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The Role of Postoperative Inflammatory Markers in Predicting Pancreatic Fistula: A Retrospective Study

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1. Abstract

1.1. Background

Postoperative pancreatic fistula (POPF) is a major complication following pancreatectomy, requiring improved risk prediction. This study aims to evaluate the.

1.2. Methods

A retrospective analysis of 78 patients undergoing pancreatectomy was conducted. Demographic, operative, and postoperative variables were analyzed. Receiver operating characteristic (ROC) curve analysis assessed the predictive performance of inflammatory markers. Univariate and multivariate logistic regression analyses identified potential risk factors.

1.3. Results

Clinically relevant POPF (grade B or C) occurred in 22 patients (28%), with a higher prevalence among males (72.7%). Preoperative inflammatory markers were not associated with POPF. ROC analysis identified optimal cutoff values for neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) on postoperative day 5 (POD 5) 5(5.19 and 153.99, respectively) as potential predictors. Univariate analysis showed significant associations between male sex (OR: 4.12, CI 95% 1.4-12.1; p = 0.01) and elevated CRP levels on POD 3 and 5 (p = 0.01) with POPF. However, multivariate analysis did not confirm these associations.

1.4. Conclusion

No inflammatory markers demonstrated an independent association with postoperative pancreatic fistula.

2. Introduction

Pancreatectomy (PT) is the standard surgery for benign and malignant pancreatic tumors in the head and periampullary region. Postoperative pancreatic fistula (POPF) is acommon complication of PT [1]. According to the International Study Group for Pancreatic Surgery (ISGPS), the incidence of POPF range from 9 to 21% [2]. The occurrence of POPF can lead to severe complications, prolonged hospital stays, and it is associated with a mortality of up to 25% [3]. POPF is defined as a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit of institutional normal serum amylase activity [2]. However, it does not reflect the severity of the POPF, and it cannot be determined in patients without an operative drain [4]. Some studies reported that systemic inflammatory markers improved the accuracy of the diagnosis of POPF. Post-operative C- reactive protein (CRP) is a well-known inflammatory marker predicting pancreatic fistula [5]. In recent years, some studies reported using the neutrophil-to-lymphocyte ratio (NLR) as a reliable marker with high specificity in diagnosing POPF [6]. Therefore, this study aimed to investigate the cut-off and the predictive significance of NLR and CRP in our population to predict POPF.

3. Methods

The Ethics committee of the Hospital Santa Casa de Misericordia (HSCMPA) approved this cross-sectional study. It followed the STROBE guidelines for observational studies.

3.1. Setting and Participants

From June 2013 to December 2022, a cross-sectional study was conducted at the Hospital Santa Casa de Porto Alegre (HSCPA), a reference public hospital in south Brazil. All the patients who underwent pancreatectomy (DPT or distal PT) were included. Patients without postoperative drain fluid amylase (DFA) reports were excluded. Also, according to the pancreatic fistula definition with the ISGPF, patients with

Biochemical grade A fistula were included in the group of non- POPF, because it has no clinical importance and is no longer referred to a true pancreatic fistula.

3.2. Data Collection and Variables

We created a data collection with the variables of interest. First, study team members reviewed the medical records of included patients to extract the following information: Pre-operative 1) demographic characteristics such as sex and age at diagnosis; 2) environmental risk factors like body mass index (BMI). Operative 1) type of surgery, 2) intraoperative blood loss, and 3) operative time. Post-operative characteristics 1) histopathological features including tumor type, pancreatic texture, and diameter of the main pancreatic duct; 2) blood examinations were conducted routinely at 3 and 5 days. The inflammatory markers included the WBC, neutrophil count, CRP, and serum amylase levels; 3) drain collection-like amylase levels at 3- and 5-days POD.

