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How to Reduce Delayed Gastric Emptying After Pancreatoduodenectomy

A Systematic Literature Review and Meta-Analysis

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Introduction: The occurrence of delayed gastric emptying (DGE) following pancreatoduodenectomy is of high clinical relevance. Despite the pivotal nature of this topic, the existing evidence is limited and often conflicting. This meta-analysis aims to assess the impact of various interventions, such as the type of surgical reconstruction (specifically pylorus resection or preservation), enhanced recovery after surgery (ERAS), epidural anesthesia (EA), as well as strategies involving nasogastric decompression on DGE.

Methods: Following the PRISMA guidelines, a systematic search was conducted. Studies that compared patients undergoing pancreatoduodenectomy regarding one of the following interventions were included: pylorus-preserving pancreaticoduodenectomy (ppPD) *versus* pylorus-resecting pancreaticoduodenectomy (prPD), ERAS *versus* no ERAS, epidural anesthesia EA *versus* no EA, nasogastric decompression *versus* no nasogastric decompression and jejunostomy/nasojejunal feeding tube placement (J/NJF) *versus* no J/NJF.

Results: The analysis included 5930 patients from 29 studies. Patients undergoing ppPD exhibited a higher incidence of DGE compared with those undergoing prPD (logOR, –0.95; 95% CI = –1.57 to –0.34; P = 0.002). Additionally, patients in the ERAS group showed reduced rates of DGE (logOR, –0.712; 95% CI = –1.242 to –0.183; P = 0.008). Lower rates of DGE were observed in patients without a J/NJF (logOR, –0.618; 95% CI, 0.39–0.84; P < 0.001).

Conclusion: In summary, our meta-analysis reveals that pylorus resection, adherence to ERAS protocols, and the absence of a J/NJF are associated with lower rates of DGE after pancreatoduodenectomy. Although these results are partially based on observational studies, they contribute valuable insights to the current understanding of interventions impacting DGE in these complex procedures.

Keywords: delayed gastric emptying, meta-analysis, pancreatic surgery

INTRODUCTION

Pancreatoduodenectomy is the surgical therapy of choice for malignant and benign conditions in the pancreatic head region. Postoperative complications include pancreatic fistula, bleeding, and delayed gastric emptying (DGE). DGE occurs in up to two-thirds of the patients, even in high-volume centers.[1]

Although harmless in nature, DGE compromises patients' quality of life, prolongs hospital stay, postpones discharge, and increases total hospital costs. DGE was defined by the International Study Group of Pancreatic Surgery (ISGPS) as the inability to normal oral food uptake by the end of the first postoperative week.[2] This condition also includes prolonged or new nasogastric tube placement. DGE can be classified into 3 different grades (A, B, C) depending on its duration and the required medical provisions.

Risk factors for the occurrence of DGE include pylorus preservation, the type of surgical reconstruction, and the occurrence of pancreatic or bile fistula or chyle leak.[3,4] Understanding the factors influencing DGE is vital for effective management or prevention. Despite the crucial nature of the topic, the evidence remains limited and often conflicting. Pylorus preservation is regularly accused of being associated with DGE. Several meta-analyses suggested that pylorus resection was associated with a decreased rate of DGE.[5–7] In contrast, Klaiber and co-workers have shown in their meta-analysis that pylorus resection is not superior compared to pylorus preservation to prevent DGE after surgery.[8]

Beside pylorus preservation, numerous risk factors for DGE were identified.[6] Due to the heterogeneity of the data, strategies to prevent DGE are not clear. The effectiveness of enhanced recovery after surgery (ERAS) protocols following pancreatoduodenectomy in reducing the rate of DGE is still unclear.[9] Research on DGE after pancreatic surgery spans various aspects, from defining the condition to identifying risk factors and evaluating the impact of surgical techniques. While several meta-analyses have been published on the topic,[5–8,10] our meta-analysis is the first to analyze multiple interventions for DGE.

We aimed to assess the outcome of several interventions with the potential to reduce DGE in pancreatic surgery, including pylorus resection or preservation, the type of surgical

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reconstruction, the use of ERAS protocols, epidural anesthesia, nasogastric decompression, and jejunostomy or nasojejunal feeding tube placement.

