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RECEIVED 23 January 2023

ACCEPTED 25 April 2023

PUBLISHED 09 May 2023

CITATION

Wu Z, Zong K, Zhou B, Yin K, Zhang A and Li M (2023) Incidence and risk factors of postoperative acute pancreatitis after pancreaticoduodenectomy: a systematic review and meta-analysis. *Front. Surg.* 10:1150053. doi: 10.3389/fsurg.2023.1150053

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Incidence and risk factors of postoperative acute pancreatitis after pancreaticoduodenectomy: a systematic review and meta-analysis

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Background: Postoperative acute pancreatitis (POAP) is a specific complication after pancreatectomy. The acute inflammatory response of the residual pancreas may affect the healing of pancreatoenteric anastomoses, leading to postoperative pancreatic fistulas (POPFs), abdominal infections, and even progressive systemic reactions, conditions that negatively affect patients' prognoses and can cause death. However, to the best of our knowledge, no systematic reviews or meta-analytic studies have assessed the incidence and risk factors of POAP after pancreaticoduodenectomy (PD).

Method: We searched PubMed, Web of Science, Embase, and Cochrane Library databases for relevant literature describing the outcomes of POAP after PD until November 25, 2022, and we used the Newcastle–Ottawa Scale to assess the quality of the studies. Next, we pooled the incidence of POAP and the odds ratios (ORs) and 95% confidence intervals (CIs) of the risk factors using a random-effect meta-analysis. I^2 tests were used to assess heterogeneity between the studies.

Results: We analyzed data from 7,164 patients after PD from 23 articles that met the inclusion criteria for this study. The subgroup results of the meta-analysis by different POAP diagnostic criteria showed that the incidences of POAP were 15% (95% CI, 5–38) in the International Study Group for Pancreatic Surgery group, 51% (95% CI, 42–60) in the Connor group, 7% (95% CI, 2–24) in the Atlanta group, and 5% (95% CI, 2–14) in the unclear group. Being a woman [OR (1.37, 95% CI, 1.06–1.77)] or having a soft pancreatic texture [OR (2.56, 95% CI, 1.70–3.86)] were risk factors of POAP after PD.

Conclusion: The results showed that POAP was common after PD, and its incidence varied widely according to different definitions. Large-scale reports are still needed, and surgeons should remain aware of this complication.

Systematic Review Registration: identifier: CRD42022375124.

KEYWORDS

postoperative acute pancreatitis, pancreaticoduodenectomy, risk factors, systematic review, meta-analysis

Introduction

Pancreaticoduodenectomy (PD) is a common surgical procedure for treating pancreatic head cancers and periampullary tumors (1). The procedure is one of the most complicated operations in hepatobiliary and pancreatic surgery, involving the removal of the pancreas,

duodenum, and biliary tract and the reconstruction of the digestive tract (2). Improvements in surgical technique, equipment progress, and perioperative management have greatly reduced the mortality rate of PD to less than 3%, but its complication rate remains high at 30%. Complications increase treatment costs, prolong the length of hospital stay, and the risk of death (3). Delayed gastric emptying (DGE), pancreatic fistulas, hemorrhage and others are common postoperative complications of PD.

Postoperative acute pancreatitis (POAP) is commonly seen after operations involving the pancreas and its surrounding tissues and organs, such as PD, central pancreatectomy, and distal pancreatectomy (4, 5). However, POAP can also occur after heart or spinal surgical procedures (6, 7). The equally severe post-ERCP pancreatitis can also lead to local or systemic complications and even organ failure. The local acute inflammation of the pancreas may slow down the healing of pancreato-enteric anastomoses and residual pancreatic necroses, resulting in pancreatic fistulas, infections, and the need for secondary interventions (8–10).

This systematic review and meta-analysis aimed to provide an understanding of the frequency of POAP after PD and to explore the odds ratio and risk factors of POAP.

Methods

We followed the PRISMA guidelines to design and implement this systematic review and meta-analysis (11, 12). We registered the study protocol in the PROSPERO database (CRD42022375124).

Eligibility criteria

Considered for inclusion were observational studies of adults who underwent open or laparoscopic pancreaticoduodenectomy, including Whipple procedure, subtotal gastric preserved pancreaticoduodenectomy (SSPPD), and PD with pylorus preservation (PPPD), and reported the number or prevalence of POAP cases. We excluded case reports, case series, letters, reviews, and conference abstracts from our analysis.

Search strategy

We searched PubMed, Web of Science, Embase, and Cochrane Library databases for relevant literature reporting the outcomes of POAP after PD from inception to November 25, 2022. We used Medical Subject Headings (MeSH) to search PubMed, Cochrane Library, and Web of Science, and Emtree terms were used to search Embase. We also scanned through citations and references to identify additional records. Our search was limited to articles in English and on human subjects.

We used the MeSH terms “Pancreaticoduodenectomy” and “Pancreatitis” for our PubMed search. The full search strategy is presented in the [Supplementary Materials](#).

Study selection

Two authors (ZW and KZ) independently screened the collected references for articles meeting our criteria. They read the headlines and abstracts to initially rule out all non-conforming studies. After the initial screening, the two authors performed full-text analyses. They read the articles and selected those to be included in our meta-analysis. Disagreements on the final inclusion of articles and the exclusion of duplicate studies were resolved through consultation between the two independent authors.

Data extraction

The data extracted for each study included the name of the first author, country, enrollment period, sample size, age, gender, POAP diagnostic criteria applied, and the number of cases of POAP. We also extracted ORs and 95% CIs for the risk factor variables.

