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Original Article

Enhanced recovery after pancreatic surgery: a systematic review

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Abstract: Background: Enhanced recovery after surgery (ERAS) program is widely used because its advantage in reducing the length of hospital stay (LOS) and morbidity rate. Patients have suffered great benefits in colonic surgery, gastric cancer surgery and liver surgery. But in pancreatic surgery, the efficacy of ERAS program remains controversial. This study aimed to gain a current, comprehensive picture of ERAS program compares with conventional care in patients undergoing pancreatic surgery. Methods: MEDLINE, EMBASE, the Cochrane Library, and the Chinese National Knowledge Infrastructure database were searched until October 2015. Risk ratios (RRs), standard mean difference (SMD) and 95% confidence intervals (CIs) were calculated. Results: The analysis included 16 studies (5 were with single cohort, and another 11 were with 2 groups). Patients in ERAS group had significantly lower morbidity (RR=0.77, 95% CI=0.70-0.84) and shorter LOS (SWD=-0.61, 95% CI=-0.94-0.26). Moreover, ERAS program would not increase mortality rates (RR=0.90, 95% CI=0.49-1.64) and readmission rates (RR=0.92, 95% CI=0.71=1.18). Nevertheless, ERAS program also helped reducing pancreatic fistula (RR=0.77, 95% CI=0.70-0.84) and digestive gastric empty rates (RR=0.66, 95% CI=0.53-0.83). Conclusion: ERAS program is safe and efficient for patients undergoing pancreatic surgery.

Keywords: Pancreatic surgery, enhanced recovery after surgery, meta-analysis, morbidity, mortality

Introduction

Enhanced recovery after surgery (ERAS) program, also referrs to ‘fast track’, ‘clinical or critical pathways’, is an integrated care pathway that takes a multi modal, evidence-based approach to optimize patient recovery. ERAS was developed by Kehlet in the early 1990s for colonic surgery [1] and now is established in selected surgical specialities [2].

Pancreatic surgery is not only a technically challenging surgical procedure but also the only curative treatment for malignancy in the periampullary region [3]. An initial mortality rate of 29% was recorded according to Whipple *et al.* [4]. With the development of the techniques and skills, the mortality of patients undergoing pancreatic surgery in specialized centers and advances in perioperative care is less than 5% [5]. But postoperative morbidity still remains high at a rate of 40-60% [5-7]. Postoperative complications, such as anastomotic leakage, pancreatic fistula (PF), and delayed gastric empty (DGE), are the main reasons for delayed recovery. Additional radiological or surgical interventions are frequently needed in patients with serious complications.

Several studies showed ERAS could significantly reduce the length of hospital stay (LOS) [8, 9] in patients undergoing pancreatic surgery. But studies still failed to find out this benefit in LOS [10]. A meta-analysis published in 2013 [11] showed that ERAS program could significantly decrease LOS and morbidity rate. We research the database and find many new published studies concerning the safety and efficacy of EARS program in patients undergoing pancreatic surgery. A significantly decreased rate of DGE [8, 12-14] and PF [15] still could be found in patients undergoing pancreatic surgery.

Thus we perform a systematic review of the available literature on ERAS pathways compared with traditional treatment in patients undergoing pancreatic surgery. We analyzed the outcome of LOS, morbidity, mortality, read-

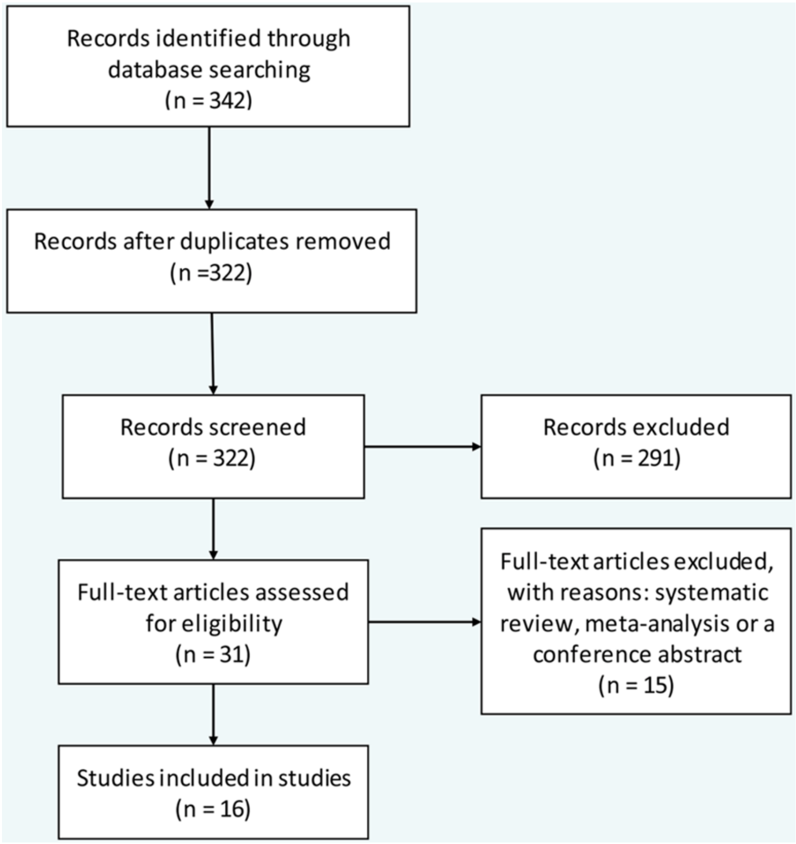


Figure 1. Selection process for trials.

mission rate, reoperation rate, DGE rate and PF rate, aimed to find out whether EARS pathway could benefit the patients undergoing pancreatic surgery.

