ORIGINAL ARTICLE

Mortality and risk factors in post-operative pancreatic fistula following pancreatoduodenectomy: A single centre experience

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INTRODUCTION

Pancreatoduodenectomy (PD) is one of the most complex surgical procedures in abdominal surgical procedure. It is offered to patients with benign pathology and malignancy. The mortality has been quite significant despite it had reduced from 25%-30% in 1980s to 2%-4% in the modern era.[1] However, perioperative morbidity remained high (30%-50%).[2]

The most dreaded complication of PD is post-operative pancreatic fistula (POPF). The International Study Group of Pancreatic Surgery (ISGPS) in 2005 further the POPF into grade A, B and C.[3] In 2016, The ISGPS updated the POPF Grade A into biochemical leak, POPF Grade B and Grade C into clinically relevant POPF (CR-POPF).[4]

The reported overall POPF rate of studies in 2001 – 2019 from as 7% - 90%. The reported pooled overall POPF is 27% (CI-95%: 23%-30%). The CR-POPF reported in the same systemic review is 7% - 45%, with the pooled CR-POPF rate of 19% (CI-95%: 17%-22%) The wide variation in the reported rates of overall POPF and CR-POPF could be due to different ethnic or societal factors (such as Body Mass Index), in surgical outcomes or some form of confounding or publication bias.[5]

The complications that follow POPF consists of intra-abdominal infection, sepsis, post-pancreatectomy haemorrhage, pseudo-aneurysm and even death. Multiple strategies have been developed to prevent POPF, these are including methods of pancreatic anastomosis, external or internal pancreatic stents, somatostatins analogues, fibrin glue or topical agent to reinforce pancreatic anastomosis.[6] Thus, it is essential to predict and take action accordingly to the risk.

Risk factors that have been identified in the literature include, male sex, Body Mass Index (BMI) >25kg/m^2, pancreatic duct diameter (PDD) < 3mm, soft pancreatic texture and blood transfusion. Pancreatic adenocarcinoma, diabetes mellitus(DM), vascular resection and preoperative chemotherapy are found to be protective factors against POPF.[7] There is tremendous effort of building risk scoring system to prognosticate as evidenced by at least 10 reported POPF scoring systems by Adamu et al.[8] Among these, the scoring systems created by Callery et al. and Mungroop et al. respectively are deemed the easiest to be implemented and have the best prognosticate ability.[8–10] The Callery et al. uses the gland texture, pathology, PDD, and intraoperative blood loss in the Fistula Risk Score.[9] The Mungroop et al. created an online calculator named as Alternative Fistula Risk Score (a-FRS) which is available at pancreascalculator.com, using pancreatic texture, BMI and PDD.[10] The Ansorge et al 2012 by using pancreatic consistency (pancreatic texture) and PDD, divided the patients into high (two risk factors), intermediate group (one risk factors), and low risk group (no risk factor). [11]

An ideal score can be helpful in prognosticate and thus implementing different strategies. Total pancreatectomy can eradicate the possibility of POPF with the risk of a brittle DM.[12] External pancreatic stent was suggested to help in preventing POPF, and to be considered in the high POPF-risk patient.[13] Expensive medication such as pasireotide can be offered in the high risk patients.[2] On the other hand, in the low risk patients, abdominal drain can be removed earlier.[14] By risk stratification, individualized management can be provided.

Until now, there is no publication on incidence of POPF in Malaysia. This study provides an opportunity to assess and examine the correlation of the risk factor and POPF after PD.

MATERIALS AND METHODS

This is a single centre retrospective observational study which conducted in Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia. This is a government own, tertiary referral centre for Hepato-pancreato-biliary surgery cases in Northern Malaysia. The data of patients in the IT system of Hospital Sultanah Bahiyah that were classified as Pancreatoduodenectomy done during the 5 years period from 01 Jan 2017 to 31 Dec 2021 are used for analysis.

Inclusion Criteria:

1. All patients who were recorded as pancreatoduodenectomy done

Exclusion Criteria:

1. Procedure abandoned.
2. Patient had undergone total pancreatectomy
3. Patient with incomplete information of the procedure

All data collected are confidential, no personal identification data of patient will be collected. Data presented will not identify individuals.

