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A Simple Classification of Pancreatic Duct Size and Texture Predicts Postoperative Pancreatic Fistula

A classification of the International Study Group of Pancreatic Surgery

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Objective: The aim of this study was to develop a classification system for pancreas-associated risk factors in pancreatoduodenectomy (PD).

Summary Background Data: Postoperative pancreatic fistula (POPF) is the most relevant PD-associated complication. A simple standardized surgical reporting system based on pancreas-associated risk factors is lacking.

Methods: A systematic literature search was conducted to identify studies investigating clinically relevant (CR) POPF (CR-POPF) and pancreas-associated risk factors after PD. A meta-analysis of CR-POPF rate for texture of the pancreas (soft vs not-soft) and main pancreatic duct (MPD) diameter was performed using the Mantel-Haenszel method. Based on the results, the International Study Group of Pancreatic Surgery (ISGPS) proposes the following classification: A, not-soft (hard) texture and MPD >3 mm; B, not-soft (hard) texture and MPD $\leq$3 mm; C, soft texture and MPD >3 mm; D, soft texture and MPD $\leq$ 3 mm. The classification was evaluated in a multi-institutional, international cohort.

Results: Of the 2917 articles identified, 108 studies were included in the analyses. Soft pancreatic texture was significantly associated with the development of CR-POPF [odds ratio (OR) 4.24, 95% confidence interval (CI) 3.67-4.89, $P < 0.01$) following PD. Similarly, MPD diameter $\leq$3 mm significantly increased CR-POPF risk compared with >3 mm diameter MPDs (OR 3.66, 95% CI 2.62–5.12, $P < 0.01$). The proposed 4-stage system was confirmed in an independent cohort of 5533 patients with CR-POPF rates of 3.5%, 6.2%, 16.6%, and 23.2% for type A-D, respectively ($P < 0.001$).

Conclusion: For future pancreatic surgical outcomes studies, the ISGPS recommends reporting these risk factors according to the proposed classification system for better comparability of results.

Keywords: pancreatic duct, pancreatic fistula, pancreatic texture, pancreaticoduodenectomy, pancreatoduodenectomy

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Pancreatoduodenectomy (PD) is the treatment of choice for malignant and symptomatic benign disease of the pancreatic head. It offers the only potential curative option for patients with pancreatic ductal adenocarcinoma (PDAC), distal bile duct cancer, or pancreatic neuroendocrine tumors. In addition, it is the treatment of choice for a range of premalignant and benign lesions such as intraductal papillary mucinous neoplasms and chronic pancreatitis.[1]

Although surgery-associated mortality after PD has decreased in specialized centers, postoperative complications are frequent and affect up to 50% of patients.[2–4] The benchmark from the International Study Group of Pancreatic Surgery (ISGPS) Evidence Map of Pancreatic Surgery[5] shows a postoperative mortality rate of 1% [99% confidence interval (CI) 0.01–0.02) in 155 randomized controlled trials (RCTs) and a clinically relevant postoperative pancreatic fistula (CR-POPF)[6,7] rate of 15% (99% CI 0.12-0.18) in 76 RCT after PD.[5]

Multiple risk factors have been identified that are associated with CR-POPF development following PD.[8] These include: *patient-associated* risk factors such as body mass index (BMI)[9] and sex[10]; *perioperative risk* factors such as volume management,[11] neoadjuvant chemotherapy,[12] and preoperative total bilirubin levels,[10];and*sur-geon-associated* risk factors such as experience in PD, anastomotic technique, frequency of pancreatic surgery, and blood loss.[13–16] Furthermore, several *pancreas-associated* risk factors have been proposed in the literature, including histology,[12] the localization,[17] and diameter of the main pancreatic duct (MPD),[9,11,18] and soft pancreatic texture.[3,19]

These factors have been combined in numerous risk scores to calculate the individual CR-POPF risk for a specific patient.[9,20–22] However, there is no uniform reporting classification enhancing the comparability of study results in pancreatic surgery. Therefore, the aims of this systematic review were to evaluate pancreatic texture and MPD diameter as the most prominent pancreas-specific risk factors for CR-POPF after PD, to develop a simple classification for reporting the pancreas-specific risk in future studies, and to validate this classification in a large cohort.

METHODS

This systematic review was reported according to the PRISMA guidelines[23] (PRISMA checklist: Supplement 1, http://links.lww.com/SLA/D34). The resources and facilities of the Department of General, Visceral and Transplantation Surgery at the University Hospital of Heidelberg, the Study Center of the German Surgical Society and the 17-center, multinational Pancreas Fistula Study Group (PFSG) database were used to conduct this study.