Methods

Literature search strategy

The following electronic databases were systematically searched until October 2015 without language restrictions: MEDLINE, EMBASE, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI). Following index words were used: pancreas *or* pancreatic, clinic pathway *or* enhanced recovery after surgery *or* fast track *or* ERAS. Relevant reviews and meta-analyses comparing ERAS and conventional care in pancreatic surgery were examined manually to identify additional eligible studies.

Inclusion criteria

(1) Trials clearly describing ERAS protocol; (2) The sample size of each group should more than 20; (3) Either the trial with a single cohort or two groups were available; (4) The reported data should conclude at least one of primary outcomes with or without secondary outcomes (primary outcome: morbidity, mortality; secondary outcome: readmission rate, DGE rate, PF rate and cost).

Types of outcome measures

Primary outcomes evaluated in the meta-analysis were mortality and morbidity. Secondary outcomes were LOS, readmission rate, DGE rate, PF rate and cost.

Data extraction

Two reviewers (Z.B.X and C.J.) independently screened the potentially eligible studies and independently extracted the following data: authors, publication year, study design, interventions, and outcomes. A third reviewer (D.L.F.) was needed when there were disagreements about study eligibility or extracted data.

Statistical analysis

All statistical calculations were performed using Stata 12.0 (Stata Corp, College Station, TX, USA). Mantel-Haenszel risk rations (RRs) with corresponding 95% confidence interval (CIs) were calculated for dichotomous outcomes (morbidity, mortality, readmission rate, reoperation rate, DGE rate and PF rate) while standard mean difference (SMD) with 95% CIs were calculated for continuous outcomes (LOS). Heterogeneity was assessed by calculating I^2. When I^2 was less than 50%, we used a fixed-effects model for meta-analysis; random-effects model was used when I^2 was more than 50%. Homogeneity between trials was assessed using the χ^2 test with the significance threshold set at $P>0.1$. To evaluate the robustness of meta-analysis results, we repeated all

Table 1. Characteristics of included studies

Author	Year	Country	Patients, n		Study design	Resection
			CC	ERAS		
Abu Hilal *et al.*	2013	England	24	20	Prospective	Whipple
Balzano *et al.*	2008	Italy	252	252	Retrospective	Whipple
Berberat *et al.*	2007	Germany	NA	255	Prospective	Whipple, total PT, distal PT, central PT, segmental PT, duodenum-preserving pancreatic head resection
Chaudhary *et al.*	2015	India	NA	200	Retrospective	Whipple, PPPD
Coolsen *et al.*	2014	Netherland	97	86	Retrospective	Whipple
Di Sebastiano *et al.*	2011	Italy	NA	145	Prospective	Whipple, distal PD, central PD, total PD, duodenum-preserving pancreatic head resection
Hore *et al.*	2014	New Zealand	NA	156	Retrospective	PD, left PT
Kennedy *et al.*	2007	America	44	91	Retrospective	Whipple, total PT
Kennedy *et al.*	2009	America	40	71	Retrospective	Distal PT, distal PT with splenectomy
Kobayashi *et al.*	2014	Japan	90	100	Retrospective	PD, SSPD
Nikfarjam *et al.*	2013	Australia	21	20	Retrospective	Whipple
Pillai *et al.*	2014	India	20	20	Retrospective	Whipple
Porter *et al.*	2000	America	68	80	Retrospective	Whipple, total PT
Robertson *et al.*	2012	England	NA	50	Prospective	Whipple
Shao *et al.*	2015	China	310	325	Retrospective	Whipple
Vanounou *et al.*	2007	America	64	145	Retrospective	Whipple, PPPD

Abbreviation: CC = conventional care; ERAS = enhanced recovery after surgery; NA = not available; PD = pancreaticoduodenectomy; PPPD = pylorus-preserving PD; PT = pancreatectomy; SSPD = subtotal stomach-preserving PD.

Table 2. Elements included in ERAS protocols

Study	Early oral intake	Goal-directed mobilization	Octreotide	Epidurals / patient controlled analgesia	Surgical drains	Nasogastric tubes	Pre-operative antibiotics	Foley catheters	Prokinetic agents	Discharge planning	Other
Abu Hilal *et al.*	+	+	-	+	+	+	-	-	+	+	-
Balzano *et al.*	+	+	-	+	+	+	-	-	-	-	+
Berberat *et al.*	+	-	+	+	-	+	+	-	+	-	+
Chaudhary *et al.*	+	-	-	-	+	+	+	+	+	+	-
Coolsen *et al.*	+	+	-	+	+	+	+	+	-	+	+
Di Sebastiano *et al.*	+	+	+	+	-	+	+	+	+	+	-
Hore *et al.*	+	+	+	+	+	-	+	+	+	+	+
Kennedy *et al.* 2007	+	+	+	+	+	+	+	+	-	+	+
Kennedy *et al.* 2009	+	+	-	+	+	+	+	+	-	+	+
Kobayashi *et al.*	+	-	-	-	+	+	-	-	+	-	+
Nikfarjam *et al.*	+	+	-	-	+	+	+	+	+	+	+

Pillai *et al.*	+	+	-	+	+	+	-	+	-	+	+
Porter *et al.*	+	-	-	-	+	+	-	+	-	-	-
Robertson *et al.*	+	+	-	+	+	+	-	+	-	+	+
Shao *et al.*	+	+	-	+	+	+	-	-	-	+	+
Vanounou *et al.*	+	+	-	-	+	+	+	+	-	-	+

Abbreviation: + = element explicitly listed in the ERAS protocol; - = element not explicitly listed in the ERAS protocol.

