The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After

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Background. *In 2005, the International Study Group of Pancreatic Fistula developed a definition and grading of postoperative pancreatic fistula that has been accepted universally. Eleven years later, because postoperative pancreatic fistula remains one of the most relevant and harmful complications of pancreatic operation, the International Study Group of Pancreatic Fistula classification has become the gold standard in defining postoperative pancreatic fistula in clinical practice. The aim of the present report is to verify the value of the International Study Group of Pancreatic Fistula definition and grading of postoperative pancreatic fistula and to update the International Study Group of Pancreatic Fistula classification in light of recent evidence that has emerged, as well as to address the lingering controversies about the original definition and grading of postoperative pancreatic fistula.*
Methods. *The International Study Group of Pancreatic Fistula reconvened as the International Study Group in Pancreatic Surgery in order to perform a review of the recent literature and consequently to update and revise the grading system of postoperative pancreatic fistula.*
Results. *Based on the literature since 2005 investigating the validity and clinical use of the original International Study Group of Pancreatic Fistula classification, a clinically relevant postoperative pancreatic fistula is now redefined as a drain output of any measurable volume of fluid with an amylase level > 3 times the upper limit of institutional normal serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula. Consequently, the former "grade A postoperative pancreatic fistula" is now redefined and called a "biochemical leak," because it has no clinical importance and is no longer referred to a true pancreatic fistula. Postoperative pancreatic fistula grades B and C are confirmed but defined more strictly. In particular, grade B requires a change in the postoperative management; drains are either left in place > 3 weeks or repositioned through endoscopic or percutaneous procedures. Grade C postoperative pancreatic fistula refers to those postoperative pancreatic fistula that require*

Accepted for publication November 15, 2016.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2016.11.014

reoperation or lead to single or multiple organ failure and/or mortality attributable to the pancreatic fistula. ***Conclusion.*** *This new definition and grading system of postoperative pancreatic fistula should lead to a more universally consistent evaluation of operative outcomes after pancreatic operation and will allow for a better comparison of techniques used to mitigate the rate and clinical impact of a pancreatic fistula. Use of this updated classification will also allow for more precise comparisons of surgical quality between surgeons and units who perform pancreatic surgery. (Surgery 2017;161:584-91.)*

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In 2005, an International working group of 37 pancreatic surgeons from all inhabited continents (the International Study Group of Pancreatic Fistula [ISGPF]) was convened to reach a universally accepted and objective definition of postoperative pancreatic fistula (POPF). Twenty-six different definitions of a POPF existed at that time, so that any critical comparison between outcomes among surgeons and clinical centers was impossible due to often different definitions of what was considered to be a POPF according to the authors of each study. Prior to this classification, no attempt to classify POPF had been accepted internationally. Based on a review of the literature by the ISGPF, a POPF was defined as an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid.[1] This condition might be related to either a leak of a pancreatic-enteric anastomosis or, alternatively, originating from the traumatized, raw pancreatic surface. A consensus was reached defining a POPF as fluid output of any measureable volume via an operatively placed drain with amylase activity greater than 3 times the upper normal serum value. Moreover, a clinical system of 3 discrete grades of POPF (grades A, B, and C) was proposed based on the complication-specific severity.

Eleven years after its definition, POPF still remains one of the most harmful complications after pancreatic resection.[2-5] Despite all the advances and technical modifications developed during this past decade to prevent POPF, the incidence of this dreaded complication still ranges between 3–45 % of pancreatic operations at high-volume centers.[6-9] Updating the ISGPF classification is both relevant and clinically important, because POPF remains the single main determinant of serious postoperative morbidity and mortality related to pancreatic resection and plays a major role in terms of operation-related mortality, morbidity, hospital stay, and economic impact.[10-12]

The aim of the present article is 2-fold: first to verify the actual usefulness of the ISGPF definition and grading of POPF both in clinical practice and for scientific purposes, and second, to update the International Study Group on Pancreatic Surgery (ISGPS) 2005 consensus statement in the light of recent evidence that has emerged.

