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Low Drain Fluid Amylase Predicts Absence of Pancreatic Fistula Following Pancreatectomy

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Abstract

Introduction—Improvements in the ability to predict pancreatic fistula could enhance patient outcomes. Previous studies demonstrate that drain fluid amylase on postoperative day 1 (DFA1) is predictive of pancreatic fistula. We sought to assess the accuracy of DFA1 and to identify a reliable DFA1 threshold under which pancreatic fistula is ruled out.

Methods—Patients undergoing pancreatic resection from November 1, 2011 to December 31, 2012 were selected from the American College of Surgeons-National Surgical Quality Improvement Program Pancreatectomy Demonstration Project data-base. Pancreatic fistula was defined as drainage of amylase-rich fluid with drain continuation >7 days, percutaneous drainage,

or reoperation for a pancreatic fluid collection. Univariate and multi-variable regression models were utilized to identify factors predictive of pancreatic fistula.

Results—DFA1 was recorded in 536 of 2,805 patients who underwent pancreatic resection, including pancreaticoduodenectomy ($n=380$), distal pancreatectomy ($n=140$), and enucleation ($n=16$). Pancreatic fistula occurred in 92/536 (17.2 %) patients. DFA1, increased body mass index, small pancreatic duct size, and soft texture were associated with fistula ($p<0.05$). A DFA1 cutoff value of <90 U/L demonstrated the highest negative predictive value of 98.2 %. Receiver operating characteristic (ROC) curve confirmed the predictive relationship of DFA1 and pancreatic fistula.

Conclusion—Low DFA1 predicts the absence of a pancreatic fistula. In patients with DFA1 <90 U/L, early drain removal is advisable.

Keywords

Pancreatectomy; Drain fluid amylase; Pancreatic fistula; American College of Surgeons-National Surgical Quality Improvement Program

Introduction

Although the mortality of pancreatectomy has improved, one of the most common complications remains pancreatic fistula. Wide variability exists in reported rates of pancreatic fistula, ranging from 2 to 46 %, likely due to variation in definition as well as in surgeon expertise.^{1–3} Recently, the International Study Group on Pancreatic Fistula (ISGPF) established a widely accepted definition for pancreatic fistula (PF) based upon clinical impact or related complications.⁴ By standardizing the definition, comparison of pancreatic fistula rates among series is enhanced. Despite numerous studies reporting risk factors for pancreatic fistula, standard evidence-based guidelines for postoperative drain management do not exist.

Initial studies in the early postoperative period revealed that drain fluid amylase on postoperative day 1 (DFA1) is a significant predictor of pancreatic fistula.^{5–10} However, these studies have shown variable results with respect to cutoff levels. Molinari et al. proposed that DFA1 $>5,000$ U/L was a significant predictor of pancreatic fistula.⁶ Since this publication, DFA1 values of $>4,000$, 350, and 100 U/L have been proposed as predictors of clinically significant fistulas.^{8–11} However, these studies were limited by either the retrospective approach, small study populations, and/or the fact that they were single-institution studies. Despite these discrepancies, each of these investigations has confirmed that DFA1 serves as a clinically useful predictor of pancreatic fistula. While DFA1 has been associated with pancreatic fistula, this factor has yet to be evaluated in a large, prospective multiinstitutional cohort, and a reliable cutoff value that can be used in guiding postoperative drain management has not been established. Therefore, the goal of this study was to evaluate the role of DFA1 as an indicator of the absence of pancreatic fistula, using a large national database of patients in the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) Pancreatectomy Demonstration Project.

Methods

Data Collection

The ACS-NSQIP is a national, multi-institutional, prospectively collected database established to identify 21 categories of 30-day postoperative morbidity and mortality at participating institutions.^{12–14} ACS-NSQIP was created to provide riskadjustment outcome data to participating hospitals for the purpose of quality improvement. The Participant Use File (PUF) details over 200 Health Insurance Portability and Accountability Act (HIPAA)-protected perioperative variables. Data collection was performed at NSQIP-participating institutions by dedicated Surgical Clinical Reviewers (SCRs) with support and oversight from a nurse coordinator. Descriptions of the qualifications, training, and auditing of data collection personnel, case inclusions criteria, sampling and data collection strategy, as well as variable and outcome definitions are available online in the ACS-NSQIP participant user guide.¹³ The Pancreatectomy Demonstration Project (PDP) was established to enhance data collection for pancreas procedures, since NSQIP complication definitions did not adequately capture procedure-specific complications, such as pancreatic fistula and delayed gastric emptying.

