Enhanced Recovery After Surgery Program in Patients Undergoing Pancreaticoduodenectomy

*l*edicine

A PRISMA-Compliant Systematic Review and Meta-Analysis

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Abstract: Enhanced recovery after surgery (ERAS) pathways are multimodal, evidence-based approaches to optimize patient outcome after surgery. However, the use of ERAS protocols to improve morbidity and recovery time without compromising safety following pancreatico-duodenectomy (PD) remains to be elucidated.

We conducted a systemic review and meta-analysis to assess the safety and efficacy of ERAS protocols compared with conventional perioperative care (CPC) in patients following PD.

PubMed, Medline, Embase, and Science Citation Index Expanded and Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library were searched between January 2000 and June 2015.

The patients who underwent PD with ERAS protocols or CPC were eligible. The studies that compared postoperative length of hospital stay (PLOS), postoperative complications, or in-hospital costs in the 2 groups were included.

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- Xubao Liu, Robert Sutton, Michael G. Raraty and Qing Xia designed the research, corrected, and approved the final manuscript; Junjie Xiong and Wei Huang developed the literature search and carried out the statistical analysis of studies; Junjie Xiong, Wei Huang, Peter Szatmary, Daniel de la Iglesia-Garciaand, Weiming Hu and Quentin M. Nunes carried out the extraction of data; Junjie Xiong, Peter Szatmary and Wei Huang wrote the manuscript.
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A meta-analysis, meta-regression, sensitivity analysis, and subgroup analysis were performed to estimate the postoperative outcomes between the 2 groups and identified the potential confounders. We used the methodological index for nonrandomized studies checklist to assess methodological qualities. Weighted mean differences (WMD) or odds ratios (OR) were calculated with their corresponding 95% confidence intervals (CI). The publication bias tests were also performed through the funnel plots.

In total, 14 nonrandomized comparative studies with 1409 ERAS cases and 1310 controls were analyzed. Implementation of an ERAS protocol significantly reduced PLOS (WMD: -4.17 days; 95%CI: -5.72 to -2.61), delayed gastric emptying (OR: 0.56; 95%CI: 0.44-0.71), overall morbidity (OR: 0.63; 95% CI: 0.54-0.74), and inhospital costs compared to CPC (all P < 0.001). There were no statistically significant differences in other postoperative outcomes. Age, gender, and ERAS component implementation did not significantly contribute to heterogeneity for PLOS as shown by meta-regression analysis.

Our study suggested that ERAS was as safe as CPC and improved recovery of patients undergoing PD, thus reducing in-hospital costs. General adoption of ERAS protocols during PD should be recommended.

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Abbreviations: CI = confidence interval, CPC = conventional perioperative care, DGE = delayed gastric emptying, ERAS = enhanced recovery after surgery, ISGPF = International Study Group of Pancreatic Fistula, ISGPS = International Study Group of Pancreatic Surgery, OR = odds ratios, PD = pancreaticoduodenectomy, PLOS = postoperative length of hospital stay, POPF = postoperative pancreatic fistula, PPPD = pylorus-preserving pancreaticoduodenectomy.

INTRODUCTION

H igh standards of perioperative management in conjunction with expert surgery are the corner stones of postoperative recovery. A formalized enhanced recovery after surgery (ERAS) program was first implemented in elective colorectal surgery.¹ ERAS involves a multidisciplinary team approach and thoughtful review of all aspects of operative and perioperative care, such as optimal pain control (including regional anesthesia), minimally invasive techniques, and aggressive postoperative rehabilitation (including nutritional support and ambulation).^{2,3} It has been further developed for joint,⁴ breast,⁵ and colorectal⁶ surgeries, consistently demonstrating significantly accelerated postoperative recovery and shortened postoperative length of hospital stay (PLOS), as well as reduced in-hospital costs, while maintaining similar safety profiles compared with conventional perioperative care (CPC) alone.⁷

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As a result, there is a consensus agreement that ERAS should be a standard practice in elective colorectal surgery.⁸

Guidelines published by the ERAS group also recommend its use in pancreaticoduodenectomy (PD); however, this recommendation was based on a very limited number of studies.⁹ A subsequent meta-analysis⁷ was only able to include 4 studies and found that ERAS reduced overall morbidity without affecting readmission rates or mortality.^{10–13} The effect of ERAS on PLOS and in-hospital costs after PD remains unexplored. This systematic review and meta-analysis incorporates the most recent published literature on this topic and aims to evaluate the effects of implementing an ERAS program following PD.

METHODS

Data Sources and Search Strategy

Major public medical and scientific databases including Medline, Embase, and Science Citation Index Expanded and Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library were searched for studies published in the English language comparing ERAS with CPC after PD, from January 2000 to June 2015. The following search terms were used, in all possible combinations: "Whipple," "pancreatticoduodenectomy," "pancreatoduodenectomy," "pancreatoduodenal resection," "ERAS program," "enhanced recovery," "fast track," "critical pathway," and "clinical pathway." Reference lists of selected articles were further examined for relevant articles during the initial search. Only comparative clinical trials with full-text descriptions were included. Final inclusion of articles was determined by consensus of 3 authors. The reporting of this systematic review is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁴

Inclusion and Exclusion Criteria

Inclusion criteria were: articles published in English in peer-reviewed journals; human studies; studies reporting at least one outcome of interest as defined below; and where multiple studies by the same institute and/or authors had overlapping enrollment times, only the higher quality study was included in the analysis.

Exclusion criteria were: abstracts, letters, editorials, reviews or guidelines, and case reports; noncomparative studies; and studies including patients undergoing procedures other than PD.

Outcomes of Interest

The primary outcome was PLOS. The secondary outcomes were rates of postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), overall morbidity, readmission, reoperation, mortality, and in-hospital costs.

PLOS was defined as the postoperative time interval in days. POPF was defined as per the International Study Group of Pancreatic Fistula (ISGPF) definition¹⁵ or as defined by the study's authors in studies conducted prior to 2005. DGE was defined according to the International Study Group of Pancreatic Surgery (ISGPS) definition¹⁶ or author's own definitions. Overall morbidity was defined as all complications from operation to discharge or within 30 days. Readmissions were defined as any hospital admission for any reason within 30 days of discharge. Reoperation was defined as the need for laparotomy as a consequence of the 1st operation within 30 days. Mortality was defined as death from any cause prior to discharge from hospital or within 30 days.

Data Extraction and Quality Assessment

Data were extracted by 2 independent observers using standardized forms. The recorded data included characteristics of included study, baseline parameters of patients, inclusion criteria for ERAS, elements of ERAS protocol, postoperative outcomes, and in-hospital costs. Means and standard deviations of the outcomes were used for meta-analysis unless otherwise mentioned. Methodologies for estimating means and standard deviations from medians and ranges have been described previously.^{17,18} The quality of included studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) checklist.¹⁹ This instrument scores 8 methodological items for noncomparative studies and an additional 4 criteria for comparative studies. The items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal scores were 16 for noncomparative studies and 24 for comparative studies.

Statistical Analysis

Meta-analysis was conducted by using Review Manager Version 5.3 software (Version 5.3 for Windows, The Cochrane Collaboration, 2014). Continuous and categorical variables were calculated as weighted mean differences or odds ratios (ORs) with their corresponding 95% confidence interval (CI), respectively. Heterogeneity was assessed using a Chi-square test, where P < 0.1 was considered significant. I^2 values were used for the evaluation of statistical heterogeneity; an I^2 value of 50% or more indicated the presence of heterogeneity.²⁰ The fixed-effects analysis²¹ was initially used for all outcomes, while the random-effects model²² was calculated when homogeneity of studies was not supported by the test. Data otherwise unsuitable for meta-analysis were described in the text.

Subgroup and sensitivity analyses were carried out by excluding each study out of each outcome measure. Subgroup analyses were performed by separately analyzing only high quality studies (MINORS score \geq 13), studies conducted in Western or Eastern countries, and studies in which n > 100. Sensitivity analyses were conducted to evaluate effects of operative technique (PD or PD with pylorus-preserving pancreatoduodectomy [PPPD]), pancreatic texture, or matching preoperative nutritional status. Meta-regression was carried out to assess the impact of age, gender, and implementation of ERAS elements (not used in >2 studies) on heterogeneity using Stata SE Version 13 Software (Stata Corp LP, TX) with a P < 0.05 considered significant. Funnel plots²³ were constructed to evaluate potential publication bias based on the PLOS, readmission, and other secondary outcomes.