Systematic Literature Search and Information Sources

The databases Medline (via PubMed), Web of Science, and Cochrane Central Register of controlled trials (CENTRAL) were searched[24] between 2006 and November 2020 without restriction of publication language. A combination of medical subject headings and free text words combined by Boolean connectors was used. An additional hand search of relevant articles was performed. According to the PICO scheme, search terms describing the following two population (P) characteristics were chosen: search terms for pancreatoduodenectomies and search terms for MPD size and pancreatic texture. The full search terms for Medline (via PubMed) were:

(pancreas[MeSH Terms] OR pancreas[tiab] OR pancreatic [-tiab]) AND (surgery[tiab] OR surgeries[tiab] OR surgical [tiab] OR removal[tiab] OR operation [tiab] OR resection* [tiab] OR laparos-cop*[tiab] OR "surgical procedures, operative"[MeSH Terms] OR "general surgery"[MeSH Terms]) OR pancreaticoduodenec-tom*[tiab] OR pancreatoduodenectom*[tiab] OR duodenopancrea-tectom*[tiab] OR Whipple[tiab] OR ppWhipple[tiab] OR Kausch-Whipple [tiab] OR PPPD[tiab] OR "pancreatic head resection"[tiab] OR pancreatectom*[tiab] OR "pancreatic resection"[tiab] ORpan-creaticoduodenectomy [MeSH Terms] OR pancreatectomy[MeSH Terms] OR "duodenum-preserving pancreatic head resection"[tiab] OR dpphr [tiab] OR "pancreatic enucleation"[tiab]

AND

((pancreas[tiab] OR pancreatic[tiab]) AND (duct[tiab] OR ducts[tiab]) AND (size[tiab] OR diameter*[tiab])) OR "small pancreatic duct" [tiab] OR "large pancreatic duct"[tiab]

OR ((pancreas[tiab] ORpancreatic[tiab]) AND texture* [tiab]) OR (("Pancreatic Ducts/diagnosis"[Mesh] OR "Pancreatic Ducts/diagnostic imaging"[Mesh]) AND (size[tiab] OR textur-e*[tiab]))

OR"soft *pancreatic parenchyma"* [tiab] OR "soft pancreas [tiab]

NOT (animals [mh] NOT humans [mh])

Study Selection

All studies providing data on the association of POPF with either pancreatic texture or MPD after PD were eligible, irrespective of disease. Only studies that used the ISGPS

definition of POPF were included. Studies lacking the above-mentioned information, animal studies, and studies reporting or investigating conservative procedures or the placement of interventional drains without surgical resection of the pancreas were excluded, as were studies published before 2006, the time of the first ISGPS POPF definition. This last limitation was chosen because of the multiplicity of adjustments of definitions, therapeutic approaches, and types of surgical interventions reported in earlier publications. Furthermore, all letters, titles without abstract, and case reports, and study protocols were excluded.

All included studies were screened and extracted by two reviewers independently (F.S., P.P.). Differences that could not be resolved were discussed with a third reviewer (A.L.M.).

Data Extraction

The data extracted were: author, year of publication, the primary investigated organ characteristics (texture yes/no, MPD yes/no, texture radiologically measured, texture measured by durom-eter), other primary investigated risk factors for POPF (somatostatin administration, enzymes, different anastomosis, drains), MPD cutoff to differentiate between a narrow and a wide duct (in millimeters), classification of gland texture (soft, hard, firm, friable, and others), sample size, number of POPF in risk and non-risk populations (small duct or soft gland), surgical procedure (PD—resection/preservation of pylorus, different techniques of anastomosis), conclusions of trial, number of grade A/B/C fistulas according to original ISGPS defini-tion,[6] and biochemical leak and B/C POPF (CR-POPF) according to the updated ISGPS definition.[7]

Risk of Bias

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2).[25] Four domains were assessed: patient selection, index parameter, reference parameter, and flow and timing. For "patient selection, the focus was to investigate whether a consecutive or random

