Research Article / Araştırma Makalesi

The Role of Inflammatory Indices in Predicting Pancreatic Fistula After Distal Pancreatectomy

Distal Pankreatektomi Sonrası Pankreatik Fistül Gelişimini Tahmin Etmede İnflamatuar İndekslerin Rolü

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Abstract

Background: The significance of inflammatory markers in forecasting pancreatic fistula development has not been thoroughly investigated in patients who have undergone distal pancreatectomy. This study seeks to assess the predictive value of postoperative inflammatory indices, particularly SII (systemic immune inflammation index), NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio), concerning the onset of pancreatic fistula in these patients.
Materials and Methods: This retrospective study analyzed patients who underwent distal pancreatectomy for pancreatic cancer between January 2020 and December 2023. Statistical analyses were performed by retrospectively examining the data obtained from the prospectively filled clinical notes of patients who developed pancreatic fistula (Grade B and C) using the SII, NLR and PLR calculated based on the laboratory results obtained on the third postoperative day.
Results: The study included 72 patients who fulfilled the established criteria. Pancreatic fistulas were observed in 25 (34.7%) of the patients. In this study, BMI and soft pancreatic tissue were statistically significant risk factors for pancreatic fistula development (p=0.02 for both). SII and NLR from the third postoperative day were statistically significant predictors of pancreatic fistula development, while postoperative PLR did not provide statistically significant results. SII was a more significant predictor of pancreatic fistula than NLR.
Conclusions: This study conveys that monitoring the increase in SII and NLR, which are inflammation-related indices, is an effective method for predicting the development of pancreatic fistula after distal pancreatectomy, whereas PLR is not effective in predicting the development of pancreatic fistula.

Keywords: Distal pancreatectomy, Pancreatic fistula, SII, NLR, PLR

Öz

Amaç: İnflamatuar belirteçlerin, distal pankreatektomi sonrası pankreatik fistül gelişimini tahmin etmedeki önemi, bu konuda yapılan çalışmalarla yeterince derinlemesine incelenmemiştir. Bu çalışma, distal pankreatektomi yapılan hastalarda postoperatif inflamatuar indekslerin, özellikle SII (sistemik immün inflamasyon indeksi), NLR (nötrofil-lenfosit oranı) ve PLR (trombosit-lenfosit oranı), pankreatik fistül gelişimi ile ilişkisini değerlendirmeyi amaçlamaktadır.
Materyal ve Metod: Bu retrospektif çalışmada, Ocak 2020 ile Aralık 2023 arasında pankreatik kanser nedeniyle distal pankreatektomi uygulanan hastalar analiz edilmiştir. İstatistiksel analizler, pankreatik fistül (B ve C dereceleri) gelişen hastaların, üçüncü postoperatif günde elde edilen laboratuvar sonuçlarına dayalı olarak hesaplanan SII, NLR ve PLR verileri retrospektif olarak incelenerek yapılmıştır.
Bulgular: Çalışmaya, belirlenen kriterlere uyan 72 hasta dahil edildi. Bu hastaların 25'inde (% 34.7) pankreatik fistül gözlemlendi. Bu çalışmada, BMI ve yumuşak pankreatik doku pankreatik fistül gelişimi için istatistiksel olarak anlamlı risk faktörleri olarak bulundu (her ikisi için p=0.02). Postoperatif üçüncü günde ölçülen SII ve NLR, pankreatik fistül gelişiminin istatistiksel olarak anlamlı prediktörleri olurken, postoperatif PLR'nin pankreatik fistül gelişimini tahmin etmede istatiksel anlamlı sonuç vermediği görüldü. SII'nin pankreatik fistül gelişiminin tahmin edilmesinde NLR'den daha güçlü bir prediktör olduğu görüldü.
Sonuç: Bu çalışma, inflamasyonla ilişkili indeksler olan SII ve NLR'deki artışın, distal pankreatektomi sonrası pankreatik fistül gelişiminin tahmin edilmesinde etkili bir yöntem olduğunu göstermektedir. Buna karşılık, PLR'nin pankreatik fistül gelişimini tahmin etmede etkili olmadığı görüldü.

Anahtar Kelimeler: Distal pankreatektomi, Pankreatik fistül, SII, NLR, PLR

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Introduction

Regardless of the surgical technique employed for pancreatic cancer, morbidity and mortality rates remain high. Complication rates following distal pancreatectomy vary between 9% and 30%, with pancreatic fistula being the most significant complication. Other general complications are bleeding, intra-abdominal abscesses, and delayed gastric emptying (1,2).