Terminology and definitions

The Connor criteria (9), Atlanta definitions (13), and International Study Group for Pancreatic Surgery (ISGPS) definition (8) have been commonly used for diagnosing POAP. The Connor criteria defines POAP as the presence of urinary trypsinogen-2 levels higher than 50 µg/l or serum amylase levels higher than the normal upper limit on postoperative days (PODs) 0 or 1 (9).

The ISGPS defines POAP as an acute inflammatory response in the remnant pancreas early after partial pancreatectomy and serum amylase activity consistently above the normal upper limit for at least 48 h postoperatively, in addition to the presence of radiologic features and disease-related management changes (8). Finally, the Atlanta POAP classification and definition requires the presence of two of the following three features: abdominal pain consistent with acute pancreatitis; serum lipase or amylase activity at least three times higher than the normal upper limit; and radiologic features of acute pancreatitis (13).

Study quality assessment

Two authors (ZW and KZ) independently assessed the quality of the studies included in the final analysis following the Newcastle–Ottawa Scale (NOS) guidelines. A third author was called to decide upon disagreements. The NOS score ranges between 7 and 9 for good quality studies, between 4 and 6 for moderate quality studies, and is lower than 4 for poor quality studies.

Statistical analysis

We handled and analyzed all data using the R 4.1.1 software. Before using the “metaprop” function to combine incidence rates, we tested the original rate and the transformed rates for normality (sample rate estimation methods are as follows: “PRAW”, “PLN”, “ PLOGIT”, “PAS”, and “PFT”), and selected the transformation with the largest *p*-value of the test result to estimate rate. Odds ratios (ORs) and 95% confidence intervals (CIs) of risk factors were combined using the “metagen” function. We included studies with only crude ORs after calculating the adjusted ORs using the “calcOddsRatio” function. We assessed heterogeneity between studies using *I*² tests. An *I*² value higher than 50% indicated significant heterogeneity among studies and the need to pool the data using a random-effects model. We performed subgroup analyses by POAP diagnostic criteria. Sensitivity analyses were conducted using the “metainf” function. Finally, we used funnel plots and conducted an Egger’s test to measure the risk of publication bias. We considered *p*-values < 0.05 as statistically significant.

Results

Study selection

Our search of PubMed, Cochrane Library, Web of Science, and Embase yielded 5,236 articles, and we manually retrieved an additional 12 articles for a total of 5,248 articles. We removed 1,344 duplicate articles and 3,785 nonconforming articles (case reports, case series, letters, reviews, and conference abstracts). Of the remaining 119 full-text articles, we excluded 96 because they were duplicated trials, failed to separately describe PD complications, or failed to describe POAP cases. Finally, we included data from 23 articles in this systematic review (Figure 1).

Characteristics of included studies

Table 1 shows the main characteristics of the patients whose data were included in this study. We analyzed data from 7,164 pancreaticoduodenectomies, including 2,344 patients with POAP.