Table 3. Outcomes in studies between patients in ERAS and conventional care group

Study	Length of stay, (median, days)		Readmission, n (%)		Morbidity, n (%)		Reoperation, n (%)		Mortality, n (%)		Pancreatic fistula, n (%)		Delayed gastric emptying, n (%)		Total cost, US dollars	
	CC	ERAS	CC	ERAS	CC	ERAS	CC	ERAS	CC	ERAS	CC	ERAS	CC	ERAS	CC	ERAS
Abu Hilal *et al.*	13 (10.5-20.5)	8.5 (7-13)	2 (10%)	1 (4%)	16 (67%)	8 (40%)	3 (1%)	1 (5%)	0 (0%)	0 (0%)	4 (17%)	4 (20%)	2 (10%)	1 (5%)	-	-
Balzano *et al.*	15 (7-102)	13 (7-110)	16 (6%)	18 (7%)	148 (59%)	119 (47%)	20 (8%)	17 (7%)	7 (3%)	9 (4%)	65 (26%)	60 (24%)	62 (25%)	35 (14%)	-	-
Berberat *et al.*	-	10	-	9 (4%)	-	105 (41%)	-	23 (9%)	-	5 (2%)	-	4 (2%)	-	20 (8%)	-	-
Chaudhary *et al.*	-	8 (4-52)	-	8 (4%)	-	69 (35%)	-	-	-	8 (4%)	-	17 (9%)	-	38 (19%)	-	-
Coolsen *et al.*	20 (9-132)	14 (7-83)	14 (14%)	11 (13%)	48 (49%)	46 (53%)	13 (13%)	7 (8%)	6 (6%)	4 (5%)	12 (12%)	11 (12%)	7 (7%)	11 (13%)	-	-
Di Sebastiano *et al.*	-	10	-	9 (6%)	-	56 (39%)	-	11 (8%)	-	4 (3%)	-	7 (7%)	-	9 (8%)	-	-
Hore *et al.*	-	11 (3-140)	-	34 (22%)	-	100 (64%)	-	22 (14%)	-	4 (3%)	-	-	-	-	-	-
Kennedy *et al.* 2007	13	7	3 (7%)	7 (8%)	19 (44%)	34 (37%)	-	-	1 (2%)	1 (1%)	4 (9%)	2 (2%)	3 (7%)	7 (8%)	240242	126566
Kennedy *et al.* 2009	10	7	10 (25%)	5 (7%)	15 (38%)	11 (16%)	-	-	1 (2%)	1 (1%)	7 (18%)	4 (6%)	-	-	26393	22806
Kobayashi *et al.*	36.3±23.8	21.9±11.9	2 (2%)	2 (2%)	60 (54%)	39 (39%)	-	-	1 (1%)	0 (0%)	25 (28%)	9 (9%)	9 (10%)	2 (2%)	-	-
Nikfarjam *et al.*	14 (8-29)	9 (7-16)	0 (0%)	3 (15%)	-	-	-	-	-	-	-	-	-	-	-	-
Pillai *et al.*	18.5 (13-38)	14 (9-26)	-	-	-	-	1 (5%)	3 (15%)	1 (5%)	2 (10%)	10 (50%)	11 (55%)	15 (75%)	7 (35%)	-	-
Porter *et al.*	15	12	10 (15%)	9 (11%)	20 (29%)	24 (30%)	1 (2%)	1 (1%)	2 (3%)	1 (1%)	5 (8%)	6 (8%)	6 (9%)	6 (8%)	47515	36627
Robertson *et al.*	-	10 (8-17)	-	2 (4%)	-	23 (46%)	-	5 (10%)	-	2 (4%)	-	6 (12%)	-	7 (14%)	-	-
Shao *et al.*	17.6±7.7	13.9±7.5	44 (14%)	43 (13%)	173 (56%)	127 (39%)	-	-	-	-	56 (18%)	53 (16%)	52 (17%)	29 (9%)	11074	9436
Vanounou *et al.*	8	8	4 (6%)	13 (9%)	40 (62%)	77 (54%)	4 (6%)	7 (5%)	1 (2%)	2 (1%)	-	-	-	-	23112	19561

Abbreviation: CC = conventional care; ERAS = enhanced recovery after surgery.

