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Original Research Article

Postoperative day 3 drain amylase versus fistula risk score: predicting clinically relevant postoperative pancreatic fistula following pancreatico-duodenectomy

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ABSTRACT

Background: Clinically relevant postoperative pancreatic fistula (CR-POPF) remains the most common cause of perioperative morbidity following pancreatico-duodenectomy (PD). Early and accurate prediction of CR-POPF can be helpful in postoperative drain management as well as stratifying patients for enhanced recovery protocol after surgery. Both fistula risk score (FRS) and postoperative drain amylase levels have been analyzed in past. However, currently there is no clear consensus regarding the ideal predictor. Present study sought to assess the utility of postoperative day 3 drain amylase (POD-3DA) level as a predictor of CR-POPF in comparison with FRS.
Methods: A retrospective analysis was done on 57 patients who underwent PD at our institute between 2014 to 2018. POPF was defined and graded in accordance with ISGPF definition. Receiver operating characteristic (ROC) analysis predicted a threshold of POD3DA >486 IU/l associated with CR-POPF. Sensitivity, specificity and odds ratios with 95%CI calculated and ROC curves were plotted for POD3DA of ≥500 IU/l and FRS (negligible/low vs. moderate/ high) as predictors of CR-POPF.
Results: Incidence of POPF and CR-POPF was 63% and 32% respectively. Sensitivity and specificity of POD3DA ≥500 and moderate/high FRS for predicting CR-POPF were 83%, 79% & 78%, 51% respectively. Difference between ROC area under the curve (AUC) for POD3DA ≥500 IU/l (0.868) and FRS (0.692) was significant (p=0.028). Combining FRS and POD3DA ≥500 IU/l improved specificity (87%) at the cost of sensitivity (67%). The negative predictive value of POD3DA <500 IU/l and negligible/low FRS were 91.2% and 83.3% respectively.
Conclusions: POD3DA level greater than 5 times of upper normal range is more precise at predicting CR-POPF, hence clinically more reliable for drain and postoperative management.

Keywords: Pancreaticoduodenectomy, Pancreatic fistula, CR-POPF, POD3DA, FRS

INTRODUCTION

One of the most common and feared postoperative complications of pancreaticoduodenectomy (PD) is Postoperative pancreatic fistula (POPF). Studies suggest the incidence of POPF varies between 5% and 45%.[1-5] Although overall mortality following PD has decreased significantly over the last decade from 25% to presently accepted rates of <5%, perioperative morbidity remains high (40-50%).[6-10] POPF remains the most common cause of increased perioperative morbidity such as intra-abdominal abscess, sepsis, haemorrhage, delayed gastric emptying, wound infection, need for reoperation, prolonged intensive care unit (ICU) stay and extended

hospitalization. This increases the costs associated with surgery and results in overall economic burden on society.[11,12] Also the POPF associated morbidity frequently delays the timely delivery of adjuvant therapies reducing overall survival.[13,14]

The International Study Group of Pancreatic Fistula (ISGPF) formed an objective definition of POPF as fluid output of any measureable volume via an operatively placed drain after post-operative day 3 with amylase level greater than 3 times the upper normal serum value and graded it as grades A, B, and C according to the complication-specific severity.[15,16] Grade B and C fistulas are collectively referred to clinically relevant POPF (CR-POPF).

As a result of the high incidence of POPF, routine practice among surgeons has been to place a drain after PD. Prospective randomized trial by Buren et al has provided level 1 data against elimination of drains in all cases of PD.[17] Optimal timing of removal of drain has been a subject of debate. Prolonged drainage is associated with increased complications, duration of hospital stay and resource utilization.[18] Prospective study by Kawai et al. reported lower rates of abdominal complications following early drain removal.[19] Randomized study by Bassi et al. suggested reduced risk of CR-POPF, if postoperative day (POD) 1 drain fluid amylase ≤5000 U/l and hence early drain removal in these patients. [18]

However significant controversy persists about the dynamic post-operative changes in drain output volume and amylase concentration and their correlation with CR-POPF. This controversy over the drain management and the significant impact of POPF on overall surgical outcome has made prediction of CR-POPF an important topic of investigation.[20,21] Currently no consensus exists regarding whether drain fluid amylase concentration or volume of drain output are important in predicting CR-POPF and whether they are more predictive on any particular post-operative day. Such a predictor would be useful in deciding timing of drain removal and identifying patients who require close monitoring.