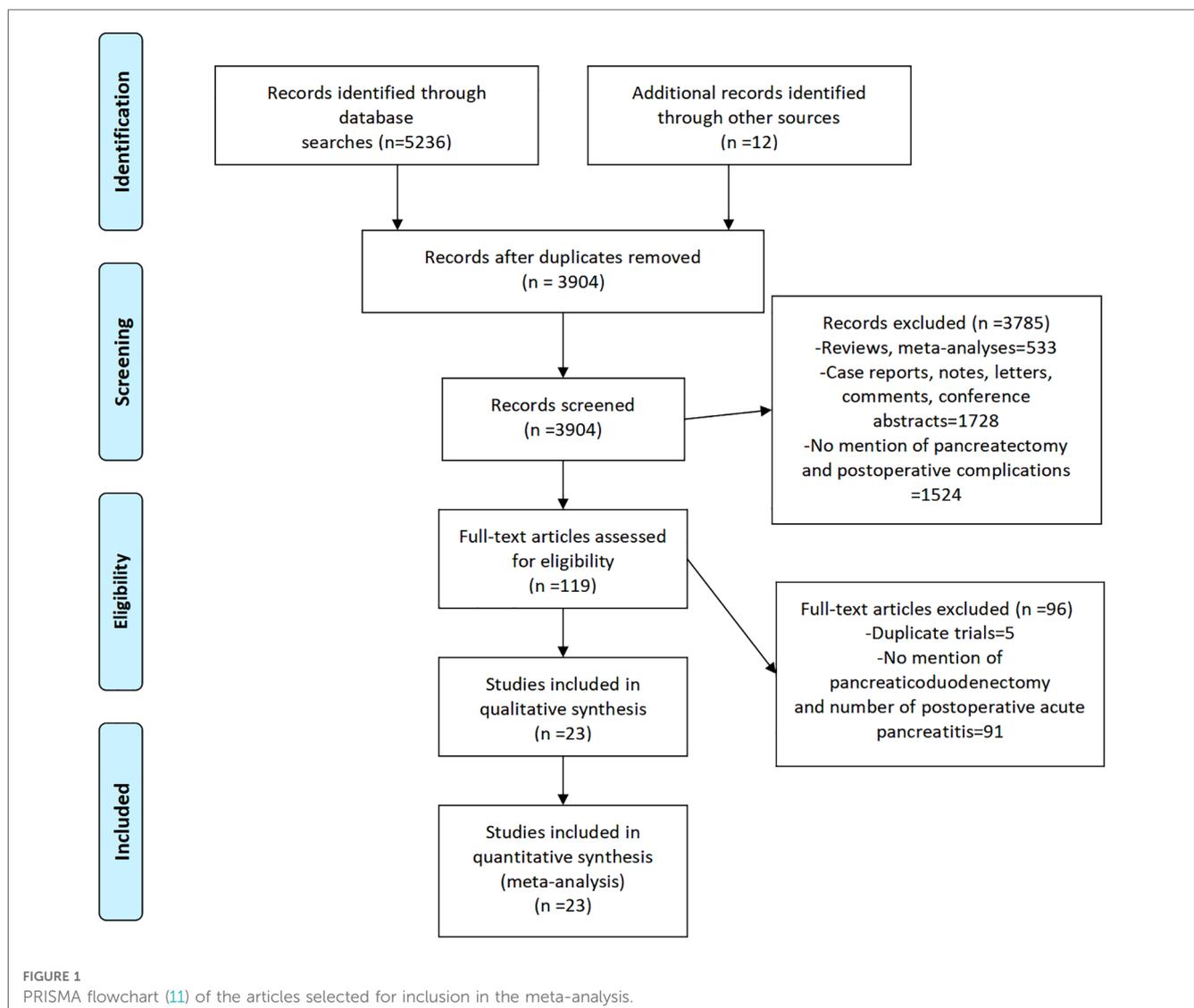


TABLE 1 Characteristics of the studies included in the systematic review and meta-analysis.

Reference	Country	Enrollment period	All patients, <i>n</i>	Age, mean (SD)/median (range), years	Gender, M/F	BMI, mean (SD)/median (range), kg/m ²	Diagnostic criteria of POAP	POAP, <i>n</i>	NOS score
Wu et al. (14)	China	2019–2021	286	62 (55–69)	176/110	NA	ISGPS	150	7
Murakawa et al. (15)	Japan	2013–2019	207	NA	NA	NA	Connor	121	8
Ikenaga et al. (42)	Japan	2015–2019	247	67 (59–73)	151/96	NA	ISGPS	9	8
Chen et al. (16)	China	2020–2021	716	63 (55–69)	423/293	22.8 (20.8–24.8)	ISGPS	152	7
Bonsdorff et al. (17)	Finland	2013–2020	508	68 (61–73)	277/231	25.5 (23.0–28.1)	Connor	202	7
Bannone et al. (18)	Italy	2016–2020	852	65 (56–72)	463/389	24 (22–26)	ISGPS	64	7
Yoo et al. (19)	South Korea	2015–2017	246	63.0 ± 9.2	152/94	24.3 ± 3.1	Connor	191	8
Paik et al. (20)	South Korea	2009–2019	163	63.4 ± 11.1	96/67	23.5 ± 3.7	Atlanta	41	6
Doussot et al. (21)	France	2020–2020	30	NA	23/7	NA	Connor	9	7
Ausania et al. (22)	Spain	2012–2018	62	NA	37/25	NA	Connor	27	6
Partelli et al. (23)	Italy	2015–2018	610	NA	308/302	NA	Connor	250	7
Chen et al. (24)	China	2010–2018	1,465	62 (54–68)	583/883	NA	Connor	770	8
Walsh et al. (25)	America	2001–2016	44	64.3 ± 14	14/30	NA	Unclear	1	7
Birgin et al. (26)	Germany	2009–2015	190	68 (59–74)	108/82	25 (23–28)	Connor	100	8
Nahm et al. (27)	Australia	2016–2017	35	67 (32–85)	18/17	NA	Connor	20	7
Kühlbrey et al. (28)	Germany	2001–2014	561	NA	NA	NA	Atlanta	200	7
Shuo et al. (29)	China	2011–2015	30	54.09 ± 9.3	52/31	NA	Unclear	1	8
Renz et al. (30)	Germany	2002–2012	300	NA	156/144	NA	Atlanta	9	7
Joliat et al. (45)	Switzerland	2002–2012	245	65 (54–75)	147/98	24.1 (21.6–26.5)	Atlanta	2	7
Dalla Valle et al. (31)	Italy	2009–2014	98	67.12 ± 10.44	55/43	24.48 ± 3.86	Unclear	3	7
Weinberg et al. (32)	Australia	2006–2012	150	67 (15–84)	89/61	26 (18–42)	Atlanta	8	6
Makni et al. (33)	Tunisia	1998–2009	80	56 ± 12.0	46/34	NA	Unclear	4	6
Räty et al. (34)	Finland	NA	39	60.2 ± 15.8	25/14	NA	Unclear	10	7

Most of the studies included in this review were conducted in Europe ($n = 11$) and Asia ($n = 8$), with a few studies conducted in the United States ($n = 1$), Oceania ($n = 1$), and Africa ($n = 1$). There were 18 articles with definite POAP diagnostic criteria, while the other five studies did not specify the diagnostic criteria (unclear group).

Meta-Analyses

POAP incidence

The final results of the meta-analysis showed a 33% (95% CI, 32–34) incidence of POAP after PD, with significant heterogeneity among studies ($I^2 = 98\%$; $P < 0.01$). Subgroup analyses by POAP diagnostic criteria showed that the POAP incidences were 15% (95% CI, 5–38) in the ISGPS group, 51% (95% CI, 42–60) in the Connor group, 7% (95% CI, 2–24) in the

Atlanta group, and 5% (95% CI, 2–14) in the unclear group (Figure 2).

Risk factor analysis for POAP

Results of our multifactorial analysis in some of the included studies showed that being a woman as well as having a small pancreatic duct diameter, soft pancreatic texture, and high body mass index (BMI) were all risk factors of POAP after PD (14, 16, 17, 26).

