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Research Article

A new marker in post-pancreatectomy fistulas; hypophosphatemia

Post-pankreatektomi fistüllerinde yeni bir belirteç; hipofosfatemi

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Abstract

Aim: Postoperative hypophosphatemia is associated with morbidity after many gastrointestinal surgeries. In this study, we aimed to investigate the relationship between hypophosphatemia and POPF, which is one of the morbidities after pancreatectomy.

Material and Methods: All adult patients who underwent pancreatectomy in our surgical oncology clinic from 2010 to 2020 were included in the patient data recording system to the Faculty of Medicine of Ankara University, Surgical Oncology clinic. Exclusions were made for those under 18, without postoperative Jackson-Pratt (jp) amylase levels, and with previous pancreatic surgery.

Results: Examination of a total of 185 patients showed that fistula occurred in 20% of cases. Statistical analysis revealed that postoperative 2nd and 3rd-day phosphorus levels are markers for pancreatic leak.

Conclusion: Decreased phosphate values after pancreatic surgery may be an indicator for pancreatic fistula, especially significant on the 2nd and 3rd postoperative days

Keywords: Pancreatectomy, Postoperative Fistula, Hypophosphatemia, Surgical Oncology, Pancreatic Leak, Phosphorus Levels

Öz

Amaç: Postoperatif hipofosfatemi, birçok gastrointestinal cerrahi sonrası morbidite ile ilişkilidir. Bu çalışmada, hipofosfatemi ile pankreatektomi sonrası morbiditelerden biri olan POPF arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: 2010 ile 2020 yılları arasında cerrahi onkoloji kliniğimizde pankreatektomi uygulanan tüm yetişkin hastalar, Ankara Üniversitesi Tıp Fakültesi, Cerrahi Onkoloji Kliniği hastaların veri kayıt sistemine dahil edildi. 18 yaşından küçük hastalar, postoperatif Jackson-Pratt (jp) amilaz seviyesi olmayan hastalar ve önceki pankreas cerrahisi olan hastalar bu çalışma dışı bırakıldı.

Bulgular: Toplam 185 hastanın takibinde fistül gelişip gelişmediği kaydedildi ve vakaların %20'sinde fistül meydana geldi. Fistül ile BMI, yaş, cinsiyet, ca-19.9 seviyeleri ve ameliyat öncesi fosfor seviyeleri, pankreas cerrahisi türü ve ameliyat sonrası günlerdeki 0-1-2-3 fosfor seviyeleri arasındaki ilişki incelendi. POPF olmayan ve olan grup arasında POPL 0 değerleri arasında istatistiksel olarak anlamlı bir fark bulunmadı (p=0.422). POPF olmayan ve olan gruplardaki POPL 1 değerlerindeki fark önemli değil (p=0.296). POPF olmayan ve olan gruplardaki POPL 2 değerlerindeki fark anlamlı (p=0.002). POPF olmayan ve olan grup arasında POPL 3 değerlerindeki fark anlamlıydı (p=0.001). İstatistiksel analiz, ameliyat sonrası 0. gün fosfor seviyeleri ve ameliyat sonrası 1. gün fosfor seviyelerinin pankreas kaçağının bir göstergesi olmadığını, ameliyat sonrası 2. ve 3. gün fosfor seviyelerinin ise çalışma grubumuzda pankreas kaçağının belirleyicisi olduğunu gösterdi.

Sonuç: Pankreas cerrahisi sonrası azalan fosfat değerleri, pankreatik fistül için bir gösterge olabilir. Fosfor seviyeleri, özellikle ameliyat sonrası 2. ve 3. günlerde kaçak açısından anlamlı bulundu.

Anahtar Kelimeler: Pankreatektomi, Postoperatif Fistül, Hipofosfatemi, Cerrahi Onkoloji, Pankreatik Sızıntı, Fosfor Seviyeleri

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Introduction

Pancreaticoduodenectomy (pd)distal pancreatectomy and total pancreatectomy is one of the most complex procedures in gastroenterological surgery and is often indicated for a variety of diseases; therefore, surgical techniques are constantly being improved(1).