METHODS

The literature search and data analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[11] The study has been registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42023405721).[12]

SEARCH STRATEGY

We searched the databases PubMed/MEDLINE, Web of Science Core Collection, Cochrane Library, and ClinicalTrials.gov using their respective online search engines. The search covered studies published from the inception of each database until February 2, 2023. The search strategies employed are detailed in Supplemental Material 1, http://links.lww.com/AOSO/A366. Two authors (R.K. and A.R.) independently assessed the titles and abstracts following a standardized procedure to determine eligibility for inclusion. Identified studies were categorized as either "retrieve" (eligible, potentially eligible, or unclear) or "do not retrieve." For studies labeled as "retrieve," two reviewers (R.K. and A.R.) independently reviewed the full text and provided recommendations for inclusion or exclusion. Discrepancies between the reviewers were resolved through consensus; in cases of unresolved disagreements, a third reviewer (J.Klo.) made the decision on whether to include the respective study. Additionally, the reference lists of the included studies were manually scrutinized to identify any additional relevant articles.

INCLUSION AND EXCLUSION CRITERIA

We only considered articles in English for inclusion. Studies that compared patients undergoing pancreatoduodenectomy regarding one of the following interventions and provided information on DGE were included: pylorus-preserving pancreaticoduodenectomy (ppPD) *versus* pylorus-resecting pancreaticoduodenectomy (prPD), ERAS no ERAS, *versus* epidural anesthesia (EA) *versus* no EA, nasogastric decompression (NGD) *versus* no nasogastric decompression and jejunostomy/nasojejunal feeding tube placement (J/NJF) *versus* no J/NJF. Excluded from consideration were review articles, case reports, case series with fewer than 5 patients, commentaries, and letters. A flowchart summarizing the study selection process was created following the guidelines outlined in the PRISMA 2020 statement (Fig. 1).

DATA COLLECTION

Data from the included studies were extracted separately by two authors (R.K. and A.R.) and stored in a dedicated database. The following descriptive data were documented for each selected

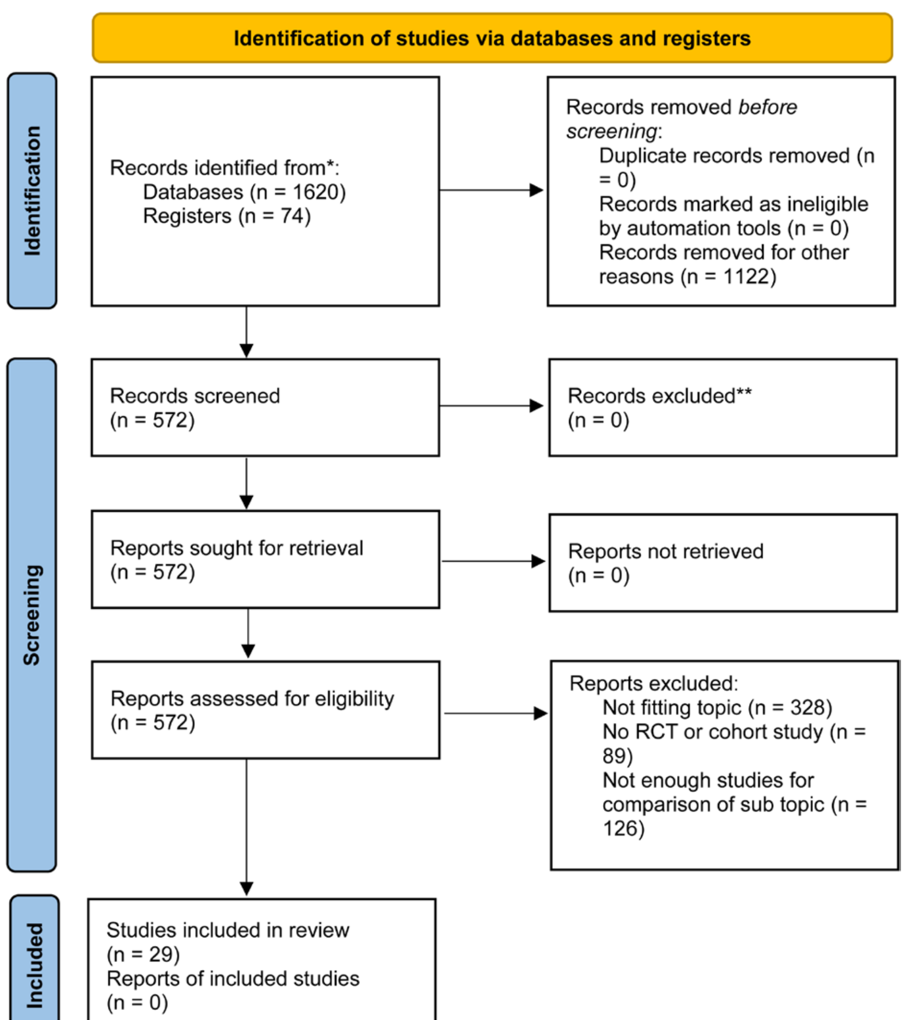

FIGURE 1. PRISMA 2020 flow chart.

