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**Critical appraisal of the techniques of pancreatic anastomosis following
pancreaticoduodenectomy: a network meta-analysis**

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ABSTRACT

Background

Postoperative pancreatic fistula (POPF) remains a major cause of morbidity following pancreaticoduodenectomy (PD). This network meta-analysis (NMA) compared techniques of pancreatic anastomosis following PD to determine the technique with the best outcome profile.

Methods

A systematic literature search was performed on the Scopus, EMBASE, Medline and Cochrane databases to identify RCTs employing the international study group of pancreatic fistula (ISGPF) definition of POPF. The primary outcome was clinically relevant POPF.

Results

Five techniques of pancreatic anastomosis following PD were directly compared in 15 RCTs comprising 2428 patients. Panreatojejunostomy (PJ) end-to-side invagination vs. PJ end-to-side duct-to-mucosa was the most frequent comparison (n=7). Overall, 971 patients underwent PJ end-to-side duct-to-mucosa, 791 patients PJ end-to-side invagination, 505 patients pancreatogastrostomy (PG) end-to-side invagination, 98 patients PG end-to-side duct-to-mucosa, and 63 patients PJ end-to-side single layer. PG duct-to-mucosa was associated with the lowest rates of clinically relevant POPF, delayed gastric emptying, intra-abdominal abscess, all postoperative morbidity and postoperative mortality, the shortest operative time and postoperative hospital stay and the lowest volume of intra-operative blood loss.

Conclusion

Duct-to-mucosa pancreatogastrostomy was associated with the lowest rates of clinically relevant POPF and had the best outcome profile among all techniques of pancreatico-anastomosis following PD.

26 **Keywords**

27 Pancreaticoduodenectomy; pancreatic anastomosis; pancreaticojejunostomy;

28 pancreaticogastrostomy

29

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1.1 INTRODUCTION

Postoperative pancreatic fistula (POPF) is considered the major factor contributing to the postoperative morbidity and mortality following pancreaticoduodenectomy (PD)¹. Although several risk factors have been identified preoperatively^{2,3}, the role of the surgical technique in preventing POPF is still under investigation. Over the last several years, multiple variations of pancreatic anastomosis after PD have been described including various modifications of pancreatojejunostomy (PJ) and pancreatogastrostomy (PG)⁴. Techniques of PG reconstruction include duct-to-mucosa (DTM)⁴ and invaginating⁴ variants. Techniques of PJ reconstruction include end-to-end (E-E) invaginating^{5,6} and binding⁶, and end-to-side (E-S) single layered closure⁷, DTM and invaginating⁴.

Meta-analyses reporting PG vs. PJ comparisons are abundant in the literature where proponents have argued that PG is significantly advantageous in lowering the rate of POPF^{8,9} while others report no significant difference^{10,11}. Pairwise comparisons of PJ variations have generally been unsuccessful in identifying relative benefit of one technique over the other¹²⁻¹⁶. Previous meta-analyses also included articles prior to the development of the international study group of pancreatic fistula (ISGPF) definition of POPF resulting in difficulty comparing POPF rates¹²⁻¹⁶. In contrast to pairwise meta-analysis, a network meta-analysis (NMA) methodology allows investigators to perform simultaneous direct and indirect comparisons through Bayesian modelling, thus maintaining randomization. This NMA aimed to compare rates of POPF amongst randomised controlled trials (RCTs) evaluating the most frequently performed techniques of pancreatic anastomosis following PD in the era of ISGPF POPF grading systems.

2.1 METHODS

The review protocol is available on Prospero (ID: CRD42019132822).

2.2 Literature Search.

A systematic search of SCOPUS, Medline, EMBASE and the Cochrane databases was performed observing validated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology¹⁷ in May of 2019 (Appendix 1).

2.3 Data selection, extraction and quality assessment.

RCTs comparing techniques of pancreatic anastomosis following PD with the ISGPF definition of POPF¹⁸ were included. Exclusion criteria were: i) non-randomised datasets ii) non-PD resections, and iii) non-ISGPF definitions of POPF. Two authors independently screened the articles (CBBR and CW). Study methodology was assessed using the Cochrane risk of bias tool¹⁹.

