# C-reactive Protein as an Early Marker for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy

Pankreatikoduodenektomi Sonrası Gelişen Postoperatif Pankreatik Fistül İçin Erken Bir Belirteç Olarak C-Reaktif Protein

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# C-reactive Protein as an Early Marker for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy

**ABSTRACT**

**Objective:** Clinically relevant postoperative pancreatic fistula (CR-POPF) remains one of the most serious complications following pancreaticoduodenectomy (PD), leading to increased morbidity and secondary adverse events. Early identification of CR-POPF risk is essential for timely intervention and optimal drain management. This study aimed to evaluate the predictive value of serum C-reactive protein (CRP) levels on postoperative day 3 (POD 3) for the development of CR-POPF.

**Material and Method:** We retrospectively analyzed 112 patients who underwent PD between March 2020 and February 2025. Patients with distal or total pancreatectomy, neoadjuvant therapy, poorly controlled diabetes, immunosuppression, or anastomotic leaks unrelated to the pancreas were excluded. Serum CRP levels, drain amylase concentration, and drainage volume were recorded on POD 3. CR-POPF was defined according to International Study Group on Pancreatic Surgery (ISGPS) criteria. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of CRP. Multivariable logistic regression was used to identify independent risk factors for CR-POPF.

**Results:** CR-POPF occurred in 17 patients (15.2%). These patients had significantly softer pancreatic texture and smaller duct diameters ($p<0.01$). ROC analysis revealed that a POD 3 CRP level >161 mg/L predicted CR-POPF with an area under the curve (AUC) of 0.77, sensitivity of 82.4%, and specificity of 66.3%. Logistic regression identified small duct diameter and soft pancreatic texture as independent predictors of CR-POPF.

**Conclusion:** Elevated POD 3 serum CRP levels are significantly associated with CR-POPF development after PD. Incorporating CRP into routine postoperative assessment may enhance early risk stratification, support clinical decision-making, and guide individualized drain management strategies.

**Keywords:** C-Reactive Protein, Drain management, Postoperative Pancreatic Fistula, Pancreaticoduodenectomy.

**ÖZET**

**Amaç:** Pankreatikoduodenektomi (PD) sonrası gelişen klinik olarak anlamlı postoperatif pankreatik fistül (CR-POPF), cerrahi sonrası morbiditenin en önemli nedenlerinden biri olup, sekonder komplikasyonlara da zemin hazırlamaktadır. CR-POPF'nin erken dönemde tanınması, zamanında müdahale ve uygun dren yönetimi açısından kritik öneme sahiptir. Bu çalışmanın amacı, postoperatif 3. gün (POD 3) serum C-reaktif protein (CRP) düzeylerinin CR-POPF gelişimini öngörmedeki değerini değerlendirmektir.

**Gereç ve Yöntem:** Mart 2020 ile Şubat 2025 arasında merkezimizde PD uygulanan 112 hasta retrospektif olarak analiz edildi. Total veya distal pankreatektomi yapılanlar, neoadjuvan tedavi alanlar, kontrolsüz diyabeti olanlar, immünsüprese hastalar ve pankreas dışı anastomoz kaçağı gelişenler çalışma dışı bırakıldı. Postoperatif 3. gün serum CRP düzeyleri, dren amilaz konsantrasyonu ve drenaj hacmi kaydedildi. CR-POPF, Uluslararası Pankreas Cerrahisi Çalışma Grubu (ISGPS) kriterlerine göre tanımlandı. ROC eğrisi analizi ile CRP düzeylerinin tanısal performansı değerlendirildi. Ayrıca, çok değişkenli lojistik regresyon analizi ile CR-POPF için bağımsız risk faktörleri belirlendi.

**Bulgular:** CR-POPF, 17 hastada (%15,2) gelişti. Bu hastalarda pankreas duktus çapı anlamlı şekilde daha dar ve doku yapısı daha yumuşaktı ($p<0,01$). ROC analizinde, POD 3 CRP düzeyi >161 mg/L olan hastalarda CR-POPF gelişimini öngörmede AUC 0,77, sensitivite %82,4 ve spesifisite %66,3 olarak bulundu. Lojistik regresyon analizinde, dar pankreatik duktus çapı ve yumuşak pankreas dokusu CR-POPF için bağımsız risk faktörleri olarak saptandı.

**Sonuç:** Pankreatikoduodenektomi sonrası 3. gün serum CRP düzeylerinin yüksek olması, CR-POPF gelişimini öngörmede anlamlı bir belirteçtir. CRP düzeylerinin rutin postoperatif değerlendirmeye dahil edilmesi, erken risk sınıflamasını kolaylaştırarak hasta yönetimi ve dren çekilme zamanlamasında klinik karar sürecine katkı sağlayabilir.

