"Mitigation strategies for post-operative pancreatic fistula after pancreaticoduodenectomy in high-risk pancreas: an evidence-based algorithmic approach"—a narrative review

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Background and Objective: Postoperative pancreatic fistula (POPF) is associated with a mortality of up to 25% apart from significant morbid sequelae related to abdominal sepsis and post pancreatectomy hemorrhage. Numerous strategies to curtail the risk of POPF and associated morbidity have been largely unsuccessful. The pancreaticoenteric anastomosis post pancreaticoduodenectomy in a high-risk pancreas represents a significant surgical and clinical challenge. In this narrative review, we present the strategies for early identification and comprehensive management of the high-risk pancreas as per the available literature and present a stepwise algorithmic approach of different fistula mitigation strategies in patients undergoing pancreaticoduodenectomy.

Methods: Medline, PubMed, Embase, Cochrane Library, and various center-specific guidelines were searched for the pancreas, pancreatic cancer, pancreatectomy, pancreatoduodenectomy, Whipple's operation, postoperative, complications, fistula, High-risk pancreas, risk assessment, different predictors, and scoring systems for the high-risk pancreas, current and emerging concepts in the development of POPF and mitigation strategies management and treatment in various combinations.

Key Content and Findings: Over the years, literature has mainly addressed the technical aspects of pancreatico-enteric anastomosis; however, the impact of different technical modifications has been at the most elusive. Recent literature has focused on other aspects like remnant ischemia, locoregional inflammation, and postoperative acute pancreatitis among others, defining their evolving role in pathophysiology of POPF. Although many pre-operative risk prediction models are available; their intra-operative implications are not clear. Furthermore, the evidence available on the mitigation strategies is limited, heterogeneous, and center specific. Fistula prediction includes numerous potentiating factors in addition to the factors described in various Fistula Risk Scores. Early identification of these high-risk scenarios allows the algorithmic application of mitigation strategies. Management of the high-risk pancreas starts in the pre-operative period by early identifications of the risk factors and then continues into the intra-operative period with strategies to decrease intraoperative blood loss, precise anastomosis, and external stenting wherever feasible; goal-directed fluid therapy as well as total pancreatectomy (TP) in certain highly selected scenarios followed by early identification of complications in the postoperative period and appropriate and early management of the same. The coherent application of these mitigation strategies provides the opportunity for the best possible outcome in this complicated scenario.

Conclusions: At present, the zero post-operative pancreatic fistulae seem unattainable, and time has come to study the strategies outside the operation theatre. Till preventive strategies become mainstream, a strategic personalized algorithmic approach may yield best outcomes.

Keywords: High-risk pancreas; postoperative pancreatic fistula (POPF); mitigation strategies; pancreaticoduodenectomy; post-operative pancreatitis; scoring systems for high-risk pancreas

Submitted Jan 15, 2022. Accepted for publication Feb 25, 2022.
doi: 10.21037/cco-22-6
View this article at: https://dx.doi.org/10.21037/cco-22-6

Introduction

Postoperative pancreatic fistula (POPF) represents a major outcome determinant post pancreaticoduodenectomy with an incidence ranging from 13–41%, that may result in significant hemorrhagic and septic complications, culminating in mortality of up to 25% in patients with grade C fistula (1-10). Development of the POPF seems inevitable in high-risk scenarios. Even though, the prediction of the risk of the development of clinically relevant POPF is complex and more than eighty different scenarios may be derived by just combining the four risk components of gland texture, duct size, underlying pathology, and blood loss; the risk prediction is extremely important to individualize the mitigation strategies in different scenarios (11-15). In addition to the surgical technique, surgeon volume and surgeon experience, adoption of the personalized approach in the form of multifactorial mitigation strategies may aid in the reduction of the clinically relevant POPF in the most vulnerable circumstances (16-18). Although considerable literature has been published on POPF, we intend to take a contemporary view in this review to provide a stepwise approach to identify a patient at high risk of pancreatic fistula and strategies that can be adopted to mitigate that risk as an algorithmic approach based on currently available literature and emerging concepts. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-6/rc).