study: first author, year of publication, sample size, group, study type, inclusion period, country where the study was conducted, score used, and mean or median follow-up time. The distribution of the following patient characteristics was documented: type of surgery, type of reconstruction, duration of surgery (minutes), blood loss (ml), patients age (mean), patients' gender (masculine and feminine), American Society of Anesthesiologists classification,[13] body mass index, and diabetes (Yes/No). The following predefined outcomes were extracted: DGE (ISGPS definition, ≥2),[2] postoperative pancreatic fistula (ISGPS definition, ≥2),[14] postpancreatectomy hemorrhage (ISGPS definition, any degree),[14] intraabdominal fluid or abscess, chyle leak, bile leak, wound infection, pulmonary complications and mortality. Meta-analysis was performed for the type of intervention: ppPD and prPD, ERAS, EA, NGD and J/NFJ.

In every observational study, the evaluation of risk of bias employed the ROBINS-I tool, while for randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 (RoB 2) tool was utilized for assessment.[15,16]

STATISTICAL ANALYSIS

The study employed SPSS software[17] for analysis. Forest plots were utilized to visually represent the effect estimate's magnitude. Log odds ratios (logORs) were computed for binary data, while weighted mean differences and relative standard deviation (SD) differences were determined for continuous data. Random-effect models were employed in the calculation of ORs. Each outcome was accompanied by reporting 95% confidence intervals (CI) and statistical significance. A P value of less than 0.05 was considered statistically significant.

RESULTS

In total 29 studies[18–46] from 10 countries published between 2007 and 2022, were included in the meta-analysis (Fig. 1). The enrolment periods of these studies ranged from 1981 to 2020. In these studies, a total of 5930 patients were included (ppPD: 908, prPD: 1371, ERAS: 346, No ERAS: 207, EA: 364, No EA: 172, NGD: 430, No NGD: 223, J/NFJ: 953, No J/NFJ: 956).

The study features, patient characteristics, and outcomes are presented in Supplemental Material 2, http://links.lww.com/AOSO/A367.

Patients undergoing ppPD experienced more DGE when compared with patients undergoing prPD (logOR, −0.95; 95% CI = −1.57 to −0.34; $P = 0.002$) (Fig. 2). In a separate analysis of the 4 available RCTs comparing the effect of pylorus resection or preservation on DGE, this effect could be observed as well but did not reach statistical significance (logOR, −0.28; 95% CI = −1.05 to 0.48; $P = 0.47$) (Fig. 3).

Concerning the other pancreas- and surgery-specific outcomes, there was no statistically significant difference between the 2 groups (Table 1).

When comparing patients with ERAS and no ERAS, patients in the ERAS group experienced lower rates of DGE (logOR, −0.712; 95% CI = −1.242 to −0.183; $P = 0.008$) (Fig. 4). Concerning the other above-mentioned outcomes, there was no statistically significant difference between the 2 groups (Table 2). A meta-analysis could not be conducted for the remaining above-mentioned outcomes due to a lack of data.

Regarding EA and NGD there was no statistically significant difference between any of the reported outcomes between the 2 groups (Supplemental Material 3, http://links.lww.com/AOSO/A368).

Concerning J/NJF, lower rates of DGE were observed in the no J/NJF group (logOR, −0.618; 95% CI = 0.39–0.84; $P < 0.001$) (Fig. 5). Concerning the other investigated outcomes there was no statistically significant difference between the 2 groups (Table 3). A comprehensive meta-analysis could not be performed for the remaining above-mentioned outcomes due to insufficient data availability.