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Table I: Baseline Demographic and Clinical Characteristics of Patient

	N (%)	Mean ± SD	Range
Demographic			
Age (years)	111 (100)	59.3 ± 12.747	19 - 82
BMI (kg/m²)*	53 (47.7)	22.61 ± 3.944	15 - 33
Gender			
Male	60 (54.1)		
Female	51 (45.9)		
Ethnic			
Malay	66 (59.5)		
Chinese	34 (30.6)		
Indian	10 (9.0)		
Other	1 (0.9)		
Diabetes Mellitus			
Yes	47 (42.3)		
No	64 (57.7)		
Comorbid			
Yes	77 (69.4)		
No	34 (30.6)		
PRE- OPERATIVE			
Pre- op Alb (g/L)	111 (100)	32.153 ± 5.3107	16 - 45
Pre- op PDD - image (cm)*	108 (97.3)	0.43 ± 0.291	0.11 - 1.5
Pre- op Biliary drainage			
No	48 (43.2)		
ERCP	51 (45.9)		
PTBD	12 (10.8)		
Neo-adjuvant therapy			
Yes	1 (0.9)		
No	110 (99.1)		
INTRA- OPERATIVE			
Operating time (hour:min:sec)	111 (100)	6:56:32 ± 1:55:23	2:06:00 - 13:15:00
Intra-op PDD (cm)*	15 (13.5)	0.36 ± 0.1298	0.2 - 0.5
Pancreas texture*			
Soft	45 (40.5)		
Hard	32 (28.9)		
Pancreatic anastomosis*			
Dunking PJ	43 (38.7)		
2 layers PJ	66 (59.5)		
3 layers PJ	1 (0.9)		
Vascular resection			
Yes	6 (5.4)		
No	105 (94.6)		
Intra-op transfusion*			
Yes	50 (45.0)		
No	55 (49.5)		
Intra-op blood loss (ml)*	45 (40.5)	889.56 ± 443.8	280 - 2500
POST- OPERATIVE			
HPE			
Pancreatic adenocarcinoma	28 (25.2)		
Pancreatitis	6 (5.4)		
Ampullary, duodenal, cystic, islet cell and other diagnosis	77 (69.4)		

*Missing data for these risk factors

Work Process

1. All patients that were classified as PD case are listed down using operating notes record.
2. The patient's information are retrieved from the IT system with data entry from.
3. The data are being analysed.
4. The workflow are as illustrated in the Diagram 1.

Variables

1. Pre-operative data: Age, ethnic, sex, BMI, PDD (on the latest preoperative imaging, measured at the location of planned pancreatic transaction by single observer with the guidance of radiologist), DM, comorbidity, preoperative biliary drainage (none, endoscopic biliary drainage, percutaneous transhepatic biliary drainage), neo-adjuvant therapy.
2. Intraoperative data: pancreatic texture (assess intraoperatively, soft or hard), vascular resection, intraoperative PDD, operation date, intraoperative blood loss, present of intra-op blood transfusion, pancreatic anastomosis (2 layers duct-to mucosa PJ [including Blumgart's and modified Blumgart's], dunking PJ, 3 layers duct-to-mucosa PJ, Pancreatogastrostomy), operating time
3. Postoperative data: Serum and drain amylase POD3 and day 5, drain removal date, date of discharge, image

Table II: Post-op drain and serum amylase, Post-op outcome, 30-day mortality and POPF result

