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REVIEW



Costs and clinical benefits of enhanced recovery after surgery (ERAS) in pancreaticoduodenectomy: an updated systematic review and meta-analysis

Lyrics Noba¹ · Sheila Rodgers¹ · Lawrence Doi¹ · Colin Chandler¹ · Deepak Hariharan² · Vincent Yip²

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Abstract

Purpose ERAS is a holistic and multidisciplinary pathway that incorporates various evidence-based interventions to accelerate recovery and improve clinical outcomes. However, evidence on cost benefit of ERAS in pancreaticoduodenectomy remains scarce. This review aimed to investigate cost benefit, compliance, and clinical benefits of ERAS in pancreaticoduodenectomy. **Methods** A comprehensive literature search was conducted on Medline, Embase, PubMed, CINAHL and the Cochrane library to identify studies conducted between 2000 and 2021, comparing effect of ERAS programmes and traditional care on hospital cost, length of stay (LOS), complications, delayed gastric emptying (DGE), readmission, reoperation, mortality, and compliance.

Results The search yielded 3 RCTs and 28 cohort studies. Hospital costs were significantly reduced in the ERAS group (SMD = -1.41; CL, -2.05 to -0.77; P < 0.00001). LOS was shortened by 3.15 days (MD = -3.15; CI, -3.94 to -2.36; P < 0.00001) in the ERAS group. Fewer patients in the ERAS group had complications (RR = 0.83; CI, 0.76-0.91; P < 0.0001). Incidences of DGE significantly decreased in the ERAS group (RR = 0.72; CI, 0.55-0.94; P = 0.01). The number of deaths was fewer in the ERAS group (RR = 0.76; CI, 0.58-1.00; P = 0.05).

Conclusion This review demonstrated that ERAS is safe and feasible in pancreaticoduodenectomy, improves clinical outcome such as LOS, complications, DGE and mortality rates, without changing readmissions and reoperations, while delivering significant cost savings. Higher compliance is associated with better clinical outcomes, especially LOS and complications.

Keywords Enhanced recovery after surgery · Pancreaticoduodenectomy · Systematic review · Meta-analysis

Introduction

In 1997, (Kehlet May 1997) introduced a multimodal approach to manage postoperative complications, which later evolved into enhanced recovery after surgery (ERAS). ERAS is a holistic and multidisciplinary pathway that incorporate various evidence-based interventions to accelerate recovery and reduce length of stay (LOS). Furthermore, it aimed to standardise care for patients undergoing specific procedures, with a view to improving clinical outcomes.

Lyrics Noba Lyrics.noba@outlook.com ERAS was initially implemented in colorectal surgery. Due to its success, it was quickly adopted in other surgical specialities.

Pancreatic surgery is traditionally associated with high mortality and complication rates. Few decades ago, mortality in pancreatic surgery was as high as 25%, but has now fallen to under 5% owing to recent advances in diagnosis, surgical techniques and improvement in perioperative care management (Gooiker et al. 2014). However, complications tend to remain very high, ranging between 40 and 60% (Lermite, et al. 2013; Kunstman et al. 2019). Complications such as postoperative pancreatic fistula and delayed gastric emptying (DGE) are identified as the primary causes of delayed recovery which often require further radiological or surgical interventions (Zhang et al. 2020).

The past decade has seen various ERAS guidelines published for multiple surgical specialties including colorectal, cardiac, orthopaedic, breast and gastrointestinal surgery. The

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first ERAS guidelines for pancreatoduodenectomy were published by the ERAS society in 2012 (Lassen et al. 2012). The updated guidelines published in 2020 contain 27 elements, covering the three phases of perioperative care (preoperative, intra-operative and postoperative), including preoperative education, minimally invasive techniques, pain control and early mobilisation and feeding (Melloul et al. 2019).

The impact of ERAS has been widely studied in various surgical specialities including upper gastrointestinal surgeries with good results. In recent years, many studies have been published on the effect of ERAS in pancreatic surgery. These studies have demonstrated that implementation of the ERAS pathway in pancreatic surgery is safe and reduces LOS and complications without increasing mortality rates and readmissions. However, evidence on cost benefit of ERAS programmes in pancreatic surgery remains scarce. A recent meta-analysis of 27 studies demonstrated significant cost savings following the implementation of the ERAS pathway in liver surgery (Noba et al. 2020). To date, no meta-analysis has been conducted to evaluate the impact of ERAS in pancreaticoduodenectomy on hospital costs. The aim of this review is to investigate cost benefit, compliance and clinical benefits of ERAS in pancreaticoduodenectomy.

Methods

Search strategy

This review was conducted in compliance with PRISMA (preferred reporting items for systematic reviews and metaanalyses) guidelines for systematic reviews and meta-analysis (Moher 2010). Multiple databases, (Medline, Embase, PubMed, CINAHL, and the Cochrane library), were searched to identify studies published between January 2000 and December 2021. The search was restricted to English language publications. A further search was conducted on the reference lists of relevant eligible studies and Systematic Reviews. The search terms such as 'ERAS', 'FTS', 'Fast track', 'Enhanced recovery', 'Clinical pathway', 'Critical pathway', 'Accelerated recovery surgery', 'Pancreas', 'Pancreatic', 'Whipple', 'Pancreatectomy', 'Pancreatoduodenectomy', 'Pancreaticoduodenectomy' were applied using Boolean operators (OR and AND).

Inclusion/exclusion criteria

Studies were eligible for inclusion if they met all of the following criteria (1) adult patients undergoing pancreaticoduodenectomy (2) compared ERAS to traditional care (3) reported at least one of the following outcomes: Hospital Costs, LOS, Complications, Compliance, Delayed Gastric Emptying (DGE), Mortality rates, Readmissions and Reoperations. Studies were excluded if they were non-elective or transplant patients, non-pancreaticoduodenectomy (PD), non-English and not comparing ERAS to traditional care.

Data extraction

Eligible studies and relevant data were retrieved and extracted by the first author. Data were extracted using a data extraction sheet agreed by all authors and were subsequently validated by other authors. Data extracted included; authors' names, year of publication, study design, patient' characteristics (ASA grade, age, sex and BMI), type of surgery, surgical techniques, outcomes measured, sample size, follow-up period and ERAS items.

Outcomes of interest

The primary outcomes for this systematic review were hospital costs. Secondary outcomes included: length of stay, compliance, complications, DGE, mortality, readmission and reoperation. LOS is defined by the total number of days a patient spent in the hospital prior to discharge.

Quality assessment

In line with the Cochrane Collaboration's risk of bias tool, the quality of the Randomised Control Trials (RCTs) were assessed against the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting (Higgins et al. 2011). See Fig. 1 for summary of risk of bias of RCTs. The methodological quality of the cohort studies were assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) (Hartling et al. 2012). The NOS has a maximum of 9 stars (Selection 4 stars, Comparability 2 stars and Exposure 3 stars).

Statistical analysis

This review was conducted using Review Manager (Rev-Man) version 5.4 (Collaboration 2020). Risk ratio was used for all dichotomous variables, weight mean difference or weight standardised mean difference for continuous variables with 95% confidence interval (CI). Statistical significance level was set at p < 0.05. Statistical heterogeneity was assessed using a chi-squared test (χ^2), I^2 statistic. A P < 0.1was considered to be a statistically significant heterogeneity. A fixed effect model was applied for pooling. Where

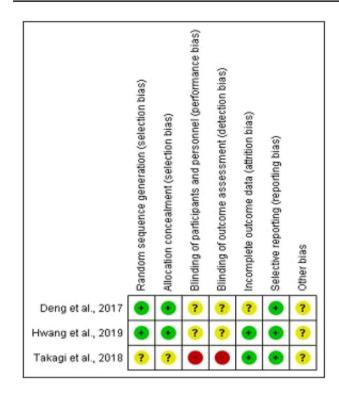


Fig. 1 Summary of risk of bias of randomised control trials

there is substantial evidence of heterogeneity ($l^2 > 60\%$), a random effect model was applied instead. Using the method recommended by (Hozo et al. 2005), study data presented as medians and interquartile ranges were converted to mean and standard deviation (SD). Standard deviation from a study with similar sample size was used with the mean as suggested by (Furukawa et al. 2006). The presence of publication bias was assessed using Funnel plots.

Results

Search results

An initial search resulted in 835 studies. After inclusion/ exclusion criteria were applied, 31 final studies were included in the meta-analysis. See Fig. 2 for the PRISMA flow chart.

Characteristics of included studies

A total of 5382 patients were included in this review (range between 41 and 635, per study), with 2776 patients in the ERAS group and 2606 patients in the traditional care group. Full details of the characteristics for included studies is shown in Table 1.

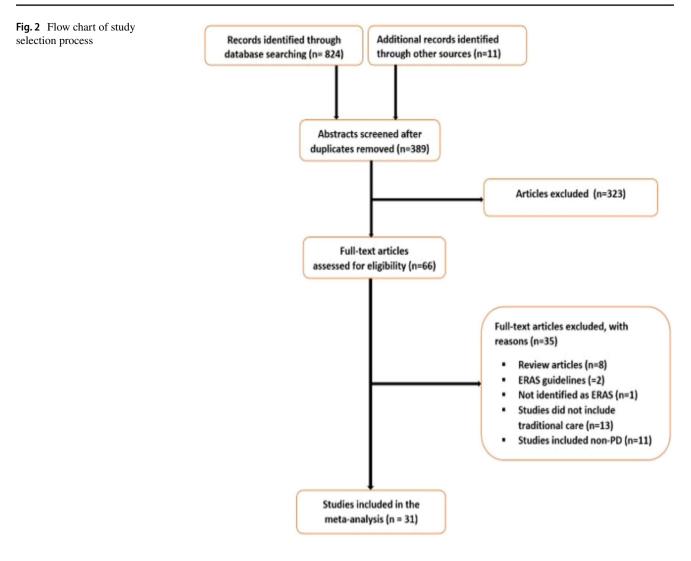
The number of ERAS items applied across the studies varied substantially. While, five studies did not provide lists of items utilised in their study (French et al. 2009; Nikfarjam et al. 2013; Shao et al. 2015; Téoule et al. 2020; Williamsson et al. 2019). A detailed list of ERAS items utilised by individual studies is shown in Table 2. Three studies were RCTs (Deng et al. 2017; Hwang et al. 2019; Takagi et al. 2019), while the remaining studies were cohort studies (Ahanatha Pillai et al. 2014; Balzano et al. 2008; Braga et al. 2014; Coolsen et al. 2014; Dai et al. 2017; French et al. 2009; Hilal et al. 2013; Joliat et al. 2015; Kagedan et al. 2017; Kennedy et al. 2007; Kobayashi et al. 2014; Kowalsky et al. 2019; Morales Soriano et al. 2015; Nikfarjam et al. 2013; Nussbaum et al. 2015; Partelli et al. 2016; Shah et al. 2016; Shao et al. 2015; Su et al. 2017; Sutcliffe et al. 2015; Téoule et al. 2020; Tremblay St-Germain et al. 2017; van der Kolk et al. 2017; Vanounou et al. 2007; Williamsson et al. 2015, 2019; Zhu et al. 2020; Zouros et al. 2016). The surgical approach was reported in six studies. Of these studies, four were open surgery (Hwang et al. 2019; Partelli et al. 2016; Braga et al. 2014; Hilal et al. 2013), one combined robotic and open surgery (Kowalsky et al. 2019), while the remaining study utilised a combination of open and laparoscopic approach (Nussbaum et al. 2015). Full details of characteristics for included studies is shown in Table 1.