2.4 Terminology and definitions

PD included the terms Whipple's procedure and pylorus-preserving PD. *Duct-to-mucosa pancreaticogastrostomy* (PG DTM) was a two-layered closure from the main pancreatic duct (MPD) to the stomach mucosa and an anchoring layer from the pancreatic capsule to the stomach wall⁴. *Invaginated pancreaticogastrostomy* (PG Inv) was an anastomosis between the stomach and pancreas where a portion of the pancreas was described to invaginate into the stomach lumen⁴. *Single layered end-to-side pancreaticojejunostomy* (PJ E-S SL) included the term total closure⁷ and described an anastomosis onto the side of jejunum with a single layer and a large luminal opening to accommodate the entire cut surface of the pancreas²⁰. *Invaginated end-to-side pancreaticojejunostomy* (PJ E-S Inv) was a side-on pancreaticojejunostomy anastomosis where the pancreas invaginated into the jejunal lumen and two layers of sutures were used to maintain this position⁴. *Duct-to-mucosa end-to-side pancreaticojejunostomy* (PJ E-S DTM), which included the term papillary-like PJ²¹, was a two-layered closure where the MPD was sutured onto a small luminal opening on the side of

the jejunum with seromuscular sutures from the pancreatic capsule to the jejunum⁴. If multiple variants of PG or PJ were reported in a single arm, outcomes were reported under the technique with the highest number of patients. *POPF* were defined as per the consensus definition from the International Study Group on Pancreatic Fistula (ISGPF)¹⁸. *Clinically relevant POPF* was ISGPF grade B or C¹⁸. *Delayed gastric emptying* was defined as per the International Study Group of Pancreatic Surgery (ISGPS)²². *Significant morbidity* was defined as Clavien Dindo classification grade of \geq III²³. *Reoperations* occurred when patients were operated for complications within the hospital admission. *Postoperative mortality* was the within 30-day mortality including combined mortality figures reporting *perioperative*, *within-hospital* and *30-day*.

2.5 Statistical Analysis

The *gemtc* package in R²⁴ (R Foundation for Statistical Computing, Austria 2014) was used to perform a random effects NMA employing Just Another Gibbs Sampler (JAGS) software. Odds ratios (OR) for dichotomous data and mean differences (MD) for continuous data were tabulated and summarised with their respective 95% credible intervals (CrI). The cells in the output tables provides the effect of the column-defining intervention relative to the row-defining intervention for separate pairwise comparisons within the NMA. Mean estimates were derived from Wan et al²⁵. For Network Maps, the thickness of the connecting line correlated with the number of comparisons made. The best and worst ranked techniques for each outcome category were determined by plotting rankograms with respective treatment rank probabilities, where rankings were determined by the relative effect values and P scores. The random effects standard deviation was determined to measure heterogeneity and the residual deviance was used to determine the relative effect of a single trial arm to explain the heterogeneity observed. A node splitting analysis of inconsistency was applied to determine the accuracy of indirect comparative estimates from available direct comparisons.

Comparison-adjusted funnel plots were constructed and visually inspected for publication bias. Because single layered closure was reported in a single study⁷, a sensitivity-analysis was performed following exclusion of that study for all relevant outcomes.

This work has been reported in line with PRISMA¹⁷ and AMSTAR²⁶ (Assessing the methodological quality of systematic reviews) guidelines.

3.1 RESULTS

Following the initial literature search, 2789 potentially relevant articles were identified.

Fourteen RCTs^{7,21,27-38} met the inclusion criteria and were included in the NMA. One additional RCT³⁹ was identified following a review of article references (Figure 1). These 15 RCTs^{7,21,27-39} were published between 2008 and 2018, including five techniques of pancreatic anastomosis following PD and a total of 2428 patients (Supplementary Table 1a (S1a)). All studies reported the 2005 ISGPF definition of POPF¹⁸. Table S1a provides a detailed summary of the characteristics for each article included in the review and Table S1b reports on all the extracted clinical data for the patients recruited in the study. Specific surgical experience and pancreatic function is summarized in Table S1c.

Five direct comparisons were extracted from all included articles and PJ E-S Inv vs. PJ E-S DTM was the most frequent comparison reported (Table S2a, Figure 2). Overall, 971 patients underwent PJ E-S DTM, 791 patients PJ E-S Inv, 505 patients PG E-S Inv, 98 patients PG E-S DTM and 63 patients PJ E-S SL.

3.2 Risk of Bias

A summary of the risk of bias assessment for seven domains of bias is shown in Figure S1 and S2. Two studies^{21,28} were at risk of a high allocation or selection bias resulting from the allocation of patients at the time of selection by the judgment of the surgeon intra-operatively.

