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Original Artical

"Association of Early Postoperative Peripancreatic Drainage Fluid Culture with Postoperative Pancreatic Fistula (POPF) and Antibiogram After Pancreaticoduodenectomy (PD) to Assess the Outcome"

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Abstract

Background: Postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD) are often accompanied by perioperative bacterial contamination which may lead to abscess, MOF and death. However the impact of intra operative bacterial contamination on surgical outcome after PD has not been assessed in depth in our country.

Aim of this study: To know the bacterial contamination and antibiogram at an earlier basis at the peripancreatic anastomotic area after PD and to assess their relation to the aggravation of POPF and septic complications.

Materials and methods: Total 24 patients were enrolled who underwent PD.Drain fluid amylase level were measured on day 1, 3 and 7 postoperatively. Peripancreatic drain fluid culture was done on day 01. According to ISGPF criteria for POPF, patients who had three times elevated (>300 IU/ml) amylase on post operative drain fluid had been considered as Pancreatic Fistula. So all patients(N=24) were divided into two groups on the basis of drain fluid culture result. Group 1(n=14)- was patient with positive culture result, Group 2(n=10)- was patient with negative culture result.

Result: The median age of 24 cases was 55years (range 32-69 years). There were 15 male and 9 female. The commonly found micro organisms in the PP drain fluid culture were Klebsiella alone 8 (57.14%) cases, E.coli 3 (21.60%)cases. Klebsiella with E.coli 1 (7%) case, with Enterobacter 1 (7%) case and Acenobacter alone in 1 (7%) case. 13 patients developed POPF (grade A/B/C) where 11 (84.6%) were C/S positive. Among them 9 developed Grade-A POPF and sensitive to colistin sulphate, meropenem, amoxiclav and linezolid. 1 was Grade B POPF and was sensitive only to colistin sulphate. 1 developed Grade C POPF, which was resistant to all the drugs and not survived eventually due to sepsis and MOF.

Preoperative raised CRP level (> 20 mg/l) was found in 17 cases (70.83%) where 12 was C/S positive which was statistically significant. Pre operative biliary stenting was done in 11 patients where 8(77%) was culture positive with statistically significant result. The Dunking procedure was also found statistically significant to develop POPF along with C/S positive cases.

Conclusion: Evidence of perioperative bacterial contamination has a strong predictive value in the development of grade-B/C POPF from grade-A where multi drug resistant polymicrobial agents may play an important role.

Key words: Pancreaticoduodenectomy(PD), Postoperative pancreatic fistula (POPF), antibiogram, drain fluid culture, biliary stenting, multidrug resistant

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Introduction:

Pancreaticoduodenectomy or Whipple's surgery is often performed as a curative surgical procedure in periampullary carcinoma, carcinoma head of pancreas or distal cholangiocarcinoma causing obstructive jaundice[1]. In some benign cases like duodenal GIST, pancreatic head lacerated injury etc, this procedure often considered[2]. As a complex surgical procedure, morbidity and mortality still remain high despite the improvements in surgical technique and postoperative management. The infections and anastomotic insufficiency particularly clinically relevant postoperative pancreatic fistula (CR POPF) are the main post operative morbidity[3]. Nearly one third of patient developed infectious complications even in high volume centers[4]. These postoperative complications such as wound infections, POPF A, B or C, intra-abdominal abscess & hemorrhage cause prolonged hospital stay of such patients and increase the cost also. Bacterial contaminations enhance the progression of grade A pancreatic fistula to grade B/C and subsequently causes intra-abdominal abscess, sepsis and even causes increased morbidity and mortality[5].

Kobayashi and colleague reported that infections of drainage fluid on 1st POD is a risk factor for development of POPF. they also found that more than 20% of bacterial cultures from peritoneal fluid revealed positive findings for bacteria[6]. Okamura and colleagues reported that 79% of bacteria isolated from incisional SSIs and 36.8% of bacteria isolated from organ/ space specific SSI foci correspond to those obtained from peritoneal fluid[7]. Nagakawa reported not all of the bacteria causing organ/space specific SSIs were from intraoperative contaminations, some were due to bacteria arising for example from leakage of the pancreatojejunostomy (PJ) or from a retrograde infection via the drainage tube. However not all microorganisms present in bile are important rather specific species of bacteria (like pseudomonas) may confer the increased risk of CR_POPF[8-9].