	N (%)	Mean ± SD
D3 drain amylase (iu/L)	111 (100)	1079.33 ± 1987.46
D5 drain amylase (iu/L)	74 (66.7)	1600.12 ± 6808.7
Serum amylase D3 (iu/L)	74 (66.7)	143.66 ± 232.679
Serum amylase D5 (iu/L)	37 (33.3)	47.27 ± 35.754
	Number (N)	**Percent (%)**
Drainage day		
>21 Days	39	35.1
≤21Days	72	64.9
IR drainage post-op		
Yes	3	2.7
No	108	97.3
IR angiography post-op		
Yes	1	0.9
No	110	99.1
Re-operation*		
Yes	20	18
Re-operation for POPF	14	12.6
Re-operation for other	6	5.4
No	91	82
Organ failure post-op		
Yes	16	14.4
No	95	85.6
30 days mortality**		
Yes	10	9
Mortality due to POPF	6	5.4
Mortality for other cause	4	3.6
No	101	91
Clinically Relevant POPF		
No	68	61.3
No POPF	43	38.7
Biochemical Leak	25	22.5
Yes	43	38.7
POPF Grade B	21	18.9
POPF Grade C	22	19.8

* Six (6) cases of re-operation for non POPF leak: 1 case for drain site bleeding, 1 for strangulated incisional hernia, 1 for bleeding cystic plate, 2 for biliary leak, 1 for chyle leak.

**Three (3) cases of patient died from pneumonia, 1 case for acute coronary event.

guided management for POPF, angiographic procedures for POPF, re-operation, POPF related organ failure, 30days mortality, histopathology examination

4. POPF grading is according to ISGPS 2016.[4]

a. Biochemical leak: Amylase > 3 times upper limit institutional normal serum amylase value (300iu/ml)
b. Grade B Pancreatic Fistula: Persistent drainage > 3weeks, Percutaneous or endoscopic specific interventions for collections, angiographic procedures for POPF related bleeding
c. Grade C Pancreatic Fistula: Reoperation, organ failure and death

Surgical Procedure

The surgery is performed by HPB surgery consultants or surgeons who are under HPB surgery subspecialty training with the supervision of HPB consultants. The procedure is started with modified Makuuchi, rooftop or mid-line skin incision. The exploratory laparotomy is performed to decide on whether there is peritoneal metastasis or liver metastasis. Pancreaticoduodenectomy is then performed in a standard way, usually by Classical Kausch-Whipple Procedure. Vascular resection such as portal vein resection is performed as deemed necessary by the operating surgeon. The pancreatic anastomosis is then selected according to the surgeon preference. All patients receive pancreatic stent insertion. Somatostatin analogue is given prior to pancreas transaction and continued for 5days. Enteral feeding is started at Day 2 if there is no contraindication.

DATA ANALYSIS

The statistical analysis will be done using SPSS ™ For Windows Version 20.0. The information collected are analysed using Student T- test for continuous data, Chi-square test for categorical data. The analysis of risk factors is performed using Multivariate logistic regression. P value of less than 0.05 is considered significant.

RESULTS

There were 150 patients listed for pancreaticoduodenectomy in Hospital Sultanah Bahiyah, Alor Setar from 01/01/2017 till 31/12/2021. Among all of them, 111 (74%) patients underwent PD and completed the procedure. Among the 39 patients whom did not proceed with the PD, 15 of them had