Sex

We included six studies with 3,474 patients in the analysis of sex (female vs. male) as a risk factor. Our results showed significant study heterogeneity ($I^2 = 53\%$). We pooled the data using a random effects model, and the results suggest that the risk of POAP after PD is approximately 1–2 times higher in women than in men (OR, 1.37; 95% CI, 1.06–1.77). Subgroup analyses

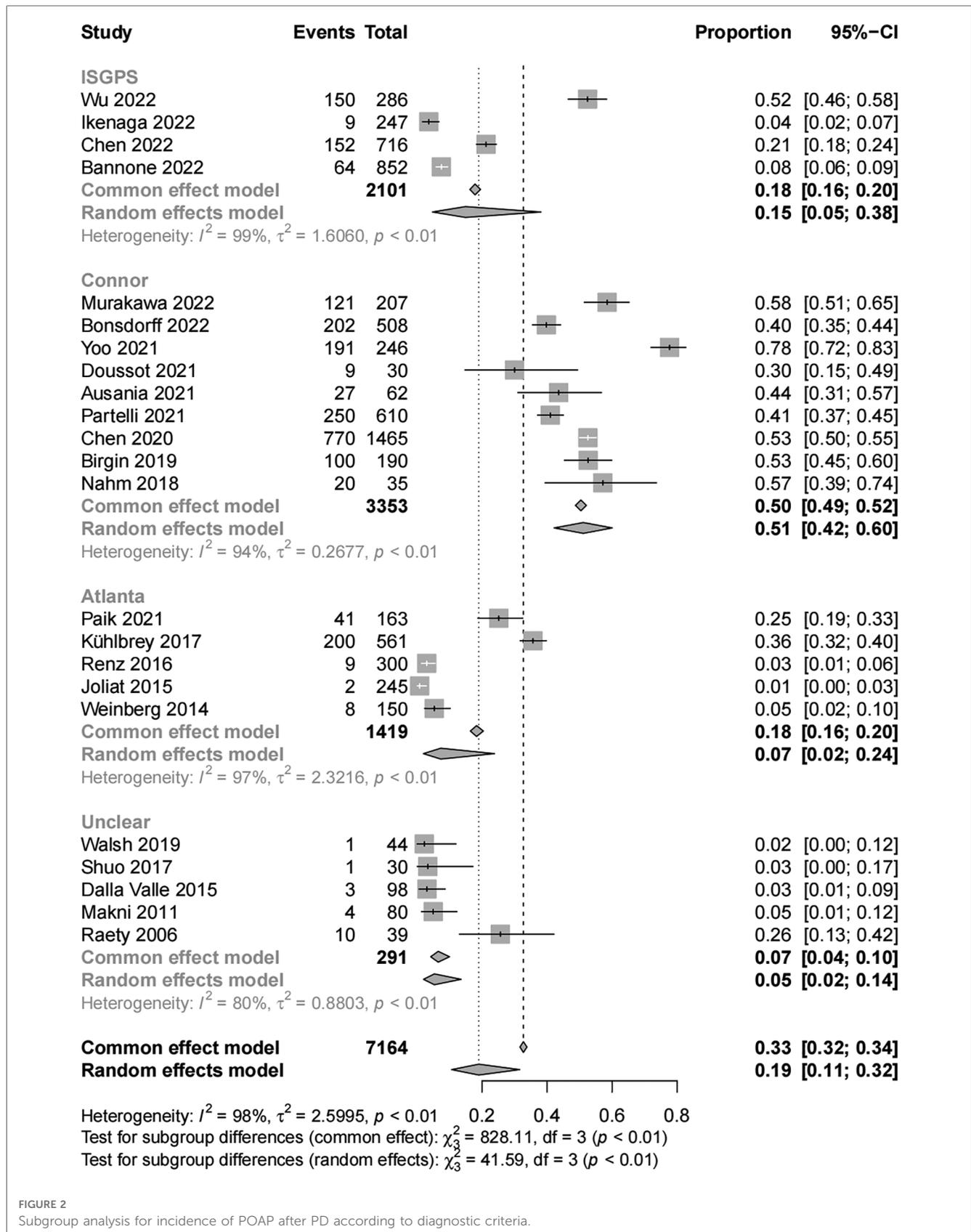


FIGURE 2 Subgroup analysis for incidence of POAP after PD according to diagnostic criteria.

were performed separately by POAP diagnostic criteria and adjusted/crude ORs. The results of the subgroup analyses by diagnostic criteria showed that the ORs were 1.64 (95% CI,

1.19–2.26) in the IGSPS group, 1.56 (95% CI, 1.24–1.96) in the Connor group, and 0.94 in the unclear group (95% CI, 0.66–1.33) (Figure 3). In addition, the results of subgroup