Ethics, Standards of Reporting, Data Availability

This systematic review was not submitted to any biomedicalethical committee for approval, and no additional consent was sought from individuals analyzed. It was performed and reported according to the PRISMA standard. All primary outcome data are fully available from the published papers. Other data are partially available and are pointed out in the tables.

RESULTS

Description of Trials Included in the Meta-analysis

The search strategy initially generated 436 relevant clinical trials. No randomized clinical trials were identified. Figure 1

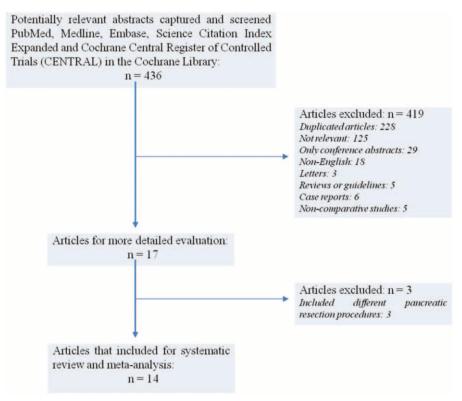


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the process of identification and inclusion of selected studies.

shows the process of selecting comparative studies using the PRISMA statement for meta-analyses.

Application of inclusion/exclusion criteria led to Application of inclusion/exclusion criteria led to 17 articles^{10–13,24–36} being subjected to detailed analysis. Of these studies, a further three^{10,32,33} were excluded as they included pancreatic resections other than PD, leaving 14 studies^{11–13,24–31,34–36} for data extraction. Patients in Sutcliff et al's study³⁴ were divided into high- and low-risk according to the risk of POPF using drain fluid amylase. As only low-risk patients were selected for all other ERAS programs, we included the patients at low-risk of POPF for analysis.

Characteristics and Quality Assessment of Included Studies

Detailed study characteristics and quality assessments are shown in Table 1. All the included studies were retrospective case–control series. Eleven studies^{11–13,24–27,30,34–36} were conducted in Western populations, and 8 studies^{11–13,26–28,30,31} had sample sizes >100. A total of 2719 patients were included with 1409 and 1310 patients in the ERAS group and CPC group, respectively. There were 12 studies^{11–13,24–26,28,29,31,34–36} with MINORS scores \geq 13.

Baseline Parameters of Patients and Inclusion Criteria for Surgery

The baseline parameters and inclusion criteria for ERAS are shown in Table 2. The mean or median age ranged from 44.2 to 70. The gender, body mass index, American Society of

Anesthesiologist score, pancreatic texture, and duct status distribution were equal for ERAS and CPC groups in most of the studies. Malignant pancreatic diseases accounted for 50% to 95% of the indications for surgery. Patients with benign pancreatic tumor, chronic pancreatitis, and other pancreatic disorders were also included for surgery.

In 6 studies^{11,24,29,30,35,36} only PD was performed, while PPPD was used as well as PD in 8 studies.^{12,13,25–28,31,34} One Japanese study²⁸ included both PPPD and subtotal stomachpreserving PD alongside PD. Eleven studies^{13,24,26–31,34–36} used the ISGPF definition for POPF. Kennedy et al¹¹ defined POPF as drainage of >30 mL with serum amylase level >3-fold for more than 10 days after surgery, while the diagnostic criteria were not described in the remaining 2 studies.^{12,25} Eight studies^{7,24,28–31,35,36} defined DGE as per ISGPS guidance, 3 studies^{11,13,26} defined it as a need for nasogastric decompression, persistent vomiting or vomiting occurring after the 10th postoperative day, and the remaining 3 studies^{12,25,34} did not state their criteria.

Essential ERAS Elements Used in Included Studies

Individual elements of different ERAS protocols used in each study are listed in Table 3. Although there were significant differences in the use of prophylactic antibiotics and octreotide, most studies used epidural and/or patient-controlled analgesia, prokinetic agents, and goal-directed mobilization and had predefined criteria for removal of drains, nasogastric tubes, and catheters as well as a preagreed discharge plan. Early oral intake was encouraged in most of studies.

Authors	Year	Country	Study Design	Group	No. of Patients	MINORS Score
Kennedy et al ¹¹	2007	USA	Case-control	ERAS	91	16/24
-				CPC	44	
Vanounou et al ¹²	2007	USA	Case-control	ERAS	145	15/24
12				CPC	64	
Balzano et al ¹³	2008	Italy	Case-control	ERAS	252	13/24
				CPC	252	
Abu Hilal et al ²⁴	2013	UK	Case-control	ERAS	20	15/24
			<i>a</i>	CPC	24	
Nikfarjam et al ²⁵	2013	Australia	Case-control	ERAS	20	13/24
D 126	0014	T. 1		CPC	21	15/04
Braga et al ²⁶	2014	Italy	Case-control	ERAS	115	17/24
C 1	2014	The Netherlands	Construction 1	CPC	115	12/24
Coolsen et al ²⁷	2014	The Netherlands	Case-control	ERAS CPC	86 97	12/24
Kobayashi et al ²⁸	2014	Japan	Case-control	ERAS	100	13/24
Kobayasili et al	2014	Japan	Case-control	CPC	90	15/24
Pillai et al ²⁹	2014	India	Case-control	ERAS	20	17/24
	2014	India	Case control	CPC	20	17/24
Nussbaum et al ³⁰	2015	USA	Case-control	ERAS	100	11/24
r ussou uni er ui	2010	0011	cube connor	CPC	142	
Shao et al ³¹	2015	China	Case-control	ERAS	325	15/24
				CPC	310	
Sutcliffe et al ³⁴	2015	UK	Case-control	ERAS	44	15/24
				CPC	37	
Morales Soriano et al ³⁵	2015	Sweden	Case-control	ERAS	50	17/24
				CPC	50	
Williamsson et al ³⁶	2015	Spain	Case-control	ERAS	41	17/24
		-		CPC	44	

TABLE 1. Study Characteristics and Quality Assessment

CPC = conventional perioperative care, ERAS = enhanced recovery after surgery, MINORS = Methodological Index for Non-Randomized Studies.

Meta-Analysis Outcomes

The postoperative outcomes are detailed in Supplementary Table 1, http://links.lww.com/MD/A928 and meta-analysis results are shown in Figures 2 and 3.

Primary Outcome

All studies reported the primary outcome: PLOS. Metaanalysis including 2719 patients showed that patients in the ERAS group had a shorter PLOS compared with those in the CPC group (weighted mean differences: -4.17 days; 95%CI: -5.72 to -2.61, P < 0.00001; Figure 2), although a moderate degree of heterogeneity was observed ($l^2 = 57\%$, P = 0.008).

Secondary Outcomes

The rates of POPF in all studies (OR: 0.88, 95%CI: 0.73– 1.08; P = 0.22; Figure 3A) or only those using the ISGPF definition (OR: 0.90, 95%CI: 0.74–1.10; P = 0.30) were similar between ERAS and CPC groups. Furthermore, there was no significant difference in POPF B/C (OR: 0.87, 95%CI: 0.66– 1.14; P = 0.32) between ERAS and CPC groups.

Compared to CPC, the incidence of DGE (OR: 0.56; 95% CI: 0.44–0.71, P < 0.0001; Figure 3B) was lower in the ERAS group. This difference remained statistically significant when only including studies adhering to the ISGPS definition (OR: 0.57, 95%CI: 0.42–0.77; P = 0.003).

The incidence of overall morbidity (OR: 0.63; 95%CI: 0.54-0.74, P < 0.00001; Figure 3C) was lower in the ERAS group.

There were no statistically significant differences in rates of readmission (OR: 1.05, 95%CI: 0.82-1.34; P=0.71; Figure 3D), reoperation (OR: 0.86, 95%CI: 0.60-1.22; P=0.39; Figure 3E), or mortality (OR: 0.95, 95%CI: 0.55-1.64; P=0.86; Figure 3F).

In-hospital costs were reported by 4 studies^{11,12,31,36} and showed that ERAS protocols significantly reduced costs. Kennedy et al¹¹ reported that the respective average costs were US \$126,566 ± 4883 in the ERAS group and \$240,242 ± 32,490 in the CPC group (P < 0.0001). Vanounou et al¹² reported decreased costs when using an ERAS protocol (a reduction from \$28,886 to \$23,344 following ERAS implementation). Shao et al³¹ also reported a reduction of costs from RMB 68,663.18 ± 26,639.74 to RMB 58,505.19 ± 34,044.92 (P < 0.001). These findings again were corroborated in the study of Williamsson et al,³⁶ with costs of €10400 (6519– 39558) and €14576 (8245–42750) in the ERAS group and CPC group (P < 0.001), respectively.