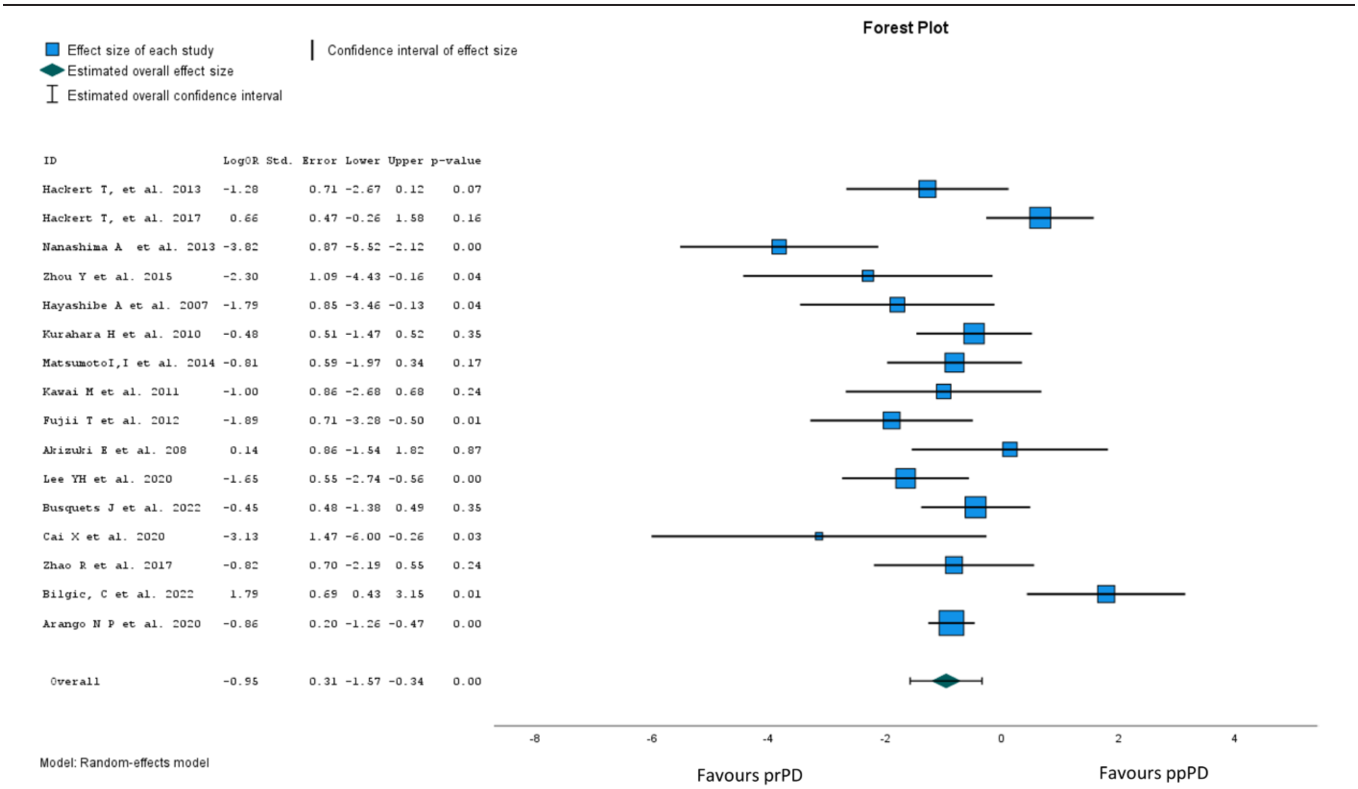

FIGURE 2. Forest plot of odds ratio (logOR) with 95% CI for DGE. The logORs presented are pylorus-preserving pancreaticoduodenectomy (ppPD) *vs.* pylorus-resecting pancreaticoduodenectomy (prPD).