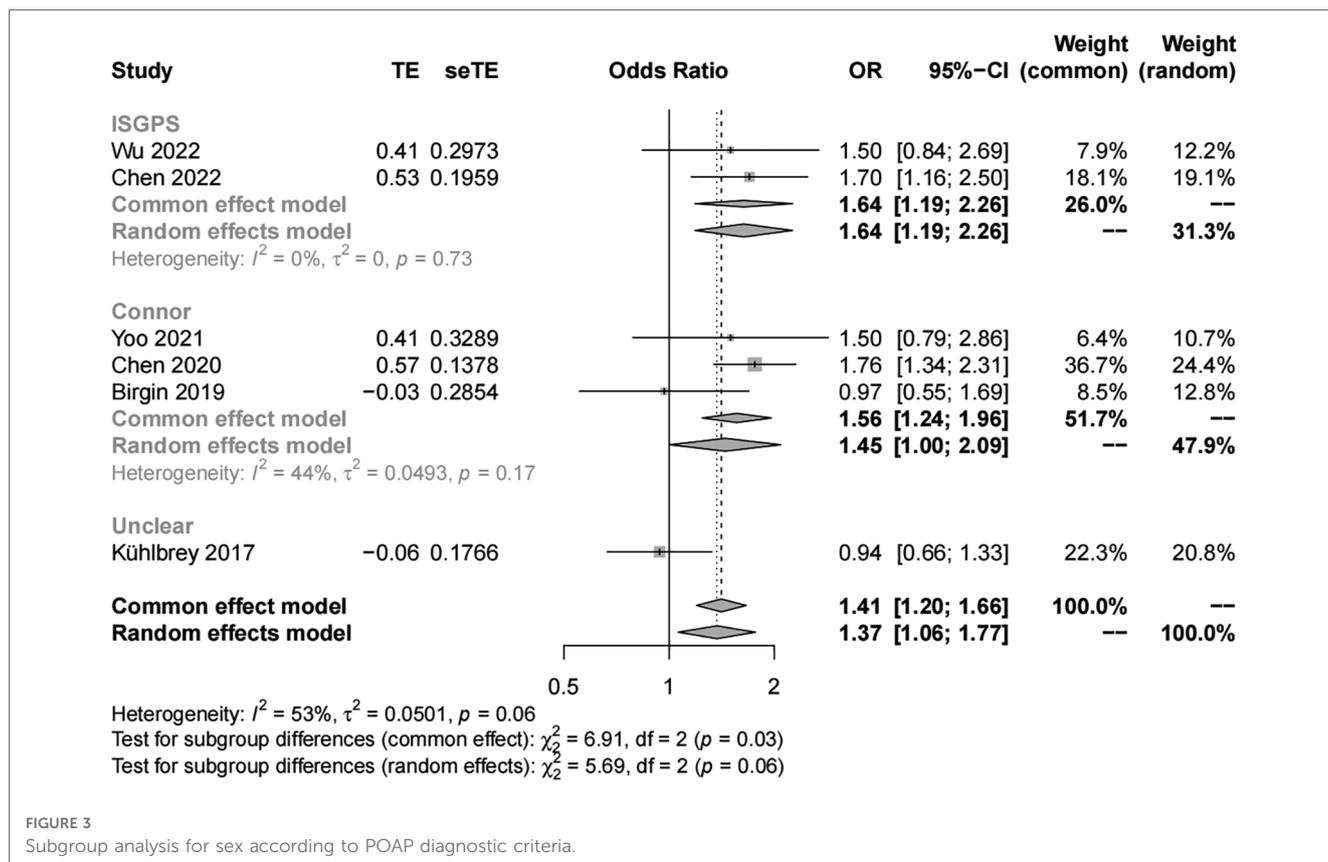


FIGURE 3 Subgroup analysis for sex according to POAP diagnostic criteria.

analyses by adjusted/crude ORs showed that the ORs were 1.71 in the adjusted group (95% CI, 1.39–2.10) and 1.03 in the crude group (95% CI, 0.78–1.34) (Figure 4).

Pancreatic texture

We included four studies with 1,419 patients in the analysis of pancreatic texture. Our results showed significant heterogeneity ($I^2 = 51\%$) and suggested that patients with a soft pancreatic texture had a higher risk (OR, 2.56; 95% CI, 1.70–3.86) of POAP after PD than those with a hard pancreatic texture (Figures 5, 6). The results of subgroup analyses according to the diagnostic criteria revealed the following ORs: 2.17 for the IGSPS group (95% CI, 1.25–3.78) and 3.38 for the Connor group (95% CI, 2.05–5.57) (Figure 5). The results of subgroup analyses according to adjusted/crude ORs showed that the ORs were 2.13 for the adjusted group (95% CI, 1.57–2.89) and 3.38 for the crude group (95% CI, 2.05–5.57) (Figure 6).

Sensitivity analysis

The results of our meta-analysis of pancreatic texture and total POAP incidence were not skewed by data from any individual study. However, in the meta-analysis of sex, the combined OR values changed after excluding individual studies (16, 24). See the Supplementary Material for details.

Publication bias

We found potential publication biases on the calculated incidence of POAP after PD. Figures 7, 8 show the funnel plots and Egger’s test results ($P = 0.024$).

Discussion

The main objective of this systematic review was to analyze the incidence of POAP after PD. This study included data from 23 studies, including 12 countries and 7,164 patients. The diagnostic criteria for POAP varied among the studies included, and the main diagnostic criteria were those from the ISGPS, the Connor criteria, and the Atlanta definition. According to the results of our meta-analysis, the overall incidence of POAP after PD was high (33%). The lack of standard POAP diagnostic criteria may have led to differences and errors in the POAP incidence calculated in the individual studies. In studies with clear diagnostic criteria, the POAP incidences were 15%, 51%, and 7% in those using the ISGPS definition, Connor criteria, and Atlanta definition, respectively. The lack of need for radiologic features of acute pancreatitis to diagnose POAP in the Connor criteria group may have caused the incidence of POAP to be significantly higher in this group compared to the other groups (9).