METHODS

After the publication of a recent article by the Heidelberg group,[13] the need for an update of the definition and grading of POPF has become evident, and a new stimulus was given to the ISGPS. All the pancreatic surgeons taking part in the original study group were contacted by e-mail. The ISGPS was redefined after confirmation by the bulk of the previous members and adding new experts who have provided substantial contributions in the field during the past decade. The study group carried out a complete review of the literature. An extensive search was conducted on PubMed and Embase of all published articles of interest in this context. The following search terms were used: "pancreatic fistula," "POPF," "pancreas leak," and "anastomotic failure." All obtained results were analyzed, and a manual inspection of the cited references also was performed to find any other related articles. An internal analysis of the institutional experiences of the ISGPS members was carried out to validate literature results. The draft of the POPF definition and updating of the grading system was circulated to all participants for comments and validation with the available local databases. Revised drafts were circulated through electronic mail for critical analysis and further modifications. Two meetings were scheduled to discuss the manuscript drafts: during the International Hepato-Pancreato-Biliary Association Conference held in Sao Paulo, Brazil, and during the European Pancreatic Club held in Liverpool, UK, both in 2016. Multiple revisions were circulated, commented, and edited electronically to all the contributing members of the ISGPS. Eventually, all members approved the final version.

RESULTS

Acceptance of the 2005 ISGPF POPF definition and grading. Since its release in the journal *Surgery* in May 2005,[1] the original article by the ISGPF has been cited 1,703 times (until December 2015 from the Web of Science Core Collection[14]), making it one of the most-ever cited articles in the pancreatic surgery literature. Of note, a recent systematic review has assessed that it is actually the 15th most-cited article of all times in the field of visceral operation.[15] In particular, as a demonstration of its acceptance and its efficacy, 10 years after its publication, the ISGPF definition and classification system has been applied to >320,000 patients reported in original studies. Conversely, our PubMed and Medline search from 2005 for the above-mentioned keywords provided few articles suggesting a different definition and grading system other than that of the original ISGPF classification.

Several articles validated the ISGPF definition and grading of POPF. Pratt et al[16] applied the classification scheme in 2007 in 176 consecutive patients. They found that all clinical outcomes were equivalent between the no fistula and the grade A fistula patients; moreover, the costs, duration of hospital and intensive care unit (ICU) stays, and the utilization of resources increased progressively from grade A to grade C POPFs. Similarly, Kim et al[17] demonstrated the progressive clinical impact of different grades of POPF, and that patients with a grade A fistula had identical outcomes to those without a fistula. Interestingly, although risk factors for clinically relevant fistulas have been established and eventually led to risk scores assessment, no predictors of grade A POPF have been found.[18] The economic implications of the development of a POPF was evaluated in a series of 755 pancreatoduodenectomies by the Verona group.[19] Of note, the ISGPF grading system allowed for a correct stratification of the patients with complications based on the POPF-related costs.

Issues related to the 2005 ISGPF POPF definition and grading. Most of the more recent publications focusing on the impact of POPF after pancreatic operation refer to either "clinically relevant" fistulas (grades B–C), or a condition where both the "no fistula" and "grade A fistula" are considered together.[5,6,11,13,20,21] As a result, there might be confusion as to whether the overall rate of POPF refers to the entire cohort of grades A, B, and C or only to the CR grades B and C POPF, questioning the clinical relevance of a grade A POPF. There is, therefore, a discrepancy in the reported literature as to what exactly are the rates of POPF; publications that include grade A POPF in their analysis regularly demonstrate rates twice as high as those that report only grades B and C POPF. A recent, multicenter, multinational report of >4,000 pancreatoduodenectomies indicated an overall POPF rate of 19.2%, of which 42.3% were biochemical (grade A) leaks; CR-POPFs occurred in 11.1% of all cases.[22] The introduction of new policies such as pancreatic resections without the use of intraperitoneal drains in individuals at negligible-low risk of POPF development has again forced the ISGPF to reconsider the actual reporting of grade A as a "fistula." In fact, such conditions would eliminate the occurrence of a biochemical leak (BL), which is clinically unimportant because in those individuals the presence of amylase-rich fluid could not be tested.