The fistula risk score (FRS) developed by Callery et al, is a four-factor score which takes into account pancreatic duct diameter, gland texture, pathology and intraoperative blood loss.[22,23] FRS classifies patients into negligible (score 0), low (score 1-2), moderate (score 3-6) or high (score 7-10) risk categories for developing POPF. Both FRS and postoperative drain amylase levels on different postoperative days have been analyzed in past as predictors of CR-POPF. However, currently there is no clear consensus regarding the ideal predictor. Hence, the present study sought to assess the utility of POD-3 drain amylase level (POD3DA) as a predictor of CR-POPF in comparison with FRS in patients undergoing PD.

METHODS

57 consecutive patients who underwent PD at Department of Surgical-Gastroenterology and Liver transplant, Bangalore medical college and research institute, Bangalore, between March 2014 to May 2018 were included. This includes patients undergoing surgery for both malignant and benign pathology. All patients underwent classical Whipple procedure.

Data collection

Current study is a retrospective analysis of data extracted from review of a prospectively maintained electronic database and patient medical records. For all patients data obtained on patient demographics, clinical history, past medical history, family and social history, physical findings, body mass index (BMI), diagnostic tests, detailed operative data, complications, postoperative interventions and outcome and histopathological data. Pancreatic duct diameter determined at the line of resection by preoperative computed tomography and magnetic resonance cholangiopancreatography. Intraoperative data included pancreatic gland texture (hard/firm or soft), estimated blood loss. Histopathologically specimen were segregated into two categories on the basis of whether the pathology associated with hard/firm pancreatic parenchyma (pancreatic adenocarcinoma and chronic pancreatitis) or normal/soft parenchyma (ampullary adenocarcinoma, duodenal carcinoma, distal cholangiocarcinoma, pancreatic head neuroendocrine tumours or cystic neoplasm or other lesions). FRS was calculated for each patient as described by Callery et al and patients are dichotomized into negligible or low risk and moderate or high risk category.[22,23] Outcome data included total length of stay in an ICU which includes any readmission to ICU due to complications and total length of postoperative hospital stay which includes rehospitalisation for complications pertaining to surgery. Drain fluid amylase level estimated on POD-3 for all patients and POPF diagnosed according to ISGPF definition. Postoperative complications recorded and graded according to International Study Group of Pancreatic Surgery (ISGPS) classification and POPF grade reviewed during follow-up.[24]

Operative procedure and perioperative management

All surgeries performed under single surgical gastroenterology unit and operative steps of PD followed as previously described.[25-27] Pancreatic remnant anastomosis done using double layer duct to mucosa technique with either jejunum (pancreaticojejunostomy (PJ)) or stomach (pancreaticogastrostomy) according to surgeon's preference. Two non-suction drains (28-32 Fr, ADK) were routinely placed at pancreatic and biliary anastomosis site. No somatostatin analogues were used perioperatively. Patients were extubated on POD-0 or 1 as per anaesthetist's decision. All patients were kept under ICU observation for first 48 hours after surgery and then transferred to general ward or HDU according to their clinical condition. Drain fluid volumes were recorded daily and constant criteria followed for drain

removal i.e. drain output of less than 50 ml over 24 hour with no POPF and no other contraindication for drain removal (e.g. bile or chyle leak or purulent discharge). In patients with POPF drain removal was done when minimal daily output (<30 ml) for 3 consecutive days or repeat drain amylase negative for POPF with no other contraindications. Patients with grade B or C POPF managed as per clinical requirement with provisions of supportive care, antibiotics, percutaneous drainage, and angio-embolisation for pseudo aneurysm and surgical exploration.

