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ORIGINAL ARTICLE

Central pancreatectomy: a comprehensive, up-to-date meta-analysis

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Abstract

Background Central pancreatectomy (CP) is the alternative to distal pancreatectomy (DP) for specific pathologies of the mid-pancreas. However, the benefits of CP over DP remain controversial. This study aims to compare the two procedures by conducting a meta-analysis of all published papers.

Methods A systematic search of original studies comparing CP vs. DP was performed using PubMed, Scopus, and Cochrane Library databases up to June 2018. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist was followed.

Results Twenty-one studies were included (596 patients with CP and 1070 patients with DP). Compared to DP, CP was associated with significantly higher rates of overall and severe morbidity ($p < 0.0001$), overall and clinically relevant pancreatic fistula ($p < 0.0001$), postoperative hemorrhage ($p = 0.02$), but with significantly lower incidences of new-onset ($p < 0.0001$) and worsening diabetes mellitus ($p = 0.004$). Furthermore, significantly longer length of hospital stay ($p < 0.0001$) was observed for CP patients.

Conclusions CP is superior to DP regarding the preservation of pancreatic functions, but at the expense of significantly higher complication rates and longer hospital stay. Proper selection of patients is of utmost importance to maximize the benefits and mitigate the risks of CP.

Keywords Central pancreatectomy · Distal pancreatectomy · Morbidity · Exocrine pancreatic insufficiency · Diabetes mellitus

Introduction

Initially, central pancreatectomy (CP) was proposed as an alternative to standard pancreatic resections such as distal pancreatectomy (DP) or pancreatico-duodenectomy for specific pathologies of the mid-pancreas, when enucleation is not possible [1]. The rationale of CP is to preserve more of the normal pancreatic parenchyma and, thus, to avoid the functional consequences of standard pancreatic resections [1].

Nowadays, CP is widely accepted as a real alternative only to DP, while for pancreatico-duodenectomy, the conservative option is duodenum-preserving pancreatic head resection [2].

Benign and low-grade malignant tumors are the main indications of the necessity of CP [1–5]. The feasibility of CP was demonstrated also for some particular malignancies of the pancreas such as metastases of other neoplasms [6] and recently also for early-stage pancreatic ductal adenocarcinoma of the neck [7]; however, malignant tumors (especially advanced pancreatic ductal carcinoma) mostly remain contraindications for CP [1].

Currently, the benefits of CP over DP remain controversial. The potential long-term functional benefits of CP should be regarded in balance with the widely reported high morbidity rates. Thus, in few series reporting at least 100 patients with CP, the overall morbidity and pancreatic fistula rates were 58–72% and 44–63%, respectively, while the incidences of endocrine and exocrine insufficiencies were 4–7.5% and 0–6%, respectively [8–10].

Two systematic reviews and meta-analyses published in 2013 have shown a significantly higher incidence of

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pancreatic fistula and overall morbidity rates of CP, but significantly lower rates of endocrine insufficiency, compared to DP [3;5]. However, these meta-analyses included studies published before December 2010, with a relatively small number of patients [3;5]. Additionally, new large series of CP were published in the last years [9–11], some of them raising the issue of safety or rationale for CP [9, 11]. Furthermore, several other important comparative studies of CP vs. DP were published after 2010 but have reached conflicting results [11–17]. Nevertheless, minimally invasive approaches (laparoscopic and robotic) have been developed for CP, showing some potential advantages [18–20].

A meta-analysis published in 2018 has shown a significantly higher incidence of pancreatic fistula and overall morbidity rates of CP, but significantly lower rates of endocrine and exocrine insufficiency, compared to DP [4]. Furthermore, CP was associated with significantly increased operative time and length of hospital stay, but with significantly lower intraoperative blood loss [4]. However, the meta-analysis of Xiao et al. [4] overlooked some published studies [11, 21, 22] and did not address some important outcomes of interest after pancreatic resections such as new-onset diabetes mellitus, severe morbidity, delayed gastric emptying, surgical site infection, and systemic complications rates.

Taking into consideration the above-mentioned aspects, a new systematic review and meta-analysis that will include all published papers comparing CP with DP and addressing additional outcomes of interest could help in understanding the value and limitations of CP.

The objective of this study was to compare intra- and postoperative outcomes of CP vs. DP by performing a systematic review and meta-analysis of all published studies.

Methods

Literature search strategy

A systematic literature search of original studies comparing CP vs. DP was performed by four independent authors (MPD, AAS, GEDP, and TD) using PubMed (Medline), Scopus, and the Cochrane Library databases up to June 2018. The following Medical Subject Heading (MESH) keywords were searched for: "median pancreatectomy," "central pancreatectomy," "central pancreatic resection," "middle pancreatectomy," "organ-preserving pancreatectomy," "parenchyma-preserving pancreatectomy," "organ-sparing pancreatectomy," "parenchyma-sparing pancreatectomy," "segmental pancreatic resection," "segmental pancreatectomy," "non-standard pancreatic resection," "nonstandard pancreatic resection," "meso-pancreatectomy," and "mesopancreatectomy." Additionally, a manual search of the reference list of the relevant articles was performed.

Study design and quality assessment

For the design of this meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist was followed [23, 24]. In order to check the overall quality of the included studies, the Newcastle-Ottawa Scale (NOS) was used [25]. Only studies with a score over 6 were considered for the present meta-analysis [25]. Additionally, to check the methodological quality of the included studies, we used the newly developed "Risk Of Bias In Non-randomized Studies of Interventions" (ROBINS-I) tool [26]. We investigated all the seven domains which could introduce bias in non-randomized studies.

Inclusion and exclusion criteria

Two different screenings of the initially retrieved articles were performed. First, two independent authors (AAS and GEDP) screened the title and abstract of obtained articles (after duplicates were removed). Studies were excluded if both authors agreed. Second, the authors checked the eligibility of the studies that passed the initial screening. No limitations were imposed by language. Only original research studies that met the following inclusion criteria were considered: (1) studies comparing the outcomes of CP vs. DP and (2) studies with sufficient available data regarding the outcomes of interest. The exclusion criteria were the following: (1) case reports, (2) studies without a control group, (3) letters to the editor and editorials, and (4) reviews that did not include original data.

Data extraction

Data extraction was performed by four authors (MPD, AAS, GEDP, and TD) and was cross double-checked. For binary data, the numbers were directly extracted from the original manuscripts. For continuous data, the standard deviation (SD) and mean (m) were obtained from the original papers. If the continuous data were reported as range and median, the formulas described by Hozo et al. were used to estimate the SD and m [27]. If continuous data were reported as standard error (SE), the SD was calculated using the following formula: $SD = SE\sqrt{n}$, where n is the sample size.