The first Pancreaticoduodenectomy (PD) was operated in the 1800s. William Halsted performed the first transduodenal local excision of the ampulla Vater tumor in 1898 (2), while in the same year Alessandro Codivilla became the first person to perform PD in Imola, Italy. In 1909, Walter Kausch performed the first successful 2-stage PD in Berlin (3) Allen Whipple et al reported the first series of PDs in 1935, and the operation has since been known as the "Whipple" operation.(4) Mortality in Whipple operations until the 1970s was over 25%.(5,6)

Mortality due to pancreatectomy in developed centers is below 5%, and morbidity due to pancreatectomy is still common and is estimated as high as 40-50%.(7,8)

The most common causes of morbidity following pancreatic resection include delayed gastric emptying, postoperative bleeding, and postoperative pancreatic fistula (POPF) (9). Pancreatic fistula is typically associated with significant perioperative morbidity such as bleeding, sepsis, longer hospital stay, and increased cost and higher perioperative mortality risk10).

POPF is a common complication of pancreatic surgery associated with increased hospital costs and prolonged hospital stay(11). The sequelae of POPF include sepsis, intra-abdominal abscess formation and intra-abdominal bleeding associated with high mortality rates(12). POPF prevalence estimates are highly variable, frequently ranging from 10% to 20% (8,13) and up to 30% following distal pancreatectomy(14,15.)As POPFs pose a significant risk and cost for both patients and hospitals, studies have focused on estimating the risk of developing POPF. Soft pancreatic parenchyma(16-18), small pancreatic duct(16,17), low surgeon/hospital volüme(19,20),and increased BMI(21,22) Pancreaticojejunostomy vs. pancreaticogastrostomy (23,24), stump closure method(25,26), internal and external drainage(27,28), and administration of somatostatin/pasireotide (29) are accepted risk factors for the development of POPF.

Hypophosphatemia is a common manifestation after various surgical procedures, as well as in patients with infections, burns, and trauma (30-32). The presence of hypophosphatemia is associated with poor outcomes, including arrhythmia, heart failure, longer hospital stays, and increased postoperative complications (33). There is new evidence that following hypophosphatemia may be associated with increased morbidity, including the development of POPF(34).

In this retrospective study, we aimed to investigate whether there is a relationship between early postoperative phosphorus low and pancreatic fistula

Materıal and Methods

All adult patients who underwent pancreatectomy in our surgical oncology clinic for any reason from 2010 to 2020 were included from the patient data recording system of Ankara University Faculty of Medicine, Surgical Oncology Clinic. Patients younger than 18 years of age, patients with no postoperative Jackson-Pratt (jp) amylase levels, and patients with previous pancreatic surgery were excluded from the study.

Age at surgery, gender, year of surgery, type of surgery, duration of surgery, body mass index (bmi), albumin levels, presence or absence of pancreatic ductaladenocarcinoma, and phosphorus levels on postoperative day 0-1-2-3 (POPL 0-1-2-3) were included as covariates.

Those with POPF more than 3 times the upper serum limit of drain amylase on the postoperative day were considered as leaks. Postoperative serum phosphorus levels, demographic characteristics and comorbidities were evaluated and phosphorus levels of the group with fistula and the group without fistula were compared in the preoperative and postoperative days using univariate analysis methods. The importance of phosphorus level as an independent variable in the development of fistula was examined by multivariance analysis. In this study, the variables of age, gender, bmi, type of surgery and preoperative albumin levels were taken. Mann-whitney-u test was used to compare continuous variables that did not show normal distribution. The repeatanova test was performed to test whether there was a difference between the phosphorus levels on the day of surgery, day 1, day 2 and day 3 without considering the pancreatic fistula status, and it was examined with bonferroni, one of the multiple comparisons tests, to find the different one or ones. Unadjusted analyzes were performed with Pearson's chi-square tests, Fisher's exact test, and anova for categorical dependent variables.

Results

A total of 185 adult patients were included in the study. Of these patients, 93 (50.2%) were male and 92 (48.8%) were female. Of the patients who underwent pancreatectomy, 130 (70.3%) underwent proximal pancreaticoduodenectomy (Whipple pancreaticoduodenectomy), 52 (28.1%) underwent distal pancreatectomy, and 3 (1.6%) underwent total pancreatectomy. All operations were performed as open surgery. The mean BMI of the patients was 25.9 (SD 0.24).), the

mean age was 57.1 (SD 1.02). 68.6% of the patients were under 65 years of age, 31.4% were 65 years or older.