Outcome measures

POPF was defined and classified by the ISGPF definition i.e. drain fluid amylase level ≥3 times the upper limit of normal serum amylase level for each specific institution on or after POD3.[17] The upper normal limit of serum amylase at our institute is 100 IU/l, hence drain amylase level ≥300 IU/l on POD3 considered as POPF. Patients with grade A POPF currently termed as Biochemical leak (BL) were clinically non-significant requiring no additional treatment or no deviation from a normal postoperative course. Grade B POPF patients required additional treatment, intensive care and prolonged hospital stay. Grade C POPF patients often had a life threatening event or morbid postoperative period. They frequently required interventional radiologic procedure like angioembolisation for post-pancreatectomy haemorrhage or dialysis or ventillatory support or relaparotomy. Grade B and C patients collectively referred to as clinically relevant POPF (CR-POPF). Postoperatively FRS was calculated for each patient using the variables described by Callery et al.[24] Patients are stratified into negligible risk (FRS-0), low risk (FRS-1 to 2), intermediate risk (FRS-3 to 6), and high risk (FRS- 7 to 10). All patients were then dichotomized into either negligible/low risk category or intermediate/ high risk category for predicting CR-POPF.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 16.0 for Windows (SPSS, Inc). For continuous variables, descriptive statistics calculated and reported as mean ± standard deviation (SD). To compare continuous variables, the Mann-Whitney U-test was used. Fisher's exact test used to compare categorical variables. The independent sample *t* test (unpaired *t* test) was used to evaluate differences in means of continuous variables. Receiver operating characteristic (ROC) curve analysis was done to identify optimum threshold level of POD3 drain amylase for predicting CR-POPF. The area under the ROC curve (AUC) is a measure of diagnostic accuracy of a test.[28] AUC of >0.75 considered to have high diagnostic accuracy indicating more than 75% of cases with the condition of interest are classified correctly.[29] ROC and AUC were used to evaluate the performance of prediction model (POD3DA ≥500 vs. FRS of intermediate/high risk). Univariate binary logistic regression analysis used to determine the association between clinicopathological factors with CR-POPF including POD3 drain fluid amylase and FRS. Multivariate binary logistic regression analysis done for variables showing significant association on univariate analysis ($p<0.05$). A $p<0.05$ was considered as statistically significant.

RESULTS

The records of 57 consecutive patients who underwent PD between March 2014 to May 2018 were analyzed. All patients underwent classic PD with intraoperative drain placement. For all patients POD3DA value was recorded from medical record. FRS was calculated for all patients using review of operative notes, anaesthesia/nursing records (for estimated blood loss) and histopathology report of excised specimen.

Data regarding demographic profiles, individual components of FRS and outcomes are summarized in Table 1. Among 57 patients, 40 (70.2%) were male and 17 (29.8%) were female with a mean age of 47±12 years (range: 15-75 years). 18 (31.57%) patients had preoperative biliary stenting. Median intraoperative blood loss was 500 ml (300-1000 ml).

Post operatively 37 (64.9%) patients developed POPF. Among them 19 (33.3%) patients had grade A/ biochemical leak, 14 (24.5%) patients had grade B and 4 (7%) patients had grade C POPF. The rate of CR-POPF (ISGPF grade B or C) was 31.57% among the study cohort. The rate of clinically significant PPH (ISGPS grade B or C) was 7% (n=4) out of which 3 patients needed relaparotomy for control of bleeding.

FRS calculated for all 57 patients stratified them into four different risk categories.[24] Among them 2 (3.5%) were negligible risk (FRS=0), 22 (38.6%) were low risk (FRS=1-2), 30 (52.6%) were moderate risk (FRS= 3-6) and 3 (5.2%) were high risk (FRS= 7-10) group. Mean FRS of the cohort was 3.36 (SD-1.702, median 3, range 0-7). Mean FRS of patients who had CR-POPF was 4.1 (SD 1.6) as opposed to 3.05 (SD 1.63) in no CR-POPF group and the difference of mean was significant ($p=0.039$). None of 2 negligible risk category patients developed CR-POPF, while 4/22 (18.2%), 12/30 (40%) and 2/3 (66.6%) patients of low, moderate and high risk categories respectively developed a CR-POPF. When patients are dichotomized into two groups i.e. negligible/low group vs. moderate/high group, the incidence of CR-POPF was significantly lower in the negligible/low group (16.6%) compared to the moderate/high group (42.4%) which was statistically significant ($p=0.047$). The sensitivity and specificity of moderate/high FRS for predicting CR-POPF was 77.8% and 51.2% respectively with a negative predictive value of 83.3%.

Table 1: Demographic information, clinical profile and outcome for study cohort.