Outcomes of interest

The primary end-points were postoperative exocrine and endocrine insufficiency (particularly new-onset and worsening diabetes mellitus), overall and severe (i.e., > grade II Dindo-Clavien) morbidity, and pancreatic fistula rates (particularly clinically relevant pancreatic fistula rates), while secondary end-points were operative time, blood loss and need for intraoperative blood transfusions, systemic complications, postoperative hemorrhage, delayed gastric emptying, surgical site infection, re-exploration for surgical complications, mortality rates, and length of hospital stay. The length of resected pancreas was also an outcome of interest.

Statistical analysis

Meta-analysis was conducted using the Cochrane Collaboration Review Manager 5.3 software. Statistical analysis was performed using the Mantel-Haenszel method for dichotomous variables and inverse variance weighting for continuous variables. Summary statistics were described in the form of odds ratio (OR) or mean difference (MD) and 95% confidence intervals (CI). The heterogeneity was assessed using Higgin's I^2. A value of $I^2 > 50\%$ was used as a threshold for heterogeneity, and p values < 0.05 were considered statistically significant. A random-effects model was used when there was heterogeneity between the studies; otherwise, a fixed-effects model was considered. When interpreting the funnel plots for publication bias, the Begg's and Egger's methods were used to test the degree of asymmetry. When a high degree of heterogeneity was observed ($I^2 >$ 50%), we additionally performed sensitivity analysis, by removing one-by-one each of the eligible studies, to evaluate the influence of a single paper on the overall results. Begg's and Egger's test and sensitivity analysis were performed using STATA, version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search, study characteristics, and quality assessment

A total of 20,399 articles were identified (PubMed, $n = 9942$; Scopus, $n = 10{,}136$; The Cochrane Library, $n = 321$). After removing the duplicates, 9479 articles were screened by title and abstract, and 168 articles were considered for full-text assessment. Of these, 21 studies [8, 11–14, 16, 17, 21, 22, 28–39] were included in the meta-analysis according to the inclusion criteria (Fig. 1).

Table 1 summarizes the characteristics of the included studies [8, 11–14, 16, 17, 21, 22, 28–39] that were published between 2000 and 2017. No randomized study was found. There were 11 studies originating from Asia [11, 13, 16, 17, 31–33, 36–39], six from Europe [12, 14, 21, 28, 29, 34], two from the USA [22, 30], and two from Europe-USA [8, 35]. Twenty studies were published in English, [8, 11–14, 16, 17, 22, 28–39], and one study was published in Italian [21]. Overall, the studies included 1666 unique patients: 596 with CP (35.8%) and 1070 patients with DP (64.2%) [8, 11–14, 16, 17, 21, 22, 28–39].

Demographic data and surgical indications for CP and DP of the included studies are summarized in Table 2.

There were considerably more females undergoing CP (65.3%) than DP (57.5%), albeit the statistical significance was not reached ($p = 0.541$). There were no statistically significant differences between CP vs. DP groups with regard to

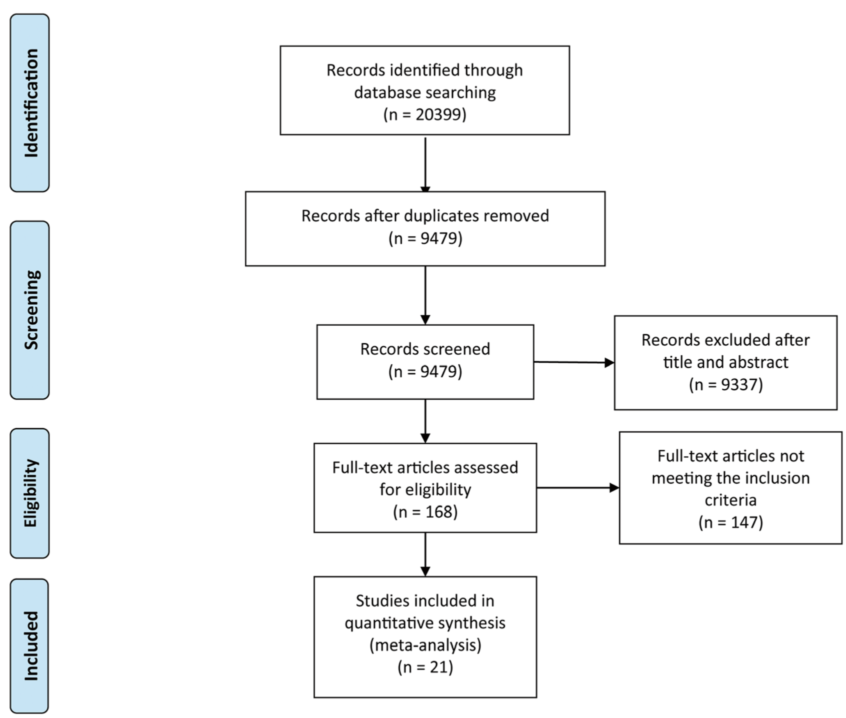

Fig. 1 Flow chart describing the process of scientific paper identification, screening, eligibility testing and inclusion

Table 1 Characteristics and quality assessment of the included studies comparing CP and DP

Author	Country	Year	Number of patients		Technique	Study design	NOS score
			CP	DP			
Yamaguchi et al. [39]	Japan	2000	10	47	NA	Retrospective	7
Falconi et al. [21]	Italy	2001	21	64	NA	Retrospective	7
Balzano et al. [28]	Italy	2003	32	21	NA	Retrospective	8
Su et al. [38]	Taiwan	2004	5	11	NA	Retrospective	7
Shibata et al. [36]	Japan	2004	10	7	NA	Retrospective	7
Muller et al. [34]	Germany	2006	40	40	Open	Prospective	8
Pratt et al. [22]	USA	2006	6	66	Open	Retrospective	7
Crippa et al. [8]	Italy-USA	2007	100	45	Open	Prospective	7
Ocuin et al. [35]	USA-UK	2008	13	18	Open	Retrospective	9
Hirono et al. [31]	Japan	2009	24	28	Open	Prospective	7
Cataldegirmen et al. [29]	Germany	2010	35	35	Open	Retrospective	7
DiNorcia et al. [30]	USA	2010	50	50	NA	Retrospective	7
Shikano et al. [37]	Japan	2010	26	35	Open	Retrospective	7
Lee et al. [33]	Korea	2010	14	188	NA	Retrospective	8
Kang et al. [32]	Korea	2011	17	22	NA	Retrospective	7
Xiang et al. [17]	China	2012	44	55	NA	Retrospective	7
Dumitrascu et al. [14]	Romania	2012	22	25	Open, laparoscopic, and robotic	Retrospective	7
Du et al. [13]	China	2013	36	26	Open	Retrospective	8
Song et al. [16]	Korea	2015	40	96	Open and laparoscopic	Retrospective	8
Dokmak et al. [12]	France	2017	35	165	Laparoscopic	Prospective	7
Lv et al. [11]	China	2017	16	26	Open	Retrospective	7

CP central pancreatectomy, *DP* distal pancreatectomy, *NOS* Newcastle–Ottawa scale, *NA* not available

age ($p = 0.644$), as shown in Table 2. Significantly fewer patients in the CP group have had comorbidities, compared to the DP group of patients (20.7% vs. 36.8%, $p = 0.002$).