3.3. Data Management

First, the pancreatic fistula was defined as a fluid output of any measurable volume, on or after the third (POD3) and five (POD5) postoperative day from an operatively positioned drain with a pancreatic amylase level more than three times the upper serum reference value. Patients were categorized as having developed a grade B or C fistula based on the definitions of the ISGPF. Grade B was a fistula involving increased amylase activity in the fluid from any drain associated with a clinically relevant condition. Whenever a grade B POPF leads to organ failure or clinical instability such that are operation is needed, the POPF becomes a grade C.

4. Statistical Methods

For categorical variables, frequencies and percentages were reported. We used median and interquartile ranges (IQR) for numerical variables due to asymmetry, verified by the Kolmogorov-Smirnov test. The Chi-Square, Fisher's Exact, and Mann-Whitney tests were applied to verify the association with the presence of a fistula. Subsequently, to identify the appropriate cutoff value of each marker, the receiver operating characteristic (ROC) curves were analyzed. The optimal cutoff values were chosen according to the highest Youden's index (sensitivity + specificity - 1). Prevalence ratio (PR) estimates for fistula were obtained with Drain/Serum Amylase, as well as adjusted estimates for variables of interest that did not compromise the analysis due to lack of data. For this analysis, Poisson regression analysis with robust variance adjustment was used. Analyzes were performed using SPSS software, version 25. The significance level adopted was 0.05.

5. Results

5.1. Demographic Characteristics

Figure 1 shows the clinical characteristics of 78 patients who underwentpancreatectomy. 22 (28%) developed POPF (16 male, 72.7%) grade B or C, and 56(72%) did not have POPF or had only biochemical leak (22 male, 39.3%) (Table 1). Themedian age was similar in POPF and non-POPF. The pre-operative inflammatorymarkers were not associated with POPF.

5.2. Operative Characteristics

66 patients underwent DPT, and 12 distal pancreatectomies (7 splenic preservation and5 partial) (Figure 1). Regarding the surgery approach, in the POPF group most of the patient underwent open pancreatectomy (88.9%), like the non-POPF group (74.1%). Table 2 shows that the mean operative time was similar in both groups (POPF 460 min and non- POPF 420 min). Finally, the blood loss in the POPF group was 600 ml versus500 ml in the non-POPF group. These variables were not statistically significant.

5.3. Postoperative Characteristics

The predictive values of postoperative inflammatory markers at each time point andtime-dependent changes were evaluated by ROC curve analyses. Table 3 shows themost optimal cutoff point to predict clinically relevant POPFs. The optimal cutoff for NLR and CRP on POD 5 were 5.19, 153.99, respectively. These post-operative markers were significantly associated with excluding POPF. The parameters PCR 3, RNL 5 and PCR 5 can predict POPF. The univariate analysis identified several factors associated with the development of postoperative pancreatic fistula. Male sex was found to be a significant risk factor, with an odds ratio (OR) of 4.12 (95% confidence interval [CI]: 1.4–12.1, p = 0.01), indicating a higher likelihood of developing the complication compared to females. Inflammatory markers, particularly the neutrophil-to- lymphocyte ratio (NLR) and C-reactive protein (CRP), also demonstrated significant associations. NLR on postoperative day 3 showed a trend toward significance (p = 0.05), while CRP levels on postoperative days 3 and 5 were significantly correlated with the occurrence of pancreatic fistula (CRP day 3: OR 1.02, 95% CI: 1.00–1.03, p = 0.01; CRP day 5: OR1.01,
95% CI: 1.00–1.02, p = 0.01). In contrast, other clinical and intraoperative parameters, including age, body mass index (BMI), pancreatic duct diameter, intraoperative blood loss, lymphocyte and neutrophil counts, operative time, and surgical approach, did not reach statistical significance (Table 4). In the multivariate analysis, none of the evaluated parameters reached statistical significance in predicting postoperative pancreatic fistula. Male sex exhibited an extremely high odds ratio (OR: 13,500,000), but the wide confidence interval (95% CI:0.00–Inf, p = 1.00) suggests a lack of reliable estimation due to model limitations or data sparsity. Similarly, inflammatory markers, including lymphocyte counts onpostoperative days 3 and 5 (OR: 0.99 and 0.98, respectively), neutrophil-to-lymphocyte ratio (NLR) on days 3 and 5 (OR: 0.22 and 0.60, respectively), and C-reactive protein (CRP) levels on days 3 and 5 (OR: 0.95 and 1.11, respectively), all had wide, unbounded confidence intervals extending to infinity and non-significant p-values (all p= 1.00) (Table 5).