Table III: Comparison of the CR-POPF incidence by crisk factors

	CR-POPF (N, %)			p-value
	No	Yes	Total (N, %)	
Ethnic				0.593
Malay	41 (62.0)	24 (37.9)	65 (58.5)	
Chinese	19 (55.9)	15 (44.1)	34 (30.6)	
Others	8 (72.7)	3 (27.3)	11 (9.9)	
Gender				0.924
Female	31 (60.8)	20 (39.2)	51 (45.9)	
Male	37 (61.7)	23 (38.3)	60 (54.1)	
DM			0.634	
No	38 (59.4)	26 (40.6)	64 (57.7)	
Yes	30 (63.8)	17 (36.2)	47 (42.3)	
Comorbid other than DM		*0.029		
No	26 (76.5)	8 (23.5)	34 (30.6)	
Yes	42 (54.5)	35 (45.5)	77 (69.4)	
Pre-op biliary drainage		0.634		
ERCP	33 (64.7)	18 (35.3)	51 (45.9)	
PTBD	8 (66.7)	4 (43.8)	12 (10.8)	
None	27 (56.3)	21 (43.8)	48 (43.2)	
Neo-adjuvant therapy		0.613		
No	67 (60.9)	43 (39.1)	110(99.1)	
Yes	1 (61.3)	0 (0.0)	1(0.9)	
Pancreas texture			0.618	
Soft	29 (64.4)	16 (35.6)	45 (40.5)	
Hard	20 (62.5)	12 (37.5)	32 (28.8)	
Pancreatic anastomosis		0.663		
Dunking PJ	25 (58.1)	18 (41.9)	43 (38.7)	
2 Layer PJ	41 (62.1)	25 (37.9)	66 (59.5)	
3 Layer PJ	1 (100.0)	0 (0.0)	1(0.9)	
Vascular resection			0.402	
No	63 (60.0)	42 (40.0)	105(94.6)	
Yes	5 (83.3)	1 (16.7)	6 (5.4)	
Intra-op transfusion			0.481	
No	34 (61.8)	21 (38.2)	55 (49.5)	
Yes	29 (58.0)	21 (42.0)	50 (45.0)	
HPE				0.18
PDAC and Pancreatitis	24(70.6)	10 (29.4)	34 (30.6)	
Ampullary, duodenal, cystic, islet cell and other diagnosis	44(57.1)	33 (42.9)	77 (69.4)	
	(Mean ± SD)	(Mean ± SD)		
Age (Years)	57.40 ± 13.684	62.30 ± 10.571	111 (100)	*0.048
BMI (kg/m^2)	22.48 ± 4.032	22.84 ± 3.878	53 (47.7)	0.753
Pre-op Alb (g/L)	32.794 ± 4.7176	31.140 ± 6.0537	111 (100)	0.11
PDD- image (cm)	0.47±0.297	0.37 ± 0.277	108(97.3)	0.099
Operating time (hour:min:sec)	6:53:13 ± 1:53:10	7:01:49 ± 1:59:59	111 (100)	0.704
Intra-op blood loss (ml)	851.67 ± 370.108	965.33 ± 569.484	45 (40.5)	0.424

*p value < 0.05, statistically significant.

bypass surgery, 18 patients were explored and biopsy only, 3 patients did not proceed for operation, 2 patients had radical cholecystectomy done and 1 patient had a total pancreatectomy done.

Of the 111 patients who had PD, their baseline characteristics are as in Table I. The postoperative drain and serum amylase concentration is reported in Table II. The mean of day 3 drain amylase is 1079± 1987 iu/L. The cut off value of D3 drain amylase level of 300iu/L is used to defined biochemical leak. The patients are graded according to ISGPS 2005 and 2016. The result is presented in the Table III. The number of patients with POPF Grade B is 21 (18.9%) and POPF Grade C is 22 (19.8%), make up total of 43 patients with CR-POPF (38.7%). The outcomes of operation are reported in Table II. There are 39 patients have drain >21days. Three (2.7%) patients have interventional radiological drainage, and one (0.9%) has angiographic intervention. There are 20 (18.0%) cases of re-operations, 14 (12.6%) of them are for POPF, 6 are for other causes including 2 for biliary leak, one for drain site bleeding, one for strangulated incisional hernia, one for bleeding cystic plate, and one for chyle leak. 16 (14.4%) developed organ failure. Ten (9.0%) cases of 30 days mortality, 6 (5.4%) of them due to POPF, 3 died for pneumonia, and one for acute coronary event.

The comparative statistical analysis is reported in Table III. The ethnicity Indian and others are combined into others for analysis. The ethnic, sex, DM, pre-op biliary drainage, neo-adjuvant therapy, pancreas texture, pancreatic anastomosis, vascular resection, intraoperative transfusion and HPE are not found have statistical significance. The age and

