Impact of enhanced recovery after surgery programs on pancreatic surgery: A meta-analysis

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Abstract

AIM
To evaluate the impact of enhanced recovery after surgery (ERAS) programs on postoperative complications of pancreatic surgery.

METHODS
Computer searches were performed in databases (including PubMed, Cochrane Library and Embase) for randomized controlled trials or case-control studies describing ERAS programs in patients undergoing pancreatic surgery published between January 1995 and August 2017. Two researchers independently evaluated the quality of the studies' extracted data that met the inclusion criteria and performed a meta-analysis using RevMan5.3.5 software. Forest plots, demonstrating the outcomes of the ERAS group vs the control group after pancreatic surgery, and funnel plots were used to evaluate potential publication bias.

RESULTS
Twenty case-control studies including 3694 patients, published between January 1995 and August 2017, were selected for the meta-analysis. This study included the ERAS group (n = 1886) and the control group (n = 1808), which adopted the traditional perioperative management. Compared to the control group, the ERAS group had lower delayed gastric emptying rates [odds ratio (OR) = 0.58, 95% confidence interval
(CI): 0.48-0.72, \( P < 0.00001 \)], lower postoperative complication rates (OR = 0.57, 95%CI: 0.45-0.72, \( P < 0.00001 \)), particularly for the mild postoperative complications (Clavien-Dindo I - II) (OR = 0.71, 95%CI: 0.58-0.88, \( P = 0.002 \)), lower abdominal infection rates (OR = 0.70, 95%CI: 0.54-0.90, \( P = 0.006 \)), and shorter postoperative length of hospital stay (PLOS) (WMD = -4.45, 95%CI: -5.99 to -2.91, \( P < 0.00001 \)). However, there were no significant differences in complications, such as postoperative pancreatic fistulas, moderate to severe complications (Clavien-Dindo III - V), mortality, readmission and unintended reoperation, in both groups.

CONCLUSION
The perioperative implementation of ERAS programs in pancreatic surgery is safe and effective, can decrease postoperative complication rates, and can promote recovery for patients.

Key words: Pancreatic surgery; Enhanced recovery after surgery; Postoperative complication; Meta-analysis

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Core tip: Enhanced recovery after Surgery (ERS) programs have been launched in a variety of surgical fields, including colorectal, orthopedics, urology, esophageal and gynecology, demonstrating favorable outcomes. Pancreatic surgery is considered a high-risk abdominal surgery, due to increased surgical trauma and high incidence of postoperative complications. In this meta-analysis we aimed to evaluate the impact of ERAS on complications of pancreatic surgery. The present study demonstrates that ERAS could reduce complication rates, especially of mild complications, delayed gastric emptying, abdominal infection and postoperative length of hospital stay, while not affecting the rates of postoperative pancreatic fistulas, reoperation, readmission and mortality during the perioperative period.

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INTRODUCTION
Enhanced recovery after surgery (ERAS; also called ‘fast track surgery’) was first introduced by Kehlet H, a Danish surgeon, in 1997[1]. ERAS is a multidisciplinary and evidence-based framework developed to decrease perioperative surgical stress, accelerate postoperative recovery and significantly reduce the postoperative length of hospital stay (PLOS). ERAS programs were initially implemented in colorectal surgery and have been shown to be effective for reducing PLOS and complications[2]. Subsequently, ERAS programs have been published in numerous areas of surgery, such as orthopedics, urology, esophageal, gynecology, breast and hepatobiliary[3-8].

An array of studies has shown that the perioperative implementation of ERAS programs can reduce PLOS without increasing complications or mortality. However, pancreatic surgery is still considered a high-risk abdominal surgery, due to the anatomical location of the pancreas and high rate of complications (30%-60%). Postoperative complications, such as postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), abdominal infection, and so on, are the main reasons for delayed recovery and the frequent need for additional interventions, without which the complications are potentially life threatening. For these reasons, the implementation of ERAS programs has lagged for pancreatic surgeries.

There had been an increasing number of ERAS programs implemented in pancreatic surgery when the ERAS group published evidence-based consensus recommendations for pancreatic surgery in 2012[9]. The benefit of implementing ERAS programs on postoperative complications in pancreatic surgery has not reached consensus. For this reason, we performed a meta-analysis of the available studies on ERAS programs compared with traditional perioperative management in patients undergoing pancreatic surgery.

