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ORIGINAL ARTICLE

Preoperative neutrophil-to-lymphocyte ratio predicts healing time for postoperative pancreatic fistula after distal pancreatectomy

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Abstract

Purpose: Postoperative pancreatic fistula is a serious complication of distal pancreatectomy. Although many studies have described the incidence and risk factors associated with postoperative pancreatic fistula (POPF), few have focused on the healing time. This study investigated the healing time and potential factors associated with the healing time of POPF after distal pancreatectomy (DP).

Methods: Among 114 patients that underwent DP in our hospital from January 2010 to December 2020, we included 88 that developed POPF. The healing time for a postoperative pancreatic fistula was defined as the interval between the completion of DP and the removal of all drains related to the treatment for POPF. Based on the definition, three cases who required additional treatment after removal of all drains were excluded from this study. Clinical factors associated with the fistula healing times were investigated in the 85 patients.

Results: The average POPF healing time was 11 ± 10 days (median: 6 days, range: 3-57). We found that the neutrophil-to-lymphocyte ratio, a marker of inflammatory and nutritional status, was the only factor independently associated with the POPF healing time; the mean healing time was significantly shorter in patients with neutrophil-to-lymphocyte ratio ≤2.1 (8 ± 6 days) than in those with neutrophil-to-lymphocyte ratio >2.1 (13 ± 12 days; *P* = .0139).

Conclusion: We demonstrated that the neutrophil-to-lymphocyte ratio could independently predict the POPF healing time after DP. These findings suggested that improving the neutrophil-to-lymphocyte ratio might shorten the healing times for POPF after DP.

KEYWORDS

distal pancreatectomy, lymphocyte, neutrophil, neutrophil-to-lymphocyte ratio, pancreatic fistula

1 | INTRODUCTION

Distal pancreatectomy (DP) is the curative treatment for various diseases that occur in the body and/or tail of the pancreas. Improvements in surgical techniques and perioperative management have reduced the incidences of postoperative morbidity and mortality after pancreatectomy. However, postoperative pancreatic fistula (POPF) remains one of the most common complications of DP; the incidence is approximately 10%-40%.[1-3] Once POPF develops, it can trigger subsequent postoperative complications, such as intra-abdominal abscess and pseudoaneurysm associated with post-pancreatectomy hemorrhage. These complications can potentially extend postoperative hospitalization, increase the treatment costs, and even lead to postoperative mortality. In this context, many investigators have identified factors predictive of the risk of developing POPF, such as obesity, nutritional status, pancreas thickness, and pancreas consistency.[4-7] Thus, predicting the risk of developing POPF has been established for patients that require DP. However, POPF continue to develop, despite the prediction. Therefore, it is important to select the appropriate POPF treatment. Although the choice of a therapeutic option plays a role in the POPF treatment, it is also important to estimate how long it might take to achieve a complete cure. To that end, we previously investigated the time needed to cure POPF after pancreaticoduodenectomy.[8,9] However, to date, few studies have investigated the time necessary for POPF to heal after DP.[10]

Recent studies have focused on whether the inflammatory and nutritional status of patients might potentially influence wound healing, the risk of postoperative complications, and even a cancer prognosis.[10-15] Additionally, several studies have reported a significant association between nutritional status and the incidence of POPF.[3,5,16,17] Considering that inflammatory and nutritional status is associated with wound healing, we reasoned that these statuses might also affect the time for POPF to heal.

Based on this background, in the present study, we aimed to assess the time needed to cure POPF after DP. Moreover, we evaluated whether factors associated with inflammatory and nutritional statuses might affect the POPF healing time.

2 | PATIENTS AND METHODS

A total of 149 consecutive patients underwent DP, from January 2010 to December 2020, in the Department of Gastroenterological Surgery, Osaka University Hospital. Among the 149 patients, 35 were excluded from this retrospective study, because they required resections of other organs, in addition to DP (21 cases), or they underwent other procedures for treating the pancreatic stump, including DP with hand-sewn stump closure (three cases) and anastomosis with intestinal tract (11 cases). Among the remaining 114 patients, 88 (77.2%) developed POPF. In the 88 patients, three cases, who required additional treatment after removal of all drainage tubes, were excluded from this study based on the definition of the POPF healing time described below. Finally, 85 patients were included in the present study. The clinical and surgical characteristics of the patients are summarized in Table 1. Furthermore, in the 85 patients, we investigated factors that might affect the POPF healing time.