Subgroup, Sensitivity, and Meta-Regression Analyses

The results of the subgroup analysis are summarized in Table 4. The results of sensitivity analysis and meta-regression

TABLE 2. Basel	ine Parë	imeters of Pat	tients and	TABLE 2. Baseline Parameters of Patients and Inclusion Criteria for Surgery	ria for Surgery				
Authors	Group	Age, years	Male/ female	Body mass index, [*] kg/m ²	ASA Classification [†] or Score	Type of Surgery	Firm Pancreas Texture n, %	Pancreatic Duct ≤3 mm n, %	Inclusive Criteria for Surgery
Kennedy et al ¹¹	ERAS CPC	63.9 ± 1.3 61.3 ± 2.0	41/50 23/21	NA NA	NA NA	PD	NA NA	AN NA	M (74%) M (70%)
Vanounou et al ¹²	ERAS	64 64	NA	NA	2/53/84/6	D/PPPD	NA	NA	M, B or CP
Balzano et al ¹³	ERAS		155/97	NA	NA	DAPPD/	100 (39.7)	127 (50.4)	M (77.7%) , B (6%) , CP (7.9%) , O (8.3%)
Abu Hilal et al ²⁴	ERAS		148/104 10/10	NA	4/15/1/0	PD	100 (42.1) NA MA	(0.cc) cc1 NA	M (/0.0%), B (4.8%), CF (9.2%), U (9.1%) M (90%), B (10%) M (01.7%), B (20%)
Nikfarjam et al ²⁵	ERAS	$(0 \ (01 - 10) \ 68 \ (45 - 81)$	10/14 13/7	NA 25 (19–42)	0/5/15/0	DAPPD	NA 13 (65.0)	14 (70.0)	M (91./%0), B (8.3%0) M (90%)
Braga et al ²⁶	CPC ERAS	$\begin{array}{c} 62 \ (15 - 81) \\ 69 \ (61 - 74) \end{array}$	12/9 66/49	24 (19-34) 23.7 (21-25)	0/9/12/0 0/4/88/23	DAPPD.	10 (76.9) 47 (40.9)	3(25.0) 45(39.1)	M (76.2%) M (85.2%)
Coolsen et al ²⁷	CPC ERAS	69 (61–74) 67 \pm 11	66/49 44/42	23.1 (21–25) NA	0/4/82/29 NA	DAPPD/	50 (43.5) NA	52 (45.2) NA	M (82.6), B (7.1%), CP (1.2%), O (9.3%)
0 C		62 ± 13	58/39	NA	NA		NA	NA	M (73.3%), B (8.3%), CP (4.1%), O (14.4%)
Kobayashi et al²°	ERAS CPC	67.5 ± 10.7 65.4 ± 10.8	61/39 62/28	21.6 ± 3.54 25.0 ± 4.54	NA NA	PD/PPPD/SSPPD	NA NA	$4.10\pm2.15^{+}$ $3.71\pm2.46^{\ddagger}$	Pancreas tumor (45%), other tumor (55%) Pancreas tumor (50%), other tumor (50%)
Pillai et al ²⁹	ERAS	44.2 ± 15.9	9/11	NA	NA	PD	NA	NA	Periampullary carcinoma (\sim 50%)
		47.6 ± 12.0	10/10	NA	NA	ļ	NA	NA	Periampullary carcinoma (~50%)
Nussbaum et al	CPC	65.5 ± 10.1 62.1 ± 11.5	39/61 67/75	26.2 ± 4.6 27.1 ± 6.5	2.9 ± 0.4 2.9 ± 0.4	ЦЧ	NA NA	NA NA	M (39%), B (16%), CP (7%), U (18%) M (66%), B (15%), CP (3%), O (17%)
Shao et al ³¹	ERAS	57.0 ± 11.5	194/131	NA	NA	DD/PPPD	NA	NA	M (80.3%), B (19.7%)
Sutcliffe et al ³⁴	ERAS	$C.21 \pm 1.7C$	184/120 NA	NA	NA	DD/PPDD	NA	NA	M (79%), B (21%) M (94%), B (6%)
	CPC	NA	NA	NA	NA		NA	NA	M (92.3%), B (7.7%)
Morales Soriano et al ³⁵	ERAS	69 (15–80)	31/19	24.3 (19.4–36.2)	2/28/20/0	ΡD	NA	NA	M (94%), B (6%)
	CPC	67 (25–81)		25.2 (16.3-33.4)	6/27/17/0		NA	NA	M (88%), B (12%)
Williamsson et al ³⁶	ERAS	61.3 (44–80)	17/24	NA	NA	PD	NA	NA	M (93%), B (7%)
	CPC	66.7 (41-84)	17/27	NA	NA		NA	NA	M (95%), B (5%)
ASA = Americs pylorus-preserving for operation. *Data are show	an Sociel g pancrea n as mea	y of Anesthesic ticoduodenector m (± standard o	ologists, C my, SSPPI deviation	ASA = American Society of Amesthesiologists, CPC = conventional perioperative canlorus-preserving pancreaticoduodenectomy, SSPPD = subtotal stomach-preserving pancoperation.	I perioperative care, E ch-preserving pancreati or median (range).	cRAS = enhanced re icoduodenectomy, M	covery after surg 1 = malignant tum	ery, NA = not avail ors, B = benign tum.	ASA = American Society of Anesthesiologists, CPC = conventional perioperative care, ERAS = enhanced recovery after surgery, NA = not available, PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy, M = malignant tumors, B = benign tumors, CP = chronic pancreatitis, O = other reasons for operation.
⁺ Mean (± standard devia	lard devi	ADA class of μ	satic duct	diameter (mm).					

TABLE 3. Frequency of Elements Included in Enhanced Recovery After Surgery (ERAS) Protocols for Pancreaticoduo-denectomy

Element	Frequency
Prophylactic antibiotics	7/14 ^{11-12,25,27,30,35,36}
Octreotide	3/14 ^{27,34,36}
Removal of drains	$13/14^{11-13,24-30,34-36}$
Epidural or patient-controlled analgesia	11/14 ^{11,13,24,26-27,29-31,34-36}
Foley catheters	$10/14^{11-12,25,27-31,34,36}$
Prokinetic agents	8/14 ^{24-30,35}
Nasogastric tubes	$13/14^{11-13,25-31,34-36}$
Early oral intake	$13/14^{11-13,25-31,34-36}$
Goal-directed mobilization	$12/14^{11-13,25-27,29-31,34-36}$
Discharge planning	11/14 ^{11,25-31,34-36}

analysis are also summarized Supplementary Tables 2 and 3, http://links.lww.com/MD/A928, respectively.

The subgroup analysis including only high quality studies yielded similar results to the primary analysis. When analyzing only studies conducted in Western countries, the results were also the same, but with abolished heterogeneity for PLOS $(I^2 = 0\%)$; expectedly, there was increased heterogeneity in studies conducted in Eastern countries ($l^2 = 86\%$), and furthermore, the reduction of overall morbidity by ERAS was also no longer statistically significant (P = 0.1). The heterogeneity for PLOS in larger studies (n > 100) was increased (77%) with consistent clinical outcomes when compared to the primary analysis. In the sensitivity analysis, studies reporting matching preoperative nutritional status, pancreatic texture, or type of procedure (PD, PD/PPPD) showed reduced heterogeneity for PLOS and a consistent reduction of PLOS by ERAS. Age, gender, and ERAS component implementation did not significantly contribute to heterogeneity for PLOS as shown by metaregression analysis.

Publication Bias

The funnel plots based on PLOS and readmission are shown in Supplementary Figure 1, http://links.lww.com/MD/ A928. There was no evidence of publication bias of PLOS, readmission, and the other secondary outcomes (data not shown).