3.3 Network Meta-analysis of Outcomes

3.3.1 Primary outcome measure

3.3.1.1 Clinically relevant POPF

Clinically relevant POPF was reported in 14 RCTs^{21,27-39} including 2305 patients (Table S2b) and four techniques (Figure S5). The findings of the NMA are summarized in Table S5. PG DTM was the best-ranked technique of pancreatico-anastomosis in 47% of comparisons followed by PG Inv in 38% of all comparisons (Table S3 and Figure 3). PJ E-S DTM and PJ E-S Inv ranked similarly in the network. The absolute rate of clinically relevant POPF in the two trials reporting PG DTM were 4%³⁴ and 15%³¹.

3.3.2 Secondary outcome measures

3.3.2.1 Intraoperative blood loss

Intraoperative blood loss was directly compared in 12 trials^{7,21,27,29-36,38} including 2055 patients (Table S2b) comparing five techniques (Figure S6). Table S6 summarizes the results of the NMA. Plotted rankograms show PJ E-S DTM was associated with the lowest volume of intraoperative blood loss in 26% of comparisons (Table S3) followed closely by both PG DTM and PJ E-S SL in 25% and 21% of all comparisons respectively (Figure S7). On sensitivity-analysis, PG DTM was the best-ranked technique in 41% of all comparisons (Table 1 and Figure S25A).

3.3.2.2 Operative time

Thirteen trials^{7,21,27-36,38} reported direct comparisons regarding operative time in 2171 patients (Table S2b) and five techniques (Figure S8). The results of the NMA are reported in Table S7. PJ E-S SL was associated with the shortest operative time compared to all other techniques of pancreatico-anastomosis in 83% of all comparisons (Figure S9 and Table S3). On sensitivity-analysis, PG DTM was the best-ranked technique in 90% of all comparisons (Table 1 and Figure S25B).

3.3.2.3 All POPF

Twelve RCTs^{7,21,27,29-34,36,37,39} were included in this network comprising 1872 patients for comparison (Table S2b) and five techniques (Figure S3). PJ E-S SL consistently reported the best rates compared to all other techniques (Table S4) in 79% of all comparisons (Table S3 and Figure S4). PJ E-S DTM ranked the worst ranked technique the most frequently (55% of all comparisons). On sensitivity-analysis, PG Inv was the best-ranked technique in 48% of all comparisons followed closely by PG DTM in 44% (Table 1 and Figure S25C).

3.3.2.4 Delayed gastric emptying

Twelve trials^{7,21,28-31,33-37,39} reported delayed gastric emptying for five techniques (Figure S10) including 2013 patients (Table S2b). PJ E-S SL was associated with odds ratios suggesting lower rates of DGE than all other techniques included in the analysis of this outcome (Table S8). Similarly, PJ E-S SL was the best technique of pancreatico-anastomosis for delayed gastric emptying in 60% of all comparisons (Figure S11 and Table S3). On sensitivity-analysis, PG DTM was the best-ranked technique in 48% of all comparisons (Table 1 and Figure S25D).

3.3.2.5 Intra-abdominal abscess

Rates of intra-abdominal abscesses were directly compared in six articles^{28-30,34,36,39} for four techniques (Figure S12) comprising 872 patients (Table S2b). Results of NMA are reported in Table S9. On review of constructed rankograms, PG DTM was the best technique of pancreatico-anastomosis in 83% of all comparisons (Table S3). PG Inv was ranked the worst technique in 55% of all comparisons (Figure S13).

3.3.2.6 All postoperative morbidity

All postoperative morbidity was reported in 11 articles^{7,27,29-34,36,37,39} including 1564 patients (Table S2b) and five techniques (Figure S14). The results of the NMA are reported in Table S10. PJ E-S SL consistently reported odds ratios suggesting lower rates of overall

postoperative morbidity when compared to all other techniques of pancreatic anastomosis, in 90% of all comparisons (Table S3) in plotted rankograms (Figure S15). PG Inv ranked the worst technique in 54% (Figure S15). On sensitivity-analysis, PG DTM was the best-ranked technique in 71% of all comparisons in the NMA (Table 1 and Figure S25C).