In this study, the POPF healing time was defined as the interval from the day of DP to the day when POPF was cured. The day of POPF cure was defined as the day that all intra-abdominal drainage tubes related to the treatment were removed.

We used the following factors to evaluate inflammatory and nutritional statuses in this study: white blood cell, neutrophil, lymphocyte, and platelet counts; albumin, total cholesterol, and C-reactive protein (CRP) levels; the prognostic nutritional index (PNI), the controlling nutritional status (CONUT); the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the modified Glasgow prognosis score (mGPS).[18-21]

Distal pancreatectomy was performed with a triple-row linear stapler, and the closure jaw was clamped carefully and slowly, at a fixed speed, over a period of at least 5 minutes.[22] Prior to the completion of pancreatic surgery, an intra-abdominal, closed-suction drainage tube was placed near the pancreas stump. In patients that also underwent spleen removal, another tube was placed at the left subphrenic space.

The POPF diagnosis was based on the definition established by the International Study Group of Pancreatic Fistula (ISGPF),[10] with the following severity grades: biochemical leakage (BL), grade B, and grade C. All patients received the same postoperative management, including the POPF treatment. Briefly, we measured the amylase concentration in the drainage fluid on the first and third postoperative days. In patients that developed POPF, octreotide was administered when the amylase concentration in the drainage fluid was >5000 U/L. The intra-abdominal drainage tube was changed every 1-2 weeks, and the drainage tube was removed when the patients were asymptomatic and imaging modalities confirmed the disappearance of the intra-abdominal cavity independently of appearance or amylase concentration in the drainage fluid through the tubes. The main pancreatic duct diameter was measured at the resection line of the pancreas on enhanced computed tomography images.

Data are described as the mean ± standard deviation for continuous variables and the number for categorical variables. Between-group differences were assessed with the Mann-Whitney *U*-test, the chi-square test, and Fisher's exact test, as appropriate. The POPF healing time was estimated with the Kaplan-Meier method, and cumulative POPF healing rates were compared between groups with the log-rank test. Cox proportional hazards models were constructed for multivariate analyses to identify independent variables that significantly affected the POPF healing time. Continuous variables were converted to categorical variables by forming groups above and below the median value for each variable. We determined the odds ratio (OR) and 95% confidence interval (CI) for each variable. Statistical analyses were performed with the JMP® software program (SAS Inc.). P values <.05 were considered statistically significant.

After an extensive dialogue with the Institutional Ethics Review Committee, patient consent for participation was obtained through an opt-out method. The present study was approved by the Institutional Ethics Review Committee (Certificate Number 20466).

TABLE 1 Perioperative characteristics of 85 individuals with POPF

Characteristic	Measurement
Preoperative factors	
Age (years)	59 ± 18
Sex (Male/Female)	39/46
Height (cm)	160.9 ± 9.3
Weight (kg)	57.0 ± 11.1
BMI (kg/m^2)	22.0 ± 3.6
Disease (Pancreatic cancer/Others)	35/40
Neoadjuvant therapy (no/yes)	69/16
White blood cells (/μL)	5185 ± 1539
Neutrophils (g/dL)	3084 ± 1113
Lymphocytes (/μL)	1515 ± 660
Platelets (10^4/μL)	26.5 ± 16.2
Albumin (g/dL)	4.0 ± 0.4
Total cholesterol (mg/dL)	188 ± 38
CRP (mg/dL)	0.16 ± 0.36
PNI	40.2 ± 3.6
NLR	2.4 ± 1.3
PLR	214.0 ± 203.9
mGPS (0/1/2)	77/8/0
CONUT (0-1/2-4/5-8/9-12)	37/37/11/0
MPD diameter (mm)	2.3 ± 2.0
Pancreas thickness (mm)	10.9 ± 3.3
Intraoperative factors	
Surgical approach (Open/Laparoscopic)	62/23
Position of pancreas dissection (Portal vein/ Body, Tail)	56/29
Operation time (min)	267 ± 86
Intraoperative blood loss (mL)	293 ± 355
Spleen preservation (no/yes)	74/11
Postoperative factors	
POPF (BL/Grade B/Grade C)	60/25/0
Amylase concentration in the drainage fluid (U/L)	
on POD1	7007 ± 8149
on POD3	8781 ± 48 539
Administration of octreotide (∓)	59/26

Note: Data are expressed as the mean ± standard deviation, for continuous variables, or the number of patients, for categorical variables.