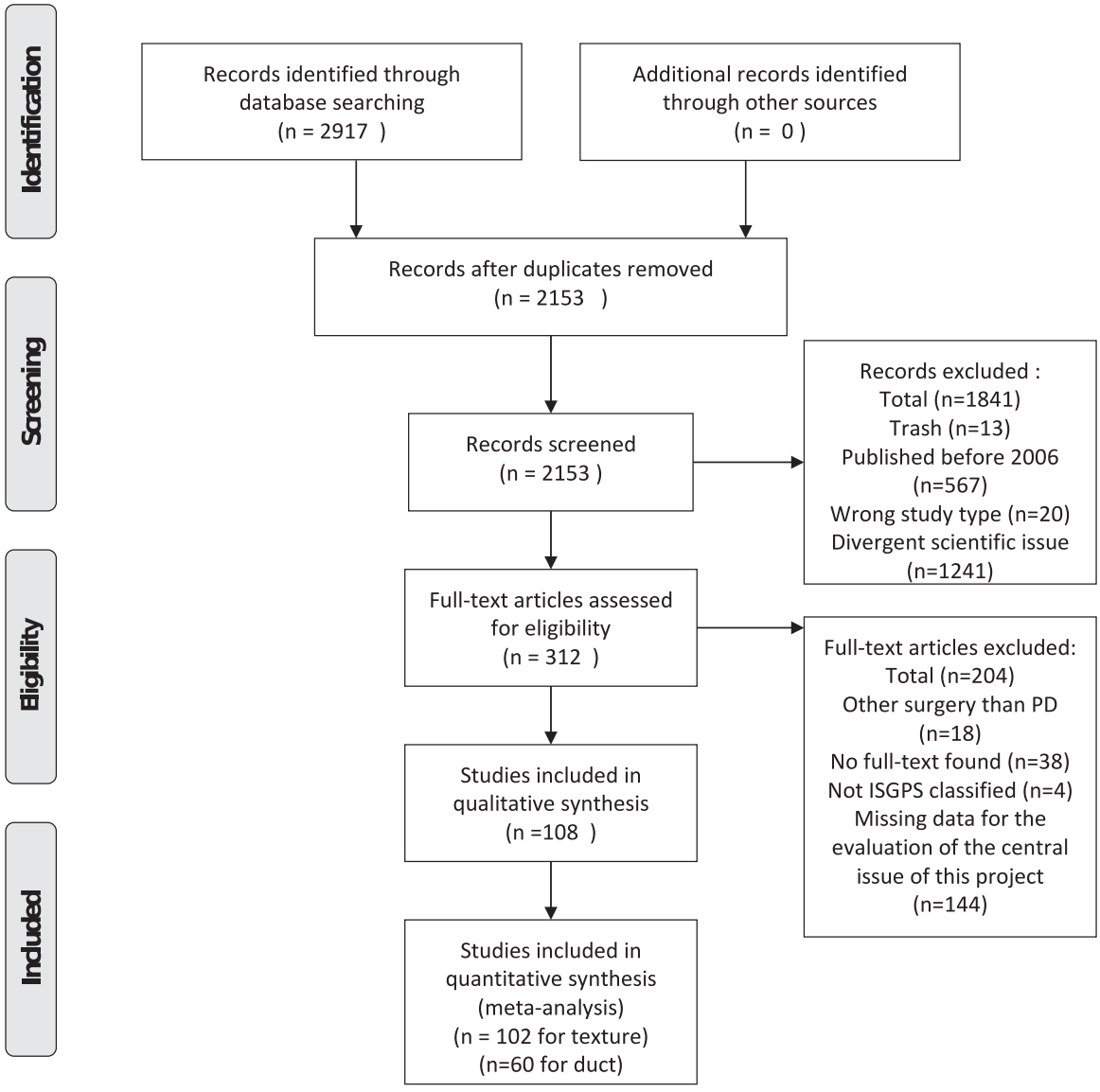

FIGURE 1. PRISMA flow chart.

population was investigated. If the selection process was not random or if there were major differences concerning the surgical procedure and/or the preoperative treatments, the risk of bias was high. The domain "index parameter" concerned the influence of individual pancreatic characteristics such as pancreatic gland texture and MPD diameter on the rate of CR-POPF. Texture had to be reported as soft and not-soft/hard. The diameter of the MPD had to be given in millimeters. A study that fulfilled all these conditions was classified as having a low risk of bias. The domain "reference parameter covered the influence of well-known con-founders on the rate of CR-POPF. At least, the texture of the pancreatic gland, the diameter of the MPD, and the BMI[9] had to be recorded and evaluated for a study to be classified as having a low risk of bias. Differences in the perioperative therapy, such as (neoadjuvant therapy, within the study population were also recorded as a high risk of bias. In the domain "flow and timing," nonprospective study design and missing data were defined as high risk of bias.

The risk of publication bias was assessed by means of funnel plots for the association of the parenchymal characteristics (texture and MPD) with CR-POPF with/without biochemical leaks.

The Proposed Classification and Its Validation

The results of the systematic reviews were discussed by the members of the ISGPS on February 6, 2020 at the third World Pancreas Forum in Bern. Based on the odds ratios (ORs) of the meta-analyses the following classification system for MPD size andtexture was developed, where the category "not-soft" comprises any pancreatic texture (eg, hard, firm, sclerotic) other than soft, whereas "soft" also includes "friable" and "brittle" tissue (Fig. 1). Based on the results from the included studies, texture and MDP should be measured intraoperatively by the surgeon (see details in the Results section and Discussion).

Type A: not-soft pancreatic texture	*AND main pancreatic duct size* $>3mm$
Type B: not-soft pancreatic texture	*AND main pancreatic duct size* $\leq 3mm$
Type C: soft pancreatic texture	*AND main pancreatic duct size* $> 3mm$
Type D: soft pancreatic texture	*AND main pancreatic duct size* $\leq 3mm$

Thereafter, this classification was validated using the PFSG database, which includes 5533 pancreatoduodenectomies carried out between 2004 and 2019. Finally, the proposal was approved by all ISPGS members, whereupon the manuscript was prepared and peer-reviewed internally to establish the classification.

Statistics

Statistical analysis was performed with the program R.[26] The comparison of low- and high-risk factors was reported as OR with 95% CIs. The studies were pooled using the Mantel-Haenszel method with a random-effects model. A P value <0.05 was considered to show a statistically significant difference. Forest plots were created for graphic presentation of the results. To assess a potential publication bias, funnel plots were created to investigate the presence of graphical asymmetry.

The main analysis included CR-POPF (ISGPS grade B/C) only. Additionally, a sensitivity analysis including also grade A fistula or biochemical leaks was conducted. Furthermore, subgroup analyses were performed for different definitions of pancreatic texture and different cut-offs for MPD diameter.