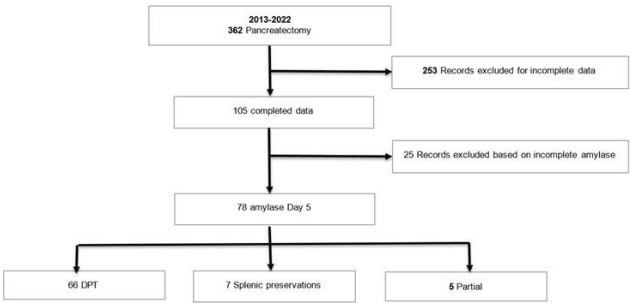

Figure 1: Flow diagram of the patient distribution in the enrolled cohorts of the study.

Table 1: Pre-operative characteristics by pancreatic fistula.

Variables		Yes	No	p-value
		n=22 (28%)	n=56 (72%)	
Sex	F	6 (27.3%)	34 (60.7%)	**0.008**
	M	16 (72.7%)	22 (39.3%)	
***Overall age**		66.5 [52.3; 75]	64 [56; 75]	0.559
Age	< 65	11 (50.0%)	31 (55.4%)	0.669
	≥ 65	11 (50.0%)	25 (44.6%)	
***Pre-operative Neutrophils**	n=19 and n=42	4733 [3397; 7106]	4152.5 [2744; 6353]	0.344
***Pre-operative Lymphocytes**	n=19 and n=42	1191 [673; 1790]	1602.5 [1179; 2130]	0.052
***NLR pre-operative**	n=19 and n=42	2.7 [1.9; 13.93]	2.5 [1.7; 4.24]	0.154
***CRP pre-operative**	n=6 and n=28	11.8 [1.5; 19.98]	22.1 [5; 41.58]	0.276
***BMI, median (IC)**	n=14 and n=46	25.9 [23.7; 30.35]	25.4 [23.6; 27.1]	0.523
BMI	< 25	7 (50.0%)	19 (41.3%)	0.565
	≥ 25	7 (50.0%)	27 (58.7%)	

*Express in median [IQR]; NLR: Neutrophil Lymphocyte ratio; CRP: C-reactive protein; BMI: body mass index.

Table 2: Surgical and post-operative characteristics by pancreatic fistula.

		Yes	No	p-value
		n=22 (28%)	n=56 (72%)	
*Neutrophils – 3 day	n=18 e n=46	8108.5 [5113.5; 11498.3]	7300.5 [5329.3; 10521]	0.601
*Lymphocytes – 3 day	n=20 e n=50	791 [628; 980.5]	1052.5 [746.3; 1466.8]	**0.028**
*NLR – 3 day	n=18 e n=46	7.8 [6.4; 13.8]	7.2 [4.6; 9.7]	0.076
*CRP – 3 day	n=6 e n=25	301.5 [247.5; 369.4]	148.4 [122.5; 202.2]	**0.008**
*Neutrophils – 5 day	n=18 e n=45	7752 [6057.5; 9664.8]	6650 [4692; 9958]	0.224
*Lymphocytes – 5 day	n=19 e n=49	825 [498; 1483]	1165 [819; 1757]	**0.042**
*NLR – 5 day	n=17 e n=45	7.2 [5.8; 13.1]	5.4 [3; 9]	**0.017**
*CRP – 5 day	n=13 e n=34	247.5 [172.4; 315.5]	100.3 [69.3; 204.7]	**0.001**
Surgical approach	Open	16 (88.9%)	40 (74.1%)	0.326
	Laparoscopic	2 (11.1%)	14 (25.9%)	
*Diameter of the main pancreatic duct (mm)	n=1 and n=11	**0.2 [0.2; 0.2]**	11 [7; 40]	---
*Intraoperative blood loss (ML)	n=11 and n=38	600 [200; 906]	500 [200; 500]	0.417
*Operative time (min)	n=14 and n=51	460 [420; 540]	420 [329; 540]	0.172