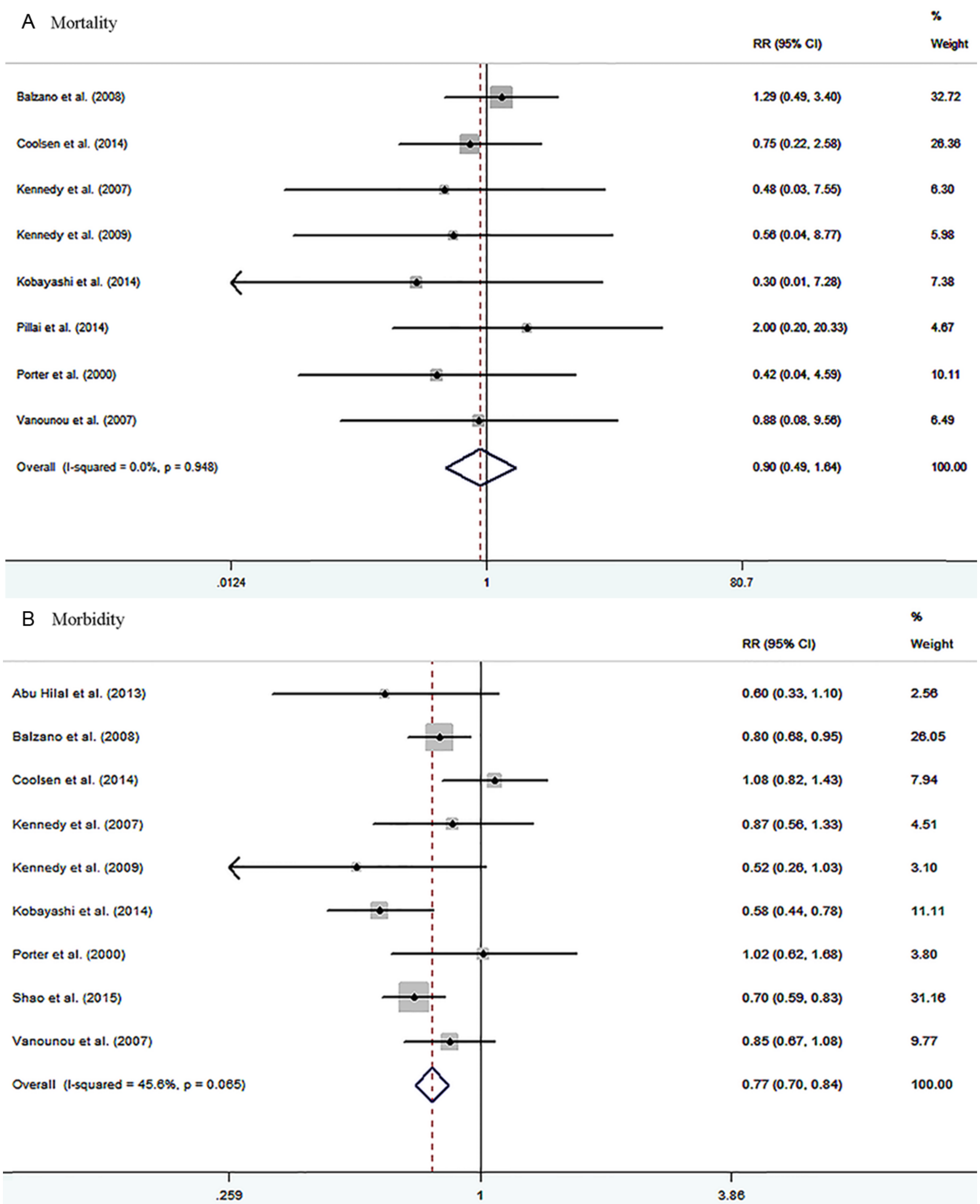


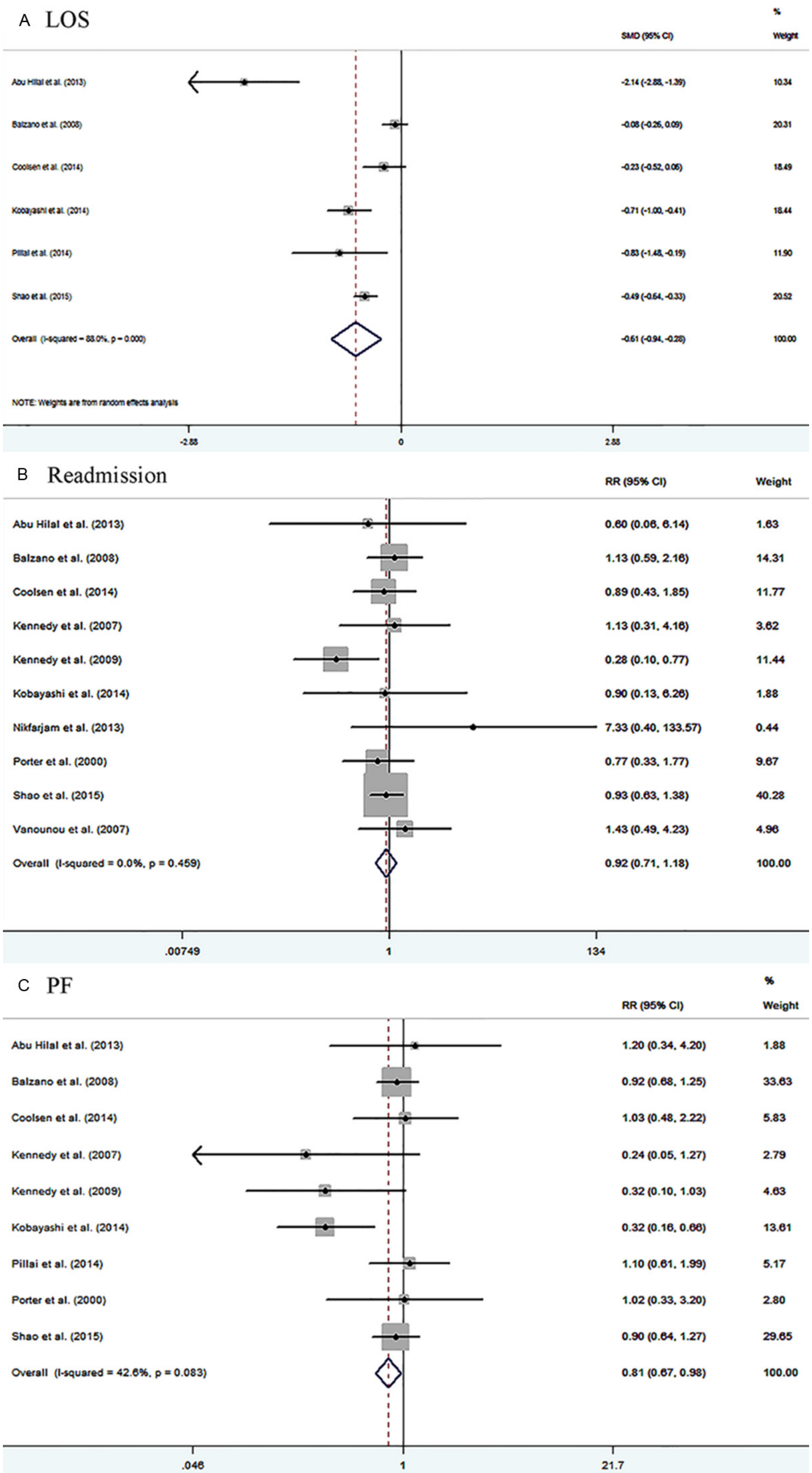
Figure 2. Mortality and morbidity in patients with ERAS program and conventional care.