DISCUSSION

The 1-stage PD, or Whipple procedure, remains one of the most technically challenging general surgical operations with extreme impact on patient physiology.³⁷ Nowadays, despite reductions in mortality of this procedure to around 5% in highvolume specialized centers,^{38¹} it is still associated with post-operative morbidity up to 60%.³⁸⁻⁴⁰ A previous systematic review⁴¹ and meta-analysis⁷ suggest that using an ERAS protocol in pancreatic resections may help to shorten PLOS and reduced overall morbidity without affecting readmission rates or mortality. When only focusing on PD, a reduction of overall morbidity was noticed without significant differences in rates of readmission and mortality by the implementation of ERAS.⁷ The PLOS and in-hospital costs, however, were not specifically analyzed.^{7,41} We included 14 studies in our meta-analysis, demonstrating that implementation of ERAS program following PD can reduce PLOS, DGE, overall morbidity and in-hospital costs without affecting POPF, reoperation, readmission, and mortality rates. The primary outcome and most of the secondary outcomes remained unchanged in the subgroup and sensitivity analyses.

A large number of factors contribute to the timing of discharge of a patient following major surgery relating both to patient recovery and the healthcare environment. Patient morbidity may significantly contribute to PLOS; however, patient baseline characteristics and inclusion criteria for surgery were over all well balanced in the ERAS and CPC groups, indicating ERAS implementation as the main factor affecting PLOS. From a patient perspective, the reduction in PLOS is associated with reduced DGE rates and earlier return to normal

		ERAS			CPC			Mean Difference		Mean D	ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Rando	om, 95% Cl
Kennedy 2007	7	0	91	13	0	44		Not estimable	2007		
Vanounou 2007	8	0	145	8	0	64		Not estimable	2007		
Balzano 2008	13	29.25	252	15	27.25	252	6.6%	-2.00 [-6.94, 2.94]	2008		
Nikfarjam 2013	9.75	5.75	20	16.25	9.25	21	7.0%	-6.50 [-11.19, -1.81]	2013		
Abu Hilal 2013	9.25	5	20	14.25	7.75	24	9.0%	-5.00 [-8.80, -1.20]	2013		
Braga 2014	14.6	9.8	115	16.1	8.9	115	13.1%	-1.50 [-3.92, 0.92]	2014		+
Coolsen 2014	13	17.75	86	20	35.25	97	3.2%	-7.00 [-14.96, 0.96]	2014	· · ·	+
Pillai 2014	15.75	8.75	20	22	12.75	20	4.1%	-6.25 [-13.03, 0.53]	2014		+
Kobayashi 2014	21.9	11.9	100	36.3	23.8	90	5.7%	-14.40 [-19.84, -8.96]	2014	←	
Shao 2015	13.94	7.45	325	17.6	7.71	310	17.3%	-3.66 [-4.84, -2.48]	2015		
Sutcliffe 2015	7	12.75	44	9	16.5	37	4.4%	-2.00 [-8.52, 4.52]	2015		
Nussbaum 2015	11	6.45	100	13	7.08	142	15.6%	-2.00 [-3.72, -0.28]	2015		
Williamsson 2015	10	10.25	50	14	12.75	50	7.3%	-4.00 [-8.53, 0.53]	2015		+
Morales Soriano 2015	14.2	9.19	41	18.7	13.44	44	6.7%	-4.50 [-9.37, 0.37]	2015		+
Total (95% CI)			1409			1310	100.0%	-4.17 [-5.72, -2.61]		•	
Heterogeneity: Tau² = 3	.28; Chi²	= 25.34	4, df = ⁻	11 (P =	0.008);	l² = 57%	6				+ +
Test for overall effect: Z	= 5.25 (P < 0.00	0001)							-10 -5 Favours ERAS	0 5

FIGURE 2. Forest plots demonstrating the primary outcome postoperative length of hospital stay in terms of ERAS versus CPC after pancreaticoduodenectomy. Pooled WMDs with 95% CIs were calculated using the random-effects model. CI = confidence interval, CPC = conventional perioperative care, ERAS = enhanced recovery after surgery, WMD = weighted mean difference.