Methodology

Medline, PubMed, Embase, Cochrane Library, and various center-specific guidelines were searched for literature regarding strategies to identify the high-risk pancreas and different fistula mitigation strategies that could be adopted in these patients undergoing pancreaticoduodenectomy. Databases were searched using combinations of POPF and high-risk pancreas based on both MeSH headings and text words. MeSH terms used included but were not limited to, the pancreas, pancreatic cancer, pancreatectomy, pancreatoduodenectomy, Whipple's operation, postoperative, complications, fistula, high-risk pancreas, risk assessment, different predictors and scoring systems for the high-risk pancreas, current and emerging concepts in the development of POPF and mitigation strategies management and treatment in various combinations.

Predicting POPF-risk scores and beyond

Various risk scores and fistula prediction nomograms have been proposed and validated in recent years (13,19-25). The common elements that have been studied in various prediction models include gland texture, high-risk pathology, pancreatic duct diameter, intra-operative blood loss, body mass index, sex, pre-operative albumin, pre-operative bilirubin, intra-abdominal fat thickness, and neoadjuvant treatment (NAT) (13,24,25). The Callery Model, also known as the original fistula risk score (o-FRS) is the most commonly used POPF predictive score (13). Alternative fistula risk score (a-FRS) by the Mungroop group included pancreatic texture, duct size, and body mass index that is simpler than o-FRS (24). The same group further proposed an updated alternative fistula risk score (ua-FRS) specifically for minimally access pancreaticoduodenectomy that was later validated for both minimally invasive and open pancreaticoduodenectomies and includes male sex as an additional risk factor (25). Kantor *et al.* proposed a modified Fistula Risk Score based on sex, BMI, preoperative total bilirubin, pancreatic ductal diameter, and gland texture. The patients were classified into four risk groups that were externally validated. This scoring system utilized a standardized national database (ACS National Surgical Quality Improvement Program) (26). Across the classifications, pancreatic duct size and texture have constantly featured in the risk score models which have led to the four-tier classification of these pancreas associated risk factors for clinically relevant POFP (CR-POPF) by the International Study Group of Pancreatic Surgery (ISGPS) in a recent systemic review of 108 relevant

Table 1 Risk factors for post-operative pancreatic fistula

(I) Patient factors
• Non-modifiable
Male sex
High BMI
Intra-abdominal fat thickness
Depth of abdomen at the level of the pancreas
Access to pancreas
• Modifiable
Pre-operative nutritional optimization
Supplemental immunonutrition
(II) Pancreas related
• Non-modifiable
High-risk etiology
Soft pancreatic texture
Broad and thick pancreas
Duct diameter <3 mm
Ongoing pancreatitis
High acinar cell density
• Modifiable
Neo-adjuvant treatment
(III) Procedure related
• Modifiable (to some extent)
Blood loss
Minimal handling of the pancreas
Documentation of adequate vascularity of the pancreatic remnant at the site of anastomosis
Transection technique

studies (27). Type-A included not-soft pancreas with duct diameter of >3 mm; Type B included not-soft texture and duct diameter <3 mm; Type C included soft texture and duct diameter >3 mm and Type D included soft texture and duct diameter <3 mm. This classification was validated in more than 5,000 patients, with CR-POPF of 23.2% in Type D as compared to 3.5% in Type A (27). All these classifications are based on intra-operative parameters that are partially subjective. Recently, predictive nomograms with high specificity have been proposed based on laboratory and clinical parameters to estimate the risk of CR-POPF on POD 1. These highly predictive models may aid in patient stratification and allocation to accelerated care pathways or early remnant pancreatectomies based on the risk of CR-POPF on POD-1 (28). Prediction scores have a strong potential to alter the surgeon behavior that starts in the pre-operative period with patient counseling that continues in the intra-operative period and culminates into focused and directed post-operative evaluation and management that potentially minimize complications and optimizes outcomes in these high-risk scenarios (19-28).