Event	BL (NO POPF)	Grade B POPF*	Grade C POPF*
Increased amylase activity > 3 times upper limit Institutional normal serum value	YES	YES	YES
Persisting peripancreatic drainage > 3 weeks	NO	YES	YES
Clinically relevant change in management of POPF#	NO	YES	YES
POPF percutaneous or endoscopic specific interventions for collections	NO	YES	YES
Angiographic procedures for POPF related bleeding	NO	YES	YES
Reoperation for POPF	NO	NO	YES
Signs of infection related to POPF	NO	YES, without organ failure	YES, with organ failure
POPF related organ failure^	NO	NO	YES
POPF related death	NO	NO	YES

Fig 1. The Revised 2016 ISGPS classification and grading of POPF: checklist for clinical use. *ISGPS*, International Study Group on Pancreatic Surgery; *POPF*, postoperative pancreatic fistula. *A clinically relevant POPF is defined as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper Institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the POPF. #Suggests prolongation of hospital or ICU stay, includes use of therapeutic agents specifically employed for fistula management or its consequences (of these: somatostatin analogues, TPN/TEN, blood product transfusion or other medications). ^Postoperative organ failure is defined as the need for re-intubation, hemodialysis, and/or inotropic agents > 24 hours for respiratory, renal, or cardiac insufficiency, respectively.

As for the maintenance of the peripancreatic drainage tube(s) at the time of hospital discharge as a threshold to define a CR-POPF, controversies have arisen with the widespread use of minimally invasive techniques for resection of the distal pancreas. In these cases, patients can be discharged from the hospital sooner, with the drains left in place and without a significant variation from the "normal" postoperative course.

Finally, the definition and grading of POPF also has revealed a divergent interpretation between grades B and C POPF concerning the use of interventional drainage (ID), either by percutaneous or endoscopic techniques These practices have become the standard of care for the initial approach to symptomatic, postoperative intra-abdominal fluid collections which are diagnosed subsequently as an un-drained POPF.[13,23] Using the 2005 ISGPF, some investigators were unclear whether the use of ID should shift a grade B POPF into the category of a grade C POPF. In the original 2005 ISGPF classification, a grade B POPF "may require repositioning of the drains," but "if an invasive procedure is needed, the grade B POPF will shift up to a grade C." As such, patients requiring ID for POPF-related collections have been categorized differently into B and C grades in the literature.[17,21,24-27]

Update of the definition of POPF. Pancreatic fistula remains an abnormal communication between the pancreatic ductal "system" and another epithelial surface containing pancreas-derived, enzyme-rich fluid. For the diagnosis, any measurable volume of drain fluid on or after postoperative day 3 with amylase level >3 times the upper limit of normal amylase for each specific institution is the necessary threshold. To be defined strictly as a POPF, however, this condition needs to be clinically relevant. Whenever an increased amylase activity is found in the fluid from an operatively placed drain, which does not impact on the clinical outcome of the patient, no fistula should be reported.

Update of POPF grading. Figure 1 summarizes the main features of the update of the ISGPF grading system. As was the case with the previous classification scale, the grade of severity may be defined only after the course of the "fistula" event has evolved completely, and its ultimate effect on the outcome can be assessed.

BL: Formerly grade A POPF. This condition applies to the original "grade A" POPF, and no longer is considered a true pancreatic fistula or an actual complication. As called a "biochemical fistula" in the literature, the BL has by definition no clinical impact. In particular, a BL implies no deviation in the normal postoperative pathway and therefore, does not affect the normal postoperative duration of stay. In some cases, a drain may remain in place even after discharge for observation purposes for up to 3 weeks after operation, before it might be considered to have a clinical impact on the patient.

The patient, however, remains clinically well, fed orally, and can adhere to an enhanced recovery pathway. If no drains are placed in individuals with negligible/low-risk of development of a POPF (hard pancreas, dilated main pancreatic duct, or operated for pancreatic cancer or chronic pancreatitis),[28-30] a BL is eliminated, because it cannot even be reported. Of note, if postoperative death occurs, that would not shift the BL into a grade C fistula, as sudden fatal conditions such as myocardial infarction, renal failure, or fatal pulmonary embolus cannot be considered as sustained by the BL.