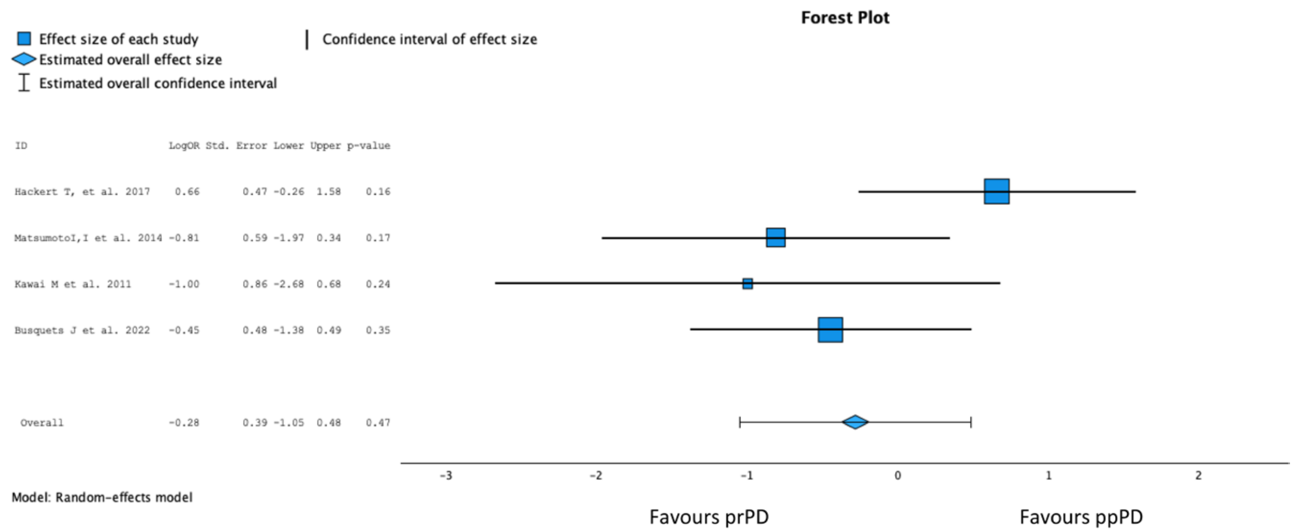

FIGURE 3. Forest plot of odds ratio (logOR) with 95% CI for DGE (only RCTs). The logORs presented are pylorus-preserving pancreaticoduodenectomy (ppPD) *vs*. pylorus-resecting pancreaticoduodenectomy (prPD).

TABLE 1.

Meta-analysis Including (logOR) With 95% CI for All Investigated Outcomes

Outcome	Effect Size (logOR)	95% CI	*P* value
POPF	−0.26	−0.58 to 0.09	0.14
PPHR	0.11	−0.47 to 0.70	0.7
IAF	−0.238	−0.600 to 0.124	0.197
CL	0.184	−0.545 to 0.913	0.621
BL	1.005	−0.272 to 2.282	0.123
WI	0.043	−0.633 to 0.719	0.902
PC	0.478	−0.335 to 1.292	0.249
Mortality	−0.057	−0.956 to 0.843	0.902
Reoperation	0.085	−0.708 to 0.878	0.833
Duration of Surgery	0.040	−0.136 to 0.216	0.654
Blood Loss	0.058	−0.173 to 0.290	0.621
Length of Stay	−0.196	−0.418 to 0.026	0.083

The logORs presented are pylorus-preserving pancreaticoduodenectomy (ppPD) *vs*. pylorus-resecting pancreaticoduodenectomy (prPD).
BL, bile leak; CL, chyle leak; IAF, intraabdominal fluid; PC, pulmonary complications; POPF, postoperative pancreatic fistula; PPHR, postpancreatectomy hemorrhage; WI, wound infection.

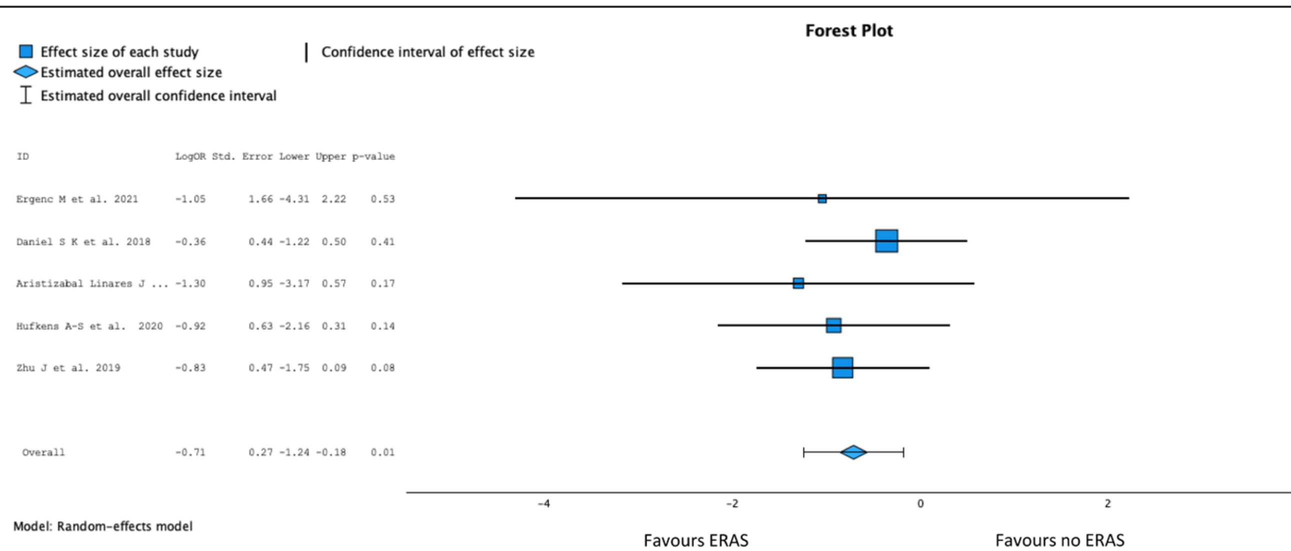

FIGURE 4. Forest plot of odds ratio (logOR) with 95% CI for DGE. The logORs presented are enhanced recovery after surgery protocols (ERAS) *vs.* no ERAS.