MATERIALS AND METHODS
Search strategy
A search was performed by two researchers (Ji HB and Wang XX) in August 2017 of the PubMed, Cochrane Library and Embase database, spanning the period from January 1995 to August 2017. The search language was restricted to English, using the search terms “enhanced recovery after surgery”, “fast track surgery”, “ERAS”, “clinical pathways”, “pancreatectomy”, “pancreatoduodenectomy” and “duodenopancreatectomy”, and using the Boolean operators “AND” and “OR”. Synonyms of all these terms were used in this search. The PubMed search strategy for the meta-analysis is shown in Table 1.

Inclusion/exclusion criteria
Studies meeting all of the following selection criteria were eligible for inclusion: (1) studies concerning patients undergoing pancreatic surgery; (2) the ERAS group implemented ERAS programs management, and the control group adopted traditional perioperative management; (3) measures in perioperative management were described in both groups; and (4) studies reported at least the following outcome measures, POPF, DGE, abdominal infection, mortality and PLOS, and explained their diagnostic criteria for postoperative complications.
Table 1 The search strategy for the PubMed database

| Search number | Description                                                                 | Number of publications |
|---------------|-----------------------------------------------------------------------------|------------------------|
| 1             | Enhanced recovery after surgery [Title/Abstract] OR ERAS [Title/Abstract] OR fast track surgery [Title/Abstract] | 3333                   |
| 2             | Clinical pathways [MeSH Terms]                                               | 5848                   |
| 3             | 1 OR 2                                                                      | 9130                   |
| 4             | Pancreatectomy [MeSH Terms] OR Pancreatectom* [Title/Abstract] OR Pancreatoduodenectomy [MeSH Terms] OR Pancreatoduodenectomy* [Title/Abstract] OR duodenopancreatectomy [MeSH Terms] OR duodenopancreatectomy* [Title/Abstract] | 21497                  |
| 5             | 3 AND 4 NGT [animals[mh] NOT humans[mh]]                                    | 69                     |
| 6             | S limited to English                                                        | 68                     |

\^Date of search: August 1, 2017.

Exclusion criteria were (1) sample size of less than 10; (2) comments, guidelines, reviews, case reports, abstracts, letters and non-comparative studies; (3) repeated publication of the same study population; and (4) incomplete clinical data.

Outcomes of interest

The outcomes of interest were POPF, DGE, PLOS, abdominal infection, mortality, readmission, unintended reoperation and occurrence of any complication within a postoperative period of 30 d. POPF was defined using the International Study Group of Pancreatic Fistula (ISGPF) guidelines describing a drain output of any measurable volume of fluid on or after postoperative day (POD) 3, with an amylase content greater than three times the serum amylase activity or as defined by the study's authors\(^{[10]}\). DGE was defined according to the International Study Group of Pancreatic Surgery's (ISGPS) recommendation that patients needing maintenance of a nasogastric tube (NGT) for > 3 d, needing to reinsert the NGT for persistent vomiting after POD 3, or unable to tolerate a solid diet by POD 7, should be considered DGE. In addition, there are another two widely used definitions for DGE after pancreatic resection (1) Yeo defined DGE as an NGT left in place for ≥ 10 d plus one of the following, or for < 10 d plus two of the following (a) repeated emesis after removal of the NGT, (b) need for prokinetic agents after POD 10, (c) need for reinsertion of the NGT, or (d) failure to progress with the diet. (2) Van Berge Henegouwen et al\(^{[11]}\) defined DGE as gastric stasis requiring NGT for ≥ 10 d or the inability to tolerate a regular diet after POD 14. PLOS was defined as the span from the day of surgery to the day of actual discharge from the hospital. Abdominal infection was defined by the study's authors. Mortality was defined as the range from the day of hospitalization to the first 30 d after actual discharge. Readmission was defined as the patient needing medical attention again within 30 d after discharge. Overall postoperative complications included any complication from the time of surgery to discharge, or within 30 d, with severity grading and classification relying on the Clavien-Dindo system\(^{[12]}\). Unintended reoperation was defined as patients with complications or other reasons that required reoperation within 30 d after discharge.

Data extraction

Data were extracted from each study by two authors (Ji HB and Wei Q) independently. The main parameters included common information (time of study publication, country, study type, and authors), characteristics of the study population (sex and age), elements of ERAS programs, and postoperative outcomes (overall complications, POPF, DGE, abdominal infection, PLOS, mortality, readmission, and unintended reoperation). All continuous outcome variables were described using the means and standard deviations for this meta-analysis. We needed to estimate means and standard deviations via the methodologies reported by Hozo et al\(^{[13]}\) if the original data were expressed as medians or ranges.