All these reports support the association of peritoneal fluid infection progresses the minor pancreatic leakage into major one, that causes severe sufferings of the patients.So, early detection of drain fluid infection and isolation of bacteria and antibiogram may prevent development of POPF after pancreaticoduodenectomy.

Material and methods

Total 24 patients with variable diagnosis underwent PD meeting the selection criteria were included in the study. Per operative bile was collected and sent for C/S. Drain fluid was collected from per operatively placed peripancreatic drain tube following PD. On first POD for C/S and amylase. Again collected for amylase only on 3rd & 7th POD. All were collected in an aseptic way by a sterile syringe and immediately capped and labelled. Drain fluid amylase level was measured by photometric technique by using Rate-Reaction method on Seimen's atellica solution machine Germany. Amylase greater than three times of upper normal value (>300IU/ml) was diagnosed as POPF. The 1st POD drain fluid culture result was found positive or negative and an antibiogram was established in case of positive cases. patients were divided into two groups(1/2) according to C/S positive or negative report respectively. Preoperative and per-operative risk factors assessed and the effect of the risk factors ware evaluated for the development of POPF following PD.

Results

The median age was 55 years (range 32-69 years). There were 15 males and 09 females. About 70% patients had co-morbidities, DM (50%), HTN (42%), COPD (8%). 20% cases were overweight (BMI>25kg/m2), 12.5% was underweight (BMI<18kg/m2). 46% had pre-operative biliary stenting (Table I).

There is no significant difference between culture positive and negative groups according to age (young or old), sex, comorbidity and nutritional status (underweight, normal or over weight group). However, the patient who underwent preoperative biliary decompression by placing stent inside the CBD, growth of microorganisms are significantly higher in PP drainage fluid after PD. WBC count and liver function test is nonsignificant in both groups but raised CRP level is found statistically significant in case of culture positive group (Table II). There is no significant difference of per operative blood loss and duration of surgery in between two groups of patients.Post operative drainage fluid culture positive result is found statistically significant in patients who underwent Dunking procedure than who underwent DTM procedure (Table III).

No POPF was seen in 3(28%) patients in group-1 and 8(72%) patients in group-2 and the difference was not significant. POPF was developed in 13 cases where 11(84%) patients were in group-1 and 2(16%) were in group-2. In further sub-classification analysis of POPF group shows Grade-A(70%), Grade-B(7%) and Grade-C(7%) was developed in group-1 cases, in contrast to group-2 cases only 2(16%) patient developed grade-A POPF and the difference between two groups was statistically significant (Table IV).

Total 58% was found C/S positive(group-1), where klebsiella alone 58%, E.coli alone 21%, Klebsiella and E.coli 7%, Klebsiella and Enterobacter 7%, Acenobacter alone 7%. 42% was C/S negative (group-2). Among either of the morbidity 13 (54%) cases developed POPF, according to ISGPF criteria there were 11(86%) grade-A, 1 (7%) grade-B and 1(7%) grade-C (who was not survived eventually). No patient had post-operative hemorrhage following PD [Fiqure 1-4].

Grade-A fistula is associated with Klebsiella alone in 7(78%) patients, E.coli alone in 2 (22%) patients. Grade-B POPF is associated with acenobacter and this patient developed severe sepsis who recovered after appropriate antibiotics. Grade-C POPF is associated combinedly with klebsiella and E.coli, who developed severe sepsis and eventually to death due to multiple organ failure (Table V).

Total 14 cases were found culture positive where 11 developed different grade of POPF(A/B/C) and 3 did not. Among that 11 POPF patients 9 was grade-A where klebsiella or E.coli was the causative organisms and all of them were sensitive to Colistin sulphate, Meropenem, Amoxiclav and Linezolid but resistant to cephalosporin group of drugs and they all were recovered well. On the other hand one patient developed grade-B POPF where Acenobacter was found in drain fluid culture and that was resistant to all the antibiotics except Colistin sulphate and the patient developed sepsis though recovered finally. One patient developed grade-C POPF where klebsiella and E.coli both combinedly was found as causative organisms and they were resistant to all the group of drugs. This patient developed MOF and eventually to death.3 patient did not developed any POPF though E.coli, Klebsiella or Enterobacter alone was found in drain fluid culture. That was sensitive to all conventional group of antibiotics and recovered without any complications. (Table VI).