	ERAS		CPC			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
Kennedy 2007	2	91	4	44	2.5%	0.22 [0.04, 1.28]	2007	←
Balzano 2008	60	252	65	252	23.5%	0.90 [0.60, 1.35]	2008	
Abu Hilal 2013	4	20	4	24	1.4%	1.25 [0.27, 5.80]	2013	
Braga 2014	35	115	36	115	11.9%	0.96 [0.55, 1.68]	2014	
Kobayashi 2014	9	100	25	90	11.4%	0.26 [0.11, 0.59]	2014	←
Pillai 2014	11	20	10	20	2.1%	1.22 [0.35, 4.24]	2014	
Coolsen 2014	11	86		97	4.7%		2014	
Williamsson 2015	11		12 14	97 50	4.7%	1.04 [0.43, 2.49]	2014	
		50				0.73 [0.29, 1.80]		
Nussbaum 2015	38	100	43	142	10.5%	1.41 [0.82, 2.42]	2015	
Morales Soriano 2015	7	41	7	44	2.7%	1.09 [0.35, 3.42]	2015	
Shao 2015	53	325	56	310	22.8%	0.88 [0.58, 1.34]	2015	
Sutcliffe 2015	4	44	3	37	1.4%	1.13 [0.24, 5.42]	2015	-
Total (95% CI)		1244		1225	100.0%	0.88 [0.73, 1.08]		
Total events	245		279					
Heterogeneity: Chi ² = 14.94, df = 11 (P = 0.1	19); I ² = 26%							0.5 0.7 1 1.5 2
Test for overall effect: Z = 1.22 (P = 0.22)								Favours ERAS Favours CPC
A								
	ERAS		CPC			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
Kennedy 2007	7	91	3	44	2.0%	1.14 [0.28, 4.63]	2007	
Balzano 2008	35	252	62	252	28.6%	0.49 [0.31, 0.78]	2007	
Abu Hilal 2013	1	202	2	232	0.9%	0.58 [0.05, 6.90]	2008	
Abu Hilai 2013 Coolsen 2014	11	20	2	24 97	0.9%		2013 2014	
						1.89 [0.70, 5.11]		
Braga 2014	11	115	17	115	8.2%	0.61 [0.27, 1.37]	2014	
Pillai 2014	7	20	15	20	5.2%	0.18 [0.05, 0.70]	2014	
Kobayashi 2014	2	100	9	90	5.0%	0.18 [0.04, 0.87]	2014	<u> </u>
Williamsson 2015	13	50	24	50	9.5%	0.38 [0.16, 0.88]	2015	
Shao 2015	29	325	52	310	25.9%	0.49 [0.30, 0.79]	2015	
Morales Soriano 2015	1	41	3	44	1.5%	0.34 [0.03, 3.42]	2015	• • • • • • • • • • • • • • • • • • • •
Sutcliffe 2015	2	44	3	37	1.7%	0.54 [0.09, 3.42]	2015	
Nussbaum 2015	17	100	23	142	8.4%	1.06 [0.53, 2.11]	2015	
Total (95% CI)		1244		1225	100.0%	0.56 [0.44, 0.71]		•
Total events	136		220					
Heterogeneity: Chi2 = 16.27, df = 11 (P = 0.1								-+++++++++
Test for overall effect: Z = 4.79 (P < 0.00001								0.05 0.2 1 5 20
	.,							Favours ERAS Favours CPC
В								
U								
J	ERAS		CPC			Odds Ratio		Odds Ratio
Study or Subgroup	ERAS Events	Total	CPC Events	Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Year	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup		Total 91		Total 44	Weight 4.4%	M-H, Fixed, 95% Cl	Year	
Study or Subgroup Kennedy 2007	Events 34	91	Events 19	44	4.4%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63]	2007	
Study or Subgroup Kennedy 2007 Vanounou 2007	Events 34 77	91 145	Events 19 40	44 64	4.4% 7.1%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24]	2007 2007	
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008	Events 34 77 119	91 145 252	Events 19 40 148	44 64 252	4.4% 7.1% 21.4%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89]	2007 2007 2008	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hial 2013	Events 34 77 119 8	91 145 252 20	Events 19 40 148 16	44 64 252 24	4.4% 7.1% 21.4% 2.4%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14]	2007 2007 2008 2013	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014	Events 34 77 119 8 69	91 145 252 20 115	Events 19 40 148 16 76	44 64 252 24 115	4.4% 7.1% 21.4% 2.4% 8.3%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32]	2007 2007 2008 2013 2014	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hial 2013 Braga 2014 Kobayashi 2014	Events 34 77 119 8 69 39	91 145 252 20 115 100	Events 19 40 148 16 76 54	44 64 252 24 115 90	4.4% 7.1% 21.4% 2.4% 8.3% 9.5%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76]	2007 2007 2008 2013 2014 2014	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilal 2014	Events 34 77 119 8 69 39 9	91 145 252 20 115 100 20	Events 19 40 148 16 76 54 5	44 64 252 24 115 90 20	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8%	M.H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39]	2007 2007 2008 2013 2014 2014 2014	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilal 2014 Coolsen 2014	Events 34 77 119 8 69 39 39 9 46	91 145 252 20 115 100 20 86	Events 19 40 148 16 76 54 5 48	44 64 252 24 115 90 20 97	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7%	M-H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10]	2007 2007 2008 2013 2014 2014 2014 2014	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pillal 2014 Coolsen 2014 Succilife 2015	Events 34 77 119 8 69 39 9 46 15	91 145 252 20 115 100 20 86 44	Events 19 40 148 16 76 54 5 48 15	44 64 252 24 115 90 20 97 37	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.58] 0.33 [0.14, 1.68] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88]	2007 2007 2008 2013 2014 2014 2014 2014 2014	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilal 2014 Coolsen 2014 Sudciffe 2015 Shao 2015	Events 34 77 119 8 69 39 9 46 15 127	91 145 252 20 115 100 20 86 44 325	Events 19 40 148 16 76 54 5 48 15 173	44 64 252 24 115 90 20 97 37 310	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70]	2007 2007 2008 2013 2014 2014 2014 2014 2014 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilal 2014 Coolsen 2014 Sutcliffe 2015 Shao 2015 Morales Soriano 2015	Events 34 77 119 8 69 39 9 46 15 127 12	91 145 252 20 115 100 20 86 44 325 41	Events 19 40 148 16 76 54 5 48 15 15 173 24	44 64 252 24 115 90 20 97 37 310 44	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilai 2014 Coolsen 2014 Sudcilfe 2015 Shao 2015	Events 34 77 119 8 69 39 9 46 15 127	91 145 252 20 115 100 20 86 44 325	Events 19 40 148 16 76 54 5 48 15 173	44 64 252 24 115 90 20 97 37 310	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70]	2007 2007 2008 2013 2014 2014 2014 2014 2014 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilal 2014 Coolsen 2014 Sucliffe 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015	Events 34 77 119 8 69 39 9 46 15 127 12	91 145 252 20 115 100 20 86 44 325 41 50	Events 19 40 148 16 76 54 5 48 15 15 173 24	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.33] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilal 2014 Cooleen 2014 Sutcliffe 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total (95% CI)	Events 34 77 119 8 69 39 9 46 15 127 127 12 32	91 145 252 20 115 100 20 86 44 325 41	Events 19 40 148 16 54 5 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilai 2014 Coolsen 2014 Suba 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total (95% CI) Total events	Events 34 77 119 8 69 9 9 46 15 127 