RESULTS

Literature Search Results

The systematic literature search identified 2153 articles, of which 1841 were excluded because of a publication date before the first ISGPS definition of POPF, inappropriate study type, or divergent research questions. The full texts of the remaining 312 articles were screened, and finally 108 studies were included in the qualitative analysis. For texture 102 studies and for duct size 60 studies were included in the quantitative analysis (Fig. 2). Details of the studies included can be found in supplement 2, http://links.lww.com/SLA/D35.

Association of Texture and POPF

A total of 66 studies[9–12,18,20,27–86] with 25,599 patients investigated the association of soft pancreatic texture and CR-POPF development. The classifications used to grade pancreatic texture differed among the studies. The most frequent classification was description of the pancreatic gland as soft versus hard based on the impression of the operating surgeon. Other terms used were "firm," "friable," "sclerotic," "medium," and "intermediate." Because of this discrepancy, differentiation between soft and not-soft was chosen for use in this systematic review and meta-analysis. Soft also includes "friable" and "brittle" tissue. "Not-soft" comprises any pancreatic texture (eg, hard, firm, sclerotic) other than soft. Soft texture was significantly associated with CR-POPF (B/C) (OR 4.24, 95% CI 3.67–4.89, $P < 0.01$ (Fig. 3).

The sensitivity analysis including also biochemical leaks showed similar results in 102 studies[9–12,18,20,27–122] for 37,259 patients with an OR of 4.28 (95% CI: 3.84–4.78, $P < 0.01$).

Association of MPD Size and POPF

A total of 37 studies[10,11,28–30,33,34,37,39,44,45,48–53,55,58–64,72,74,75,77,81,83,87,87,123–125] with 14,471 patients investigated MPD diameter as a risk factor for CR-POPF, applying different cut-offs. Irrespective of the cut-off, duct diameter was associated with CR-POPF (OR 3.14, 95% CI 2.53–3.90, $P < 0.01$) (Fig. 4). Similar results were obtained if only studies were included that used intraoperative measurements of the MPD (29 studies; OR 3.25; 95% CI 2.52–4.17, $P < 0.01$)

A sensitivity analysis including also biochemical leaks showed similar results irrespective of the chosen cut-off with an OR of 3.14 (95%CI 2.73–3.61, $P < 0.01$). The 60 studies ana-lyzed[10,11,28–30,33,34,37,39,44,45,47–55,58–64,69,72,74,75,77,81,83,87–103,120,121,123–128] included 23,932 patients. Again, results were comparable when including only the 49 studies that assessed the MPD intraoperatively (OR 3.21, 95% CI 2.70–3.81, $P < 0.01$) The studies included for analysis used different cutoff values for MPD diameter. Twelve studies[10,44,55,59,63,72,75,77,81,83,123,124] including 4660 patients classified MPD diameter of $\leq$ 3mm as a high risk for CR-POPF development (OR 2.99, *95%* CI 2.17–4.13, $P < 0.01$). Another 20 studies[11,29,30,33,37,39,44,45,48–51,58,61,62,64,74,79,87,125] with 9067 patients used MPD diameter of $\leq$3 mm as the high-risk cut-off, although the results were comparable (OR 3.66, 95% CI 2.62–5.12, $P < 0.01$).

One study used an MPD cut-off of exactly ≤ 5 mm,[34] without a significant association with CR-POPF (176 patients; OR 1.01, 95% CI 0.45–2.29, $P = 0.97$), whereas another study chose to classify glands with MPD diameter <5 mm as high