The main indications for surgery (72.9% of patients) were benign, borderline, or low-grade malignant pancreatic lesions in both groups of patients: 73.9% in the CP group and 72.5% in the DP group, with no statistically significant differences between the groups ($p = 0.54$), as shown in Table 2. However, significantly more patients with neuroendocrine tumors were included in the CP group, compared to the DP group of patients (20% vs. 15%, $p = 0.01$), as shown in Table 2. Furthermore, significantly more patients with malignancies

Table 2 Demographics and surgical indications of the included studies comparing CP and DP

Parameter	Central pancreatectomy ($n = 596$)	Distal pancreatectomy ($n = 1070$)	*p* value
Gender (M/F)	194:389	330:615	0.541[a]
Age, years (mean (SD))	52.81 (± 7.98)	52.97 (± 5.71)	0.644[b]
Benign lesions (*n*, %))	356 of 482 (73.9%)	679 of 937 (72.5%)	0.54[a]
Neuroendocrine tumors (*n*, (%))	97 of 482 (20%)	141 of 937 (15%)	0.01[a]
Malignant tumors (*n*, (%))	29 of 482 (6%)	117 of 937 (12.5%)	0.001[a]
Laparoscopic procedures (*n*, (%))	61 of 393 (15.5%)	263 of 605 (24.4%)	< 0.001[a]
Robotic procedures (*n*, (%))	0 of 393 (0%)	2 of 605 (0.3%)	0.522[a]
Open procedures (*n*, (%))[c]	332 of 393 (84.5%)	340 of 605 (56.2%)	< 0.001[a]
Comorbidities	40 of 193 (20.7%)	102 of 277 (36.8%)	0.002[a]

M male, *F* female, *SD* standard deviation

[a] Fisher's exact test

[b] Mann-Whitney test

[c] Nine studies did not report the type of surgical technique (203 patients in CP group and 465 in DP group)

were observed in the DP group when compared to the CP group (12.5% vs. 6%, $p = 0.001$), as shown in Table 2.

Not all the included studies reported the operative technique. Out of 21 studies, 12 reported the specific operative technique. Nine of them reported only the open technique used [8, 11, 13, 22, 29, 31, 34, 35, 37], and one of the studies reported using only laparoscopic technique [12]. Two other studies reported using both open and laparoscopic techniques [14, 16]. Only one study reported using robotic technique [14]. There were 672 open interventions (332 in the CP group and 340 in the DP group), 324 laparoscopic procedures (61 in the CP group and 263 in the DP group), and 2 robotic interventions (in the DP group). The number of laparoscopic procedures was significantly higher in the DP group of patients, compared to the CP group (24.4% vs. 15.5%, $p < 0.001$), as shown in Table 2.

All 21 articles included in the meta-analysis [8, 11–14, 16, 17, 21, 22, 28–39] were considered to be of good quality by having a score higher than six on the NOS, as shown in Table 1. It is worth mentioning that only four studies [8, 12, 31, 34] have had a prospective design, as shown in Table 1. We performed qualitative assessment also using the ROBINS-I tool. All the authors discussed and agreed on the confounding factors. Confounding domains were related to comorbidities (cardiac, renal, hepatic, diabetes, obesity), gender, age, smoking status, type, and size of tumor. Throughout the studies, data regarding these factors were several times inconsistently reported. MPD and AAS separately analyzed each of the included studies. Together with TD and GEDP, we agreed on the definitive qualitative assessment. As expected, because all studies were not randomized and the most were retrospective, the overall risk was moderate in 16 studies, and low and serious in only 3, respectively 2 studies (Supplementary Table 1).

Outcomes of meta-analysis comparing CP with DP

The meta-analysis assessed three categories of data: intraoperative, early postoperative, and long-term outcomes.

Intraoperative outcomes

The operative time was reported in 19 out of the 21 studies. The I^2 value was 93%. The operative time was significantly shorter in the DP group when compared to the CP group (mean (± SD)) 206.48 (± 74.19) vs. 251.22 (± 60.34) min (MD 53.09; 95% CI 29.76, 76.42; $p < 0.0001$) (Fig. 2a). The funnel plot (Supplementary Fig. 1A) suggested data heterogeneity, also confirmed by the Egger's publication bias plot (Supplementary Fig. 1B). The Egger's and Begg's tests revealed p values of 0.007 and 0.008, respectively, altogether suggesting the presence of publication bias. By performing sensitivity analysis (sequential removal of each eligible study), we observed that our results are robust and stable. The omission of the study of Yamaguchi et al. [39] would have influenced the most the pooled estimate, but also this study was inside the lower and upper limits of the 95% CI (Supplementary Fig. 1C).

Only 12 studies reported data regarding the necessity of intraoperative blood transfusions. The I^2 value was 0%. No statistically significant differences were observed between the groups (in CP group 34 patients—9.4% vs. DP group 66 patients—9.9% needed blood transfusion) (OR 0.65; 95% CI 0.40, 1.05; $p = 0.08$) (Fig. 2b). The funnel plot (Supplementary Fig. 2A) suggested no publication bias, also confirmed by the Egger's plot (Supplementary Fig. 2B). The Egger's and Begg's tests revealed p values of 0.776 and 0.533, respectively.

Seventeen studies reported data regarding intraoperative blood loss. The I^2 value was 69%. The mean (± SD) blood loss in the CP group was 401.92 (± 326.06) ml, while in the DP group, it was 533.43 (± 431.70) ml. No statistically significant differences were observed between the groups (MD − 58.97; 95% CI − 122.27, 4.33; $p = 0.07$) (Fig. 2c). The funnel plot (Supplementary Fig. 3A) was symmetrical; also, the Egger's publication bias plot suggested no bias (Supplementary Fig. 3B). The absence of publication bias was confirmed by Egger's and Begg's tests, with p values of 0.622 and 0.174, respectively. By performing sensitivity analysis (sequential removal of each eligible study), we observed that our results are robust and stable. All studies were between the lower and upper limit of the 95% CI (Supplementary Fig. 3C).