127 12 32 587	91 145 252 20 115 100 20 86 44 325 41 50	Events 19 40 148 16 76 54 5 48 15 15 173 24	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.33] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Baizano 2008 Abu Hial 2013 Braga 2014 Kobayashi 2014 Pilai 2014 Coolsen 2014 Sucliffe 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total (95% CI) Total events Heterogeneity: Chi ^o = 16.17, df = 11 (P = 0.1000)	Events 34 77 119 8 69 39 9 9 46 15 127 12 32 587 13); P = 32%	91 145 252 20 115 100 20 86 44 325 41 50	Events 19 40 148 16 54 5 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.33] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilali 2013 Shaqa 2014 Kobayashi 2014 Pilali 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total events Heterogeneily: Chi² = 16.17, df = 11 (P = 0: Test for overall effect: Z = 5.52 (P < 0.0007)	Events 34 77 119 8 69 39 9 9 46 15 127 12 32 587 13); P = 32%	91 145 252 20 115 100 20 86 44 325 41 50	Events 19 40 148 16 54 5 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.33] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Baizano 2008 Abu Hial 2013 Braga 2014 Kobayashi 2014 Pilai 2014 Coolsen 2014 Sucliffe 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total (95% CI) Total events Heterogeneity: Chi ^o = 16.17, df = 11 (P = 0.1000)	Events 34 77 119 8 69 39 9 9 46 15 127 12 32 587 13); P = 32%	91 145 252 20 115 100 20 86 44 325 41 50	Events 19 40 148 16 54 5 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.33] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilali 2013 Shaqa 2014 Kobayashi 2014 Pilali 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total events Heterogeneily: Chi² = 16.17, df = 11 (P = 0: Test for overall effect: Z = 5.52 (P < 0.0007)	Events 34 77 119 8 69 39 9 9 46 15 127 12 32 587 13); P = 32%	91 145 252 20 115 100 20 86 44 325 41 50	Events 19 40 148 16 54 5 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.33] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Varounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilali 2013 Shaqa 2014 Kobayashi 2014 Pilali 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total events Heterogeneily: Chi² = 16.17, df = 11 (P = 0: Test for overall effect: Z = 5.52 (P < 0.0007)	Events 34 77 119 8 69 39 9 46 15 127 12 32 587 13): I ² = 32%	91 145 252 20 115 100 20 86 44 325 41 50	Events 40 148 16 76 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44 50	4.4% 7.1% 21.4% 2.4% 8.3% 9.5% 0.8% 5.7% 2.9% 29.6% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92] 0.63 [0.54, 0.74]	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Baizano 2008 Abu Hial 2013 Braga 2014 Kobayashi 2014 Pilali 2014 Colsero 2014 Sutcliffe 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total (95% CI) Total events Heterogeneity: Chi ² = 16.17, df = 11 (P = 0. Test for overall effect: Z = 5.52 (P < 0.00001)	Events 34 77 119 8 69 9 9 46 15 127 12 32 587 13); P = 32% 1) ERAS	91 145 252 20 115 100 20 86 44 325 41 50 1289	Events 19 40 148 16 54 5 48 15 173 24 34	44 64 252 24 115 90 20 97 37 310 44 50 1147	4.4% 7.1% 2.14% 8.3% 9.5% 9.5% 2.9% 2.9% 4.5% 3.4%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.64 [0.37, 1.92] 0.63 [0.54, 0.74] Odds Ratio	2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H, Fixed, 95% CI
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilala 2014 Coolsen 2014 Sucifie 2015 Shao 2015 Morales Soriano 2015 Villiamsson 2015 Total (95% CI) Test for overall effect: Z = 5.52 (P < 0.0000)	Events 34 37 119 8 69 9 9 46 15 127 12 32 587 13); I ² = 32% 1) ERAS Events	91 145 252 20 115 100 20 20 86 44 325 41 50 1289	Events 19 40 148 16 76 48 15 173 24 34 652 CPC Events	44 64 22 24 115 90 20 97 37 310 44 50 1147	4.4% 7.1% 21.4% 8.3% 9.5% 0.8% 5.7% 2.9% 2.9% 4.5% 3.4% 100.0%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92] 0.63 [0.54, 0.74] Odds Ratio M+H, Fixed, 95% Cl	2007 2008 2013 2014 2014 2014 2015 2015 2015 2015 2015	M-H, Fixed, 95% Cl
Study or Subgroup Kennedy 2007 Vanounou 2007 Balzano 2008 Abu Hilal 2013 Braga 2014 Kobayashi 2014 Pilali 2014 Coolsen 2014 Sutcliffe 2015 Shao 2015 Morales Soriano 2015 Williamsson 2015 Total (95% CI) Total events Hetoregonethy: Ch ^a = 16.17, df = 11 (P = 0 Test for overall effect: Z = 5.52 (P < 0.00001	Events 34 37 119 8 69 39 9 46 15 127 12 32 13); P = 32% 1) ERAS Events 7	91 145 252 20 115 100 20 86 44 325 41 50 1289 1289	Events 19 40 148 16 76 48 15 173 24 34 652 Events	44 64 252 24 115 90 20 97 37 310 44 50 1147	4.4% 7.1% 21.4% 4.3% 9.5% 9.5% 0.8% 5.7% 2.9% 2.96% 4.5% 3.4% 100.0% Weight 3.1%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.31, 1.88] 0.51 [0.37, 0.70] 0.34 [0.14, 0.85] 0.44 [0.37, 0.74] 0.63 [0.54, 0.74] Odds Ratio M+H, Fixed, 95% Cl 1.14 [0.28, 4.63]	2007 2008 2013 2014 2014 2014 2015 2015 2015 2015 2015 2015 2015	M-H, Fixed, 95% CI
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Study or Subgroup Kennedy 2007 Vanounou 2007 Baizano 2008 Abu Hial 2013 Braga 2014 Kobayashi 2014 Pilali 2015 Shac 2015 Morales Soriano 2015 Williamsson 2015 Total (95% Cl) Total events Heterogeneity: Chi* = 16.17, df = 11 (P = 0. Test for overall effect: Z = 5.52 (P < 0.0000)	Events 34 77 119 8 69 9 9 46 15 127 12 32 587 13); P = 32% 1) ERAS Events 7 7 13 18 13 14	91 145 252 20 115 100 20 86 44 325 41 50 1289 Total 91 145 252 20 20 145 252 20 20 20 15 100 115 20 20 20 115 100 20 20 20 20 20 20 20 20 20	Events 19 40 148 16 76 54 55 48 173 24 34 652 Events 3 18 2 0 12	44 64 252 20 90 97 37 310 44 50 1147 1147 Total 44 64 252 24 21 115	4.4% 7.1% 2.14% 8.3% 9.5% 9.5% 4.5% 3.4% 100.0% Weight 3.1% 4.1% 1.2%	M+H, Fixed, 95% Cl 0.78 [0.38, 1.63] 0.68 [0.37, 1.24] 0.63 [0.44, 0.89] 0.33 [0.10, 1.14] 0.77 [0.45, 1.32] 0.43 [0.24, 0.76] 2.45 [0.64, 9.39] 1.17 [0.66, 2.10] 0.76 [0.37, 1.07] 0.54 [0.37, 0.70] 0.34 [0.14, 0.85] 0.84 [0.37, 1.92] 0.63 [0.54, 0.74] 0.63 [0.54, 0.74] 0.63 [0.54, 0.74] 0.63 [0.54, 0.74]	2007 2008 2013 2014 2014 2014 2015 2015 2015 2015 2015 2015 2015 2015	M-H, Fixed, 95% CI
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FIGURE 3. Forest plots demonstrating secondary outcomes in terms of ERAS versus CPC after pancreaticoduodenectomy. (A) Postoperative pancreatic fistula; (B) delayed gastric emptying; (C) overall morbidity; (D) readmission rate; (E) reoperation rate; and (F) mortality. CPC = conventional perioperative care, ERAS = enhanced recovery after surgery.

