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SYSTEMATIC REVIEWS AND META-ANALYSIS

# Mortality and postoperative complications after different types of surgical reconstruction following pancreaticoduodenectomy—a systematic review with meta-analysis

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## Abstract

**Background** Pancreaticoduodenectomy/PD is a technically demanding pancreatic resection. Options of surgical reconstruction include (1) the child reconstruction defined as pancreatojejunostomy/PJ followed by hepaticojejunostomy/HJ and the gastrojejunostomy/GJ “the standard/s-Child,” (2) the s-child reconstruction with an additional Braun enteroenterostomy “BE-Child,” or (3) Isolated-Roux-En-Y-pancreaticojejunostomy “Iso-Roux-En-Y,” in which the pancreas anastomosis is reconstructed in a separate loop after the GJ. Yet, the impact of these reconstruction methods on patients’ outcome has not been sufficiently compared in a systematic manner.

**Methods** A systematic review and meta-analysis were conducted according to the Preferred-Reporting-Items-for-Systematic-review-and-Meta-Analysis/PRISMA-guidelines by screening Pubmed/Medline, Scopus, Cochrane Library and Web-of-Science. Articles meeting predefined criteria were extracted and meta-analysis was performed.

**Results** Nineteen studies were identified comparing BE-Child or Isolated-Roux-En-Y vs. s-Child. Compared to s-Child neither BE-Child ($p = 0.43$) nor Iso-Roux-En-Y ($p = 0.94$) displayed an impact on postoperative mortality, whereas BE-Child showed less postoperative complications ($p = 0.02$). BE-Child ($p = 0.15$) and Iso-Roux-En-Y ($p = 0.61$) did not affect postoperative pancreatic fistula/POPF in general, but BE-Child was associated with a decrease of clinically relevant POPF ($p = 0.005$), clinically relevant delayed gastric emptying/DGE B/C ($p = 0.004$), bile leaks ($p = 0.01$), and hospital stay ($p = 0.06$). BE-Child entailed also an increased operation time ($p = 0.0002$) with no impact on DGE A/B/C, hemorrhage, surgical site infections and pulmonary complications.

**Conclusion** BE-Child is associated with a decreased risk for postoperative complications, particularly a decreased risk for clinically relevant DGE, POPF, and bile leaks, whereas Iso-Roux-En-Y does not seem to affect the clinical course after PD. Therefore, BE seems to be a valuable surgical method to improve patients’ outcome after PD.

**Keywords** Braun enteroenterostomy · Braun anastomosis · Child reconstruction · Iso-Roux-En-Y-reconstruction · Pancreas surgery · Pancreaticoduodenectomy

## Introduction

Incidence of postoperative complications after partial pancreaticoduodenectomy/PD did not alter within the last decades with morbidity rates reaching up to 60%, whereas mortality rates could be successfully dropped down to 3–5% in specialized high volume centers [1–4]. In this context, delayed gastric emptying/DGE and postoperative pancreatic fistula/POPF belong to the most feared complications after PD. Although DGE also occurs in other upper GI operations such as partial gastrectomy or esophagectomy with vagotomy [5–10], it is especially common after PD with an incidence

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of nearly 50% [11–14]. In contrast to other postoperative complications, DGE is not a life-threatening complication, but patients after pancreatic surgery followed by DGE suffer from a decreased quality of life and a prolonged hospital stay [2, 15–17]. In contrast to DGE, the incidence of overall POPF is less common and ranging around 20–30% [18, 19] and 20% for clinically relevant grade B/C POPF [18, 19]. Importantly, mortality increases especially in the presence of clinical relevant POPF grades B and C up to 20% [20, 21]. Moreover, Pratt et al. could demonstrate that an increasing degree of clinical relevant POPF negatively impacted economic and healthcare resources [22, 23].

To reduce the risk for postoperative mortality and morbidity, several surgical reconstruction techniques were introduced including the Child reconstruction. This reconstruction method is defined as pancreaticojejunostomy/PJ followed by hepaticojejunostomy/HJ and by gastrojejunostomy/GJ (s-Child, Fig. 1a) and could be performed with an optional Braun enteroenterostomy/BE (BE-Child Fig. 1b) [24]. Another reconstruction technique is the Isolated-Roux-En-Y-reconstruction/Iso-Roux-En-Y, which involves one jejunal loop for the HJ and GJ and an additional loop for the PJ (Fig. 1c). Here, Hochwald et al. were the first authors who described a beneficial effect of an additional BE to reduce DGE after classical Whipple operations in 2010 [25]. In this study, DGE defined according to ISGPS (Braun $n = 5/7\%$ vs. no Braun $n = 11/31\%$, $P = 0.003$) or to the inability to have oral intake by postoperative day 10 (Braun $n = 7/10\%$, no Braun $n = 9/26\%$, $P < 0.05$) was crucially reduced in the presence of Braun enteroenterostomy. In this study, no impact could be observed on the occurrence of POPF (Braun $n = 12/17\%$ vs. no Braun $n = 5/14\%$, $P = 0.79$) [25]. Accordingly, other studies could already identify BE as an independent, protective factor for DGE in patients even after pylorus-preserving PD/PPPD (OR 16.489, 95%-CI 1.287–211.195, $p = 0.031$) [26].

To assess the impact of reconstruction techniques after PD and PPPD, several systematic reviews with meta-analysis have been performed [27, 28]. Here, a potential protective effect of an additional BE after PD could be shown for DGE A/B/C ($p = 0.0007$), DGE grade B ($p = 0.02$), DGE grade C ($p < 0.00001$), morbidity ($p = 0.0003$), and length of hospital stay/LOS ($p = 0.03$) but not for pancreatic fistula in general [28]. Accordingly, Klaiber et al. could recently show that no superiority could be proven for double loop reconstructions including studies with a gastrojejunostomy and pancreaticojejunostomy in a separate jejunal loop against single loop reconstructions after PD for mortality ($p = 0.75$), morbidity ($p = 0.84$), DGE (0.77), and POPF ($p = 0.57$) [27]. Although these systematic reviews with meta-analysis were well conducted and performed, ours is the only meta-analysis that included a comparison of all three different techniques, whereas previous reports only compared two reconstructions in total. Moreover, unfortunately, both studies missed to capture the impact of BE-Child and Iso-Roux-En-Y against s-Child for clinically relevant DGE grade B/C and POPF grade B/C. Therefore, we decided to perform an up-to-date systematic review with meta-analysis including the recently published RCT of [26, 29, 30] and to include both reconstruction techniques BE-Child and Iso-Roux-En-Y against s-Child in one single clinical systematic review. Therefore, this is the first systematic review with meta-analysis that included clinically relevant DGE G/C and POPF B/C defined according to the recommendation of the ISPGS [31, 32] in separate meta-analysis.

## Material and methods

### Study design

According to the advice of the Cochrane network, reporting guideline of The Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) [33] guidelines was considered for this systematic review with meta-analysis. The following search terms were chosen to screen databases in April 2017: "pancreas," "resection," "pancreatic," "Braun anastomosis," "Braun enteroenterostomy," "Roux-En-Y," "pancreatic fistula," "pancreatic leakage," and "delayed gastric emptying." To provide an adequate overview of the current literature, databases of Pubmed/Medline, Web of Science, Scopus and The Cochrane Library were chosen for screening and identification process which is in line with the recommendation for surgical systematic review with meta-analysis by Goossen et al. [34]. Although no period was defined, the first study comparing BE-Child vs. s-Child was published in 2010 by Hochwald et al. [25] and 2008 for the comparison of Iso-Roux-En-Y vs. s-Child [35]. All studies with human pancreatic resections comparing the effect of s-Child vs. BE-Child or vs. Iso-Roux-En-Y were eligible to be included. The entire systematic review and meta-analysis protocol was registered at PROSPERO (CRD42017060838).

### Inclusion and exclusion criteria

After removing duplicates, three reviewers (SS, IED, and TV) independently screened the current literature for inclusion in the database of the systematic review. If inconstancy occurred during data extraction, studies were presented to two independent reviewers (DW, GOC). For study selection, the following inclusion and exclusion criteria were used:

1. Surgical techniques:

All studies were critically reviewed for the surgical reconstruction procedure. For this purpose, two reviewers