The risk models should include modifiable factors and non-modifiable factors which may be variously classified as patient-related, pancreas-related, and procedure-related factors, as shown in *Table 1*.

Emerging concepts

Most of the pancreatic literature over the years has focussed on the strategies to enhance the mechanical integrity of pancreatico-enteric anastomosis (1,11,12,17,19). The results have been at the most misleading, inconsistent, skewed, and centre specific. Recently the notion that POPF develops due to gradual failure of pancreatico-enteric anastomosis has been challenged and it is believed that a high-risk pancreas with high acinar cell density is prone to early intra-operative leakage of proteolytic juice due to acinar cell disruption and post-operative acute pancreatitis (POAP) related to pancreatic handling, manipulation, alteration of the blood supply, and ischemia, which finally culminates into POPF (29-35). The evidence for focal ischemia at the pancreatic transection may be direct as suggested by the absence of brisk bleeding from the cut surface, absence of flow on Doppler ultrasonography and ischemia on ICG enhanced images, and indirectly by high local lactate to pyruvate ratio in perianastomotic fluid collected by microdialysis techniques (33-35). The finding that POAP is integral in the development of POPF has opened novel research gateways in the prediction, prevention and management of POPF. Recently ISGPS has come up with consensus statement regarding the definition and classification of post pancreatectomy acute pancreatitis (PPAP). PPAP has been recently identified as one of the strongest predictors of POPF and being an early event in the operative course, early identification and prevention may significantly reduce the complications related to the consequences of PPAP. Presently there is no specific treatment or mitigation strategy available to prevent or treat PPAP, ISGPS calls for RCTs to study specific treatments addressing PPAP and to

reduce the morbidity related to it (36,37).

Discussion (mitigation strategies)

Mitigation strategy 1: *Identifying those high-risk patients with high-risk pancreas-beyond the pancreatic texture and duct size*

Pancreatic surgeons are aware of the fact that predicting CR-POPF is not like one size fits all. Although the 4 element/10-point o-FRS is most commonly used for segregating the patients into the negligible, low, moderate, and high-risk groups, we believe that apart from these, there are equally important factors that may push a moderate risk group into a POPF C category (38-47). These factors may be termed as the *potentiators* and include the male sex, high BMI, body fat distribution impairing access during the surgery, broad and thick pancreas, ongoing acute pancreatitis, a not-soft but brittle pancreas. These factors have not been addressed adequately in the literature.

These inconsistencies could be addressed by risk profiling every individual patient using all the above-mentioned factors and creating nomograms that would adequately determine the risk of CR-POPF and more importantly POPF C in an individual patient (19-23).

The patients at high risk of CR-POPF should be identified early in the pre-operative planning. The use of a Contrast-enhanced computed tomography-guided fistula risk score may help in the early identification of potential high-risk patients and help in the better application of the mitigation strategies (48). Apart from high-risk etiology, male sex, and high BMI, CT may provide information about the pancreatic attenuation that is an indirect indicator of pancreatic texture, duct size, duct volume, remnant size and volume, ongoing inflammation, skeletal muscle index, visceral fat distribution and depth of the abdomen at the level of the pancreatic remnant (43-51). Lapshyn *et al.* studied eleven pre-operative baseline and radiological parameters to develop a POPF risk calculator using binominal regression. They developed a simple POPF risk calculator based on gender and radiological features of maximum MPD diameter and pancreatic gland diameter at the anticipated resection margin with the area under the curve (AUC 0.756–0.808) comparable to the established scores like fistula risk score (AUC 0.74–0.79) and the alternative fistula risk score (AUC 0.72–0.79). They also developed a nomogram visual risk scale that could be easily adapted in pre-operative stratification models (52). In another recent study by Perri *et al.*, a pre-operative risk tree model was created using radiological main pancreatic duct diameter and body mass index, that was externally validated. They identified low, intermediate, and high-risk groups with significantly different post-operative pancreatic fistula rates in different groups (53). These scoring systems are easily adaptable and may aid in altering the surgeon's behavior regarding the application of the mitigation strategies.