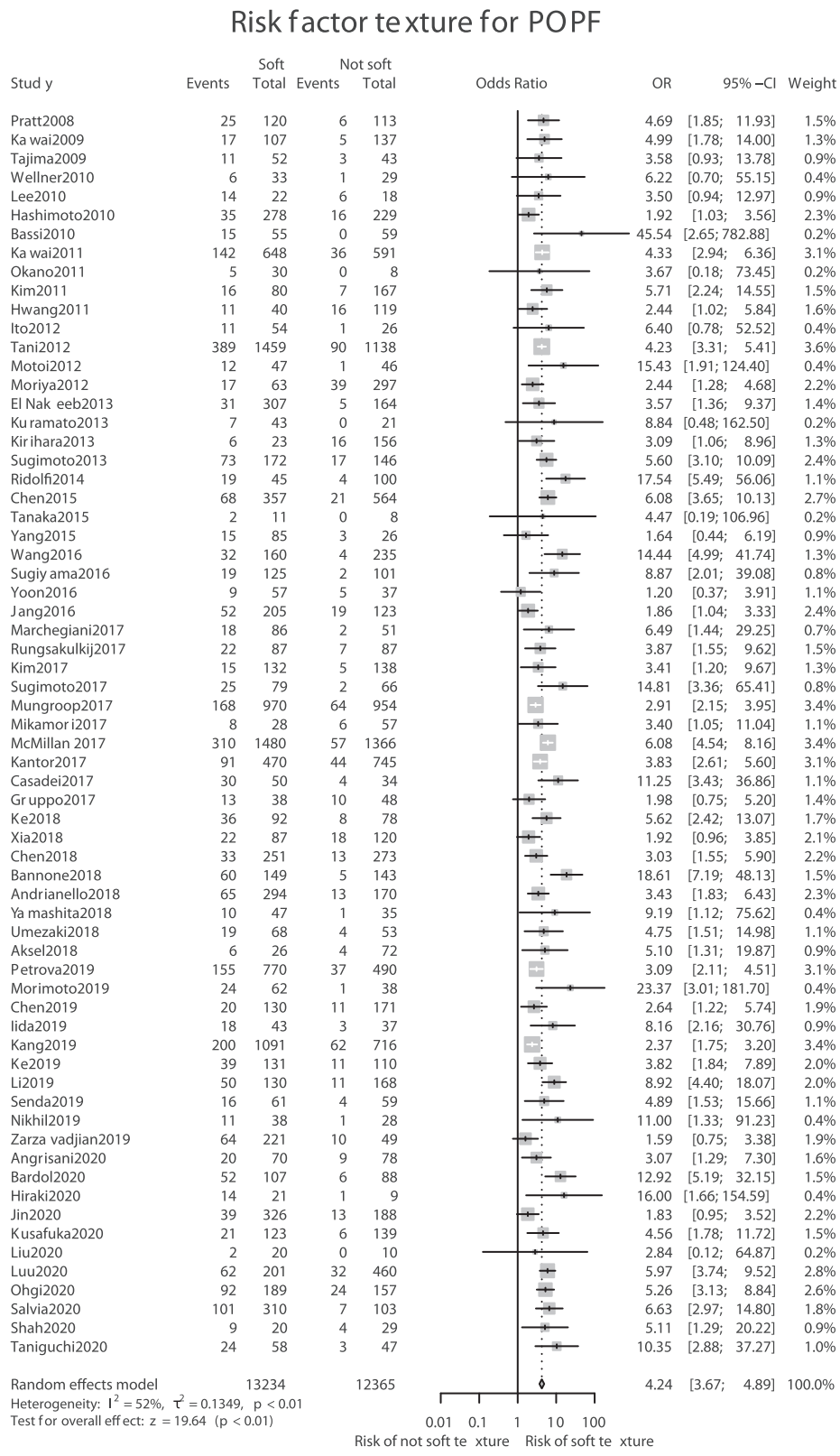

FIGURE 2. Meta-analysis of pancreatic texture (soft vs not-soft) and clinically relevant postoperative pancreatic fistula, defined as POPF B or C according to the ISGPS.