Grade B POPF. This grade refers to a properly defined fistula involving increased amylase activity in the fluid from any drain in association with a clinically relevant condition. A grade B POPF requires a change in the management of the expected postoperative pathway. Unlike the BL, the pancreatic drains might be left in place for an extended period (defined as 3 weeks/21 days after operation), or there may be a need to reposition the operatively placed drains through interventional, image-guided means to "decompress" an undrained intra-abdominal fluid collection.[31] Alternatively, percutaneous or endoscopic ID is warranted for the same purpose. If a POPF-related hemorrhage or pseudo-aneurism occurs, transfusions and/or angiography usually are necessary. Whenever reoperation is needed or organ failure occurs, the fistula shifts to a grade C POPF. In most cases, the POPF is associated with signs of mild infection (leucocytosis and mild fever) requiring only antibiotic administration; however, once single or multiple organ dysfunctions occurs, the fistula would shift to a C grade POPF. Finally, if sudden death occurs (eg, secondary to myocardial infarction, fatal pulmonary embolus, or renal failure), the grade B POPF might shift into a C in case the fistula represents the initiating/triggering factor.

Because of these grade B POPF-related complications, patients may be kept on nothing per mouth and supported with either enteral or parenteral nutrition and sometimes therapeutic somatostatin analogues. In the vast majority of cases, transfer to an ICU is not necessarily warranted but might be chosen. ICU use alone does not necessarily shift the grade B POPF to a grade C POPF without evidence of organ failure. Many patients with a grade B POPF need long-standing, intra-abdominal drainage and are even discharged with these drains in place.

Grade C POPF. Whenever a grade B POPF leads to organ failure or to clinical instability such that a reoperation is needed, the POPF becomes a grade C. Often, stay in an ICU is necessary, and the hospital stay becomes excessively prolonged secondary to the POPF-related problems. For the purpose of POPF classification, postoperative organ failure is defined as the need for reintubation, hemodialysis, and/or use of inotropic agents for >24 hours because of respiratory, renal, or cardiac insufficiency, respectively. Reoperation usually is performed after attempts at percutaneous and/or endoscopic ID have failed to improve the clinical

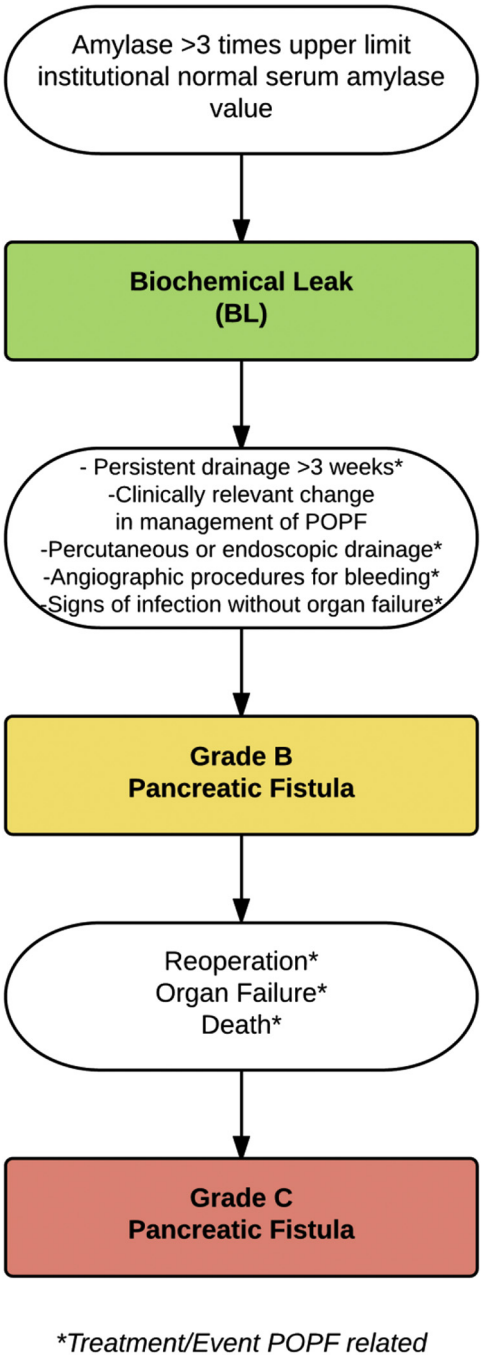

Fig 2. Flow chart for BL and POPF grade definition. *BL*, Biochemical leak; *POPF*, postoperative pancreatic fistula.