Although the impact of the pre-operative nutritional rehabilitation on POPF has not been studied in the randomized trials, there is some evidence from prospective and retrospective studies that lower prognostic nutritional index and sarcopenia were significantly associated with POPF (18,54-56). All the dedicated pancreatic centers should consider pre-operative nutritional rehabilitation as the standard of care. Pre-operative and post-operative immuno-nutrition may decrease the incidence of POAP in the high-risk pancreas and consequently CR-POPF (57-63).

The NAT is being increasingly used in resectable and borderline resectable pancreatic head cancers. There is some evidence from population-based databases that NAT is associated with reduced POPF. Similar findings were noted in a retrospective study of 79 patients with periampullary carcinoma who underwent neoadjuvant chemoradiotherapy. NAT in selected cases may mitigate the risk of CR-POPF. This strategy may be adopted in a resectable uncinate process adenocarcinoma with CT-FRS suggestive of the high-risk pancreas, where a delay in adjuvant treatment due to CR-POPF may seriously impact the final survival outcome (64-71).

Intraoperative mitigation strategies: *All that can be done should be done here*

Operative strategies are the prime determinants of the outcome of the patients at high risk of CR-POPF. Carefully selected intraoperative strategies may mitigate the risk of POPF C. The anticipated risk of POPF C should bring out the best in the pancreatic surgeon. He should take charge of the situation and communicate concerns and strategies to the surgical and anesthesia team (72,73).

One of the important factors that have been constantly undervalued in the mitigation strategies is intra-operative blood loss (74,75). Although its contribution cannot be addressed in human randomized trials due to obvious reasons, a recent multicenter propensity score-matched analysis concluded that high intraoperative blood loss is an independent predictor of CR-POPF occurrence apart

from being a quality indicator of pancreaticoduodenectomy. Minimizing the blood loss, particularly in the scenario of a high-risk pancreas may act as the gamechanger and is the attainable objective that the pancreatic surgeon should strive for. Even though blood loss during surgery may be impacted by many physiological, tumour-related, and technical factors that may be difficult to control even for an expert surgeon, however a proactive mindset and strategically minimizing blood loss at the steps like pancreatic transection and uncinate dissection may still be achievable (74).

Intra-operatively a scenario of the high-risk pancreas (Type D, o-FRS 7-10) may be intimidating even for a senior pancreatic surgeon. A surgeon may adapt some type of a technical mitigation strategy like Pancreaticogastrostomy, dunking, isolated limb reconstruction, isolated limb reconstructions, total pancreatectomies along with an adjuvant strategy like trans anastomotic stents, intraperitoneal drains, tissue sealants, prophylactic octreotide, and intraoperative hydrocortisone (72,73,76). Out of all these mitigation strategies, a multi-institutional study that analyzed the mitigation strategies used by 62 surgeons across 17 high volume centers, use of external stenting was associated with reduced CR-POPF. External stents were specifically studied in high-risk scenarios in French and Japanese randomized controlled trials, both of which concluded the reduced rate of CR-POPF in the soft pancreas with non-dilated ducts. However, converse results were noted with internal trans anastomotic stents that led to the termination of a large multicentre RCT from the United States (77-84). Externalized trans anastomotic stents need to achieve complete diversion of the pancreatic juice away from the anastomosis. This function cannot be achieved by the routine infant feeding tubes and as such, they are more likely to malfunction. In a prospective risk-stratified observational study from Verona, Italy authors concluded that specialized size-specific externalized trans anastomotic stents when used appropriately in the high-risk pancreas may considerably mitigate CR-POPF occurrence. The authors also highlighted the increase in morbidity associated with stent malfunction (85,86).