Abbreviations: BL, biochemical leakage; BMI, body mass index; CONUT, controlling nutritional status; CRP, C-reactive protein; mGPS, modified Glasgow prognosis score; MPD, main pancreatic duct; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; POD, postoperative day; POPF, postoperative pancreatic fistula.

3 | RESULTS

Among the 114 patients that underwent DP, 88 (77.2%) developed POPF. Of the 88 patients, three patients were excluded from this study, as they required additional treatment after removal of all drainage tubes. Among the 85 patients, the POPF severity grades were BL (n = 60) and grade B (n = 25); no patient exhibited grade C POPF. No patients were discharged from the hospital or died after surgery before the POPF was cured. Patient characteristics are shown in Table 1.

The average POPF healing time was 11 ± 10 days (median, 6 days; range 3-57). Individual POPF healing times are shown in Figure 1. The POPF healing time was significantly longer in patients with grade B than in those with BL (22 ± 11 days vs 6 ± 2 days; $P < .001$). The cumulative POPF healing rates were calculated with

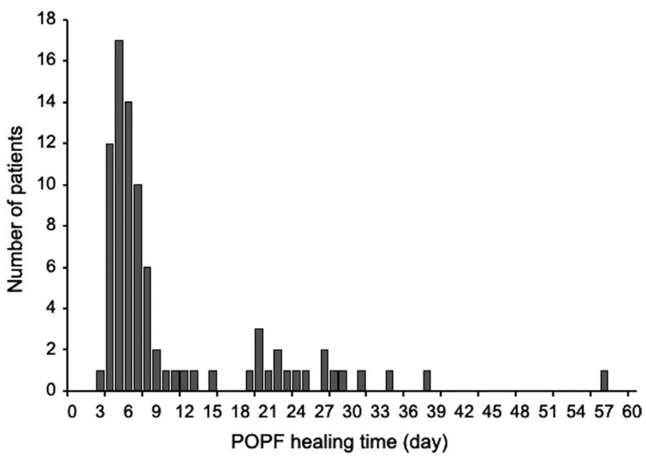

FIGURE 1 Individual POPF healing times. Each bar indicates the number of patients that experienced the indicated POPF healing time. POPF, postoperative pancreatic fistula

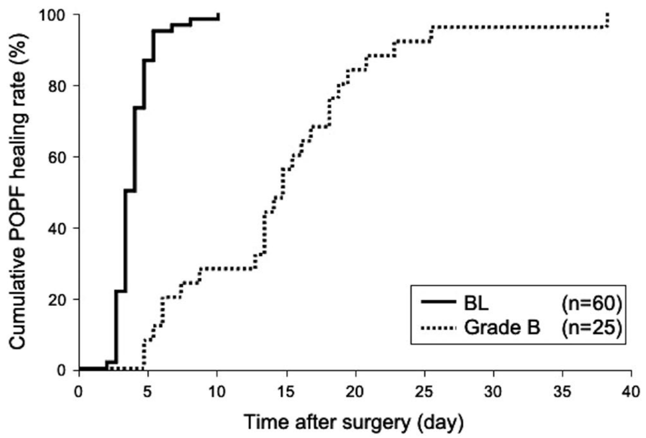

FIGURE 2 Cumulative POPF healing rate in patients, stratified by the POPF grade, defined by the ISGPF. The cumulative POPF healing rate was calculated with the Kaplan-Meier method. The healing time was significantly shorter in patients with BL than in patients with grade B ($P < .0001$). BL, biochemical leak; ISGPF, International Study Group of Pancreatic Fistula; POPF, postoperative pancreatic fistula

the Kaplan-Meier method (Figure 2). This result was consistent with the definition of POPF.[10]