Quality assessment

The quality assessment of each study was done by two authors (Zhu WT and Ji HB) independently via the Methodological Index for Non-Randomized Studies (MINORS) checklist. It was then summarized by a French surgeon, and if there was a disagreement, the third researcher was involved in the negotiation or adjudication, until a consensus was achieved. The MINORS checklist includes eight methodological items for non-comparative studies and an additional four items for comparative studies. The items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The overall ideal scores were 24 for comparative studies.

Statistical analysis

The meta-analysis was performed using RevMan5.3.5 software (Ji HB and Wang HB). Continuous and categorical variables were calculated as weighted mean differences (WMDs) or odds ratios (ORs) with their corresponding 95% confidence interval (CI), respectively. Heterogeneity was assessed using a chi-square test, where \( P > 0.05\) was considered non-significant. \( I^2 \) values were used for the evaluation of statistical heterogeneity, and the \( I^2 \) value of 50% or more indicated the presence of substantial heterogeneity.
Scores > 12.

RESULTS

Pancreatic fistula
Eighteen studies reported the rates of POPF. The overall results (OR = 0.87, 95%CI: 0.74-1.03, \(P = 0.10\); Figure 2), or only those using the ISGPF definition (OR = 0.90, 95%CI: 0.76-1.07, \(P = 0.24\)), showed that there were no significant differences present in either group. Furthermore, there was no significant difference in A (OR = 1.05, 95%CI: 0.81-1.36, \(P = 0.71\)), B (OR = 1.13, 95%CI: 0.85-1.51, \(P = 0.40\)), and C (OR = 0.90, 95%CI: 0.60-1.33, \(P = 0.59\)) grade of POPF between the ERAS group and control group.

DGE
Eighteen studies reported the rates of DGE. Compared to the control group, the ERAS group had a lower incidence of DGE (OR = 0.58, 95%CI: 0.48-0.72, \(P < 0.00001\); Figure 3). The difference persisted when including only studies that adopted the ISGPS definition (OR = 0.50, 95%CI: 0.39-0.65, \(P < 0.00001\)).

Postoperative complications
The rate of overall postoperative complications was lower in the ERAS group (OR = 0.57, 95%CI: 0.45-0.72, \(P < 0.00001\); Figure 4). Additionally, the incidence of mild postoperative complications (Clavien-Dindo I-II), which relies on the Clavien-Dindo definition of severity and classification, was lower in the ERAS group (OR = 0.71, 95%CI: 0.58-0.88, \(P = 0.002\); Figure 5). There were no statistically significant differences in the moderate to severe complication rates (Clavien-Dindo III-V) between the ERAS group and control group (OR = 0.90, 95%CI: 0.73-1.11, \(P = 0.32\)).

Abdominal infection
A total of 12 studies reported the rates of abdominal infection. The incidence of abdominal infection was lower (OR = 0.70, 95%CI: 0.54-0.90, \(P = 0.006\); Figure 6) in the ERAS group.

PLOS
A total of 13 studies reported the PLOS, and they showed that the ERAS group had shorter PLOS (WMD = -4.45, 95%CI: -5.99 to -2.91, \(P < 0.00001\); Figure 7) than the control group.

In addition, there were no significant differences in rates of mortality (OR = 0.85, 95%CI: 0.54-1.36, \(P = 0.51\); Figure 8), readmission (OR = 1.04, 95%CI: 0.83-1.30, \(P = 0.75\); Figure 9), and unintended reoperation (OR = 0.87, 95%CI: 0.63-1.20, \(P = 0.40\); Figure 10).

Subgroup analysis
The subgroup analysis, which included only larger...
This analysis revealed that no single study generated an overall significant effect. We aimed to investigate the influence of a single study on the overall results by omitting one study in each turn. This analysis revealed that no single study generated an overall significant effect.

### Sensitivity analysis

We aimed to investigate the influence of a single study on the overall results by omitting one study in each turn. This analysis revealed that no single study generated an overall significant effect.
especially strong influence on the results, with estimates ranging from an OR of 0.54 to 0.62 (Table 4).

**Publication bias**

Funnel plots based on the incidence of POPF and mortality were used to evaluate potential publication bias in this study (Figure 11). There was no evidence of publication bias of POPF, mortality or other outcomes of this study (other figures not shown).

