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Postoperative C-Reactive Protein as a Predictor of Postoperative Pancreatic Fistula after Pancreaticoduodenectomy

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ABSTRACT

Introduction

Postoperative pancreatic fistula (POPF) has adverse effects on the outcomes of patients after Pancreaticoduodenectomy PD. Thus, an accurate predictor of POPF is essential. This study aimed to identify C-Reactive Protein (CRP) on the first postoperative day (POD1) as a predictor of clinically relevant postoperative pancreatic fistula (CR-POPF).

Methods

It was a prospective observational study performed at Tribhuvan University Teaching Hospital, Nepal, from March 2019 to November 2019. Forty-nine patients who underwent PD were enrolled in the study. Demography, clinicopathological characteristics, postoperative complications, and CRP on POD1 were recorded. Statistical analyses were performed to identify the association of POD1 CRP with CR-POPF.

Results

The mean age was 56.94 ± 10.10 years, with a nearly equal gender distribution. Clinically relevant postoperative pancreatic fistula (CR-POPF) occurred in 13 patients (26.5%). Patients with CR-POPF had higher mean postoperative day 1 serum C-reactive protein (CRP) levels (123.84 ± 42.90 mg/L) compared to those without CR-POPF (93.35 ± 67.02 mg/L); however, the difference was not statistically significant ($p = 0.134$). No significant associations were found between CR-POPF and preoperative or intraoperative variables, including pancreatic duct diameter, gland texture, and operative time.

Conclusion

Although serum CRP levels on postoperative day 1 were higher in patients who developed clinically relevant POPF, the difference was not statistically significant in this study. Therefore, CRP alone may not be a reliable early predictor of CR-POPF.

Keywords

C-reactive protein; pancreaticoduodenectomy, postoperative pancreatic fistula

INTRODUCTION

Pancreaticoduodenectomy (PD) is a potentially curative treatment for periampullary neoplasms.[1] Although postoperative mortality after PD has reduced to rates below 5% in referral centers, morbidity rates remain high.[2]

Postoperative pancreatic fistula (POPF) is considered the "Achilles heel "of PD and is the most dreaded complication (20–40%).[3-5] A previous study done in our center showed that the overall morbidity was 58%, with a pancreatic fistula rate of 13%.[6]

Early prediction of POPF after PD is essential for patient management and better post-operative outcomes. Patients with biochemical or no leak may have early abdominal drain removal, early initiation of oral nutrition, and reduced hospital stay, while patients with CR-POPF require close observation and may benefit from specific complications-related treatment.[7] The importance of early postoperative drain fluid amylase levels after PD, serum amylase and lipase, and C-reactive protein (CRP) levels for predicting POPF has been studied.[8, 9] But the gold standard for early POPF prediction and definitive management guidelines is still lacking. The study aimed to assess the value of serum CRP on POD1 as a predictor of CR-POPF.

METHODS

This was a prospective observational study conducted at the Department of GI and General Surgery, TUTH, Kathmandu, Nepal, from March 2019 to November 2019. All patients who underwent PD were eligible to participate in the study.

A nonprobability (convenience) sampling method was used. Written informed consent was obtained from all the patients. Ethical clearance was obtained from the Institutional Review Board on 15 March 2019 [391(6-11) E2/075/76]. All patients admitted to the Department of GI and General Surgery and undergoing pancreaticoduodenectomy were included in the study. Patients were excluded if they met any of the following criteria: age less than 16 years, decline to participate, or mortality before postoperative day 3. Serum CRP was sent on the first post-operative day. The presence of CR-POPF was determined according to the International Study Group of Pancreatic Surgery (ISGPS) guideline 2016,[10] which refers to any measurable volume of drain fluid on or after postoperative day 3 with amylase level >3 times the upper-limit of normal amylase for each specific institution, associated with a clinically relevant development/condition related directly to POPF. The study population was divided into two groups: CR-POPF present and absent. Serum quantitative CRP was sent on the first postoperative day. The pancreatic consistency was graded as soft, firm, or hard by the operating surgeon intraoperatively, and the pancreatic duct diameter was measured using a measuring scale. Preoperative and intraoperative variables, and the histopathological report of the resected specimen were recorded in a proforma. The data were entered in an Excel sheet and analyzed using SPSS version 20.0.