The pathological diagnosis of the majority of the patients was adenocarcinoma (78.4%). Whipple procedure was performed in 70% of the patients, distalpancreatectomy in 28.1% and total pancreatectomy in 1.6% (table 1).

Table 1 Baseline variables	
N=185	
Male (n,%)	93(%50.3)
Type of pancreatectomy(n,%)	
Distal	52(%28.1)
Proksimal	130(%70.3)
Total	3(%1.6)
Age (mean,SD)	57.1(1.02)
Age <65 (n,%)	127(68.6)
Age ≥65 (n,%)	58(31.4)
Pancreaticcancer(n,%)	145(78.4)
BMI(mean,SD)	25.9 (0.24)
Lenght of procedure (min; mean, SD)	300(111.3)
EBL (mean, SD)	710.5(940)
Charlson Comorbidity Index Score (n, %)	
0	
1	
2 or more	
Fistula patient (n,%)	37(%20)
POPL 0 phosphate (mean, SD)	3.75(0.84)
POPL 1 phosphate (mean, SD)	3.63(1.21)
POPL 2 phosphate (mean, SD)	2.92(1.28)
POPL 3 phosphate (mean, SD)	2.57(1.27)

It was noted whether fistula developed or not in the follow-up of a total of 185 patients who underwent pancreatic surgery. Accordingly, fistula occurred in 20% of the cases.The relation between fistula development and BMI, age, gender, CA-19.9 levels, preoperative phosphor levels, type of pancreatic surgery, pancreatic specimen pathology, phosphorus levels on postoperative days 0-1-2-3 was looked at.

The difference in POPL 0 values in the group with and without POPF was not significant (p=0.422). The difference in POPL 1 values in the groups with and without POPF was not significant (p=0.296).

The difference in POPL 2 values in the groups with and without POPF was significant (p= 0.002). The difference in POPL 3 values in the group with and without POPF was significant (p=0.001). Statistical analysis showed that postoperative Day 0 phosphorus levels and postoperative Day 1 phosphorus levels were not a marker for pancratic leak, whereas phosphorus levels on post operative Days 2 and 3 are markers in our study group for pancreatic leak (figüre 1).

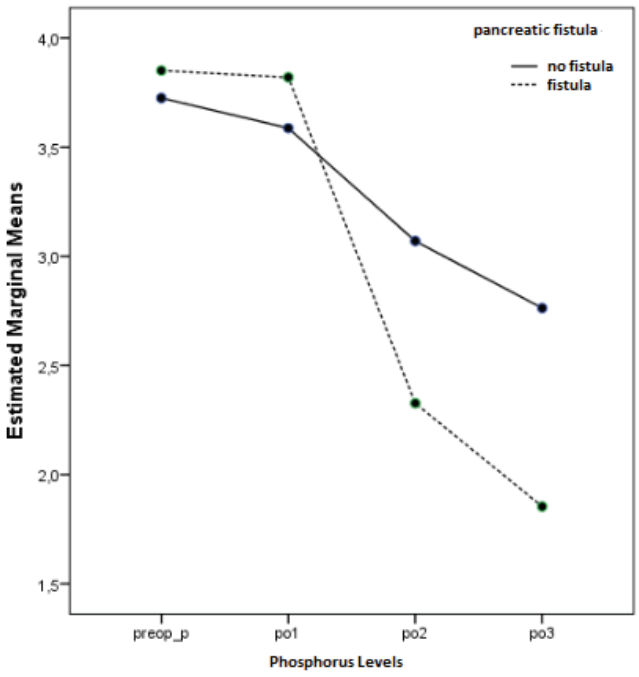

Figure 1.

After determining that the level of POPL values is an independent and important variable, the cut-off value was determined in the ROC analysis and its sensitivity and specificity were determined in the prediction of whether there would be fistula or not.

The area under the curve (AUC) relative to the ROC curve was 0.789, p<0.001. When the cutoff value was taken as 1.6 for POPL values, the sensitivity was determined as 88.4% and the specificity as 62.2%. If the p value is above 1.6 on the postoperative Day 3, there will be no leakage with a prediction of 88%. in the opposite case (p value < 1.6), the estimated leakage is 62.2% (figüre 2).