**DISCUSSION**

ERAS requires surgical, nursing, anesthesia, nutritionist and other specialties to work together and uses a series of optimal and evidence-based management measures to lessen perioperative surgical stress while promoting the recovery of organ function in the early postoperative period [34,35]. ERAS programs were initially implemented in colorectal surgery, with recommendations for each step...
to achieve optimal perioperative care[36]. Subsequently, ERAS programs had been launched in numerous fields of surgery, such as orthopedics, urology, esophageal and gynecology.

The literature from these disciplines has suggested that standardizing ERAS measures could reduce the incidence of complications, accelerate recovery for patients, reduce hospitalization costs and save medical resources in perioperative care[34,4,7,8]. Pancreatic surgery is an effective treatment of pancreatic tumors, periampullary tumors, duodenal tumors and distal bile duct tumors. Currently, despite surgical techniques, anesthesia, and preoperative imaging assessment making great progress and the mortality of the procedure rates of DGE, POPF, readmission, and mortality. Kagedan et al[39] analyzed 10 studies suggesting that the ERAS group had only shorter PLOS and no differences in other complications. As mentioned above, we may reasonably conclude that the influence of ERAS programs on the postoperative complications of pancreatic surgery is controversial. Hence, the application of ERAS programs in the perioperative period of pancreatic surgery is still being explored in our practices.

The main measures of the ERAS programs include no bowel preparation and clear fluids until 2-3 h before surgery, multimodal analgesia of postoperative, clear fluids or food intakes, enhanced mobilization and removal of the drainage tube in early period. The ERAS group had shorter PLOS and lower postoperative complication rates; however, there were no significant differences in rates of DGE, POPF, readmission, and mortality. Kagedan et al[39] analyzed 10 studies suggesting that the ERAS group had only shorter PLOS and no differences in other complications. As mentioned above, we may reasonably conclude that the influence of ERAS programs on the postoperative complications of pancreatic surgery is controversial. Hence, the application of ERAS programs in the perioperative period of pancreatic surgery is still being explored in our practices.

The main measures of the ERAS programs include no bowel preparation and clear fluids until 2-3 h before surgery, multimodal analgesia of postoperative, clear fluids or food intakes, enhanced mobilization and removal of the drainage tube in early period. The ERAS group had reduced time of fasting in the preoperative period, which can decrease the insulin resistance in the postoperative period. We adopted multimodal

| Study or Subgroup | ERAS group | Control group | Odds Ratio | Year |
|-------------------|------------|---------------|------------|------|
|                    | Events     | Total | Events | Total | Weight | M-H, Fixed, 95%CI |                  |
| Vanoueu T         | 53         | 145   | 32     | 64    | 13.7%  | 0.58 [0.32, 1.04] | 2007             |
| Abu Hilal M       | 6          | 20    | 13     | 24    | 4.0%   | 0.36 [0.10, 1.26] | 2013             |
| Coolen MM         | 20         | 86    | 17     | 97    | 6.0%   | 1.43 [0.69, 2.94] | 2014             |
| Braga M           | 46         | 115   | 54     | 115   | 15.8%  | 0.75 [0.40, 1.39] | 2014             |
| Yui R             | 52         | 57    | 40     | 52    | 1.8%   | 3.12 [1.02, 9.58] | 2014             |
| Partell S         | 7          | 22    | 26     | 66    | 4.3%   | 0.72 [0.26, 2.00] | 2015             |
| Joliat GR         | 18         | 74    | 30     | 87    | 10.2%  | 0.61 [0.31, 1.22] | 2015             |
| Morales Soriano R | 6          | 41    | 12     | 44    | 4.8%   | 0.46 [0.15, 1.36] | 2015             |
| Williamson C      | 25         | 50    | 29     | 50    | 7.1%   | 0.72 [0.33, 1.59] | 2015             |
| Zouros E          | 15         | 75    | 15     | 50    | 7.0%   | 0.58 [0.25, 1.34] | 2016             |
| Bai X             | 55         | 124   | 30     | 63    | 10.8%  | 0.88 [0.48, 1.61] | 2016             |
| Dai J             | 32         | 68    | 68     | 98    | 14.4%  | 0.39 [0.21, 0.74] | 2017             |

Total (95%CI) 877 810 100.0% 0.71 [0.58, 0.88]
Total events 335 366
Heterogeneity: Χ² = 16.67, df = 11 (P = 0.12); I² = 34%
Test for overall effect: Z = 3.15 (P = 0.002)