Demographics	CR-POPF N (%)	No CR-POPF N (%)	P value[a,b]
n=57	18 (31.6)	39 (68.4)	
Age (years) (Mean±SD)	51.27±6.7	47.17±4.8	0.227
Gender			
Female	5 (27.7)	12 (30.7)	1.000
Male	13 (72.2)	27 (69.2)	
Body mass index, Kg/m^2			
Smoking			
Yes	7 (38.8)	13 (33.3)	0.768
No	11 (61.1)	26 (66.6)	
Preoperative biliary stenting			
Yes	9 (50)	9 (23.07)	0.065
No	9 (50)	30 (76.92)	
FRS components	Median (range)		
Pancreatic duct size (mm)	4 (2-8)	5 (2-10)	0.262
Estimated blood loss (ml)	600 (350-1000)	450 (300-700)	0.0001
Pathology	N (%)	N (%)	
Pancreatic adenocarcinoma or Pancreatitis	3 (16.6)	7 (17.9)	1.000
Ampullary carcinoma, Duodenal carcinoma, distal cholangiocarcinoma, NET, Cystic neoplasm or others	15 (83.3)	32 (82.1)	
Soft gland	11 (61.1)	23 (58.9)	1.000
Firm/hard gland	7 (38.9)	16 (40.9)	
Pancreatic anastomosis	N (%)	N (%)	
Pancreatico-gastrostomy	3 (16.6)	0	0.027
Pancreatico-jejunostomy	15 (83.3)	39 (100)	
Outcomes	Median (Range)		
PoD3DA (IU/l)	671 (450-2867)	155 (14-4719)	0.042
Postoperative hospital stay (days)	17 (6-45)	9 (6-15)	0.0001
Clinically significant post pancreatectomy haemorrhage[c]	3 (16.6)	1 (2.56)	0.231

[a]Fisher's exact test; [b]Unpaired *t* test; [c]International study group of pancreatic surgery (ISGPS) post-pancreatectomy complications.

Table 2: Comparison between POD3DA and FRS as a predictor of CR-POPF.

		(%CR-POPF)	P value	AUC*	95% CI
FRS (n=57)	Negligible/ low	16.6	0.04	0.692	0.592-0.781
	Moderate/ high	42.4			
POD3DA (n=57)	<500 IU/l	9.6	<0.001	0.868	0.785-0.927
	≥500 IU/l	65.2			
FRS vs. POD3DA	**AUC diff.**	**SE**		**Z statistic**	**Adjusted P value**
	0.175	0.08	0.028	2.194	0.028

*Area under the ROC curve (AUC).

Similar analyses of POD3 drain fluid amylase undertaken for all patients. The mean POD3DA was 916 IU/l in CR-POPF group and 447 IU/l in patients with no CR-POPF and the difference of mean between the two group was significant (p=0.042). In Figure 1 the distribution of PoD3 drain amylase in patients who developed CR-POPF and those who did not is plotted (box plot). An analysis by ROC was performed on the cohort who had CR-POPF, which revealed a significant correlation between POD3 drain amylase levels and CR-POPF (AUC = 0.868, 95% CI 0.78-0.92). The optimal threshold for POD3 drain amylase level for predicting CR-POPF was >486 IU/l with sensitivity of 94.4% and specificity of 79.5%. This value was corrected to 500 IU/l (5 times of upper limit of normal serum amylase at our institute, normal range 60-100 IU/l) for clinical convenience and subsequently validated (Fishers exact test). A total of 23 patients had a POD3DA of ≥500 IU/l, out of which 15 (65.2%) developed CR-POPF and only 3 (9.6%) out of

31 patients with POD3DA <500 developed CRPOPF (p<0.001). A PoD3 drain amylase level ≥500 IU/l was strongly associated with the occurrence of CR-POPF (sensitivity 83%, specificity 79%; p<0.001) with positive predictive value of 65.2% and negative predictive value of 91.2%. The sensitivity, specificity and the AUC of the ROC curve are presented in Table 2 and 3.

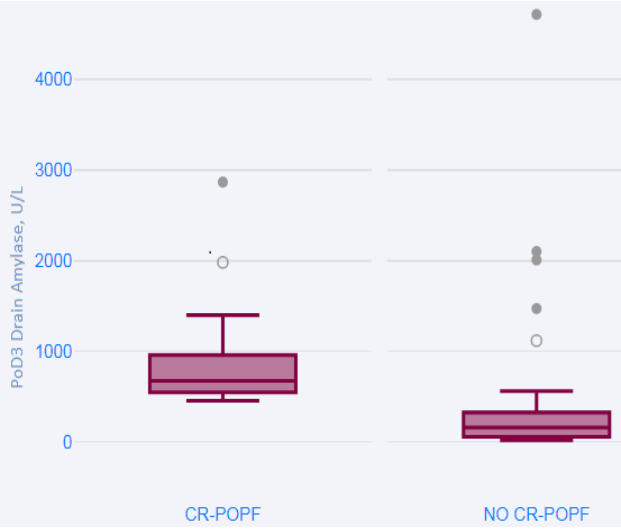

Figure 1: Distribution of POD3DA in patients with or without CR-POPF.