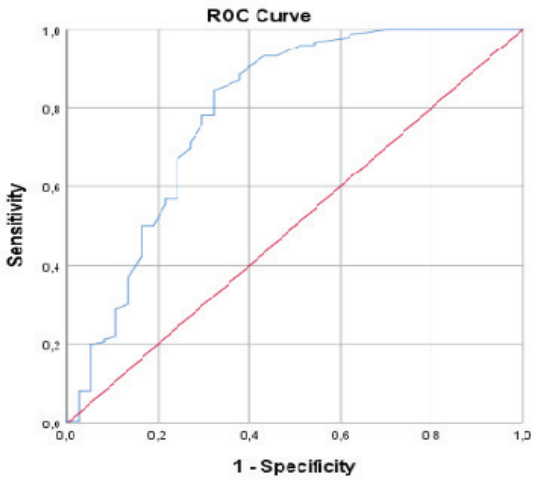

Figure 2.

It showed that 1 unit decrease in phosphorus level on the postoperative day 3 also increased the probability of pancreatic leak by 3.1. Considering gender, 2.6 times more pancreatic leak was observed in male gender in our study. (P=0.029)

The relationship between pancreatic fistula and age (categorical) was not significant (p=0.154)

No relationship was found between pancreatic fistula and age. (P = 0.615) BMI was associated with pancratic fistula and increased BMI was found to be associated with pancreatic leak.(.p=0.001). As the BMI rate increases, the risk of fistula development also increases. There was no relationship between pancreatic fistula development and preoperative ca-19.9 levels (.p=0.564)

The relationship between pancreatic fistula and operation was not significant (p=0.078). The relationship between pancreatic fistula and pathology result was not significant.(p=1.00)

After pancreatic surgery, 15 of 185 patients died in the first week due to surgery and complications.

POPF was present in 6 of these 15 patients, and there was no significant relationship between POPF and these deaths (p=0.083).

The median life expectancy was 33 months in those without POPF, and 29 months in those with POPF. There was no significant difference in survival probability between those with and without POPF (p=0.286) (log-rank test)(figure -3) Table 2.

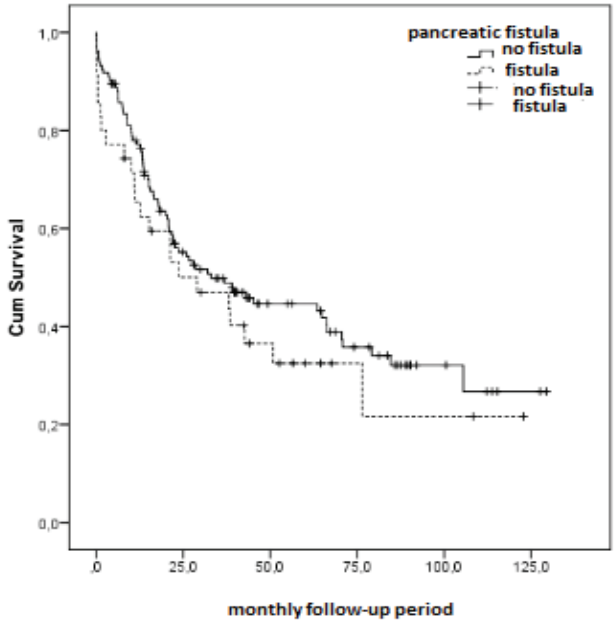

Figure 3.

Table -2			
	fistula	No fistula	P value
Male (n, %)	24(25.8)	69(74.2)	0.047
Age (mean,SD)	56.11 (11.9)	57.43(14.4)	0.615
BMI(mean,SD)	30.1(2.21)	24.8(2.72)	0.001
CA-19,9(mean,SD)	226.6(450.2)	316.8(630.8)	0.433
Adenokarsinom	29	116	1.00
Pankreatikoduodenktomi	30	100	0.78
POPL 0 (mean,SD)	3.85 (0.6)	3.72 (0.9)	0.422
POPL 1 (mean,SD)	3.82 (1.14)	3.58 (1.53)	0.296
POPL2 (mean,SD)	2.32 (1.31)	3.07 (1.24)	0.002
POPL3 (mean,SD)	1.85 (1.16)	2.76 (1.24)	0.001

Dicussion

This retrospective study showed that early postoperative low phosphorus levels are a risk factor and marker reliably associated with POPF. POPL 2 and POPL 3 serum phosphate levels were significantly lower in patients who developed POPF. The reason why we did not include POPL 4 and POPL5 in the study was that low phosphorus levels were usually replaced on the 4th and 5th days. In addition, while male gender and increased BMI were found to be associated with pancreatic fistula in our study, it was

found that age, CA-19.9 levels, type of pancreatic surgery performed and pancreatic specimen pathology were not associated with pancreatic fistula.