Figure 5 Forest plots demonstrating the outcomes of mild complications.

| Study or Subgroup | ERAS group | Control group | Odds Ratio | Year |
|-------------------|------------|---------------|------------|------|
|                    | Events     | Total | Events | Total | Weight | M-H, Fixed, 95%CI |                  |
| Abu Hilal M       | 2          | 20    | 0      | 24    | 0.3%   | 6.62 [0.30, 146.37] | 2013             |
| Coolen MM         | 14         | 86    | 15     | 97    | 8.5%   | 1.06 [0.48, 2.35] | 2014             |
| Nussbaum DP       | 16         | 100   | 25     | 142   | 12.5%  | 0.89 [0.45, 1.77] | 2014             |
| Kobayashi S       | 5          | 100   | 5      | 90    | 3.6%   | 0.89 [0.25, 3.20] | 2014             |
| Yui R             | 2          | 57    | 10     | 52    | 7.3%   | 0.15 [0.03, 0.73] | 2014             |
| Nussbaum DP       | 6          | 50    | 9      | 100   | 3.8%   | 1.38 [0.46, 4.12] | 2014             |
| Williamson C      | 6          | 50    | 2      | 50    | 1.3%   | 3.27 [0.63, 17.07] | 2015             |
| Morales Soriano R | 3          | 41    | 2      | 44    | 1.3%   | 1.66 [0.26, 10.46] | 2015             |
| Shao Z            | 46         | 325   | 69     | 310   | 43.8%  | 0.58 [0.38, 0.87] | 2015             |
| Bai X             | 10         | 124   | 9      | 63    | 7.9%   | 0.53 [0.20, 1.37] | 2016             |
| Zouros E          | 1          | 75    | 0      | 50    | 0.4%   | 2.03 [0.08, 50.92] | 2016             |
| Dai J             | 2          | 68    | 16     | 98    | 9.2%   | 0.16 [0.03, 0.70] | 2017             |

Total (95%CI) 1096 1120 100.0% 0.70 [0.54, 0.90]
Total events 113 162
Heterogeneity: Χ² = 18.46, df = 11 (P = 0.07); I² = 40%
Test for overall effect: Z = 2.72 (P = 0.006)

Figure 6 Forest plots demonstrating the outcomes of abdominal infection.
analgesia in the postoperative period, which was able to reduce the stress caused by pain. The programs, such as, no bowel preparation before surgery, clear fluids or food intakes, enhanced mobilization in the early postoperative period which may promote rehabilitation of gastrointestinal function[39].

The ERAS programs aimed to reduce the incidence of complications and accelerate recovery for patients. Among them, gastrointestinal function rehabilitation is an important part of the rapid recovery in abdominal surgery. In addition, the early postoperative oral feeding, which may play an important role in the gastrointestinal function rehabilitation in the postoperative period. This is because early postoperative oral feeding is more in line with human physiology of the digestive tract, and which may have a beneficial effect on immunological, inflammatory and nutritional status. In addition, early postoperative oral feeding can promote the recovery of gastrointestinal motility, protect the gastrointestinal mucosal barrier, shorten time to gas and stools passage, and reduce the incidence of complications.

A total of 20 studies and 3694 patients were included in our meta-analysis. Compared with the control group, the ERAS group had lower rates of DGE, lower postoperative complication rates, particularly lower mild postoperative complication rates, lower abdominal infection rates, and shorter PLOS. However, no significant differences existed in POPF, moderate
### Table 1: Meta-analysis of Intended Reoperation