Pancreatic Fistula definition was revised in 2016. According to this new definition, drain amylase levels that indicate a grade A fistula are considered biochemical leaks rather than true pancreatic fistulas (3).

In the literature, it is stated that deaths after distal pancreatectomy are 3% and morbidity varies between 22% and 47%. The rate of pancreatic fistula development after surgery are between 15% and 31%. Since there is no anastomosis in distal pancreatectomy, pancreatic fistulas that arise after the procedure typically close on their own and seldom necessitate reoperation (2-4).

Methods like closing the pancreatic stump with staples or stitches, using tissue adhesives, administering prophylactic octreotide and using cautery or scalpel techniques for cutting the pancreas, have not proven effective in preventing pancreatic fistula formation after distal pancreatectomy. Fistula development rate may be affected by patient-related factors rather than the surgical approach itself. Reasons such as advanced age, obesity, intraoperative bleeding, high ASA score, concurrent splenectomy, vascular resection, and hypoalbuminemia have been associated with an increased risk of developing pancreatic fistula (1,4,5).

In last years, a broader array of biological markers has been increasingly utilized in clinical practice due to their cost-effectiveness and easy accessibility. One such markers are the complete blood count (CBC), that is a straightforward, widely available, and economical test. This test provides detailed counts of various blood cell types, including neutrophils, platelets, and lymphocytes. From these counts, several inflammation-related indices can be derived, such as the systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). Many researchs have shown significant associations between these inflammation-related indices and a wide range of diseases, including infectious, neoplastic, metabolic, autoimmune, and cardiovascular diseases (6,7).

The role of inflammatory markers in predicting the development of pancreatic fistulas hasn't been extensively studied in patients who have had distal pancreatectomy. This research aims to evaluate the predictive significance of postoperative inflammatory indices, specifically SII, NLR, and PLR, in relation to the occurrence of pancreatic fistulas in these individuals.

Materials and Methods

Study design

Postoperative pancreatic fistula (POPF) was categorized according to the criteria established by the International Study Group on Pancreatic Fistula (ISGPF) (3). Data regarding laboratory results for patients who experienced pancreatic fistula (Grades B and C) were collected through a retrospective review of prospectively maintained clinical records.

The study included patients aged 18 to 75 who underwent distal pancreatectomy for pancreatic ductal adenocarcinoma between January 2020 and December 2023 in Atılım University Faculty of Medicine-affiliated Medicana International Ankara Hospital. Those with benign conditions, other malignancies aside from adenocarcinoma, individuals who received palliative surgery, patients with distant metastases (M1), concurrent malignancies, different surgical procedures apart from distal pancreatectomy, autoimmune diseases, a history of previous malignancy, and those who had neoadjuvant chemotherapy or radiotherapy were excluded.

Parameters such as age, sex, BMI, stump closure technique, tumor diameter, number of metastatic lymph nodes, and pancreatic texture were evaluated. The consistency of the pancreatic tissue, whether firm or soft, was subjectively assessed by the operating surgeon through palpation based on their experience, after resection and immediately before the pancreaticojejunostomy.

A drain was routinely inserted intraperitoneally to monitor patients during the postoperative period. Antibiotics (ceftriaxone 1gr and metronidazole 500mg) were administered to all patients for five days postoperatively. Ocreotide was not routinely used in the postoperative period. Blood cell counts were obtained on postoperative day (POD) 3. All blood cell counts will be represented as count*10^3/μL.

SII = [platelet count (PLT) x neutrophil count (NC)] / lymphocyte count (LC)

NLR = neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

Statistical Methods

Statistical analysis was performed using SPSS v27, with a significance threshold set at $p < 0.05$. The normality of continuous variables was assessed using Skewness and Kurtosis tests. Data that conformed to a normal distribution are presented as mean ± standard deviation (SD). For data that did not follow a normal distribution, results are shown as median (25th–75th percentile). Categorical variables are reported as counts and percentages. The Independent-samples t-test, Mann–Whitney U test and chi-squared test were used to compare the groups.

The predictive value of variables was assessed using a receiver operating characteristic (ROC) curve, with the occurrence of Grade B and C pancreatic fistula defined as the primary endpoint for this analysis. Areas under the ROC curve (AUROC) were calculated for postoperative SII, NLR, and PLR. The results of the ROC analysis, including sensitivity and specificity, were examined, and the highest values were determined as cut-off points. Consequently, AUROC, confidence intervals (CI), and p-values were compared.

Results

Between January 2020 and December 2023, 121 patients who underwent distal pancreatectomy in our clinic were evaluated. The study included a total of 72 patients who fulfilled the established criteria. An open surgery including splenectomy was performed on all patients. Pancreatic fistulas were observed in 25 (34.7%) of the patients. Patient information, including age, gender, body mass index (BMI), pathological results, pancreatic stump closure, and the condition of pancreatic tissue in the presence of pancreatic fistula, is presented in Table 1.