Twenty-four pancreas-specific variables classified by operative phase (preoperative, operative, and postoperative) were included to assess the quality of pancreatic surgery. Patients undergoing pancreatic resection at 43 institutions participating in the Procedure-Targeted Pancreatectomy Program (see “Acknowledgment” section) were enrolled in the ACS-NSQIP PDP between November 2011 and December 2012. A complete list of the 24 variables is presented in Table 1. Pathology data were recorded only during the last seven of the 14-month study period. More than 200 patient variables routinely captured in ACS-NSQIP also were linked with the pancreatectomy-specific variables.

Inclusion and Exclusion Criteria

All patients underwent partial pancreatectomy, including pancreaticoduodenectomy, distal pancreatectomy, and enucleation. Patients who underwent total pancreatectomy were excluded. Only patients with a recorded DFA1, which by default meant that drains were placed at the time of surgery, were included. In addition, patients with missing pancreatic fistula data were excluded.

Data Definition

Pancreatic duct size at the site of the transected pancreas was noted by preoperative imaging or as specified by the surgeon in the operative report. The sizes were categorized as <3, 3–6, and >6 mm, or unknown if not stated. Pancreatic gland texture was classified as soft (normal), intermediate (indurated), hard (firm or fibrotic), or unknown, as noted by the operating surgeon in the operative report. Intra-abdominal drains placed at the time of the initial operation were specified by the surgeon in the operative note and recorded as yes, no, or unknown.

Pancreatic fistula was defined as persistent drainage (a drain output of any measurable volume of fluid on or after post-operative day (POD) 3) of amylase-rich fluid (an amylase

content greater than three times the serum amylase activity) in addition to the following: drain continuation >7 days, percutaneous drainage, or reoperation for a pancreatic fluid collection. The attending surgeon also had the option to determine a clinical diagnosis of pancreatic fistula. Clinically relevant pancreatic fistulas included those requiring percutaneous drainage or reoperation as well as those resulting in mortality. Prolonged drainage without the measurement of drain amylase was not considered to be a pancreatic fistula. Postoperative day 1 drain amylase was recorded as the highest chemical amylase level from any drain on POD 1. Drain output volume was not collected. All complications that occurred by 30 days postoperatively were recorded per ACS-NSQIP methodology.¹²

Statistical Analysis

Comparisons of patient demographic and postoperative variables between groups were evaluated using chisquare and unpaired t tests as appropriate. Logistic regression models were performed to analyze potential prognostic factors for pancreatic fistula. Only factors which had a p value <0.10 on univariate analysis were included in the multi-variable model. Receiver operating characteristic (ROC) curves were created based upon previously cited and newly established DFA1 cutoff levels in this study.^{6,8-11}

On final multi-variable analysis, p values <0.05 were considered statistically significant. Negative predictive value was defined as the proportion of patients without PF among those who had a negative test result. Positive predictive value was defined as the proportion of patients who had PF among those with a positive test result. All statistical analyses were performed using SPSS software (version 21, SPSS Inc., Chicago, IL).

Results

Data Acquisition and Patient Selection

A total of 2,805 patients underwent pancreatic surgery at the 43 institutions enrolled in the ACS-NSQIP PDP. As noted in Fig. 1, 2,269 patients were excluded. Therefore, the total study population included 536 patients.

Demographic, Pancreatic Fistulas, and Mortality Data

The mean age of the study patients was 62.7 years (range, 19.2 to 94.2 years) with 48.9 % males and 51.1 % females (Table 2). Mean operative time was 350 min (range, 66 to 1,122 min). Types of resection included 380 pancreaticoduodenectomy (70.9 %), 140 distal pancreatectomy (26.1 %), and 16 enucleations (3.0 %). The most common pathology within the DFA1 group was adenocarcinoma. The overall pancreatic fistula rate was 17.2 %. Pancreatic fistulas developed in 37.5 % of patients after enucleation, in 17.4 % of pancreaticoduodenectomy patients, and in 14.3 % of patients after distal pancreatectomy. The overall 30-day mortality rate was 1.5 % (8/536).