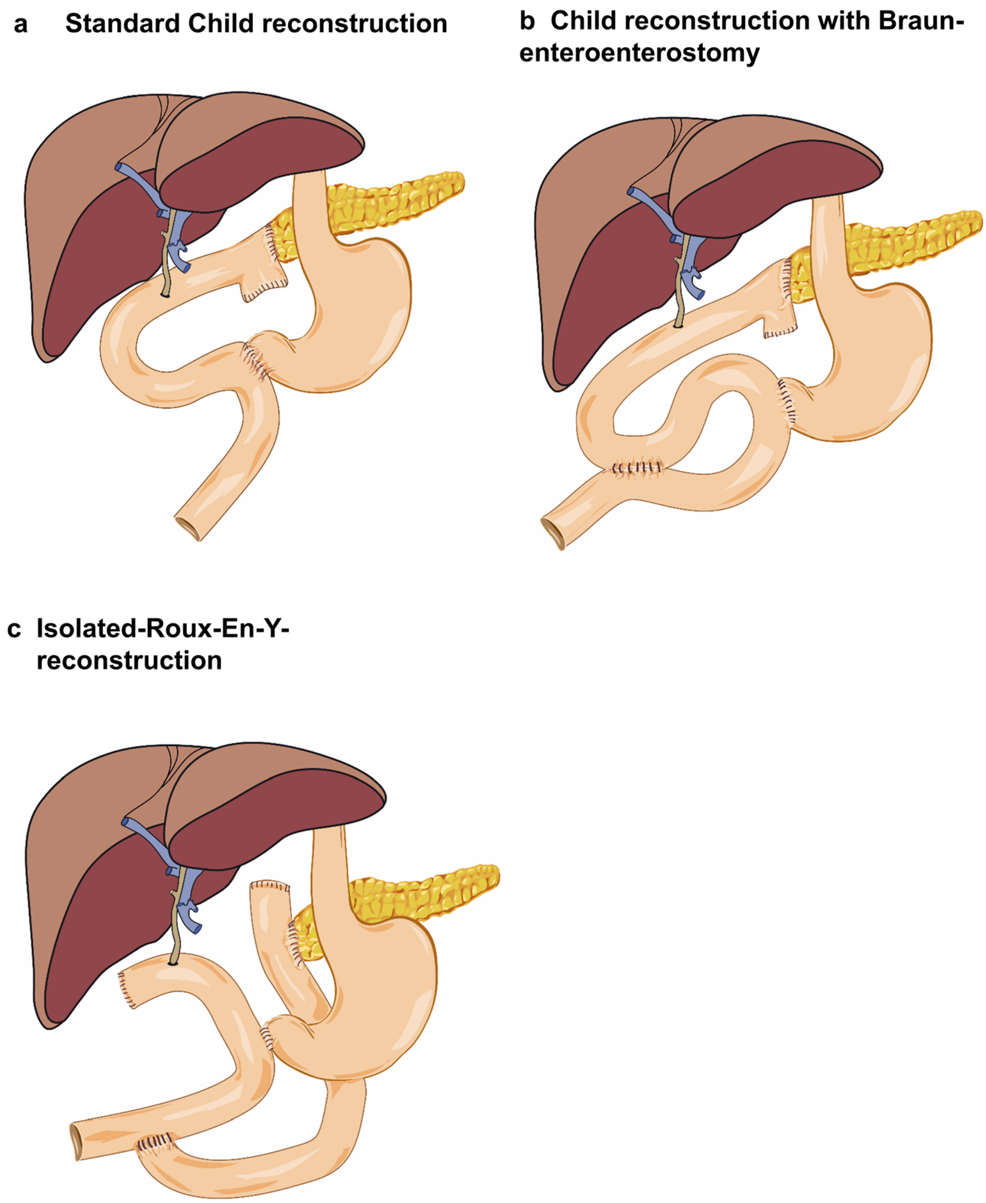


**Fig. 1** The most common used surgical reconstruction techniques after PD. Illustrates the different surgical reconstruction technique after pancreaticoduodenectomy. Reconstruction techniques using one single jejunal loop to connect the pancreas and biliary anastomosis with the gastrojejunostomy/GJ were defined as s-Child (**a**). In accordance, BE-Child was defined as s-Child with an additional enteroenterostomy between the afferent and efferent loop of the GJ facilitate the drainage of pancreatic juice and bile (**b**). The Isolated-Roux-En-Y-reconstruction uses a jejunal loop for the biliary and the gastric anastomosis and an additional isolated jejunal loop to drain the pancreatic juice (**c**)

independently screened the "Material and Method" part of each manuscript included in the systematic review. All studies providing a direct comparison of patients after pancreaticoduodenectomy followed by s-Child vs. BE-Child or Iso-Roux-En-Y with an isolated loop for the PJ were eligible for this systematic review. Three experienced pancreatic surgeons (GOC, DW, HF) supervised this process and were consulted for any inconsistencies or questions regarding the surgical technique in the considered studies.

2. Histology:

There was no limitation regarding the indication for pancreatic head resection. All patients with benign or malignant diseases were included in our systematic review.

3. Study design

Since the primary focus of the study was to concentrate on the immediate complications after PD, all studies were included regardless of their design or length of follow-up.

4. Language and time restrictions

All studies published in English-language, peer-reviewed journals until April 2017 were included in the systematic review and meta-analysis.

5. Definition of severity of postoperative pancreatic fistula (POPF) and delayed gastric emptying/DGE

For meta-analysis of POPF grade A/B/C and DGE A/B/C, no restrictions of studies regarding their definitions of DGE and POPF were made. In contrast, to guarantee a consistent definition of the severity of DGE and POPF, only studies with a DGE grade B/C and POPF grade B/C according to the definition of the International Study Group of Pancreatic Surgery/ISGPS were included in the meta-analysis of clinically relevant DGE and clinically relevant POPF [21, 31, 32]. As no study was performed before the introduction of the new definition of clinically relevant POPF of the ISGPS in 2016, the definition of clinically relevant POPF and DGE of 2005 and 2008 were considered for stratification [31, 32].

6. Selection bias

Only one study per institution was included in this study. After conducting the database of systematic review, four independent reviewers (SS, RS, TV, DR) analyzed the full-text articles for the exact number of patients, mortality rates, postoperative complications, and perioperative parameters. Meta-analysis was conducted by two reviewers (SS, IED), and an overall RR or mean differences were estimated.

## Data extraction

Exact amount of patients with postoperative complications or the exact risk ratio/RR with the corresponding 95%-confidence interval/95%-CI and/or the exact $p$ value were extracted and pooled in meta-analysis of postoperative complications including mortality, postoperative complications, DGE; POPF, bile leaks, hemorrhage, surgical site infections, and pulmonary infections. Continuous variables including LOH, operation length or perioperative blood loss were presented as the mean differences with corresponding standard deviations to be pooled in the meta-analysis. Accordingly, to control for relevant patient characteristics (age, gender, body mass index/BMI), perioperative data (type of anastomosis, pancreas texture, mean main pancreatic diameter, main pancreatic duct diameter < 3 mm), and histology, odds ratios/OR and mean differences were included in the analysis.

## Statistical analysis

Statistical analyses were performed with the Review Manager Software (Review Manager/RevMan, Version 5.3, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). In this study, heterogeneity was estimated using the inconsistency statistic ($I^2$) and defined as follows: If $I^2$ was zero or less than 50%, the absence or a low level of heterogeneity was assumed. As RCT, prospective studies, and retrospective studies were included in the meta-analysis, RR and OR were pooled using the Mantel–Haenszel method for random effects and expressed as pooled RRs with associated 95%-CI and $p$ value. In cases of continuous variables, the mean difference was estimated using the inverse variance model for random effects pooling mean of length of hospital stay, blood loss and operation time with their corresponding 95%-CI or $p$ value in the different meta-analyses. In addition, odds ratios/OR of multivariate logistic regression models with their corresponding 95%-CI or $p$ values were extracted and pooled in meta-analysis using the generic inverse variance model for random effects. To compare patient characteristics between BE-Child vs. s-Child and Iso-Roux-En-Y vs. s-Child, respectively, the unpaired student's $t$ test was estimated using StatsDirect Statistical Software (StatsDirect Ltd., Version 3.0.167). A two-sided $p$ value was calculated of each meta-analysis, and a level of significance of $\alpha = 0.05$ was used. As study design and surgical technique may interfere with study results, subgroup analyses were introduced depending on the design of the included study (RCT vs. prospective studies vs. retrospective studies) and of the surgical procedure (PPPD vs. PD). Moreover, sensitivity analysis were performed of all parameters including more than one study.

## Quality assessment and risk of publication bias

The methodological quality of each included studies was assessed by using the Risk Of Bias in Non-randomized Studies—of Interventions tool (ROBINS-I) [36]. ROBINS-I provided a detailed framework for assessment and judgment of the risk of bias including confounding bias, selection bias, or bias occurring due to different definition or explanation of interventions, missing data, measurement of outcome, or reporting results [36]. Afterwards, an overall estimated risk of bias was estimated of each study. Each domain of ROBINS-I is determined to have a low, moderate, serious, or critical risk of bias. It is important to note that the ROBINS-I score was assigned for each study of the systematic review regardless of the initial design of the original study [36]. Quality assessment reflects how well a specific result is associated to the intent of the systematic review regardless of the primal objective of the included study. Consequently, quality assessment and overall risk of bias refer to this specific systematic review and not to intended goal of the original study.

Additionally, as a recommendation of the Cochrane Collaboration, the presence of publication bias was assessed only in meta-analyses containing more than 10 studies [37]. For this purpose, Funnel plots were performed using Review Manager Software and the Egger's test [38] was performed using StatsDirect Statistical Software (Version 3.0.167). Publication bias was excluded, if the Funnel plot showed a symmetrical distribution of the included studies, which was evaluated by the $p$ value of the Egger test ($p > 0.05$).

## Results

### Screening and identification process of the systematic review

After screening the databases for the predefined search terms, a total of 2908 studies were identified, of which 13 [25, 26, 29, 30, 39–47] and 6 [48–52] studies met the inclusion criteria and were included in the systematic review comparing the postoperative outcome of patients with BE-Child or Iso-Roux-En-Y vs. s-Child (Fig. 2). Two RCTs with a total of 367 participants [48, 49] and 3 retrospective studies with 298 patients [50–52] were included in the systematic review comparing the outcome of patients with Iso-Roux-En-Y vs. s-Child. Furthermore, 3 RCTs with 158 patients [26, 29, 30], 3 prospective studies with 352 patients [25, 39, 40], and 7 retrospective studies [41–47] with 1897 patients were included in the analysis of BE-Child vs. s-Child. Characteristics of the different studies are summarized in Table 1. As patient characteristics (sex, gender, BMI), type of anastomosis of the pancreaticojejunostomy, pancreas texture, main pancreatic duct diameter, and the extent of surgical procedure as well as the indication for surgery itself may influence the results of our meta-analysis, the included studies were screened for differences of these parameters (Table 2). Here, no relevant differences ($p > 0.05$) could be observed in the comparison between patients with BE-Child vs. s-Child and Iso-Roux-En-Y vs. s-Child, respectively.