The length of resected pancreas was reported only by five studies. The I^2 value was 96%. As expected, the length of resected pancreas was significantly larger in the DP group of patients with a mean (± SD) of 10.70 cm (± 1.92) compared to the CP group 4.77 cm (± 0.99) (MD − 5.50; 95% CI − 7.24, − 3.75; $p < 0.0001$) (Supplementary Fig. 4A). The funnel plot (Supplementary Fig. 4B) was symmetrical; the Egger's and Begg's tests did not indicate any publication bias, with p-values of 0.693 and 0.432, respectively, also confirmed by the Egger's publication bias plot (Supplementary Fig. 4C).

Early postoperative outcomes

The overall morbidity rate was reported by 16 out of 21 studies. The I^2 value was 45%. The overall morbidity rate was significantly higher in the CP group ($n = 232$, 50.8%) when compared to the DP group ($n = 255$, 39.9%) (OR 1.90; 95% CI 1.45, 2.48; $p < 0.0001$) (Fig. 3a). The Funnel plot (Supplementary Fig. 5A) revealed relative symmetry, while Egger's publication bias plot (Supplementary Fig. 5B) suggests minimal asymmetry. Also, both Egger's ($p = 0.085$) and Begg's test ($p = 0.034$) have borderline values.

Nineteen studies reported the overall pancreatic fistula rate, and 16 studies reported the incidence of clinically relevant pancreatic fistula (i.e., grade B-C). The I^2 value was 24% for studies assessing the overall pancreatic fistula rate and 41% for studies assessing the clinically relevant pancreatic fistula

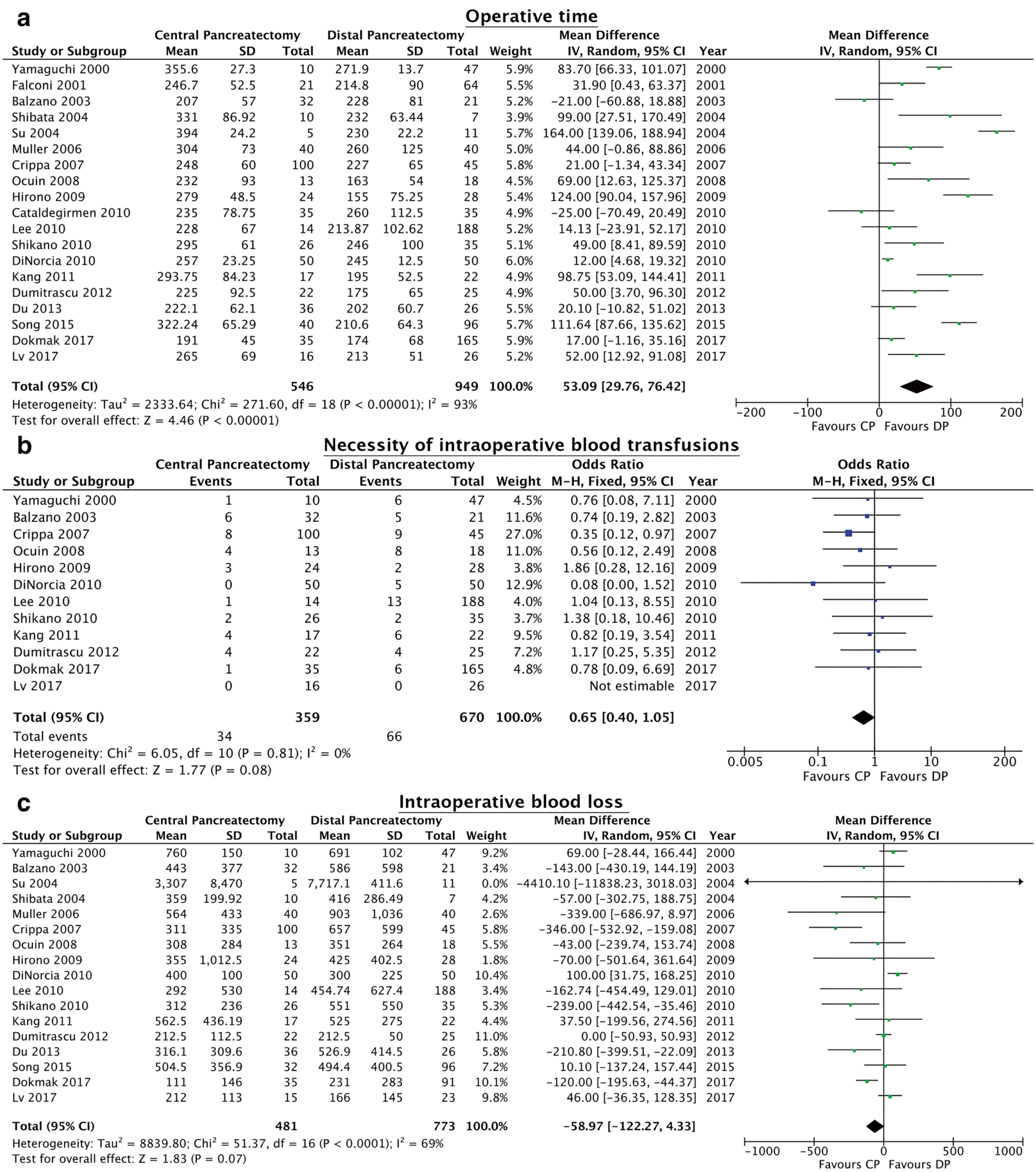

Fig. 2 Forest plots comparing intraoperative parameters. **a** Operative time. **b** Necessity of intraoperative blood transfusions. **c** Intraoperative blood loss

rate. Most of the studies [8, 12–14, 17, 22, 29–35, 37] used the International Study Group of Pancreatic Fistula definition and grading of pancreatic fistula [40].

The overall pancreatic fistula rate was significantly higher in the CP group ($n = 209$, 38.7%) when compared to the DP group ($n = 232$, 24.6%) (OR 2.01, 95% CI 1.54, 2.61, $p < 0.0001$) (Supplementary Fig. 6A). The funnel plot (Supplementary Fig. 6B) showed minimal asymmetry; the Egger's publication bias plot (Supplementary Fig. 6C) partially supported this view, while Egger's and Begg's test for publication bias showed borderline p values of 0.03 and 0.042, respectively.