outcome, and is specifically addressed to treat the fistula.[16] Obviously, reoperation potentially is associated with relevant morbidity and mortality. In addition to the above, if a subsequent POPF-specific mortality takes place even without a reoperation, the POPF becomes a grade C POPF. Each of these 3 defining scenarios occurs during approximately a third of grade C POPFs, and they are commonly concurrent.[32]

DISCUSSION

The conclusions of the 2005 ISGPF publication suggested that the use of the proposed classification of POPF would confirm its clinical value and allow accurate comparison across different surgical practices internationally.[1] Indeed, 11 years later, the ISGPS has re-evaluated the impact of this original classification and can attest that the original goals in creating the classification have been reached. We now speak a common language for many aspects of pancreatic operation, and POPF has become a standardized definition in our clinical lexicon. The number of citations of the original 2005 ISGPF article (n = 1,707) and the almost universal acceptance of the definition and classification of POPF reinforces this concept. The use of the ISGPF classifications have provided the ability to better assess the efficacy of numerous operative approaches and mitigation strategies, and analyse surgical performance.[22,33,34] The strength of the original 2005 ISGPF classification was both its brevity and objective simplicity as well as its clinical applicability. The same need for conciseness and simplicity is the basis of the current update. Several articles have validated the grading system used by the ISGPF and have confirmed its usefulness and acceptance from a clinical, financial, and academic point of view. Therefore, the current update needs to preserve this objectivity. With this update, we preserve 3 grades of severity. First: a condition that has no clinical implications (BL) but still implies a situation that is not absolutely normal (ie, increased amylase activity in the drainage fluid), cannot be totally ignored, but also cannot be called a "fistula." Indeed, as a result, many surgical series since 2005 have excluded grade A from their analysis of outcomes. Second, grade B reflects the occurrence of clinically relevant morbidity from a pancreatic fistula that impacts the postoperative course (prolonging hospitalization) but only requires therapeutic agents and less-invasive treatment or percutaneous, endoscopic, or angiographic interventional procedures. Third, grade C involves a more serious, systemic condition characterized by POPF-related organ failure, possibly requiring operative intervention and/or burdened by substantial morbidity or even death.

In order to clarify and further expand the previous validated classification, several simple but relevant modifications have been introduced in the present update (Fig 2). The first change is to rename the former "grade A POPF" into "BL." Our aim is to avoid the implication of this condition being called a "fistula," because it has no clinical relevance. This update will allow for a better and clearer identification of what is meant by the "fistula rate" of an operative series, because use of the original classification of POPF could refer either to the overall occurrence of all grades of POPFs (grades A, B, and C) or only to those having a clinical impact (only grades B and C). Moreover, the striking differences in the rates of grade A POPFs found in the literature, ranging from almost zero to 50%, underline how clinicians have either over- or underestimated this condition.[13,19,20] This distinction is important, because some groups sample the amylase activity in the drainage fluid on a regular basis; in contrast, others think that the amylase activity in the fluid is unimportant from the clinical standpoint when there are no symptoms, and the drains are removed even in the presence of increased amylase levels in the drainage fluid. Others do not place a drain at the time of resection, and therefore, the defining "threshold" of an increased drain amylase level is not even discoverable. Of note, the finding of an increased amylase activity in the drainage fluid is, however, not normal and implies some "leakage" of pancreatic exocrine secretions from somewhere in the pancreas, either from the anastomosis or from the parenchyma across a cut or traumatized surface of the gland. Nevertheless, it should not be called a "fistula," but likewise it also cannot be ignored, but rather it should be referred to a BL-clinically unimportant. Therefore, with this updated classification, a former grade A should no longer be called a fistula nor need to be quantitated in the calculation of the POPF rate.