meta-analyses using the other type of model (fixed- or random-effects); we judged the result to be reliable if both models gave the same meta-analysis results. Publication bias was assessed using Egger's test and funnel plots [16, 17] in Stata 12.0.

Results

Characteristics of the included studies

Initial searching of literature databases revealed 342 published clinical trials satisfied


A LOS
SMD (95% CI)
%
Weight
Abu Hilal et al. (2013)
-2.14 (-2.88, -1.39)
10.34
Balzano et al. (2008)
-0.08 (-0.26, 0.09)
20.31
Coolsen et al. (2014)
-0.23 (-0.52, 0.06)
18.49
Kobayashi et al. (2014)
-0.71 (-1.00, -0.41)
18.44
Pillai et al. (2014)
-0.83 (-1.48, -0.19)
11.90
Shao et al. (2015)
-0.49 (-0.64, -0.33)
20.52
Overall (I-squared = 88.0%, p = 0.000)
-0.61 (-0.94, -0.28)
100.00
NOTE: Weights are from random effects analysis
-2.88
0
2.88
B Readmission
RR (95% CI)
Weight
Abu Hilal et al. (2013)
0.60 (0.06, 6.14)
1.63
Balzano et al. (2008)
1.13 (0.59, 2.16)
14.31
Coolsen et al. (2014)
0.89 (0.43, 1.85)
11.77
Kennedy et al. (2007)
1.13 (0.31, 4.16)
3.62
Kennedy et al. (2009)
0.28 (0.10, 0.77)
11.44
Kobayashi et al. (2014)
0.90 (0.13, 6.26)
1.88
Nikfarjam et al. (2013)
7.33 (0.40, 133.57)
0.44
Porter et al. (2000)
0.77 (0.33, 1.77)
9.67
Shao et al. (2015)
0.93 (0.63, 1.38)
40.28
Vanounou et al. (2007)
1.43 (0.49, 4.23)
4.96
Overall (I-squared = 0.0%, p = 0.459)
0.92 (0.71, 1.18)
100.00
.00749
1
134
C PF
RR (95% CI)
%
Weight
Abu Hilal et al. (2013)
1.20 (0.34, 4.20)
1.88
Balzano et al. (2008)
0.92 (0.68, 1.25)
33.63
Coolsen et al. (2014)
1.03 (0.48, 2.22)
5.83
Kennedy et al. (2007)
0.24 (0.05, 1.27)
2.79
Kennedy et al. (2009)
0.32 (0.10, 1.03)
4.63
Kobayashi et al. (2014)
0.32 (0.16, 0.66)
13.61
Pillai et al. (2014)
1.10 (0.61, 1.99)
5.17
Porter et al. (2000)
1.02 (0.33, 3.20)
2.80
Shao et al. (2015)
0.90 (0.64, 1.27)
29.65
Overall (I-squared = 42.6%, p = 0.083)
0.81 (0.67, 0.98)
100.00
.046
1
21.7