TABLE 2.

Meta-analysis Including (logOR) With 95% CI for All Investigated Outcomes

Outcome	Effect Size (logOR)	95% CI	*P* Value
POPF	−0.185	−0.709 to 0.340	0.490
PPHR	−0.504	−1.406 to 0.399	0.274
IAF	−1.345	−3.246 to 0.556	0.166
BL	−1.026	−2.496 to 0.444	0.171
WI	−0.588	−1.305 to 0.129	0.108
Mortality	0.042	−1.352 to 1.436	0.953
Readmission	−0.422	−1.654 to 0.810	0.502
Duration of Surgery	−0.049	−0.309 to 0.210	0.709
Blood Loss	−0.559	−1.730 to 0.612	0.349
Length of Hospital Stay	−0.930	−2.738 to 0.879	0.314

The logORs presented are Enhanced Recovery after Surgery protocols (ERAS) vs no ERAS.

BL, bile leak; IAF, intraabdominal fluid; POPF, postoperative pancreatic fistula; PPHR, postpancreatectomy haemorrhage; WI, wound infection.

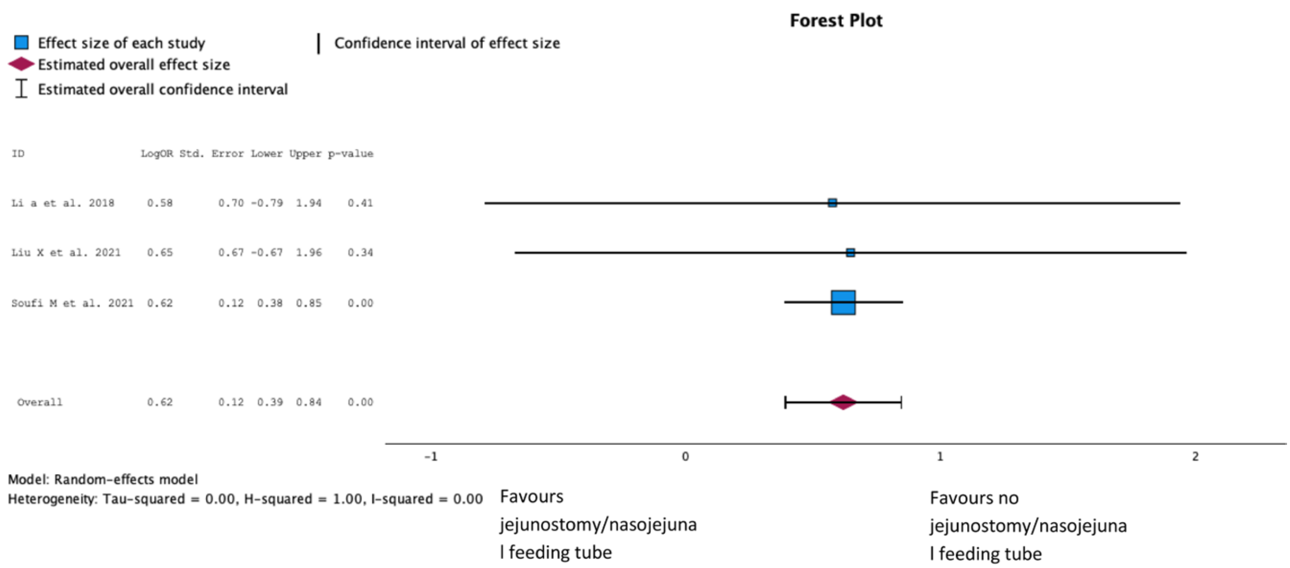

FIGURE 5. Forest plot of odds ratio (logOR) with 95% CI for DGE. The logORs presented are jejunal/nasojejunal feeding tube (J/NJF) *vs*. no J/NJF.

TABLE 3.

Meta-analysis Including (logOR) With 95% CI for All Investigated Outcomes

Outcome	Effect Size (logOR)	95% CI	*P* Value
POPF	0.7	−0.28 to 0.43	0.70
IAF	−0.05	−0.33 to 0.23	0.74
WI	0.033	−0.31 to 0.37	0.85
Mortality	0.17	−1.5 to 1.8	0.83
Readmission	0.19	−0.05 to 0.43	0.12
Length of Hospital Stay	0.32	−0.03 to 0.66	0.07

The logORs presented are jejunal/nasojejunal feeding tube (J/NJF) vs no J/NJF.

