JCTEI
JOURNAL OF CLINICAL TRIALS AND EXPERIMENTAL INVESTIGATIONS
Year: 2025 Volume: 4 Issue: 3

LETTER

10.5281/zenodo.17163030

Postoperative pancreatic fistula after pancreatic cancer surgery: Past and present of ISGPS classification

Correspondence
Melih Can Gul, Afyonkarahisar State Hospital Department of Gastroenterology, Surgery Afyonkarahisar, Türkiye

e-mail
opdrmelihcangul@gmail.com

Received: 1 September 2025
Revised: 12 September 2025
Accepted: 18 September 2025
Published: 30 September 2025

ORCID ID of the author(s):
MCG: 0000-0002-6165-1144

Melih Can Gul[1]

1. *Afyonkarahisar State Hospital Department of Gastroenterology Surgery, Afyonkarahisar, Türkiye*

To the Editor,

Postoperative pancreatic fistula (POPF) is a frequent and consequential complication after cancer-related pancreatic resections. Even in high-volume centers, reported incidence after pancreatoduodenectomy ranges from ~5% to 30% (1–3), and distal pancreatectomy historically reaches 30–40% in some series (2). POPF prolongs hospitalization and drives secondary problems—abscess, sepsis, hemorrhage, and delayed gastric emptying—despite overall perioperative mortality falling below 5% in specialized units (4,5). Although Grade C events are uncommon (<5%), they carry a grave prognosis, with postoperative mortality reported up to 20–30% when organ failure or erosive bleeding occurs (4,6).

Before 2005, heterogeneous, center-specific criteria produced wide variation in reported fistula rates and impeded benchmarking (4). The International Study Group on Pancreatic Fistula (ISGPF) addressed this by proposing the first consensus definition and severity grading in 2005: any drain output on/after postoperative day 3 with amylase >3× the upper normal serum level constituted a POPF, stratified into Grades A–C by clinical impact (4). Broad adoption standardized reporting (4,7), yet accumulating experience exposed limitations and ambiguities, prompting critical reassessment by the community (5,8).

2005 ISGPF classification of POPF

The 2005 ISGPF classification introduced three grades of POPF severity based on clinical impact and management (4). Grade A represented an asymptomatic "biochemical leak" with no effect on recovery, Grade B required therapeutic interventions or prolonged drainage but without organ failure, and Grade C denoted life-threatening fistulas leading to organ failure, reoperation, or death (4).

Table 1 summarizes the original criteria, showing that only Grades B and C were clinically relevant. Grade A inflated overall POPF rates since many patients labeled as having a fistula had outcomes indistinguishable from those without one (5,8). Clinical studies later demonstrated that Grade A had no prognostic significance, prompting many surgeons to advocate its exclusion and to focus on "clinically relevant POPF" (CR-POPF, Grades B/C) (9,10).

Cite as: Gul MC. Postoperative pancreatic fistula after pancreatic cancer surgery: Past and present of ISGPS classification. J Clin Trials Exp Investig. 2025;4(3):97-101.

Table 1: ISGPF 2005 Definition and Grading of Postoperative Pancreatic Fistula (original consensus criteria (4)).

Criteria	Grade A (Transitory POPF)	Grade B (Clinically Relevant POPF)	Grade C (Severe POPF)
Drain fluid amylase >3× normal serum amylase on/after POD3	**Yes** (meets POPF biochemical definition)	**Yes**	**Yes**
Impact on patient's clinical course	None (no change in management)	Yes – requires deviation in management	Yes – major deviation; life-threatening
Requires special treatment (e.g. nutritional support, octreotide, antibiotics)	No	Yes (often required)	Yes (always required)
Imaging (CT/Ultrasound) evidence of fluid collection	No (usually none)	Possible (may be present)	Yes (typically present)
Persistent drainage > 3 weeks	No	Often yes (prolonged drainage)	Yes (persistent fistula)
Interventional procedures (percutaneous or endoscopic) for POPF	No	Sometimes (e.g. drain placement)	Often (if needed to avoid surgery)
Reoperation due to POPF	No	No	Yes (required in many cases)
Organ failure (POP*-related)	No	No	Yes (single or multi-organ failure)
Postoperative mortality (attributable to POPF)	No	No	Possible (any death due to POPF)

**POPF: postoperative pancreatic fistula.* Grade A = transient biochemical leak with no clinical morbidity; Grade B = fistula requiring therapeutic intervention or affecting recovery but without organ failure; Grade C = fistula causing organ failure, reoperation, or mortality (4).

Another weakness of the 2005 system was inconsistency between Grades B and C. Certain interventions, such as percutaneous drainage or angiographic procedures, were variably classified, leading to heterogeneity across studies (8,11). Similarly, the rule that a drain left in place for more than three weeks automatically constituted Grade B became outdated as enhanced recovery protocols normalized safe discharge with drains (8). These discrepancies underscored the need for refinement and set the stage for the 2016 ISGPS update.