*Express in median [IQR]; NLR: Neutrophil Lymphocyte ratio; NLR: Neutrophil Lymphocyte ratio; CRP: C-reactive protein; DFA: drain fistula amylase; DSA: drain serum amylase; DSAR: drain/ serum amylase ratio.

Table 3: Inflammatory markers for clinically relevant postoperative pancreatic fistula.

Parameter	n	AUC (CI 95%)	p-value	Cut-Off ≥	Sensitivity	Specificity	PPV (%)	NPV (%)
NLR – 3 day	64	0.644 (0.500; 0.788)	0.076	5.69	94.40%	37.00%	37.00%	94.40%
CRP – 3 day	31	0.853 (0.696; 1.000)	**0.008**	274.06	83.30%	88.00%	62.50%	95.65%
NLR – 5 day	62	0.698 (0.567; 0.829)	**0.017**	5.19	100.00%	44.40%	40.48%	100.0%
CRP – 5 day	47	0.805 (0.673; 0.938)	**0.001**	153.99	92.30%	67.60%	52.17%	95.83%

AUC: Area under the curve, NPV: Negative predictive value; PPV: Positive predictive value.

6. Discussion

We conducted a retrospective analysis of patients who underwent pancreatectomy at aregional reference hospital in Brazil. This analysis revealed that NLR was more than 5.19 and CRP more than 154 at POD5 can predict POPF. The percentage of POPF was 27.3%. We think that the high rate of POPF was due to the lack of a unified protocol to diagnose POPF with DFA. It was a common practice to analyze DFA only for patient with clinical suspicion of POPF. Also, our study identified male sex, elevated NLR on day 3, and CRP on days 3 and 5 as significant predictors of postoperative pancreatic fistula (POPF) in univariate analysis, highlighting the role of systemic inflammation. However, in multivariate analysis, none of these factors remained statistically significant, likely due to sample size limitations, multicollinearity, or model overfitting. CRP increases in response to inflammation and infection after 48-72h10.Numerous reports have indicated that the serum CRP level on the POD 3 is a valuable indicator for anticipating CR-POPF [11,12]. Our findings corroborated this by demonstrating that the serum CRP levels on POD 3 and 5 were significantly elevated in patients with POPF compared to non-POPF. This observation strengthens the connection between CRP levels on POD 3 and 5 and the occurrence of POPF. However, it is worth noting that the specificity is low in our population. Given these inherent individual differences,

Table 4: Univariate analysis.

Parameter	OR	Lower 95%CI	Upper 95%CI	p- value
Sex [T.M]	4.12	1.4	12.1	0.01
Age	0.98	0.942	1.02	0.29
BMI	1.07	0.899	1.26	0.46
Diameter of the main pancreatic duct (mm)	0.00	0	Inf	1.00
Intraoperative blood loss (ML)	1.00	0.999	1	0.28
Lymphocytes – 3 day	1.00	0.998	1	0.06
Lymphocytes – 5 day	1.00	0.998	1	0.06
Pre-operative Lymphocytes	1.00	0.999	1	0.22
Neutrophils – 3 day	1.00	1	1	0.48
Neutrophils – 5 day	1.00	1	1	0.50
Pre-operative Neutrophils	1.00	1	1	0.54
NLR pre-operative	1.13	0.991	1.28	0.07
NLR – 3 day	1.09	1	1.18	0.05
NLR – 5 day	1.08	0.995	1.16	0.07
Operative time (min)	1.00	0.999	1.01	0.16
CRP pre-operative	0.97	0.921	1.03	0.31
CRP – 3 day	1.02	1	1.03	0.01
CRP – 5 day	1.01	1	1.02	0.01
Surgical approach [T open]	2.80	0.57	13.7	0.21

Table 5: Multivariate analysis.