| Study or Subgroup | ERAS group | Control group | Odds Ratio | Year |
|-------------------|------------|---------------|------------|------|
| Kennedy EP        | 7          | 91            | 3          | 44   | 2.5%  1.14 [0.28, 4.63] | 2007 |
| Vanounou T        | 13         | 145           | 4          | 64   | 3.4%  1.48 [0.46, 4.72] | 2007 |
| Balzano G         | 18         | 252           | 16         | 252  | 10.1% 1.13 [0.56, 2.28] | 2008 |
| Kennedy EP        | 5          | 71            | 10         | 40   | 8.1%  0.23 [0.07, 0.72] | 2009 |
| Abu Hilal M       | 1          | 20            | 2          | 24   | 1.2%  0.58 [0.05, 6.90] | 2013 |
| Coolen MM         | 11         | 86            | 14         | 97   | 7.8%  0.87 [0.37, 2.03] | 2014 |
| Braga M           | 14         | 115           | 12         | 115  | 7.1%  1.19 [0.52, 2.70] | 2014 |
| Nussbaum DP       | 31         | 100           | 36         | 142  | 13.9% 1.32 [0.75, 2.33] | 2014 |
| Nussbaum DP       | 15         | 50            | 20         | 100  | 6.3%  1.71 [0.79, 3.73] | 2014 |
| Pillai SA         | 0          | 20            | 0          | 20   | Not estimable | 2014 |
| Shao Z            | 43         | 325           | 44         | 310  | 26.5% 0.92 [0.59, 1.45] | 2015 |
| Partelli S        | 3          | 22            | 11         | 66   | 3.2%  0.79 [0.20, 3.14] | 2015 |
| Morales Soriano R | 4          | 41            | 4          | 44   | 2.4%  1.08 [0.25, 4.64] | 2015 |
| Zouros E          | 5          | 75            | 3          | 50   | 2.3%  1.12 [0.26, 4.91] | 2016 |
| Bai X             | 11         | 124           | 2          | 63   | 1.6%  2.97 [0.64, 13.83] | 2016 |
| Dai J             | 0          | 68            | 6          | 98   | 3.6%  0.10 [0.01, 1.88] | 2017 |

| Total (95%CI)     | 1605       | 1529          | 100.0%     | 1.04 [0.83, 1.30] |

| Total events      | 181        | 187           |            |                  |

### Figure 9: Forest plots demonstrating the outcomes of readmission.

| Study or Subgroup | ERAS group | Control group | Odds Ratio | Year |
|-------------------|------------|---------------|------------|------|
| Vanounou T        | 7          | 145           | 4          | 64   | 6.8%  0.76 [0.21, 2.70] | 2007 |
| Balzano G         | 17         | 252           | 20         | 252  | 24.1% 0.84 [0.43, 1.64] | 2009 |
| Abu Hilal M       | 0          | 20            | 3          | 24   | 4.0%  0.15 [0.01, 3.08] | 2013 |
| Nussbaum DP       | 10         | 100           | 18         | 142  | 17.3% 0.77 [0.34, 1.74] | 2014 |
| Yui R             | 1          | 57            | 1          | 52   | 1.3%  0.91 [0.06, 14.94] | 2014 |
| Pillai SA         | 3          | 20            | 1          | 20   | 1.1%  3.35 [0.32, 35.36] | 2014 |
| Coolen MM         | 7          | 86            | 13         | 97   | 14.5% 0.57 [0.22, 1.51] | 2014 |
| Braga M           | 14         | 115           | 12         | 115  | 13.6% 1.19 [0.52, 2.70] | 2014 |
| Morales Soriano R | 5          | 41            | 5          | 44   | 5.5%  1.08 [0.29, 4.05] | 2014 |
| Partelli S        | 1          | 22            | 3          | 66   | 1.9%  1.00 [0.10, 10.14] | 2015 |
| Zouros E          | 4          | 75            | 2          | 50   | 2.9%  1.35 [0.24, 7.68] | 2016 |
| Bai X             | 4          | 124           | 1          | 63   | 1.7%  2.07 [0.23, 18.89] | 2016 |
| Dai J             | 2          | 68            | 5          | 98   | 5.1%  0.56 [0.11, 2.99] | 2017 |

| Total (95%CI)     | 1125       | 1087          | 100.0%     | 0.87 [0.63, 1.20] |

| Total events      | 75         | 88            |            |                  |

### Figure 10: Forest plots demonstrating the outcomes of unintended reoperation.
to severe complications, mortality, readmission or unintended reoperation in both groups.

Many factors, such as age, nutritional status, and serious comorbidity, can influence patients’ postoperative complication rates and the process of postoperative recovery\cite{41, 42}. The patients’ demographic data in the included studies was basically identical, so these influences may be eliminated for the outcomes in this study. In addition, all of the included studies described the diagnostic criteria for postoperative complications. Therefore, to a certain extent, information bias was possible, because some complications did not have national criteria. Second, only retrospective case control studies were included in this analysis. Therefore, to a certain extent, the outcomes of this study may be influenced by the selection bias. Third, the degree of implementation of ERAS programs and the compliance of patients may be different between studies. Finally, there was no evidence