To investigate which factors could significantly determine the POPF healing time, we performed a univariate analysis of potentially influential factors (Table 2). In this analysis, we only included factors that were clearly known prior to surgery to establish a predictive model with preoperative factors. The univariate analysis showed that the NLR and body weight were significantly related to the POPF healing time. Patients with NLR ≤2.1 had significantly shorter POPF healing times than those with NLR >2.1 (healing times: 8 ± 6 days vs 13 ± 12 days; *P* = .0139). Patients with body weights ≤56.0 kg also had significantly shorter POPF healing times than those with body weights >56.0 kg (healing times: 8 ± 7 days vs 13 ± 12 days; *P* = .0341). The univariate analysis also identified one marginally

TABLE 2 Univariate and multivariate analysis results for POPF healing times among patients that underwent a distal pancreatectomy

		Univariate			Multivariate		
Factors	Number	OR	95% CI	*P* value	OR	95% CI	*P* value
Preoperative factors							
Age (years) (≤63 vs >63)	41/44	1.0414	0.6762-1.6040	.8411			
Sex (Male vs Female)	39/46	0.7272	0.4676-1.1310	.1216			
Height (cm) (≤162 vs >162)	43/42	1.2765	0.8191-1.9840	.5567			
Weight (kg) (≤56 vs >56)	44/41	1.5390	0.9924-2.3867	.0341	1.4696	0.9456-2.2839	.0870
BMI (kg/m^2) (≤21 vs >21)	44/41	1.2784	0.8303-1.9684	.2235			
Disease (Pancreatic cancer vs Others)	39/46	0.7841	0.5037-1.2204	.2386			
Neoadjuvant therapy (no vs yes)	69/16	0.6115	0.3497-1.0691	.0555			
White blood cells (/μL) (≤4960 vs >4960)	43/42	0.9389	0.6068-1.4528	.7575			
Neutrophils (g/dL) (≤2893 vs >2893)	42/43	1.3373	0.8657-2.0656	.1522			
Lymphocytes (/μL) (≤1379 vs >1379)	42/43	0.8669	0.5603-1.3412	.4836			
Platelets (10^4/μL) (≤22.0 vs >22.0)	42/43	0.8104	0.5269-1.2463	.2964			
Albumin (g/dL) (≤4.0 vs >4.0)	45/40	0.9628	0.6256-1.4817	.8511			
CRP (mg/dL) (≤0.04 vs >0.04)	48/37	1.3054	0.8441-2.0187	.1911			
Total cholesterol (mg/dL) (≤190 vs >190)	44/41	0.9552	0.6187-1.4749	.8218			
PNI (≤40.1 vs >40.1)	43/42	0.9897	0.6444-1.5197	.9588			
NLR (≤2.1 vs >2.1)	41/44	1.6685	1.0613-2.6232	.0139	1.5995	1.0167-2.5164	.0422
PLR (≤160.7 vs ≥160.7)	42/43	0.9141	0.5907-1.4145	.6600			
mGPS (0 vs 1 or 2)	77/8	1.0994	0.5273-2.2923	.7840			
CONUT (0 or 1 vs 2-12)	37/48	0.9762	0.6304-1.5117	.9064			
MPD diameter (mm) (≤1.9 vs >1.9)	44/41	1.0254	0.6669-1.5766	.9012			
Pancreas thickness (mm) (≤10.4 vs >10.4)	46/39	1.1731	0.7611-1.8079	.4304			
Intraoperative factors							
Surgical approach (Open/Laparoscopic)	61/24	0.7462	0.4571-1.2183	.1947			
Position of pancreas dissection (Portal vein/Body, Tail)	56/29	0.8346	0.5301-1.3139	.3935			
Operation time (min) (≤244 vs >244)	43/42	0.9156	0.5958-1.4069	.6614			
Intraoperative blood loss (mL) (≤170 vs >170)	44/41	1.1018	0.7161-1.6953	.6311			
Spleen preservation (∓)	74/11	0.5791	0.3014-1.1120	.0641			