The patient who died on 17th POD after PD [Fiqure 5]. He was diabetic & hypertensive and no history preoperative biliary stenting. CRP and WBC count was raised. Dunking method of PJ anastomosis was done. Both klebsiella & E.coli was found in PP drain fluid culture result & both was resistant to all the antibiotics. He developed severe sepsis then MOF & expired eventually.

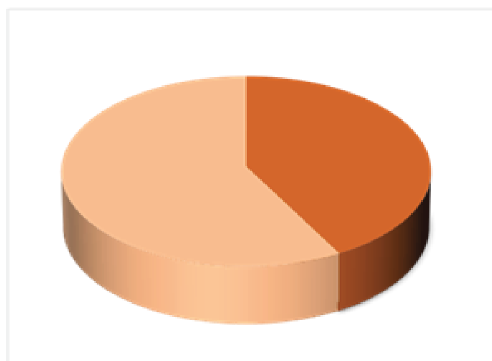

Fig-1: Distribution of culture result with percentage(N=24)

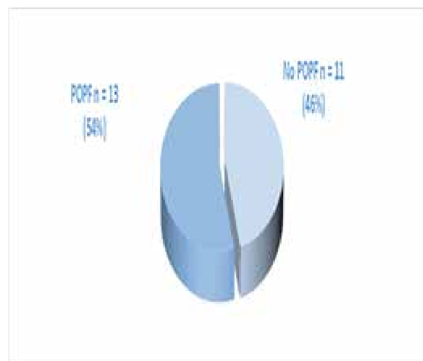

Fig-2 : Distribution of POPF after PD

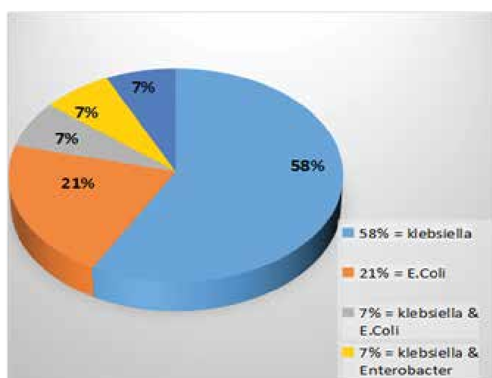

Fig-3: Distribution of presence of microorganisms.

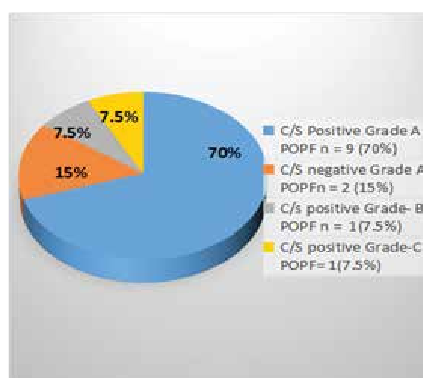

Fig-4: Distribution of development of POPF according to culture result

Table-I: Comparison of clinico - demographic variables between two groups (N=24)

Variables (N=24) n	Group-1 (n=14) Culture positive [n(%)]	Group-2 (n=10) Culture negative [n(%)]	P value
Age (years)			
32-50(7)	5(72)	2(28)	0.112ns
51-69(17)	9(53)	8(47)	0.730ns
Sex			
Male (15)	9(60)	6(40)	0.281ns
Female(9)	5(55)	4(35)	0.407ns
Comorbidity(17)	**11(65%)**	**6(35%)**	
DM (6)	4(67)	2(33)	0.259ns
HTN (6)	5(83)	1(17)	0.129ns
DM+HTN (4)	1(25)	3(75)	0.185ns
COPD (1)	1(100)	0	0.322ns
BMI(kg/m2)			
<18 (2)	0	2(100)	0.083ns
18-25 (18)	11(61)	7(39)	0.193ns
>25 (4)	3(75)	1(25)	0.186ns
Preoperative biliary stenting			
yes (11)	8(73)	3(27)	0.043s
No (13)	6(46)	7(54)	0.230ns

Chi square test was done to measure the level of significance (s=significant, ns= non significant).