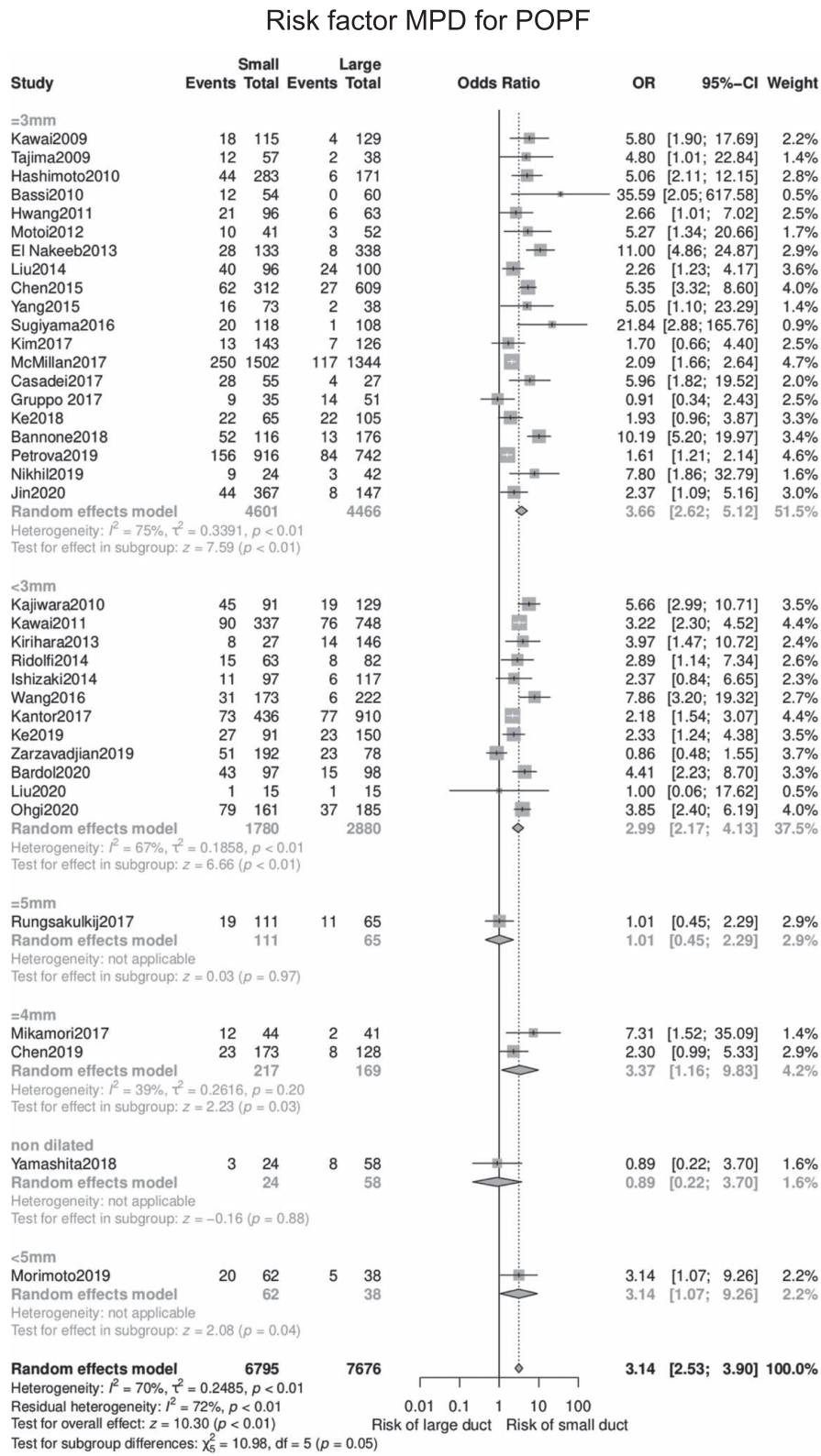

FIGURE 3. Meta-analysis of main pancreatic duct size and clinically relevant postoperative pancreatic fistula, defined as POPF B or C according to the ISGPS.

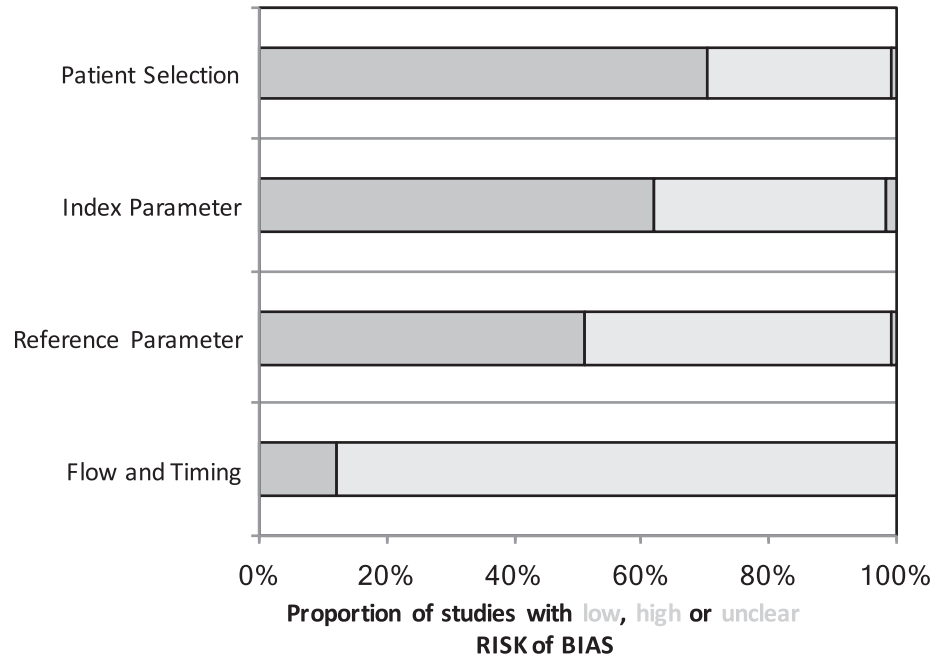

FIGURE 4. Risk of bias of the included studies according to QUADAS-2 analysis.[25]

risk,[53] with borderline significant results (100 patients; OR 3.14, 95% CI 1.07–9.26, $P = 0.04$).

One study[60] defined the duct as nondilated versus dilated to differentiate between a high-risk and a low-risk gland, with no significant association with CR-POPF (82 patients; OR 0.89, 95% CI 0.22-3.70, $P = 0.88$), whereas 2 studies[52,69] had the MPD cut-off at 4 mm, with a significant association between MPD <4mm and CR-POPF (386 patients; OR 3.37; 95% CI 1.16-9.83, $P = 0.03$).

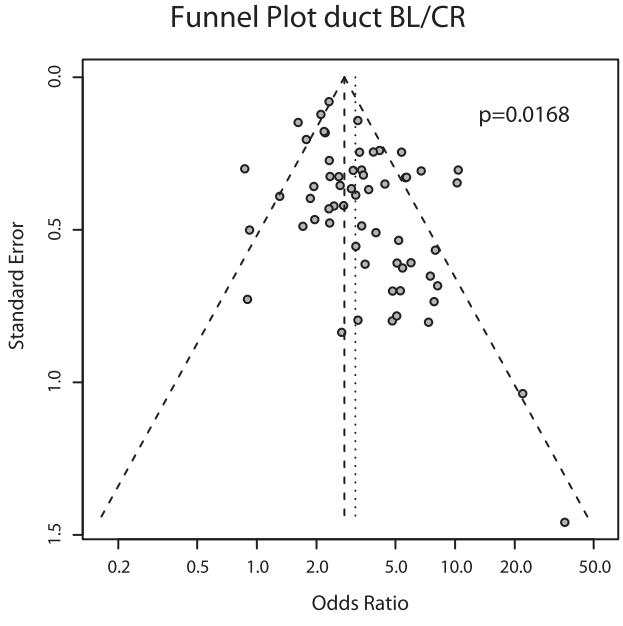

FIGURE 5. Funnel Plot for publications investigating the association between main pancreatic duct size and post-operative pancreatic fistula.