**Anahtar Sözcükler:** C-Reaktif Protein, Dren yönetimi, Postoperatif Pankreatik Fistül, Pankreatikoduodenektomi.

## Introduction

Advancements in pancreatic surgery and perioperative management have significantly reduced postoperative morbidity and mortality. However, clinically relevant postoperative pancreatic fistula (CR-POPF) remains a common and serious complication that may also predispose patients to other postoperative adverse events (1,2). Consequently, numerous methods have been investigated to predict POPF in advance, and various risk factors have been identified (3–6).

Drain management plays a critical role in pancreatic surgery, both in preventing postoperative complications and enhancing patient recovery. Accurate prediction of CR-POPF allows for better decision-making regarding the duration of drain placement. Early drain removal in low-risk patients and prolonged drainage in high-risk cases are key strategies that directly affect clinical outcomes. Prolonged drainage beyond necessity has been associated with increased risk of complications. In clinical practice, drain removal is generally performed based on the surgeon's assessment, once the risk of POPF is deemed minimal. Therefore, early prediction of POPF is crucial for optimizing the timing of drain removal, which can accelerate recovery and facilitate earlier hospital discharge (7,8).

Complications associated with POPF include intra-abdominal abscess, delayed gastric emptying, hemorrhage, sepsis, and mortality. Early diagnosis of POPF enables timely interventions such as antibiotic therapy or initiation of parenteral nutrition, before clinical deterioration occurs. Furthermore, in patients who do not develop POPF, early transition to enteral feeding may contribute to improved recovery (3,9).

C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver. It begins to rise approximately six hours after the onset of inflammation, peaks around 48 hours, and—due to its relatively constant plasma half-life of approximately 19 hours—typically begins to decline by the third postoperative day in the absence of ongoing inflammatory stimuli (10,11). In recent years, CRP has been studied extensively for its predictive value in detecting anastomotic leakage following colorectal surgery and infectious complications after major abdominal operations (12,13). These findings have led to increasing interest in the potential role of CRP as a predictive marker for the development of CR-POPF after pancreatic resections (14–16).

The aim of this study was to evaluate the predictive value of serum C-reactive protein (CRP) levels on postoperative day 3 (POD 3) for the development of CR-POPF in patients undergoing pancreaticoduodenectomy (PD).

## Material and Method

Patients who underwent pancreaticoduodenectomy (PD) at our institution between March 2020 and February 2025 were retrospectively analyzed using prospectively collected clinical data. Patients aged 18 to 75 years who underwent PD were included in the study. Approval of the study was obtained from the Ethics Committee of Medicana International Ankara Hospital (Decision no: 2023/43, Date: 14.12.2023), and the study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective design of the study.

Exclusion criteria were as follows: patients who underwent total or distal pancreatectomy, those with unresectable tumors, immunosuppressed individuals, patients with a history of chronic steroid use or rheumatologic disease, those who received neoadjuvant therapy, patients with poorly controlled diabetes mellitus (HbA1c >10), and those who developed biliary or intestinal anastomotic leaks. CR-POPF was defined according to the criteria established by the International Study Group on Pancreatic Surgery (ISGPS) (17). All surgical procedures were performed by a single hepatobiliary surgeon (M.K.) with over 20 years of experience. A 10-mm flat silicone drain was routinely placed posterior to the pancreatojejunostomy. POD 1 was defined as the first 24-hour period following completion of surgery. Drain amylase levels were measured on postoperative days (POD) 1 and 3, and thereafter as clinically indicated. On POD 3, serum CRP levels (mg/L), drain amylase levels (U/L), drainage volume (mL), and drain fluid appearance (e.g., serous, pancreatic leak, biliary leak, or intestinal leak) were routinely assessed. The reference range for serum CRP levels in our institution is 0–5 mg/L. Octreotide was not used in either the preoperative or postoperative period. Preoperative

biliary drainage was not routinely performed.

Drain removal on POD 3 was considered for patients whose drain amylase concentrations and drainage volumes were below institutional threshold values, whose drain output was serous, who had stable vital signs, and who tolerated oral intake (18). In patients deemed to be at high risk for CR-POPF on POD 3, reassessment was performed on POD 5, and drains were removed if appropriate. Patients clinically suspected of having CR-POPF were further evaluated with close vital sign monitoring and radiological imaging (abdominal ultrasonography or computed tomography). However, the final decision regarding drain removal was made by the operating surgeon based on an overall clinical assessment, which included intraoperative findings, postoperative course, and patient-specific factors. As such, some degree of subjectivity may have influenced the timing of drain removal, especially in borderline cases with inconclusive clinical parameters.