The results were expressed in either mean ± SD or median (range) for the quantitative (continuous) data, and differences between the 2 groups were compared using the Student t-Test as a parametric test and Mann–Whitney U-Test as a nonparametric test. The categorical data were expressed in numbers (percentages) and compared using the χ^2 test (non-parametric test) or Fisher's exact test (non-parametric test). The P value < 0.05 was taken as statistically significant.

RESULTS

Among 52 patients evaluated for eligibility, three were excluded due to unresectable diseases. Thus, 49 patients were included in the final study cohort. The mean age of the patients was 56.94 ± 10.10 years. There were 25 (51%) males and 24 (49%) females. The mean Body Mass Index (BMI) was 20.30 ± 2.97 kg/m². Almost half of the patients had a main pancreatic duct diameter of less than or

Table 1. Demography and clinical characteristics of the patients (N=49).

Variables		No.
Age (years), mean± SD		56.94 ± 10.10
Gender		
Male		25 (51%)
Female		24 (49%)
BMI (Kg/m²), mean ± SD		20.30 ± 2.97
NRI, mean ± SD		95.67 ±11.24
ASA SCORE	1	36 (73.50%)
	2	12 (24.50%)
	3	1 (2%)
KARNOFSKY	100	48 (98%)
	90	1 (2%)
ECOG	0	1 (2%)
	1	48 (98%)
Operative time (min), mean±SD		352.55±83.07
Soft pancreatic gland		42 (85.70%)
Hard/firm pancreatic gland		7 (14.30%)
Main pancreatic duct diameter≤3mm		22 (44.89%)

Table 2. Histopathological diagnosis (N=49)

Variables	Number (%)
Benign	4 (8.2)
Malignant (n=45)	
Ampullary carcinoma	25 (51)
Distal Cholangiocarcinoma	6(12.2)
Pancreatic ductal adenocarcinoma	3(6.1)
Duodenal adenocarcinoma	3(6.1)
Gastric adenocarcinoma	2 (4.1)
Colonic adenocarcinoma	2(4.1)
Gall Bladder carcinoma	1(2%)
Neuroendocrine carcinoma	1(2%)
Ampullary GIST	1(2%)

equal to 3mm, and most of them had soft pancreas (Table 1).

Ampullary carcinoma was the most common cancer in the study cohort (Table 2).

The preoperative and intraoperative variables and post-operative CRP did not show association with the presence of CR-POPF (Table 3).

DISCUSSION

Pancreaticoduodenectomy (PD) remains a cornerstone in the management of periampullary neoplasms. Despite advances in surgical techniques and perioperative care that have significantly reduced mortality to below 5% in high-volume centers,[5, 11] the morbidity following PD continues to be a concern, with postoperative pancreatic fistula (POPF) being the most frequent and challenging complication, reported in 20–40% of cases.[12-14]

In our study, the incidence of clinically relevant POPF (CR-POPF) was 26.5%, consistent with the range reported in the literature.[12-14] A previous study conducted at our center reported a lower rate of pancreatic fistula (13%);[6] however, this may reflect changes in diagnostic criteria, surgical practices, or patient selection over time. The most common cancer in this study was ampullary carcinoma, which is consistent with a previous study from our center.[15] This may explain why the majority of patients had a soft pancreatic texture and a pancreatic duct diameter of less than 3 mm..

Several studies have emphasized the importance of early identification of patients at risk for CR-POPF to enable timely intervention, such as modifying drain management, initiating targeted therapy, or delaying oral intake.[16] Biochemical markers, particularly serum and drain fluid amylase, lipase, and C-reactive protein (CRP), have been proposed as predictive tools.[17, 18] Among these, CRP is a readily available, low-cost marker with potential utility in early postoperative risk stratification.

In the present study, although postoperative day 1 (POD1) serum CRP levels were higher in patients who developed CR-POPF (123.84 ± 42.90 mg/L) compared to those who did not (93.35 ± 67.02 mg/L), the difference was not statistically significant (p = 0.134). This aligns with some previous studies that have questioned the discriminatory power of CRP alone for predicting POPF.[17, 18] However, other studies have reported a stronger correlation