In this study, BMI and the presence of soft pancreatic tissue were identified as statistically significant risk factors for the development of postoperative pancreatic fistula (POPF).

In this study, the cut-off values for the postoperative inflammatory indices were established as follows: the SII was set at 1881, resulting in 92% sensitivity and 51% specificity; the NLR at 8.4, which also achieved 92% sensitivity and 51% specificity; and the PLR at 170, which yielded a sensitivity of 55% and specificity of 68%. Postoperative SII and NLR were found to be statistically significant predictors of POPF development, with SII showing a stronger predictive capability than NLR. In contrast, postoperative PLR did not yield statistically significant results for predicting POPF. The comparisons of AUROC, CI, and p-values for postoperative SII, NLR, and PLR are illustrated in Table 2 and Figure 1.

Table 1. Patient Characteristics, Pathological Findings and Pancreatic Fistula Outcomes

	Pancreatic Fistula (+)	Pancreatik Fistula (-)	p
Age	61.8 (±6.1)	58.7 (±8.9)	0.08
Gender			
Male	10 (13.9%)	20 (27.8%)	0.8
Female	15 (20.8%)	27 (37.5%)	
Body Mass Index (BMI)	30.4 (±3.8)	28.3 (±2.6)	**0.02**
Stump Closure Technique			
Stapler	24 (33.3%)	41 (56.9%)	0.4
Suture	1 (1.4%)	6 (8.4%)	
Pancreatic Tissue			
Soft	14 (19.4%)	13 (18.1%)	**0.02**
Firm	11 (15.3%)	34 (47.2%)	
Tumor Size (mm)	45.4 (±21.8)	39.8 (±23.6)	0,3
Metastatic lymph node	0 (0-2)	0 (0-1)	0.33

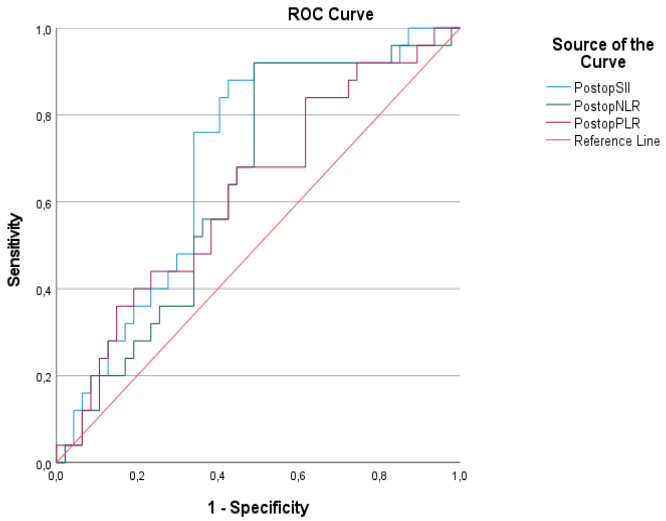

Figure 1. Comparison of postoperatif SII, NLR and PLR with ROC analysis to predict pancreatic fistula development of patients

Table 2. Comparison of postoperatif SII, NLR and PLR with ROC analysis to predict pancreatic fistula development of patients

	AUROC	Confidence Interval (CI)	Std. Error	p value
Postoperative SII	0.70	0.57-0.82	0.63	**0.006**
Postoperative NLR	0.64	0.51-0.77	0.66	**0.05**
Postoperative PLR	0.62	0.48-0.76	0.69	0.08

Discussion

The mortality rate following pancreatic resection has declined in recent years to less than 4% in high-volume centers; however, morbidity remains significantly high. Among the complications that arise after distal pancreatectomy, pancreatic fistula is the most prevalent and is a major contributor to morbidity (4,5). Predicting the onset of pancreatic fistula is challenging, yet early detection is crucial for improving patient prognosis. In examining the dynamics of circulating immune cells in cancer patients, neutrophilia serves as an indicator of systemic inflammatory response, while lymphopenia reflects host immunosuppression. Additionally, the role of thrombocytosis in cancer progression underlies the significance of SII, NLR, and PLR scores. Schlanger et al. demonstrated that significant changes occur in the populations of circulating immune cells following tumor resection, noting that total counts of neutrophils, monocytes, and platelets, as well as NLR, PLR, and SII, increase significantly after surgery (8).