### Table 3 Results of Subgroup Analysis

| Outcomes of interest | Studies | Patients | OR/WMD | 95%CI | P-value | Heterogeneity P-value | I² | % |
|----------------------|---------|----------|--------|-------|---------|----------------------|-----|----|
| Studies with cases ≥ 100 | | | | | | | | |
| POPF | 14 | 3067 | 0.87 | 0.73-1.03 | 0.11 | 0.02 | 48 |
| DGE | 14 | 3117 | 0.58 | 0.47-0.71 | <0.00001 | 0.07 | 39 |
| Overall complications | 14 | 3045 | 0.57 | 0.45-0.72 | <0.00001 | 0.06 | 46 |
| Mild complications | 9 | 1470 | 0.74 | 0.59-0.93 | 0.009 | 0.07 | 46 |
| Abdominal infection | 10 | 2087 | 0.67 | 0.51-0.87 | 0.003 | 0.07 | 42 |
| PLOS | 10 | 2394 | -4.64 | -3.77 to -2.91 | <0.00001 | 0.09 | 65 |
| Mortality | 15 | 2802 | 0.83 | 0.51-1.37 | 0.47 | 1 | 0 |
| Readmission | 12 | 2877 | 1.05 | 0.83-1.33 | 0.68 | 0.23 | 22 |
| Unintended reoperation | 9 | 1955 | 0.85 | 0.60-1.21 | 0.38 | 0.96 | 0 |
| MINORS score > 12 | | | | | | | | |
| POPF | 15 | 2784 | 0.84 | 0.70-1.00 | 0.05 | 0.13 | 30 |
| DGE | 16 | 2949 | 0.52 | 0.42-0.64 | <0.00001 | 0.12 | 31 |
| Overall complications | 16 | 3008 | 0.56 | 0.44-0.71 | <0.00001 | 0.01 | 51 |
| Mild complications | 11 | 1504 | 0.67 | 0.54-0.83 | 0.0003 | 0.24 | 21 |
| Abdominal infection | 10 | 1791 | 0.63 | 0.46-0.85 | 0.002 | 0.05 | 46 |
| PLOS | 11 | 2272 | -4.35 | -3.97 to -2.72 | <0.00001 | 0.03 | 66 |
| Mortality | 16 | 2523 | 0.96 | 0.56-1.65 | 0.89 | 0.99 | 0 |
| Readmission | 13 | 2598 | 1.09 | 0.84-1.33 | 0.52 | 0.82 | 0 |
| Unintended reoperation | 11 | 1787 | 0.96 | 0.65-1.41 | 0.83 | 0.94 | 0 |

CI: Confidence interval; DGE: Delayed gastric emptying; MINORS score: Methodological Index for Non-Randomized Studies checklist; OR: Odds ratio; PLOS: Postoperative length of hospital stay; POPF: Postoperative pancreatic fistula; WMD: Weighted mean difference.

### Table 4 Results of sensitivity analysis by omitting one study in each turn

| Studies | OR | 95%CI | P-value |
|---------|----|-------|---------|
| Omitting Vanounou et al\cite{31} | 0.56 | 0.44-0.72 | <0.00001 |
| Omitting Kennedy et al\cite{32} | 0.56 | 0.44-0.71 | <0.00001 |
| Omitting Balzano et al\cite{33} | 0.56 | 0.43-0.73 | <0.0001 |
| Omitting Kennedy et al\cite{34} | 0.56 | 0.46-0.74 | <0.0001 |
| Omitting Abu Hilal et al\cite{35} | 0.56 | 0.45-0.73 | <0.0001 |
| Omitting Yui et al\cite{36} | 0.56 | 0.44-0.72 | <0.0001 |
| Omitting Kobayashi et al\cite{37} | 0.56 | 0.45-0.74 | <0.0001 |
| Omitting Coolsen et al\cite{38} | 0.54 | 0.43-0.69 | <0.0001 |
| Omitting Braga et al\cite{39} | 0.55 | 0.43-0.71 | <0.0001 |
| Omitting Pillai et al\cite{40} | 0.57 | 0.45-0.73 | <0.0001 |
| Omitting Joliat et al\cite{41} | 0.57 | 0.45-0.73 | <0.0001 |
| Omitting Partelli et al\cite{42} | 0.55 | 0.44-0.68 | <0.0001 |
| Omitting Williamson et al\cite{43} | 0.56 | 0.44-0.71 | <0.0001 |
| Omitting Morales Soriano et al\cite{44} | 0.58 | 0.46-0.74 | <0.0001 |
| Omitting Shao et al\cite{45} | 0.57 | 0.44-0.74 | <0.0001 |
| Omitting Zouros et al\cite{46} | 0.57 | 0.44-0.73 | <0.0001 |
| Omitting Bai et al\cite{47} | 0.56 | 0.44-0.71 | <0.0001 |
| Omitting Dai et al\cite{48} | 0.62 | 0.52-0.71 | <0.0001 |
| Overall effect | 0.57 | 0.45-0.72 | <0.0001 |

CI: Confidence interval; OR: Odds ratio.
to indicate that major publication bias existed in these studies, and potential publication bias is impossible to completely rule out in small studies. Hence, these factors had some influence on our results.