### The impact of surgical reconstruction on mortality and postoperative complications after PD

Mortality rates were 1.7% ($n = 15$) for patients with BE-Child and 1.9% ($n = 11$) in patients with s-Child. There was no difference in mortality (RR 0.72, 95%-CI 0.32–1.61; $p = 0.47$, $I^2 = 0\%$) (Fig. 3a). In contrast, BE-Child was associated with less postoperative complications compared with s-Child [161 patients (39.8%) after BE-Child vs. 212 (52.9%) after s-Child, RR 0.80, 95%-CI 0.66–0.97; $p = 0.002$, $I^2 = 29\%$, Fig. 3b]. Subgroup analysis of RCT could not detect any differences for mortality (RR 0.33, 95%-CI 0.01–7.58; $p = 0.49$, $I^2$ = na) (Fig. 3a) and for postoperative complications (RR 0.92, 95%-CI 0.55–1.54; $p = 0.75$, $I^2 = 29\%$) (Fig. 3b).

Furthermore, 5 studies [48–52] including 665 patients were pooled in the meta-analysis comparing the risk for postoperative mortality after Iso-Roux-En-Y vs. s-Child. Here, there was no clinically relevant impact of the Iso-Roux-En-Y vs. s-Child on overall mortality (HR 1.03, 95%-CI 0.39–2.77; $p = 0.95$, $I^2 = 0\%$) (Fig. 3c) or for overall postoperative complications (RR 1.03, 95%-CI 0.86–1.23; $p = 0.73$, $I^2 = 0\%$) (Fig. 3d).

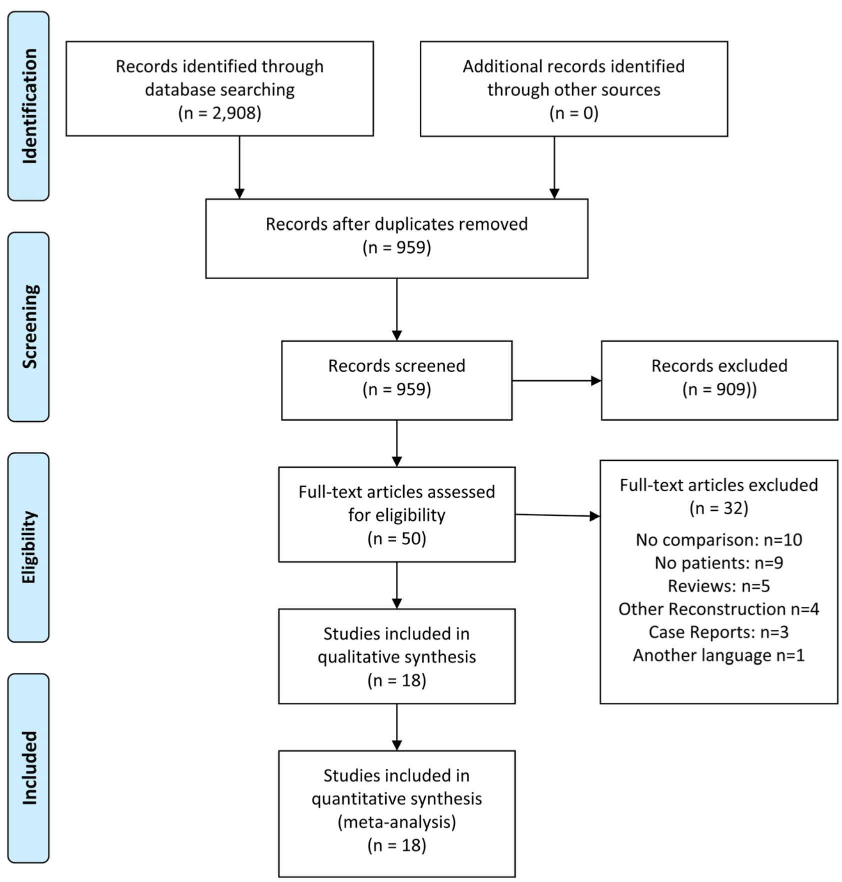


**Fig. 2** Flowchart of the screening and the identification-process. A flowchart of the screening and the identification-process was conducted according to the PRISMA-Guidelines. Here, a total of 2908 studies were identified comparing the outcome of patients after pancreas resection with BE-Child or Iso-Roux-En-Y vs. s-Child. After exclusion, only 18 studies were eligible to be included in our current systematic review

**Table 1** Characteristics of the included studies

| Author | Reconstruction-Type | Data collection | Study type | Definition of POFP and DGE | Typ of pancreas resection |
|---|---|---|---|---|---|
| Ke et al. 2013 [48] | Iso-Roux-En-Y (n=107) vs. s-Child (n=109) | 2006-2012 | RCT | POPF: ISGPF[31] | PD |
| Tani et al. 2014 [49] | Iso-Roux-En-Y (n=75) vs. s-Child (n=76) | 2009-2012 | RCT | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |
| Ballas et al. 2010 [50] | Iso-Roux-En-Y (n=42) vs. s-Child (n=46) | 1994-2006 | RS | ISGPF | PD+PPPD |
| Kaman et al. 2008 [51] | Iso-Roux-En-Y (n=60) vs. s-Child (n=51) | 1994-2006 | RS | POPF: >3x serum amylase, >50 ml/d lasting <7 days<br>DGE: na | PD+PPPD |
| Perwaiz et al. 2006 [52] | Iso-Roux-En-Y (n=53) vs. s-Child (n=55) | 2003-2007 | RS | POPF: ISGPF[31] | PD |
| Fujieda et al. 2017 [29] | BE-Child (n=34) vs. s-Child (n=34) | 2011-2016 | RCT | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PPPD |
| Hwang et al. 2016 [26] | BE-Child (n=30) vs. s-Child (n=30) | 2013-2014 | RCT | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PPPD |
| Kakaei et al. 2015 [30] | BE-Child (n=15) vs. s-Child (n=15) | 2013 | RCT | na | PD |
| Hochwald et al. 2009 [25] | BE-Child (n=70) vs. s-Child (n=35) | 2001-2006 | PS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |
| Meng et al. 2015 [39] | BE-Child (n=98) vs. s-Child (n=105) | 2009-2014 | PS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |
| Nikfarjam et al. 2012 [40] | BE-Child (n=24) vs. s-Child (n=20) | 2009-2011 | PS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |
| Cordesmeyer et al. 2014 [41] | BE-Child (n=51) vs. s-Child (n=62) | 2004-2011 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PPPD |
| Hu et al. 2016 [42] | BE-Child (n=172) vs. s-Child (n=367) | 2012-2015 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD+PPPD |
| Liu et al. 2014 [43] | BE-Child (n=40) vs. s-Child (n=156) | 2013 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD+PPPD |
| Wang et al. 2013 [44] | BE-Child (n=32) vs. s-Child (n=30) | 2008-2012 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |
| Watanabe et al. 2015 [45] | BE-Child (n=98) vs. s-Child (n=87) | 2008-2013 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PPPD |
| Xu et al. 2015 [46] | BE-Child (n=206) vs. s-Child (n=201) | 2000-2013 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |
| Zhang et al. 2014 [47] | BE-Child (n=347) vs. s-Child (n=48) | 2009-2013 | RS | POPF: ISGPF[31]<br>DGE: ISGPS[32] | PD |

All relevant characteristics of the included studies of the systematic review were summarized in this table

*BE-Child*, Child reconstruction with an additional Braun enteroenterostomy; *Iso-Roux-En-Y*, Reconstruction with an isolated pancreaticojejunostomy according to Roux-En-Y; *vs.*, versus; *POPF*, postoperative pancreatic fistula; *DGE*, delayed gastric emptying; *RCT*, prospective, randomized controlled trial; *PS*, prospective trial without randomization; *RS*, retrospective study; *ISGPF*, International Study Group for Pancreatic Fistula; *ISGPS*, International Study Group for Pancreatic Surgery; *PD*, pancreaticoduodenecotmy; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *na*, not available

Moreover, all studies, which showed sufficient data for a comparison of patients' characteristics, perioperative data, and histological diagnosis, were included in sensitivity meta-analysis of postoperative complications (Table 2, see ESM Figures 1–4).

## The impact of surgical reconstruction on POPF after pancreatic surgery

One hundred fifty-one patients (20.4%) presented POPF grade A/B/C after pancreatic resection with BE-Child, whereas 223 patients (36.7%) had POPF after s-Child. Nevertheless, no clinically relevant risk difference could be observed in the overall pooled meta-analysis of POPF grade A/B/C with a RR of 0.88 (RR 0.88, 95%-CI 0.74–1.05; $p = 0.15$, $I^2 = 0\%$) (Fig. 4a). Similarly, the meta-analysis comparing the impact of Iso-Roux-En-Y vs. s-Child did not identify any relevant difference for developing POPF grade A/B/C either (RR 0.92, 95%-CI 0.67–1.27; $p = 0.61$, $I^2 = 0\%$) (Fig. 4b). However, in the sub-analysis of clinically relevant, i.e., POPF grade B/C, only 53 patients (9.8%) with BE-Child displayed clinically relevant POPF grade B/C whereas nearly the double number of patients with s-Child ($n = 107$; 19.9%) demonstrated grade B/C POPF. Consequently, the meta-analysis revealed a two-fold increased risk for developing POFP grade B/C in patients with s-Child (RR 0.50, 95%-CI 0.31–0.81; $p = 0.005$, $I^2 = 46\%$) (Fig. 4c). The subgroup analysis of RCT was not able to detect any relevant difference for POPF grade A/B/C (RR