Predictors of Pancreatic Fistula

Results of univariate analysis revealed four significant predictors of pancreatic fistula including BMI greater than 30 kg/m² (p <0.012), soft pancreatic gland texture (p <0.001), small pancreatic duct size (p <0.001), and DFA1 (p <0.001). Among obese patients, 25.4 %

experienced PF. In patients with a pancreatic duct <3 mm, 29.3 % had a PF. In patients with a soft gland texture, a PF occurred in 27.5 %.

Multi-variable logistic regression analysis was performed incorporating all variables with p value <0.1 on univariate analysis. In addition to BMI, pancreatic duct size, and gland texture, DFA1, analyzed as a continuous variable, was strongly associated with pancreatic fistula (Table 3).

Comparison of Patients with Known DFA1 vs. Unknown DFA1

Due to the large number of patients who were excluded secondary to unmeasured DFA1, further comparison between these groups was performed. No significant difference existed in age, gender, diabetes, BMI, smoking status, presence of jaundice, biliary stent placement, neoadjuvant therapy, intra-operative transfusion, or mean operative times comparing patients who did and did not have DFA1 recorded (Table 4). In addition, no difference was observed in the incidence of pancreatic fistula between groups [17.2 % (92/536) with known DFA1 vs. 16.0 % (16/2,078) with unknown DFA1; $p=0.524$].

Correlation Between DFA1 and Pancreatic Fistula Formation

Table 5 depicts the sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) at varying cutoff levels of DFA1. A strong correlation existed between pancreatic fistula and DFA1 ($p<0.001$), confirmed by the area under the ROC curve (c-statistic) of 0.761 (Fig. 2, 95 % CI 0.711–0.810). As the DFA1 cutoff value decreased, both the sensitivity and NPV improved. Among multiple DFA1 cutoff values, 90 U/L demonstrated the highest NPV (98.2 %). When subanalyses of the 380 pancreaticoduodenectomy and 180 distal pancreatectomy patients were performed, these cutoff levels were similar. For pancreaticoduodenectomy, the sensitivity and NPV for DFA1 < 90 U/L were 95.5 and 97.9 %, respectively. For distal pancreatectomy both the sensitivity and NPV were 100 % for DFA1 < 90 U/L. For the 16 enucleation patients, the sensitivity and NPV were 100 % for DFA1 < 2,500 U/L. The incidence of pancreatic fistula at each cutoff level of DFA1 is demonstrated in Fig. 3. These pancreatic fistula rates at the various DFA1 cutoff levels were similar for the pancreaticoduodenectomy and distal pancreatectomy patients. At DFA1 < 90 U/L, three of 141 pancreaticoduodenectomy patients (2.1 %) developed a pancreatic fistula whereas none of the distal pancreatectomy ($n=23$) nor the enucleation patients ($n=2$) developed a fistula.

Discussion

Pancreatic fistula may significantly prolong a patient's post-operative course and complicate management, increasing the need for antibiotics, drainage of intra-abdominal collections, and/or reoperation. Former studies have investigated factors associated with pancreatic fistula following pancreatectomy, including predictive preoperative risk factors, surgical technique, modified drain regimens, administration of somatostatin, and drain fluid amylase levels.^{2, 5–11, 15–24} Our study uses data from a large multi-institutional collaborative to establish a DFA1 value of 90 U/L, under which pancreatic fistula is very unlikely. This

value can be used to guide early drain removal and provide risk stratification, which may expedite postoperative care and improve outcomes.