Parameter	OR	Lower 95%CI	Upper 95%CI	p- value
Sex [T.M]	13500000.00	0.00	Inf	1.00
Lymphocytes – 3 day	0.99	0.00	Inf	1.00
Lymphocytes – 5 day	0.98	0.00	Inf	1.00
NLR – 3 day	NLR3	0.22	0.00	Inf
NLR – 5 day	0.60	0.00	Inf	1.00
CRP – 3 day	0.95	0.00	Inf	1.00
CRP – 5 day	1.11	0.00	Inf	1.00

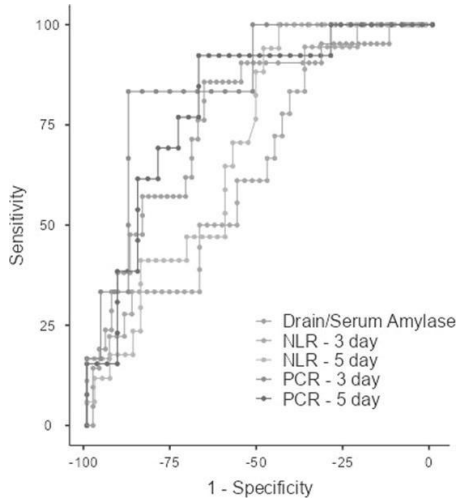

Figure 2: Receiver operating characteristic (ROC) curve of inflammatory markers on postoperative pancreatectomy.

relyingsolely on CRP might not accurately predict the onset of POPF.NLR is a new alternative to exclude POPF. Garnier et al.6, in a recent prospectivestudy of 648 patients who underwent PD, reported that NLR less than 8.5 on postoperativeday 3 may be a simple, independent, cost-effective, and easy-to-use criterion for excluding POPF. Moreover, Solaini et al. [13], in a retrospective study of 378 patients withPD, showed that an NLR of 12.3 on POD2 was significantly correlated with POPF. Contrary, our diagnostic model of NLR was sensitive but not specific in detecting POPF.NLR was 5.69 and 5.19 on POD3 and 5, respectively. Of course, as with every surrogatemarker, NLR cannot guarantee a POPF alone. It can be combined with other markers likeCRP to improve the diagnosis of POPF.

7. Limitations and Strengths

This study has several limitations. First, the small sample size may have reduced thestatistical power, limiting the ability to detect independent predictors of POPF in themultivariate analysis. Between 2013 and 2019, our hospital had no protocol for collectingDFA in the postoperative patient who underwent PD. Another issue is the wideconfidence intervals and unbounded estimates, particularly for male sex, suggest possiblemodel instability due to data sparsity. Second, potential multicollinearity amonginflammatory markers, such as CRP and NLR, may have influenced the results, makingit difficult to determine their true independent effects. Third, the study did not accountfor other important clinical variables, such as pancreatic texture which is known to impactPOPF risk. Lastly, as this is a retrospective study, inherent biases and unmeasuredconfounders cannot be ruled out. Despite these limitations, this study has severalstrengths. First, it provides valuable insights into the association between systemicinflammatory markers and POPF, reinforcing the potential role of CRP and the NLR asearly predictors. Second, the analysis includes both univariate and multivariate models,allowing for a comprehensive evaluation of risk factors

while highlighting potentialstatistical challenges in predicting POPF. Third, the study focuses on a clinicallysignificant complication, contributing to the growing body of evidence aimed atimproving postoperative outcomes. Future research with larger, prospective cohorts andmore comprehensive variable inclusion is necessary to validate these findings andimprove risk stratification for POPF.

8. Conclusion

In conclusion, this study found no independent association between inflammatory markers and postoperati.

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