Another mitigation strategy that is at an end of the spectrum is upfront TP in patients with the high-risk pancreas. Recent studies have shown improved postoperative outcomes in patients post TP at high volume centers. Even though an RCT to compare TP with PD in patients with high-risk pancreas may not be considered ethical at present, a recent retrospective study by Marchegiani *et al.* concluded that TP in the high-risk pancreas may be associated with significantly lower POPF related morbidity like post-pancreatectomy hemorrhage, delayed gastric emptying and sepsis, although with comparable mortality and cancer-specific quality of life and low diabetes-related quality of life (72,87,88). Similar conclusions were made in a single-center observational study by Capretti *et al.* (89). At present TP may not be recommended for all the patients with the high-risk pancreas, however the patients at the end of the spectrum with high o-FRS (8-10) along with other potentiating factors like high BMI, male sex, body fat distribution impairing access during the surgery, broad and thick pancreas, ongoing acute pancreatitis, a not-soft but brittle pancreas with adenocarcinoma of the uncinate process that will require early post-operative adjuvant treatment where early post-operative benefits may overweigh long term quality of life outcomes (87).

It needs to be reinstated that a specific reconstruction technique should not be promoted and a standardized institutional concept of pancreatic anastomosis that is constantly audited, analyzed, and enhanced by documentation and interpretation of the surgical quality may provide the best possible outcomes in most of the scenarios. Pancreaticojejunostomy done meticulously with a standardized institutional technique using finer delayed absorbable sutures and magnifying loupes increase the chances of the most optimal outcome of the anastomosis (90-100).

Regarding technical mitigation strategies like dunking or invagination of the pancreatic stump, some poorly designed RCTs without risk stratification have shown some value of dunking reconstruction on CR-POPF, the same was not shown in other RCTs as well as in the multi-institutional study that analyzed more than 5,000 pancreaticoduodenectomies. Similarly, isolated limb reconstruction has shown some benefit in small studies, but they were poorly designed without any risk stratification of the patients. Pancreaticogastrostomy *vs.* pancreaticojejunostomy have resulted in conflicting outcomes in meta-analysis due to variability in the studies. In the 5 RCTs published in ISGPS-era, only two were risk-stratified. Although no benefit was seen in the soft pancreas, PG did benefit when duct size was <3 mm. In the RECOPANC study, no significant difference was noted between PG and PJ in the rate of POPF. However, PG was associated with increased post-pancreatectomy hemorrhage (97-100). Similarly, occlusion of the pancreatic duct without

reconstruction either by ligation, glue occlusion, or stapled closure have largely been ineffective and may precipitate lethal postoperative pancreatitis. Regarding the adjuvant strategies like tissue patches and sealants; patches and sealants were not able to decrease the incidence of CR-POPF in high-risk scenarios. This was uniformly seen in the RCTs, Cochrane review, and multicenter studies (101-106).

Some of the adjuvant strategies although not studied extensively may benefit in these scenarios like the flooring of the surgical bed with native tissues like vascularized falciform ligament or mobilized omentum and may mitigate hemorrhagic complications in presence of CR-POPF. Similarly, the placement of drains in high-risk cases has been supported in some randomized trials (107,108).

Numerous clinical studies and randomized trials have addressed the use and efficacy of somatostatin analogs in the prevention of POPF (109-122). The results have been largely contentious. Although there was an initial enthusiasm regarding the efficacy of Pasireotide in the prevention of CR-POPF after a single-center RCT by Allen *et al.* in 2014, similar results were not confirmed in the subsequent studies (67,112-115). The use of prophylactic Octreotide as a mitigation strategy was found to be independently associated with higher CR-POPF in a multi-institutional study by Ecker (84). In a retrospective study by McMillan *et al.*, authors have suggested that octreotide use may potentiate POPF risk (122). Apart from impaired wound healing associated with octreotide use, poor splanchnic blood flow associated with its use may potentiate POAP in high-risk pancreas finally culminating into CR-POPF.