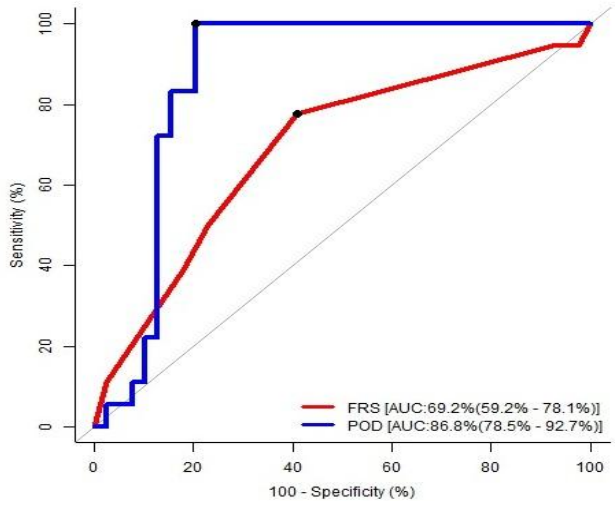

Figure 2: ROC analysis comparing POD3DA≥500 IU/l and FRS (moderate/high).

The comparison of the AUC for the ROC curve between the two predictive tests (POD3DA ≥500 IU/l vs. dichotomized FRS-moderate/high) revealed a statistically significant difference in predicting the development of CR-POPF (Figure 2). The AUC for POD3DA ≥500 IU/l was 0.868 and the AUC for FRS-moderate/high risk patients was 0.692. Hence POD3DA ≥500 IU/l was found to be statistically superior in predicting CR-POPF (p=0.028). When both POD3DA ≥500 IU/l and moderate/ high-FRS are combined, the sensitivity decreased to 67% for predicting CR-POPF and it did not prove to be superior to either of the individual test (Table 2).

Table 3: Comparison of sensitivity and specificity for predicting CR-POPF between POD3DA vs. dichotomized FRS (moderate/high and negligible/low).

	Sensitivity (%)	Specificity (%)
FRS (moderate/ high)	78	51
POD3DA ≥500 IU/l	83	79
POD3DA + FRS (moderate/high)	67	87

DISCUSSION

CR-POPF continues to be the major cause of morbidity post PD. The ability to make a reliable prediction of postoperative CR-POPF may enable surgeons to individualize the postoperative management strategy and minimize the morbidity associated with CR-POPF. In spite of some published evidence against routine placement of intraoperative drains after PD, majority of institutions follow a routine placement of drain.[30,31] Few studies have advocated omitting drains in patients having negligible or low risk of POPF by FRS as well as early removal of drains in patients with POD1DA below a predesignated cut-off.[32-34] This study is an effort to externally validate the effectiveness of FRS as a predictive test of CR-POPF. Also this study is the first to document POD3 drain amylase level (POD3DA <5 times of upper normal serum range) as an objective marker to predict patients with low risk for CR-POPF for whom early drain removal and enhanced postoperative recovery may be predicted.

Studies have been done previously to demonstrate POD1DA level as a predictor of CR-POPF with various cut-off levels. Bassi et al from Verona and subsequently Vollmer et al, advocated the benefit of early drain removal after PD if POD1DA <5000 IU/l.[20,33] They demonstrated reduction in incidence of CR-POPF (11.2% vs. 20.6%, p=0.001) as well as reduced incidence of severe complications, reoperation, percutaneous drainage and overall hospital stay (all p<0.05) with this selective drain management. A meta-analysis by Giglio et al, including 13 studies advocated a PoD1DA cut-off of 350 U/L (sensitivity 91%) for predicting the likelihood of developing CR-POPF.

However according to ISGPF definitions, presence of POPF can be ascertained based on drain amylase level only on or after POD3. Hence a drain fluid amylase level on POD3 which can diagnose a POPF as well as predict or exclude a CR-POPF is felt to be of more value. Srivastava et al demonstrated a POD3DA <666 IU/l effectively predicts the absence of CR-POPF following PD.[35] However a value of 666 IU/l may be difficult to reproduce as the normal range of serum amylase differs

from institute to institute and it was felt that a more standardized value of PoD3 drain amylase level might be of value in predicting the presence or absence of CR-POPF.