Sensitivity analysis and publication bias

Funnel plots for LOS and readmission rates were used to assess publication bias as shown in Figs. 3, 4. The asymmetry of the funnel plots suggested no evidence of publication bias. In the presence of heterogeneity, a sensitivity analysis was conducted to test the reliability of the results.

Hospital costs

Ten studies evaluated hospital costs (3378 patients). Four of the studies measured hospital costs in US dollar (Takagi et al. 2019; Kennedy et al 2007; Kowalsky et al. 2019; Vanounou et al. 2007), two in Chinese yuan (Shao et al. 2015; Dai et al. 2017), two in euros (Joliat et al. 2015; Williamsson et al. 2015), one each in Canadian dollar (Kagedan et al. 2017) and South Korean won (Hwang et al. 2019). The pooled analysis suggested hospital costs were significantly lower in the ERAS group compared to the traditional care group (SMD = -1.41; CL, -2.05 to -0.77; P < 0.00001). However, there was significant evidence of heterogeneity observed in the studies ($\chi^2 = 389.50$; df = 9; P < 0.00001; $I^2 = 98\%$). Similarly, in the subgroup analysis of studies conducted in different continents, hospital costs were lower



in the ERAS group in studies conducted in North America (SMD = -2.76; CL, -4.54 to -0.98; P = 0.002) and East Asia (SMD = -0.35; CL, -0.47 to -0.23; P < 0.00001), while there was no difference in studies conducted in Europe (SMD = -1.02; CL, -2.18-0.14); P = 0.08). There was evidence of substantial heterogeneity in studies conducted in North America ($\chi^2 = 257.00$; df = 3; P < 0.00001; $I^2 = 99\%$) and Europe ($\chi^2 = 18.84$; df = 1; P < 0.0001; $I^2 = 95\%$). On the contrary, there no evidence of heterogeneity in studies conducted in Asia ($\chi^2 = 1.93$; df = 3; P = 0.59; $I^2 = 0\%$). There was a significant difference in hospital costs across the three continents ($\chi^2 = 18.16$; df = 3; P = 0.0004; $I^2 = 83.5\%$). See Fig. 5.

Length of stay

Length of stay was reported in all studies. Pooling of all results demonstrated a significant reduction in LOS in the ERAS group compared to the traditional care group (MD = -3.15; CI, -3.94 to -2.36; P < 0.00001), with evidence of

heterogeneity ($\chi^2 = 513.70$; df = 30; P < 0.00001; $I^2 = 94\%$). In addition, a subgroup analysis demonstrated a shorter LOS after implementation of ERAS in studies conducted in North America (MD = -2.45; CI, -3.42 to -1.48; P < 0.00001), Europe (MD = -2.23; CI, -3.67 to -0.79; P = 0.002) and Asia (MD = -4.99; CI, -7.57 to -2.41; P = 0.0002). There was no significant difference in LOS in the three continents ($\chi^2 = 4.56$; df = 3; P = 0.21, $I^2 = 34.3\%$). See Fig. 6.

Complication rates

Twenty-five reported incidences of complications. Overall complications were reported in thirty-four studies (4454 patients). A total of 2417 patients experienced complications, 1101 patients in ERAS groups compared to 1316 in traditional care groups. One study reported no complication in both the ERAS and traditional groups (Nikfarjam et al. 2013). The meta-analysis revealed a significant reduction in rates of complication in the ERAS group (RR = 0.83; CI, 0.76–0.91; P < 0.0001), however, there was evidence of

Table 1 Ch	Characteristics of included studies	OI IIICIAACA												
Studies	Study	Type of	Surgery	ASA Grade		Age		Sex		BMI		Sample size	ize	†NOS (9*)
	design	surgery	approach	Pre-ERAS	ERAS	Pre-ERAS	ERAS	Pre- ERAS	ERAS	Pre-ERAS	ERAS	Pre- ERAS	ERAS	
				ΛΙ/Π/Π/Ι	VI/III/II/			M/F	M/F					
Balzano et al. (2008)	Cohort study	Qddd/Qd	Ns	Ns	N_{S}	62.9 (26–84)	64.3 (33–88)	148/104	155/97	Ns	Ns	252	252	9
Braga et al. (2014)	Cohort study	PD/PPPD Open	Open	4/82/29/0/0	4/88/23/0/0	69 (61–74)	69 (61–74)	66/49	66/49	23.1 (21–25)	23.7 (21–25)	115	115	7
Coolsen et al. (2014)	Cohort study	DPPD/PD	$N_{\rm S}$	SN	$N_{ m S}$	62±13	67±11†	58/39	44/42	$N_{\rm S}$	Ns	76	86	Ś
Dai et al. (2017)	Cohort study	DPPD/PD	$\mathbf{N}_{\mathbf{S}}$	15/75/8/0/0	18/44/6/0/0	59.2 (14–83)	58.5 (18–69)	51/47	34/34	22.94 (14.95– 34.64)	21.48 (18.55- 28.40)	98	68	5
Deng et al. (2017)	RCT	PPPD/PD Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns	51.3±15.0	54.5±12.7	46/37	46/30	I-II (64)/ III-IV (19)	I–II (54)/ III–IV (22)	83	76	
French et al. (2009)	Cohort study	Qddd/Qd	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns	66.2 (10.3)	53.8 (11.6)	Ns	$N_{\rm S}$	$N_{\rm S}$	$\mathbf{N}_{\mathbf{S}}$	49	6	5
Hilal et al. (2013)	Cohort study	PD	Open	6/15/3/0/0	4/15/1/0/0	70 (61–76)	68.5 (65–72)	10/14	10/10	Ns	$N_{\rm S}$	24	20	5
Hwang et al. (2019)	RCT	PD/ PPPD/ SSPD	Open	18/100/6/0/0	9/99/15/0/0	62.9+9.2	63.3+9.2	81/43	72/51	24.2+3.0	24.3+3.1	124	123	
Joliat et al. (2015)	Cohort study	DPPD/PD	Ns	I/II (67)/20/0/0	I/II (50)/24/0/0	67 (55–75)	67.5 (57–74)	56/31	39/35	24·2 (22·1– 27·3)	23·9 (22·1– 26·7)	87	74	5
Kagedan et al. (2017)	Cohort study	CId	Open	$N_{\rm S}$	Ńs	65.5 (58–74)	65 (56–74)	31/43	74/47	Ns	$\mathbf{N}_{\mathbf{S}}$	74	121	5
Kennedy et al. (2007)	Cohort study	CId	Ns	C	Ńs	61.3±2.0	63.9 ± 1.3	23/21	41/50	N_{S}	$\mathbf{N}_{\mathbf{S}}$	44	91	5
Kobayashi et al. (2014)	Cohort study	PD/ PPPD/ SSPD	Ns	Ns	Ns	65.4 ± 10.8	67.5±10.7	62/28	61/39	25.0±4.54	21.6 ± 3.54	06	100	2
Kowalsky et al. Jun. (2019)	Cohort study	DJ	Robotic/ Open	0/12/106/5	0/14/103/14	66.3±10.4	68.2±9.8	70/61	64/59	28.2±6.3	26.8±5.9	131	123	6

Table 1 (continued)	ntinued)													
Studies	Study	Type of	Surgery	ASA Grade		Age		Sex		BMI		Sample size	ze	†NOS (9*)
	design	surgery	approach	Pre-ERAS	ERAS	Pre-ERAS	ERAS	Pre- ERAS	ERAS	Pre-ERAS	ERAS	Pre- ERAS	ERAS	
				ΛΙ/Π/ΙΙ/Ι	VI/III/II/			M/F	M/F					
Morales Soriano, et al. (2015)	Cohort study	Dd	$N_{ m S}$	$N_{ m S}$	I (21)/II-III (20)	66.7 (41–84)	61.3 (44–80)	27/17	24/17	Ns	$N_{ m S}$	44	41	7
Nikfarjam et al. Jan. (2013)	Cohort study	N DA/DA Ns		Ns	0/5/15	62 (15–81)	68 (45–81)	12/9	13/7	24 (19–34)	25 (19–42)	21	20	Ś
Nussbaum et al. (2015)	Cohort study	D	Open/Lap Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	62.1+11.5	65.5+10.1	67/75	39/61	27.1+6.5	26.2+4.6	142	100	9
Partelli et al. (2016)	Cohort study	Qddd	Open	5/42/1/0/0	2/13/7/0/0	77.5 (75–82)	77 (75–82)	33/33	14/8	25 (18–32)	25 (21–31)	66	22	Ś
Ahanatha Pillai et al. (2014)	Cohort study	DD	$ m N_{s}$	Ns	$N_{ m S}$	47.6±12.0	44.2±15.9	10/10	11/9	Ns	$\mathbf{N}_{\mathbf{S}}$	20	20	L
Shah et al. (2016)	Cohort study	DPPD/PD	Ns	7/27/12/2/0	18/79/36/9/0	59.1 ± 10.4	61.9±9.1	30/16	84/58	21.5±2.7	21.5 ± 2.5	46	142	5
Shao et al. (2015)	Cohort study	DPPD/PD	Ns	Ns	$N_{\rm S}$	57.05±12.30	56.96 ± 11.50	184/126	194/131	Ns	Ns	310	325	L
Su, et al. (2017)	Cohort study	PD	Ns	>II (5)	>11 (5)	61±11	62 ± 9	18/13	19/12	22.7±2.8	22.4±3.0	31	31	6
Sutcliffe et al. (2015)	Cohort study	Qd/Qddd	Ns	Ns	$N_{\rm S}$	66 (35–83)	67 (18–83)	37/28	40/25	25.4±4.4	27.3±5.8	65	65	2
Takagi et al. (2019)	RCT	DPPD/ SSPPD/ PD	Ns	6/26/5/0/0	3/23/11	66.8 (9.3)	67.8 (9.7)	20/17	20/17	21.7 (2.8)	22.1 (3.0)	37	37	
Téoule et al. (2020)	Cohort study	Qd/Qddd	Ns	6/39/27/3/ (72)	11/71/65/0 (1)	64.2	65.6	87/60	90/58	25.7	25.6	147	148	5
Tremblay St- Germain, et al. (2017)	Cohort study	PPD/PD Ns		0/15/55/4/0	0/17/49/17/0	66 (24–84)	65 (29–85)	31/43	44/39	25 (15–36)	26 (16-45)	74	83	2