3.3.2.7 Significant postoperative morbidity

This outcome was reported infrequently, in five articles^{27,30,31,33,36} including 855 patients (Table S3 and Figure S16). The results of the NMA are reported in Table S11 and PG Inv was associated with odds ratios that trended towards lower rates of significant postoperative morbidity. PG Inv was observed as the best method of pancreatic anastomosis in 38% of all comparisons and PJ E-S Inv followed closely with 36% of all comparisons (Figure S17).

3.3.2.8 Reoperations

Ten RCTs^{21,27,28,30,31,33,34,36,37,39} reported on this outcome in 1644 patients (Table S2b) and four techniques (Figure S18). No significant odds ratios were observed on NMA of this outcome (Table S12). Constructed rankograms revealed that PJ E-S Inv performed the best in 39% of all comparisons however, all four techniques of pancreatic anastomosis performed similarly (Table S3 and Figure S19). In all the studies that reported on reoperations, none reported on specific interventions for POPF.

3.3.2.9 Postoperative hospital stay

The duration of hospital stay following PD was directly compared in fourteen RCTs^{7,21,27-37,39} (Figure S20) comprising 2308 patients (Table S2b). The findings from the NMA are summarized in Table S13. PJ E-S SL ranked the best technique of pancreatic anastomosis in 52% of all comparisons (Table S3 and Figure S21). On sensitivity-analysis, PG DTM was the best-ranked technique in 69% of all comparisons (Table 1 and Figure S25F).

3.3.2.10 Postoperative mortality

Ten studies^{7,21,27,30,32-37} reported rates of postoperative mortality in 1915 patients and five techniques (Figure S22). PJ E-S SL was consistently ranked as the best technique of pancreatic anastomosis with significantly better odds ratios in all comparisons (Table S14). Constructed rankograms also found PJ E-S SL was the best-ranked technique in 88% of all comparisons (Figure S23 and Table S3). On sensitivity-analysis, PG DTM was the best-ranked technique in 37% of all comparisons followed closely by PJ E-S Inv in 29% and PJ E-S DTM in 27% (Table 1 and Figure S25G).

All the relative odds ratios and mean differences with corresponding CrI for the sensitivity-analysis are reported in Figure S26.

3.4 Risk of heterogeneity, inconsistency and publication bias

Significant heterogeneity was demonstrated in the outcomes intraoperative blood loss, all postoperative morbidity and postoperative hospital stay (Appendix 2). Appendix 2 provides a detailed analysis of the potential contributors. Inconsistency was not found within this dataset. Publication bias was assessed through review of constructed comparison adjusted funnel plots (Figure S24). No publication bias was observed for the outcomes; all POPF, DGE, intra-abdominal abscess, all postoperative morbidity and reoperations (Figure S24 C, E, F, G and I respectively). Publication bias was observed for the remaining outcomes (Figure S24A, B, D, H, J, K).

4.1 DISCUSSION

The present NMA showed that PG DTM consistently ranked as the best technique of pancreatic anastomosis with lowest rates of clinically relevant POPF and the best outcome profile among all techniques of pancreatoco-anastomosis following PD. As PJ ES SL was

reported in a single dataset, a sensitivity-analysis was undertaken to eliminate bias. By limiting the inclusion of RCTs to those reporting ISGPF POPF grades and eliminating the potential bias associated with single dataset reporting, this NMA employed valid comparisons in a dataset reflective of current practices.

A previous NMA comparing various pancreatic stump anastomosis techniques⁴⁰ found no relative benefit between four techniques. The authors categorized interventions into PG, PJ DTM, PJ Inv and binding PJ and included articles reporting definitions of POPF beyond that of the validated ISGPF definition¹⁸, introducing significant heterogeneity into the analysis. The authors further pooled all PG variants into a single arm, ignoring the evident variability in technique between PG Inv and PG DTM. Additionally, a limited four outcomes were explored and no consideration of subgroup or sensitivity-analysis of the network by exclusion of binding PJ was made due to single study reporting. The authors reported difficulty in exploring other known risk factors for POPF including MPD diameter and octreotide use similar to the experience of this current study.