In patients with the high-risk pancreas, an important mitigation strategy is avoiding near-zero fluid balance which may potentiate the POAP in these patients. Studies have shown that even though a liberal fluid strategy is associated with mucosa edema and swelling of the jejunal limb that may potentiate anastomotic failure, a near-zero fluid balance may result in transient hypoperfusion that may precipitate inflammatory response and stump ischemia in patients with the high-risk pancreas. Clear communication with the anesthesia team is necessary to promote tailored fluid management in these high-risk scenarios (123-127).

Considering CR-POPF as a consequence of remnant hypoperfusion and inflammation, adjuvant mitigation strategies like perioperative steroids and NSAID therapy have been studied (128-131). The use of single-dose intra-operative Dexamethasone has yielded conflicting results, whereas Sandini *et al.* reported lower post-operative complications and improved survival with intra-operative Dexamethasone. A study by Newhook *et al.* failed to demonstrate similar benefits (129,130). Studies have suggested that in the high-risk pancreas with higher acinar cell density at the cut margin, hydrocortisone use may decrease the overall complication rate by preventing the inflammatory response generated at the time of pancreatic transection (128). Regarding NSAIDS, the efficacy of Diclofenac to reduce post ERCP pancreatitis could not be reproduced in patients after pancreaticoduodenectomy. Behman *et al.* reported a non-significant increase in pancreatic fistula in post-pancreaticoduodenectomy patients receiving NSAIDs in the early postoperative period (131).

Other strategies without much evidence from literature like securing a feeding jejunostomy and the use of Braun's jejunojejunostomy may also be implemented in these high-risk scenarios (82-84).

Post-operative mitigation strategies: *proactive*, *pre-emptive*, *and aggressive*

No definitive recommendation could be made but vigilant behavior may enhance outcomes. Nutritional optimization should be continued with supplemental Immunonutrition. Enteral nutrition is the preferred mode and may aid in spontaneous closure in patients who develop CR-POPF (132).

Drain management using the risk-stratified pancreatectomy care pathways has the potential to reduce the median hospital stay and hospital costs. In a study by Newhook *et al.*, risk stratification led to a unique drain fluid cut-off in each risk group to rule out POPF. This approach leads to a significant shift from the standard assessment strategy for drain fluid amylase to a stratified and titrated approach that in turn promotes individualized data-driven drain management and facilitates accelerated management in a significant proportion of patients (133). Post-operatively drain management should be algorithmic and supported by the data from the high-volume centers (133-138). Since all high-risk patients are likely to have drains, drain removal should be guided by drain fluid amylase, drainage volume, the character of the effluent, and the clinical condition of the patient. All the drains should be actively managed to prevent clogging and promote drainage. In patients with the high-risk pancreas, drains should be strategically removed by documenting a persistently low or decreasing drain fluid amylase on a postoperative day 5 or 7 in the absence of any change in the character of effluent that may appear sinister. These extra days may aid in the identification of a selective group of patients with the high-risk pancreas that

may manifest CR-POPF later in the hospital course (133). In these high-risk patients raised serum amylase levels and C-reactive protein levels may also act as predictors of POPF development (133-138).

Once the CR-POPF develops, these patients should be managed with a Step-up approach. A 24-hour and 365 days access to interventional radiology is the prime requirement in the step-up pathway. Any deviation from a normal recovery or a sinister drain output should prompt cross-sectional imaging. All the undrained collections should be drained. Safe radiological drainage is possible in most of the peripancreatic collections; lesser sac collections may be managed by endoscopic drainage. Any significant drop in hemoglobin or intra or extraluminal bleeding and any hemodynamic instability should prompt an urgent evaluation with a CT angiography followed by conventional angiography. Arterial aneurysms or hemorrhagic points should be managed using embolization or stenting (139,140).