Risk of Bias

The QUADAS-2 analysis shows a high risk of bias in all evaluated domains in a number of the studies included (Fig. 5; Supplement 3, http://links.lww.com/SLA/D36). Detailed assessment is shown in supplement 2, http://links.lww.com/SLA/D35. For "patient selection", 31 of 108 studies (28.7%) were at high risk of bias due to differences in selection criteria. Thirty-nine of 108 studies (36.1%) were at high risk of bias due to missing data for pancreatic texture and/or the diameter of the MPD or to major differences in the classification of these characteristics. Another 52 of 108 studies (48.2%) did not consider relevant confounding factors or had major differences in the perioperative treatment. Finally, 95 of 108 studies (88.0%) were judged to be at high risk of bias due the retrospective study design.

Additionally, the association of POPF including biochemical leaks and MPD size showed significant asymmetry ($P = 0.0168$). It is therefore very likely that studies without significant association were withheld, resulting in publication bias (Fig. 6). The funnel plots of the remaining metaanalyses can be found in supplement 4, http://link-s.lww.com/SLA/D37.

ISGPS Proposal

The results of the meta-analyses were discussed with the ISGPS members on February 6, 2020 at the third World Pancreas Forum in Bern. Based on the ORs of CR-POPF for pancreatic texture and MPD size, the members proposed a simple, sensible classification (Fig. 1) with the goal of facilitating reporting and enabling the comparison of pancreas-associated fistula risk factors among studies in the future. The category "soft" also includes brittle or friable tissue. The category "not-soft" contains any pancreatic texture (eg, hard, firm or sclerotic) other than "soft, brittle, or friable." As most studies in our meta-analysis used intraoperative evaluation of pancreatic texture via palpation by the surgeon (Supplement 2, http://links.lww.com/SLA/D35), we recommend applying this method for assessment of pancreatic texture. Furthermore, intraoperative palpation has been shown to correlate well with durometer measure-ments.[12,129] Similarly,

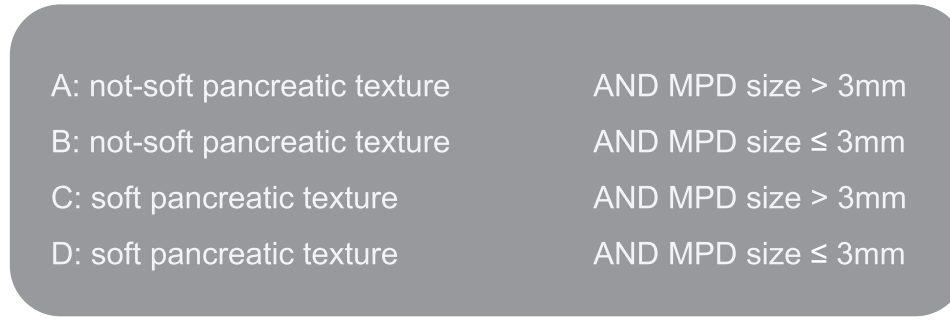

FIGURE 6. ISGPS consensus classification on risk of POPF based on pancreatic texture and main pancreatic duct size The category "soft" also includes brittle or friable tissue. The category "not-soft" contains any pancreatic texture (eg, hard, firm, or sclerotic) other than "soft, brittle or friable".

MPD diameter should be measured intraoperatively at the transection site of the pancreatic remnant (site of anastomosis), as this was the method most frequently used in the included studies.

Validation of the ISGPS Proposal

Finally, the ISGPS proposal was applied to an independent cohort comprising 5533 patients of the PFSG. The rates of CR-POPF differed significantly among the grades: 3.5%, 6.2%, 16.6%, and 23.2% for grades A, B, C, and D, respectively (overall $P < 0.001$) (Table 1).

DISCUSSION

The aims of this systematic review were to evaluate pancreatic texture and MPD size as risk factors for POPF after PD and to develop a consensus for standardized reporting of pancreas- associated risk factors. The results of the meta-analysis show a significant association of both of these factors with the development of CR-POPF with the association being stronger for soft pancreatic texture than for small MPD size. The association was stronger for soft pancreatic texture than for small MPD size. The quantitative results are limited by the inherent risk of bias due to retrospective designs and failure to include confounding factors in some of the included studies. To improve comparability of studies, the ISGPS herewith suggests a straightforward, 4-teir reporting classification (Fig. 1).