In scenarios involving strong triggers of systemic inflammatory response, such as sepsis, malignancy, and trauma, platelet proliferation is stimulated by pro-inflammatory cytokines in addition to the presence of neutrophilia and lymphopenia. The potential significance of SII arises from the specific interplay between neutrophils, lymphocytes, and platelets, all of which play critical roles in various inflammatory processes. The Systemic Immune-Inflammation Index (SII), introduced into the literature in 2014, is a novel biomarker that was initially utilized to predict prognosis in various types of cancer (9). It has also proven to be a valuable marker for examining the interaction between thrombocytosis and immune inflammation in the context of sepsis, postoperative complications, and cerebrovascular diseases (10). In this retrospective study, we identified a cut-off value for SII of 1881, which was shown to predict the development of pancreatic fistula with a sensitivity of 92% and specificity of 51%, achieving statistical significance ($p = 0.006$).

NLR was defined by Zahorec in 2001 and has been proposed as a simple, reliable, and cost-effective parameter for assessing various conditions, including sepsis and trauma, in critically ill patients (11,12). In this study, the cut-off value for NLR was determined to be 8.4. This ratio was found to effectively predict the occurrence of pancreatic fistula in patients who underwent distal pancreatectomy, showing a sensitivity of 92% and a specificity of 51%, with statistical significance ($p = 0.05$).

PLR was first introduced by Smith et al. (13). In this study, a cut-off value of 170 was identified for PLR, which exhibited 68% specificity and 55% sensitivity; however, this result was not statistically significant in predicting fistula development ($p = 0.08$).

Qi et al. conducted a study evaluating the relationship between inflammatory markers and postoperative complications, finding a significant correlation between postoperative SII and NLR values and the occurrence of anastomotic leakage in patients who underwent low anterior resection for rectal cancer. Notably, preoperative values were not significant for predicting anastomotic leakage (14). In this article, we focus on evaluating postoperative blood results in relation to the development of pancreatic fistula.

Ma et al. showed that SII, NLR, and PLR are significant predictors of pancreatic fistula development in patients undergoing pancreaticoduodenectomy (7). In this retrospective study, a statistically significant association was found between SII and NLR with the occurrence of pancreatic fistula, while PLR did not demonstrate a significant relationship. The lack of significance for PLR may be attributed to the inclusion of patients with fever in the study. Conversely, complications such as bile leakage and anastomotic leakage are not typically encountered following distal pancreatectomy. Thus, we propose that inflammatory markers may be more effective in predicting pancreatic fistula development in distal pancreatectomy than in pancreaticoduodenectomy. The statistically significant findings related to PLR in patients undergoing pancreaticoduodenectomy may also be influenced by the presence of additional complications beyond pancreatic fistula.

Various studies have explored both preoperative and postoperative inflammatory markers, yielding mixed results regarding their significance (7,14-16). Surgical trauma may trigger an exaggerated inflammatory response or suppress cell-mediated immunity, as evidenced by research indicating that surgical trauma significantly impacts the immune system (17,18). The challenge lies in determining whether complications stem from preoperative tumor immunology, are a consequence of surgical stress post-tumor removal, or arise from blood count changes after complications occur. In this study, we analyzed SII, NLR, and PLR derived from postoperative blood results.

Limitations

A key limitation of this study is the small patient cohort, underscoring the need for further research with larger sample sizes to validate these findings.

Conclusions

This study revealed that increases in the SII and NLR, both of which are inflammation-related indices, are associated with a heightened risk of complications. Furthermore, SII was found to be a statistically more significant predictor of pancreatic fistula compared to NLR. The affordability and straightforward calculation of these markers may facilitate the early prediction of pancreatic fistula in the postoperative period.

Ethical Approval: *Ethics committee approval number '45' dated 18.12.2023 was received from Atılım University Faculty of Medicine-affiliated Medicana International Ankara Hospital for this study. This manuscript adheres to the principles outlined in the Declaration of Helsinki (2013).*

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Analysis and interpretation: M.K.
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Critical revision of manuscript: M.K.
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References