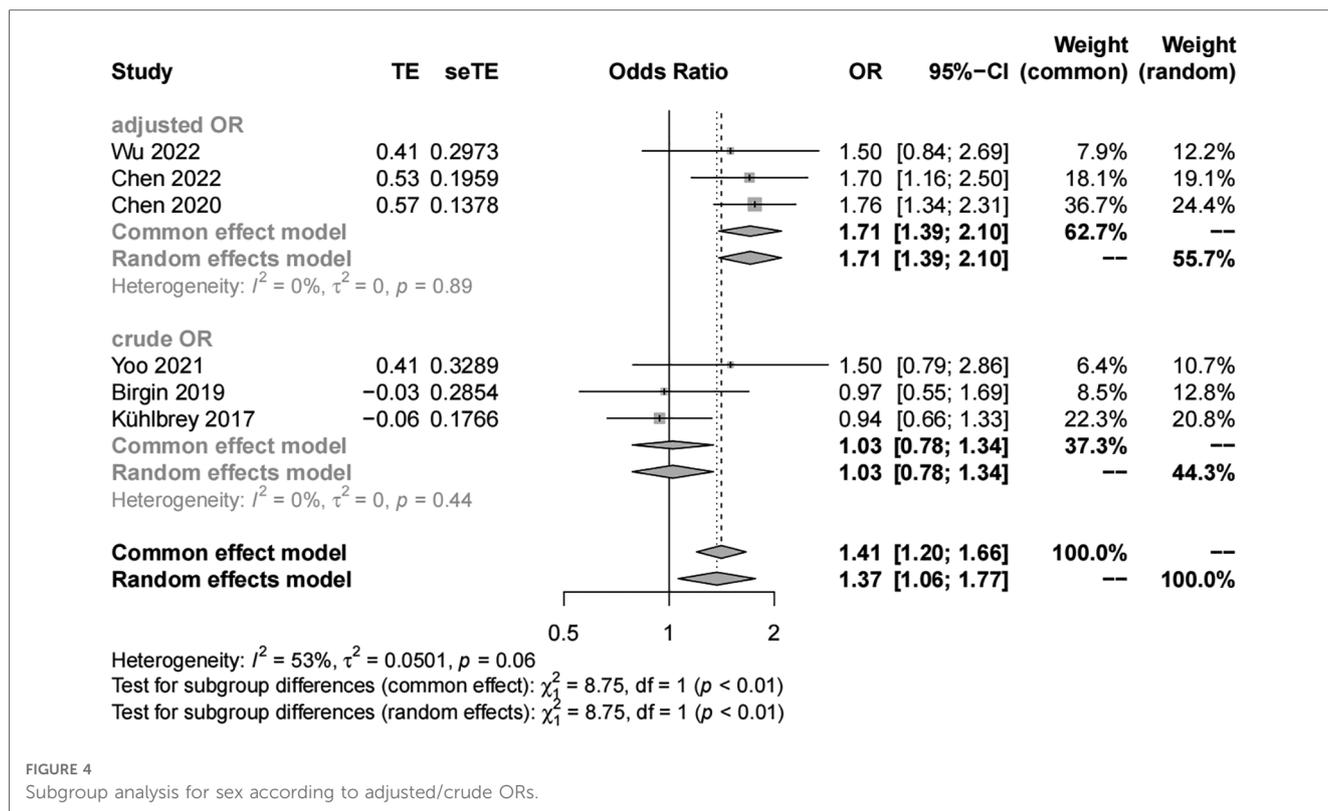


FIGURE 4 Subgroup analysis for sex according to adjusted/crude ORs.

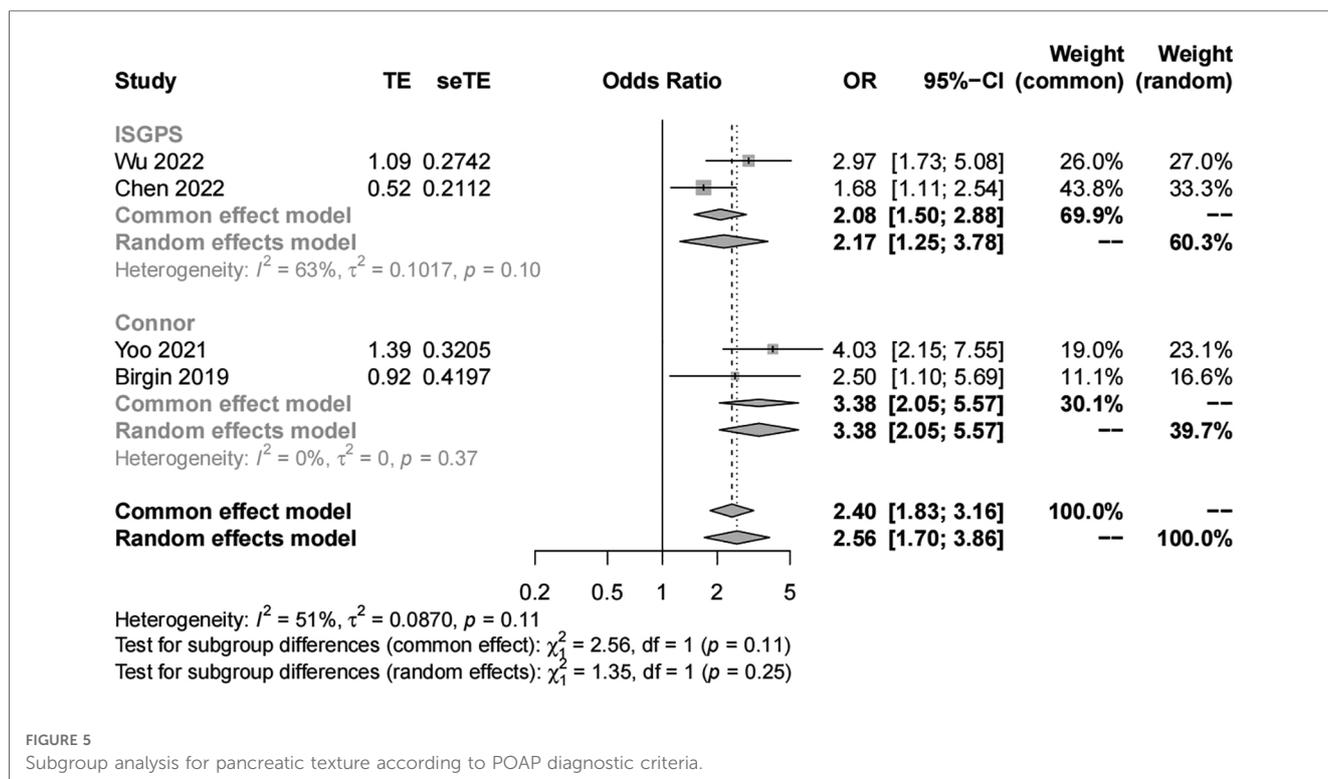


FIGURE 5 Subgroup analysis for pancreatic texture according to POAP diagnostic criteria.