By calculating the POPF formation rate, sensitivities, and specificities at different serum phosphate thresholds in POPL 3, we were able to determine a serum phosphate threshold lower than 1.6 as predictive for the 62% fistula risk.

In previous studies, many causes of pancreatic fistula such as age, gender, BMI, pancreatic parenchymal stiffness, type of surgery performed, pancreatic duct width, pancreatic pathology were investigated(12,25,26). In fact, the aim of this study was to investigate whether phosphorus levels could be a marker rather than causing pancreatic leak.

There are few studies suggesting that hypophosphatemia following pancreatectomy can predict leakage-related complications, and our findings are consistent with existing studies(34).

It has been known for years that hypophosphatemia is common in hospital populations and seen in burn and trauma patients, but recently, there are rare studies showing that it may be associated with organ-related complications after gastric, colorectal and pancreatic surgery(35). Eransadot et al. described a consistent hypophosphatemia pattern in a large number of patients following three different

gastrointestinal operations. In addition, low phosphate levels were associated with an increased risk of organ-specific complications, independent of other established risk factors. They stated that early postoperative hypophosphatemia may predict early identification of patients at risk of organ-specific complications(35). Although there are very few studies on hypophosphatemia and pancreatic surgery, there are many studies on the relationship between liver surgery and hyposphataemia. This is because hypophosphatemia is a common phenomenon following hepatic resection(36. While hypophosphatemia is associated with poor outcomes after pancreatic surgery, hypophosphatemia after hepatectomy is associated with good results. Initially it was only predicted to be a result of reduction along the growth of the liver. Although it has been proven that the active incorporation of phosphate into the liver reaches its maximum level in the immediate first 72 hours after hepatectomy (37), this cannot clarify the mechanism of hypophosphatemia.

In a study mentioned in the literature, there was a significant increase in phosphate excretion in the urinary system after hepatectomy. They hypothesized that it was caused by an unidentified phosphaturic protein resulting in postoperative renal phosphate loss (38). This opinion is confirmed by urinary phosphate increases emerging within the first few hours postoeratively. In addition, an experimental animal study in the literature revealed a phosphaturic protein associated with urinary phosphate loss after hepatectomy(39).In fact, in the light of the above literature; Any factor causing hypophosphatemia; The lack of decrease in serum phosphate levels in the early postoperative period suggests that it is associated with a much more significant risk of mortality or non-fatal postoperative liver dysfunction after hepatectomy. In a study by Zheng et al., which was also recently declared in the literature, "serum nicotinamidephosphoribosyl-transferase (NAMPT)" as the main cornerstone; It is understood that they defined it as a phosphaturic touchstone that plays a leading role in phosphatauria and related hypophosphatemia in the period after hepatectomy or pancreatectomy(40). Thus it appears that the mechanism of hypophosphatemia following both procedures may actually be similar, despite opposing prognostic implications. In addition, low serum phosphate levels plays an important role in onset sepsis and infection, as different proinflammatory cytokines are correlated with hypophosphatemia(41). On the other hand; Even if the hypophosphatemia pathway that occurs after partial liver or pancreas resection has gained more and more attention and studies have increased (40), unfortunately, the relationship between POPF and hypophosphatemia is still not clear. Because the relationship between POPF and hypophosphatemia is not clearly known, the therapeutic results of phosphorus replacement remain unclear. Large sample and prospective studies are needed to reveal this relationship.

The limitations of our study were the retrospective nature of our study, insufficient records related to pancreatic parenchyma and ductal structure in our data, and the number of our patients and therefore the number of POPF patients was not high.

In summary, in our study, by calculating the POPF formation rate, sensitivities and specificities at different serum phosphate threshold values in POPL 3, we were able to determine a serum phosphate threshold value less than 1.6 as an estimator for the 62% fistula risk. Hypophosphatemia can be interpreted as a marker with good sensitivity but poor specificity. Evaluating the severity and timing of hypophosphatemia after pancreatectomy provides an opportunity for early detection of possible fistula-related complications.