IAF, intraabdominal fluid; POPF, postoperative pancreatic fistula; WI, wound infection.

We did not conduct separate analyses for RCTs regarding ERAS, EA, and J/NJF because only 1 RCT was conducted for each intervention. No RCTs were available regarding NGD.

For the non-RCTs, ROBINS-I analysis revealed that the majority of studies (18/22) did not systematically control confounding via a regression analysis or the Cochrane-Mantel-Haenszel method. Four studies[12,19,35,42] analyzed potential confounding factors, but did not systematically adjust data. All studies except Akizuki et al[18] were categorized as "low risk of bias" for domains "bias in classification of interventions" and "bias in selection of participants into the study". For the domains "bias due to deviations from intended interventions", "bias in measurement of the outcome", and "bias in selection of the reported result", all studies were categorized as "low risk of bias". For the RCTs, all studies were categorized as "low risk of bias" for domains "bias due to missing outcome data" and "bias in measurement of the outcome". For "bias arising from the randomization process", 3 studies were categorized as "high risk of bias", because they did not conduct external institutional randomization or they did not use sealed envelopes.[24,29,33] For the domain "bias due to deviations from intended intervention", 2 studies were categorized as "high risk of bias". For the domain "bias in selection of the reported result", all studies were categorized as "low risk of bias" except Ergenc et al[24] ("some concerns"), because there was no prepublished study protocol or preregistered clinical study publicly available. (Supplemental Material 4, http://links.lww.com/AOSO/A369 and 5, http://links.lww.com/AOSO/A370).

DISCUSSION

In this comprehensive systematic review and meta-analysis, we investigated the impact of various surgical and perioperative approaches on DGE after pancreatoduodenectomy. Our meta-analysis yielded 3 primary findings: (1) patients undergoing ppPD had a higher incidence of DGE compared with those undergoing prPD; (2) patients in the enhanced recovery after surgery group exhibited reduced rates of DGE; and (3) patients without placement of a feeding jejunostomy showed lower rates of delayed gastric emptying compared with the group with jejunostomy formation.

The significance of DGE in pancreatoduodenectomy cannot be overstated. Patients afflicted with DGE frequently experience extended hospitalization periods, leading to escalated healthcare expenses and heightened utilization of medical resources. Moreover, patients with DGE often necessitate supplementary medical interventions and nutritional support, thereby prolonging the recovery process and placing additional strain on both patients and healthcare systems. Additionally, DGE can impede the timely initiation of adjuvant therapies leading to impaired long-term outcomes.

The choice of ppPD *versus* prPD is comparable to Goethe's Gretchenfrage among hepatio-pancreato-biliary surgeons: how do you deal with it? Since decades, there has been an ongoing debate about whether preservation or resection of the pylorus is associated with lower rates or even prevention of DGE after pancreatoduodenectomy. Initially described in 2007, the first trial on DGE examined the effects of erythromycin on gastric emptying following pancreatoduodenectomy. This prospective, randomized, placebo-controlled trial demonstrated that erythromycin administration accelerated gastric emptying in patients undergoing pancreatic surgery.[47] Afterwards numerous randomized and non-randomized studies addressed this question and several systematic reviews and meta-analyses summarized their results.

The latest meta-analysis included 3 RCTs and 8 nonrandomized studies, comprising a total of 992 patients. In this study, the superiority of prPD *versus* ppPD concerning DGE (OR, 2.71; 95% CI = 1.48–4.96; P = 0.001) was observed when both RCTs and non-RCTs were included.[8] In contrast, no significant difference was observed in a subgroup analysis only including RCTs (OR, 1.60; 95% CI = 0.57–4.47; P = 0.37).[8] As referred, in our analysis, ppPD was associated with higher rates of DGE. In our subgroup analysis including 4 RCTs, this trend could be observed but did not reach statistical significance.