Abbreviations: 95% CI, 95% confidence interval; BL, biochemical leakage; BMI, body mass index; CONUT, controlling nutritional status; CRP, C-reactive protein; mGPS, modified Glasgow prognosis score; MPD, main pancreatic duct; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; POD, postoperative day; POPF, postoperative pancreatic fistula.

significant factor: the presence/absence of neoadjuvant therapy. The average POPF healing times were 8 ± 5 days in patients that received neoadjuvant therapy and 11 ± 10 days in the group without neoadjuvant therapy (*P* = .0555). On the other hand, no significant associations with the POPF healing time were found for age, sex, height, disease, white blood cells, neutrophils, lymphocytes, platelets, albumin, CRP, total cholesterol, PNI, PLR, mGPS, CONUT, the main pancreatic duct diameter, or pancreas thickness.

Next, to identify independent factors that significantly affected the POPF healing time, we performed a multivariate analysis of the two factors that showed significance in the univariate analyses, NLR and body weight. The multivariate analysis showed that NLR was the only independently significant factor for POPF healing time (OR: 1.5995, 95% CI: 1.02-2.51, *P* = .0422). Body weight was a marginally significant factor for POPF healing time (OR: 1.4696, 95% CI: 0.95-2.28, *P* = .0870). We also performed a univariate analysis of potentially influential intraoperative factors on the POPF healing time, including surgical approach, position of pancreas dissection, operation time, intraoperative blood loss, and presence/absence of spleen preservation. However, while the presence/absence of spleen preservation was marginally significant, the other factors were not significantly associated with the POPF healing time.

Based on these results, we performed a Kaplan-Meier analysis to calculate the cumulative POPF healing rates for patients with NLR values above and below the median value (Figure 3). The cumulative rate for the NLR ≤2.1 group was significantly higher than that of the NLR >2.1 group (*P* = .0139). This trend was confirmed in cases with patients with grade B POPF (healing times: NLR ≤2.1 group; 17 ± 8 days vs NLR >2.1 group; 24 ± 12 days) (OR: 2.1858, 95% CI: 0.88-5.46, *P* = .0776), while those with BL POPF did not exhibit the trend (healing times: NLR ≤2.1 group; 6 ± 2 days vs NLR >2.1 group; 6 ± 2 day) (OR: 1.1000, 95% CI: 0.65-1.85, *P* = .6535). Furthermore, persistent drainage (>3 weeks), which is one of the factors that determine the ISGPF grade, was observed significantly more frequently in the NLR >2.1 group (10/44 patients; 22.7%) than in the NLR ≤2.1 group (3/41 patients; 7.3%; *P* = .0431).[10]

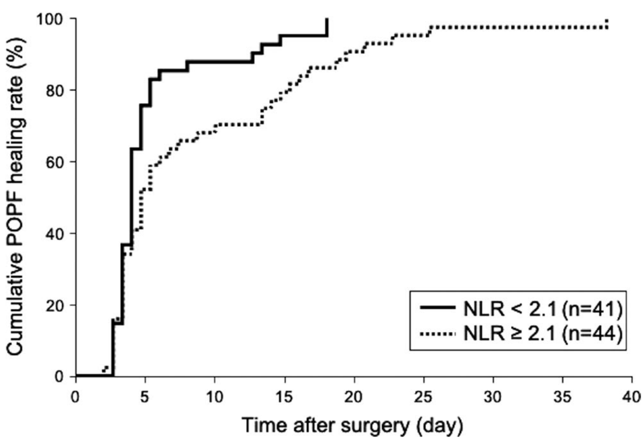

FIGURE 3 Cumulative POPF healing rate in patients, stratified by the NLR. The cumulative POPF healing rate was calculated with the Kaplan-Meier method. The healing time was significantly shorter for patients with NLR ≤2.1 than for patients with NLR >2.1 (*P* = .0139). NLR, neutrophil-to-lymphocyte ratio; POPF, postoperative pancreatic fistula