Table II: Comparison of preoperative biochemical parameters between two groups (N=24)

Variables N=24	Group-1 Culture positive(n=14),(%)	Group-2 Culture negative(n=10),(%)	P value
WBC			
>11000/cc (11)	6(55)	5(45)	0.646ns
<11000/cc (13)	8(62)	5(38)	0.230ns
CRP			
>20 mg/L (17)	11(65)	6(35)	0.034s
<20 mg/L (7)	3(43)	4(57)	0.613ns
Serum Bilirubin			
>3 mg/dl (18)	10(56)	8(44)	0.087ns
<3 mg/dl (6)	4(67)	2(33)	0.524ns
INR			
>1.5 (4)	4(100)	0	1.00ns
<1.5 (20)	10(50)	10(50)	0.076ns
Serum Albumin (gm/dl)			
>3.5 (12)	6(50)	6(50)	0.069ns
<3.5 (12)	8(67)	4(33)	0.432ns

Chi square test is used to detect the level of significance (s=significant, ns=non significant)

Table III: Comparison of intraoperative parameter between two groups of patients.

Variables N=24	Group-1 Culture positive(n=14),(%)	Group-2 Culture negative(n=10),(%)	P value
Blood loss			
>400 ml (12)	8(67)	4(33)	0.103
<400 ml (12)	6(50)	6(50)	1.000
Procedure			
DTM (18)	9(50)	9(50)	1.000
Dunking (6)	5(83)	1(17)	0.029S
Duration of surgery			
>6 hours (12)	8(67)	4(33)	0.103
<6 hours (12)	6(50)	6(50)	1.000

Chi square test was used to detect the level of significance

Table IV: Comparison of the occurrence of POPF between two groups of patients.

Variables (N=24)	Group-1 C/S positive(14) n(%)	Group-2 C/S negative(10) n(%)	P value
No POPF (11)	3(28)	8(72)	0.843a
POPF (13)			
A (11)	9(70)	2(16)	0.009b
B (1)	1(7)	0	0.018b
C (1)	1(7)	0	0.018b

The level of significance has been detected by Chi square test(a) and Fisher's exact test(b).

Table V: Association of drain fluid culture positive patient with the development of POPF grading.

Types of Micro organisms (n=14) (%)	POPF(11)		
	Grade-A(9) n(%)	Grade-B(1) n(%)	Grade-C(1) n(%)
Klebsiella (8) (58)	7(88)	0	0
E.coli (3) (21)	2(67)	0	0
Acenobacter(1) (7)	0	1(100)	0
Klebsiella & Enterobacter(1) (7)	0	0	0
Klebsiella & E.coli (1) (7)	0	0	1(100)

Table VI: Association of antibiogram of culture positive patient with POPF or No POPF and their outcome.

	Variables			
	Microorganisms	Antibiotic Sensitivity	Antibiotic Resistant	Outcome
POPF (n=11)				
Grade-A(9)	Klebsiella or E.coli	Colistin sulphate Meropenem Amoxyclav Linezolid	Cephalosporin Penicillin	Recovered
Grade-B(1)	Acenobacter	Colistin sulphate only	All others	Sepsis but Recovered
Grade-C(1)	Klebsiella & E.coli	None	All groups	MOF then Death
No POPF(3)	E.coli(1) Klebsiella(1) Klebsiella & Enterobacter(1)	All groups	None	Recovered with no complication

Grade- B POPF

Grade- C POPF

Fig-5: POPF and their complications (according to grading) after PD

Courtesy : Department of HBP and LTx surgery BSMMU, 2022

Discussion:

Perioperative bacterial contamination may play an important role in the development of POPF after pancreaticoduodenectomy(PD).The importance of early postoperative PP drain fluid culture and antibiogram after PD has been assessed in many studies to know the presence of microorganisms in the perioperative anastomotic area and their association with the postoperative outcome to prevent or reduce consequence of POPF.

In this study,the patients were divided into two groups: group-I was culture positive (58%) and group-II was culture negative(42%).

Tatsuo Hata et al.2019 investigated the impact of early postoperative drainage fluid culture positivity on the development of CR-POPF after PD in 465 cases and found culture positive in PP drainage fluid from 26% of patients[6]. Kota Nakamura et al.,2020 investigated microbiological data for PP drain culture on POD-1.They found 34% positive result in their series with a strong association with POPF[10-11].

