



A new perspective on post-operative pancreatic fistulas: the impact of post-pancreatectomy acute pancreatitis

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Pancreatoduodenectomy (PD) is frequently utilized to treat both malignant and benign disease of the pancreatic head, duodenum, and periampullary region. While surgical techniques and operative technology have improved over the years, PD remains associated with significant post-operative morbidity, affecting upwards of 50% patients (1,2). Notably, post-operative pancreatic fistula (POPF) remains a significant complication, with clinically relevant fistulas occurring in 10–20% of cases (3,4). Significant emphasis has been placed on accurately classifying POPF to optimize mitigation strategies and identify potential causes (5). In this regard, multiple technical aspects of PD have been extensively evaluated for association with POPF, including utilization of pancreatic duct stent placement, various pancreaticojejunostomy anastomotic techniques, and intra-peritoneal drainage (6,7). However, despite these efforts, POPF rates remain high and continue to be a significant issue following PD.

Post-pancreatectomy acute pancreatitis (PPAP) is a common occurrence after PD that has recently garnered more attention for its association with other postoperative complications. The International Study Group for Pancreatic Surgery (ISGPS) has formalized a definition for PPAP according to radiologic and laboratory findings following pancreatic surgery (8). PPAP is defined as an acute inflammatory condition of the pancreatic remnant that begins within the first three postoperative days after

partial pancreatectomy and is characterized by (I) sustained postoperative serum hyperamylasemia greater than the institutional upper limit of normal for at least 48 hours, (II) clinically relevant features, and (III) radiologic alterations consistent with PPAP. Risk factors for PPAP have been extensively investigated and include soft pancreatic texture, receipt of neoadjuvant treatment, gender, and pancreatic ductal diameter (9,10).

In a recent issue of *Annals of Surgery*, Chen and colleagues investigated the risk and clinical significance of POPF after PPAP among patients undergoing PD (11). In their retrospective study of 817 patients who underwent open or minimally invasive PD, they observed that POPF occurred in 159 (19.5%) patients. Of these, 73 (45.9%) cases of POPF occurred following PPAP, as defined by ISGPS criteria. When compared to non-POPF cases, PPAP-associated POPF was associated with higher body mass index (BMI), higher rate of non-dilated main pancreatic duct, soft pancreatic texture, and non-PDAC pathology. When compared to non-PPAP-associated POPF, PPAP-associated POPF was associated with a trend towards younger age, female gender, lower rate of preoperative biliary drainage, and softer pancreatic texture. Compared to all patients, PPAP-associated POPF was associated with higher common Fistula Risk Score (FRS). On subsequent multivariable logistic regression, factors associated with development of PPAP-associated POPF included greater

intraoperative blood loss, small pancreatic duct size, and soft pancreatic texture. In contrast, non-PPAP-associated POPF was linked to different risk factors, including age. Importantly, there were no significant differences in postoperative outcomes between PPAP-associated POPF and non-PPAP-associated POPF. However, the authors observed that PPAP-associated POPF presented with unique radiologic features.

These findings by Chen and colleagues contribute to the growing body of evidence linking PPAP to the development of POPF (10,12-14). Retrospective studies by Bellotti *et al.* (55.0% vs. 11.6%, $P < 0.001$) and Wu *et al.* (33.3% vs. 12.5%, $P < 0.001$) have similarly reported a strong association between PPAP and POPF compared to patients without PPAP (10,12). Across multiple studies, further analysis of factors associated with PPAP-related POPF identified similar risk factors as those described by Chen and colleagues, including smaller duct size and softer pancreatic texture (10,12,14). Ultimately, these findings by Chen and colleagues corroborate previously recognized risk factors and challenge the conventional dogma that POPF solely results from breakdown or leakage of the pancreatic stump or anastomosis. Their finding of temporal development of PPOF following PPAP, alongside unique risk factors for PPAP-associated PPOF, suggests that PPOF following PPAP should be recognized as a potential complication secondary to PPAP. This prompts the consideration of additional PPOF subtypes and underscores the necessity for innovative prevention strategies. While surgeons have focused on refining surgical techniques to reduce POPF, additional efforts and attention may also need to be directed towards minimizing PPAP in post-PD patients.

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