Studies	Study	Type of	Surgery	ASA Grade		Age		Yac		DIMI		Sample size	ze	†NOS (9*)
	design	surgery	approach	Pre-ERAS	ERAS	Pre-ERAS	ERAS	Pre- ERAS	ERAS	Pre-ERAS	ERAS	Pre- ERAS	ERAS	
				VI/II/II/I	VI/III/II/			M/F	M/F					
Kolk et al. (2017)	Cohort study	DD	N_{S}	Ns	Ns	66 (58–72)	66 (57–72)	35/17	56/39	N_{S}	Ns	52	95	5
Vanounou et al. (2007)	Cohort study	PPPD/PD Ns	$N_{\rm S}$	1/33/30/0/0	2/53/84/6/0	64	64	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	$\mathbf{N}_{\mathbf{S}}$	64	145	Ś
Wil- liamsson et al. (2015)	Cohort study	$\mathbf{N}_{\mathbf{S}}$	$N_{\rm S}$	6/27/17/0/0	2/28/20/0/0	67 (25–81)	69 (15–80)	26/24	31/19	25·2 (16·3– 33·4)	25-2 (16-3- 24-3 (19-4- 50 33-4) 36-2)	50	50	7
Wil- liamsson et al. (2019)	Cohort study	D	$N_{\rm S}$	Ns	$N_{ m S}$	Ns	SN	$N_{\rm S}$	Ns	Ns	Ns	50	55	5
Zhu et al. (2020)	Cohort study	DD	$N_{\rm S}$	21/33/15/0/0	17/34/13	64.1 ± 11.5	64.3±7.9	32/37	27/37	42	44	69	64	L
Zouros et al. (2016)	Cohort study	PPD/PD Ns	Ns	18/27/5/0/0	26/33/16/0/0	63.9±11.6	65.9 ± 10.5	34/16	46/29	$\mathbf{N}_{\mathbf{S}}$	$\mathbf{N}_{\mathbf{S}}$	50	75	×

coduodenectomy, Ns not stated

 $^{\dagger}Newcastle-Ottawa quality assessment scale (maximum 9 stars)$

Table 2 Summary of ERAS items	Imary OF EK												
ERAS items	Balzano et al. (2008)	Braga et al. (2014)	Coolsen et al. (2014)	Dai et al. (2017)	Deng et al. (2017)	Hilal et al. (2013)	Hwang et al. (2019)	Joliat et al. (2015)	Kagedan et al. (2017)	Kennedy et al. (2007)	Kobayashi et al. (2014)	Kowalsky et al. Jun. (2019)	Morales Soriano, et al. (2015)
Preopera- tive coun- selling	Ns	+	+	+	+	+	+	+	Ns	+	+	Ns	Ns
Prehabilita- tion	Ns	$N_{\rm S}$	$N_{\rm S}$	Ns	Ns	N_{S}	Ns	Ns	Ns	$N_{\rm S}$	Ns	$N_{\rm S}$	Ns
Avoid Pre- operative biliary drainage	Ns	I	Ns	I	Ns	Ns	+	Ns	$ m N_{S}$	$\mathbf{N}_{\mathbf{S}}$	I	Ns	I
Preopera- tive smok- ing and alcohol cessation	Ns	Ns	Ns	Ns	Ns	Ns	+	Ns	Ns	Ns	Ns	+	Ns
Preopera- tive nutri- tion	N_{S}	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	N_{S}	$\mathbf{N}_{\mathbf{S}}$	+	Ns
Avoid Periopera- tive oral immunon- utrition	Ns	I	Ż	Ns	Ns	Ns	I	Ns	Ns S	Ns	Ns	Ns	Ns
Preop- erative fasting and treat- ment with carbohy- drates	$\Sigma_{\rm S}$	Ns	+	+	Ns	+	+	+	Ns	Ns.	$\Sigma_{\rm s}$	+	Š
Pre-anaes- thetic medica- tion	Ns	I	I	Ns	Ns	Ńs	+	Ns S	Ns	Ns	Ns	Ńs	Ns
Anti-throm- Ns botic prophy- laxis	Ns	Ns	+	Ns	Ns	+	+	+	Ns	+	I	Ss	Ns

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Table 2 (continued)	tinued)												
ERAS items	Balzano et al. (2008)	Braga et al. (2014)	Coolsen et al. (2014)	Dai et al. (2017)	Deng et al. (2017)	Hilal et al. (2013)	Hwang et al. (2019)	Joliat et al. (2015)	Kagedan et al. (2017)	Kennedy et al. (2007)	Kobayashi et al. (2014)	Kowalsky et al. Jun. (2019)	Morales Soriano, et al. (2015)
Fluid bal- ance	Ns	+	+	+	+	+	+	+	Ns	+	$N_{\rm S}$	+	Ns
Early removal of Peri- anasto- motic drainage	$ m N_S$	Not used	+ POD4	+ POD3	+ POD7 -10	+ POD4	+ POD3	+ POD 3/4	+ POD3	+ POD3	+ POPOD5	+ POD35	+ POPOD4
Avoid Soma- tostatin analogues	Ns	I	+	Ns	I	I	+	+	$\mathbf{N}_{\mathbf{S}}$	Ns	I	I	I
Removal of Urinary drainage	Ns	$\mathbf{N}_{\mathbf{S}}$	+POD2	+POD1	+ POD3	+ POD3	+	+ POD3	Ns	+ POD2	$\mathbf{N}_{\mathbf{S}}$	Ns	+POD3
Prevention of DGE	Ns	Ns	Ns	$N_{\rm S}$	$N_{\rm S}$	$N_{\rm S}$	+	Ns	$N_{\rm S}$	Ns	$N_{\rm S}$	$N_{\rm S}$	N_{S}
Stimulation of bowel movement	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	$ m N_{ m S}$	Ns	Ns	+ Chew gum	$\mathbf{N}_{\mathbf{S}}$	Ns	$ m N_{S}$	Ns	Ns	Ns
Postop- erative artificial nutrition	Ns	+	Ns	$\mathbf{N}_{\mathbf{S}}$	Ńs	Ns	I	Ns.	Ns	Ns	+	$\mathbf{N}_{\mathbf{S}}$	+
Early and scheduled mobiliza- tion	+POD1	+ POD1	+POD1	+POD1	+ POD1/2	+	+	+ POD0	+POD1	+POD1	SU	+	+ POD4
Minimal invasive surgery	$\mathbf{N}_{\mathbf{S}}$	Ns	$\mathbf{N}_{\mathbf{S}}$	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	Ns	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns	+	Ns
Systemic audit	Ns	N_{S}	Ns	Ns	$N_{\rm S}$	Ns	+	+	$\mathbf{N}_{\mathbf{S}}$	Ns	N_{S}	Ns	Ns

Table 2 (continued)	ntinued)												
ERAS items	Nussbaum et al. (2015)	Partelli et al. (2016)	Ahanatha Pillai et al. (2014)	Shah et al. (2016)	Su et al. (2017)	Sutcliffe et al. (2015)	Takagi et al. (2019)	Tremblay St-Germain, et al. (2017)	Kolk et al. (2017)	Vanounou et al. (2007)	Williamsson et al. (2019)	Zhu et a. (2020)	Zouros et al. (2016)
Preoperative counselling	Ns	+	+	+	+	+	+	+	+	+	+	+	+
Prehabilitation	Ns	N_{S}	$N_{\rm S}$	N_{S}	$N_{\rm S}$	N_{S}	Ns	Ns	Ns	$N_{\rm S}$	N_{S}	Ns	Ns
Avoid Preopera- tive biliary drainage	Ns	I	Ns	S	$N_{\rm s}$	Ns	1	1	Ns	Ns	S	Used	I
Preoperative smoking and alcohol cessation	Ns	$ m N_{S}$	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	$ m N_{S}$	Ns	Ns
Preoperative nutrition	$N_{\rm S}$	$N_{\rm S}$	$N_{\rm S}$	$\mathbf{N}_{\mathbf{S}}$	$\mathbf{N}_{\mathbf{S}}$	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	+	$N_{\rm S}$	N_{S}	1	$N_{\rm S}$
Avoid Periop- erative oral immunonu- trition	Ns	Ns	Ns	Ns	Ns	$N_{\rm S}$	1	Ns	+	Ns	Ns	Ns	Ns
Preoperative fasting and treatment with carbo- hydrates	Ns	Ňs	Ns	$\mathbf{N}_{\mathbf{S}}$	I	+	+	$\mathbf{z}_{\mathbf{s}}$	Ns	Ns	+	Ns	+
Pre-anaes- thetic medication	Ns	Ns	Ns	Ns	$N_{\rm S}$	Ns	Ns	Ns	Ns	I	Ns	Ns	1
Anti- thrombotic prophylaxis	$\mathbf{N}_{\mathbf{S}}$	+	Ns	Ns	$N_{\rm S}$	+	+	+	+	+	+	Ns	Ns
Antimicrobial prophylaxis and skin preparation	Ns	+	Ns	Ns	+	Ns	Ns	Ns	+	+	+	Ż	Ňs
Epidural analgesia	+	+	+	Ns	+	+	+	+	+	$N_{\rm S}$	+	+	+
Postoperative intravenous and per oral analgesia	+ POD4/5	+ POD3	Ns	+ POD 4	+ POD 3	Ns	Ns	+POD2	Ns	Ns	Ns	Ns Ns	+ POD3
Wound catheter and transversus abdominis plane (TAP) block	Š	Ns.	sz	$\mathbf{z}_{\mathbf{s}}$	s	SZ	s Z	+D3	ž	Š	Ns	sz	Ŝ

ERAS items	Nussbaum et al. (2015)	Partelli et al. (2016)	Ahanatha Pillai et al. (2014)	Shah et al. (2016)	Su et al. (2017)	Sutcliffe et al. (2015)	Takagi et al. (2019)	Tremblay St-Germain, et al. (2017)	Kolk et al. (2017)	Vanounou et al. (2007)	Williamsson et al. (2019)	Zhu et a. (2020)	Zouros et al. (2016)
Postoperative nausea and vomiting (PONV) prophylaxis	Ńs	z	+	Ns	+	+	S	S	+	Ns	+	s	NS
Avoiding hypothermia	Ns	Yes	Ns	Ns	$N_{\rm S}$	+	+	Ns	Ns	$N_{\rm S}$	$N_{ m s}$	+	+
Postoperative glycaemic control	$N_{\rm S}$	+	+	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	+	+	+	$N_{\rm S}$	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns
Avoid Nasogastric intubation	Ns	I	I	I	Ns	I	+	I	I	I	I	I	I
Fluid balance	Ns	+	+	$N_{\rm S}$	÷	N_{S}	+	Ns	+	Ns	+	+	+
Early removal of Peri- anastomotic drainage	+	+ POD3	+ POD3	+ POD5/6	$\mathbf{Z}_{\mathbf{S}}$	+ POD3	+	+POD3	+	+	+ POD 3	+D4-5	+ POD5
Avoid Soma- tostatin analogues	I	+	Ns	I	Ns	I	Ns	I	$\mathbf{N}_{\mathbf{S}}$	$N_{\rm S}$	Ns	$\mathbf{N}_{\mathbf{S}}$	I
Removal of Urinary drainage	+ POD2	+ POD1	+POD2	+ POD1	+ POD 2	+POD1/2	+ POD2/3	+ POD3	$\mathbf{N}_{\mathbf{S}}$	+	+ POD 6	+D1	+ POD2
Prevention of DGE	Ns	$N_{\rm S}$	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	Ns	N_{S}	Ns	N_{S}	Ns	Ns
Stimulation of bowel movement	$N_{ m S}$	Ns	Ns	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	$\mathbf{N}_{\mathbf{S}}$	Ns	$N_{\rm s}$	Ns	+ Chewing gum
Postoperative artificial nutrition	Ns	Ns	Ns	Ns	+	$\mathbf{N}_{\mathbf{S}}$	Ns	Ns	$N_{\rm S}$	Ns	Ns	Ns	+
Early and scheduled mobiliza- tion	+ POD2	+POD1	+ POD1	+ POD2	+ POD 1	+	+	+POD1	+POD1	su	+	SU	+ PODI
Minimal invasive surgery	+	1	Ns	Ns	I	Ns	Ns	$N_{\rm S}$	Ns	I	Ns	$\mathbf{N}_{\mathbf{S}}$	$N_{\rm S}$
Systemic audit Ns	t Ns	N_{S}	$N_{\rm S}$	N_{S}	N_{S}	N_{S}	Ns	N_{S}	Ns	$N_{\rm S}$	N_{S}	N_{S}	Ns
Ns not stated, POD + Policy applied Dolicy not confied	<i>Ns</i> not stated, <i>POD</i> postoperative day + Policy applied	perati ve day											

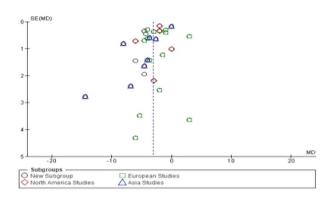


Fig. 3 Funnel plots for length of stay

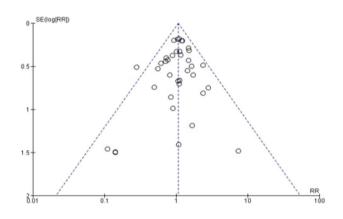


Fig. 4 Funnel plots for readmission rates

substantial heterogeneity ($\chi^2 = 60.31$; df = 23; P < 0.0001; $l^2 = 62\%$). Eighteen studies provided data on major complications (2608 patients). 553 patients had major complications, 268 patients in ERAS vs 285 patients in traditional care. Pooling the results demonstrated that major complications were comparable in both groups (RR = 0.96; CL, 0.83–1.11; P = 0.57), with no significant evidence of heterogeneity ($\chi^2 = 24.03$, df = 17; P = 0.12; $l^2 = 29\%$). See Figs. 7, 8.