Pairwise comparisons of PG vs PJ have largely failed to form consistent conclusions regarding the better technique⁸⁻¹¹. Although proponents have argued that PG is associated with lower rates of all POPF^{8,9} historical definitions of POPF beyond the ISGPF¹⁸ were included. There also remains an abundance of meta-analyses reporting no significant differences between groups^{10,11}. Importantly, although PG DTM performed consistently well in most of the outcomes examined in this NMA, the only direct comparison was between PG DTM and PJ E-S DTM. Despite this, the findings from recent observational cohorts have further echoed the conclusions from this NMA^{41,42}. Multiple variations of the PJ anastomosis have been described⁴ but only two techniques were available for recruitment into this NMA

among the RCTs in the ISGPF era. E-E PJ was previously compared in two RCTs reporting invaginated, binding and single layered variants^{5,6} but were dated prior to the ISGPF consensus statement. Importantly, pairwise investigations have largely failed to identify any significant benefit of one PJ technique over the other¹²⁻¹⁶.

The anastomotic technique remains a known risk factor for the development of POPF following PD⁴³. The PG DTM technique is a relatively undemanding technique to perform and provides structural integrity of the anastomosis through tension free suturing and is thought to reduce the tendency for ischaemia and anastomotic breakdown³¹. The largely acidic environment in the stomach is thought to inhibit the pancreatic proteolytic breakdown of the anastomosis improving rates of leakage^{30,34,44,45}. Furthermore, unlike the PJ DTM variant, the PG DTM technique also allows for the drainage of minor ducts and reduces the dead space^{16,34}. Globally, PJ is performed in a significantly greater frequency than PG (88.7% vs .9.7%) with a particular tendency towards PJ in North America⁴⁶. This may be explained in part by the lack of North American RCTs showing the relative benefit of PG³², reflecting regional bias in adopting the results of certain trials. Further investigation into the relative efficacy of pancreatic reconstruction techniques following PD is warranted and remains an area of particular interest. Indeed, one trial comparing Cattell-Warren versus Blumgart techniques of pancreaticojejunostomy following PD (ISRCTN registry: ISRCTN52263879)⁴⁷ in the UK trial registry and aims to provide further data to clarify the ongoing debate regarding the best technique of pancreatic reconstruction. Confirmation of the observations in this NMA would encourage DTM PG in preference to other techniques in the future and potentially reduced POPF rates and thereby limit prolonged hospital admissions and healthcare costs⁴⁸.

Several limitations exist within the methodology of this review. As previously mentioned, the PG DTM was directly compared to PJ E-S DTM alone and in only two studies. However, consistency in the direct and indirect comparisons was established through node-splitting, confirming the validity of the comparative rankings. This NMA is also limited in its ability to form conclusions regarding the efficacy of stenting with each method and the authors did not explore gastro-enteric anastomotic techniques. It is important to note that there remains no evidence to support the use of routine stenting in the current literature⁴⁹. Confounding variables including cardiopulmonary exercise testing scores, types of sutures, and the specific interventions for POPF were also not controlled for. In addition, surgeons may not have personal equipoise between several pancreatic anastomosis techniques, such that they may strongly prefer one technique over another, and this may be a mechanism that influences trial outcomes⁵⁰. This mechanism has the potential to be transferred to the NMA, although the effect is not measurable. Future trials should aim to compare PG DTM with other pancreatic anastomosis techniques to confirm the findings of this NMA and investigate the long-term influence of anastomotic technique.

5.1 CONCLUSION

PG DTM is consistently ranked as the best method of pancreatic reconstruction following PD in this NMA of 15 RCTs. This technique was associated with the lowest rates of clinically relevant POPF, delayed gastric emptying, intrabdominal abscess and all postoperative morbidity, the shortest operative time and postoperative hospital stay and the lowest volume of intra-operative blood loss.

Provenance and peer review

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Table 1. Rank probability of being the best ranked technique of pancreatic anastomosis following pancreatico-duodenectomy in all direct and indirect comparison within the network meta-analysis. Results of subgroup analysis of all articles including the ISGPF definition¹⁸ of POPF. Results of a sensitivity-analysis of all techniques of pancreatic anastomosis reported in

Technique	Rank probability of coming first ranked technique of pancreatic anastomosis										
	Intraoperative blood loss	Operative time	All POPF	Clinically relevant POPF	DGE	Intraabdominal abscess	All postoperative morbidity	Significant postoperative morbidity	Reoperations	Postoperative hospital - stay	postoperative mortality
<i>PG DTM</i>	0.414*	0.897*	0.436	0.465*	0.475*	0.829*	0.714*	0.224	0.235	0.687*	0.370*
<i>PG Inv</i>	0.205	0.018	0.478*	0.384	0.314	0.023	0.083	0.375*	0.256	0.014	0.075
<i>PJ E-S DTM</i>	0.350	0.010	0.010	0.033	0.141	0.023	0.091	0.235	0.122	0.250	0.265
<i>PJ E-S Inv</i>	0.031	0.076	0.077	0.120	0.070	0.125	0.111	0.364	0.388*	0.049	0.290

more than a single dataset (by removal of Sun et al⁷).