**Table 2** Distribution of relevant patients' characteristics within the different meta-analysis

| | BE-Child | s-Child | p-value | Studies | | Sensitivity analysis of postoperative complications | Sensitivity analysis of crPOPF | Sensitivity analysis of crDGE |
|---|---|---|---|---|---|---|---|---|
| BE-Child vs. s-Child | | | | | | | | |
| Patient demographics | | | | | | | | |
| Age (mean) | Na | Na | Na | $n = 6$ [26, 30, 39, 44, 46, 47] | MD: 0.99 (95%-CI: (-)0.86-2.84), $p = 0.29$ | RR: 0.76 (95%-CI: 0.76-0.96); $p = 0.02$ | RR: 0.33 (95%-CI: 0.18-0.59=; $p = 0.0002$ | RR: 0.28 (95%-CI: 0.12-0.65); $p = 0.003$ |
| BMI (mean) | Na | Na | Na | $n = 2$ [39, 44] | MD: -0.34 (95%-CI: (-)1.43-0.70; $p = 0.50$ | RR: 0.82 (95%-CI: 0.53-1.27); $p = 0.36$ | Na | Na |
| Gender | | | | | | | | |
| Man | 544 | 377 | $p = 0.6225$ | $n = 11$ [25, 26, 29, 30, 39, 40, 41, 44–47] | OR: 0.99 (95%-CI: 0.79-1.13); $p = 0.90$ | RR: 0.80 (95%-CI: 0.66-0.97); $p = 0.02$ | RR: 0.50 (95%-CI: 0.31-0.81); $p = 0.005$ | RR: 0.40 (95%-CI: 0.22-0.75); $p = 0.0004$ |
| Woman | 406 | 261 | $p = 0.4478$ | $n = 11$ [25, 26, 29, 30, 39, 40, 41, 44–47] | OR: 1.01 (95%-CI: 0.82-1.25); $p = 0.90$ | | | |
| Resection technique | | | | | | | | |
| Classical Whipple | 792 | 454 | $p > 0.999$ | $n = 11$ [25, 26, 29, 30, 39, 40, 41, 44–47] | Na | Na | Na | Na |
| Pylorus-preserving Whipple | 202 | 224 | $p > 0.999$ | $n = 11$ [25, 26, 29, 30, 39, 40, 41, 44–47] | Na | Na | Na | Na |
| Other surgical data | | | | | | | | |
| Mean pancreatic duct diameter | Na | Na | Na | $n = 1$ [47] | MD: 0.00 (95%-CI: (-)0.04-0.04); $p = 1.00$ | Na | Na | RR: 0.64 (95%-CI: 1.29); $p = 0.21$ |
| Pancreatic duct <3mm | 32 | 31 | $p = 0.899$ | $n = 2$ [40, 44] | OR: 0.85 (95%-CI: 0.37-2.00); $p = 0.72$ | Na | Na | Na |
| Soft pancreatic tissue | 290 | 107 | $p = 0.5735$ | $n = 5$ [29, 40, 44, 45, 47] | OR: 1.16 (95%-CI: 0.82-1.63); $p = 0.40$ | RR: 0.98 (95%-CI: 0.67-1.44); $p = 0.94$ | RR: 0.77 (95%-CI: 0.51-1.17); $p = 0.23$ | RR: 0.41 (95%-CI: 0.19-0.86); $p = 0.02$ |
| Type of anastomosis | | | | | | | | |
| Duct to mucosa | 229 | 215 | $p = 0.4835$ | $n = 7$ [29, 26, 30, 40, 44–46] | OR: 0.23 (95%-CI: 0.02-2.15); $p = 0.20$ | RR: 0.85 (95%-CI: 0.67-1.07); $p = 0.16$ | RR: 0.58 (95%-CI: 0.32-1.08); $p = 0.08$ | RR: 0.28 (95%-CI: 0.16-0.52); $p < 0.0001$ |
| Invagination | 210 | 202 | $p = 0.9525$ | $n = 7$ [29, 26, 30, 40, 44–46] | OR: 4.40 (95%-CI: 0.47-41.60); $p = 0.20$ | | | |
| Pathology | | | | | | | | |
| Pancreatic cancer | 249 | 159 | $p = 0.8479$ | $n = 9$ [25, 26, 29, 30, 39, 44–47] | OR: 0.85 (95%-CI: 0.64-1.12); $p = 0.24$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| IPMN | 31 | 38 | $p = 0.9063$ | $n = 9$ [25, 26, 29, 30, 39, 44–47] | OR: 0.69 (95%-CI: 0.41-1.17); $p = 0.17$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Bile duct cancer | 167 | 61 | $p = 0.7494$ | $n = 9$ [25, 26, 29, 30, 39, 44–47} | OR: 0.85 (95%-CI: 0.64-1.12); $p = 0.24$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Ampullary cancer | 60 | 32 | $p = 0.4894$ | n = 9 [25, 26, 29, 30, 39, 44–47] | OR: 1.71 (95%-CI: 0.71-4.11); $p = 0.23$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Duodenal cancer | 19 | 24 | $p = 0.8585$ | n = 9 [25, 26, 29, 30, 39, 44–47] | OR: 0.62 (95%-CI: 0.29-1.30); $p = 0.21$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Neuroendocrine tumors | 25 | 17 | $p = 0.6955$ | n = 9 [25, 26, 29, 30, 39, 44–47] | OR: 0.64 (95%-CI: 0.31-1.32); $p = 0.23$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Chronic pancreatitis | 27 | 6 | $p = 0.7576$ | n = 9 [25, 26, 29, 30, 39, 44–47] | OR: 0.98 (95%-CI: 0.40-2.38); $p = 0.96$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | |

**Table 2** (continued)

| | BE-Child | s-Child | p-value | Studies | | Sensitivity analysis of postoperative complications | Sensitivity analysis of crPOPF | Sensitivity analysis of crDGE |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Others | 135 | 54 | $p = 0.8506$ | n = 9 [25, 26, 29, 30, 39, 44–47] | OR: 0.91 (95%-CI: 0.40-2.07); $p = 0.82$ | RR: 0.80 (95%-CI: 0.64-1.00); $p = 0.05$ | RR: 0.53 (95%-CI: 0.29-0.95); $p = 0.03$ | RR: .38 (95%-CI: 0.20-0.73); $p = 0.003$ |
| Iso-Roux vs. s-Child | Iso-Roux-en-Y | s-Child | p-value | Studies | | Sensitivity analysis of morbidity | Sensitivity analysis of crPOPF | Sensitivity analysis of crDGE |
| Patient demographics | | | | | | | | |
| Age (mean) | Na | Na | Na | n = 4 [48, 49, 51, 52] | MD: -0.18 (95%-CI: -(-)1.48-1.11); $p = 0.78$ | RR: 1.01 (95%-CI: 0.83-1.21); $p = 0.95$ | Na | Na |
| BMI (mean) | Na | Na | Na | n = 4 [48, 49, 51, 52] | MD: 0.10 (95%-CI: (-)0.42-0.62); $p = 0.70$ | RR: 1.01 (95%-CI: 0.83-1.21); $p = 0.95$ | Na | Na |
| Gender | | | | | | | | |
| Man | 193 | 191 | $p = 0.8576$ | n = 5 [48, 49, 50–52] | OR: 0.96 (95%-CI: 0.70-1.31); $p = 0.80$ | RR: 1.01 (95%-CI: 0.83-1.21); $p = 0.95$ | Na | Na |
| Woman | 143 | 137 | $p = 0.9891$ | n = 5 [48, 49, 50–52] | OR: 1.04 (95%-CI: 0.76-1.43); $p = 0.79$ | | | |
| Biliary stenting | 55 | 57 | $p = 0.488$ | n = 3 [49, 51, 52] | OR: 0.94 (95%-CI: 0.59-1.48); $p = 0.77$ | RR: 1.04 (95%-CI: 0.81-1.34); $p = 0.76$ | RR: 1.11 (95%-CI: 0.50-2.47); $p = 0.79$ | RR: 3.04 (95%-CI: 0.63-14.59); $p = 0.16$ |
| Resection technique | | | | | | | | |
| Classical Whipple | 333 | 307 | $p = 0.3768$ | n = 5 [48, 49, 50–52] | OR: 1.11 (95%-CI: 0.79-1.55); $p = 0.56$ | RR: 1.01 (95%-CI: 0.83-1.21); $p = 0.95$ | RR: 1.11 (95%-CI: 0.50-2.47); $p = 0.79$ | RR: 3.04 (95%-CI: 0.63-14.59); $p = 0.16$ |
| Pylorus-preserving Whipple | 8 | 26 | $p = 0.3768$ | n = 5 [48, 49, 50–52] | OR: 0.20 (95%-CI: 0.08-0.48); $p = 0.0003$ | RR: 1.01 (95%-CI: 0.83-1.21); $p = 0.95$ | RR: 1.11 (95%-CI: 0.50-2.47); $p = 0.79$ | RR: 3.04 (95%-CI: 0.63-14.59); p=0.16 |
| Other surgical data | | | | | | | | |
| Mean pancreatic duct diameter | Na | Na | Na | n = 3 [48, 49, 52] | MD: 0.00 (95%-CI: (-)0.05-0.05); $p = 0.97$ | RR: 0.99 (95%-CI: 0.80-1.22); $p = 0.92$ | RR: 1.11 (95%-CI: 0.50-2.47); $p = 0.79$ | RR: 3.04 (95%-CI: 0.63-14.59); $p = 0.16$ |
| Soft pancreatic tissue | 129 | 121 | $p = 0.9507$ | n = 4 [48, 49, 51, 52] | OR: 1.07 (95%-CI: 0.74-1.56); $p = 0.71$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| Type of anastomosis | | | | | | | | |
| Duct to mucosa | 292 | 285 | $p = 0.6842$ | n = 4 [48, 49, 51, 52] | OR: 2.04 (95%-CI: 0.48-8.62); $p = 0.33$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | RR: 1.11 (95%-CI: 0.50-2.47); $p = 0.79$ | RR: 3.04 (95%-CI: 0.63-14.59); $p = 0.16$ |
| Invagination | 3 | 6 | $p = 0.6842$ | n = 4 [48, 49, 51, 52] | OR: 0.49 (95%-CI: 0.12-2.07); $p = 0.33$ | | | |
| Pathology | | | | | | | | |
| Pancreatic cancer | 117 | 108 | $p = 0.7939$ | n = 4 [48, 49, 51, 52] | OR: 1.11 (95%-CI: 0.79-1.55); $p = 0.56$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| IPMN | 11 | 16 | $p = 0.8117$ | n = 4 [48, 49, 51, 52] | OR: 0.64 (95%-CI: 0.28-1.50); $p = 0.31$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| Bile duct cancer | 62 | 54 | $p = 0.561$ | n = 4 [48, 49, 51, 52] | OR: 1.20 (95%-CI: 0.79-1.82); $p = 0.40$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| Ampullary cancer | 65 | 65 | $p = 0.915$ | n = 4 [48, 49, 51, 52] | OR: 0.95 (95%-CI: 0.63-1.43); $p = 0.80$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |

**Table 2** (continued)

| | BE-Child | s-Child | p-value | Studies | | Sensitivity analysis of postoperative complications | Sensitivity analysis of crPOPF | Sensitivity analysis of crDGE |
|---|---|---|---|---|---|---|---|---|
| Duodenal cancer | 16 | 21 | $p = 0.3701$ | n = 4 [48, 49, 51, 52] | OR: 0.73 (95%-CI: 0.37-1.44); $p = 0.36$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| Neuroendocrine tumors | 3 | 2 | $p = 0.7846$ | n = 4 [48, 49, 51, 52] | OR: 1.54 (95%-CI: 0.25-9.50); $p = 0.64$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| Chronic pancreatitis | 5 | 5 | $p = 0.8722$ | n = 4 [48, 49, 51, 52] | OR: 0.96 (95%-CI: 0.25-3.26); $p = 0.90$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |
| Others | 19 | 20 | $p = 0.2571$ | n = 4 [51, 48, 52, 49] | OR: 0.80 (95%-CI: 0.40-1.60); $p = 0.53$ | RR: 1.01 (95%-CI: 0.86-1.21); $p = 0.95$ | Na | Na |

*BE-Child*, Child reconstruction with an additional Braun enteroenterostomy; s-Child: standard Child reconstruction; *MD*, mean difference; *95%-CI*, 95%-Confidence-interval; *OR*, odds ratio; *BMI*, body mass index; *IPMN*, intraductal papillary-mucinous neoplasms; *Iso-Roux*, Reconstruction with an isolated pancreaticojejunostomy; *na*, not available

0.33, 95%-CI 0.01–7.58; $p = 0.49$, $I^2$ = na) or for clinically relevant POPF (RR 0.83, 95%-CI 0.40–1.73; $p = 0.62$, $I^2$ = 0%) between BE-Child and s-Child. In addition, no protective effect of an Isolated-Roux-En-Y compared to s-Child was present in the meta-analysis (HR 1.11, 95%-CI 0.50–2.47; $p = 0.79$, $I^2$ = na) (Fig. 4d).

According to postoperative complications, sensitivity analysis was performed for clinically relevant POPF and provided in Table 2 and ESM Figures 1–4 (Table 2, see ESM Figures 1–4). In this context, no differences could be observed regarding the rates of the pancreas texture, the main pancreatic duct, and of type of anastomosis (Table 2). In accordance, the overcalled pooled RR of the sensitivity analysis tended to show a potential benefit of an additional BE although no statistical significance could be observed, which should be interpreted as a consequence of a low number of included studies (Table 2, see ESM Figures 1–4).

## The impact of surgical reconstruction on DGE after pancreatoduodenectomy

Whereas only 54 patients (22.7%) suffered from postoperative DGE after BE-Child, it were 101 patients (36.9%) with s-Child. As a consequence, the overall pooled RR showed that BE-Child is associated with a slightly decreased, but non-significant risk for DGE compared to s-Child (RR 0.72, 95%-CI 0.46–1.14; $p = 0.16$, $I^2 = 53\%$) (Fig. 5a). No effect was seen comparing the impact of Iso-Roux-En-Y against s-Child for DGE grade A/B/C either (RR 1.19, 95%-CI 0.82–1.75; $p = 0.36$, $I^2 = 0\%$) (Fig. 5b). This protective effect of a BE was even more visible after stratifying patients into clinically relevant DGE grade B/C according to ISGPS [32]. Here, 77 patients (8.3%) displayed DGE grade B/C after PD with BE-Child vs. 139 patients (18.7%) after s-Child. Accordingly, the overall RR of 0.40 showed a strongly reduced risk for clinically relevant DGE grade B/C in patients with BE-Child (RR 0.40, 95%-CI 0.22–0.75; $p = 0.004$, $I^2 = 73\%$) (Fig. 5c). No protective effect was visible in the comparison of Iso-Roux-En-Y vs. s-Child (RR 3.04, 95%-CI 0.63–14.59; $p = 0.16$, $I^2$ = na) (Fig. 5d). Subgroup analysis of RCT comparing the effect of BE-Child vs. s-Child could not detect any relevant differences for DGE grade A/B/C (RR 0.59, 95%-CI 0.31–1.12; $p = 0.11$, $I^2 = 0\%$) (Fig. 5a) or for clinically relevant DGE B/C (RR 0.41, 95%-CI 0.22–1.90; $p = 0.25$, $I^2 = 54\%$) (Fig. 5c). Also, the overall pooled RR of RCT comparing Iso-Roux-En-Y against s-Child was not able to detect any benefit of Iso-Roux-En-Y for DGE Grade A/B/C (RR 1.01, 95%-CI 0.63–1.64; $p = 0.96$, $I^2 = 0\%$) (Fig. 5b). To identify BE as an independent factor for DGE, a total of 4 OR of multivariate regression models [26, 43, 45, 46] could be identified and pooled in meta-analysis identifying BE as an independent, protective factor against clinically relevant DGE after PD (OR 4.59, 95%-CI 2.86–7.36; $p < 0.0001$; $I^2$ = 0%) (see ESM Figure 5).

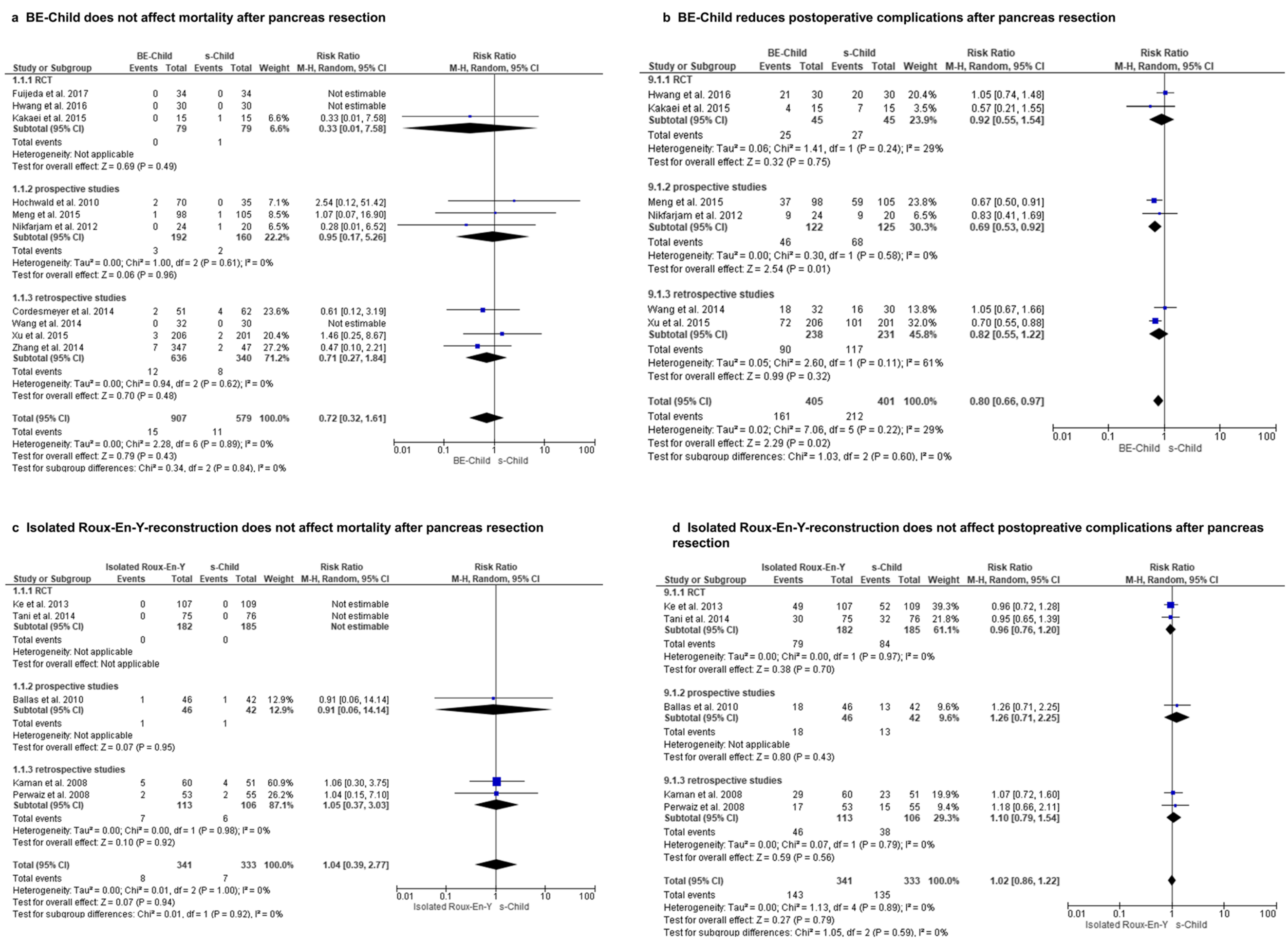


**Fig. 3** The impact of BE-Child or Iso-Roux-En-Y vs. s-Child on overall mortality and postoperative complications after pancreatic head resection. Forest plot of quantitative data comparing the incidence of postoperative mortality between patients with BE-Child (**a**) or Iso-Roux-En-Y (**c**) and s-Child. Meta-analysis of patients for the comparison of postoperative complications between patients with BE-Child vs. s-Child (**b**) and Iso-Roux-En-Y vs. s-Child (**d**). Studies were stratified from their study design into RCT; prospective studies and retrospective studies. Data were shown as risk ratio (RR) with their corresponding 95%-CI and $p$ value using the Mantel–Haenszel random effects models. RCT randomized controlled trial, M-H Mantel–Haenszel model; CI confidence interval

In addition, sensitivity analyses were performed for the comparison of BE-Child/Iso-Roux-En-Y vs. s-Child for clinically relevant DGE confirming the superiority of BE-Child vs. s-Child for clinically relevant DGE (Table 2, see ESM Figures 1–4). Here, all sensitivity analysis but one showed a clinical benefit of an additional BE to prevent clinically relevant DGE (Table 2, see ESM Figures 1–4).