Conclusion

Decreased phosphate values after pancreatic surgery may be a warning for pancreatic fistula. Phosphorus levels were found to be significant in our study in terms of leakage, especially on the 2nd and 3rd postoperative days. In larger patient groups and with meta-analyses, it is possible that phosphorus level will enter the literature widely as a leak indicator, with possible positive results.

Evaluating the severity and timing of hypophosphatemia after pancreatectomy provides an opportunity for early detection of possible fistula-related complications. Future studies should prospectively examine the relationship between phosphorus levels and pancreatic fistula and investigate the effect on leakage rates and decrease in morbidity and mortality due to leakage after early or prophylactic phosphorus replacement, and the physiopathological relationship between phosphorus level and POPF should be examined.

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References

1. W. Kimura, “Strategies for the treatment of invasive ductal carcinoma of the pancreas and how to achieve zero mortality for pancreaticoduodenectomy,” J. Hepatobiliary. Pancreat. Surg., vol. 15, no. 3, pp. 270–277, May 2008, doi: 10.1007/s00534-007-1305-7.
2. W. S. HALSTED, “Contributions to the Surgery of the Bile Passages, Especially of the Common Bile-Duct,” Bost. Med. Surg. J., vol. 141, no. 26, pp. 645–654, Dec. 1899, doi: 10.1056/nejm189912281412601.

3. KAUSCH and W., "Die Resektion des Mittleren Duodenums-line Typische operation. Verlauzige Mitter-lung," Zentralbl Chir., vol. 39, p. 1350, 1909, Accessed: Jun. 02, 2021. [Online]. Available: https://ci.nii.ac.jp/naid/10016079236.
4. J. M. Howard, "Development and progress in resective surgery for pancreatic cancer," in World Journal of Surgery, Sep. 1999, vol. 23, no. 9, pp. 901–906, doi: 10.1007/s002689900597.
5. J. J. Monge', E. S. Judd, and R. P. Gage, "Radical Pancreatoduodenectomy: A 22-Year Experience with the Complications, Mortality Rate, and Survival Rate *." Accessed: Jun. 02, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1408901/.
6. P.B.Lansing,J.B.Blalock,andJ.L.Ochsner,"Pancreatoduodenectomy: a retrospective review 1949 to 1969.," Am. Surg., vol. 38, no. 2, pp. 79–86, Feb. 1972, Accessed: Jun. 02, 2021. [Online]. Available: https://europepmc.org/article/med/4333406.
7. J. L. Cameron, T. S. Riall, J. Coleman, and K. A. Belcher, "One thousand consecutive pancreaticoduodenectomies," Ann. Surg., vol. 244, no. 1, pp. 10–15, Jul. 2006, doi: 10.1097/01.sla.0000217673.04165.ea.
8. C. Bassi, M. Falconi, R. Salvia, G. Mascetta, E. Molinari, and P. P. Pederzoli, "Management of complications after pancreaticoduodenectomy in a high volume centre: Results on 150 consecutive patients," Dig. Surg., vol. 18, no. 6, pp. 453–457, 2001, doi: 10.1159/000050193.
9. K. Søreide and K. J. Labori, "Risk factors and preventive strategies for post-operative pancreatic fistula after pancreatic surgery: a comprehensive review," Scandinavian Journal of Gastroenterology, vol. 51, no. 10. Taylor and Francis Ltd, pp. 1147–1154, Oct. 02, 2016, doi: 10.3109/00365521.2016.1169317.