Table IV: Logistic Regression Analysis for Risk Factor

Univariate Logistic Regression						
		Coeff.	OR	95% C.I. for OR		p-value
				Lower	Upper	
Age		0.033	1.033	1.000	1.033	0.052
Gender Male		-0.037	0.964	0.448	2.073	0.924
DM	-0.188	0.828	0.381	1.800	0.624	
Comorbid		0.996	2.708	1.090	6.732	0.032*
Preop Albumin		-0.060	0.934	0.854	1.022	0.137
Pre-op biliary drainage	No					0.635
	ERCP	-0.355	0.701	0.312	1.575	0.390
	PTBD	-0.442	0.643	0.170	2.428	0.515
PDD Pre-op image		-1.229	0.293	0.067	1.282	0.293
Pancreatic Anastomosis	Duct-to-mucosa PJ**	-0.190	0.827	0.378	1.808	0.634
Intra-op transfusion		0.159	1.172	0.536	2.562	0.690
HPE (Pancreatic Ca or pancreatitis)		-0.588	0.556	0.234	1.319	0.183
		Multivariate Logistic Regression				
		Coeff.	OR	95% C.I. for OR		p-value
				Lower	Upper	
Age		0.024	1.024	0.982	1.069	0.269
Gender Male		-0.051	0.951	0.365	2.473	0.917
DM		-0.411	0.663	0.255	1.727	0.400
Comorbid		1.257	3.514	1.085	11.385	0.036*
Preop Albumin		-0.068	0.934	0.854	1.022	0.137
Pre-op biliary drainage	No					0.481
	ERCP	-0.538	0.584	0.219	1.557	0.282
	PTBD	-0.679	0.507	0.109	2.354	0.386
PDD Pre-op image		-1.312	0.269	0.048	1.503	0.135
Pancreatic Anastomosis	Duct-to-mucosa PJ**	-0.260	0.771	0.303	1.964	0.585
Intra-op transfusion		0.279	1.322	0.517	3.385	0.560
HPE (Pancreatic Ca or pancreatitis)		-0.522	0.593	0.215	1.636	0.313
Nagelkerke R Square	0.218					
Hosmer and Lemeshow Test	0.385					

* p-value < 0.05
** 2-layer and 3-layer duct-to-mucosa group are combined as duct-to-mucosa PJ group

comorbidities other than DM have statistically significant difference. Between CR-POPF and no CR-POPF group, the student t-test analysis reported no different of means in BMI, Pre-op albumin, PDD (image), operating time and intra-op blood loss volume.

The Table IV shows the results of logistic regression analysis. The 2-layers and 3-layers duct-to-mucosa PJ are combined as duct-to-mucosa group in pancreatic anastomosis variable analysis. The Univariate Logistic Regression are conducted, and comorbid other than DM is found to be significant predicting factor. The OR is 2.708 (CI 95%: 1.090-6.732, p-value 0.032) All the other factors are not statistically significant. Multivariate analysis is performed, and comorbidity other than DM found to be a significant risk factor with OR 3.529 (CI 95%: 1.092-11.404, p-value = 0.035). The Nagelkerke pseudo R^2 = 0.223, Hosmer and Lemeshow test p-value =0.228. This means that the model is not strong, but it is consider fit as p-value of the Hosmer & Lemeshow test is >0.05.

DISCUSSION

The overall CR-POPF incidence in this study is 38.7%. The reported pooled CR-POPF rate in systematic review by Sivesh K. Kamarajah et al. is 19% (CI 95%: 17-22).5 The CR-POPF for all the studies included in the systemic review is between 7% - 45%, the reported wide range may be explained by the different population and social economy factor of the centres.[5] Our rate of CR-POPF of the local centre is within the reported range. The 30days mortality related to POPF is 5.4%. The hospital death reported by an Amsterdam paper to be 1% - 16%.[15] The 30days mortality of our centre is within the range.

The patients who have none DM morbidity experience a significant higher CR-POPF rate. This association is further supported by logistic regression analysis. Our study did not explore the specific co-morbidities as the FRS and a-FRS does not include pre-morbid disease. A 2020 systematic review by Sivesh et al. suggested a link between cardiovascular disease and CR-POPF, where pre-operative chronic pulmonary obstructive pulmonary disease and pre-operative hypertension were correlated with all POPF which including biochemical leak.[5] Age was found to be significantly different. The mean age of the group of patients who developed CR-POPF is older. The similar finding is found in the Zhao Z. et al. in 2023, where group older than 62.5-year-old has higher POPF rate (14.9%) compare to the younger group (6.9%).[16] It was proposed that senile patients carried more comorbidity, and suboptimal fitness which cause poor healing of the anastomosis. The univariate and multivariate logistic