Delayed gastric emptying (DGE)

Twenty-six studies supplied data on DGE (4734 patients). Of these, three studies recorded DGE according to their own centre definition (Kennedy et al. 2007; Su et al. 2017; Braga et al. 2014), two studies did not state how DGE was evaluated (Sutcliffe et al. 2015; Tremblay St-Germain et al. 2017), while the remaining studies defined DGE according to the International Study Group of Pancreatic Surgery (ISGPS) (Wente et al. 2007). Cases of DGE were recorded in 774 patients, with 322 being in the ERAS group compared to 452 in traditional care. The pooled analysis demonstrated

significantly fewer cases of DGE in the ERAS group (RR = 0.72; CI, 0.55–0.94; P = 0.01). However, there was evidence of substantial heterogeneity ($\chi^2 = 79.42$; df = 25; P < 0.00001; $l^2 = 69\%$). See Fig. 9.

Mortality rates

Mortality rates were reported in 30 studies (5341 patients). Eight studies reported zero mortality (Deng et al. 2017; Takagi et al. 2019; Su et al. 2017; Williamsson et al. 2015; Zhu et al. 2020; Dai et al. 2017; Hilal et al. 2013). In one study (Shao et al. 2015), mortality rates were substantially higher than normal (12% in the ERAS group vs 17.1% in the traditional care group), this was likely due to long-term follow up in the study (ranged from 1.3 to 48 months). A total of 192 deaths occurred in the studies, 84 patients in the ERAS, compared to 108 in the traditional care. On pooling the results, the number of deaths was significantly lower in the ERAS group (RR = 0.76; CI, 0.58–1.00; P=0.05) and there was no evidence of heterogeneity (χ^2 =10.12; df=21; P=0.98; I^2 =0%). See Fig. 10.

Readmission rates

Twenty-eight studies supplied data for readmissions (5101 patients). Following hospital discharge, 561 patients were readmitted within 30 days (297 in ERAS compared to 264 in traditional care). There was no difference in ERAS and traditional care after pooling the results (RR=1.07; CI, 0.91–1.25; P=0.40), with no evidence of heterogeneity observed ($\chi^2=18.46$; df=25; P=0.82; $l^2=0\%$). See Fig. 11.

Reoperation rates

Reoperation rates were reported in fourteen studies (2419 patients). A total of 166 patients had to be reoperated, 81 patients in ERAS and 85 in traditional care. A pooled analysis found both groups to have similar reoperation rates (RR=0.98; CI, 0.73–1.31; P=0.88). There was no evidence of heterogeneity ($\chi^2=9.55$, df=13; P=0.73; $I^2=0\%$). See Fig. 12.

Compliance

Six studies evaluated overall compliance to key elements of the ERAS pathway. Two of these studies compared rates of compliance to ERAS items between ERAS group and traditional care group. Compliance was significantly higher in ERAS group, ranging 81.2–90.3% in ERAS group compared to 34.9–43.8% in traditional care. The remaining four studies did not compare compliance between the two groups. (Joliat et al. 2015) reported 70% rates of compliance in the ERAS group, while (Van der Kolk et al. 2017) reported 80% compliance during intensive care and 60% for the surgical ward period,

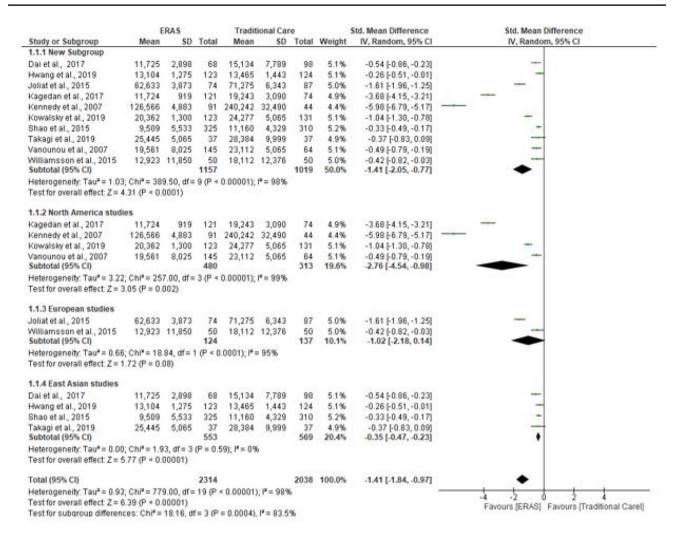


Fig. 5 Forest plot of hospital cost, ERAS vs traditional care; subgroup analysis (North America, Europe and Asia studies)

respectively. Similarly, Zouros et al. (Zouros et al. 2016) found compliance to 13 key ERAS items to be > 74%, with 100% compliance in five of the 13 key elements. However, (Braga et al. 2014) recorded the lowest compliance (ranged between 38 and 66%). Two studies investigated correlation between compliance and clinical outcomes. In these studies, higher compliance was associated with fewer complications (Zouros et al. 2016; Braga et al. 2014) and shorter Length of stay (Zouros et al. 2016).

Discussion

Pancreatoduodenectomy is the most common treatment for pancreatic cancer. However, it remains one of the most complex and challenging procedures (Navarro 2017). Despite the significant improvement in outcomes such as mortality rate, complications remain as high as 60% (Lermite et al. 2013; Kunstman et al. 2019) and are the main reason for delayed discharge (Zhang et al. 2020).

This present meta-analysis included a total of 31 studies and 5382 patients making it the largest study to date on this topic. Previous systematic reviews and meta-analyses have concluded that implementation of ERAS pathways may reduce length of hospital stay and overall complications in pancreatoduodenectomy without increasing rates of mortality and readmission (Coolsen et al. 2013; Bin Ji et al. 2018; Kagedan et al. 2015; Kuemmerli et al. 2022; Sun et al. 2020; Wang et al. 2020; Xiong et al. 2016).

With regard to the primary outcome, this review pooled sufficient data to investigate the impact of ERAS on hospital costs in pancreaticoduodenectomy. Three previous reviews included data on hospital costs in their analysis (Coolsen