The concept of early drain removal following pancreaticoduodenectomy was proposed as a method to reduce overall morbidity.¹ A prospective randomized trial by Bassi et al. demonstrated an association between early drain removal (POD 3 vs. POD 5) and a decreased incidence of pancreatic fistula in patients with DFA1 < 5,000 U/L (pancreatic fistula 1.8 %, drain removal at POD 3 vs. 26.3 %, drain removal at POD 5, $p=0.0004$). In this study, the timing of drain removal was the strongest independent predictor associated with pancreatic fistula formation.¹ Furthermore, in a prospective non-randomized analysis by Kawai et al., an association of decreased morbidity was observed with respect to pancreatic fistula and intra-abdominal infections when drains were removed early (POD 4 vs. POD 8). When drains were removed on POD 4, the pancreatic fistula rate was only 4 % compared to 23 % when drains were removed on POD 8 ($p=0.0038$). The duration of drain placement was the only independent risk factor discovered for intra-abdominal infections.⁵ Based on these two studies, the current evidence suggests that early drain removal is associated with a decreased risk of pancreatic fistula. The present study adds substantially to the current literature by enhancing the surgeon's ability to understand the risk of pancreatic fistula at each DFA1 cutoff, so that early drain removal can be confidently recommended. However, in the dataset, only 24 % of patients had a recorded DFA1, suggesting that surgeons are not incorporating DFA1 evaluation into their routine postoperative pathway. This postoperative management strategy is clearly an area with substantial opportunity for future quality improvement.

The association between drain fluid amylase level and pancreatic fistula formation has been established in multiple recent series,⁸⁻¹¹ although these studies were limited by small size, variable pancreatic fistula definition, and primarily single-institution focus. The concept of using DFA1 to predict the presence of pancreatic fistula was initially proposed by Molinari et al., who found that a DFA1 level of 5,000 U/L distinguished high and low risk groups. Although DFA1 5,000 U/L was associated with high sensitivity (93 %), the specificity was low (84 %).⁶ Subsequent studies identified lower but more varied DFA1 cutoff values, 4,000 and 350 U/L, providing additional evidence by which to recommend optimal timing of drain removal^{8,9} (Table 6). Following these studies, a simple drain removal algorithm was proposed by Nissen and colleagues, in which DFA was evaluated daily in patients who underwent pancreaticoduodenectomy, revealing a NPV of 84 % when DFA1 was < 100 U/L. Drains were removed at a mean of 1.8 postoperative days, compared to the standard of 5 days. This algorithm allowed for safe and early drain removal guided by this threshold (< 100 U/L).¹¹ Recently, another single institution study revealed that DFA1 < 100 U/L was associated with very low risk of pancreatic fistula (sensitivity of 96 % and NPV of 96 %).¹⁰

The present multi-institutional series mirrors the finding that, as the DFA1 decreases, the NPV increases. We observed a high NPV of 98.2 % at DFA1 < 90 U/L. At a DFA1 of < 90 U/L, 30.4 % of the patients in our cohort (166/536) could undergo early drain removal. A minimal false negative rate of 3.3 % was observed in the group with a DFA1 of < 90 U/L. In addition, DFA1 was independently associated with pancreatic fistula controlling for BMI, small duct size, and pancreas texture. The ability of DFA1 to predict pancreatic fistula was

low across all cutoff values, with the highest PPV of 37.2 %, respectively, at 5,000 U/L. Thus, DFA1 is not an accurate predictor of the presence of a pancreatic fistula.

Across all potential DFA1 cutoff values, NPV and PPV differed by minimal increments and varied along a continuum. The implications of these small differences in NPV at each cutoff suggest that surgeons should consider the clinical consequences of early drain removal at each level in order to guide management, rather than defining one “ideal” DFA1 value. For example, at a DFA1 threshold of <90 U/L, the surgeon accepts a 3.3 % false negative rate, or 3/166 patients (1.8 %) experience a pancreatic fistula. The DFA1 values should be considered in the context of the individual patient’s overall clinical picture and the surgeon’s comfort level with small differences in NPV at each cutoff.

A clear strength of the present study was the employment of nationally validated trained SCRs who prospectively entered potential risk factors for pancreatic fistula development using the ACS-NSQIP PDP database. In addition to standard NSQIP variables, a list of pancreas-specific variables was created via the PDP, providing a unique opportunity to study pancreatic resection-related national outcomes and practice patterns (Table 1). A total of 2,805 cases of pancreas surgery at 43 institutions were recorded in the PDP. This study is the first multi-institutional analysis of low DFA1 as a predictor of the absence of pancreatic fistula using this dataset and confirms its utility for this purpose.