10. "Butturini G, Daskalaki D, Molinari E et al (2008)... - Google Akademik." https://scholar.google.com/scholar?hl=tr&as_sdt=0%2C5&q=+Butturini+G%2C+Daskalaki+D%2C+Molinari+E+et+al+%282008%29+Pancreatic+fistula%3A+definition+and+current+problems.+J+Hepato+Biliary+Pancreat+Surg+15%3A247–251&btnG= (accessed Jun. 02, 2021).
11. C. Bassi, C. Dervenis, G. Butturini, A. Fingerhut, C. Y.- Surgery, and undefined 2005, "Postoperative pancreatic fistula: an international study group (ISGPF) definition," Elsevier, Accessed: Jun. 02, 2021. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0039606005002291.
12. Y. M. Yang, X. D. Tian, Y. Zhuang, W. M. Wang, Y. L. Wan, and Y. T. Huang, "Risk factors of pancreatic leakage after pancreaticoduodenectomy," World J. Gastroenterol., vol. 11, no. 16, pp. 2456–2461, Apr. 2005, doi: 10.3748/wjg.v11.i16.2456.
13. J. B. IV, D. Rattner, … A. W.-A. of, and undefined 2001, "Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization," jamanetwork.com, Accessed: Jun. 02, 2021. [Online]. Available: https://jamanetwork.com/journals/jamasurgery/article-abstract/391232.
14. T. Hackert, J. Werner, M. B.-T. Surgeon, and undefined 2011, "Postoperative pancreatic fistula," Elsevier, Accessed: Jun. 02, 2021. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1479666X10002738.
15. B. K. P. Goh, "Critical Appraisal of 232 Consecutive Distal Pancreatectomies With Emphasis on Risk Factors, Outcome, and Management of the Postoperative Pancreatic Fistula A 21-Year Experience at a Single Institution." Accessed: Jun. 02, 2021. [Online]. Available: https://jamanetwork.com/journals/jamasurgery/article-abstract/401940.
16. B. Suc, S. Msika, A. Fingerhut, … G. F.-A. of, and undefined 2003, "Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: prospective," ncbi.nlm.nih.gov, Accessed: Jun. 02, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/pmc1513966/.
17. A. El Nakeeb et al., "Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience)," World J. Surg., vol. 37, no. 6, pp. 1405–1418, Jun. 2013, doi: 10.1007/s00268-013-1998-5.
18. M. Shimoda, M. Katoh, I. Yukihiro, J. Kita, T. Sawada, and K. Kubota, "Body mass index is a risk factor of pancreatic fistula after pancreaticoduodenectomy," Am. Surg., vol. 78, no. 2, pp. 190–194, Feb. 2012, doi: 10.1177/000313481207800237.
19. J. L. Mueller et al., "Lower phosphate levels following pancreatectomy is associated with postoperative pancreatic fistula formation," HPB, vol. 21, no. 7, pp. 834–840, Jul. 2019, doi: 10.1016/j.hpb.2018.10.017.
20. J. McPhee, J. Hill, G. Whalen, … M. Z.-A. of, and undefined 2007, "Perioperative mortality for pancreatectomy: a national perspective," ncbi.nlm.nih.gov, Accessed: Jun. 02, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1933570/.
21. M. Shimoda, M. Katoh, I. Yukihiro, J. Kita, T. Sawada, and K. Kubota, "Body mass index is a risk factor of pancreatic fistula after pancreaticoduodenectomy," Am. Surg., vol. 78, no. 2, pp. 190–194, Feb. 2012, doi: 10.1177/000313481207800237.
22. S. Gaujoux, A. Cortes, A. Couvelard, S. Noullet, L. C.- Surgery, and undefined 2010, "Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy," Elsevier, Accessed: Jun. 02, 2021. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0039606009007971.
23. A. Mckay et al., "Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy," ingentaconnect.com, 2006, doi: 10.1002/bjs.5407.