Table 3. Predictors of CR-POPF

Variable	CR-POPF		p value
	Absent (n=36)	Present (n=13)	
Age	47.31 (±11.11)	55.92(±6.81)	0.68
Female	16(66.7%)	8(33.30%)	0.46
ASA 3	1(100%)	0(0%)	0.82
Karnofsky 90	35(72.9%)	13(27.1%)	1
BMI	20.32(±2.9)	20.9(±3.26)	0.95
NRI	94.82(±12.4)	98.01(±6.4)	0.39
Duration of operation	339.17(±71.4)	389.62(±103.4)	0.06
Main pancreatic duct (≤3mm)	16(74.1%)	6(24.9%)	0.1
Hard pancreas	7 (100%)	0	0.21
Soft pancreas	29(69.04%)	13(30.95%)	
Intra-operative blood transfusion	13(72.72%)	5(27.77%)	0.06
CRP mg/L	93.35(±67.02)	123.84(±42.90)	0.13

between elevated CRP levels and the development of POPF.[17, 19, 20]

The lack of a statistically significant association in our findings may be attributed to the small sample size and limited number of CR-POPF events. Moreover, variability in baseline inflammation, surgical technique, and intraoperative factors may influence postoperative CRP levels, thereby reducing specificity for POPF.

Soft pancreatic texture and small main pancreatic duct diameter are well-established intraoperative risk factors for CR-POPF.[21, 22] In our cohort, although the majority of patients with CR-POPF had a soft pancreas and duct size ≤3 mm, these variables did not reach statistical significance, possibly due to the same limitations noted above.

This study highlights the need for larger prospective studies to determine the utility of POD1 CRP as a standalone marker or as part of a predictive model incorporating multiple variables. A multimodal approach, including clinical, radiological, and laboratory parameters, may provide more robust early prediction of POPF, guiding clinicians in postoperative management decisions.

This study has several limitations that should be considered when interpreting the results. First, the sample size was relatively small, which may have limited the statistical power to detect significant associations between serum CRP levels and the development of clinically relevant postoperative pancreatic fistula (CR-POPF). Second, the study was conducted at a single institution, potentially limiting the generalizability of the findings to other settings with different surgical techniques, patient populations, or perioperative care protocols.

Third, only CRP levels on postoperative day 1 were evaluated, without considering dynamic changes or trends over subsequent days, which may provide better predictive value. Additionally, the study did not include other potential predictors such as drain fluid amylase levels or radiological findings, which may have improved the accuracy of POPF prediction. Finally, although the study was prospective, potential observer or selection biases inherent to non-randomized observational designs cannot be fully excluded.

CONCLUSION

Although serum CRP levels on postoperative day 1 were higher in patients who developed clinically relevant POPF, the difference was not statistically significant in this study. Therefore, CRP alone may not be a reliable early predictor of CR-POPF. Future studies with larger sample sizes and incorporation of additional clinical and biochemical markers are needed to establish a robust predictive model.

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CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

NK: conceptualization, methodology, data collection; NM: writing, original draft, conceptualization, methodology, data collection; RSB: conceptualization, investigation, resources, editing; PJL: conceptualization, investigation, resources, editing

DECLARATION

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REFERENCES

1. Wolfgang CL, Pawlik TM. Pancreaticoduodenectomy: time to change our approach? Lancet Oncol. 2013;14(7):573-5. Epub 20130502. doi: 10.1016/S1470-2045(13)70159-1. PubMed PMID: 23643140.
2. 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. Dig Surg. 2001;18(6):453-7; discussion 8. doi: 10.1159/000050193. PubMed PMID: 11799295.
3. de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ. Incidence and management of pancreatic leakage after pancreatoduodenectomy. Br J Surg. 2005;92(9):1117-23. doi: 10.1002/bjs.5047. PubMed PMID: 15931656.
4. Harnoss JC, Ulrich AB, Harnoss JM, Diener MK, Buchler MW, Welsch T. Use and results of consensus definitions in pancreatic surgery: a systematic review. Surgery. 2014;155(1):47-57. Epub 20131025. doi: 10.1016/j.surg.2013.05.035. PubMed PMID: 24694359.
5. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg. 2006;10(9):1199-210; discussion 210-1. doi: 10.1016/j.gassur.2006.08.018. PubMed PMID: 17114007.
6. Lakhey PJ, Bhandari RS, Ghimire B, Khakurel M. Perioperative outcomes of pancreaticoduodenectomy: Nepalese experience. World J Surg. 2010;34(8):1916-21. doi: 10.1007/s00268-010-0589-y. PubMed PMID: 20517610.
7. 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(2):207-14. doi: 10.1097/SLA.0b013e3181e61e88. PubMed PMID: 20622661.
8. Hiyoshi M, Chijiiwa K, Fujii Y, Imamura N, Nagano M, Ohuchida J. Usefulness of drain amylase, serum C-reactive protein levels and body temperature to predict postoperative pancreatic fistula after pancreaticoduodenectomy. World J Surg. 2013;37(10):2436-42. doi: 10.1007/s00268-013-2149-8. PubMed PMID: 23838932.
9. Palani Velu LK, McKay CJ, Carter CR, McMillan DC, Jamieson NB, Dickson EJ. Serum amylase and C-reactive protein in risk stratification