The second important change in the POPF grading system is regarding the "grey area" in the original 2005 classification of the use of ID procedures and whether the need for such procedures should move the grade of severity from grade B to grade C POPF. This lack of clarity in the original definition of severity has led to different interpretations in the literature. As pointed out by Hackert et al,[13] some series have included the need for percutaneous ID of an intra-abdominal collection with increased amylase activity in the grade B group,[21,24,27] others in the C group,[25,26] and others by shifting a grade B to a grade C POPF.[17,32] The

different clinical impact of ID versus a reoperation for POPF is obvious, as demonstrated by the zero mortality rate associated with percutaneous or endoscopic ID alone compared with a mortality of ≥35% of the need for operative intervention.[13] Because the type of interventional procedure has a strong prognostic implication, it is now suggested using reoperation as the interventional parameter to shift a grade B POPF into a grade C POPF. This concept applies also to the hemorrhage related to a POPF, which is potentially a life-threatening condition, but might be recognized early as "sentinel bleeding" and then managed through interventional endoscopic stenting or embolization without developing organ failure or requiring operative reintervention. Whenever one or both of these 2 conditions are met, they shift a grade B to grade C POPF.

Here, we emphasize that the presence of organ failure, either single or multiple, always shifts the grade from a grade B to a grade C POPF. This condition often implies concomitant sepsis, as the International Consensus for Sepsis and Septic shock has recently redefined[35]; however, in order to make it easy to assess and report, postoperative organ failure in relation to the POPF definition has been strictly defined according to the required intervention for the system failure. Similarly, any death related to a POPF, regardless of how it is treated along the way, should be categorized a grade C fistula as well. A word of caution must be used every time sudden death occurs in a patient with a grade B POPF. In most of these cases, fistula-related sepsis and/or bleeding play a crucial role in triggering processes eventually leading to death. Only in exceptional cases are a grade B POPF and a patient's sudden death completely unrelated, and in those cases, a grade C fistula should not be reported.

We are aware that the grade B POPF is a heterogeneous clinical condition, and a critical factor in determining its burden is the degree of severity of the infection occurring because of the fistula itself.[36] There has been a substantial amount of debate whether to stratify the grade B category into subcategories depending on the severity of infection to some extent, or the resources used to treat it; however, we maintain that our aim to keep this classification simple would be better accomplished by keeping this grade of severity simple as well.

Whether this update will follow the successful acceptance of the original POPF definition and grading is a matter of further validation and use; however, we think that the practice of sharing and comparing the outcomes of different surgical series using this updated classification of POPF still remains the main determinant of outcome after pancreatectomy. A simple, objective, and useful definition and classification of POPF remains the fundamental step to developing methods to prevent and treat this postoperative condition.

REFERENCES

1. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.
2. Miller BC, Christein JD, Behrman SW, et al. Assessing the impact of a fistula after a pancreaticoduodenectomy using the Postoperative Morbidity Index. HPB (Oxford) 2013;15:781-8.
3. Callery MP, Pratt WB, Kent TS, et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 2013; 216:1-14.
4. Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. Ann Surg 2007;246:281-7.
5. Vallance AE, Young AL, Macutkiewicz C, et al. Calculating the risk of a pancreatic fistula after a pancreaticoduodenectomy: a systematic review. HPB (Oxford) 2015;17:1040-8.
6. Bassi C, Buchler MW, Fingerhut A, et al. Predictive factors for postoperative pancreatic fistula. Ann Surg 2015;261:e99.
7. Bassi C, Butturini G, Molinari E, et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. Dig Surg 2004;21:54-9.
8. Zhang H, Zhu F, Shen M, et al. Systematic review and meta-analysis comparing three techniques for pancreatic remnant closure following distal pancreatectomy. Br J Surg 2015;102:4-15.
9. Xiong JJ, Tan CL, Szatmary P, et al. Meta-analysis of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Br J Surg 2014;101:1196-208.
10. Allen PJ, Gonen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med 2014;370:2014-22.
11. Malleo G, Pulvirenti A, Marchegiani G, et al. Diagnosis and management of postoperative pancreatic fistula. Langenbecks Arch Surg 2014;399:801-10.
12. Vollmer CM Jr, Sanchez N, Gondek S, et al. A root-cause analysis of mortality following major pancreatectomy. J Gastrointest Surg 2012;16:89-102; discussion 102-3.
13. Hackert T, Hinz U, Pausch T, et al. Postoperative pancreatic fistula: we need to redefine grades B and C. Surgery 2016; 159:872-7.
14. Web of Science Core Collection 2015. Available from: http://wokinfo.com; 2015.
15. Muller M, Gloor B, Candinas D, et al. The 100 most-cited articles in visceral surgery: a systematic review. Dig Surg 2016;33:509-19.
16. Pratt WB, Maithel SK, Vanounou T, et al. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg 2007;245:443-51.
17. Kim WS, Choi DW, Choi SH, et al. Clinical validation of the ISGPF classification and the risk factors of pancreatic fistula formation following duct-to-mucosa pancreaticojejunostomy by one surgeon at a single center. J Gastrointest Surg 2011;15:2187-92.