24. C. Bassi, M. Falconi, E. Molinari, … R. S.-A. of, and undefined 2005, "Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study," ncbi.nlm.nih.gov, Accessed: Jun. 02, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1409871/.
25. M. K. Diener, H. P. Knaebel, S. T. Witte, I. Rossion, M. Kieser, and C. M. Seiler, "DISPACT trial: a randomized controlled trial to compare two different surgical techniques of DIStal PAnCreaTectomy-study rationale and design," Clin. Trials, vol. 5, no. 5, pp. 534–545, 2008, doi: 10.1177/1740774508096140.
26. M. Ridolfini, S. Alfieri, … S. G.-W. journal of, and undefined 2007, "Risk factors associated with pancreatic fistula after distal pancreatectomy, which technique of pancreatic stump closure is more beneficial?," ncbi.nlm.nih.gov, Accessed: Jun. 02, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4434639/.
27. I. G. Van Buren, … M. B.-A. of, and undefined 2014, "A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage," cdn.journals.lww.com, Accessed: Jun. 02, 2021. [Online]. Available: https://cdn.journals.lww.com/annalsofsurgery/FullText/2014/04000/A_Randomized_Prospective_Multicenter_Trial_of.1.aspx.
28. R. Poon, S. Fan, C. Lo, K. Ng, … W. Y.-A. of, and undefined 2007, "External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized," ncbi.nlm.nih.gov, Accessed: Jun. 02, 2021. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/pmc1959348/.
29. P. J. Allen et al., "Pasireotide for Postoperative Pancreatic Fistula," N. Engl. J. Med., vol. 370, no. 21, pp. 2014–2022, May 2014, doi: 10.1056/nejmoa1313688.
30. J. J. Pomposelli et al., "Life-Threatening Hypophosphatemia After Right Hepatic Lobectomy for Live Donor Adult Liver Transplantation," Elsevier, vol. 7, no. 7, pp. 637–642, 2001, doi: 10.1053/jlts.2001.26287.
31. I. Hessov, N. G. Jensen, and A. Rasmussen, "Prevention of hypophosphatemia during postoperative routine glucose administration," Acta Chir. Scand., vol. 146, no. 2, pp. 109–114, Jan. 1980, Accessed: Jun. 02, 2021. [Online]. Available: https://europepmc.org/article/med/6774541.
32. A. Rasmussen, H. H. Kimose, and I. Hessov, "Severity of postoperative hypophosphatemia in relation to glucose administration and renal handling of phosphate," Acta Chir. Scand., vol. 154, no. 11–12, pp. 617–621, Nov. 1988, Accessed: Jun. 02, 2021. [Online]. Available: https://europepmc.org/article/med/3232477.
33. I. Giovannini, C. Chiarla, and G. Nuzzo, "Pathophysiologic and clinical correlates of hypophosphatemia and the relationship with sepsis and outcome in postoperative patients after hepatectomy," Shock, vol. 18, no. 2, pp. 111–115, 2002, doi: 10.1097/00024382-200208000-00003.
34. "Early post-operative hypophosphatemia as a novel... - Google Akademik." https://scholar.google.com/scholar?q=Early post-operative hypophosphatemia as a novel predictor of anastomotic failure after pancreatic resection: a risk-prediction tool. Oral Presentation (accessed Jun. 02, 2021).
35. E. Sadot et al., "Hypophosphatemia as a Predictor of Organ-Specific Complications Following Gastrointestinal Surgery: Analysis of 8034 Patients," World J. Surg., vol. 43, pp. 385–394, 2019, doi: 10.1007/s00268-018-4726-3.
36. "Hypophosphataemia after major hepatectomy and the risk of post-operative hepatic insufficiency and mortality: an analysis of 719 patients | Elsevier Enhanced Reader." https://reader.elsevier.com/reader/sd/pii/S1365182X15314957?token=A7012E1AF021466A68DB899D844311933107C9B23C7438303FB6403E7D8E5B710CE57BF839AE0C3F19F55673917A5588&originRegion=eu-west-1&originCreation=20210913163841 (accessed Sep. 13, 2021).
37. D. Kooby, K. Zakian, S. Challa, C. Matei, H. P.-C. research, and undefined 2000, "Use of phosphorous-31 nuclear magnetic resonance spectroscopy to determine safe timing of chemotherapy after hepatic resection," AACR, vol. 60, pp. 3800–3806, 2000, Accessed: Sep. 13, 2021. [Online]. Available: https://cancerres.aacrjournals.org/content/60/14/3800.short.
38. R. R. Salem and K. Tray, "Hepatic Resection-Related Hypophosphatemia Is of Renal Origin as Manifested by Isolated Hyperphosphaturia," Ann. Surg., vol. 241, no. 2, p. 343, Feb. 2005, doi: 10.1097/01.SLA.0000152093.43468.C0.
39. K. Nomura et al., "Hepatectomy-Related Hypophosphatemia: A Novel Phosphaturic Factor in the Liver-Kidney Axis," J. Am. Soc. Nephrol., vol. 25, no. 4, pp. 761–772, Apr. 2014, doi: 10.1681/ASN.2013060569.
40. J. Zheng et al., "Hypophosphatemia after Hepatectomy or Pancreatectomy: Role of the Nicotinamide Phosphoribosyltransferase," J. Am. Coll. Surg., vol. 225, no. 4, pp. 488-497.e2, Oct. 2017, doi: 10.1016/J.JAMCOLLSURG.2017.06.012.
41. V. Barak, A. Schwartz, I. Kalickman, B. Nisman, G. Gurman, and Y. Shoenfeld, "Prevalence of Hypophosphatemia in Sepsis and Infection: The Role of Cytokines," Am. J. Med., vol. 104, no. 1, pp. 40–47, Jan. 1998, doi: 10.1016/S0002-9343(97)00275-1.