## The impact of surgical reconstruction on hemorrhage, surgical site infections, pulmonary complication, blood loss, length of hospital stay, and operation time

Next, the database of the systematic review was screened for data of perioperative blood loss, operation time, postoperative hemorrhage, surgical site infections (SSI), pulmonary complications, bile leaks, and length of hospital stay (LOH). No clinically relevant impact of BE-Child vs. s-Child was detected on hemorrhage (RR 1.17, 95%-CI 0.69–1.97; $p = 0.56$, $I^2 = 0\%$), on SSI (RR 0.97, 95%-CI 0.67–1.42; $p = 0.89$, $I^2 = 0\%$), on pulmonary infections (RR 1.00, 95%-CI 0.45–2.23; $p = 0.99$, $I^2 = 45\%$), or on perioperative blood loss (mean difference 0.29 ml, 95%-CI − 0.02–0.61; $p = 0.06$, $I^2 = 78\%$) (Table 3). However, patients after BE-Child tended to have shorter LOH (mean difference − 1.39 days, 95%-CI − 2.81–0.04; $p = 0.06$, $I^2 = 0\%$) with a decreased risk for postoperative bile leaks (RR 0.52, 95%-CI 0.31–0.88; $p = 0.01$, $I^2 = 0\%$) and a longer operation time (mean difference 17.72 min, 95%-CI 8.27–3.66; $p = 0.0002$, $I^2 = 0\%$) compared with s-Child (Table 3). Sensitivity analysis of bile leaks including RCT was performed to allow a deeper insight of an additional BE on bile leaks. Here, no patient in the BE-Child group (0/30) and 2 patients in the s-Child group (2/30) showed a postoperative bile leak (RR 0.33, 95%-CI 0.04–3.08, $p = 0.33$, $I^2 = 0\%$).

In accordance with BE-Child, the same meta-analysis was conducted comparing the postoperative outcome between patients after Iso-Roux-En-Y vs. s-Child. In line with the meta-analysis of

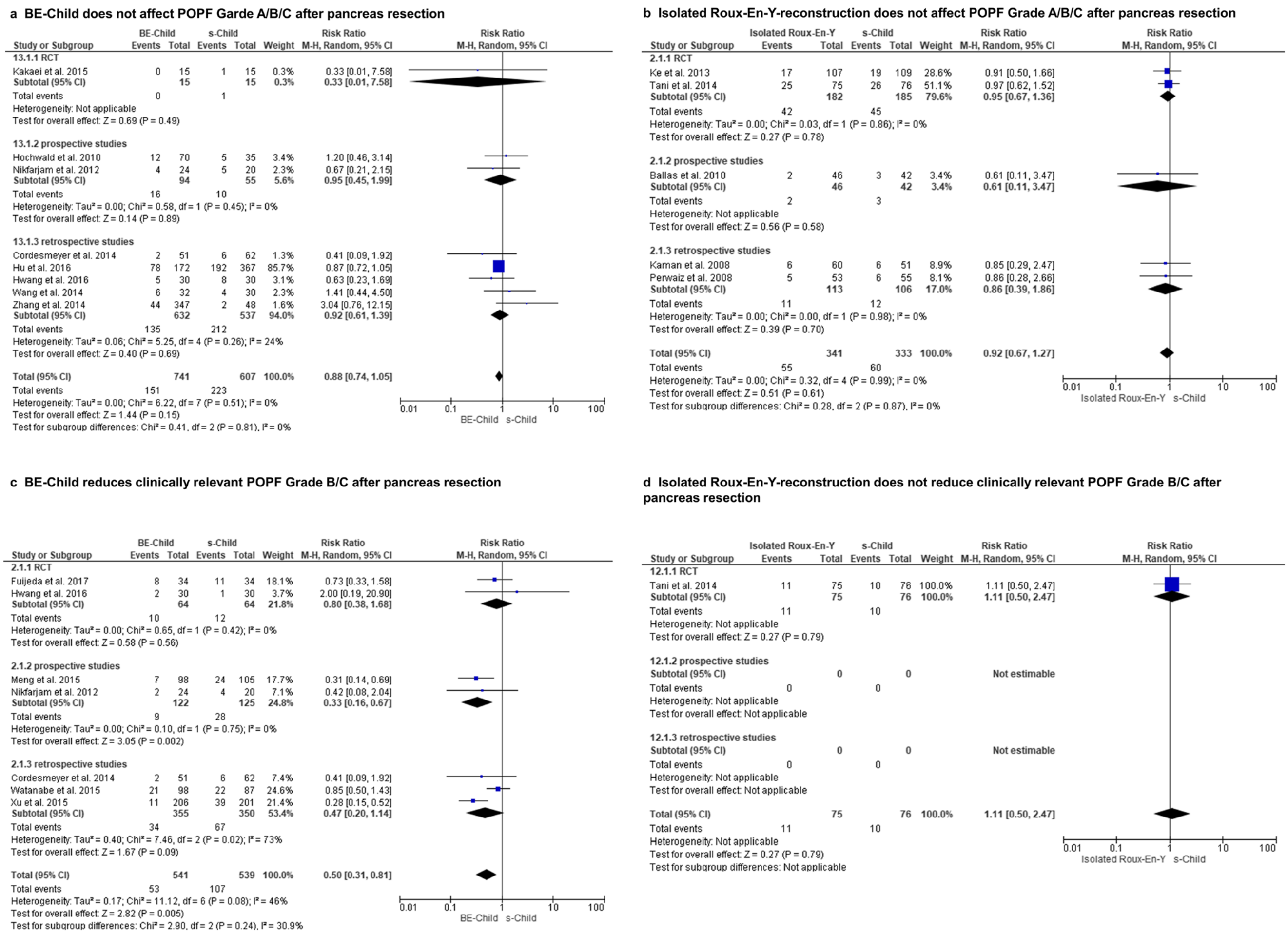


**Fig. 4** The impact of BE-Child or Iso-Roux-En-Y vs. s-Child on POPF after pancreatic head resection. Meta-analysis of any kind of POPF comparing the postoperative outcome between BE-Child vs. s-Child (**a**) and Iso-Roux-En-Y vs. s-Child (**b**). Quantitative data of clinically relevant POPF according to the definition of ISGPS were pooled in (**c**) for meta-analysis of BE-Child and s-Child and in (**d**) for Iso-Roux-En-Y and s-Child. Studies were stratified from their study design into RCT; prospective studies and retrospective studies. Risk ratios (RR) were calculated by the Mantel–Haenszel random effects models. POPF postoperative pancreatic fistula; ISPGS International Study Group for Pancreatic Surgery; RCT randomized controlled trial; M-H Mantel–Haenszel model; CI confidence interval

BE-Child, no clinically relevant effect was visible for the risk of developing postoperative hemorrhage (RR 1.79, 95%-CI 0.72–4.44; $p = 0.21$, $I^2 = 0\%$), of SSI (RR 0.89, 95%-CI 0.56–1.41; $p = 0.61$, $I^2 = 0\%$), of pulmonary infections (RR 1.18, 95%-CI 0.69–2.02; $p = 0.55$, $I^2 = 0\%$) or of a clinically relevant perioperative blood loss (mean difference: − 30.99 ml, 95%-CI − 55.74–−6.23; $p = 0.01$, $I^2 = 0\%$) (Table 3). In contrast to BE-Child, also no impact of Iso-Roux-En-Y was observed in the meta-analysis on bile leaks (RR 1.24, 95%-CI 0.41–3.78; $p = 0.70$, $I^2 = 11\%$), on operation time (mean difference 29.17, 95%-CI − 7.45–65.80; $p = 0.12$, $I^2 = 88\%$) or on LOH (mean difference − 0.38 days, 95%-CI − 1.69–0.94; $p = 0.58$; $I^2 = 56\%$) (Table 3).

## The effect of BE and Iso-Roux-En-Y in classical PD and PPPD

To provide a detailed insight on the impact of BE after PD, studies were stratified from classical PD and PPPD. Importantly, whereas no single study could be identified that included solely PPPD in the comparison of Iso-Roux-En-Y against s-Child, meta-analysis comparing the effect of BE-Child vs. s-Child on mortality, postoperative complications, POPF, clinically relevant POPF, DGE, and clinically relevant DGE were performed including subgroup analysis depending on studies included patients with PD or PPPD or PD+PPPD. Here, no effect of BE on mortality could be observed in patients undergoing classical PD (RR 0.76, 95%-CI 0.30–1.91; $p = 0.56$, $I^2 = 0\%$) whereas no calculation of RR was able in the meta-analysis of PPPD (see ESM Figure 6a). The meta-analysis of postoperative complications revealed a strong decreased risk for postoperative complications after classical PD (RR 0.73, 95%-CI 0.62–0.86; $p = 0.0002$, $I^2 = 0\%$) whereas no effect was detectable in the subgroup analysis of patients undergoing PPPD (RR 1.05, 95%-CI 0.74–1.48; $p = 0.78$, $I^2 =$ na) (see ESM Figure 6b).