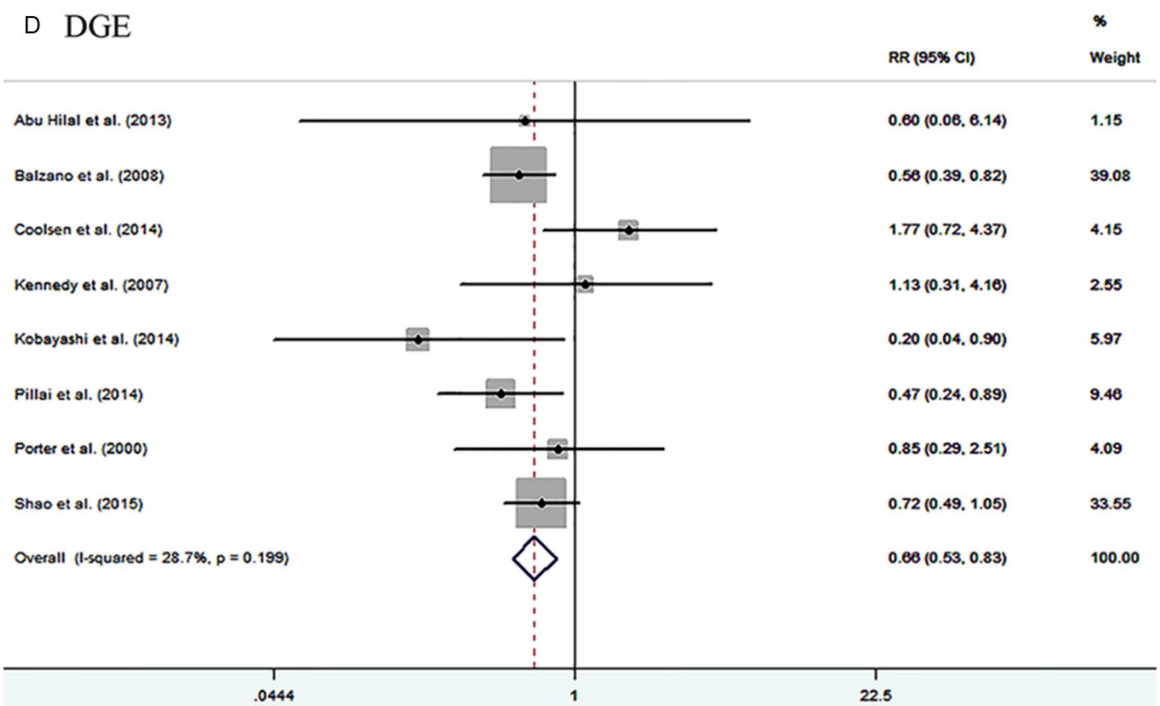


Figure 3. Postoperative outcomes in patients with ERAS program and conventional care.

our selection criteria (**Figure 1**). After removing 20 duplicates, we were left with 322 potentially eligible trials. We excluded 291 trials based on abstract review because the study design or outcomes data did not satisfy the inclusion criteria. After reading the full text of the remaining 31 trials, we excluded 15 trials (systematic reviews, meta-analyses or a conference abstract). Finally 16 studies [8-10, 12-15, 18-26] (conventional care group, n=1030; ERAS group, n=2016) were enrolled. Among which 5 studies [18-21, 26] were single cohort study, another 11 studies [8-10, 12-15, 22-25] have both conventional care and ERAS group. The characteristics of the included studies are shown in **Table 1**. Pancreatic surgery in our analysis includes classic Whipple, pancreatectomy (PT), and pancreaticoduodenectomy (PD). ERAS program includes early oral intake, goal-directed mobilization, octreotide, epidurals or patient controlled analgesia, surgical drains, nasogastric tubes, pre-operative antibiotics, Foley catheters, prokinetic agents, discharge planning, and other procedures (**Table 2**).

Therapy outcomes

Mortality

Together 14 studies concerned about mortality, 5 of them were single cohort studies [14, 18-21, 24, 26] and another 9 studies [8-10, 12, 13, 15, 22, 23, 25] have 2 group design. Totally 8 studies were eligible to conduct meta-analysis (Abu Hilal *et al.* [8] reported mortality rate of 0%, thus this study was not included in meta-analysis). No significant difference was found between conventional care and ERAS group (RR=0.90, 95% CI=0.49-1.64, I^2=0%) (**Table 3**; **Figure 2**).

In studies with single cohort, mortality rate varied from 2% to 4% in ERAS group. In ERAS group, mortality rate of all 14 studies is less than 5% except Pillai *et al.*'s study (10%) [12].

Morbidity

Together 14 studies [8-10, 13-15, 18-26] concerned about morbidity, among which 5 were single cohort studies [14, 18-21, 24, 26], with the morbidity rate varying from 35% to 64% in ERAS cohort. Meta-analysis was conducted in studies with 2 group design [8-10, 13-15, 22, 23, 25], and we found that patients in ERAS group had less morbidity rate than patients in conventional care group (RR=0.77, 95% CI=0.70-0.84, I^2=46%) (**Table 3**; **Figure 2**).

Length of hospital stay

All studies reported the outcome of LOS. Together, 5 of them were single cohort studies

[14, 18-21, 24, 26], and their findings of LOS varied from 8 to 11 days (median) in ERAS cohort. Meta-analysis was conducted in another 11 studies [8-10, 12-15, 22-25], and found patients undergoing ERAS care had significant shorter LOS than the patients in conventional care group (SWD=-0.61, 95% CI=-0.94--0.26, I^2=88%) (**Table 3**; **Figure 3**).

Readmission

Together 13 studies [8-10, 13-15, 18-26] reported the data about readmission, among which 5 were single cohort studies [14, 18-21, 24, 26], with the readmission rate varying from 4% to 22% in ERAS cohort. Meta-analysis was conducted in studies with 2 group design [8-10, 13-15, 22-25], and we found the difference was similar between 2 groups (RR=0.92, 95% CI=0.71-1.18, I^2=0%) (**Table 3**; **Figure 3**).

Pancreatic fistula

Together 13 studies [8, 9, 12-15, 18-20, 22, 23, 25, 26] concerned about PF. In studies with a single cohort [18-20, 26], PF rates varied from 2% to 12%. Meta-analysis was conducted in studies with 2 group design [8, 9, 12-15, 22, 23, 25], and we found that patients in ERAS group had significantly less PF rate than patients in conventional care group (RR=0.77, 95% CI=0.70-0.84, I^2=46%) (**Table 3**; **Figure 3**).

Delayed gastric empty

Together 12 studies [8, 9, 12-15, 18-20, 23, 25, 26] concerned about DGE. The DGE rate in studies with a single cohort [18-20, 26] varied from 8% to 19%. In studies with 2 group design [8, 9, 12-15, 23, 25], meta-analysis was conducted and found that patients in ERAS group had significantly less DGE rate than patients in conventional care group (RR=0.66, 95% CI=0.53-0.83, I^2=29%) (**Table 3**; **Figure 3**).