Clear limitations of this study include significant gaps in data collection, which resulted in a large number of patients being excluded. This limitation likely occurred due for several reasons, including that many surgeons did not routinely obtain DFA1 levels. In addition, some surgeons did not utilize drains. We attempted to address this potential for sampling bias by comparing patients we excluded to patients in our final cohort and observed minimal differences. However, the potential for unmeasured differences persists. Secondly, the time that DFA1 was collected was not standardized, and variations likely existed in the assay for amylase across institutions. Finally, this study did not define pancreatic fistula under the exact definition as the ISGPF, and thus, the data is likely not be comparable to other series that use this definition.

As many surgeons did not routinely measure drain amylase level, our study may not have captured all of the clinically silent (grade A) fistulae. Similarly, not all patients with pancreatic fistulas managed only with octreotide, antibiotics, or total parenteral nutrition (grade B fistulas) were captured. Thus, the overall pancreatic fistula rate was likely underestimated. However, the PDP pancreatic fistula definition was consistent across all institutions and was entered by trained clinical nurse reviewers to ensure data reliability. Despite this limitation, the overall pancreatic fistula incidence of 17.2 % is similar to studies that employ the ISGPF definition for grade B and C fistulas. Lastly, the dataset did not include information on pancreatic fistula grade, and thus, conclusions could not be made regarding the association between DFA1 and fistula grade. However, a subanalysis (data not shown) which focused on patients with clinically relevant pancreatic fistulas requiring percutaneous drainage, reoperation, or death resulted in a ROC and c-statistic (0.738) which were very comparable to the overall analysis.

Conclusions

To date, this analysis is the largest prospective multi-center investigation assessing the prognostic ability of DFA1 to rule out pancreatic fistula. Decreasing DFA1 levels were associated with high NPV, with the best results (98.2 %) observed at DFA1 levels <90 U/L. These values may be used to guide early drain removal, potentially avoiding drain-related complications and decreasing pancreatic fistula in patients undergoing pancreatic resection.

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References

1. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, Talamini, Pederzoli P. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg.* 2010; 252(2):207–14. [PubMed: 20622661]
2. Moskovic DJ, Hodges SE, Wu M, Brunicaudi FC, Hilsenbeck SG, Fisher WE. Drain data to predict clinically relevant pancreatic fistula. *HPB.* 2010; 12:472–481. [PubMed: 20815856]
3. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, Clavien PA. Assessment of complications after pancreatic surgery. *Ann Surg.* 2006; 244:931–9. [PubMed: 17122618]
4. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an International Study Group (ISGPF) definition. *Surgery.* 2005; 138(1):8–13. [PubMed: 16003309]
5. Kawai M, Tani M, Terasawa H, Ina S, Hirono S. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection; prospective study for 104 consecutive patients. *Ann Surg.* 2006; 244:1–7. [PubMed: 16794381]
6. Molinari E, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, Falconi M, Pederzoli P. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula. *Ann Surg.* 2007; 246(2):281–7. [PubMed: 17667507]
7. Shintchi H, Wada K, Traverso L. The usefulness of drain data to identify a clinically relevant pancreatic anastomotic leak after pancreaticoduodenectomy? *J Gastrointest Surg.* 2006; 10:490–8. [PubMed: 16627213]
8. Sutcliffe RP, Battula N, Haque A, Ali A, Srinivasan P, Atkinson S, Rela M, Heaton N, Prachalias A. Utility of drain fluid amylase measurement on the first postoperative day after pancreaticoduodenectomy. *World J Surg.* 2012; 36(4):879–83. [PubMed: 22354484]
9. Kawai M, Kondo S, Yamaue H, Wada K, Sano K, Motoi F, Unno M, Satoi S, Kwon A, Hatori T, Yamamoto M, Matsumoto J, Murakami Y, Doi R, Ito M, Miyakawa S, Shintchi H, Natsugoe S, Nakagawara H, Ohta T, Takada T. Predictive risk factors for clinically relevant pancreatic fistula analyzed in 1,239 patients with pancreaticoduodenectomy: multicenter data collection as a project study of pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci.* 2011; 18(4):601–8. [PubMed: 21491103]
10. Israel JS, Rettammel RJ, Levenson GE, Hanks LR, Cho CS, Winslow ER, Weber SM. Does postoperative drain amylase predict pancreatic fistula after pancreatectomy? *J Am Coll Surg.* May; 2014 218(5):978–87. pii: S1072-7515(14)00134-3. doi: 10.1016/j.jamcollsurg. 2014.01.048. E pub Feb 18. [PubMed: 24680573]
11. Nissen NN, Menon VG, Puri V, Annamalai A, Boland B. A simple algorithm for drain management after pancreaticoduodenectomy. *Am Surg.* 2012; 78(10):1143–6. [PubMed: 23025959]