Accordingly, BE did not seem to affect the incidence of all kind of POPF in patients undergoing classical PD (RR 1.27,

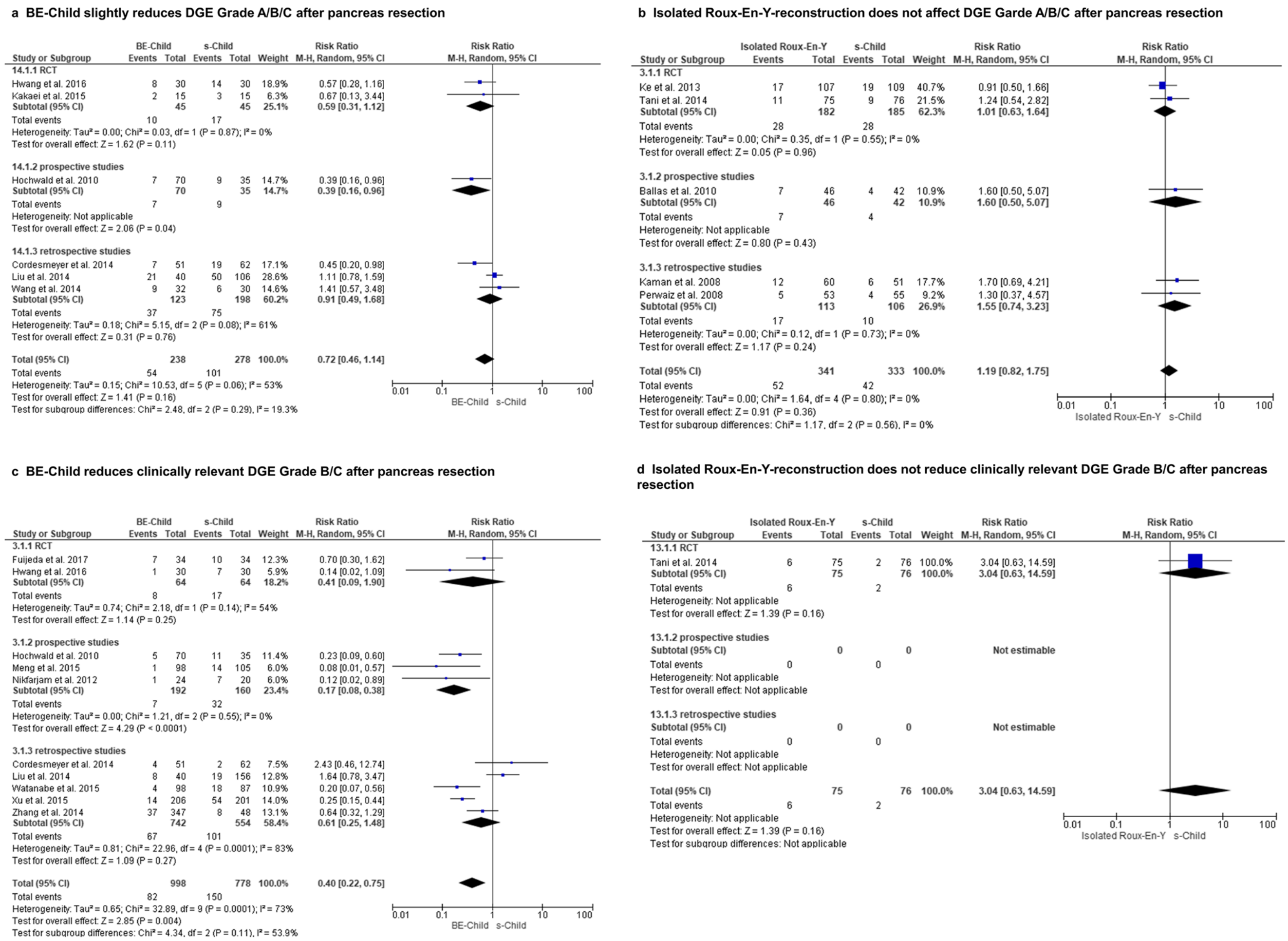


**Fig. 5** The impact of BE-Child or Iso-Roux-En-Y vs. s-Child on DGE after pancreatic head resection. Risk ratio for DGE between BE-Child (**a**) or Iso-Roux-En-Y (**b**) vs. s-Child after pancreatic head resection. Data of clinically relevant DGE according to ISGPS were summarized in (**c**) for BE-Child vs. s-Child and (**d**) for Iso-Roux-En-Y vs. Child. Meta-analysis were performed using the Mantel–Haenszel random effects models and subgroups were introduced depending on the study design. DGE delayed gastric emptying; ISPGS International Study Group for Pancreatic Surgery; M-H Mantel–Haenszel model; CI confidence interval; RCT randomized controlled trial

95%-CI 072–2.25; $p = 0.41$, $I^2 = 0\%$) or PPPD (RR 0.59, 95%-CI 0.23–1.52; $p = 0.28$, $I^2 = 0\%$) (see ESM Figure 7a). In contrast, no effect of BE was detectable for clinically relevant POPF in patients undergoing PPPD (RR 0.83, 95%-CI 0.54–1.28; $p = 0.40$, $I^2 = 0\%$), whereas patients after classical PD and an additional BE showed a strong diminished risk for clinically relevant POPF (RR 0.30, 95%-CI 0.19–0.48; $p < 0.00001$, $I^2 = 0\%$) (see ESM Figure7b). Whereas no effect was visible for all kind of DGE (classical PD: RR 0.73, 95%-CI 0.41–1.28; $p = 0.27$, $I^2 = 49\%$; PPPD: RR 0.57, 95%-CI 0.28–1.16; $p = 0.12$, $I^2 =$ na%) (see ESM Figure 7c), the subgroup analysis of clinically relevant DGE B/C revealed a strongly reduced risk in patients undergoing classical PD (RR: 0.27, 95%-CI 0.12–0.64; $p = 0.003$, $I^2 = 62\%$) and PPPD (RR 0.32, 95%-CI 0.11–0.93; $p = 0.04$, $I^2 = 57\%$) (see. ESM Figure 7d).

However, no effect could be observed of Iso-Roux-En-Y in patients with PD and PPPD for mortality (PD: RR 1.04, 95%-CI 0.15–7.10; $p = 0.97$, $I^2 =$ na; PPPD: RR 1.03, 95%-CI 0.93–2.77; $p = 0.94$, $I^2 = 0\%$) and for postoperative complications (PD: RR 0.98, 95%-CI 0.79–1.22; $p = 0.83$, $I^2 = 0\%$; PPPD: RR 1.13, 95%-CI 0.81–1.57; $p = 0.46$, $I^2 = 0\%$) (see ESM Figure 8a–b). Moreover, also no relevant differences was were detectable in the sensitivity analysis of POPF (PD: RR 0.94, 95%-CI 0.67–1.33; $p = 0.74$, $I^2 = 0\%$; PPPD: RR 0.92, 95%-CI 0.67–1.27; $p = 0.61$, $I^2 = 0\%$), clinically relevant POPF according to ISGPS (PD: RR 1.11, 95%-CI 0.50–2.47; $p = 0.79$, $I^2 =$ na), DGE (PD: RR 1.05, 95%-CI 0.67–1.64; $p = 0.84$, $I^2 = 0\%$; PPPD: RR 1.68, 95%-CI 0.81–3.39; $p = 0.16$, $I^2 = 0\%$) and clinically relevant DGE according to ISGPS (PD: RR 3.04, 95%-CI 0.63–14.59; $p = 0.16$, $I^2 =$ na; PPPD: RR 1.11, 95%-CI 0.47–2.63; $p = 0.81$, $I^2 = 13\%$) (see ESM Figure 9a–d).

**Table 3** Meta-Analysis comparing the effect of BE-Child or Iso-Roux-En-Y vs. s-Child on hemorrhage, surgical site infection/SSI, pulmonary complication, perioperative blood loss, length of operation and length of hospital stay/LOH

| | | Total HR: | Total $I^2$ | Studies |
|---|---|---|---|---|
| Hemorrhage | Iso-Roux-En-Y vs. s-Child | RR: 1.79, 95%-CI: 0.72-4.44, p=0.21 | 0% | n=4 [49–52] |
| | BE-Child vs. s-Child | RR: 1.17, 95%-CI: 0.69-1.97, p=0.56 | 0% | n=8 [26, 30, 39, 40, 44–47] |
| SSI | Iso-Roux-En-Y vs. s-Child | RR: 0.89, 95%-CI: 0.56-1.41, p=0.61 | 0% | n=4 [48–50, 52] |
| | BE-Child vs. s-Child | RR: 0.97, 95%-CI: 0.67-1.42, p=0.89 | 0% | n=8 [25, 26, 30, 39, 40, 44, 45, 47] |
| Pulmonary Complications | Iso-Roux-En-Y vs. s-Child | RR: 1.18, 95%-CI: 0.69-2.02, p=0.55 | 0% | n=4 [48–51] |
| | BE-Child vs. s-Child | RR: 1.00, 95%-CI: 0.45-2.23, p=0.85 | 45% | n=6 [25, 30, 39, 40, 45, 47] |
| Bile leaks | Iso-Roux-En-Y vs. s-Child | RR: 1.24, 95%-CI: 0.41-3.78, p=0.70 | 11% | n=3 [48, 49, 51] |
| | BE-Child vs. s-Child | RR: 0.52, 95%-CI: 0.31-0.88, *p=0.01* | 0% | n=9 [25, 26, 30, 39, 41, 44–47] |
| Blood loss | Iso-Roux-En-Y vs. s-Child | Mean Difference:-30.99, 95%-CI: -55.74--6.23, *p=0.01* | 0% | n=3 [48, 49, 51] |
| | BE-Child vs. s-Child | Mean Difference: 0.29, 95%-CI: -0.02-0.61, p=0.06 | 78% | n=6 [26, 30, 39, 44, 46, 47] |
| Hospital stay | Iso-Roux-En-Y vs. s-Child | Mean Difference: -0.38, 95%-CI: -1.69-0.94, p=0.58 | 56% | n=5 [48, 49, 51–52] |
| | BE-Child vs. s-Child | Mean Difference: -1.37, 95%-CI: -2.77-0.03, *p=0.05* | 0% | n=4 [26, 39, 44, 46] |
| Operation time | Iso-Roux-En-Y vs. s-Child | Mean Difference: 29.17 95%-CI: -7.45-65.80, p=0.12 | 88% | n=5 [48–52] |
| | BE-Child vs. s-Child | Mean Difference: 17.72 95%-CI: 8.27-3.66, *p=0.0002* | 0% | n=5 [26, 30, 39, 44, 46] |