Study or Subgroup	Mean	SD	Total	Mean	ional Ca SD		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.1.1 New Subgroup									
Balzano et al., 2008	13	29.8	252	15	27.5	252	0.8%	-2.00 [-7.01, 3.01]	
Braga et al., 2014	14.6	9.8	115	16.1	8.9	115	1.7%	-1.50 [-3.92, 0.92]	
Coolsen et al., 2014	14	21.9	86	20	35.5	97	0.4%	-6.00 [-14.45, 2.45]	
Dal et al., 2017	7.5	3.8	68	12	15.6	98	1.3%	-4.50 [-7.72, -1.28]	
Deng et al., 2017		8							
	15		76	19	10	83	1.5%	-4.00 [-6.80, -1.20]	
French et al., 2009	17.1	6.2	9	22.4	19.6	49	0.5%	-5.30 [-12.12, 1.52]	
Hilal et al., 2013	8.5	1.7	20	13	2.9	24	2.1%	-4.50 [-5.88, -3.12]	
Hwang et al., 2019	11	1.7	123	11	1	124	2.4%	0.00 [-0.35, 0.35]	1
Joliat et al., 2015	15	3.8	74	19	4.3	87	2.2%	-4.00 [-5.25, -2.75]	-
Kagedan et al., 2017	9	2	121	11	2.6	74	2.3%	-2.00 [-2.69, -1.31]	-
Kennedy et al., 2007	7	3.7	91	13	4	44	2.1%	-6.00 [-7.41, -4.59]	
Kobayashi et al., 2014	21.9	11.9	100	36.3	23.8	90	0.7%		
Kowalsky et al., 2019	6	1.15	123	8	1.5	131	2.4%	-2.00 [-2.33, -1.67]	-
Morales Soriano et al., 2015	14.2	1.3	41	18.7	1.9	44	2.3%	-4.50 [-5.19, -3.81]	_
Nikfarjam et al., 2013	8	2.6	20	14	6.1	21	1.5%	-6.00[-8.85, -3.15]	
Nussbaum et al., 2015	11	2.8	100	13	2.4	142	2.3%	-2.00 [-2.68, -1.32]	
Partelli et al., 20216	14	13.3	22	11	18.5	66	0.5%	3.00 [-4.13, 10.13]	
Pillai et al., 2014	14	4.9	20	18.5	7.2	20	1.1%	-4.50 [-8.32, -0.68]	
Shah et al., 2016	7.8	1.6	142	12.1	3	46	2.3%	-4.30 [-5.21, -3.39]	~
Shao et al., 2015	13.9	7.5	325	17.6	7.7	310	2.2%	-3.70 [-4.88, -2.52]	-
Su et al., 2017	8	2.9	31	16	3.5	31	2.0%	-8.00 [-9.60, -6.40]	
Sutcliffe et al., 2015	9	2.6	65	10	2	65	2.3%	-1.00 [-1.80, -0.20]	-
Takagi et al., 2019	20.1	5.4	37	26.9	13.5	37	0.9%	-6.80 [-11.49, -2.11]	
Téoule et al., 2020	14	2.9	148	15	2.6	147	2.3%	-1.00 [-1.63, -0.37]	-
Tremblay St-Germain et al., 2017	8	8.9	83	11	16.8	74	1.0%	-3.00 [-7.28, 1.28]	
ran der Kolk et al., 2017	10	2	95	13	2.3	52	2.3%	-3.00 [-3.74, -2.26]	-
Vanounou et al., 2007	8	6.8	145	8	6.8	64	1.8%	0.00 [-2.00, 2.00]	
	10	1.5	50	14	1.5	50	2.4%		-
Williamsson et al., 2015								-4.00 [-4.59, -3.41]	
Williamsson et al., 2019	13	3.8	55	10	1.5	50	2.2%	3.00 [1.91, 4.09]	
Zhu et al., 2020	10.9	3.4	84	13.5	4	69	2.2%	-2.60 [-3.86, -1.34]	
Zouros et al., 2016	10.6	6.9	75	14.3	8.5	50	1.5%	-3.70 [-6.53, -0.87]	
Subtotal (95% CI) Heterogeneity: Tau [#] = 3.65; Ch/ [#] = 1	513 70 d	er = 30	2776	100011	F= 949	2606	53.6%	-3.15 [-3.94, -2.36]	
1.1.2 North America Studies Kagedan et al., 2017	9	2	121	11	2.6	74	2.3%	-2.00 [-2.69, -1.31]	-
Kennedy et al., 2007	7	3.7	91	13	4	44	2.1%	-6.00 [-7.41, -4.59]	
Kowalsky et al., 2019	6	1.15	123	8	1.5	131	2.4%	-2.00 [-2.33, -1.67]	-
Nussbaum et al., 2015	11	2.8	100	13	2.4	142	2.3%	-2.00 [-2.68, -1.32]	-
Tremblay St-Germain et al., 2017	8	8.9	83	11	16.8	74	1.0%	-3.00 [-7.28, 1.28]	
Vanounou et al., 2007	8	6.8	145	8	6.8	64	1.8%	0.00 [-2.00, 2.00]	
Subtotal (95% CI)			663		000	529	12.0%	-2.45 [-3.42, -1.48]	•
Heterogeneity: Tau*= 0.99; Ch/*= : Test for overall effect Z = 4.96 (P <			- 0.000	10 (), r =	00.30				
1.1.3 European Studies									
Balzano et al., 2008	13	29.8	252	15	27.5	252	0.8%	-2.00 [-7.01, 3.01]	
	14.6	9.8	115	16.1	8.9	115	1.7%	-1.50 [-3.92, 0.92]	
Brada et al., 2014		21.9			35.5	97	0.4%	-6.00 [-14.45, 2.45]	
	14								
Coolsen et al., 2014	14		86	20	19.6	49	0.5%	-5 301-12 12 1 52	
Coolsen et al., 2014 French et al., 2009	17.1	6.2	9	22.4	19.6	49	0.5%	-5.30 [-12.12, 1.52]	
Coolsen et al., 2014 French et al., 2009 Hilal et al., 2013	17.1 8.5	6.2 1.7	9 20	22.4 13	2.9	24	2.1%	-4.50 [-5.88, -3.12]	-
Coolsen et al., 2014 French et al., 2009 Hilal et al., 2013 Joliat et al., 2015	17.1 8.5 15	6.2 1.7 3.8	9 20 74	22.4 13 19	2.9 4.3	24 87	2.1% 2.2%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75]	7
Coolsen et al., 2014 French et al., 2009 Hilal et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015	17.1 8.5 15 14.2	6.2 1.7 3.8 1.3	9 20 74 41	22.4 13 19 18.7	2.9 4.3 1.9	24 87 44	2.1% 2.2% 2.3%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81]	=
Coolsen et al., 2014 French et al., 2009 Hilal et al., 2013 Doliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216	17.1 8.5 15 14.2 14	6.2 1.7 3.8 1.3 13.3	9 20 74 41 22	22.4 13 19 18.7 11	2.9 4.3 1.9 18.5	24 87 44 66	2.1% 2.2% 2.3% 0.5%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13]	=
Coolsen et al., 2014 French et al., 2009 Hillai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutciliffe et al., 2015	17.1 8.5 15 14.2 14 9	6.2 1.7 3.8 1.3 13.3 2.6	9 20 74 41 22 65	22.4 13 19 18.7 11 10	2.9 4.3 1.9 18.5 2	24 87 44 66 65	2.1% 2.2% 2.3% 0.5% 2.3%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20]	
Coolsen et al., 2014 French et al., 2009 Hillai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2020	17.1 8.5 15 14.2 14 9 14	6.2 1.7 3.8 1.3 13.3 2.6 2.9	9 20 74 41 22 65 148	22.4 13 19 18.7 11 10 15	2.9 4.3 1.9 18.5 2 2.6	24 87 44 66 65 147	2.1% 2.2% 2.3% 0.5% 2.3% 2.3%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.63, -0.37]	
Coolsen et al., 2014 French et al., 2009 Hillal et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Féoule et al., 2020 ran der Kolk et al., 2017	17.1 8.5 15 14.2 14 9 14 10	6.2 1.7 3.8 1.3 13.3 2.6 2.9 2	9 20 74 41 22 65 148 95	22.4 13 19 18.7 11 10 15 13	2.9 4.3 1.9 18.5 2 2.6 2.3	24 87 44 66 65 147 52	2.1% 2.2% 2.3% 0.5% 2.3% 2.3% 2.3%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.63, -0.37] -3.00 [-3.74, -2.26]	
Coolsen et al., 2014 French et al., 2009 Hillai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2017 Williamsson et al., 2017	17.1 8.5 15 14.2 14 9 14	6.2 1.7 3.8 1.3 13.3 2.6 2.9 2 3.8	9 20 74 41 22 65 148 95 55	22.4 13 19 18.7 11 10 15	2.9 4.3 1.9 18.5 2 2.6 2.3 1.5	24 87 44 66 65 147 52 50	2.1% 2.2% 2.3% 0.5% 2.3% 2.3% 2.3% 2.2%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.63, -0.37]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutoliffe et al., 2015 Téoule et al., 2015 Téoule et al., 2020 ran der Kolk et al., 2017 Williamsson et al., 2019 Zouros et al., 2016	17.1 8.5 15 14.2 14 9 14 10	6.2 1.7 3.8 1.3 13.3 2.6 2.9 2	9 20 74 41 22 65 148 95 55 75	22.4 13 19 18.7 11 10 15 13	2.9 4.3 1.9 18.5 2 2.6 2.3	24 87 44 66 55 147 52 50 50	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.3% 2.2% 1.5%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -1.00 [-1.83, -0.37] -3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-9.14, -0.9] -3.70 [-6.53, -0.87]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Partelli et al., 2015 Sutcliffe et al., 2015 Téoule et al., 2015 Tan der Kolk et al., 2017 Williamsson et al., 2019 Zouros et al., 2016 Subtotal (95% CI)	17.1 8.5 15 14.2 14 9 14 10 13 10.6	6.2 1.7 3.8 1.3 13.3 2.6 2.9 2 3.8 6.9	9 20 74 41 22 65 148 95 55 75 1057	22.4 13 19 18.7 11 10 15 13 10 14.3	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5	24 87 44 66 65 147 52 50 50 1098	2.1% 2.2% 2.3% 0.5% 2.3% 2.3% 2.3% 2.2%	$\begin{array}{c} -4.50 \left[+5.88 , -3.12 \right] \\ -4.00 \left[+5.25 , -2.75 \right] \\ -4.50 \left[+5.19 , -3.81 \right] \\ 3.00 \left[+4.13 , 10.13 \right] \\ -1.00 \left[+1.80 , -0.20 \right] \\ -1.00 \left[+1.63 , -0.37 \right] \\ -3.00 \left[3.74 , -2.26 \right] \\ 3.00 \left[1.91 , 4.09 \right] \end{array}$	
Coolsen et al., 2014 French et al., 2009 Hala et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2015 Tan der Kolk et al., 2017 Williamsson et al., 2019 Zouros et al., 2016 Subtotal (95% CI) Heterogeneity: Tau# = 5.08; Chi# = 1	17.1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d	6.2 1.7 3.8 1.3 13.3 2.6 2.9 2 3.8 6.9	9 20 74 41 22 65 148 95 55 75 1057	22.4 13 19 18.7 11 10 15 13 10 14.3	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5	24 87 44 66 65 147 52 50 50 1098	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.3% 2.2% 1.5%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -1.00 [-1.83, -0.37] -3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-9.14, -0.9] -3.70 [-6.53, -0.87]	
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Coolsen et al., 2014 French et al., 2019 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2016 Subtilite et al., 2017 Williamsson et al., 2019 Zouros et al., 2019 Zouros et al., 2019 Zouros et al., 2019 Test for overall effect Z = 3.03 (P = 1.14 Asia Studies Dai et al., 2017	17.1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d :0.002) 7.5	6.2 1.7 3.8 1.3 13.3 2.6 2.9 2 3.8 6.9 #= 12 3.8	9 20 74 41 22 65 148 95 55 75 1057 (P < 0.0	22.4 13 19 18.7 11 10 15 13 10 14.3 00001); 12	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5 ₹= 93%	24 87 44 66 65 147 52 50 50 1098 98	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.2% 1.5% 21.1%	- 4.50 [-5.88, -3.12] - 4.00 [-5.25, -2.75] - 4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] - 1.00 [-1.80, -0.20] - 1.00 [-1.80, -0.20] - 1.00 [-1.63, -0.37] - 3.00 [-3.74, -2.26] 3.00 [1.91, 4.09] - 3.70 [-6.53, -0.87] - 2.23 [-3.67, -0.79]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Parielli et al., 20216 Sutellife et al., 2015 Téoule et al., 2010 ran der Kolk et al., 2017 Williamsson et al., 2019 Zouros et al., 2016 Subtotal (95% CI) Heterogeneity: Tau ^a = 5.08; Chi ^a = 1 Test for overall effect Z = 3.03 (P = 1.1.4 Asia Studies Dai et al., 2017 Deng et al., 2017	17.1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d 0.002) 7.5 15	6.2 1.7 3.8 1.3 2.6 2.9 2 3.8 6.9 # = 12 3.8 8 8	9 20 74 41 22 65 148 95 55 75 1057 (P < 0.0 88 76	22.4 13 19 18.7 11 15 13 10 14.3 100001); 12 19	2.9 4.3 1.9 18.5 2 2.6 2.3 1.5 8.5 ■ ■ 93%	24 87 44 66 65 147 52 50 1098 98 83	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.2% 1.5% 21.1%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.25, -2.75] -4.50 [-5.19, -3.81] -1.00 [-1.80, -0.20] -1.00 [-1.63, -0.37] -3.00 [-3.74, -2.26] -3.00 [-3.74, -2.26] -3.00 [-3.74, -2.26] -3.00 [-5.3, -0.79] -2.23 [-3.67, -0.79] -4.50 [-7.72, -1.28] -4.00 [-6.80, -1.20]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2017 Williamsson et al., 2017 Williamsson et al., 2017 Subtotal (95% CI) Heterogeneity: Tau [*] = 5.08; Chi [#] = : Test for overall effect $Z = 3.03$ ($P =$ 1.1.4 Asia Studies Dai et al., 2017 Deng et al., 2017 Hwang et al., 2019	17.1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d :0.002) 7.5 15 11	6.2 1.7 3.8 1.3 2.6 2.9 2 3.8 6.9 #= 12 3.8 8 1.7	9 20 74 41 22 65 55 75 1057 (P < 0.0 68 76 123	22.4 13 19 18.7 11 10 15 13 10 14.3 100001); 12 19 11	2.9 4.3 1.9 18.5 2.6 6.3 1.5 8.5 ₽ = 93% 15.6 10 1	24 87 44 66 65 147 52 50 1098 98 83 124	2.1% 2.2% 2.3% 0.5% 2.3% 2.3% 2.2% 1.5% 21.1%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -3.00 [-3.74, -2.26] 3.00 [1.91, 4.09] -3.70 [-6.53, -0.87] -2.23 [-3.67, -0.79] -4.50 [-7.72, -1.28] -4.00 [-6.80, -1.20] 0.00 [-0.35, 0.35]	