12. American College of Surgeons. National Surgical Quality Improvement Program: American College of Surgeons. 2013. available at <http://site.acsnsqip.org/downloads/>
13. American College of Surgeons. National Surgical Quality Improvement Program: Participation User Guide. 2013. available at http://site.acsnsqip.org/wp-content/uploads/2013/10/ACSNSQIP.PUF_UserGuide.2012.pdf
14. Parikh P, Shiloach M, Cohen ME, Bilimoria KY, Ko CY, Hall BL, Pitt HA. Pancreatectomy risk calculator: an ACS-NSQIP resource. *HPB*. 2010; 12:488–497. [PubMed: 20815858]
15. Sato N, Yamaguchi K, Chijiwa K, Tanaka Masao. Risk analysis of pancreatic fistula after pancreatic head resection. *Arch Surg*. 1998; 133:1094–1098. [PubMed: 9790207]
16. Lin JW, Cameron JL, Yeo CJ, et al. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointestinal Surg*. 2004; 8:951–959.
17. El Nakeeb A, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, Hamdy E, Atef E, El Hanafy E, El-Geidie A, Wahab M, Abdallah T. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). *World J Surg*. Mar 15.2013 [Epub ahead of print].
18. Heslin MJ, Harrison LE, Brooks AD, Hochwald SN, Coit DG, Brennan MF. Is intra-abdominal drainage necessary after pancreaticoduodenectomy? *J Gastrointest Surg*. 1998; 2:373–378. [PubMed: 9841995]
19. Kelly KJ, Greenblatt DY, Wan Y, Rettamel RJ, Winslow E, Cho CS, Weber SM. Risk stratification for distal pancreatectomy utilizing ACS-NSQIP: preoperative factors predict morbidity and mortality. *J Gastrointest Surg*. 2011; 15:250–261. [PubMed: 21161427]
20. Greenblatt DY, Kelly KJ, Rajamanickam V, Wan Y, Handon T, Rettamel R, Winslow ER, Cho CS, Weber SM. Preoperative factors predict perioperative morbidity and mortality after pancreaticoduodenectomy. *Ann Surg Oncol*. 2011; 18:2126–2135. [PubMed: 21336514]
21. 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. [PubMed: 18175170]
22. Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Colt D, Merchant N, Brennan M. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Ann Surg*. 2001; 234:487–93. [PubMed: 11573042]
23. Correa-Gallego C, Brennan MF, D'Angelica M, Fong Y, DeMatteo RP, Kingham P, Jarnagin WR, Allen PJ. Operative drainage following pancreatic resection analysis of 1122 patients resected over 5 years at a single institution. *Ann Surg*. 2013; 258(6):1051–8. [PubMed: 23360918]
24. Van Buren G, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, Vollmer C, Velanovich V, Riall T, Muscarella P, Trevino J, Nakeeb A, Schmidt CM, Behrns K, Ellison C, Barakat O, Perry KA, Drebin J, House M, Abdel-Misih S, Silberfein EJ, Goldin S, Brown K, Mohammed S, Hodges SE, McElhany A, Issazadeh M, Jo E, Qianxing M, Fisher WE. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Ann Surg*. 2014; 259(4):605–610. [PubMed: 24374513]

Fig. 1.
Patient selection: inclusion and exclusion criteria

Fig. 2.
ROC curve (c-statistic=0.761; $p<0.001$; 95 % CI 0.711–0.810)

Fig. 3.
Pancreatic fistula rates according to DFA1 cutoff level

Table 1

ACS-NSQIP Pancreatectomy Demonstration Project: pancreas-related variables

Pancreas-specific variables		
Preoperative	Intra-operative	Postoperative
Preoperative jaundice	Operative approach	POD#1 highest drain amylase
Biliary stent placement	Pancreatic duct size	Date of last drain removal
Neoadjuvant chemotherapy	Pancreatic gland texture	Pancreatic fistula
Neoadjuvant radiation	Vascular resection	Percutaneous drainage
	Pylorus preservation	Delayed gastric emptying
	Method of pancreatic reconstruction	Pathology
	Ante vs. retrocolic enteric reconstruction	Malignant type
	Intra-operative drain placement	T-stage
		N-stage
		M-stage
		Benign type
		Tumor size