In 2021, Martin et al. (9) added radiologic features of acute pancreatitis to the Connor criteria and found that 58% of patients with hyperamylasemia did not develop acute pancreatitis

based on postoperative radiologic features. The researchers concluded that postoperative hyperamylasemia (POH) cannot be equated with POAP (35). The lack of analysis of the degree of

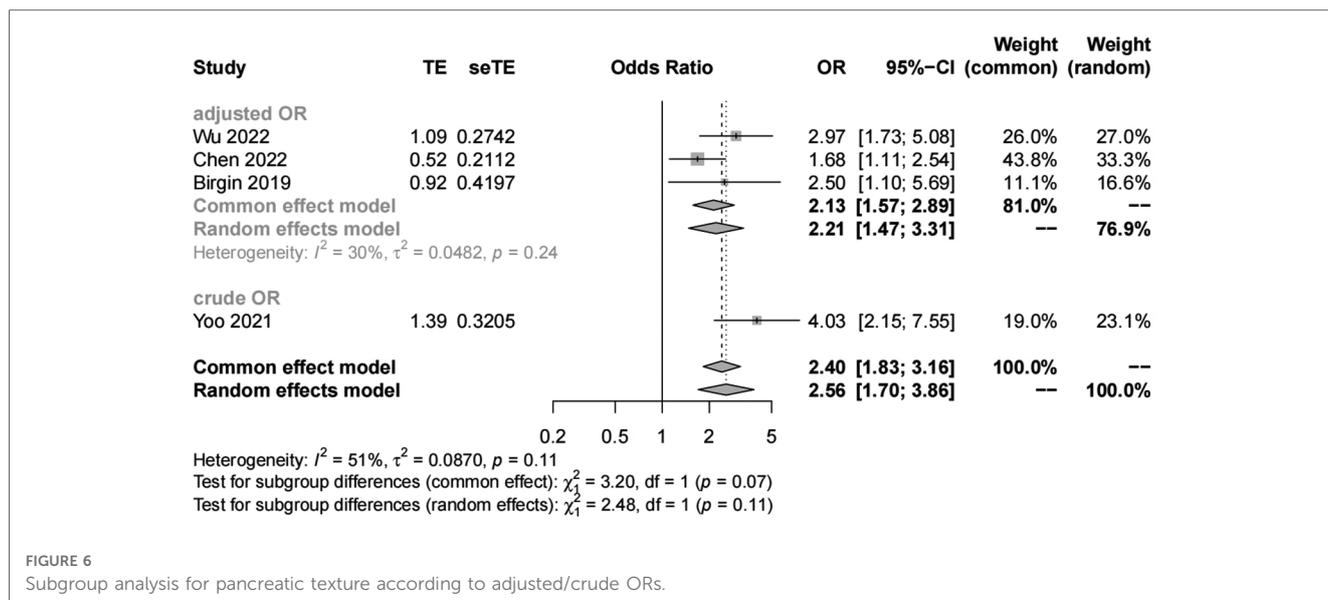


FIGURE 6 Subgroup analysis for pancreatic texture according to adjusted/crude ORs.

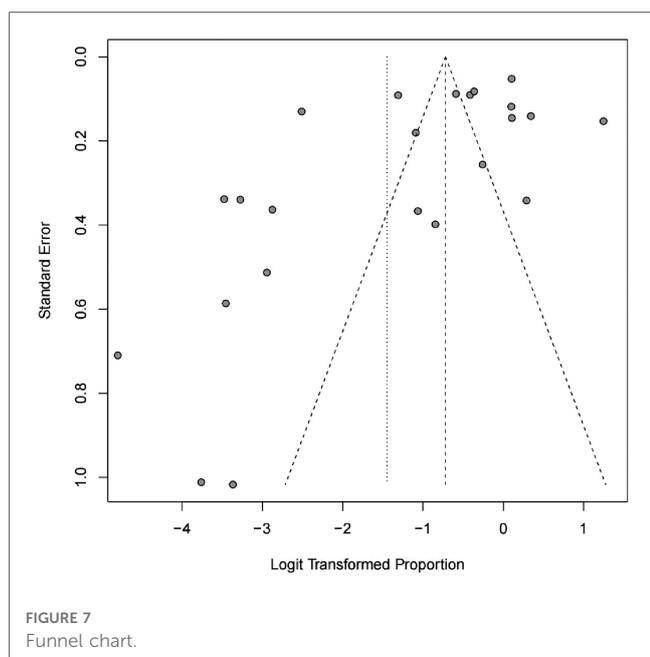


FIGURE 7 Funnel chart.

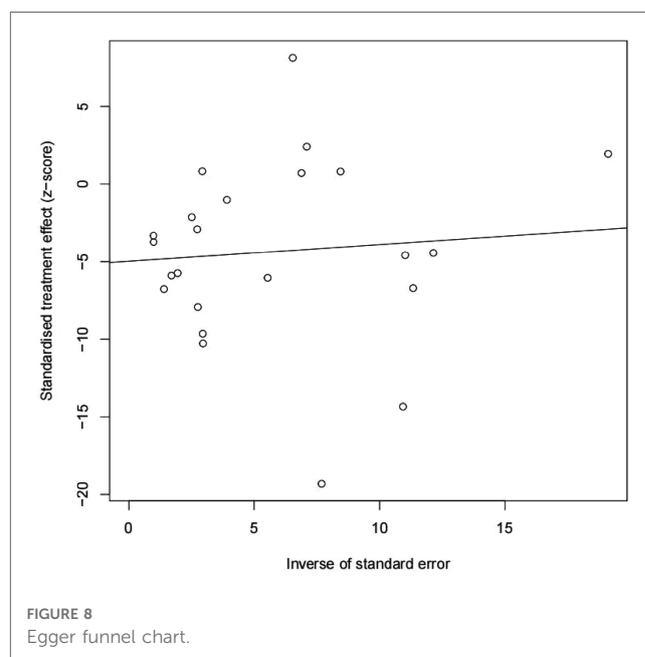


FIGURE 8 Egger funnel chart.

residual pancreatic necrosis, a limitation of the Connor criteria, makes studies using this definition also lack a relevant clinical imaging diagnostic basis. The POAP cases in the Connor criteria group included many patients without radiologic features and clinical symptoms of pancreatitis.