The incidence of clinically relevant POPF in the current cohort is 31%, which is within expected range when compared to the reported incidence of CR-POPF in literature.[36,37] The 7% rate of clinically significant PPH in this cohort is also within expected range as found in literature.[38] The mean FRS of 3.36, this cohort is comparable to 3.54 as reported by Callery et al, in the multi-institutional study to validate FRS indicating the baseline risk of the study cohort is comparable to the study cohort used to validate FRS.[39]

CONCLUSION

Both POD3DA ≥500 IU/l and moderate/high FRS are effective in predicting the development of CR-POPF in the current study with sensitivity of 94% and 78% respectively. However the ROC curve showed the superiority of POD3DA ≥500 IU/l over moderate/high FRS in predicting CR-POPF (AUC 0.868 vs. 0.692, AUC diff. 0.175, p=0.028). The difference in specificity between the two groups is also significant (79.5% vs. 51.2%, p<0.05). This indicates POD3DA <500 IU/l is more accurate in ruling out CR-POPF than negligible/low FRS group. When both moderate/high FRS and POD3DA ≥500 IU/l were combined, it achieved a high specificity (87.2%) as opposed to low sensitivity (66.7%). Out of 24 patients with negligible/low FRS, 13 (54%) developed POPF and 4 (16.6%) developed CR-POPF which can not be ignored. Hence the present study recommends against non-placement of intraoperative drain in negligible/low FRS category patients. However drains should be removed as early as on postoperative day 3 if the POD3DA <500 IU/l in these patients thereby avoiding the potential morbidity associated with prolonged drainage. The high negative predictive value of POD3DA more than equal to 5 times of normal serum upper range (≥500 IU/l) in association with negligible/low FRS risk category might be highly precise in identifying patients at low risk for CR-POPF and associated morbidity. Such patients therefore can be put on enhanced recovery protocol with early drain removal and early discharge, thus saving health care resources.

Limitations

This study is limited by its retrospective nature and non-randomized analysis in a small cohort of patient operated at a single institute. With regards to data pertaining to gland texture no standardized criteria was applied and subjective variation has to be accounted. Although this analysis of prospectively maintained data gives a non-ambiguous positive correlation, this is a preliminary investigation and further validation of the result is necessary and is currently on-going.

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REFERENCES

1. Callery MP, Pratt WB, Vollmer CM Jr. (2009) Prevention and management of pancreatic fistula. J Gastrointest Surg. 2009;13:163-73.
2. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. Dig Surg. 2004;21:54-9.
3. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt, HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997;226:248-57.
4. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol. 2005;11:2456-61.
5. Vallance AE, Young AL, Macutkiewicz C. Calculating the risk of a pancreatic fistula after a pancreaticoduodenectomy: a systematic review. HPB (Oxford). 2015;17:1040-8.
6. YeoCJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s:pathology, complications and outcomes. Ann Surg. 1997;226:248-57.
7. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, deWit LT, Busch OR et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg. 2000;232:786-95.
8. DeOliveira ML, Winter JM, Schafer M, Cunnigham SC, Cameron JL, Yeo CJ, et al. Assesment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg. 2006;244:931-7.
9. Relles DM, Burkhart RA, Pucci MJ, Sendecki J, Tholey R, Drueding R, et al. Does resident experience affect outcomes in complex abdominal surgery? Pancreaticoduodenectomy as an example. J Gastrointest Surg. 2014;18:279-85.
10. Ahmad SA, Edwards MJ, Sutton JM. Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1302 patients. Ann Surg. 2012;256:529-37.
11. Abbott DE, Tzeng CWD, McMillan MT, Callery MP, Kent TS, Christein JD, et al. Pancreas fistula risk prediction: implications for hospital costs and payments. HPB. 2017;19:140-6.
12. Enestvedt CK, Diggs BS, Cassera MA, Hammil C, Hansen PD, Wolf RF. Complications nearly double