Table 2Demographics and diagnoses for patients with known *DFA1* (*n*=536)

	Number of subjects (%)
Age, mean (years)	62.7±12.7
Gender	
Male	262 (48.9)
Female	274 (51.1)
Mean operative time (min)	350.7±165.1
Procedure type	
Pancreaticoduodenectomy	380 (70.9)
Distal pancreatectomy	140 (26.1)
Enucleation	16 (3.0)
Malignant histopathology	
Adenocarcinoma	121 (22.5)
Neuroendocrine tumor	25 (4.6)
Ampullary carcinoma	18 (3.4)
IPMN	11 (2.1)
Duodenal carcinoma	8 (1.5)
Distal cholangiocarcinoma	5 (0.9)
Other	5 (0.9)
Benign	100 (18.7)
Unknown	243 (45.3)

IPMN intra-ductal papillary mucinous neoplasm

Table 3

Univariate and multi-variable regression analyses of risk factors for pancreatic fistulas in patients with known DFA1 ($n=536$)

Variable	PF rate (%)	Univariate p value	Multi-variable p value	OR; 95 % CI
Gender		0.995		
Male	45/262 (17.2 %)			
Female	47/274 (17.2 %)			
BMI		0.012*	0.008*	
<25	30/229 (13.1)			Referent
25–30	29/175 (16.6)			1.072; 0.525–2.191
>30	33/130 (25.4)			2.880; 1.386–5.982
Diabetes		0.180	N/A	
Insulin	5/57 (8.8 %)			
Non-insulin	10/63 (15.9)			
No	77/416 (18.5)			
Smoking		0.528	N/A	
Yes	22/115 (19.1)			
No	70/421 (16.6)			
Presence of jaundice		0.337	N/A	
No	63/358 (17.6)			
Yes	27/173 (15.6)			
Unknown	2/5 (40.0)			
Stent placement		0.217	N/A	
No	58/342 (17.0)			
Yes	32/190 (16.8)			
Unknown	2/4 (50.0)			
Neoadjuvant chemotherapy		0.216	N/A	
No	82/483 (17.0)			
Yes	8/49 (16.3)			
Unknown	2/4 (50.0)			
Neoadjuvant radiation		0.229	N/A	
No	88/503 (17.5)			
Yes	2/27 (7.4)			
Unknown	2/6 (33.3)			
Vascular resection		0.871	N/A	
None	72/420 (17.1)			
Vein (portal or SMV)	5/40 (12.5)			
Artery (celiac, hepatic, or SMA)	3/15 (20.0)			
Vein and artery	0/1 (0)			
Unknown	12/60 (20.0)			
Transfusion		0.262	N/A	
Yes	0/6 (0)			

Variable	PF rate (%)	Univariate <i>p</i> value	Multi-variable <i>p</i> value	OR; 95 % CI
No	92/530 (17.4)			
Pancreatic duct size		<0.001 *	0.037 *	
<3 mm	46/157 (29.3)			5.325; 1.172–24.192
3–6 mm	21/187 (11.2)			2.888; 0.634–13.157
>6 mm	4/62 (6.5)			Referent
Pancreatic gland texture		<0.001 *	0.017 *	
Soft	49/178 (27.5)			2.864; 1.393–5.888
Intermediate	7/44 (15.9)			1.796; 0.635–5.081
Hard	17/180 (9.4)			Referent
Pathology		0.159	N/A	
Benign	12/100 (12)			
Malignant	40/193 (20.7)			
Unknown	40/243 (16.5)			
DFA1	92/536 (17.2)	<0.001 *	0.028 *	1.021; 1.002–1.041

Multi-variable logistic regression was performed based on variables identified in univariate analysis with a *p* value <0.10

* *p*<0.05, statistical significance

Table 4

Comparison of patient characteristics, intra-operative, and postoperative outcomes for all patients with known pancreatic fistula data ($n=2614$; $p<0.05$)