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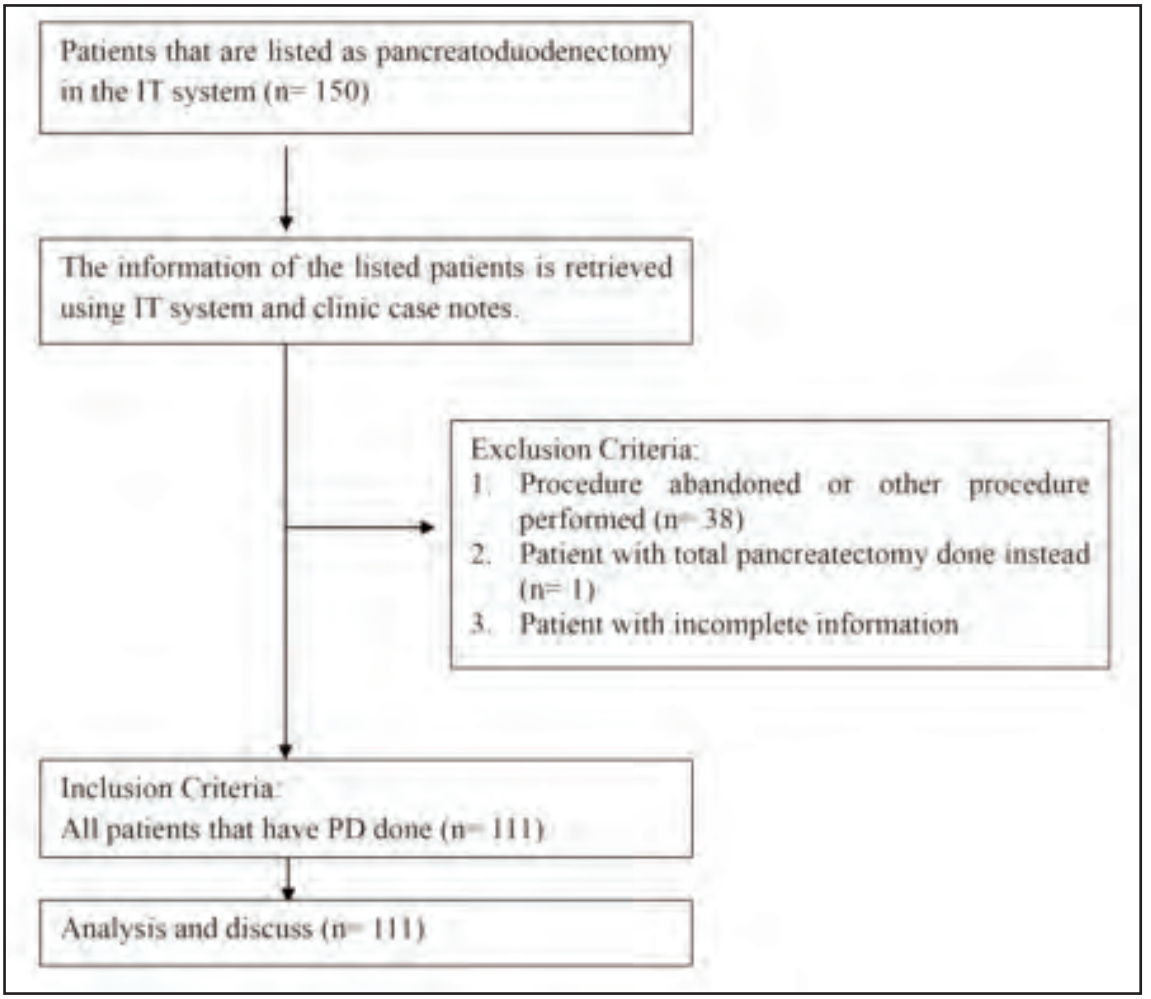

regression found that only none DM comorbidity can predict the CR-POPF, with the OR 3.514 (CI 95%: 1.085-11.385, p-value = 0.035). The age is not a predictor. More efforts should be invested into studying the comorbidity in the population.