2016 ISGPS update – "Clinically Relevant" redefined

In 2016, the ISGPS updated the POPF definition to focus only on clinically relevant fistulas (5). Elevated drain amylase without clinical impact is now termed a "biochemical leak" and excluded from POPF incidence, addressing prior overestimation and confusion about Grade A (5,10,12). Early studies confirmed that reclassification lowered reported rates by 30–50%, particularly after distal pancreatectomy (10,12).

The revision also clarified the boundary between Grades B and C. Grade B requires a deviation from routine care—such as prolonged drainage, antibiotics, nutritional support, or image-guided intervention—without organ failure or reoperation (5). Grade C denotes critical fistulas causing organ failure, necessitating reoperation, or leading to death (5,11). Only organ failure directly attributable to POPF is included, avoiding misclassification of unrelated events (5,8).

As shown in Table 2, the new framework eliminated Grade A, defined biochemical leaks as non-complications, and provided stricter criteria for Grades B and C (5).

Table 2: ISGPS 2016 updated definition and grading of POPF (new criteria emphasizing clinical impact (5)).

Criteria	Biochemical Leak (Former "Grade A")	Grade B (Clinically Significant)	Grade C (Critical)
Drain fluid amylase >3× normal (after POD3)	Yes (by definition)	Yes	Yes
Impact on clinical course / change in management	**No** (no clinical impact; trivial leak)	**Yes** (requires active management)	**Yes** (major impact; intensive management)
Requires prolonged drainage (>3 weeks)	No	Yes (often required)	Yes (persistent fistula)
Requires invasive intervention (percutaneous or endoscopic procedure for POPF or related complication)	No	Yes (e.g. drain placement, angiographic bleeding control)	Yes (often in addition to surgery)
Requires reoperation for POPF	No	**No**	**Yes** (surgical re-intervention)
Organ failure attributable to POPF	No	**No**	**Yes** (single or multi-organ)
POPF-related postoperative death	No	No	Yes (any mortality due to POPF)

**POPF: postoperative pancreatic fistula.* Grade A = transient biochemical leak with no clinical morbidity; Grade B = fistula requiring therapeutic intervention or affecting recovery but without organ failure; Grade C = fistula causing organ failure, reoperation, or mortality.

Biochemical leak: elevated drain amylase without adverse clinical sequelae – not considered a true fistula (5). Grade B: POPF requiring a deviation in patient management (e.g. therapeutic agents, image-guided drainage) but no organ failure or reoperation. Grade C: POPF causing organ failure, necessitating reoperation, and/or resulting in death (5). All Grade B/C are considered clinically relevant POPF.

Overall, the 2016 update has been widely adopted, improving uniformity and clinical relevance in reporting (5,7,12). By excluding trivial leaks and sharpening Grade B/C criteria, it allows surgeons to concentrate on patients needing real intervention and enables more consistent comparisons across studies (8,10,12).

Clinical impact and ongoing considerations

The 2016 ISGPS classification reduced reported POPF rates by excluding clinically insignificant leaks and emphasized that only fistulas altering clinical course should be considered complications (10,12).

In research, focusing on clinically relevant fistulas (Grade B/C) improved risk factor analysis, identifying variables such as soft gland, small duct, high BMI, and blood loss (9,13-15).

Proposals to subclassify Grade B into B1–B3 highlight its clinical heterogeneity, ranging from prolonged drains to major interventions, and early data suggest outcome correlations (11,16).

Clinically, Grade B requires additional support such as antibiotics, nutritional therapy, or radiologic intervention, whereas Grade C denotes life-threatening complications often requiring ICU care and reoperation. This system has standardized research endpoints, with most trials now reporting CR-POPF rates; many technical modifications show reduced overall POPF but no significant difference when focusing on Grade B/C (17–20).

Conclusions

The classification of postoperative pancreatic fistula has evolved significantly, moving from inconsistent definitions to a standardized framework that enables meaningful comparison across studies. The ISGPF's initial definition provided the first step toward uniformity, while the ISGPS 2016 update refined the system by removing clinically insignificant cases and clearly distinguishing moderate from severe fistulas.

This evolution reflects the surgical community's ongoing efforts to improve outcome reporting and patient care. Ultimately, surgeons now share a common language when addressing postoperative fistulas, which translates into better understanding, prevention, and treatment of this complication in pancreatic cancer surgery.

Conflict of interest: The authors report no conflict of interest.

Funding source: No funding was required.

Ethical approval: Not applicable. This paper is a Letter to the Editor.

Informed consent: Not applicable.

