01$											
Fixed effect model	**1766**			**1621**				−3.33	[−3.76; −2.89]	100.0%	--
Random effects model								−3.89	[−4.98; −2.81]	--	100.0%
Heterogeneity: $I^2 = 78\%$, $\tau^2 = 3.5689$, $p < 0.01$											

−20   −10   0   10   20

FIGURE 8 | Forest plots demonstrating LOS of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.
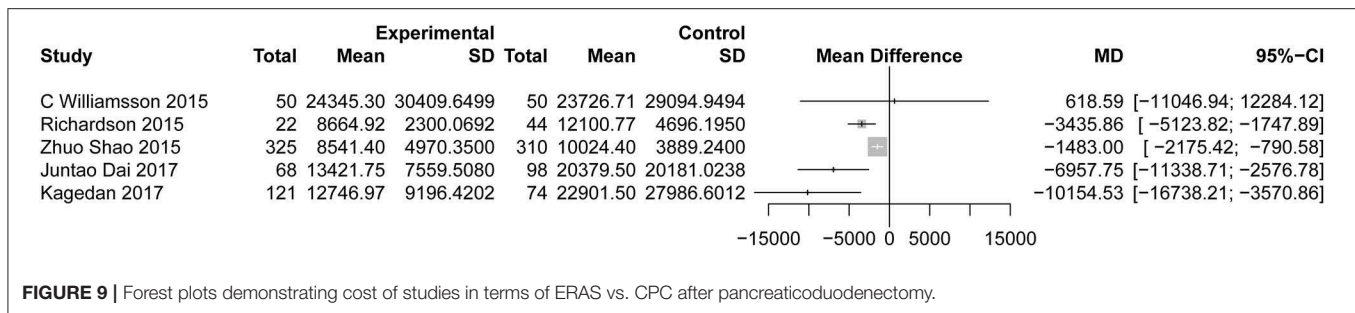
Study	Total	Experimental Mean	SD	Total	Control Mean	SD	Mean Difference	MD	95%-CI
C Williamsson 2015	50	24345.30	30409.6499	50	23726.71	29094.9494		618.59	[−11046.94; 12284.12]
Richardson 2015	22	8664.92	2300.0692	44	12100.77	4696.1950		−3435.86	[−5123.82; −1747.89]
Zhuo Shao 2015	325	8541.40	4970.3500	310	10024.40	3889.2400		−1483.00	[−2175.42; −790.58]
Juntao Dai 2017	68	13421.75	7559.5080	98	20379.50	20181.0238		−6957.75	[−11338.71; −2576.78]
Kagedan 2017	121	12746.97	9196.4202	74	22901.50	27986.6012		−10154.53	[−16738.21; −3570.86]

−15000   −5000 0 5000   15000

FIGURE 9 | Forest plots demonstrating cost of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy.

been shown that constructing the duodenojejunostomy in an antecolic (as opposed to a retro-colic) fashion results in reduced DGE (6). Thus, we need more data to certify that ERAS can decrease the rate of DGE. It should be noted that early postoperative oral intake does not worsen anastomotic leakage in colorectal surgery (45). Early postoperative oral intake has been avoided in patients undergoing PD with the concern that it may stimulate pancreatic exocrine secretion, resulting in an increased incidence of PF (32).

The purpose of ERAS protocols is to reduce patient stress; so it is important that guidelines mention several major measures: preoperative counseling with various information, avoiding oral bowel preparation and limiting fluid intake. The first measure can eliminate patients' preoperative anxiety (46), and the next one can decrease the incidence of anastomotic insufficiency (47), and liquid management can also reduce anastomotic fistula; this recommendation is also mentioned in the ERAS published in 2018. The included studies did not report the choice of incision at the surgeon's discretion, which should be of a length sufficient to ensure good exposure, so it cannot provide the evidence for clinical treatment. Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely in the guidelines. An important measure is the early removal of the nasogastric duct, which can reduce the incidence of PF, consistently with the outcomes of many studies. Studies have shown that the carbohydrate beverage given to patients on the night before surgery and 2∼4 h before surgery can alleviate the above stress response to some extent. To sum up, the ERAS program appears to be feasible in pancreaticoduodenectomy.

This meta-analysis not only provides evidence for using ERAS guidelines but also shows a new result regarding infection. ERAS can reduce incisions and lung infections. At the same time, the main outcome of this study was not LOS but the effect of the surgery itself, which has significant impact on clinical outcomes. The study incorporated all observational studies that contained large data groups to support the results reported and to increase the accuracy of the results.

This study has three main limitations: (1) it is unlikely that truly blinded, case-control studies regarding ERAS protocols will be performed due to a lack of feasibility. (2) It is very difficult to compare the incidence rates between different treatment centers according to the confirmed case, as the study reported the

complication classification scheme (Clavien classification), and a suggestion for grading the complications based on the treatment intervention was to use a compound endpoint, which would reduce the required sample size study and improve objectivity and comparability. (3) Only two studies were randomized controlled trials (48, 49); therefore, data contained in these studies cannot be effectively analyzed.

CONCLUSION

In conclusion, this meta-analysis showed a decrease in the rates of PF, infection, LOS and hospital costs without increasing the incidence of mortality, readmission, or reoperation in patients undergoing pancreatic duodenal surgery when ERAS protocols were applied in the patients' perioperative care. This is the time to promote the use of ERAS pathways as a protocol to restore patients' health after a complex and delicate surgery. With continued improvement in outcome results, ERAS protocols will attain the standard for primary abdominal surgeries.

DATA AVAILABILITY

The datasets for this manuscript are not publicly available because all the data is in the manuscript. Requests to access the datasets should be directed to YF, fuyan_taihe0601@163.com.

AUTHOR CONTRIBUTIONS

CZ and YF had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JL, YC, and CZ designed the study. JL, YC, and Z-DH developed and tested the data collection forms. H-YG, Y-PW, and QZ acquired the data. YC, H-YG, and Z-DH conducted the analysis and interpreted the data. YC drafted the manuscript. CZ and YF had guarantor. All authors critically revised the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00687/full#supplementary-material

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