PG Pancreatico-gastrostomy; *PJ* Pancreatico-jejunostomy; *E-S* End to side; *Inv* Invaginated

* indicates the technique of pancreatic stump management following pancreatico-duodenectomy with the highest probability of ranking first. *POPF* Postoperative pancreatic fistula; *Clinically relevant POPF* international study group of pancreatic fistula (ISGPF)¹⁸ grades B and C postoperative pancreatic fistula; ¥ as defined by a Clavien Dindo²³ complication grade of ≥ 3

Figure 1. PRISMA flow chart of literature search strategy. ¥ Trial investigators were contacted however no data was available.

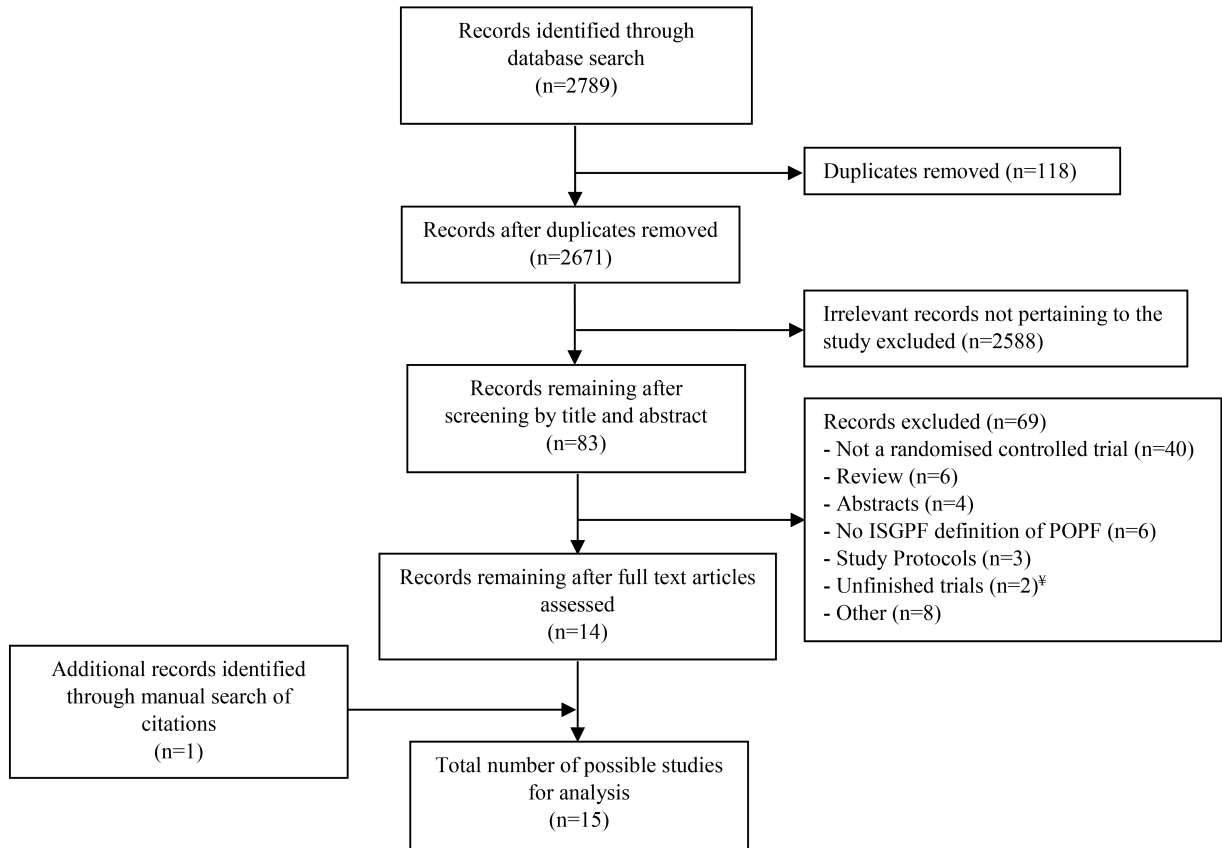
ISGPF International study group of pancreatic fistula; *POPF Postoperative pancreatic fistula*.