Of note, compared to the meta-analysis of Klaiber and co-workers, we were able to include one more RCT concerning the comparison between ppPD and prPD. The inclusion of 4 studies underlines the value of the data obtained in our study. Hence, we conclude that pylorus resection should be performed during pancreatoduodenectomy. This is in line with the recent data on minimally invasive pancreatic surgery. De Graaf and co-workers demonstrated in their retrospective cohort study that robotic pancreatoduodenectomy (where pylorus resection is commonly performed) is not associated with an increased rate of DGE compared with open (pylorus-preserving) pancreaticoduodenectomy.[48]

In our study, the ERAS group exhibited reduced rates of DGE. This correlates to the available evidence concerning other surgical specialties. The implementation of ERAS protocols has consistently been associated with reduced rates of DGE in various surgical procedures. Studies in gynecologic and colorectal procedures,[49–53] distal pancreatectomy,[54] and abdominal wall reconstruction[55] have all reported shorter hospital stays, reduced opioid use, and improved patient satisfaction, which are all factors that can contribute to a lower risk of DGE. The specific components of ERAS pathways, such as patient education, multimodal analgesia, and early ambulation, have been shown to facilitate early recovery and discharge, further reducing the risk of DGE.[56,57] Kuemmerli and co-workers demonstrated the favorable effects of ERAS protocols on DGE after pancreatoduodenectomy before. They discovered that ERAS was linked to reduced rates of DGE (risk difference, −0.11; 95% CI = −0.22 to −0.01; P = 0.039) with earlier oral food intake and reduced time to pass first stool.[58] In line with these findings are the data from an early meta-analysis from 2018 regarding the effect of ERAS on DGE. The authors also describe reduced rates of DGE in the ERAS group compared with conventionally treated patients after pancreatoduodenectomy.[59]

Finally, patients without the placement of a feeding jejunostomy showed lower rates of delayed gastric emptying. The use of jejunostomy in pancreatic surgery has been explored in various studies. Jejunostomy can be safely used for enteral nutrition in patients with severe acute pancreatitis and those undergoing pancreatic surgery.[60,61] However, Waliye et al[62] suggested that routine placement of jejunostomy tubes during pancreatoduodenectomy may not be necessary, as it did not significantly decrease morbidity or mortality. In a propensity score case-matched analysis, feeding jejunostomy was associated with increased rates of DGE compared with surgery without feeding tube placement (26.8% *vs*. 16.4%; P < 0.001).[43] These findings corroborate our analysis and collectively suggest that while jejunostomy can be a useful tool in highly selected cases, its routine use may not be necessary during pancreatoduodenectomy.

This meta-analysis has several limitations. Primarily, it relies not only on RCTs but also on observational studies, introducing heterogeneity in outcome definitions and treatments. The retrospective design across multiple studies raises concerns about potential selection bias. The results stem from nonrandomized, uncontrolled comparisons of patients with diverse backgrounds, lacking a clear distinction between groups receiving several therapies across all studies. Despite adhering to PRISMA guidelines (Supplemental Material 6, http://links.lww.com/AOSO/A371) for transparency and standardized reporting, a notable risk of bias persists. Therefore, caution is warranted in the interpretation and application of the data. This study is also subject to confounding variables and bias and is hampered by the quality of the pooled studies underlying the analysis. Regarding ERAS, a protective effect was observed, aligning with contemporary practices aimed at minimizing NGD, promoting early ambulation, and reducing narcotic use—though the exact definition of ERAS was not explicitly stated across the studies. Interestingly, NGD and epidural anesthesia did not impact DGE rates when analyzed independently, suggesting a synergistic effect with bundled ERAS care. It is important to note that insufficient RCTs were available for ERAS, epidural anesthesia, NGD use, or J/NJ tube feeds, highlighting the limitations in interpreting the data and drawing well-supported conclusions. The meta-analysis' strength lies in its inclusion of all available studies providing comparative information on various approaches to reduce DGE in patients undergoing pancreatoduodenectomy, encompassing a large number of patients.

In conclusion, our meta-analysis demonstrates that factors such as pylorus resection, adherence to ERAS protocols, and the absence of jejunostomy are linked to reduced occurrences of delayed gastric emptying in patients undergoing pancreatoduodenectomy. These results provide valuable insights that contribute to the ongoing comprehension of interventions influencing delayed gastric emptying in individuals undergoing pancreatic surgery.

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AUTHOR CONTRIBUTIONS

Conceptualization and design: A.R., J.Kle. J.Klo. initiated the meta-analysis, outlining the research questions, objectives, and methodology, and ensuring the study's design was robust and comprehensive. Literature search and data collection: A.R. and R.K. were responsible for conducting a thorough literature search and identifying relevant studies for inclusion. J.Klo. assisted in screening the studies and extracting critical data, ensuring accuracy and consistency. Data analysis: A.R. took the lead on statistical analysis. Original draft preparation: A.R. and J.Klo. drafted the initial manuscript, focusing on articulating the study's findings and integrating the data analysis into a cohesive narrative. Y.S. contributed to the writing of specific sections, such as bias analysis. All authors participated in reviewing and editing the manuscript.

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