18. Pratt WB, Callery MP, Vollmer CM Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. World J Surg 2008;32:419-28.
19. Daskalaki D, Butturini G, Molinari E, et al. A grading system can predict clinical and economic outcomes of pancreatic fistula after pancreaticoduodenectomy: results in 755 consecutive patients. Langenbecks Arch Surg 2011;396:91-8.
20. Roberts KJ, Sutcliffe RP, Marudanayagam R, et al. Scoring system to predict pancreatic fistula after pancreaticoduodenectomy: a UK multicenter study. Ann Surg 2015;261:1191-7.
21. Keck T, Wellner UF, Bahra M, et al. Pancreatogastrostomy Versus Pancreatojejunostomy for RECOnstruction After PANCreatoduodenectomy (RECOPANC, DRKS 00000767): perioperative and long-term results of a multicenter randomized controlled trial. Ann Surg 2016;263:440-9.
22. McMillan MT, Soi S, Asbun HJ, et al. Risk-adjusted outcomes of clinically relevant pancreatic fistula following pancreatoduodenectomy: a model for performance evaluation. Ann Surg 2016;264:344-52.
23. Lermite E, Sommacale D, Piardi T, et al. Complications after pancreatic resection: diagnosis, prevention and management. Clin Res Hepatol Gastroenterol 2013;37:230-9.
24. Reid-Lombardo KM, Farnell MB, Crippa S, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 2007;11:1451-8; discussion 1459.
25. Goh BK, Tan YM, Chung YF, et al. Critical appraisal of 232 consecutive distal pancreatectomies with emphasis on risk factors, outcome, and management of the postoperative pancreatic fistula: a 21-year experience at a single institution. Arch Surg 2008;143:956-65.
26. Frymerman AS, Schuld J, Ziehen P, et al. Impact of postoperative pancreatic fistula on surgical outcome—the need for a classification-driven risk management. J Gastrointest Surg 2010;14:711-8.
27. Fuks D, Piessen G, Huet E, et al. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. Am J Surg 2009;197:702-9.
28. McMillan MT, Fisher WE, Van Buren G 2nd, et al. The value of drains as a fistula mitigation strategy for pancreatoduodenectomy: something for everyone? Results of a randomized prospective multi-institutional study. J Gastrointest Surg 2015;19:21-30; discussion 30-1.
29. McMillan MT, Malleo G, Bassi C, et al. Drain management after pancreatoduodenectomy: reappraisal of a prospective randomized trial using risk stratification. J Am Coll Surg 2015;221:798-809.
30. McMillan MT, Malleo G, Bassi C, et al. Multicenter, prospective trial of selective drain management for pancreatoduodenectomy using risk stratification. Ann Surg 2016. [Epub ahead of print].
31. Barreto G, D'Souza MA, Shukla PJ, et al. The gray zone between postpancreaticoduodenectomy collections and pancreatic fistula. Pancreas 2008;37:422-5.
32. McMillan MT, Vollmer CM Jr, Asbun HJ, et al. The characterization and prediction of ISGPF grade C fistulas following pancreatoduodenectomy. J Gastrointest Surg 2016;20:262-76.
33. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761-8.
34. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-5.
35. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
36. Gebauer F, Kloth K, Tachezy M, et al. Options and limitations in applying the fistula classification by the International Study Group for Pancreatic Fistula. Ann Surg 2012;256:130-8.