Acknowledgments: None

Peer-review: Externally. Evaluated by independent reviewers working in at least two different institutions appointed by the field editor.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributions

Research concept and design: MCG

Data analysis and interpretation: MCG

Collection and/or assembly of data: MCG

Writing the article: MCG

Critical revision of the article: MCG

Final approval of the article: MCG

All authors read and approved the final version of the manuscript.

References

1. Pulvirenti A, Marchegiani G, Pea A, Allegrini V, Esposito A, Casetti L, et al. Clinical Implications of the 2016 International Study Group on Pancreatic Surgery Definition and Grading of Postoperative Pancreatic Fistula on 775 Consecutive Pancreatic Resections. Ann Surg. 2018;268(6):1069-75.
2. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8-13.
3. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161(3):584-91.
4. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg. 2007;245(3):443-51.
5. Hackert T, Hinz U, Pausch T, Fesenbeck I, Strobel O, Schneider L, et al. Postoperative pancreatic fistula: We need to redefine grades B and C. Surgery. 2016;159(3):872-7.
6. Hassenpflug M, Hinz U, Strobel O, Volpert J, Knebel P, Diener MK, et al. Teres ligament patch reduces relevant morbidity after distal pancreatectomy (DISCOVER randomized controlled trial). Ann Surg. 2016;264(5):723-30.
7. Vallance AE, Young AL, Macutkiewicz C, Roberts KJ, Smith AM. Calculating the risk of a pancreatic fistula after a pancreaticoduodenectomy: a systematic review. HPB (Oxford). 2015;17(11):1040-8.
8. Bassi C, Buchler MW, Fingerhut A, Sarr M. Predictive factors for postoperative pancreatic fistula: a consensus statement. Ann Surg. 2015;261(4):e99-e101.
9. Malleo G, Pulvirenti A, Marchegiani G, Butturini G, Salvia R, Bassi C. Diagnosis and management of postoperative pancreatic fistula. Langenbecks Arch Surg. 2014;399(7):801-10.
10. Roberts KJ, Sutcliffe RP, Marudanayagam R, Hodson J, Isaac J, Muiesan P. Scoring system to predict pancreatic fistula after pancreaticoduodenectomy: a UK multicenter study. Ann Surg. 2015;261(6):1191-7.
11. Kim WS, Choi DW, Choi SH, Heo JS, Kim MJ, Song SC, et al. Clinical validation of the ISGPF classification and risk factors of pancreatic fistula formation following duct-to-mucosa pancreaticojejunostomy. J Gastrointest Surg. 2011;15(12):2187-94.
12. Keck T, Wellner UF, Bahra M, Klein F, Sick O, Niedergethmann M, et al. Pancreatogastrostomy versus pancreatojejunostomy for reconstruction after pancreatoduodenectomy (RECOPANC trial): perioperative and long-term results of a multicenter randomized controlled trial. Ann Surg. 2016;263(3):440-9.
13. Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study

Group. J Gastrointest Surg. 2007;11(11):1451-8.

14. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score (Fistula Risk Score) to predict pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013;216(1):1-14.

15. Maggino L, Malleo G, Bassi C, Allegrini V, McMillan MT, Borin A, et al. Decoding Grade B pancreatic fistula: a clinical and economic analysis and subclassification proposal. Ann Surg. 2019;269(6):1146-53.

16. Merdrignac A, Garnier J, Dokmak S, Regenet N, Lesurtel M, Mabrut JY, et al. Effect of the Use of Reinforced Stapling on the Occurrence of Pancreatic Fistula After Distal Pancreatectomy: Results of the REPLAY (REinforcement of the Pancreas in distaL pAncreatectomY) Multicenter Randomized Clinical Trial. Ann Surg. 2022;276(5):769-75.

17. Cai H, Lu F, Zhang M, Cai Y, Wang X, Li Y, et al. Pancreaticojejunostomy without pancreatic duct stent after laparoscopic pancreatoduodenectomy: preliminary outcomes from a prospective randomized controlled trial. Surg Endosc. 2022;36(5):3629-36.

18. Miao Y, Lu Z, Yeo CJ, Vollmer CM Jr, Fernandez-Del Castillo C, Ghaneh P, et al. Management of the pancreatic transection plane after left (distal) pancreatectomy: Expert consensus guidelines by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2020;168(1):72-84.

19. Xia W, Zhou Y, Lin Y, Yu M, Yin Z, Lu Xi, et al. A Predictive Risk Scoring System for Clinically Relevant Pancreatic Fistula After Pancreaticoduodenectomy. Med Sci Monit. 2018;24:5719-28.

20. Hong S, Wang H, Yang S, Yang K. External stent versus no stent for pancreaticojejunostomy: a meta-analysis of randomized controlled trials. J Gastrointest Surg. 2013;17(8):1516-25.