Surgical intervention should not be used as an end of the spiral thing, it should be considered early in patients not improving after radiological interventions. Most common scenarios where relaparotomy is used include multiple small inspissated inaccessible collections with persistent patient deterioration, inability to attain complete drainage after multiple radiological interventions, catastrophic hemorrhage requiring urgent bleeding control, and clot evacuation. Relaparotomies are challenging and the decisions are made after evaluating the degree of damage and the residual anatomy. Establishing wide drainage of infected collections after abdominal lavage benefits most of the patients with a collection that isn't radiologically controlled. In situations of complete pancreatic dehiscence or necrotizing pancreatitis, a salvage completion pancreatectomy may be indicated. Historically it has been associated with mortality of up to 42%. In a multicenter cohort study and meta-analysis by Groen *et al.*, mortality was significantly higher after completion of pancreatectomy (56% *vs.* 32%) when compared to pancreas preserving procedures after relaparotomy (141). However, we believe that this procedure was mostly undertaken at the end of the spiral when physiological compromise was severe. Other strategies include disconnection followed by exteriorization and bridge stenting may be used in some scenarios. Revising pancreaticoenteric anastomosis and switching to other techniques is not feasible in most of these scenarios and should not be done (141-150).

The patients who develop these complications should be managed in a dedicated intensive care unit. Supportive care with inotropic support, ventilatory support, judicious blood transfusion, and coagulopathy correction may be required. Nutritional optimization and surgical wounds should be aggressively managed.

Conclusions

The challenge of pancreatico-enteric anastomosis in a high-risk scenario is complex, with potentially catastrophic clinical and economic consequences. The literature addressing the mechanical aspects of high-risk pancreatico-enteric anastomosis has largely been unyielding. This review highlights the concept of an individualized personalized approach to this vulnerable scenario. Early identification of these high-risk scenarios allows the algorithmic application of mitigation strategies. Management of the high-risk pancreas starts in the pre-operative period by early identifications of the risk factors and then continues into the intra-operative period with strategies to decrease intraoperative blood loss, precise anastomosis, and external stenting wherever feasible, goal-directed fluid therapy as well as TP in certain selected scenarios followed by early identification of complications in the postoperative periods and appropriate and early management of the same. The coherent application of these mitigation strategies provides the opportunity for the best possible outcomes in this complicated scenario as highlighted in an algorithmic pattern in the next section.

The road ahead

At present, the zero post-operative pancreatic fistulae seem unattainable, and time has come to study the strategies outside the operation theatre. Future studies need to focus on the strategies to decrease the localized inflammatory response that result in the prevention of POAP which seems to be a major determinant in the development of CR-POPF. Till preventive strategies become mainstream, a strategic personalized algorithmic approach may yield the best possible results.

The algorithm-adaptability and habit formation

Although at present there is a paucity of high-quality evidence regarding the strategies to mitigate the POPF following pancreaticoduodenectomy in high-risk scenarios, there is sufficient data available from high volume centers that may be compiled to present a comprehensive algorithm

that may promote adaptability and habit formation in these high-risk scenarios. Even though post-operative mitigation strategies are partly adapted in most of the high-volume pancreatic centers, the maximum benefit may only be attained if comprehensive post pancreatectomy care pathways are adapted. We present a comprehensive algorithm based on the available data from the high-volume centers and the experience of masters in pancreatic surgery (*Figure 1*).