	Known DFA1 N=536 (%)	Unknown DFA1 N=2,078 (%)	<i>p</i> value
Gender			0.390
Male	262 (48.9)	1,059 (51.0)	
Female	274 (51.1)	1,019 (49.0)	
Diabetes			0.943
Insulin	57 (10.6)	231 (11.1)	
No	416 (77.6)	1,600 (77.0)	
Non-insulin	63 (11.8)	247 (11.9)	
BMI (kg/m ²)			0.097
<25	229 (42.7)	784 (37.7)	
25–30	175 (32.6)	720 (34.6)	
>30	132 (24.6)	574 (27.6)	
Smoking			0.734
Yes	115 (21.5)	460 (22.1)	
No	421 (78.5)	1,618 (77.9)	
Presence of jaundice			0.680
No	358 (66.8)	1,402 (67.5)	
Yes	173 (32.3)	648 (31.2)	
Unknown	5 (0.9)	28 (1.3)	
Stent placement			0.286
No	342 (63.8)	1,399 (67.3)	
Yes	190 (35.4)	662 (31.9)	
Unknown	4 (0.7)	17 (0.8)	
Neoadjuvant chemotherapy			0.281
No	483 (90.1)	1,916 (92.2)	
Yes	49 (9.1)	148 (7.1)	
Unknown	4 (0.7)	14 (0.7)	
Neoadjuvant radiation			0.158
No	503 (93.8)	1,971 (94.9)	
Yes	27 (5.0)	72 (3.5)	
Unknown	6 (1.1)	35 (1.7)	
Vein resection			0.040
None	420 (78.4)	1,682 (80.9)	
Vein (portal or SMV)	40 (7.5)	189 (9.1)	
Artery (celiac, hepatic, or SMA)	15 (2.8)	51 (2.5)	
Vein and artery	1 (0.2)	5 (0.2)	
Unknown	60 (11.2)	151 (7.3)	

	Known DFA1 N=536 (%)	Unknown DFA1 N=2,078 (%)	<i>p</i> value
Intra-operative transfusion			0.739
Yes	6 (1.1)	27 (1.3)	
No	530 (98.9)	2051 (98.7)	
Mean operative time (min)			0.586
	350.7±7.16	320.6±3.3	
Pancreatic duct size (mm)			0.512
<3 mm	157 (29.3)	424 (20.4)	
3–6 mm	187 (34.9)	581 (28.0)	
>6 mm	64 (11.9)	196 (9.4)	
Pancreatic gland texture			0.619
Soft	178 (33.2)	487 (23.4)	
Intermediate	44 (8.2)	144 (6.9)	
Hard	180 (33.6)	530 (25.5)	
Pancreatic fistula			0.524
Yes	92 (17.2)	333 (16.0)	
No	444 (82.8)	1,745 (84.0)	

Table 5Pancreatic fistula rates associated with DFA1 cutoffs ($p=0.000$)

DFA1 cutoff (U/L)	Se (%)	Sp (%)	NPV (%)	PPV (%)
5,000	39.1	86.0	87.2	36.7
2,500	59.8	79.1	90.5	37.2
1,000	75.0	67.1	92.8	32.1
350	81.5	54.5	93.4	27.1
90	96.7	36.5	98.2	24.0

Se sensitivity, *Sp* specificity, *NPV* negative predictive value, *PPV* positive predictive value

Table 6

Recent studies evaluating DFA1 as a predictor of pancreatic fistula

Study	<DFA1 cutoff (U/L)	No. of patients	PF rate (%)	Se/Sp/PPV/NPV (%); ROC AUC	<i>p</i> value
Molinari et al. ⁶	5,000	137	19.7	93/84/59/98; 0.922	<0.001
Kawai et al. ⁹	4,000	1,239	30.2	62/89/85/51; 0.840	<0.001
Sutcliffe et al. ⁸	350	70	12.9	100/79/41/100; 0.962	<0.0001
Nissen et al. ¹¹	100	76	11.0	NR/NR/NR/84; NR	N/A
Israel et al. ¹⁰	100	63	43	96/69/71/96; 0.903	<0.0001

NR not recorded, *Se/Sp/PPV/NPV* sensitivity, specificity, positive predictive value, and negative predictive value, *AUC* (c-statistic) area under the curve