Additional meta-analyses were conducted to assess the impact of BE-Child and Iso-Roux-En-Y against s-Child on postoperative outcome. BE-Child was associated with a decreased risk for bile leaks a shortened length of hospital stay but an increased operation time compared to s-Child. In contrast, Iso-Roux-En-Y was only associated with a slight decrease blood loss and does not seem to affect the postoperative outcome of patients in a clinical relevant way

Statistically relevant p-value are in italic

*BE-Child*, Child reconstruction with an additional Braun enteroenterostomy; *Iso-Roux-En-Y*, Reconstruction with an isolated pancreaticojejunostomy according to Roux-En-Y; *vs.*, versus; *LOH*, length of hospital stay; *RR*, risk ratio; *95%-CI*, 95%-confidence-interval

## Quality assessment and investigation of publication bias

In this systematic review, only 2 of 18 studies had a "serious" risk of bias, whereas none of the studies harbored critical risk of bias according to ROBINS-I criteria. Importantly, the majority of included studies provided an adequate and detailed definition of their surgical procedure, which is reflected by the low risk of the interventional bias. Moreover, the equal definition of POPF and DGE according to the ISGPS [31, 32] used in our systematic review contributes to an overall low risk of bias of measurement of outcome and reported results (see ESM Table 1).

Yet, only the meta-analysis of postoperative mortality and of clinically relevant DGE of BE-Child vs. s-Child included sufficient studies for the assessment of publication bias. Here, Funnel plots showed an equal distribution of the included studies, which was confirmed by the Eggers' test of the meta-analysis of mortality (see ESM Figure 10a, $p = 0.6905$) and of clinically relevant DGE (see ESM Figure 10b, $p = 0.572$). Thus, there were no relevant publication bias in the meta-analysis.

## Discussion

This is the first systematic review with meta-analysis comparing the effect of BE-Child vs. s-Child including data of prospective, retrospective and randomized controlled studies. BE-Child seem to be the safest procedure compared to Iso-Roux-En-Y vs. s-Child, regarding decreased overall postoperative complications, risk for clinically relevant POPF, clinically relevant DGE and bile leaks.

Beside BE-Child, serval surgical techniques were introduced to reduce the incidence of DGE and POPF. However, whereas classical PD seems to exhibit a decreased incidence of DGE compared to PPPD [53], neither the type of pancreatic anastomosis, i.e., pancreaticogastrostomy/PG vs. PJ [54], or the route of the GJ (antecolic vs. retrocolic) seem to influence the occurrence of DGE in patients undergoing PD [55]. Moreover, Hackert et al. compared the postoperative outcome of patients undergoing PPPD vs. pylorus resecting PPPD [56]. Importantly, no difference on postoperative mortality, DGE and POPF could be observed [56]. In line with these studies, routinely, surgically placed intraperitoneal drains [57, 58], pancreatic duct stents [59], type of anastomosis (invagination vs. duct-to-mucosa pancreaticojejunostomy) [60], and somatostatin analogues [61] were on spotlight of current research to minimize the risk for postoperative adverse events after pancreatic resection. Of these, only somatostatin analogues could be associated with a reduction of clinically relevant POPF which should be critically considered as most RCT analyzing the impact of somatostatin analogues after pancreas resection included patients undergoing PD and distal pancreatectomy in the same study population [61]. In contrast, no clear consensus could be reached regarding the installation of prophylactic, intraperitoneal drains [57, 58], pancreatic duct stents [59], and type of anastomosis [60]. Importantly, no relevant differences in patient characteristics, operative data, and histological diagnosis (which might bias study results) could be observed in our current meta-analysis. Moreover, the majority of sensitivity analysis confirmed the possible protective effect of an additional BE—especially for clinically relevant DGE and POPF—although one should mention that the power of sensitivity analysis were crucially affected by a decreased amount of included studies. Nevertheless, in contrast with the other mentioned surgical modifications, solely the additional BE after child reconstruction seems to reduce the incidence of DGE, which was even more present for clinically relevant DGE grade B/C and clinically relevant POPF grade B/C after pancreatic head resection in our current meta-analysis. Therefore, we decided to include a paragraph on the clinically impactful risk factors in our manuscript.

The reason for this decreased risk of DGE and POPF after BE-Child may be due to eased outflow of pancreatic and biliary juice and prevention of the stasis of these gastrointestinal juices, providing a physical relief for the PJ and HJ and with this less pressure on the jejunal loop and subsequently on the anastomoses. In this context, Hochwald et al. were the first authors who compared the clinical outcome of patients after PD with BE-Child vs. s-Child [25]. In accordance with our meta-analysis, this study showed a decreased risk for developing clinically relevant DGE in patients with BE ($p = 0.003$) and a decreased median length of hospital stay ($p < 0.05$). Besides, BE was associated with a decreased time to tolerate oral liquids ($p = 0.01$) and solid diets ($p = 0.01$). Importantly, by dual radionuclide simultaneous biliary and gastric scintigraphy on postoperative day 7, the authors showed that patients after PD with BE-Child had a median bile reflux of 0% and a diminished incidence of clinically relevant DGE (BE-Child: $N = 2/7\%$ vs. Child: $n = 11/31\%$; $p = 0.003$) [25]. These findings were underlined by Wang et al. in 2013 who reported that alkaline reflux gastritis and marginal ulcers were less present in patients after PD and BE-Child compared to patients with s-Child [44]. Although no effect was detectable on DGE in general, patients with BE-Child displayed a decreased incidence of overall postoperative complications after PD (BE-Child: $n = 6/24.1\%$ vs. s-Child: $n = 12/50\%$, $p = 0.025$). Taken these findings into account, one could assume that alkaline bile reflux might play an essential role for the development of DGE in patients after PD.

Besides bile reflux, one well-known risk factor for the development of DGE is clinically relevant POPF [43]. In the presence of clinically relevant POPF, patients showed a nearly fivefold increased risk for DGE compared to patients without clinically relevant POPF (OR 4.718, 95%-CI 1.664–13.381). Accordingly, the current meta-analysis showed that the presence of BE not even decreases the incidence of clinically relevant POPF (BE-Child: $n = 53/9.8\%$ vs. s-Child: $n = 107/19.9\%$) but also of clinically relevant DGE (BE-Child $n = 82/8.2\%$ vs. s-Child: $n = 150/19.2\%$). Our current systematic review could identify three RCTs comparing the effect of BE-Child vs. s-Child [26, 29, 30]. Of these, only two RCTs [26, 29] with a total amount of 64 patients (min. 30, max. 34) per study arm could be included in our sensitivity analysis of the impact of BE-Child vs. s-Child on clinically relevant POPF (RR 0.83, 95%-CI 0.40–1.73; $p = 0.62$) and DGE (RR 0.41, 95%-CI 0.09–1.90; $p = 0.25$) after PPPD. Besides, especially the results of the RCT of Hwang et al. should be critically interpreted as their reported incidence of clinically relevant POPF (BE-Child: $n = 2/6\%$ vs. s-Child: $n = 1/3\%$) were extremely low in both arms. Therefore, this low number of participants in both RCTs not only limits the power of the included RCTs but also of our current meta-analysis as this low number of patients did not seem appropriate to allow any founded statement on the impact of an additional BE after PPPD on POPF but also on DGE. In addition, no single multivariate analysis could be identified that analyzed BE as an independent factor for POPF in patients after PPPD. Thus, the answer for the question of the true impact of BE-Child vs. s-Child after Whipple's procedure remains unclear and more RCTs with an adequate number of patients are urgently needed to address this topic. Moreover, the low number of patients within the study makes it impossible to stratify patients in subgroups according to the PPPD or classical Whipple's procedure. After introducing subgroups, 2 studies with 128 patients and 1 study with 60 patients could be included in the meta-analysis on mortality and postoperative complications, respectively. These low numbers of patients were not sufficient to allow any statement on the impact of BE after PPPD underlying the need for a well-designed RCT.

Some limitation and deficits of the present study need to be underlined: one major limitation of the systematic review was the varying definitions of DGE in the different studies, especially in studies comparing the postoperative outcome between Iso-Roux-En-Y and s-Child. Here, one study could be included in the meta-analysis for clinically relevant DGE according to ISGPS. Another limitation is caused that the majority of patients within the different meta-analysis were extracted from retrospective studies. This low number of patients included by the RCT harbors the risk that study effect could be seriously affected by bias of the retrospective analysis.

## Conclusion

Our current meta-analysis revealed a potential beneficial effect of BE-Child after PD for reducing postoperative complications and protecting patients against clinically relevant DGE and POPF. Moreover, our systematic review noticed that the 3 RCT comparing BE-Child and s-Child exhibited low power (low number of patients) for detecting clinically relevant DGE and POPF. Here, more RCTs with an adequate sample size are needed to underline the findings of our present study.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflicts of interest.

**Ethical approval** For this type of study, formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.



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