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Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2017 Williamsson et al., 2017 Williamsson et al., 2017 Subtotal (95% CI) Heterogeneity: Tau ^a = 5.08; Chi ^a = : Test for overall effect Z = 3.03 (P = 1.1.4 Asia Studies Dai et al., 2017 Deng et al., 2017 Hwang et al., 2019 Kobayashi et al., 2014 Pillai et al., 2014 Shah et al., 2016	17.1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d :0.002) 7.5 15 11 21.9 14 7.8	6.2 1.7 3.8 1.3 2.9 2.9 2.9 2.9 3.8 6.9 #= 12 3.8 1.7 1.9 1.6	9 20 74 41 22 65 148 95 575 1057 (P < 0.0 (P < 0.0 68 76 123 100 20 20 142	22.4 13 19 18.7 11 10 15 13 10 14.3 00001); 12 19 11 36.3 12.1	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5 ₹= 93% 15.6 10 1 23.8 7.2 3	24 87 44 66 50 50 1098 98 83 124 90 20 46	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.2% 1.5% 21.1%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.25, -2.75] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] -3.70 [-6.53, -0.87] -2.23 [-3.67, -0.79] -4.50 [-7.72, -1.28] -4.50 [-5.7, -0.75] -14.40 [-19.84, 8.96] Not estimable Not estimable	
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Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Parielli et al., 20216 Sutellife et al., 2017 Téoule et al., 2010 an der Kolk et al., 2017 Williamsson et al., 2019 Zouros et al., 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 5.08; Chi ^p = 1 Test for overall effect Z = 3.03 (P = 1 1.1.4 Asia Studies Dai et al., 2017 Deng et al., 2017 Hotsayashi et al., 2014 Shab et al., 2016 Shao et al., 2017	17.1 8.5 14.2 14 9 14 10 13 10.6 181.53, d :0.002) 7.5 15 11 21.9 14 7.8 13.9	6.2 1.7 3.8 1.3 2.6 2.9 2 3.8 6.9 11 11 9 1.6 7.5	9 20 74 41 22 65 148 95 55 75 1057 (P < 0.0 (P < 0.0 68 76 123 100 142 325	22.4 13 19 18.7 11 10 15 13 10 14.3 100001); 12 19 11 36.3 18.5 12.1 17.6	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5 ₹= 93% 15.6 10 1 23.8 7.2 3 7.7	24 87 44 66 50 50 1098 98 83 124 90 46 310	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.2% 1.5% 21.1%	- 4.50 [-5.88, -3.12] - 4.00 [-5.25, -2.75] - 4.50 [-5.19, -3.81] - 3.00 [-4.13, 10.13] - 1.00 [-1.80, -0.20] - 1.00 [-1.80, -0.20] - 3.00 [-3.74, -2.26] - 3.00 [-3.74, -2.26] - 3.00 [-3.74, -2.26] - 3.00 [-3.74, -2.26] - 3.70 [-6.53, -0.79] - 2.23 [-3.67, -0.79] - 4.50 [-5.72, -1.28] - 4.00 [-6.35, -0.35] - 14.40 [-19.84, -8.96] Not estimable Not estimable - 3.70 [-4.88, -2.52]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20215 Subcliffe et al., 2015 Téoule et al., 2015 Subcliffe et al., 2017 Milliamsson et al., 2017 Milliamsson et al., 2017 Milliamsson et al., 2017 Subtotal (95% CI) Heterogeneity: Tau ^a = 5.08; Chi ^a = : 1.1.4 Asia Studies Dai et al., 2017 Hwang et al., 2017 Hwang et al., 2017 Hwang et al., 2017 Kobayashi et al., 2014 Pillai et al., 2016 Shab et al., 2015 Su et al., 2017 Takagi et al., 2019 Zu et al., 2019	17:1 8:5 15 14:2 14 9 9 14 10 13 10:6 181:53, d 181:53, d 181:53, d 181:53, d 181:53, d 181:53, d 191:2 193 14 7:8 13:9 8 8	6.2 1.7 3.8 1.3 2.6 2.9 2 3.8 6.9 #=12 3.8 8 1.7 11.9 4.9 7.5 2.9	9 20 74 41 22 65 55 55 55 55 55 55 75 105 7 (P < 0. 42 325 31 37 36 4	22.4 13 19 18.7 11 10 15 13 10 14.3 100001); 12 19 11 36.3 18.5 12.1 17.6 16 16	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5 7= 93% 15.6 10 1 23.8 7.2 3.7 7.7 3.5	24 87 44 665 147 52 50 50 1098 83 124 90 83 124 90 46 310 31 37 69	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-5.3, -0.77] -2.23 [-3.67, -0.79] -4.50 [-7.72, -1.28] -4.00 [-6.80, -1.20] 0.00 [-0.35, 0.35] -14.40 [-1844, -8.96] Not estimable -3.70 [-4.88, -2.52] -8.00 [-9.60, -6.40] -6.60 [-1.49, -2.11] -2.60 [-3.86, -1.34]	
Coolsen et al., 2014 French et al., 2019 Helial et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20215 Subcliffe et al., 2015 Téoule et al., 2015 Autor an der Kolk et al., 2017 Williamsson et al., 2017 Williamsson et al., 2017 Milliamsson et al., 2017 Milliamsson et al., 2017 Subtotal (95% CI) Heterogeneity: Tau [#] = 5.08; Chi [#] = : 1.1.4 Asia Studies Dai et al., 2017 Henge et al., 2017 Hwang et al., 2017 Hwang et al., 2017 Hwang et al., 2014 Pillai et al., 2016 Shab et al., 2015 Su et al., 2017 Takagi et al., 2019 Zouros 2019	17:1 8:5 15 14:2 14 9 14 10 13 10:6 181.53, d 0:0002) 7:5 15 15 15 11 21.9 14 7:8 13.9 8 20.1	6.2 1.7 3.8 1.3 1.3 2.6 2.9 2 3.8 8.9 ± = 12 3.8 8.7 1.9 4.9 4.9 5.4	9 20 74 41 22 65 55 55 75 1057 (P < 0.0 (P < 0.0 102 20 142 325 31 37	22.4 13 19 18.7 11 10 15 13 10 14.3 100001); 12 19 11 36.3 18.5 12.1 17.6 26.9	2.9 4.3 1.9 18.5 2.6 2.3 1.5 8.5 1.5 8.5 1.5 6 10 1 2.3.8 7.2 3 7.2 3,7 3,5 13.5	24 87 44 66 50 50 1098 83 124 90 20 46 310 31 37	2.1% 2.2% 2.3% 2.3% 2.3% 2.2% 2.1.1% 1.5% 2.4% 0.7% 2.2% 2.2% 0.7%	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.25, -2.75] 3.00 [-4.13, 10.13] -1.00 [-1.63, -0.37] -1.00 [-1.63, -0.37] -3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] -3.70 [-6.53, -0.67] -2.23 [-3.67, -0.79] -2.23 [-3.67, -0.79] -4.50 [-7.72, -1.28] -4.00 [-6.80, -1.20] 0.00 [-0.35, 0.35] -14.40 [-19.84, 8-96] Not estimable -3.70 [-4.88, -2.52] -8.00 [-9.60, -6.40] -6.80 [-11.49, -2.11]	
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Braga et al., 2014 Coolsen et al., 2014 French et al., 2019 Hilai et al., 2013 Joliat et al., 2015 Morales Sociano et al., 2015 Partelli et al., 2015 Téoule et al., 2015 Téoule et al., 2015 Téoule et al., 2017 Williamsson et al., 2019 Zouros et al., 2016 Subtotal (95% CI) Heterogeneity: Tau" = 5.08; Chi" = : Test for overall effect Z = 3.03 (P = 1.1.4 Asia Studies Dai et al., 2017 Deng et al., 2017 Dia et al., 2017 Dai et al., 2017 Subtotal (95% CI) Heterogeneity: Tau" = 11.82; Chi" = Test for overall effect Z = 3.79 (P = Test for overall effect Z = 3.79 (P =	17:1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d 0.002) 7.5 15 15 15 121.9 14 7.8 13.9 8 20.1 10.9 = 169.06,	6.2 1.7 3.8 1.3 1.3 2.6 2.9 9 2 3.8 6.9 4 1.7 3.8 8 1.7 11.9 4.9 4.9 7.5 2.9 5.4 3.4	9 200 74 41 22 55 55 55 55 55 55 55 55 55 55 55 55	22.4 13 13 18.7 11 10 15 13 10 14.3 10 00001); 12 11 36.3 18.5 12.1 17.6 16 26.9 13.5	2.9 4.3 1.9 18.5 2.3 1.5 8.5 7= 93% 15.6 10 1 23.8 7.2 3.5 13.5 4	24 87 44 66 65 50 50 1098 83 124 90 20 6 310 31 37 842	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.2% 2.5% 21.1% 1.5% 2.4% 0.7% 2.2% 0.9% 2.2% 13.2%	- 4.50 5.88, -3.12] - 4.00 5.25, -2.75] - 4.50 5.19, -3.81] 3.00 4.13, 10.13] - 1.00 -1.80, -0.20] - 1.00 -1.63, -0.37] - 3.00 -3.74, -2.26] 3.00 -3.74, -2.26] 3.00 -3.74, -2.26] - 3.70 -6.53, -0.87] - 2.23 -3.67, -0.79] - 4.50 -7.72, -1.28] - 4.00 -6.80, -1.20] 0.00 -0.35, 0.35] - 14.40 -1.986] Not estimable - 3.70 -4.88, -2.52] - 8.00 -3.66, -6.40] - 6.80 -11.49, -2.11] - 2.60 -3.86, -1.34] - 4.99 -7.57, -2.41]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2015 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2017 Williamsson et al., 2017 Williamsson et al., 2017 Williamsson et al., 2017 Subtotal (95% CI) Heterogeneity: Tau ^a = 5.08; Chi ^a = 1 1.1.4 Asia Studies Dai et al., 2017 Dung et al., 2017 Hwang et al., 2019 Kobayashi et al., 2014 Philai et al., 2016 Shao et al., 2017 Takagi et al., 2017 Takagi et al., 2017 Takagi et al., 2019 Subtotal (95% CI)	17:1 8:5 15 14:2 14 9 14 10 13 10:6 181.53, d 0:0002) 7:5 15 15 15 15 121.9 14 7:5 15 11 21.9 14 7:5 13.9 14 20.0 13.9 14 20.0 15 15 15 15 15 15 15 15 15 15 15 15 15	6.2 1.7 3.8 1.3 1.3 2.6 2.9 2 3.8 6.9 ff = 12 3.8 1.7 3.8 6.9 ff = 12 3.8 1.7 3.8 6.9 ff = 12 3.8 1.7 3.8 6.9 ff = 12 3.8 6.9 ff = 12 4.9 1.6 5.9 ff = 12 4.9 1.6 5.4 4.9 1.7 4.9 1.6 5.4 4.9 1.7 1.7 1.8 1.8 1.8 1.8 1.8 1.8 1.8 1.8	9 200 74 41 22 55 55 75 75 105 70 (P < 0.1 (P < 0.1 105 105 105 105 105 105 105 105 105 10	22.4 13 19 18.7 11 16.7 13 10 14.3 000001); 12 11 36.3 18.5 12.1 17.6 12.1 17.6 13.5 000001);	2.9 4.3 1.9 18.5 2.3 1.5 8.5 15.6 10 1 2.3.8 5 15.6 10 1 2.3.8 7.7 7.3 5 13.5 4 ₽ ₽ = 96%	24 87 44 66 65 50 50 1098 83 124 98 83 124 90 20 20 20 20 46 310 31 37 842 5075	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3% 2.3	-4.50 [-5.88, -3.12] -4.00 [-5.25, -2.75] -4.50 [-5.19, -3.81] 3.00 [-4.13, 10.13] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -1.00 [-1.80, -0.20] -3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-3.74, -2.26] 3.00 [-5.3, -0.77] -2.23 [-3.67, -0.79] -4.50 [-7.72, -1.28] -4.00 [-6.80, -1.20] 0.00 [-0.35, 0.35] -14.40 [-1844, -8.96] Not estimable -3.70 [-4.88, -2.52] -8.00 [-9.60, -6.40] -6.60 [-1.49, -2.11] -2.60 [-3.86, -1.34]	
Coolsen et al., 2014 French et al., 2009 Hilai et al., 2013 Joliat et al., 2013 Morales Soriano et al., 2015 Partelli et al., 20216 Sutcliffe et al., 2015 Téoule et al., 2015 Téoule et al., 2017 Williamsson et al., 2017 Williamsson et al., 2017 Subtotai (95% CI) Heterogeneity: Tau [*] = 5.08; Chi [#] =: Test for overall effect Z = 3.03 (P = 1.1.4 Asia Studies Dai et al., 2017 Deng et al., 2017 Hwang et al., 2019 Kobsyashi et al., 2014 Pillai et al., 2016 Shao et al., 2015 Su et al., 2017 Takagi et al., 2019 Zhu et al., 2020 Subtotai (95% CI) Heterogeneity: Tau [*] = 11.82; Chi [#] =	17.1 8.5 15 14.2 14 9 14 10 13 10.6 181.53, d 0.002) 7.5 15 15 15 15 11 21.9 14 7.8 20.1 10.9 8 20.1 10.9 8 20.1 10.9 9 44.2 15 15 15 15 15 15 15 15 15 15 15 15 15	6.2 1.7 3.8 1.3 1.3 2.9 2.9 2.3 8 6.9 2.9 2.3 8 6.9 4 1.7 1.8 6.9 4 1.7 1.3 3.8 6.9 4 1.7 1.3 3.8 6.9 4 1.7 1.3 3.8 6.9 4 1.7 1.7 1.3 3.8 6.9 4 1.7 1.7 1.8 1.8 1.3 1.8 1.3 1.8 1.8 1.8 1.8 1.8 1.8 1.8 1.8	9 200 74 41 22 55 55 75 75 105 70 (P < 0.1 (P < 0.1 105 105 105 105 105 105 105 105 105 10	22.4 13 19 18.7 11 16.7 13 10 14.3 000001); 12 11 36.3 18.5 12.1 17.6 12.1 17.6 13.5 000001);	2.9 4.3 1.9 18.5 2.3 1.5 8.5 15.6 10 1 2.3.8 5 10 1 2.3.8 7.7 7.2 3.5 13.5 4 ₽ ₽ = 96%	24 87 44 66 65 50 50 1098 83 124 98 83 124 90 20 20 20 20 46 310 31 37 842 5075	2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.2% 2.5% 21.1% 1.5% 2.4% 0.7% 2.2% 0.9% 2.2% 13.2%	- 4.50 5.88, -3.12] - 4.00 5.25, -2.75] - 4.50 5.19, -3.81] 3.00 4.13, 10.13] - 1.00 -1.80, -0.20] - 1.00 -1.63, -0.37] - 3.00 -3.74, -2.26] 3.00 -3.74, -2.26] 3.00 -3.74, -2.26] - 3.70 -6.53, -0.87] - 2.23 -3.67, -0.79] - 4.50 -7.72, -1.28] - 4.00 -6.80, -1.20] 0.00 -0.35, 0.35] - 14.40 -1.986] Not estimable - 3.70 -4.88, -2.52] - 8.00 -3.66, -6.40] - 6.80 -11.49, -2.11] - 2.60 -3.86, -1.34] - 4.99 -7.57, -2.41]	