nutrition and enteric function, as well as lower levels of pain and quicker return to preoperative levels of mobility resulting in an overall improvement in the postoperative experience. Although pain and mobility levels were not specifically reported by all individual studies, they were included in the measure of overall morbidity, a reduction of which was seen in the ERAS group in this analysis. Factors relating to the healthcare environment can also delay discharge and, amongst others, these include availability of community support and transportation.⁴² Healthcare systems also function in entirely different cultural and economical environments. In the UK, it is common practice to discharge patients from hospital early and continue care in

Study or Subgroup	ERAS Events	Total	CPC Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% Cl
Vanounou 2007	7	145	4	64	7.9%	0.76 [0.21, 2.70]	2007	
Balzano 2008	17	252	20	252	27.9%	0.84 [0.43, 1.64]	2008	
Abu Hilal 2013	1	20	3	24	3.9%	0.37 [0.04, 3.85]	2013	← • · · · · · · · · · · · · · · · · · ·
Coolsen 2014	7	86	13	97	16.8%	0.57 [0.22, 1.51]	2014	
Pillai 2014	3	20	1	20	1.3%	3.35 [0.32, 35.36]	2014	
Braga 2014	14	115	12	115	15.8%	1.19 [0.52, 2.70]	2014	
Morales Soriano 2015	5	41	5	44	6.3%	1.08 [0.29, 4.05]	2015	
Nussbaum 2015	10		18			0.77 [0.34, 1.74]	2015	
Nussbaum 2015	10	100	18	142	20.1%	0.77 [0.34, 1.74]	2015	
Total (95% CI)		779		758	100.0%	0.86 [0.60, 1.22]		-
Total events	64		76					
Heterogeneity: Chi ² = 3.30, df = 7 (P = 0.8	86); l ² = 0%							-+ + + + + + +
Test for overall effect: Z = 0.85 (P = 0.39)	1							0.1 0.2 0.5 1 2 5 10
Ξ								Favours ERAS Favours CPC
Studu or Suboroun	ERAS	Total	CPC	Total	Woight	Odds Ratio	Voar	Odds Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	Odds Ratio M-H, Fixed, 95%, Cl
Vanounou 2007		145		164	3.4%	M-H, Fixed, 95% Cl 2.28 [0.20, 25.41]	2007	
	Events 2		Events 1	164 44	3.4% 5.0%	M-H, Fixed, 95% Cl 2.28 [0.20, 25.41] 0.48 [0.03, 7.82]	2007 2007	
Vanounou 2007 Kennedy 2007	Events 2 1	145 91	Events 1 1	164	3.4%	M-H, Fixed, 95% Cl 2.28 [0.20, 25.41]	2007	
Vanounou 2007 Kennedy 2007 Balzano 2008	Events 2 1 9	145 91 252	Events 1 1 7	164 44 252	3.4% 5.0%	M-H, Fixed, 95% Cl 2.28 [0.20, 25.41] 0.48 [0.03, 7.82] 1.30 [0.48, 3.54]	2007 2007 2008	
Vanounou 2007 Kennedy 2007 Balzano 2008 Abu Hilal 2013	Events 2 1 9 0	145 91 252 20	Events 1 1 7 0	164 44 252 24	3.4% 5.0% 25.1%	M-H, Fixed, 95% Cl 2.28 [0.20, 25.41] 0.48 [0.03, 7.82] 1.30 [0.48, 3.54] Not estimable	2007 2007 2008 2013	
Vanounou 2007 Kennedy 2007 Batzano 2008 Abu Hilai 2013 Piliai 2014 Kobayashi 2014 Braga 2014	Events 2 1 9 0 2	145 91 252 20 20	Events 1 7 0 1	164 44 252 24 20	3.4% 5.0% 25.1% 3.3%	M-H, Fixed, 95% Cl 2.28 (0.20, 25.41] 0.48 (0.03, 7.82] 1.30 (0.48, 3.54] Not estimable 2.11 (0.18, 25.35]	2007 2007 2008 2013 2014	
Vanounou 2007 Karendy 2007 Balzana 2006 Abu Hill 2013 Pillia 2014 Kobayashi 2014 Braga 2014 Cochen 2014	Events 2 1 9 0 2 0 4 4 4	145 91 252 20 20 100 115 86	Events 1 1 7 0 1 1 1 4 6	164 44 252 24 20 90 115 97	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0%	MH, Fixed, 95%; Cl 2.28 (0.20, 25.41) 0.48 (0.03, 7.82) 1.30 (0.48, 3.54) Not estimable 2.11 (0.18, 25.36) 0.30 (0.01, 7.38) 1.00 (0.24, 4.10) 0.74 (0.20, 2.71]	2007 2007 2008 2013 2014 2014 2014 2014	
Vanounou 2007 Kennedy 2007 Balzano 2008 Abu Hilal 2013 Pilai 2014 Braga 2014 Coolean 2014 Coolean 2014 Suddiffe 2015	Events 2 1 9 0 2 0 4 4 4 2	145 91 252 20 20 100 115 86 44	Events 1 1 7 0 1 1 4 6 0	164 44 252 24 20 90 115 97 37	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9%	MH. Fixed, 95%; Cl 2.28 (0.20; S; A1] 0.48 (0.03; 7; 82] 1.30 (0.48; 3: 54] Not estimable 2.11 (0.18; 25: 35] 0.30 (0: 07; 7: 38] 1.00 (0: 24, 4.10) 0.74 (0: 20; 2: 71) 4.41 (221; 94: 84]	2007 2007 2008 2013 2014 2014 2014 2014 2014	
Vanounou 2007 Kanendy 2007 Balzano 2008 Aub Hial 2013 Pilia 2014 Kobayashi 2014 Braga 2014 Coolsen 2014 Sukofile 2015 Nussbaum 2015	Events 2 1 9 0 2 0 4 4 4 2 1	145 91 252 20 100 115 86 44 100	Events 1 1 7 0 1 1 1 4 6 0 0 4	164 44 252 24 20 90 115 97 37 142	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9% 12.2%	MH. Fixed, 55%, CI 2.28 (0.20, 28.41) 0.48 (0.30, 7.82) 1.30 (0.48, 3.54) Not estimatile 2.11 (0.18, 25.35) 0.30 (0.01, 7.38) 1.00 (24, 4.10) 0.74 (0.20, 2.71) 4.41 (0.21, 94.84) 0.35 (0.04, 3.17)	2007 2007 2008 2013 2014 2014 2014 2014 2014 2015 2015	
Vanounou 2007 Kennedy 2007 Balzano 2008 Abu Hill 2013 Pillal 2014 Braga 2014 Coolten 2014 Sutdiffic 2015 Nuasbaum 2015 Morales Soriano 2015	Events 2 1 9 0 2 0 4 4 2 1 2 1 0	145 91 252 20 20 100 115 86 44 100 41	Events 1 1 7 0 1 1 1 1 4 6 0 0 4 2	164 44 252 24 20 90 115 97 37 142 44	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9%	M-H., Fixed, 55%, CI 2.28 (0.20, 25.41] 0.48 (0.03, 7.82] 1.30 (0.48, 3.54] Not estimable 2.11 (0.16, 25.35] 0.30 (0.01, 7.38] 1.00 (0.24, 4.10] 0.74 (0.22, 271] 4.41 (0.21, 94.84] 0.35 (0.04, 3.17] 0.20 (0.01, 4.40]	2007 2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	
Vanounou 2007 Kernedy 2007 Balzano 2008 Abu Hial 2013 Pilia 2014 Kobayashi 2014 Braga 2014 Coolem 2014 Sukcifie 2015 Nussbaum 2015	Events 2 1 9 0 2 0 4 4 4 2 1	145 91 252 20 100 115 86 44 100	Events 1 1 7 0 1 1 1 4 6 0 0 4	164 44 252 24 20 90 115 97 37 142	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9% 12.2%	MH. Fixed, 55%, CI 2.28 (0.20, 28.41) 0.48 (0.30, 7.82) 1.30 (0.48, 3.54) Not estimatile 2.11 (0.18, 25.35) 0.30 (0.01, 7.38) 1.00 (24, 4.10) 0.74 (0.20, 2.71) 4.41 (0.21, 94.84) 0.35 (0.04, 3.17)	2007 2008 2013 2014 2014 2014 2014 2014 2015 2015	
Vanounou 2007 Kennedy 2007 Balzano 2008 Abu Hill 2013 Pillal 2014 Braga 2014 Coolten 2014 Sutdiffic 2015 Nuasbaum 2015 Morales Soriano 2015	Events 2 1 9 0 2 0 4 4 2 1 2 1 0	145 91 252 20 20 100 115 86 44 100 41	Events 1 1 7 0 1 1 1 1 4 6 0 0 4 2	164 44 252 24 20 90 115 97 37 142 44	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9% 12.2%	M-H., Fixed, 55%, CI 2.28 (0.20, 25.41] 0.48 (0.03, 7.82] 1.30 (0.48, 3.54] Not estimable 2.11 (0.16, 25.35] 0.30 (0.01, 7.38] 1.00 (0.24, 4.10] 0.74 (0.22, 271] 4.41 (0.21, 94.84] 0.35 (0.04, 3.17] 0.20 (0.01, 4.40]	2007 2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	
Vanounou 2007 Kennedy 2007 Balzana 2008 Abu Hilla 2013 Pillila 2014 Kobayashi 2014 Braga 2014 Coolten 2014 Suddiffe 2015 Morales Soriano 2015 Williamason 2015	Events 2 1 9 0 2 0 4 4 2 1 2 1 0	145 91 252 20 20 100 115 86 44 100 41 50	Events 1 1 7 0 1 1 1 1 4 6 0 0 4 2	164 44 252 24 20 90 115 97 37 142 44 50	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9% 12.2% 8.9%	M-H, Fixed, 95%, CI 2.28 (0.20, 25.41] 0.48 (0.03, 7.82] 1.30 (0.46, 3.54] Not estimatile 2.11 (0.18, 25.35] 0.30 (0.01, 7.38] 1.00 (0.24, 4.10] 0.74 (0.20, 2.71] 4.41 (0.21, 94.84] 0.35 (0.04, 3.17] 0.20 (0.01, 4.40] Not estimatie	2007 2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	
Vanounou 2007 Kenneky 2007 Balzano 2008 Abu Hila 2013 Pillal 2014 Braga 2014 Cookens 2014 Sutcliffe 2015 Nusisbaum 2015 Williamsson 2015 Williamsson 2015	Events 2 1 9 0 2 0 4 4 2 1 0 0 2 5 25	145 91 252 20 20 100 115 86 44 100 41 50	Events	164 44 252 24 20 90 115 97 37 142 44 50	3.4% 5.0% 25.1% 3.3% 5.8% 14.4% 20.0% 1.9% 12.2% 8.9%	M-H, Fixed, 95%, CI 2.28 (0.20, 25.41] 0.48 (0.03, 7.82] 1.30 (0.46, 3.54] Not estimatile 2.11 (0.18, 25.35] 0.30 (0.01, 7.38] 1.00 (0.24, 4.10] 0.74 (0.20, 2.71] 4.41 (0.21, 94.84] 0.35 (0.04, 3.17] 0.20 (0.01, 4.40] Not estimatie	2007 2007 2008 2013 2014 2014 2014 2014 2015 2015 2015	M-H. Fixed, S5% CI
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FIGURE 3. (Continued)

the community if required through the use of specialist community nursing and therapy staff. In countries including China and India, not all patients have medical insurance or are able to fund convalescent periods in hospital, contributing to a higher heterogeneity observed in our analysis which was reduced when analyzing only studies from Western centers.

There is substantial and ever increasing evidence for optimal practice relating to individual components of operative and perioperative management, both specific to pancreatic resections and surgery in general. The ERAS programs utilize these data to plan idealized care, limiting variability of outcome while maintaining patient-specific and individualized management through the use of treatment protocols, targets/objectives for staff and patients as well as embedding early warning systems to identify problems. Indeed, members of local multidisciplinary teams often receive specific training relating to ERAS components following its introduction, and this may in part explain the identified patient benefits. It is self-evident, therefore, that each specialist unit included in this meta-analysis has developed and implemented their own individual ERAS protocol, which differs slightly in details (e.g., how early the drain or Foley was removed) to that of all others. This is also a likely source for the observed heterogeneity seen in this metaanalysis. Finally, there was heterogeneity in the definitions of the outcome measures. For addressing this issue, we performed a meta-regression analysis to assess the impact of ERAS elements on heterogeneity for PLOS and found that none of the parameters contributed significantly to heterogeneity.

ERAS pathways have previously been shown to reduce healthcare costs in a number of surgical procedures, including pancreatic surgery.^{5,11,43} PLOS correlates with costs,⁴⁴ so it was not surprizing that in the 4 studies reported this outcome there

was a reduction of in-hospital costs in each center, resulting in overall reduction in in-hospital costs in the EARS group in our meta-analysis. There was a 10-fold difference between the costliest and the cheapest center, with the greatest reductions reported by the centers with the highest costs. Naturally, clinical pathways require resources to develop, implement and maintain,⁴⁵ but this cost will be offset somewhat by savings generated by the protocols. Nevertheless, the emphasis when developing a service clearly has to remain with improving patient care, and the reductions in morbidity reported in this meta-analysis supports implementation of ERAS protocols following PD on those grounds.

We base our analysis on best, currently available evidence, consisting exclusively of retrospective studies. Clearly, blinded implementation of such an ERAS protocol is impossible, and simultaneous prospective cohorts of patients impractical, which is why only retrospective cohorts have been published to date. Therefore, to a certain extent, selection bias may affect the results of the study. Prospective study designs such as crossover trials or use of national and international prospective databases are of course possible, and also allow detailed evaluation of individual elements within protocols.46 However, one could argue that it is not necessary to trial a protocol that simply implements a summation of best available evidence into daily practice. As such, we conclude that implementation of a locally agreed, standardized perioperative protocol designed and implemented in the spirit of ERAS can enhance recovery in patients undergoing PD.