In our study, female gender was found as weak understood risk factor for culture positive.The effect of diabetes mellitus(DM) on C/S positive POPF following PD is controversial. Srivastava et al.,2001 investigated 120 patients with pancreatic and periampullary tumors and found that patients with DM had an increased incidence of POPF[12]. Chu et al.,2010 also reported that DM was an independent risk factor for POPF after adjusting of age, comorbidities, BMI, preoperative albumin level, type of operation, surgery time and pancreatic quality[13-14]. Though in our study we didn’t got any correlation with the presence of DM & culture positive POPF development. Total 11 patients were found preoperatively stented by ERCP. Among them 75% were culture positive and all developed POPF. Preoperative biliary stenting and development of low grade POPF with bacterial contamination has been found a strong predictor in our study.

Regarding the preoperatively measured LFT and inflammatory markers(WBC,CRP) only raised CRP level has been found an association with PP drainage fluid culture.

M. Kawa et al.,2009 have stated that leucocyte count > 9800/cc is a predictive factor for CR-POPF (grade-B). Though in our series it was found non significant [15].

In this study, the types of PJ anastomotic procedure has been found a very strong predictive factor in culture positive cases. Dunking procedure was done in 6 cases, where 83% of them found culture positive with a statistically significant P value(0.029) in comparison to DTM procedure where the culture positive was only 50%.

We got a significant relation of perioperative bacterial contamination and POPF development. Among 24 cases, 14 was found culture positive where 11(79%) developed POPF as 9 grade-A, 1 grade-B and 1 grade-C with statistically significant P value(<0.05). 3(21%) culture positive cases did not developed any POPF. 10 cases were culture negative and only 2 of them developed POPF(grade-A) which was not significant statistically.

In our series the isolated microorganisms are aerobic gram negative bacilli as- Klebsiella(71%), E.coli (28%), Enterobacter (7%) and Acenobacter (7%). K Okanu et al., 2015 found in his study the commonly detected bacteria were Enterococcus (11%), Enterobacter (5%), Klebsiella(4%), Pseudomonas(3%) and MRSA(3%) [11]. But in our study Klebsiella(71%) was the dominantly found microorganism, some where along with E.coli.

We also got the antibiogram result along with fluid culture. In our study almost all the conventional group of antibiotics are found resistant to the microorganisms. In culture positive grade-A POPF cases the sensitive antibiotics are colistin sulphate, meropenem, amoxiclav and Linezolid only. Martin loos et al.,2018 has found in their study that culture positive grade-A POPF were sensitive to second generation cephalosporin group of drugs[16-17]. Though in our study we found the group as resistant.

One patient developed grade-B POPF where the isolated microorganism (Acenobacter) was sensitive only to colistin sulphate and developed severe sepsis. Though the patient was recovered finally after an aggressive treatment.

One patient in our study developed grade-C POPF and even though the isolated microorganisms were klebsiella and E.coli they were rersistant to all group of drugs.The patient developed MOF and eventually expired on 17th POD.

Yoko Kitagawa et al.,2020 showed in their study that grade-C POPF was associated with candida species along with Enterobacter and sensitive to

antifungal and cephalosporin groups. Though in our study candida has not been found in any case[18-19].

The present study has some limitations. The first, short study period and short sample size. Second,outcome observed up to hospital discharge only. Third, only uni-variate analysis was done; multivariate could not be done due to small sample size.

In conclusion, peri-operative bacterial contamination is a strong predictor for the development of POPF after PD, So early detection of contamination by PP drain fluid culture should be a routine protocol after PD and a proper antibiogram has to be established in all cases to prevent grade-B/C POPF from grade-A which may be fatal later on.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the corresponding authors on reasonable request.

Ethical Statement

The studies involving human participants were reviewed and approved by IRB board, BSMMU, Dhaka, Bangladesh. The patients/participants provided their written informed consent to participate in this study.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed.