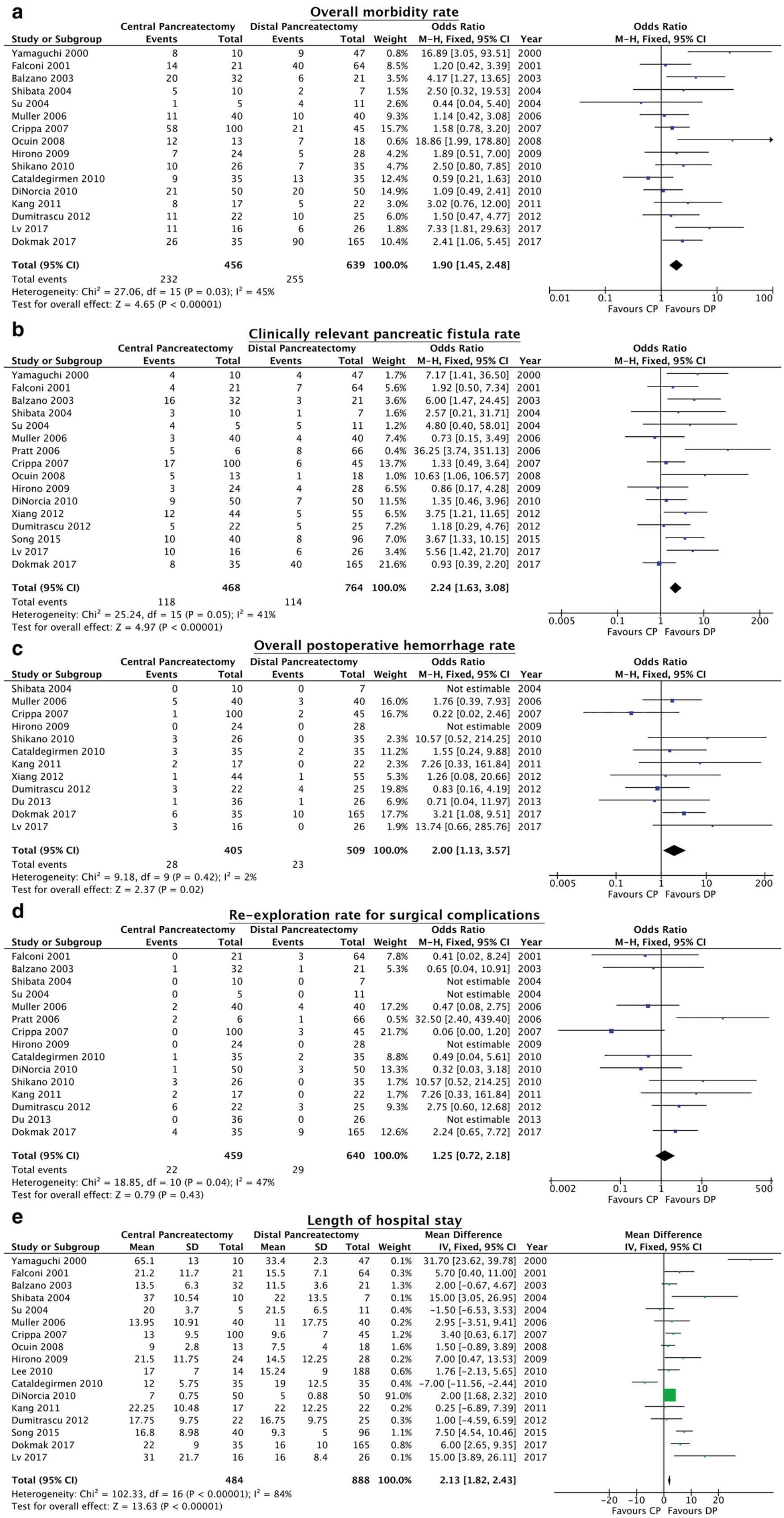

Fig. 3 Forest plots comparing early postoperative outcomes. **a** Overall morbidity rate. **b** Clinically relevant pancreatic fistula rate. **c** Overall postoperative hemorrhage rate. **d** Re-exploration rate for surgical complications. **e** Length of hospital stay

The clinically relevant pancreatic fistula rate was also significantly higher in the CP group ($n = 118$, 25.2%) when compared to the DP group ($n = 114$, 14.9%) (OR 2.24; 95% CI 1.63, 3.08; $p < 0.0001$) (Fig. 3b). The funnel plot and Egger's publication bias plot altogether suggested no publication bias (Supplementary Figs. 7A and 7B), which was confirmed by Egger's test ($p = 0.693$) and Begg's test ($p = 0.462$).

Twelve studies reported data of overall postoperative hemorrhage rate. The I^2 value was 2%. Most of the studies [8, 13, 14, 16, 17, 29–32, 35, 37] used the International Study Group of Pancreatic Surgery definition and grading of postpancreatectomy hemorrhage [41]. Significantly higher rates of overall postoperative hemorrhage were observed in the group of patients with CP ($n = 28$, 6.9%) when compared to the DP group ($n = 23$, 4.5%) (OR 2.0; 95% CI 1.13, 3.57; $p = 0.02$) (Fig. 3c). The funnel plot (Supplementary Fig. 8A) and Egger's publication bias plot (Supplementary Fig. 8B) suggested no publication bias, confirmed by Egger's test ($p = 0.982$) and Begg's test ($p = 0.592$).

Only six studies reported clinically relevant postoperative hemorrhage rate (i.e., grade B-C). The I^2 value was 0%. No significant differences were observed between the CP group ($n = 12$; 10.4%) and the DP group ($n = 7$; 0.41%) (OR 1.99; 95% CI 0.79, 5.00; $p = 0.14$) (Supplementary Fig. 9A). The funnel plot (Supplementary Fig. 9B) revealed no asymmetry; hence, no publication bias was detected.

Only 7 out of 21 studies reported the overall delayed gastric emptying rate. The I^2 value was 0%. Most of the studies [8, 14, 17, 29, 30, 32, 37] used the International Study Group of Pancreatic Surgery definition and grading of delayed gastric emptying [42]. Only six patients (2.7%) in the CP group and five patients (1%) in the DP group were reported to have delayed gastric emptying. No significant differences were observed between the groups (OR 1.53; 95% CI 0.46, 5.07; $p = 0.49$) (Supplementary Fig. 10A). The funnel plot (Supplementary Fig. 10B) and Egger's publication bias plot (Supplementary Fig. 10C) suggest no publication bias, confirmed by Egger's test ($p = 0.092$) and Begg's test ($p = 0.308$). The relevance of these statistical tests, under these specific circumstances (small sample size), is minimal.