There are probably many different reasons why CR-POPF rates are higher following PD with soft pancreatic tissue, including the increased exocrine function of soft glands,[56] the association of soft glands with smaller MPD, and the higher number of side branches in soft glands.[130] Furthermore, soft pancreatic tissue—as well as friable/brittle glands, which were included in the soft texture group in this systematic review—results in a lack of suture-holding capacity, and even ischemic or necrotic processes due to compression of the suture, ultimately leading to anastomotic failure.[131] In addition, a lower degree of fibrosis, as present in soft pancreatic glands, is a risk factor for POPF development.[132,133] Eshmuminov et al published a systematic review concerning the impact of a soft pancreatic gland on the development of CR-POPF according to the updated ISGPS definitions and the results presented here are in line with their findings.[19]

Similarly, the association of a narrow MPD with the incidence of POPF is multifactorial. First of all, pancreatic anastomosis creation is technically more challenging with a small MPD than with a more dilated duct. Second, small MPDs are associated with postoperative acute pancreatitis.[134] Most studies have used MPD diameter of ≤ 3 mm as a cut-off to differentiate between high-risk and low-risk glands. Considering the results of our meta-analysis, this cut-off seems reasonable for classification purposes, due to the clear results in comparison with higher cutoff values; however, it should be pointed out that MDP size is probably a continuous risk factor for CR-POPF development, as has been explored in previous stud-ies.[20,21,135]

We recommend evaluating pancreatic texture intraoperatively via palpation of the gland by an experienced surgeon. This method was used most frequently in the included studies and has been shown to correlate well with durometer measurements.[12,129] Similarly, MPD diameter should be measured intraoperatively at the transection site of the pancreatic remnant (site of anastomosis), as this was the method most frequently used in the included studies. Probing of the duct should be avoided or limited to once, not to distort MPD diameter.

The proposed classification does not aim to calculate the individual CR-POPF risk for a specific patient. This is better done by using one of the many fistula risk scores which, besides pancreas-inherent factors, include nonpancreatic risk factors.[9,10,20–22] However, few of these scores have been as extensively validated as the fistula risk score by Vollmer et al,[20,21,136–38] and no consensus on the clinical consequences[135,138] of implementing these scores in everyday clinical practice has been reached because interventional efficacy trials are sparse in the literature so far. Therefore, the aim of this systematic review was not to establish yet another fistula risk score to evaluate the individual CR-POPF risk of a given patient, but rather to provide a simple reporting classification of organ-specific risks for CR-POPF following PD. This seems essential for several reasons. First, as was evident from the heterogeneous trials in our systematic review, studies investigating pancreatic surgery lack a standardized risk factor and reporting of

TABLE 1. CR-POPF for Grade A-D Anastomoses in 5533 Patients of the Pancreatic Fistula Study Group

		No. of Patients Without CR-POPF	No. of Patients *With CR-POPF*	*Rates*	*P*
A	Not-soft pancreatic texture and MPD > 3 mm	1533	56	3.5%	0.002
B	Not-soft pancreatic texture and MPD ≤ 3 mm	854	56	6.2%	<0.001
C	Soft pancreatic texture and MPD >3 mm	847	169	16.6%	<0.001
D	Soft pancreatic texture and MPD ≤3 mm	1547	471	23.2%	
		4781	752	15.7%	Overall $P < 0.001$

confounders. The current proposal addresses this shortcoming with regard to 2 of the most prominent pancreas-inherent risk factors, thus enabling transparent comparison of future studies. The proposed system could be especially useful as a reporting tool for baseline characteristics in future clinical trials exploring the efficacy of surgical or perioperative mitigation strategies to address CR-POPF. Second, the proposal is useful for auditing, as it allows standardization and comparison between centers and can be easily implemented. Third, it can be used in everyday clinical practice as a simple tool to guide intraoperative management in high-risk anastomoses (groups C and D).

Palpation of the pancreas by the surgeon is the method most frequently used to determine the texture of the gland. However, other ways of measuring the texture of the parenchyma, such as CT measurement, pathologic staining, and direct measurement with a durometer, may also be used, as studies show good correlation between these measurements and surgeons' judgment.[52,129] Furthermore, texture and MPD size can also be determined at the resected PD specimen. Therefore, the proposal can readily be implemented in the minimally invasive era, once the pancreatic head specimen has been removed.

Limitations

Our study has several limitations. First, only studies that appeared after publication of the first ISGPS POPF definition were included. This restriction was necessary due to the myriad different POPF definitions before publication of the ISGPS consensus,[6,7] impeding comparison of results. Second, the methodological quality of some of the included studies was limited, as can be seen in the risk of bias analysis (Figs. 5 and 6; Supplement 2, http://links.lww.com/SLA/D35). However, as only studies with standardized ISGPS definition of POPF were included and results were consistent over time and across countries, the proposed classification is based on sound evidence. Third, the classification explores only the most prominent pancreas-inherent risk factors and focuses entirely on the pancreatic gland itself, neglecting numerous other risk factors. This simplification is inherent in the objective of the classification itself, that is, to provide a simple reporting tool for comparison and clinical decision-making.

In conclusion, the ISGPS recommends reporting MPD size and pancreatic texture according to the proposed classification system for better comparability of study results, clinical decision-making, and auditing.

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