In summary, the results from our present study demonstrate that the implementation of ERAS programs could reduce overall complication rates, especially of mild complications, DGE, rates of abdominal infection, and PLOS, while not affecting the rates of POPF, reoperation, readmission, and mortality during the perioperative period for pancreatic surgery. The perioperative period for pancreatic surgery is safe and effective to implement ERAS programs that can decrease postoperative complication rates and promote recovery. However, in the future, we need to include more high-quality and strict prospective studies to assess the contributions of individual program components.

ARTICLE HIGHLIGHTS

Research background
Enhanced recovery after surgery (ERAS) is a multidisciplinary and evidence-based framework, developed to decrease perioperative surgical stress, accelerate postoperative recovery and significantly reduce the postoperative length of hospital stay (PLOS). ERAS programs have been launched in a variety of other fields of surgery, such as colorectal, orthopedics, urology, esophageal, and gynecology, and have demonstrated favorable outcomes. The implementation of ERAS programs has lagged surrounding pancreatic surgeries because of the anatomical location of the pancreas and the high rate of postoperative complications (30%-60%). It is very important to promote the postoperative recovery for this high-risk abdominal surgery via implementing ERAS programs during the perioperative period.

Research motivation
ERAS requires surgical, nursing, anesthesia and other specialties to work together and uses a series of optimal or evidence-based management measures to lessen perioperative surgical stress while promoting the recovery of organ function in the early postoperative period. The implementation of ERAS programs may play a very important role in the perioperative period for pancreatic surgery.

Research objectives
This study evaluated the impact of ERAS programs on postoperative complications and PLOS of pancreatic surgery.

Research methods
Computer searches were performed in databases (including PubMed, Cochrane Library, and Embase) for randomized controlled trials or case-control studies describing ERAS programs in patients undergoing pancreatic surgery published between January 1995 and August 2017. Two researchers independently evaluated the quality of the studies’ extracted data that met inclusion criteria and performed a meta-analysis using RevMan5.3.3 software. Forest plots, demonstrating the outcomes of the ERAS group versus the control group after pancreatic surgery, and funnel plots were used to evaluate potential publication bias.

Research results
Twenty case-control studies, published between January 1995 and August 2017, including 3694 patients, were selected for the meta-analysis. They included the ERAS group (n = 1886) and control group (n = 1808), which adopted the traditional perioperative management. Compared to the control group, the ERAS group had lower delayed gastric emptying (DGE) rates (odds ratio (OR) = 0.58, 95% confidence interval (CI): 0.48-0.72, P < 0.00001), lower postoperative complication rates (OR = 0.57, 95%(CI): 0.45-0.72, P < 0.00001), particularly for mild postoperative complications (Clavien-Dindo I - II) (OR = 0.71, 95%(CI): 0.58-0.88, P = 0.002), lower abdominal infection rates (OR = 0.70, 95%(CI): 0.54-0.90, P = 0.006) and shorter PLOS (weighted mean difference (WMD) = -4.45, 95%(CI): -5.99 to -2.91, P < 0.00001). However, there were no significant differences in postoperative pancreatic fistulas (POPF), moderate to severe complications (Clavien-Dindo III - IV), mortality, readmission and unintended reoperation in both groups.

Research conclusions
The results from our present study demonstrate that the implementation of ERAS programs could reduce overall complication rates, especially of mild complications, DGE, rate of abdominal infection and PLOS, while not affecting the rates of POPF, reoperation, readmission and mortality during the perioperative period for pancreatic surgery. The perioperative period for pancreatic surgery is safe and effective to implement ERAS programs that can decrease postoperative complication rates and promote recovery.

Research perspectives
We need to include more high-quality and strict prospective studies to assess the contributions of individual program components, such as clear fluids or food intakes in the early period, and removal of the drainage tube.

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