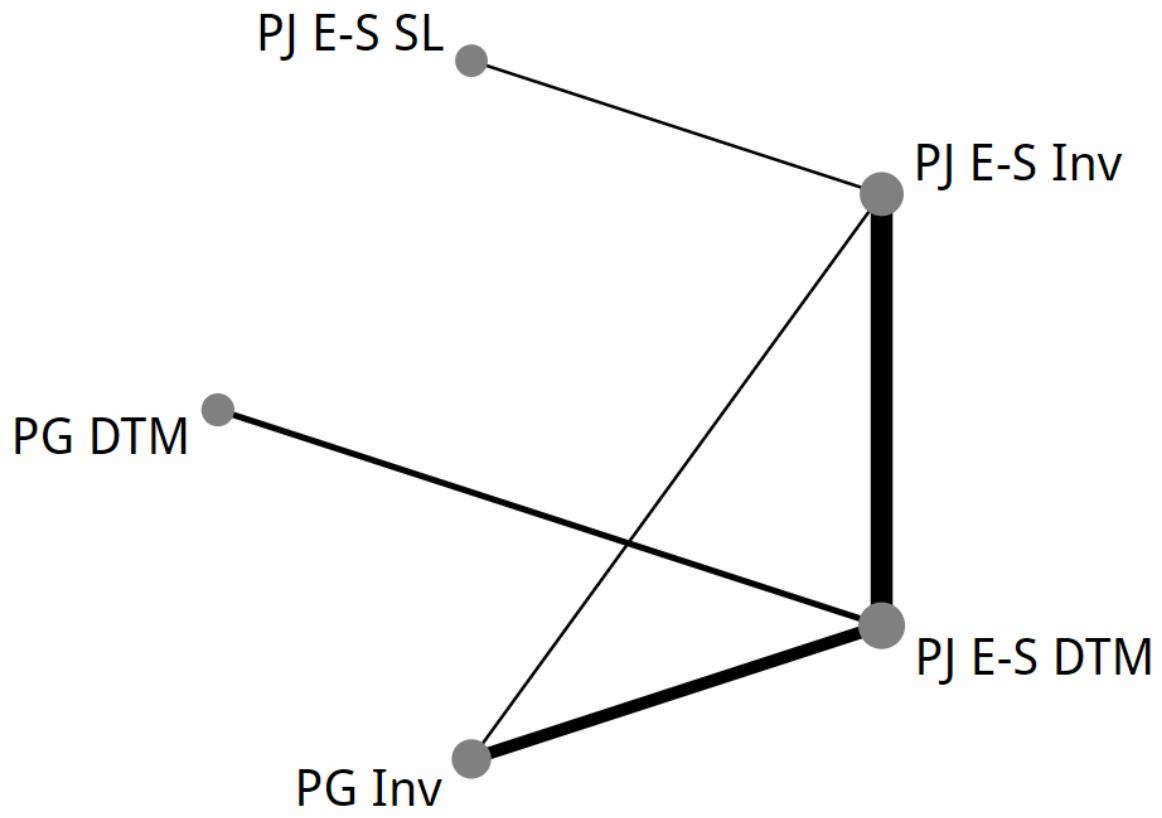
Figure 2. Network map of all direct comparisons of techniques for pancreatic anastomosis following pancreaticoduodenectomy reported by all included articles in the network meta-analysis. The thickness of the line correlates with the number of comparisons made.