In summary, the present study shows that ERAS protocols reduced PLOS, DGE and overall morbidity without adversely affecting rates of POPF, readmission, reoperation, or mortality during PD, thereby reducing healthcare costs. Following ERAS

TABLE 4. Results of Subgroup Analysis

No. of Studies	No. of Patients	OR/ WMD	95% CI	P Value	Heterogeneity <i>P</i> Value	$I^2, \%$
12	2204	1.54	6 28 2 60	~0.00001	0.01	57
12	2294	-4.34	-0.38, -2.09	<0.00001	0.01	57
10	2044	0.91	0.65 1.01	0.06	0.24	22
			,			0
			· · · · · · · · · · · · · · · · · · ·			12
			· · ·			0
			· · · · · · · · · · · · · · · · · · ·			0
10	1718	1.12	0.60, 2.11	0.72	0.82	0
11	1854	-2.77	-3.89, -1.64	<0.00001	0.48	0
			· · · · · · · · · · · · · · · · · · ·			0
						22
-			· · ·			0
	1854	1.11	0.82, 1.50		0.72	0
			0.58, 1.18		0.92	0
10	1913	0.95	0.54, 1.68	0.86	0.78	0
3	865	-7.83	-14.75, -0.91	0.03	0.0007	86
3	865	0.63	0.26, 1.54	0.31	0.02	74
3	865	0.40	0.26, 0.62	<0.0001	0.23	31
3	865	0.60	0.33, 1.11	0.10	0.06	64
3	865	0.92	0.59, 1.43	0.71	0.98	0
2	230	0.96	0.16, 5.70	0.96	0.34	0
			,			
8	2328	-4.02	-6.371.66	0.0008	0.0006	77
			,			
7	2119	0.82	0.57.1.17	0.28	0.03	57
			· · ·			50
			,			32
			· · ·			0
			,			0
			· · · · · · · · · · · · · · · · · · ·			0
	12 10 10 11 12 6 10 11 9 9 9 11 7 10 3 3 3 3 3 3 3 3	12 2294 10 2044 10 2044 11 2253 12 2294 6 1112 10 1718 11 1854 9 1604 9 1604 9 1604 9 1604 9 1604 9 1571 11 1854 7 1497 10 1913 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 3 865 4 2328 7 2119 7 <td>12 2294 -4.54 10 2044 0.81 10 2044 0.47 11 2253 0.60 12 2294 1.01 6 1112 0.96 10 1718 1.12 11 1854 -2.77 9 1604 0.98 9 1604 0.65 9 1571 0.70 11 1854 1.11 7 1497 0.83 10 1913 0.95 3 865 0.63 3 865 0.60 3 865 0.40 3 865 0.92 2 230 0.96 8 2328 -4.02 7 2119 0.67 7 2086 0.63 8 2328 1.08 5 1368 0.83 </td> <td>12 2294 -4.54 $-6.38, -2.69$ 10 2044 0.81 0.65, 1.01 10 2044 0.47 0.36, 0.61 11 2253 0.60 0.51, 0.71 12 2294 1.01 0.75, 1.35 6 1112 0.96 0.63, 1.48 10 1718 1.12 0.60, 2.11 11 1854 -2.77 -3.89, -1.64 9 1604 0.98 0.77, 1.25 9 1604 0.98 0.77, 1.25 9 1604 0.65 0.49, 0.87 9 1571 0.70 0.57, 0.86 11 1854 1.11 0.82, 1.50 7 1497 0.83 0.58, 1.18 10 1913 0.95 0.54, 1.68 3 865 0.60 0.33, 1.11 3 865 0.60 0.33, 1.11 3 865 0.92 0.59, 1.43 2 230<td>12 2294 -4.54 $-6.38, -2.69$ <0.00001 10 2044 0.81 0.65, 1.01 0.06 10 2044 0.47 0.36, 0.61 <0.00001 11 2253 0.60 0.51, 0.71 <0.00001 12 2294 1.01 0.75, 1.35 0.96 6 1112 0.96 0.63, 1.48 0.86 10 1718 1.12 0.60, 2.11 0.72 11 1854 -2.77 $-3.89, -1.64$ <0.00001 9 1604 0.98 0.77, 1.25 0.90 9 1604 0.65 0.49, 0.87 0.003 9 1571 0.70 0.57, 0.86 0.0007 11 1854 1.11 0.82, 1.50 0.49 7 1497 0.83 0.58, 1.18 0.30 10 1913 0.95 0.54, 1.68 0.86 3 865 0.60 0.33, 1.11 0.10 3 865 0.60 0.33, 1.11 0.10 3 <</td><td>12 2294 -4.54 $-6.38, -2.69$ <0.00001</td> 0.01 10 2044 0.81 0.65, 1.01 0.06 0.24 10 2044 0.47 0.36, 0.61 <0.00001</td> 0.77 11 2253 0.60 0.51, 0.71 <0.00001	12 2294 -4.54 10 2044 0.81 10 2044 0.47 11 2253 0.60 12 2294 1.01 6 1112 0.96 10 1718 1.12 11 1854 -2.77 9 1604 0.98 9 1604 0.65 9 1571 0.70 11 1854 1.11 7 1497 0.83 10 1913 0.95 3 865 0.63 3 865 0.60 3 865 0.40 3 865 0.92 2 230 0.96 8 2328 -4.02 7 2119 0.67 7 2086 0.63 8 2328 1.08 5 1368 0.83	12 2294 -4.54 $-6.38, -2.69$ 10 2044 0.81 0.65, 1.01 10 2044 0.47 0.36, 0.61 11 2253 0.60 0.51, 0.71 12 2294 1.01 0.75, 1.35 6 1112 0.96 0.63, 1.48 10 1718 1.12 0.60, 2.11 11 1854 -2.77 -3.89, -1.64 9 1604 0.98 0.77, 1.25 9 1604 0.98 0.77, 1.25 9 1604 0.65 0.49, 0.87 9 1571 0.70 0.57, 0.86 11 1854 1.11 0.82, 1.50 7 1497 0.83 0.58, 1.18 10 1913 0.95 0.54, 1.68 3 865 0.60 0.33, 1.11 3 865 0.60 0.33, 1.11 3 865 0.92 0.59, 1.43 2 230 <td>12 2294 -4.54 $-6.38, -2.69$ <0.00001 10 2044 0.81 0.65, 1.01 0.06 10 2044 0.47 0.36, 0.61 <0.00001 11 2253 0.60 0.51, 0.71 <0.00001 12 2294 1.01 0.75, 1.35 0.96 6 1112 0.96 0.63, 1.48 0.86 10 1718 1.12 0.60, 2.11 0.72 11 1854 -2.77 $-3.89, -1.64$ <0.00001 9 1604 0.98 0.77, 1.25 0.90 9 1604 0.65 0.49, 0.87 0.003 9 1571 0.70 0.57, 0.86 0.0007 11 1854 1.11 0.82, 1.50 0.49 7 1497 0.83 0.58, 1.18 0.30 10 1913 0.95 0.54, 1.68 0.86 3 865 0.60 0.33, 1.11 0.10 3 865 0.60 0.33, 1.11 0.10 3 <</td> <td>12 2294 -4.54 $-6.38, -2.69$ <0.00001</td> 0.01 10 2044 0.81 0.65, 1.01 0.06 0.24 10 2044 0.47 0.36, 0.61 <0.00001	12 2294 -4.54 $-6.38, -2.69$ <0.00001 10 2044 0.81 0.65, 1.01 0.06 10 2044 0.47 0.36, 0.61 <0.00001 11 2253 0.60 0.51, 0.71 <0.00001 12 2294 1.01 0.75, 1.35 0.96 6 1112 0.96 0.63, 1.48 0.86 10 1718 1.12 0.60, 2.11 0.72 11 1854 -2.77 $-3.89, -1.64$ <0.00001 9 1604 0.98 0.77, 1.25 0.90 9 1604 0.65 0.49, 0.87 0.003 9 1571 0.70 0.57, 0.86 0.0007 11 1854 1.11 0.82, 1.50 0.49 7 1497 0.83 0.58, 1.18 0.30 10 1913 0.95 0.54, 1.68 0.86 3 865 0.60 0.33, 1.11 0.10 3 865 0.60 0.33, 1.11 0.10 3 <	12 2294 -4.54 $-6.38, -2.69$ <0.00001

OR = odds ratio, WMD = weighted mean differences, CI = confidence interval, MINORS = Methodological Index for Non-Randomized Studies.

implementation, data should be collected and published, preferably through the use of national or international databases, allowing future analysis of the relative contributions of individual protocol components.

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