1. Oneil Machado N. Pancreatic fistula after pancreatectomy: definitions, risk factors, preventive measures, and management. International journal of surgical oncology. 2012;2012(1):602478.
2. Ecker BL, McMillan MT, Allegrini V, Bassi C, Beane JD, Beckman RM, et al. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. Ann Surg. 2019;269(1):143-9. doi: 10.1097/sla.0000000000002491. PubMed PMID: 28857813.
3. 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.
4. Goh BK, Tan YM, Chung YF, Cheow PC, Ong HS, Chan WH, et al. 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. Arch Surg. 2008;143(10):956-65. doi: 10.1001/archsurg.143.10.956. PubMed PMID: 18936374.
5. Knaebel HP, Diener MK, Wente MN, Büchler MW, Seiler CM. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. Br J Surg. 2005;92(5):539-46. doi: 10.1002/bjs.5000. PubMed PMID: 15852419.
6. Jiao Y, Zhang X, Liu M, Sun Y, Ma Z, Gu X, et al. Systemic immune-inflammation index within the first postoperative hour as a predictor of severe postoperative complications in upper abdominal surgery: a retrospective single-center study. BMC Gastroenterol. 2022;22(1):403. Epub 20220827. doi: 10.1186/s12876-022-02482-9. PubMed PMID: 36030214; PubMed Central PMCID: PMC9419130.
7. Ma M, Li G, Zhou B, Li K, Wu Z, Kong L, et al. Comprehensive analysis of the association between inflammation indexes and complications in patients undergoing pancreaticoduodenectomy. Front Immunol. 2023;14:1303283. Epub 20231123. doi: 10.3389/fimmu.2023.1303283. PubMed PMID: 38077320; PubMed Central PMCID: PMC10702568.
8. Schlanger D, Popa C, Pașca S, Seicean A, Al Hajjar N. The role of systemic immuno-inflammatory factors in resectable pancreatic adenocarcinoma: a cohort retrospective study. World J Surg Oncol. 2022;20(1):144. Epub 20220506. doi: 10.1186/s12957-022-02606-1. PubMed PMID: 35513845; PubMed Central PMCID: PMC9074307.
9. Uluç K, Turan H. Prognostic Value of Systemic Immune-Inflammation Index (SII), Platelet-Lymphocyte Ratio (PLR) and Neutrophil-Lymphocyte Ratio (NLR) in Predicting Mortality in Pneumosepsis Patients in Intensive Care Unit. Harran Üniversitesi Tıp Fakültesi Dergisi. 2024;21(3):490-5.
10. Islam MM, Satici MO, Eroglu SE. Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, and delta neutrophil index: An extensive literature review. Turk J Emerg Med. 2024;24(1):8-19. Epub 20240108. doi: 10.4103/tjem.tjem_198_23. PubMed PMID: 38343523; PubMed Central PMCID: PMC10852137.
11. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102(1):5-14. PubMed PMID: 11723675.
12. Menges T, Engel J, Welters I, Wagner RM, Little S, Ruwoldt R, et al. Changes in blood lymphocyte populations after multiple trauma: association with posttraumatic complications. Crit Care Med. 1999;27(4):733-40. doi: 10.1097/00003246-199904000-00026. PubMed PMID: 10321662.
13. Smith RA, Bosonnet L, Ghaneh P, Sutton R, Evans J, Healey P, et al. The platelet-lymphocyte ratio improves the predictive value of serum CA19-9 levels in determining patient selection for staging laparoscopy in suspected periampullary cancer. Surgery. 2008;143(5):658-66. Epub 20080328. doi: 10.1016/j.surg.2007.12.014. PubMed PMID: 18436014.
14. Qi XY, Tan F, Liu MX, Xu K, Gao P, Yao ZD, et al. Serum and peritoneal biomarkers for the early prediction of symptomatic anastomotic leakage in patients following laparoscopic low anterior resection: A single-center prospective cohort study. Cancer Rep (Hoboken). 2023;6(4):e1781. Epub 20230131. doi: 10.1002/cnr2.1781. PubMed PMID: 36718787; PubMed Central PMCID: PMC10075299.
15. Hoshimoto S, Hishinuma S, Shirakawa H, Tomikawa M, Ozawa I, Ogata Y. Validation and clinical usefulness of pre- and postoperative systemic inflammatory parameters as prognostic markers in patients with potentially resectable pancreatic cancer. Pancreatology. 2020;20(2):239-46. Epub 20191214. doi: 10.1016/j.pan.2019.12.004. PubMed PMID: 31862230.
16. Liu CQ, Yu ZB, Gan JX, Mei TM. Preoperative blood markers and intra-abdominal infection after colorectal cancer resection. World J Gastrointest Surg. 2024;16(2):451-62. doi: 10.4240/wjgs.v16.i2.451. PubMed PMID: 38463368; PubMed Central PMCID: PMC10921215.
17. Kohl BA, Deutschman CS. The inflammatory response to surgery and trauma. Curr Opin Crit Care. 2006;12(4):325-32. doi: 10.1097/01.ccx.0000235210.85073.fc. PubMed PMID: 16810043.
18. Ni Choileain N, Redmond HP. Cell response to surgery. Arch Surg. 2006;141(11):1132-40. doi: 10.1001/archsurg.141.11.1132. PubMed PMID: 17116807.