Most of the studies show that male sex is a risk factor for POPF.[5,7] But, Zhang JY et al. shows the different result which is similar to us.[17] PDD on the pre-operative imaging is a commonly studied factor for PD. Many scoring systems use PDD as one of the predicting factors.[5,7,9,10] Small duct size is associated with normal pancreas with a preserved endocrine function and usually represents difficult anastomosis. Small duct size is also correlated with more post-operative acute pancreatitis.[18,19] In our study, PDD is slightly smaller in CR-POPF group but it was not significant statistically (0.37cm vs 0.47cm, p = 0.099).

CR-POPF rate does not differ in the DM group and non-diabetic group in this study, even though the previous study found that DM is protective for POPF.[20] Pancreatic texture is a well-established predicting factor for POPF. This is confirmed by the multiple studies.[5,7–10,17,20] Histological research explains that patients with POPF usually has more pancreatic fat with less pancreatic fibrosis and low blood vessel density on the specimen.[21] Scoring system a-FRS included the BMI in the mathematic model.[10] Moreover, systematic review by Kamarajah et al. in year 2020 shows that BMI (> 25kg/m^2) is a significant risk factor.[5] However, our data cannot draw conclusion regarding BMI. Pre-op serum albumin is known to be correlated with serious complications follow PD, as reported in Narongsak et al. 2019.[22] But, Kamarajah et al. and Zhang B et al. showed the different conclusion.[5,7] Pre-operative biliary drainage (PBD) was reported to reduce CR-POPF or overall postoperative complications, although it is not shown in our result.[23,24]

Intra-operative blood loss was reported to increase risk of POPF, as reported by Callery et al.[9] It was hypothesized that sudden blood loss may lead to ischaemia and poor healing of the pancreatic anastomosis. This maybe compromised by the tissue oedema resulted from the aggressive fluid resuscitation in response to the blood loss. Intraoperative blood transfusion is related to large volume blood loss and is associated with POPF.[5,7]

Pancreaticogastrostomy was reported to be superior to pancreatojejunostomy in term of POPF rate.[25] However, recent meta-analysis shows that POPF rate in PG and PJ group are almost similar.[5] In our centre, the preferred anastomotic method is PJ, where no PG was performed. Methods that are

used including dunking technique and duct-to-mucosa PJ and there is no difference of POPF. Operative time does not differ significantly in this study which is in line with the study by Ke Z. et al.[26]

Callery et al. showed that the pancreatic adenocarcinoma or pancreatitis are associated with lower POPF rate, while other pathology is higher. The maybe theorized as other pathology are commonly related with a soft pancreas.[9] Our analysis revealed a lower but not statistically significant CR-POPF rate in patients with pancreatic ductal adenocarcinoma or pancreatitis.

The pathophysiology of POPF remained complex. The formation of POPF may not be just due to mechanical disruption of the anastomosis. Potential mechanism suggests the role of postoperative pancreatitis in the development of POPF.[27] Intraoperative amylase concentration in immediate intraoperatively derived fluid is highly predictive of the POPF. The local activation of pancreatic enzyme may lead to postoperative pancreatitis, and finally POPF.[28] Thus, the strategy should include methods to strengthen the pancreatic anastomosis, and to prevent the postoperative pancreatitis. Few methods have been proposed included the use of trypsin inhibitors (ulinastatin) and intravenous hydrocortisone.[29–31]

LIMITATIONS

This paper acknowledges certain limitations. First, the retrospective nature of the investigation introduces the possibility of selection bias. Second, missing data limit the analysis of potential risk factors. Third, the design with a small sample size may be insufficiently power to detect significant result. Finally, the variability in surgeon competency and experience could potentially biased the complications rate.

CONCLUSION

The CR-POPF rate is 38.7% and 30-days mortality associated with CR-POPF is 5.4%. Age and percentage of non-DM comorbidity are significantly higher in CR-POPF group patient compared to no CR-POPF group, where logistic regression identify none DM comorbidity as the sole predicting factor.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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