Fig. 6 Forest plot of length of stay, ears vs traditional care; subgroup analysis (North America, Europe and Asia studies)

	ERA	5	Traditiona	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Balzano et al., 2008	119	252	148	252	6.1%	0.80 [0.68, 0.95]	
Braga et al., 2014	69	115	76	115	5.6%	0.91 [0.74, 1.11]	
Coolsen et al., 2014	46	86	48	97	4.3%	1.08 [0.82, 1.43]	_
Dai et al., 2017	34	68	89	98	4.8%	0.55 [0.43, 0.70]	
French et al., 2009	5	9	26	49	1.5%	1.05 [0.55, 1.99]	
Hilal et al., 2013	8	20	16	24	1.7%	0.60 [0.33, 1.10]	
Hwang et al., 2019	64	123	68	124	5.0%	0.95 (0.75, 1.20)	
Joliat et al., 2015	50	74	71	87	5.7%	0.83 [0.69, 1.00]	
Kennedy et al., 2007	34	91	19	44	2.7%	0.87 (0.56, 1.33)	
Kobayashi et al., 2014	39	100	54	90	4.1%	0.65 (0.48, 0.88)	
Morales Soriano et al., 2015	12	41	24	44	2.0%	0.54 (0.31, 0.93)	
Nikfarjam et al., 2013	0	20	0	21		Not estimable	
Nussbaum et al., 2015	43	100	53	142	4.0%	1.15 [0.84, 1.57]	
Partelli et al., 20216	17	22	43	66	4.3%	1.19 [0.89, 1.58]	
Shah et al., 2016	21	142	15	46	1.8%	0.45 (0.26, 0.80)	
Shao et al., 2015	127	325	173	310	6.0%	0.70 [0.59, 0.83]	
Sulet al., 2017	18	31	26	31	3.7%	0.69 [0.49, 0.97]	
Sutcliffe et al., 2015	26	65	35	.65	3.3%	0.74 [0.51, 1.08]	
Takagi et al., 2019	23	37	32	37	4.3%	0.72 [0.54, 0.95]	
Téoule et al., 2020	114	148	114	147	6.7%	0.99 [0.88, 1.12]	-
Tremblay St-Germain et al., 2017	56	83	51	74	5.3%	0.98 [0.79, 1.21]	
Vanounou et al., 2007	77	145	40	64	4.9%	0.85 [0.67, 1.08]	
Williamsson et al., 2015	32	50	38	50	4.6%	0.84 (0.65, 1.09)	
Williamsson et al., 2019	40	55	32	50	4.6%	1.14 [0.87, 1.48]	
Zouros et al., 2016	27	75	25	50	2.9%	0.72 [0.48, 1.08]	
Total (95% CI)		2277		2177	100.0%	0.83 [0.76, 0.91]	•
Total events	1101		1316				17 C
Heterogeneity: Tau# = 0.03; Chi# = 6	60.31, df=	23 (P		= 62%			0.2 0.5 1 2 5
Test for overall effect: Z = 4.00 (P <		1					0.2 0.5 1 2 Favours [ERAS] Favours [Traditional

Fig. 7 Forest plot of overall complication rates, ERAS vs traditional care

	ERA	5	Traditiona	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Braga et al., 2014	23	115	22	115	8.0%	1.05 [0.62, 1.77]	
Coolsen et al., 2014	26	86	31	97	10.5%	0.95 [0.61, 1.46]	_ _
Dai et al., 2017	2	68	21	98	6.2%	0.14 [0.03, 0.57]	
Hilal et al., 2013	2	20	3	24	1.0%	0.80 [0.15, 4.33]	
Hwang et al., 2019	15	123	10	124	3.6%	1.51 [0.71, 3.23]	
Joliat et al., 2015	32	74	41	87	13.6%	0.92 [0.65, 1.29]	
Morales Soriano et al., 2015	6	41	10	44	3.5%	0.64 [0.26, 1.61]	
Partelli et al., 20216	10	22	17	66	3.1%	1.76 [0.95, 3.26]	———
Sulet al., 2017	2	31	4	31	1.4%	0.50 [0.10, 2.53]	
Sutcliffe et al., 2015	15	65	15	65	5.4%	1.00 [0.53, 1.87]	
Takagi et al., 2019	6	37	6	37	2.2%	1.00 [0.35, 2.82]	
Téoule et al., 2020	46	148	39	147	14.2%	1.17 [0.82, 1.68]	
Tremblay St-Germain et al., 2017	24	83	27	74	10.3%	0.79 [0.50, 1.25]	
van der Kolk et al., 2017	12	95	13	52	6.1%	0.51 [0.25, 1.03]	
Vanounou et al., 2007	13	145	4	64	2.0%	1.43 [0.49, 4.23]	
Williamsson et al., 2015	7	50	5	50	1.8%	1.40 [0.48, 4.12]	
Williamsson et al., 2019	16	55	7	50	2.7%	2.08 [0.93, 4.63]	
Zouros et al., 2016	11	75	10	50	4.3%	0.73 [0.34, 1.60]	
Total (95% CI)		1333		1275	100.0%	0.96 [0.83, 1.11]	•
Total events	268		285				2 A 4 2 2
Heterogeneity: Chi ² = 24.03, df = 11	7 (P = 0.12)	5; P= 2	9%				
Test for overall effect: Z = 0.56 (P =	1						0.05 0'2 1 5 20 Favours [ERAS] Favours [Traditional Care



et al. 2013; Kagedan et al. 2015; Xiong et al. 2016), however, these data were not pooled. By contrast, this review included 10 studies on hospital costs, making it the first meta-analysis to confirm that implementation of ERAS can achieve significant cost savings in pancreatoduodenectomy. The reduction in hospital costs was also observed in the subgroup analysis of studies conducted in North America and East Asia, thereby strengthening the findings of this review.

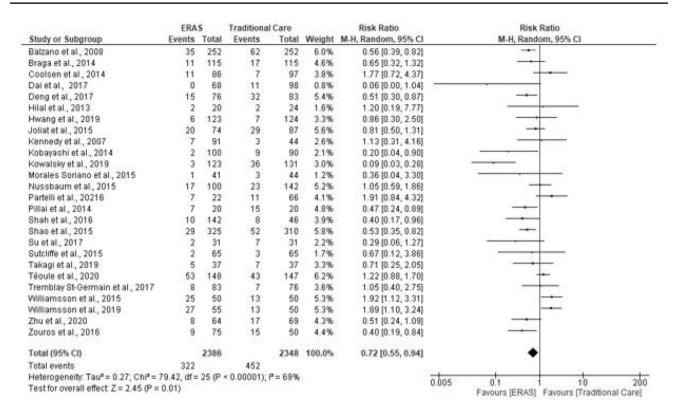


Fig. 9 Forest plot of DGE, ERAS vs traditional care

However, hospital costs varied significantly. This variation may be due to how medical costs are calculated from one centre to another. This emphasises the need for a standardised method of reporting medical costs.

Regarding secondary outcomes, this review found a significant reduction in length of stay of 3.15 days following implementation of ERAS protocols; a finding that is consistent with previous reviews on pancreatic surgery (Kuemmerli et al. 2022; Sun et al. 2020; Wang et al. 2020; Xiong et al. 2016). However, it is worth noting the presence of heterogeneity in the LOS. Despite conducting a sensitivity analysis, the heterogeneity still existed. The presence of heterogeneity could be due to several reasons, for example, how length of stay is calculated. Some studies reported LOS as either total LOS or postoperative LOS, whilst the majority of the studies did not state whether LOS was calculated as total length of stay or postoperative length of stay. Furthermore, the model of healthcare delivery differs significantly from one country to another, along with cultural ethos. For example, in countries such as the United Kingdom, it is a standard practice for a postoperative patient to be discharged from hospital to continue rehabilitation in the community. Whereas this practice is rare in many other countries and may not be affordable to patients without health insurance (Xiong et al. 2016). This review also demonstrated that ERAS reduces cases of overall complications and delayed gastric emptying (DGE). A separate analysis was conducted to investigate the impact of ERAS on major complications. This finding was consistent with previous reviews (Bin Ji et al. 2018; Sun et al. 2020), major complications did not change in the ERAS group.

Contrary to previous reviews, mortality rates were significantly lower in the ERAS group. However, this result was swayed in favour of ERAS by a study that conducted a long-term follow-up (Shao et al. 2015). When this study was excluded from the meta-analysis, there was no significant difference between both groups (RR = 0.80; 0.55–1.17; P = 0.25). Therefore, the long-term impact of the ERAS pathway should be investigated further in high-quality randomised control trials (RCTs). Meanwhile, introduction of an ERAS pathway did not reduce readmissions and reoperations compared to traditional care.