Referrences

1. Chinikar R, Patricio D, Gosse J, Ickx B, Delhaye M, Closset J, El Moussaoui I, Hites M, Navez J. Perioperative antimicrobial prophylaxis in patients undergoing pancreatoduodenectomy: retrospective analysis of bacteriological profile and susceptibility. Acta Chirurgica Belgica. 2021 Nov 23:1-8
2. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. New England Journal of Medicine. 2003 Nov 27;349(22):2117-27.
3. 3.Butturini G, Daskalaki D, Molinari E, Scopelliti F, Casarotto A, Bassi C. Pancreatic fistula: definition and current problems. Journal of hepato-biliary-pancreatic surgery. 2008 May;15:247-51.
4. Butturini G, Marcucci S, Molinari E, Mascetta G, Landoni L, Crippa S, Bassi C. Complications after pancreaticoduodenectomy: the problem of current definitions. Journal of hepato-biliary-pancreatic surgery. 2006 May;13:207-11.
5. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M, International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005 Jul 1;138(1):8-13.
6. Kobayashi S, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Infection control for prevention of pancreatic fistula after pancreaticoduodenectomy. Hepato-gastroenterology. 2013 Jun 1;60(124):876-82.
7. Osakabe H, Nagakawa Y, Kozono S, Takishita C, Nakagawa N, Nishino H, Suzuki K, Shirota T, Hosokawa Y, Akashi M, Ishizaki T. Causative bacteria associated with a clinically relevant postoperative pancreatic fistula infection after distal pancreatectomy. Surgery Today. 2021 Nov;51(11):1813-8.
8. Nagakawa Y, Matsudo T, Hijikata Y, Kikuchi S, Bunso K, Suzuki Y, Kasuya K, Tsuchida A. Bacterial contamination in ascitic fluid is associated with the development of clinically relevant pancreatic fistula after pancreatoduodenectomy. Pancreas. 2013 May 1;42(4):701-6.
9. Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients/with invited commentary. Digestive surgery. 2001 Jul 1;18(6):453-8.
10. Hata T, Mizuma M, Motoi F, Nakagawa K, Masuda K, Ishida M, Morikawa T, Hayashi H, Kamei T, Naitoh T, Unno M. Early postoperative drainage fluid culture positivity from contaminated bile juice is predictive of pancreatic fistula after

pancreaticoduodenectomy. Surgery today. 2020 Mar;50:248-57.

11. Nakamura K, Sho M, Kinoshita S, Akahori T, Nagai M, Nakagawa K, Takagi T, Ikeda N. New insight into the association between bile infection and clinically relevant pancreatic fistula in patients undergoing pancreatoduodenectomy. Journal of Hepato-Biliary-Pancreatic Sciences. 2020 Dec;27(12):992-1001.

12. Srivastava S, Sikora SS, Pandey CM, Kumar A, Saxena R. Determinants of pancreaticoenteric anastomotic leak following pancreaticoduodenectomy. ANZ journal of surgery. 2001 Sep;71(9):511-5.

13. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, Kooby DA. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. Journal of the American College of Surgeons. 2010 Apr 1;210(4):463-73.

14. Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients/with invited commentary. Digestive surgery. 2001 Jul 1;18(6):453-8

15. Kawai M, Tani M, Hirono S, Ina S, Miyazawa M, Yamaue H. How do we predict the clinically relevant pancreatic fistula after pancreaticoduodenectomy?—an analysis in 244 consecutive patients. World journal of surgery. 2009 Dec;33:2670-8.

16. Loos M, Strobel O, Legominski M, Dietrich M, Hinz U, Brenner T, Heininger A, Weigand MA, Büchler MW, Hackert T. Postoperative pancreatic fistula: Microbial growth determines outcome. Surgery. 2018 Dec 1;164(6):1185-90.

17. Abe K, Kitago M, Shinoda M, Yagi H, Abe Y, Oshima G, Hori S, Yokose T, Endo Y, Kitagawa Y. High risk pathogens and risk factors for postoperative pancreatic fistula after pancreatectomy; a retrospective case-controlled study. International Journal of Surgery. 2020 Oct 1;82:136-42.

18. Osakabe H, Nagakawa Y, Kozono S, Takishita C, Nakagawa N, Nishino H, Suzuki K, Shirota T, Hosokawa Y, Akashi M, Ishizaki T. Causative bacteria associated with a clinically relevant postoperative pancreatic fistula infection after distal pancreatectomy. Surgery Today. 2021 Nov;51(11):1813-8.

19. Abe K, Kitago M, Shinoda M, Yagi H, Abe Y, Oshima G, Hori S, Yokose T, Endo Y, Kitagawa Y. High risk pathogens and risk factors for postoperative pancreatic fistula after pancreatectomy; a retrospective case-controlled study. International Journal of Surgery. 2020 Oct 1;82:136-42.