Seven studies reported surgical site infectious complications and four studies systemic complications. For surgical site infections, the I^2 value was 0%. No significant differences were observed between the CP group ($n = 14$; 8.1%) and the DP group ($n = 18$; 4.7%) (OR 1.89; 95% CI 0.90, 3.98; $p = 0.09$) (Supplementary Fig. 11A). The funnel plot (Supplementary Fig. 11B) and Egger's publication bias plot (Supplementary Fig. 11C) indicated no publication bias, confirmed by Egger's test ($p = 0.37$) and Begg's test ($p = 0.133$).

For systemic complications, the I^2 value was 10%. No significant differences were observed between the CP group ($n = 31$; 17.1%) and the DP group ($n = 24$; 9.1%) (OR 1.30; 95% CI 0.68, 2.48; $p = 0.43$) (Supplementary Fig. 12A). The funnel plot (Supplementary Fig. 12B) and Egger's publication bias plot (Supplementary Fig. 12C) indicated no publication bias, confirmed by Egger's test ($p = 0.252$) and Begg's test ($p = 0.734$).

Only five studies reported the rate of severe surgical complications (i.e., > grade II Dindo-Clavien). The I^2 value was 0%. Significantly higher rates of severe postoperative complications were observed in the CP group ($n = 33$, 23.4%) when compared to the DP group ($n = 21$, 9.8%) (OR 3.07; 95% CI 1.62, 5.81; $p = 0.006$) (Supplementary Fig. 13A). The funnel plot (Supplementary Fig. 13B) shows no asymmetry; Egger's publication bias plot (Supplementary Fig. 13C) and the p-values for Egger's and Begg's tests, 0.776 and 0.806, respectively, suggest no publication bias.

Fifteen studies reported the re-exploration rate for surgical complications. The I^2 value was 47%. In the CP group, 22 patients (4.8%) required re-exploration, while in the DP group, 29 patients (4.5%) required re-exploration. No significant differences were observed between the groups (OR 1.25; 95% CI 0.72, 2.18; $p = 0.43$) (Fig. 3d). The funnel plot (Supplementary Fig. 14A) shows no asymmetry; Egger's publication bias plot (Supplementary Fig. 14B) and the p values for Egger's and Begg's tests, 0.694 and 0.640, respectively, suggest no publication bias.

The length of hospital stay was reported by 17 out of 21 studies. The I^2 value was 84%. Patients from the CP group had a mean (± SD) stay of 16.86 (± 8.76) days and had a significantly longer length of hospital stay when compared to the DP group, which had 15.30 (± 9.08) days (MD 2.13; 95% CI 1.82, 2.43; $p < 0.0001$) (Fig. 3e). The funnel plot (Supplementary Fig. 15A) and Egger's publication bias plot (Supplementary Fig. 15B) indicated no publication bias, which was confirmed by Egger's test ($p = 0.299$) and Begg's test ($p = 0.484$). By performing sensitivity analysis (sequential removal of each eligible study), we observed that our results are robust and stable. The omission of the study of Yamaguchi et al. [39] and DiNorcia et al. [30] would have influenced the most the pooled estimate, but also these two studies were inside the lower and upper limits of the 95% CI (Supplementary Fig. 15C). The operative mortality was reported by 18 studies out of 21 studies. The I^2 value was 0%. The mortality was differently assessed between studies, varying from in-hospital, to 30, and 90 days, respectively. There were a total of three deaths, all in the CP group (0.6%) and no deaths in the DP group (0%), without any significant differences between the groups (OR 3.66; 95% CI 0.56, 23.97; $p = 0.18$) (Supplementary Fig. 16A), and no publication bias was observed (Supplementary Fig. 16B).

Long-term postoperative outcomes

Out of 21 studies, 14 reported the overall rate of endocrine insufficiency (i.e., new onset or worsening of diabetes mellitus). The I^2 value was 0%. Significantly lower rates of overall endocrine insufficiency were observed in the CP group ($n = 29$; 6.7%) when compared to the DP group ($n = 145$; 22.3%) (OR 0.19; 95% CI 0.12, 0.29; $p < 0.0001$) (Fig. 4a). The funnel plot (Supplementary Fig. 17A) and Egger's publication bias plot (Supplementary Fig. 17B) indicated no publication bias, confirmed by Egger's test ($p = 0.721$) and Begg's test ($p = 0.381$).

Nineteen out of 21 studies reported the onset of newly diagnosed diabetes mellitus. The I^2 value was 0%. Significantly lower rates of new postoperative onset of diabetes mellitus were observed in the CP group ($n = 21$; 3.8%) when compared to the DP group ($n = 150$; 17.9%) (OR 0.17; 95% CI 0.11, 0.27; $p < 0.0001$) (Fig. 4b). The funnel plot (Supplementary Fig. 18A) and Egger's publication bias plot (Supplementary Fig. 18B) indicated no publication bias, which was confirmed by Egger's test ($p = 0.103$) and Begg's test ($p = 0.405$).

Ten of 21 studies reported the worsening of preexisting diabetes mellitus. The I^2 value was 0%. Significantly lower rates of worsening diabetes mellitus were observed in the CP group ($n = 1$; 0.3%) when compared to the DP group ($n = 23$; 4.4%) (OR 0.13; 95% CI 0.04, 0.41; $p = 0.0004$) (Fig. 4c). The funnel plot (Supplementary Fig. 19A) and Egger's publication bias plot (Supplementary Fig. 19B) indicated no publication bias, which was confirmed by Egger's test ($p = 0.904$) and Begg's test ($p = 1$).

The postoperative exocrine insufficiency rate was reported in 13 out of 21 studies. The I^2 value was 30%. Most of the studies reported the endocrine insufficiency based on clinical signs, while only few ones used specific paraclinical tests [29, 36, 39]. Statistically significant lower rates of exocrine insufficiency were observed in the CP group ($n = 35$; 8.6%), compared to the DP group ($n = 48$; 9.1%) (OR 0.58; 95% CI 0.36, 0.94; $p = 0.03$) (Supplementary Fig. 20A). The funnel plot (Supplementary Fig. 20B) and Egger's publication bias plot (Supplementary Fig. 20C) indicated no publication bias, confirmed by Egger's test ($p = 0.405$) and Begg's test ($p = 0.466$). It is worth mentioning that exocrine insufficiency was heterogeneously defined among the analyzed studies and, thus, the clinical value of this specific analysis should be regarded with caution.

The main outcomes of interest analyzed in the present meta-analysis are summarized in Table 3.

Discussion

Although the number of publications reporting CP has increased in recent years [3–5], CP remains an uncommon type of pancreatic resection. CP represents less than 5% of total pancreatic resections even in high-volume centers [8, 14, 29]. In only two single-center large series (≥ 100 patients), the rates of overall and severe morbidity (i.e., Clavien-Dindo grade ≥ 3) are substantial (62–72% and 15%, respectively). The same results were observed for the overall and clinically relevant pancreatic fistula rates (62.1–63% and 26.7–44%, respectively) [9, 10]. Notably, operative mortality of 3% was reported in one of these series of CP [9].