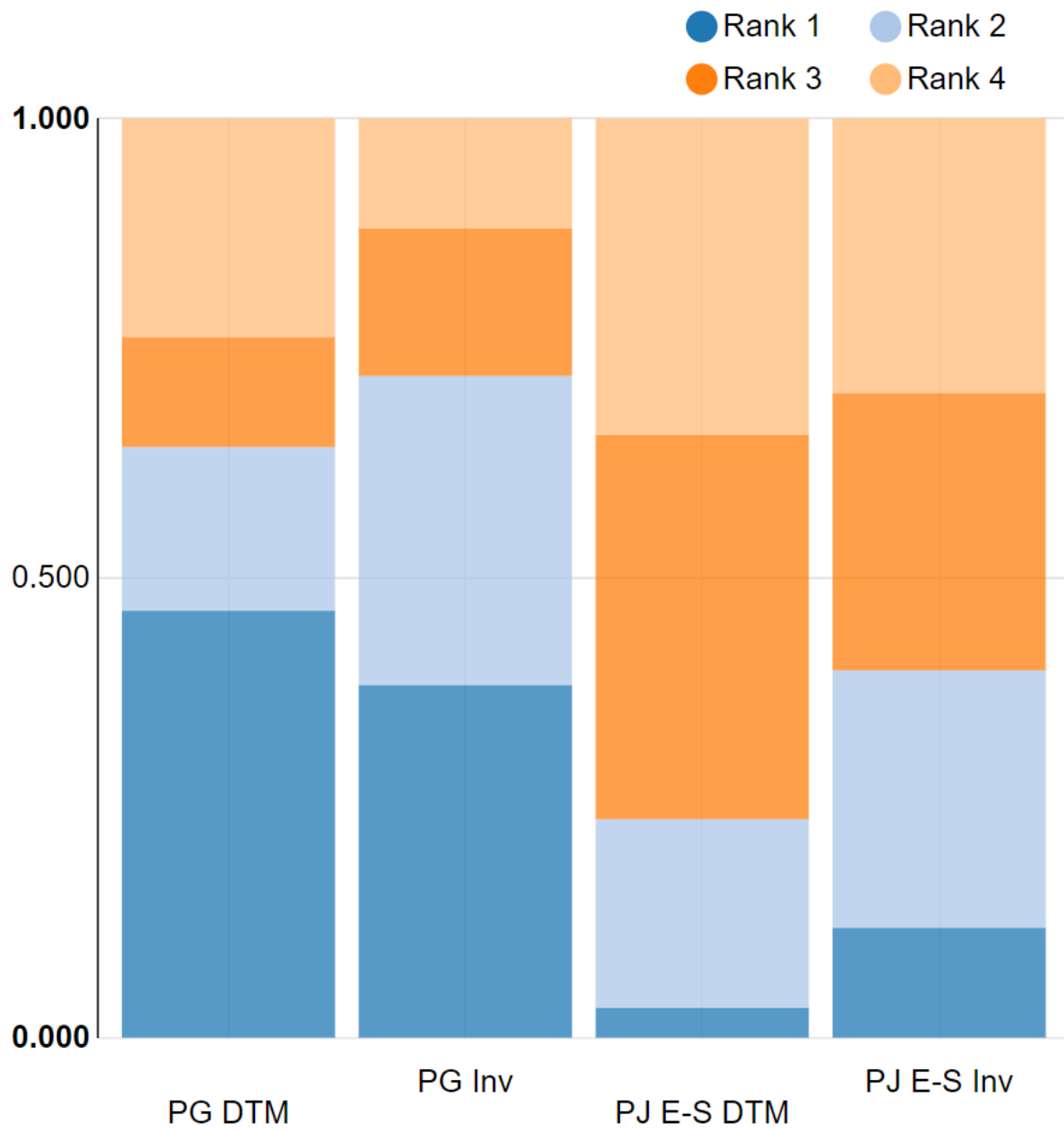
PG Pancreatico-gastrostomy; *PJ* Pancreatico-jejunostomy; *E-S* End to side; *DTM* Duct-to-Mucosa; *Inv* Invaginated; *SL* Single Layered.

Figure 3. Rankogram of clinically relevant postoperative pancreatic fistula. Rank 1 correlates with the lowest rates of clinically relevant postoperative pancreatic fistula.

PG Pancreatico-gastrostomy; *PJ* Pancreatico-jejunostomy; *E-S* End to side; *DTM* Duct-to-Mucosa; *Inv* Invaginated.







- Network meta-analysis of pancreatic anastomosis following Pancreaticoduodenectomy
- Five techniques compared in fifteen RCTs and 971 patients
- Duct-to-Mucosa Pancreaticogastrostomy was the best ranked technique overall

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

CBBR: Conception, literature search, data extraction, drafting of the manuscript
CIW: Literature search, data extraction, drafting of the manuscript
SKK: Drafting of the manuscript, critical revisions
BL: Conception, Review and critical revisions
GS: Review and critical revisions
JJF: Review and critical revisions
SW: Review and critical revisions
SP: Conception, Review and critical revisions

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

Chathura Ratnayake and Sanjay Pandanaboyana

The data has been extracted from all referenced studies for this meta-analysis.

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