Regardless of the diagnostic criteria, the high incidence of POAP deserves the attention of surgeons. In particular, the activation of pancreatic enzymes after POAP may lead to prolonged healing time or even non-healing of the pancreatic-intestinal anastomoses, resulting in postoperative pancreatic fistulas (POPFs), localized fluid accumulation in the abdominal cavity, infections, and even serious systemic complications (8, 9, 14, 35, 36). Some POAP may include acute necrotizing pancreatitis, which may pose serious hazards and

even require secondary surgery for total pancreatectomy (10). Moreover, POAP is an independent risk factor of POPFs and DGE and may also increase the incidence of other serious complications and postoperative mortality (9, 27, 32, 34). Thus, prompt POAP diagnoses during the early postoperative period and treatment have the potential to improve patients' postoperative prognoses, reduce the incidence of more serious postoperative complications, and shorten the length of stay after pancreatic resections.

Some studies have suggested that the risk factors for acute pancreatitis after pancreatic resection include being a woman, not having received neoadjuvant therapy, and the presence of a soft pancreatic texture, a small main pancreatic duct diameter, or high C-reactive protein levels (14, 16, 17, 26, 37). We only

included sex and the pancreatic texture as variables for our meta-analysis due to the small number of studies analyzing the other risk factors associated with POAP after PD. Our results showed that women had a higher risk of acute pancreatitis after PD than men, and patients with soft pancreatic textures (as judged intraoperatively by the surgeons) had a higher risk of POAP after surgery than patients with hard pancreatic textures. The heterogeneity in this respect that we observed may be due to differences in study diagnostic criteria and adjusted risk ratios in some of the included studies. A possible reason for woman being a risk factor for POAP is that woman have a higher body fat ratio which makes the pancreas softer. However, gender did not show a statistical difference in the multifactorial analysis in some of the studies reviewed in this systematic review, which were conducted without uniform confounding factors as well as classification methods. BMI, oncology, and neoadjuvant therapy were not included in some studies' multifactorial analysis, which may have led to biased results in some studies. Therefore, the conclusion that woman was a risk factor for POAP needs further validation. Moreover, a soft pancreatic texture has been recognized as an important risk factor for the development of pancreatic fistulas after pancreatic surgery (38, 39). A soft pancreatic texture used to be a sign of a small degree of pancreatic tissue fibrosis, even if the percentage of acinar cells or adipose tissue in the pancreas could not be determined without qualitative and quantitative histological analyses. Several studies have now reported results indicating a correlation between the density of acinar cells at the pancreatic cut edge and the occurrence of pancreatitis and postoperative pancreatic fistula after pancreatectomy (27, 40, 41).

The mechanisms of acute pancreatitis after pancreatic resection surgery are unclear. The possible factors that trigger its appearance or aggravation are direct injury to the pancreatic tissues during surgery (such as clamping of pancreatic tissue, dissection of pancreatic tissues, or reconstruction operation of pancreatic-intestinal anastomosis); pancreatic tissue ischemia caused by pulling, clamping, or dissection of surrounding vessels; use of drugs during anesthesia; and intraoperative/postoperative hypoxia or unstable blood pressure (37, 42–44). Maintaining perioperative vital signs as stable as possible, reducing intraoperative clamping of pancreatic tissues and surrounding vessels, and reducing unnecessary pancreatic tissue suturing operations seem to be important to prevent POAP.

Strengths and limitations

The main strength of this study is that, to the best of our knowledge, it is the first meta-analysis of the incidence and risk factors of POAP after PD. Also, we analyzed the incidence and risk factors in subgroups according to the diagnostic criteria of POAP. Finally, the studies we included were from different countries, and most had adequate sample sizes. However, we are also aware of our study's limitations.

The type of disease requiring PD surgery varied across studies, and we could not analyze those as a subgroup in this meta-analysis. In addition, we were not able to include some risk factors in the analysis because of the different definitions of POAP and the small number of relevant studies we found. Moreover, all the studies included were in English, and the lack of studies published in other languages and local journals may have introduced biases. Finally, we found publication bias in our meta-analysis, possibly because studies with positive results were more likely to be published than others.

In conclusion, we found that POAP is common after PD surgery. Differences in the incidence of POAP are due to the use of different diagnostic criteria, and being a woman and presenting a soft pancreas texture during surgery are risk factors for POAP. However, the current studies are few and limited to retrospective analyses; more prospective multicenter studies with large populations and uniform criteria are still needed to strengthen the analysis of POAP.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#), further inquiries can be directed to the corresponding author.

Author contributions

The ideas were created by ZW and ML. The articles search and data analysis were carried out by KY and AZ. ZW and KZ selected the articles, extracted the data, and wrote the first draft of the article. BZ and ML double-checked the information and revised the article. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to express our heartfelt gratitude to all of the authors whose studies were included in this systematic review.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at <https://www.frontiersin.org/articles/10.3389/fsurg.2023.1150053/full#supplementary-material>.

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