The numbers of ERAS items utilised across all studies varied significantly. None of the studies included in this review applied all 27 items in the ERAS guidelines for pancreatoduodenectomy (Lassen et al. 2012; Melloul et al. 2019), with some studies using as little as six items. This is likely to be due to most studies being conducted

	ERA	s	Traditiona	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Balzano et al., 2008	9	252	7	252	6.3%	1.29 [0.49, 3.40]	
Braga et al., 2014	4	115	4	115	3.6%	1.00 (0.26, 3.90)	
Coolsen et al., 2014	4	86	6	97	5.1%	0.75 [0.22, 2.58]	
Daietal., 2017	0	68	0	98		Not estimable	
Deng et al., 2017	0	76	0	83		Not estimable	
rench et al., 2009	0	9	3	49	1.0%	0.71 [0.04, 12.78]	· · · · · · · · · · · · · · · · · · ·
Hilal et al., 2013	0	24	0	20		Not estimable	
Iwang et al., 2019	0	123	0	124		Not estimable	
Joliat et al., 2015	3	74	4	87	3.3%	0.88 [0.20, 3.81]	
Kagedan et al., 2017	1	121	1	74	1.1%	0.61 [0.04, 9.63]	
Kennedy et al., 2007	1	91	1	44	1.2%	0.48 [0.03, 7.55]	
Kobayashi et al., 2014	0	100	1	90	1.4%	0.30 [0.01, 7.28]	
Kowalsky et al., 2019	0	123	3	131	3.0%	0.15 [0.01, 2.91]	
Morales Soriano et al., 2015	0	41	2	44	2.2%	0.21 [0.01, 4.33]	
Nussbaum et al., 2015	1	100	2	142	1.5%	0.71 [0.07, 7.72]	
Partelli et al., 2016	1	22	1	66	0.4%	3.00 (0.20, 45.98)	
Pillai et al., 2014	2	20	1	20	0.9%	2.00 [0.20, 20.33]	
Shah et al., 2016	1	142	2	46	2.7%	0.16 [0.02, 1.75]	
Shao et al., 2015	40	325	53	310	48.6%	0.72 [0.49, 1.05]	
Sulet al., 2017	0	31	0	31		Not estimable	
Sutcliffe et al., 2015	2	65	2	65	1.8%	1.00 [0.15, 6.89]	
Fakagi et al., 2019	0	37	0	37		Not estimable	
léoule et al., 2020	7	148	9	147	8.1%	0.77 [0.30, 2.02]	
Fremblay St-Germain et al., 2017	0	83	3	74	3.3%	0.13 [0.01, 2.43]	
van der Kolk et al., 2017	1	95	0	52	0.6%	1.66 (0.07, 39.95)	
/anounou et al., 2007	2	145	1	64	1.2%	0.88 [0.08, 9.56]	
Villiamsson et al., 2015	0	50	0	50		Not estimable	
Williamsson et al., 2019	2	55	0	50	0.5%	4.55 (0.22, 92.62)	
Zhu et al., 2020	0	64	0	69		Not estimable	
Zouros et al., 2016	3	75	2	50	2.2%	1.00 [0.17, 5.77]	
Total (95% CI)		2760		2581	100.0%	0.76 [0.58, 1.00]	6 · · · · ·
Total events	84		108				Q \$8
Heterogeneity: Chi ² = 10.12, df = 21 Test for overall effect: Z = 1.99 (P =		i); i* = 0	%				0.002 0.1 1 10 50 Favours [experimental] Favours [control]

Fig. 10 Forest plot of mortality rates, ERAS vs traditional care

before the first ERAS guidelines for pancreatoduodenectomy were published in 2012 (Lassen et al. 2012). The key ERAS items identified were preoperative education and counselling, minimum fasting and administration of carbohydrate drinks prior to surgery, epidural analgesia, intravenous fluids restriction, prevention of hypothermia, early removal of urinary catheters and abdominal drains, early oral intake, early mobilisation, early commencement of oral analgesia and prevention of postoperative nausea and vomiting (PONV). Early oral intake and early mobilisation were the most common interventions and were implemented in thirty-one studies, while preoperative carbohydrate drinks were the least implemented intervention and were on only administered 2–3 h prior to surgery in thirteen studies.

Most of the studies included did not investigate compliance to the ERAS pathway. When investigated, compliance rates were found to be significantly higher in the ERAS group in studies comparing compliance between the two groups (Takagi et al. 2019; Su et al. 2017). In studies that investigated compliance to key elements of ERAS in the ERAS group (Zouros et al. 2016; Braga et al. 2014), poor compliance was more prevalent in the postoperative ERAS elements particularly, oral analgesia, resumption of free fluids and normal diet and removal of abdominal drain and nasogastric tube. Moreover, patients with poor compliance experienced higher incidence of complications and prolonged hospital stay. Hence, flagging patients with poor compliance to key postoperative ERAS items may allow early identification of patients group that require additional care or further investigation.

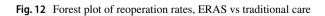
It is worth mentioning the limitations in this current review.

(1) The presence of heterogeneity was observed in hospital costs, LOS, overall complications and DGE. Where there was evidence of heterogeneity, sensitive analyses were conducted to investigate the influence of a single study by eliminating a study at each round. Despite this analysis, it was not possible to reduce the presence of heterogeneity below substantial level. Although, a random effect was used where heterogeneity could not be eliminated, however, it is not certain how this would have impacted the reliability of findings of this review.

	ERA	s	Traditional	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Balzano et al., 2008	18	252	16	252	6.1%	1.13 [0.59, 2.16]	
Braga et al., 2014	14	115	12	115	4.6%	1.17 (0.56, 2.41)	
Coolsen et al., 2014	11	86	14	97	5.0%	0.89 [0.43, 1.85]	
Daietal, 2017	0	68	6	98	2.0%	0.11 [0.01, 1.93]	· · · · · · · · · · · · · · · · · · ·
Deng et al., 2017	1	76	1	83	0.4%	1.09 [0.07, 17.16]	· · · · · · · · · · · · · · · · · · ·
Hilal et al., 2013	1	20	2	24	0.7%	0.60 (0.06, 6.14)	
Hwang et al., 2019	21	123	14	124	5.3%	1.51 [0.81, 2.84]	
Kagedan et al., 2017	20	121	12	74	5.7%	1.02 [0.53, 1.96]	
Kennedy et al., 2007	7	91	3	44	1.5%	1.13 [0.31, 4.16]	
Kobayashi et al., 2014	2	100	2	90	0.8%	0.90 (0.13, 6.26)	
Kowalsky et al., 2019	36	123	32	131	11.8%	1.20 [0.80, 1.80]	
Morales Soriano et al., 2015	4	41	4	44	1.5%	1.07 [0.29, 4.01]	
Nikfarjam et al., 2013	3	20	0	21	0.2%	7.33 [0.40, 133.57]	
Nussbaum et al., 2015	31	100	36	142	11.3%	1.22 [0.81, 1.84]	
Partelli et al., 20216	3	22	11	66	2.1%	0.82 [0.25, 2.67]	
Pillai et al., 2014	Ő	20	0	20	P.0.44	Not estimable	
Shah et al., 2016	16	142	3	46	1.7%	1.73 [0.53, 5.66]	
Shao et al., 2015	43	325	44	310	17.1%	0.93 [0.63, 1.38]	
Sutcliffe et al., 2015	5	65	9	65	3.4%	0.56 [0.20, 1.57]	
Takagi et al., 2019	ő	37	3	37	1.3%	0.14 (0.01, 2.67)	
Téoule et al., 2020	10	148	6	147	2.3%	1.66 [0.62, 4.44]	
Tremblay St-Germain et al., 2017	8	83	10	74	4.0%	0.71 [0.30, 1.71]	
van der Kolk et al., 2017	12	95	9	52	4.4%	0.73 [0.33, 1.62]	
Vanounou et al., 2007	13	145	4	64	2.1%	1.43 [0.49, 4.23]	
Williamsson et al., 2015	0	50	3	50	1.3%	0.14 [0.01, 2.70]	
Williamsson et al., 2019	13	55	5	50	2.0%	2.36 [0.91, 6.16]	
Zhu et al., 2020	0	64	0	69	2.0.0	Not estimable	
Zouros et al., 2016	5	75	3	50	1.4%	1.11 [0.28, 4.44]	
Total (95% CI)		2662		2439	100.0%	1.07 [0.91, 1.25]	•
Total events	297		264				
Heterogeneity: Chi#= 18.46, df= 25		r = 0					0.005 0.1 1 10
Test for overall effect: Z = 0.83 (P =		199	32				0.005 0.1 10 Favours [ERAS] Favours [Traditional Car

Fig. 11 Forest plot of readmission rate, ERAS vs traditional care

	ERA	s	Traditional	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Events Total Weight M-H, Fixed, 95% Cl M	M-H, Fixed, 95% CI		
Balzano et al., 2008	17	252	20	252	24.2%	0.85 [0.46, 1.58]	
Braga et al., 2014	14	115	12	115	14.5%	1.17 [0.56, 2.41]	
Daietal., 2017	2	68	5	98	4.9%	0.58 [0.12, 2.89]	
Deng et al., 2017	3	76	1	83	1.2%	3.28 [0.35, 30.83]	· · · · · · · · · · · · · · · · · · ·
Hwang et al., 2019	6	123	2	124	2.4%	3.02 [0.62, 14.69]	
Morales Soriano et al., 2015	5	41	5	44	5.8%	1.07 [0.33, 3.44]	
Nussbaum et al., 2015	10	100	18	142	18.0%	0.79 [0.38, 1.64]	
Partelli et al., 20216	1	22	3	66	1.8%	1.00 (0.11, 9.13)	
Pillai et al., 2014	1	20	3	20	3.6%	0.33 [0.04, 2.94]	
Sulet al., 2017	1	31	0	31	0.6%	3.00 [0.13, 70.92]	
Tremblay St-Germain et al., 2017	6	83	10	74	12.8%	0.53 [0.20, 1.40]	
/anounou et al., 2007	7	145	4	64	6.7%	0.77 (0.23, 2.55)	
Milliamsson et al., 2019	4	55	0	50	0.6%	8.20 [0.45, 148.52]	
Zouros et al., 2016	4	75	2	50	2.9%	1.33 [0.25, 7.01]	
Total (95% CI)		1206		1213	100.0%	0.98 [0.73, 1.31]	
Total events	81		85				
Heterogeneity: Chi# = 9.55, df = 13	(P = 0.73)	P = 09	6				adas al da ak
Test for overall effect. Z = 0.16 (P = 0.88)							0.005 0.1 1 10 20 Favours [experimental] Favours [control]



- (2) None of the studies included in this review adopted current ERAS guidelines, which may have contributed to significant evidence of heterogeneity. A future study solely based on current ERAS guidelines on pancreaticoduodenectomy.
- (3) Most of the studies do not specify surgical approach applied in the surgeries; therefore, this review was unable to reach a conclusion on the additional benefits of minimally invasive approach in ERAS protocols. A future high quality RCTs is recommended to obtain this useful information.

Conclusion

This current review demonstrated that the implementation of ERAS is safe and feasible in pancreaticoduodenectomy, improves clinical outcomes such as length of stay, complications, DGE and mortality rates, without changing readmission and reoperation rates, while delivering significant cost savings. High levels of compliance can be achieved in ERAS and is associated with better clinical outcomes especially LOS and complications.

Evidently, successful implementation of ERAS is dependent on compliance to key elements. Therefore, early identification of patients with poor compliance may ensure this group are given additional care to maximise clinical outcomes.

Author contributions Conceptualization of the study: LN, SR, LD, CC, DH and VY. Literature search, Data extraction and Data analysis: LN and Drafting of manuscript and critical revision of the work: LN, SR, LD, CC, DH and VY. All authors read and approved the final manuscript.

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Data availability All data generated or analysed during this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent and ethical approval Not required for this type of study.

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