In cases of sudden reduction or cessation of drainage, 10 mL of sterile saline was used to irrigate the drain in order to exclude mechanical obstruction. All patients received intravenous (or oral, if tolerated) antibiotic therapy consisting of ceftriaxone (2 × 1000 mg/day) and metronidazole (3 × 500 mg/day) for five days postoperatively.

Demographic data and postoperative complications—including CR-POPF, hemorrhage, intra-abdominal infection or abscess, and delayed gastric emptying (DGE) were recorded. Postoperative complications were classified according to ISGPS criteria (19–21).

*Statistical Analysis*

Statistical analysis was performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed by Skewness and Kurtosis tests. Normally distributed data are presented as mean ± standard deviation (SD), while non-normally distributed data are expressed as median (min-max). Categorical variables are reported as counts and percentages. Group comparisons were performed using the independent-samples t-test, the Mann–Whitney U test, or the chi-square test, as appropriate.

For ROC analysis, the development of CR-POPF was defined as the primary endpoint. Areas under the receiver operating characteristic (ROC) curve were calculated to evaluate CRP levels as predictors of POPF. ROC analysis was conducted based on patients' CRP values on the POD 3. The results of the ROC analysis, including sensitivity and 1-specificity values, were examined, and CRP values with the highest sensitivity and specificity were selected as cut-off points. Finally, the Area Under the Curve (AUC) and p-values were compared.

Multivariable logistic regression analysis was conducted to identify factors associated with the development of pancreatic fistula. The dependent variable was the presence of pancreatic fistula (yes/no), and the independent variables included age, gender, BMI, pancreatic duct diameter (mm), pancreatic texture (soft/hard), vascular repair, and pathology(benign/malign). The significance of each variable in the model was assessed using the Wald test, with a p-value < 0.05 considered statistically significant.

### Results

A total of 112 patients who met the inclusion criteria were enrolled in the study, comprising 70 males and 42 females. Postoperative complications occurred in 24 patients (21.4%). The most frequent complication was clinically relevant postoperative pancreatic fistula (CR-POPF), observed in 17 patients (15.2%), followed by intra-abdominal infection in 9 patients (8.0%), postoperative bleeding in 8 patients (7.1%), and delayed gastric emptying in 6 patients (5.4%). Notably, some patients experienced more than one type of complication. Early postoperative mortality occurred in two patients due to Grade C postoperative pancreatic fistula.

Patients who developed CR-POPF had significantly smaller pancreatic duct diameters and softer pancreatic texture (*p<0.01* for both). No significant differences were found between the groups regarding age, body mass index (BMI), gender distribution, vascular reconstruction frequency, or pathological diagnosis (*p>0.05* for all). A detailed comparison of clinical and demographic characteristics between patients with and without CR-POPF is shown in Table I.

Multivariate logistic regression analysis identifying independent predictors of clinically relevant

postoperative pancreatic fistula (CR-POPF) is presented in Table II. Among the variables included in the model, CRP level on postoperative day 3, pancreatic duct diameter, and pancreatic texture were found to be statistically significant independent predictors. Specifically, each 1 mg/L increase in CRP level on POD 3 was associated with a 2% increase in the odds of developing CR-POPF (OR=1.02; 95% CI, 1.01–1.03; *p=0.002*). Additionally, a 1 mm increase in pancreatic duct diameter was associated with a 64% reduction in the odds of CR-POPF (OR = 0.36; 95% CI, 0.19–0.71; *p=0.003*). The presence of hard pancreatic texture also significantly decreased the risk compared to soft texture (OR = 0.25; 95% CI, 0.06–0.92; *p=0.04*). Other variables assessed in the model—including age, gender, BMI, vascular reconstruction, and pathology type—were not significantly associated with the occurrence of CR-POPF (p>0.05 for all).