the cost of care after pancreaticoduodenectomy. Am J Surg. 2012;204:332-8.
13. Aloia TE, Lee JE, Vauthey JN, Abdalla EK, Wolff RA, Varadhachary GR, et al. Delayed recovery after pancreaticoduodenectomy: a major factor impairing the delivery of adjuvant therapy? J Am Coll Surg. 2007;204:347-55.
14. Vollmer CM Jr, Sanchez N, Gondek S, McAuliffe J, Kent TS, Christein JD, et al. The Pancreatic Surgery Mortality Study Group. A root-cause analysis of mortality following major pancreatectomy. J Gastrointest Surg. 2012;16:89-102.
15. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8-13.
16. 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;161:584-591.
17. Van Buren G, 2nd, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. Ann Surg. 2014;259:605-12.
18. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg. 2010;252:207-14.
19. Kawai M, Tani M, Terasawa H, Ina S, Hirono S, Nishioka R, et al. 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.
20. Butturini G, Daskalaki D, Molinari E, Scopelliti F, Casarotto A, Bassi C. Pancreatic fistula: definition and current problems. J Hepatobiliary Pancreat Surg. 2008;15:247-51.
21. Balzano G, Zerbi A, Cristallo M, Di Carlo V. The unsolved problem of fistula after left pancreatectomy: the benefit of cautious drain management. J Gastrointest Surg. 2005;9:837-42.
22. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013;216:1-14.
23. Pratt WB, Callery MP, Charles M, Vollmer Jr. Risk prediction for development of pancreatic fistula using the isgpf classification scheme. World J Surg. 2008;32:419-28.
24. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Post-pancreatectomy hemorrhage(PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-5.
25. Jamieson NB, Foulis AK, Oien KA, Going JJ, Glen P, Dickson EJ, et al. Positive mobilization margins alone do not influence survival following pancreatico-duodenectomy for pancreatic ductal adenocarcinoma. Ann Surg. 2010;251:1003-10.
26. Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg. 2006;10:1338-45.
27. Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg. 2004;139:718-25.
28. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem. 1993;39:561-77.
29. Robertson EA, Zweig MH. Use of receiver operating characteristic curves to evaluate the clinical performance of analytical systems. Clin Chem. 1981;27:1569-74.
30. Petrowsky H, Demartines N, Rousson V, Clavien PA. Evidence based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. Ann Surg. 2004240:1074-84.
31. Correa-Gallego C, Brennan MF, D'Angelica M, Fong Y, Dematteo RP, Kingham TP et al. Operative drainage following pancreatic resection: analysis of 1122 patients resected over 5 years at a single institution. Ann Surg. 2013;258(6):1051-8.
32. McMillan MT, Malleo G, Bassi C, Butturini G, Salvia R, Roses RE et al. Drain management after pancreatoduodenectomy: reappraisal of a prospective randomized trial using risk stratification. J Am Coll Surg. 2015;221:798-809.
33. McMillan MT, Malleo G, Bassi C, Allegrini V, Casetti L, Drebin JA, et al. Multicenter, prospective trial of selective drain management for pancreatoduodenectomy using risk stratification. Ann Surg. 2016;1:1-10.
34. Bertens KA, Crown A, Clanton J, Alemi F, Alseidi AA, Biehl T, et al., What is a better predictor of clinically relevant postoperative pancreatic fistula (CR-POPF) following pancreaticoduodenectomy (PD): postoperative day one drain amylase (POD1DA) or the fistula risk score (FRS)? HPB (Oxford). 2017;19(1):75-81.
35. Srivastava M, Kumaran, V, Nundy S. Does drain amylase < 666 IU/L on the third post-operative day effectively predicts the absence of a high-impact postoperative pancreatic fistula following pancreaticoduodenectomy?. HPB. 2016;18:e111.
36. Giglio MC, Spalding DRC, Giakoustidis A, Zarzavadjian Le Bian A, Jiao LR, Habib NA, et al. Meta-analysis of drain amylase content on postoperative day 1 as a predictor of pancreatic fistula following pancreatic resection. BJS. 2016;103:328-36.

37. Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C et al. Pancreatic anastomosis leakage after pancreaticoduodenectomy in 1507 patients: a report from the Pancreatic Anastomotic leak Study Group. J Gastrointest Surg. 2007;11:1451-8.
38. Welsch T, Eisele H, Zschabitz S, Hinz U, Buchler MW, Wente MN. Critical appraisal of the International Study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreaticoduodenectomy. Langenbecks Arch Surg. 2011;396:783-91.
39. Miller BC, Christein JD, Behrman SW, Drebin JA, Pratt WB, Callery MP, et al. Multi-institutional external validation of the fistula risk score for pancreaticoduodenectomy. J Gastrointest Surg. 2014;18:172-80.

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