Enucleation has emerged as an alternative to pancreatic resections (including CP) for selected patients with benign and low-grade malignant pathology. Recent data on enucleation have shown shorter operative time, lower intraoperative blood loss, and postoperative hemorrhage rates, with better functional outcomes [43–45]. In addition, enucleation is associated with less morbidity when compared to CP [45]. However, few studies associated enucleation with increased pancreatic fistulae rates when compared to typical pancreatic resections [43, 45]. Nevertheless, CP and enucleation have different indications and CP should be used whenever enucleation is not technically feasible, mainly due to the proximity of the lesion to the main pancreatic duct.

To the best of our knowledge, this is the largest meta-analysis comparing CP and DP that includes all published studies and explores multiple outcomes of interest for pancreatic resections. Thus, it permits to assess the current clinical value and limitations of CP and to accurately determine the indications for CP.

As previous meta-analyses have shown [3–5], significantly shorter operative time was observed for DP when compared to CP ($p < 0.0001$). This is not unexpected, because it is widely known that CP is a more complex and, time-consuming surgical procedure, compared to DP. Nevertheless, substantial publication bias was observed and further studies are necessary to confirm these findings.

In the present meta-analysis, no significant differences between the groups were observed for both the necessity of intraoperative blood transfusions ($p = 0.08$) and intraoperative blood loss ($p = 0.07$), as previous meta-analyses have already shown [1, 4, 5].

The present meta-analysis associated CP with significantly higher overall and severe morbidity, overall and clinically relevant pancreatic fistula, and overall hemorrhage rates (p values < 0.05). It is widely accepted that CP is more technically challenging when compared to DP. This is partly due to the fact that CP implies the presence of two pancreatic stumps, and at least one pancreatico-digestive anastomosis. On the other hand, DP implies no anastomosis, and there is only one pancreatic stump as a potential source of complications. Previous meta-analyses have shown significantly higher overall morbidity and pancreatic fistula rate in the CP group [3–5]. However, only one previous meta-analysis explored the rate of clinically relevant pancreatic fistula between the groups, showing no significant differences [5]. Postoperative bleeding was previously explored in one meta-analysis showing no significant differences between the groups [5]. Noteworthy, the present meta-analysis shows for the first time that the rate

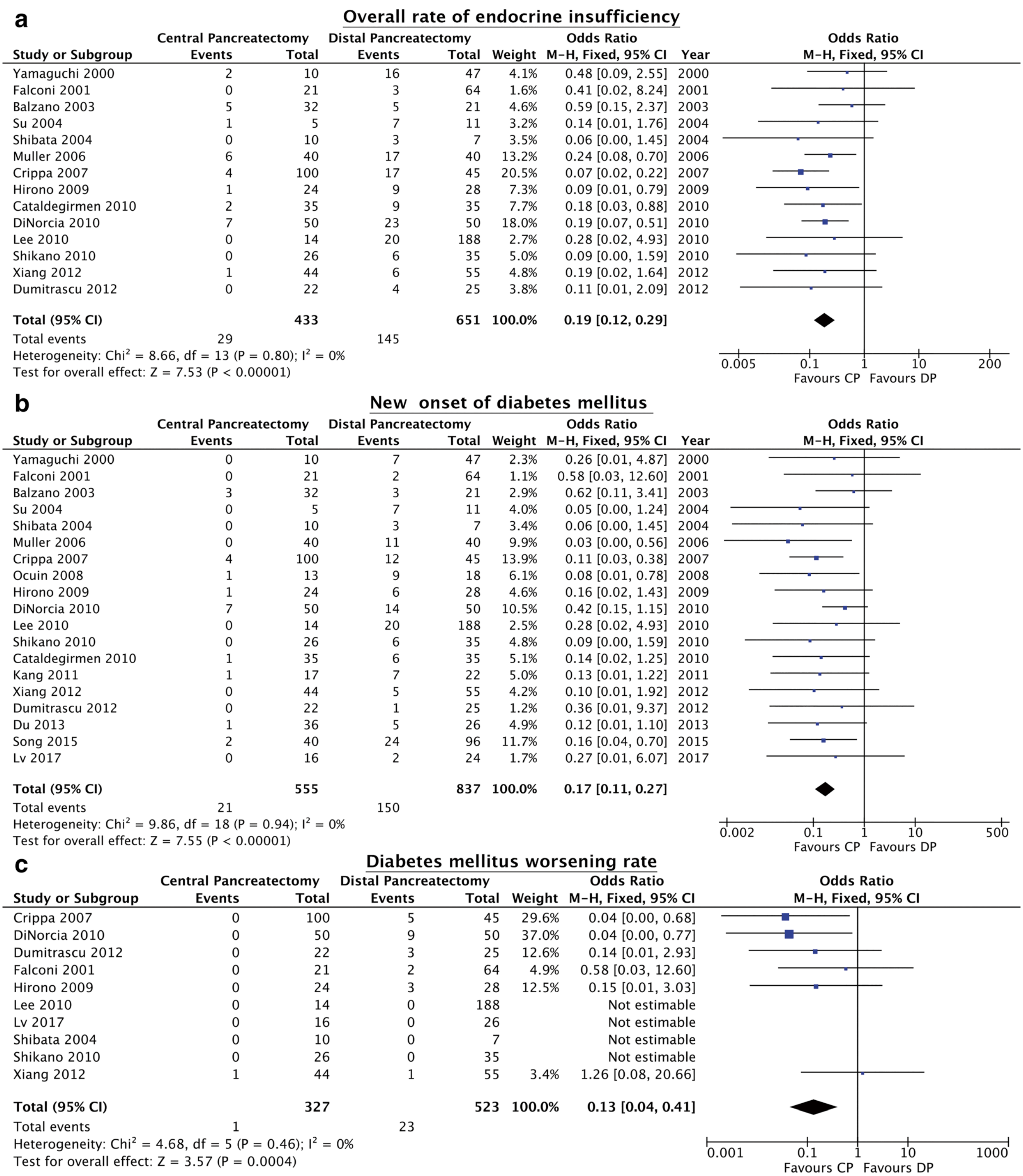

Fig. 4 Forest plots comparing long-term postoperative outcomes. **a** Overall rate of endocrine insufficiency. **b** New onset diabetes mellitus rate. **c** Worsening diabetes mellitus rate

of severe morbidity (i.e., > grade II Dindo-Clavien) is significantly higher for CP, compared to DP ($p = 0.006$).