**Table I.** Comparison of Clinical and Demographic Variables Between Patients with and Without CR-POPF

| Variable | CR-POPF (n = 17) | Non-POPF (n = 95) | *p-value* |
|---|---|---|---|
| Age (years) | 66.4±9.9 | 62.7±12.4 | *0.3* |
| Gender, n (%)<br>Female<br>Male | 5 (29.4%)<br>12 (70.6%) | 37 (38.9%)<br>58 (61.1%) | *0.4* |
| Body Mass Index (BMI, (kg/m²)) | 26.9±4.4 | 27.4±3.9 | *0.6* |
| Pancreatic texture, n (%)<br>Soft<br>Hard | 11(64.7%)<br>6 (35.3%) | 18 (18.9%)<br>77 (81.1%) | *<0.01* |
| Pancreatic duct diameter (mm) | 3.4±1.1 | 4.6±1.7 | *<0.01* |
| Vascular Reconstruction, n (%) | 3 (17.6%) | 21 (22.1%) | *0.7* |
| Pathology, n (%)<br>Benign<br>Malign | 2 (11.8%)<br>15 (88.2%) | 12 (12.6%)<br>83 (87.4%) | *0.9* |

*Values are presented as mean ± standard deviation or number (percentage), as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of C-reactive protein (CRP) levels on postoperative day 3 (POD 3 CRP) for clinically relevant postoperative pancreatic fistula (CR-POPF). The analysis demonstrated good diagnostic accuracy, with an area under the curve (AUC) of 0.777 (95% CI: 0.680–0.874; *p<0.001*). A CRP cut-off value of 161 mg/L yielded a sensitivity of 82.4% and a specificity

of 66.3% in identifying patients at risk for CR-POPF. The ROC curve for POD 3 CRP levels is illustrated in Figure I.

**Table II.** Multivariate Logistic Regression Analysis for Predictors of CR-POPF

| Variable | B (SE) | Wald | p-value | OR (Exp(B)) [95% CI] |
|---|---|---|---|---|
| Age | 0.04 (0.03) | 1.81 | *0.18* | 1.05 [0.98–1.11] |
| Gender | 0.86 (0.74) | 1.36 | *0.24* | 2.36 [0.56–10.06] |
| BMI | 0.00 (0.09) | 0.00 | *0.99* | 1 [0.84–1.19] |
| Pancreatic Duct Diameter | –1.01 (0.34) | 8.93 | *0.003* | 0.36 [0.19–0.71] |
| Pancreatic Texture | -1.38 (0.66) | 4.35 | *0.04* | 0.25 [0.06–0.92] |
| Vascular Reconstruction | 0.50 (0.90) | 0.31 | *0.58* | 1.64 [0.28–9.52] |
| Pathology | 1.42 (0.97) | 1.37 | *0.24* | 4.15 [0.38–45.16] |
| CRP (POD 3, mg/L) | 0.02 (0.01) | 9.56 | *0.002* | 1.02 [1.01–1.03] |

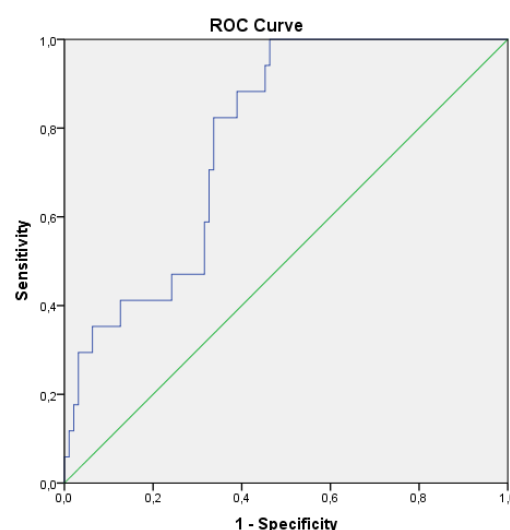*OR = odds ratio; CI = confidence interval; SE = standard error



**Figure I.** Receiver operating characteristic (ROC) curve of postoperative day 3 CRP levels for predicting CR-POPF. The area under the curve (AUC) was 0.777 (95% CI: 0.680–0.874), indicating good diagnostic accuracy

### Discussion

In pancreatic surgery, the most significant complication is the development of CR-POPF. This condition not only increases morbidity due to primary effects such as peritonitis, but also predisposes patients to secondary complications, including hemorrhage and intra-abdominal infections (22). To date, there is no perfect test that can predict CR-POPF with 100% accuracy. We believe that the

most critical factor in this context is the experience of the hepatopancreatobiliary (HPB) surgeon.

An experienced pancreatic surgeon evaluates the patient holistically taking into account preoperative factors such as malnutrition, receipt of neoadjuvant therapy, or comorbidities; intraoperative findings including pancreatic texture (soft vs. hard) and the diameter of the pancreatic duct; as well as postoperative indicators such as vital signs, laboratory results, drain amylase concentration, drainage volume, and the appearance of the drain fluid. Such a comprehensive and integrative approach is essential for optimal management and early identification of CR-POPF risk.