Cost

Altogether 5 studies reported the data of overall cost during hospitalization [10, 14, 22, 23, 25] (**Table 3**). In these 5 studies, 4 studies [10, 14, 23, 25] found patients in ERAS group cost significantly less than conventional group (the costs in conventional group and ERAS group were $ 240242 and $ 126566 in Kennedy *et al. 2007*'s study; $ 47515 and $ 36627 in Porter *et al.*'s study; $ 11074 and $ 9436 in Shao *et al.*'s study; $ 23112 and $ 19561 in Vanounou *et al.*'s study). However, Kennedy *et al. 2009* [22] found the difference of costs between ERAS group ($ 22806) and conventional group ($ 26393) was not significant.

Risk factors

Balzano *et al.* [13] conducted multivariable logistic regression analysis for DGE, and found the only significant independent factor influencing DGE was the fast-track program [odds ratio (OR)=0.477, P=0.005].

Nikfarjam *et al.* [24] also found fast track recovery program (OR=37.1, 95% CI=4.08-338, P<0.001) was the only factor independently associated with postoperative discharge (less than 8 days). Berberat *et al.* [18] used univariate analysis to detect significant predictors of early discharge (less than 10 days) and found the occurrence of the first stool (P=0.011), normal food (P<0.001), complete mobilization (P<0.001), transfer to the ward (P<0.001), and early removal of intra-abdominal drains (P=0.019) correlated significantly with early discharge. Chaudhary *et al.* found that hypoalbuminemia (RR=2.44, 95% CI=1.26-4.75, P=0.009), elevated body mass index (RR=1.11, 95% CI=1.04-1.19, P=0.003) and the preoperative presence of respiratory comorbidities (RR=5.35, 95% CI=1.61-17.80, P=0.029) emerged as independent variables contributing to a longer hospital stay (more than 8 days). Di Sebastiano *et al.* [20] found that lack of jaundice (OR=2.6, 95% CI=1.1-6.1, P=0.029) and early normal food intake (OR=3.1, 95% CI=1.3-7.2, P=0.008) retained independent power for predicting early discharge (less than 10 days).

Multivariable regression analysis in Coolsen *et al.* [9] showed that without ERAS (P=0.003) and the presence of complications (P<0.001) were independent predictors of longer postoperative LOS. In Shao *et al.*'s study [14], the presence of complications was the only predictor of readmission (OR=5.112, 95% CI=1.922-13.598, P=0.001).

Sensitivity analysis and publication bias

To evaluate the robustness of meta-analysis results, we repeated all meta-analyses using the other type of model (fixed- or random-effects). We found the result to be reliable that

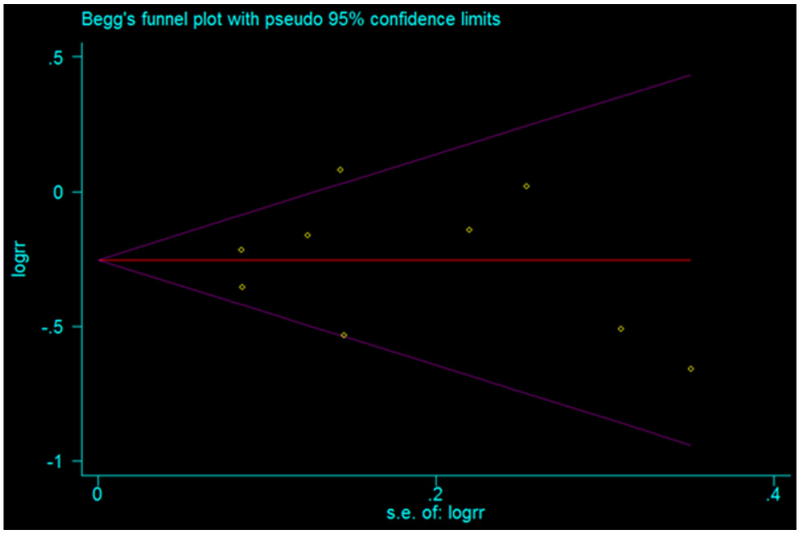


Figure 4. Publication bias of morbidity rate.

both models gave the same meta-analysis results.

Funnel plots were generated and analyzed using Egger's tests in order to assess the risk of publication bias in all included studies. The funnel plots for morbidity appeared to be symmetrical, suggesting the absence of bias. This was corroborated by Egger's test (t=-0.06, *P*=0.956) (**Figure 4**).

Discussion

ERAS programs are widely used in colonic surgery [27, 28], hepatobiliary surgery [29, 30], gastric cancer [31] and other abdominal surgery [32]. And ERAS programs are proved to be efficient in reducing LOS and morbidity [33, 34]. Since pancreatic surgery is the one of the most challenging surgeries, the efficacy and safety of ERAS is still under controversial. We conducted this systematic review to evaluate the efficacy and safety of ERAS program in patients undergoing pancreatic surgery. In our analysis, we found that patients in ERAS group had significantly lower morbidity rates and shorter LOS. Moreover, ERAS program would not increase the mortality rate and readmission rate. Nevertheless, ERAS programs also help to save the expense.