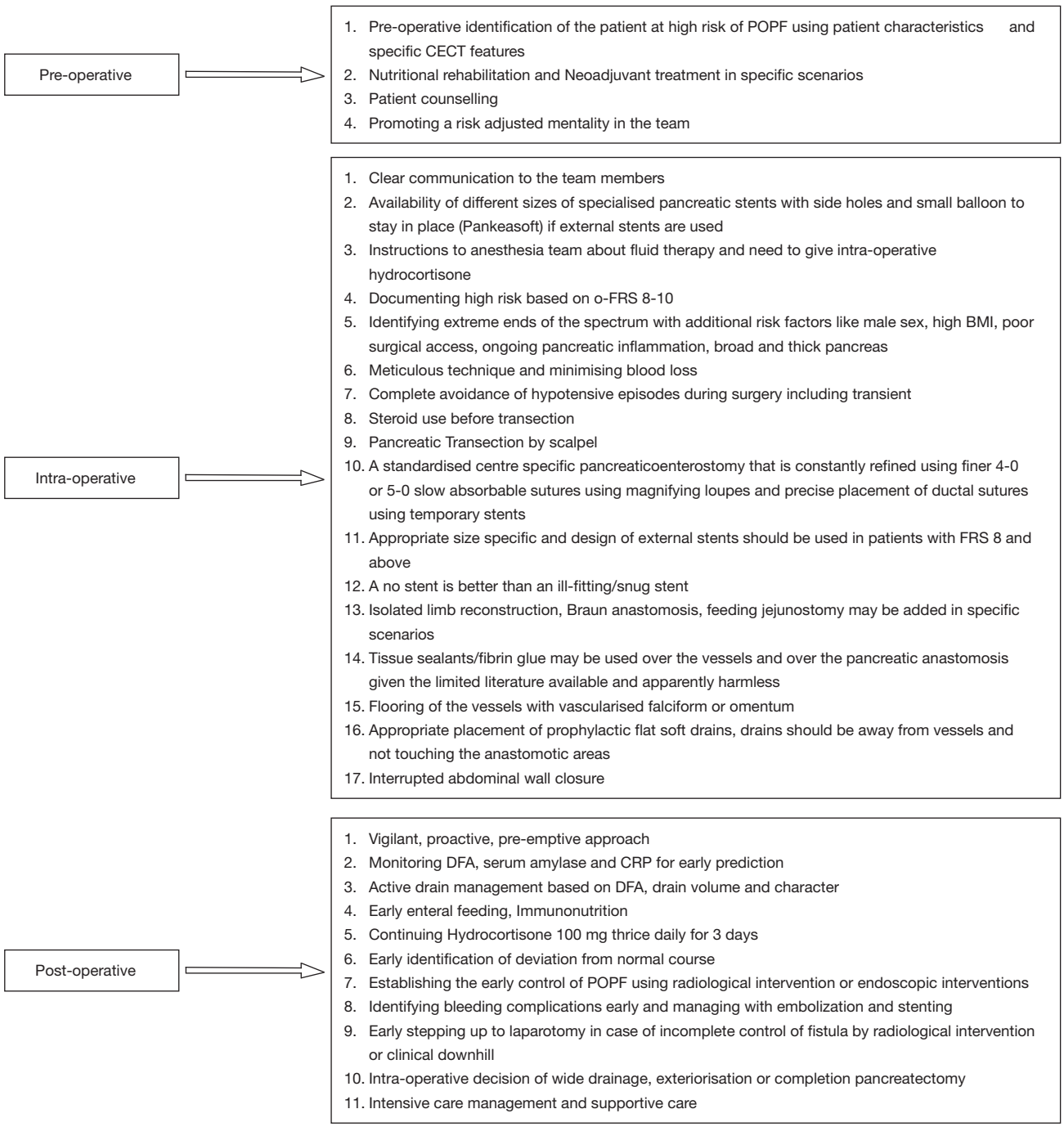

Figure 1 Adaptability and habit-forming Algorithm. POPF, postoperative pancreatic fistula; CECT, contrast enhanced tomography; FRS, Fistula Risk Score; DFA, drain fluid amylase; CRP, C-reactive protein.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Savio George Barreto) for the series "Unresolved Issues in Pancreatic Cancer" published in *Chinese Clinical Oncology*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-22-6/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-6/coif). The series "Unresolved Issues in Pancreatic Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Parray AM, Chaudhari VA, Shrikhande SV, Bhandare MS. "Mitigation strategies for post-operative pancreatic fistula after pancreaticoduodenectomy in high-risk pancreas: an evidence-based algorithmic approach"—a narrative review. Chin Clin Oncol 2022;11(1):6. doi: 10.21037/cco-22-6