Bassi et al. (8) identified soft pancreatic texture, delayed drain removal, median albumin and serum amylase levels on postoperative day (POD) 1, and preoperative weight loss greater than 10% as risk factors for CR-POPF. In contrast, Kawai et al. (7) reported that intraoperative bleeding, longer operative time, and early drain removal were significant risk factors, suggesting that neither preoperative factors nor pancreatic tissue characteristics reliably predicted POPF risk. According to this study, a small pancreatic duct diameter and soft pancreatic texture were also identified as significant risk factors for CR-POPF in our clinic. Therefore, we believe that pancreatic surgeons should consider institution-specific risk profiles when managing their patients postoperatively.

Guilbaud et al. (14) reported that a CRP level >100 mg/L on POD 1 was predictive of CR-POPF with an AUC of 0.70. Welsch et al. (22) showed that a POD 4 CRP level >140 mg/L predicted inflammatory postoperative complications with an AUC of 0.86. Hashimoto et al. (4) demonstrated that a CRP level <150 mg/L on POD 3, when combined with drain amylase values, improved the prediction of POPF. Mintziras et al. (23) identified a CRP level >203 mg/L on POD 3 as an independent risk factor for CR-POPF. In this study, a CRP level >161 mg/L on POD 3 was found to be a significant risk factor for CR-POPF, with an AUC of 0.77. Although the cutoff values vary slightly across studies, these thresholds may assist in the early identification of patients at higher risk for CR-POPF.

However, when applying such cutoffs in clinical practice, the potential trade-off between missed diagnoses and false positives must be carefully considered. Although the proposed CRP cut-off value (>161 mg/L on POD 3) demonstrated good predictive performance, it is essential to reflect on the clinical implications of false-positive and false-negative results. For instance, patients with elevated CRP levels who do not develop CR-POPF may be subjected to unnecessarily prolonged drain placement. This, in turn, may increase the risk of intra-abdominal infections due to retrograde contamination or irritation from the drain itself. Additionally, false-positive interpretations could lead to unnecessary imaging studies, delays in initiating oral intake, and prolonged hospital stay (8,24). Conversely, false-negative cases—patients with CRP levels below the cut-off who still develop clinically relevant fistulas—also warrant caution. These cases highlight the limitations of relying solely on a single laboratory parameter and underscore the importance of comprehensive clinical evaluation. Therefore, we believe that HPB surgeons should not base postoperative decisions solely on CRP values but rather integrate them with clinical judgment, intraoperative findings, and institutional experience for individualized drain management.

HPB surgeons must evaluate all relevant risk factors when assessing CR-POPF risk. Among these, the most used conventional method is measuring the drain amylase concentration. However, in certain clinical scenarios—such as patients with ascites, chylous drainage due to extensive lymphadenectomy, those who have undergone vascular procedures, or in cases where the abdomen has been irrigated with saline—the drain amylase concentration may be misleadingly low. Similarly, obstructed drains may yield falsely low drainage volumes, or the fluid collection may not be adequately captured if it forms away from the drain site. Therefore, the use of an objective laboratory parameter like CRP may provide additional guidance to HPB surgeons. From this perspective, this study showed that CRP levels on POD 3, an increasingly recognized inflammatory marker, were significantly associated with the development of POPF and could support HPB surgeons in early risk assessment and postoperative decision-making. In patients in whom drain amylase levels fail to predict CR-POPF,

elevated CRP levels exceeding the defined cutoff may warrant further evaluation with non-invasive and cost-effective imaging modalities such as ultrasonography, potentially revealing clinically silent CR-POPF that would otherwise remain undetected. Recent studies have underscored the advantages of early drain removal in low-risk patients undergoing pancreatic surgery (24,25). Early identification of CR-POPF allows timely intervention before the complication progresses to more severe outcomes. Therefore, accurate recognition of low-risk patients is critical for safe early drain removal, and we believe that serum CRP levels constitute a valuable element of this risk stratification process and should not be overlooked.

One of the main limitations of this study, in addition to its retrospective design, is the relatively low number of patients with CR-POPF. Moreover, serum CRP levels may also be elevated due to non-pancreas-specific infectious or inflammatory conditions, such as respiratory tract infections or urinary tract infections. Therefore, such confounding factors should be taken into account when interpreting CRP values in the postoperative setting.

## Conclusion

In patients undergoing PD, POD 3 serum CRP levels represent a strong early indicator of CR-POPF risk and should be adopted as a routine part of postoperative decision-making for patient and drain management.

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