The present meta-analysis did not identify any significant differences between the groups regarding delayed gastric emptying ($p = 0.49$), surgical site infections ($p = 0.09$), re-exploration for surgical complications ($p = 0.43$), systemic complications ($p = 0.43$), and mortality rates ($p = 0.18$). Out of these later parameters, only mortality and re-exploration

Table 3 Outcomes of interest analyzed in the meta-analysis comparing CP and DP

Outcome	Studies	Patients	OR/MD (95% CI)	p value	I^2
Intraoperative					
Operative time (min)	19	1495	53.09 (29.76–76.42)	< 0.0001	93%
Intraoperative blood transfusions	12	1029	0.65 (0.40–1.05)	0.08	0%
Intraoperative blood loss (ml)	17	1254	− 58.97 (− 122.27–4.33)	0.07	69%
Early postoperative outcomes					
Overall morbidity rate	16	1095	1.90 (1.45–2.48)	< 0.0001	45%
Severe (i.e., > grade II Dindo-Clavien) morbidity rate	5	356	3.07 (1.62–5.81)	0.0006	0%
Clinically relevant pancreatic fistulae rate	16	1232	2.24 (1.63–3.08)	< 0.0001	41%
Overall postoperative hemorrhage rate	12	914	2.00 (1.13–3.57)	0.02	2%
Re-exploration rate for surgical complications	15	1099	1.25 (0.72–2.18)	0.43	47%
Length of hospital stay	17	1372	2.13 (1.82–2.43)	< 0.0001	84%
Long-term outcomes					
Overall rate endocrine insufficiency	14	1084	0.19 (0.12–0.29)	< 0.0001	0%
New onset of DM	19	1392	0.17 (0.11–0.27)	< 0.0001	0%
DM worsening rate	10	850	0.13 (0.04, 0,41)	0.0004	0%
Overall exocrine insufficiency	13	936	0.58 (0.36–0.94)	0.03	30%

DM diabetes mellitus

rates were explored in previous meta-analyses [3–5]. No significant differences of mortality between the groups were previously reported [4, 5], as it was the case in the present meta-analysis. For re-laparotomy rates, previous meta-analyses reached conflicting results: One meta-analysis has shown significantly lower rates for the CP group [3], while other two reported similar results [4, 5] to those reported in the present meta-analysis.

The present meta-analysis has shown significantly longer hospital stay after CP, compared to DP. Similar results were previously reported in two meta-analyses [3, 4], while one did not identify any significant differences between the groups [5]. The more prolonged hospital stay after CP appears to be related to higher morbidity rates (particularly severe morbidity), compared to the DP.

Regarding the long-term outcomes, the present meta-analysis has shown significantly lower rates of overall endocrine insufficiency, new-onset, and worsening diabetes rates in the CP group, compared to DP ($p < 0.05$). Significantly lower rates of overall exocrine insufficiency were observed in the CP group, compared to the DP group ($p = 0.03$), but there was a large heterogeneity regarding the definition of exocrine insufficiency in the studies. Two previous meta-analyses [4, 5] have shown similar results to the present one for overall exocrine insufficiency, while one meta-analysis [3] did not show any significant differences between the groups. It is worth mentioning that although previous meta-analyses [3–5] have shown similar results for overall endocrine insufficiency rates, this is the first meta-analysis to show significantly lower rates for new-onset and worsening of diabetes mellitus in CP group, compared to DP group.

The better functional results for CP over DP are correlated with the significantly higher remnant pancreatic parenchyma volume in the CP group, which is a predictor of exocrine insufficiency after pancreatectomy [46]. Furthermore, several other factors such as underlying pathologies might influence the development of endocrine and exocrine insufficiencies after pancreatic resections [47]. Therefore, the new-onset and worsening of diabetes mellitus better assess the functional endocrine impact of CP and DP, compared to the more general overall endocrine insufficiency.

The results of the present meta-analysis should be regarded with caution because there are some limitations discussed below.

No randomized studies were included, and most of the included studies have a retrospective design.

There were significant differences in surgical indications between the patients' groups. Thus, significantly more patients in the CP group had neuroendocrine tumors, compared to the DP group (20% vs. 15%, $p = 0.01$). Neuroendocrine tumors were associated with significantly higher rates of postoperative pancreatic fistula after pancreatic resections in multiple studies [48–50]. This might explain in part the higher rates of postoperative pancreatic fistula in the CP group in the present meta-analysis.

Most of the studies did not explicitly report if the DP was performed with or without splenectomy. Only two studies specifically compared the outcomes of patients with CP vs. patients with spleen-preserving DP [14, 33]. Splenectomy during DP may potentially increase the risk of pancreatic fistula [50].

In the present meta-analysis, significantly more patients underwent a laparoscopic approach in the DP group, compared to the CP group (24.2% vs. 10.1%, $p < 0.001$). Minimally invasive approaches have become the standard for DP in many surgical centers, while minimally invasive CP is by far more technically demanding, and only a few centers have experience with these procedures. Laparoscopic DP appears to be associated with significantly shorter hospital stays and reduced pancreatic fistula rates, compared to the open DP [51]. Unfortunately, the analyzed studies did not specifically report outcomes for minimally invasive CP and DP, hence a subgroup analysis was not possible. Moreover, a recent meta-analysis has shown that minimally invasive spleen-preserving DP is associated with significantly lower pancreatic fistula rates and shorter operative time, compared to DP and splenectomy [52]. Altogether, this might explain in part the shorter hospital stay and reduced morbidity rates in the DP group of patients, compared to the CP group.

In summary, this meta-analysis favors CP for better preservation of pancreatic functions but also shows significant drawbacks for CP when compared to DP: increased rates of complications, including severe complications. Hence, this could be the reason why CP was not widely adopted in many surgical centers. The potential functional benefits of CP should be judged taking into consideration the potential harm of this procedure. Proper selection of patients for CP is crucial not only to maximize the functional benefits but also to mitigate the effects of potential complications.

CP should be used for patients with benign and low-grade malignant lesions of the mid pancreas when enucleation is not feasible as alternative to DP when there is a functionally meaningful distal remnant pancreas, in young patients with no associated diabetes mellitus and no significant comorbidities in order to be able to overcome the potential postoperative complications, particularly the severe ones.

Conclusions

CP is superior to DP regarding the preservation of pancreatic functions but at the expense of higher complication rates (including severe complications) and a longer hospital stay. However, the evidence for clinical practice provided by the current meta-analyses is limited because there are few important limitations. Thus, the results of the present meta-analysis should be used with caution in clinical decision-making. Proper selection of patients is of utmost importance to maximize the benefits and mitigate the risks of CP.

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Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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