of pancreas-specific complications after pancreaticoduodenectomy. Br J Surg. 2016;103(5):553-63. Epub 20160222. doi: 10.1002/bjs.10098. PubMed PMID: 26898605.

10. 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(3):584-91. Epub 20161228. doi: 10.1016/j.surg.2016.11.014. PubMed PMID: 28040257.
11. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg. 1993;217(5):430-5; discussion 5-8. doi: 10.1097/00000658-199305010-00002. PubMed PMID: 8098202; PubMed Central PMCID: PMC1242815.
12. 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):1-14. Epub 20121102. doi: 10.1016/j.jamcollsurg.2012.09.002. PubMed PMID: 23122535.
13. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8-13. doi: 10.1016/j.surg.2005.05.001. PubMed PMID: 16003309.
14. 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(1):54-9. Epub 20031230. doi: 10.1159/000075943. PubMed PMID: 14707394.
15. Maharjan N, Bhandari RS, Lakhey PJ. Predictive Factors Associated With Survival in Periampullary Cancers Following Pancreaticoduodenectomy: A Retrospective Analysis. Cureus. 2023;15(12):e50607. Epub 20231215. doi: 10.7759/cureus.50607. PubMed PMID: 38226083; PubMed Central PMCID: PMC10788477.
16. Buyukkasap AC, Dikmen K, Yavuz A, Altiner S, Gobut H, Emral AC, et al. Predictive value of drain fluid amylase level on postoperative day one after pancreatic resection for predicting postoperative pancreatic fistula. Turk J Surg. 2024;40(1):19-27. Epub 20240323. doi: 10.47717/turkjsurg.2024.6292. PubMed PMID: 39036006; PubMed Central PMCID: PMC11257726.
17. Malya FU, Hasbahceci M, Tasci Y, Kadioglu H, Guzel M, Karatepe O, et al. The Role of C-Reactive Protein in the Early Prediction of Serious Pancreatic Fistula Development after Pancreaticoduodenectomy. Gastroenterol Res Pract. 2018;2018:9157806. Epub 20180128. doi: 10.1155/2018/9157806. PubMed PMID: 29619047; PubMed Central PMCID: PMC5830281.
18. Ji Y, Shen Z, Li J, Zhou Y, Chen H, Li H, et al. Drain fluid volume combined with amylase level predicts clinically relevant postoperative pancreatic fistula after pancreaticoduodenectomy: A retrospective clinical study. J Gastroenterol Hepatol. 2023;38(12):2228-37. Epub 20231003. doi: 10.1111/jgh.16364. PubMed PMID: 37787385.
19. Al Hussan M, Qiao S, Abuheit EMI, Abdun MA, Al Mahamid M, Guo H, et al. The Role of C-reactive Protein and Procalcitonin in Predicting the Occurrence of Pancreatic Fistula in Patients who Underwent Laparoscopic Pancreaticoduodenectomy: a Retrospective Study. Zentralbl Chir. 2023;148(6):508-15. Epub 20231005. doi: 10.1055/a-2157-7550. PubMed PMID: 37798903.
20. Sakamoto T, Yagyu Y, Uchinaka EI, Morimoto M, Hanaki T, Tokuyasu N, et al. Predictive Significance of C-reactive Protein-to-albumin Ratio for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy. Anticancer Res. 2019;39(11):6283-90. doi: 10.21873/anticanres.13838. PubMed PMID: 31704858.
21. Ansorge C, Strommer L, Andren-Sandberg A, Lundell L, Herrington MK, Segersvard R. Structured intraoperative assessment of pancreatic gland characteristics in predicting complications after pancreaticoduodenectomy. Br J Surg. 2012;99(8):1076-82. Epub 20120504. doi: 10.1002/bjs.8784. PubMed PMID: 22556164.
22. 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 J Surg. 2009;33(12):2670-8. doi: 10.1007/s00268-009-0220-2. PubMed PMID: 19774410.