According to guidelines for ERAS program in patients undergoing PD, there were available evidences and recommendations given for 27 care items [35]. Together 19 items were strong recommended: patients should receive dedicated preoperative counseling routinely; one month of abstinence before surgery is beneficial for daily smokers and alcohol abusers; mechanical bowel preparation should not be used; intake of clear fluids up to 2 h before anesthesia is recommended before elective surgery and intake of solids should be withheld 6 h before anesthesia; low-molecular-weight heparin reduces the risk of thromboembolic complications, and administration should be continued for 4 weeks after hospital discharge; antimicrobial prophylaxis should be used in a single-dose manner at 30-60 min before skin incision and repeated intraoperative doses may be necessary depending on the half-life of the drug and duration of procedure; the benefits of using different pharmacological agents should depend on the patient's postoperative nausea and vomiting history, type of surgery and type of anesthesia; the choice of incision is at the surgeon's discretion, and should be of a length sufficient to ensure good exposure; intraoperative hypothermia should be avoided by using cutaneous warming; postoperative glycemic control; not pre-emptive routinely use nasogastric tubes; keep perioperative fluid balance; early removal of perianastomotic drain; somatostatin analogues is not warranted; transurethral catheters can be removed safely on postoperative day 1 or 2 unless otherwise indicated; artificial nutrition should be considered selectively in patients with DGE of long duration; patients should be cautioned to begin carefully and increase intake according to tolerance over 3-4 days and enteral tube feeding should be given only on specific indications and parenteral nutrition should not be employed routinely; early and scheduled mobilization is needed; and systematic improves compliance and clinical outcomes.

As with all ERAS programs, not all patients were eligible for it from the beginning to the end. A small proportion of patients will fail fast track surgery and require additional intensive care unit (ICU) resources. Lee *et al.* [36] studied factors associated with failure of ERAS protocol in patients undergoing major hepatobiliary and pancreatic (HBP) surgery to estimate the incidence and identify the associated risk factors. A retrospective cohort study enrolled 194 adult patients undergoing major HBP surgery found 25 failures after HBP surgery (12.9%). Smoking (RR=2.21, 95% CI=1.10-4.46), high preoperative alanine transaminase/glutamic-pyruvic transaminase (RR=3.55, 95% CI=1.68-7.49) and postoperative morbidities (RR=2.69, 95% CI=1.30-5.56) were associated with failures of ERAS. Compared with those successful implementation patients, failures of ERAS had longer ICU stay (median 19 *vs.* 25 h, $P<0.001$) and longer postoperative in-hospital e care (median 7 *vs.* 13 days, $P=0.003$).

Postoperative pain treatments help patients to release pain which make patients more likely to have early mobilization. Early mobilization promotes the peristalsis of digestive tract and consequently reduce the incidence of DEG [37]. Thus patients are more likely to have early oral intake. Thus, peripheral nutrition is reduced and nasogastric tube is early removed. Early mobilization stimulates the movement of the muscle of urine bladder. Thus, catheter is early removed. With less residual tubes inside the body, the incidence of postoperative infection and other complications would reduce. Thus the morbidity rate is reduced. In our risk factors analysis, less morbidity were all associated with early discharge. It is no wonder that LOS would reduce in ERAS group.

DGE is one of the most common complications of pancreatic surgery, the incidence varies from 20% to 30% [38]. DGE was used to define as a need for a nasogastric tube or emesis after postoperative 10 days [39, 40]. Nowadays DGE is stratified into Grade A, B C according to its clinical impact [41]. Erythromycin therapy has been used to reduce the clinical impact of DGE [42]. Recently antecolic reconstruction is more frequently used for reducing postoperative DGE [43, 44]. Fasting state impairs the peristaltic activity of the stomach and small intestine. Furthermore, the fed state is characterized by more forceful peristaltic waves of contraction. Thus early postoperative feeding could also efficiently reduce DGE [45]. Nevertheless, early mobilization also promotes the peristalsis of digestive tract and consequently reduce the incidence of DEG [37].

In pancreatic surgery, a stent is commonly placed in a pancreato-enteroanastomosis. Although no significant difference in the incidence of PF was found between internal and external drainages [46]. Patients without a stent still have a higher incidence of PF than patients with external drainage [47]. In ERAS group, patients were with 'no stent' which may lead to a risk of PF development. However, a significantly lower of PF was detected in ERAS group which meant that perioperative management might have been effective.

We carefully searched the Pubmed database and found 2 systematic review [11, 48] previous evaluated EARS program in patients underwent pancreatic surgery. In Coolsen *et al.*'s study [11], there was a significant difference in complication rates in favor of the ERAS group. Moreover, introduction of an ERAS protocol did not result in an increase in mortality or readmissions. Incidence of DGE and PF did not differ significantly between groups. In their analysis, only 4 studies were included [10, 13, 23, 25]. Limited studies and limited sample size may lead to some bias. Kagedan *et al.* [48] only conducted descriptive analysis of the studies. In our analysis, both descriptive analysis and meta-analysis were conducted. We also added new published studies since 2013 in our analysis. Totally 16 studies were enrolled and our findings, which were a little different from Coolsen *et al.*'s study. We found patients in ERAS group had significantly lower incidence of PF and DGE.

Our systematic review has several limitations. First, some of the included trials were retrospective trials, which can lead to some bias. We conducted sensitivity analysis and publication bias analysis and found no obvious bias was found. Furthermore, the heterogeneity of all pooled results was acceptable ($I^2<50\%$), except LOS ($I^2=88\%$). Thus our results still remain reliable. Secondly, PD procedures were not performed in all studies, which may influenced our final result. However, according to the origin analysis, surgery method was not the risk factors.

In conclusion, patients in ERAS group had significantly lower incidence of morbidity and shorter LOS. Moreover, ERAS program would not increase the mortality rate and readmission rate. Nevertheless, ERAS programs also help to reduce PF and DGE rate. Future studies with larger sample size and better study design are urgently needed to evaluate the effects of ERAS in patients undergoing pancreatic surgery.

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Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the experiments: Z.B.X. Performed the experiments: Z.B.X. and C.J. Analyzed the data: Z.B.X., C.J., and D.L.F. Contributed reagents/materials/analysis tools: Z.B.X. and D.L.F. Wrote the paper: Z.B.X. and D.L.F.

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