4 | DISCUSSION

Postoperative pancreatic fistula is one of the most important postoperative complications of DP, and it is associated with secondary postoperative complications. Most previous studies have focused on the incidence of POPF and factors associated with POPF development.[1-3] From the clinical point of view, it is also important to know how long it takes to completely cure POPF after it develops. In this context, this study investigated the POPF healing time after DP. Furthermore, we investigated inflammatory and nutritional status markers, based on previous reports that showed a relationship between nutritional status and wound healing.[11,23,24] Our results demonstrated that NLR was the only independent factor that could predict the POPF healing time. Unfortunately, it remains unclear why NLR was the independent factor predictive of the POPF healing time. In general, good inflammatory and nutritional status have been reported to be one of the important factors in wound healing.[11,23,24] Furthermore, it would be expected that the healing capacity is potentially associated with the POPF cure. We speculate that these may have caused the significant association between lower NLR and the shorter healing time. The present study implemented two novel approaches that improved the interpretation of our results in the context of managing patients that plan to receive DP. First, to the best of our knowledge, no previous study has investigated the healing time of all POPF after DP. Although Andrianello et al[25] investigated the POPF healing time after DP, they included only patients with grade B/C POPF; in contrast, the present study also included patients with BL POPF. Based on the ISGPF definition of POPF, BL and grade B/C are determined during the postoperative course, because on postoperative day 3, when POPF development is evaluated based on the fluid amylase level, in most cases, it is not possible to differentiate the grade. Nevertheless, for predicting the healing time, it is desirable to include both grade B/C and BL in the analyses. Thus, our study approach was more informative than the approach used previously by Andrianello et al. Second, in the cohort studied by Andrianello et al, 24.8% of patients had been discharged with a drain. That feature could potentially make it difficult to calculate the healing time, because the removal of the last drain, which was used in the healing time calculation, might have been based on the patients' visits to the hospital, rather than the status of the wound. Thus, the calculations for healing times might have been inaccurate. In contrast, in the present study, the last drain was removed during postoperative hospitalization in all cases. Thus, our study approach ensured that the POPF healing time was closely monitored after the DP.

To our knowledge, the present study was the first to examine the clinical impact of inflammatory and nutritional statuses on the POPF healing time after DP. In the study by Andrianello et al, the only factor investigated related to the inflammatory or nutritional status was the albumin level. Thus, the relationship between the POPF healing time and the inflammatory and nutritional status had not been investigated thoroughly.

To assess the clinical relevance of the results from our study, it is important to consider whether clinical advantages could be obtained from a shortened POPF healing time after DP. We considered that a shortened POPF healing time provided three definite clinical advantages. First, a shorter healing time could reduce the risk of postoperative complications secondary to POPF, such as intra-abdominal abscesses, pseudoaneurysms associated with post-pancreatectomy hemorrhage, and postoperative mortality. Second, a shorter healing time could reduce the cost of POPF treatments. Third, a shorter POPF healing time could reduce the delay in starting postoperative adjuvant therapy in patients with pancreatic cancer, where adjuvant chemotherapy is strongly recommended, due to the postoperative prognosis.[26-28]

Taken together, our findings suggested that these advantages might potentially be gained by improving the inflammatory and nutritional status in patients that develop POPF. Indeed, previous studies showed that improving the nutritional status could reduce the incidence of POPF.[5,29,30] Therefore, comprehensively improving nutritional status might be important for both the prevention and healing of POPF. This hypothesis requires prospective validation in future studies.

The present study had some limitations. First, as mentioned above, it remains unclear why the NLR was significantly associated with the POPF healing time in cases after DP. Clarifying the mechanism underlying the shorter POPF healing time in the NLR ≤2.1 group would help improve the surgical outcomes of DP. Second, we did not clarify the reason for the inconsistency that NLR was significantly associated with the POPF healing time, but there was no significant relationship between the POPF healing time and the other factors potentially associated with the inflammatory or nutritional status. This may be caused by the small-scale patient cohort. A potential explanation for the lack of a relationship between the platelet count and the POPF healing time might be that the platelet counts were influenced by splenic function. Indeed, splenic function was affected by the diseases that were treated with DP. Lastly, our analysis for the identification of factors significantly determining the healing time was performed only with preoperative factors, not intraoperative factors, in order to establish a predictive model with preoperative factors. Actually, we confirmed that several intraoperative factors were insignificant, but considering a possibility that influential factors exist among other intraoperative factors, our results should be validated with other investigations using more intraoperative factors in the future.

In summary, we showed that the POPF healing time after DP was significantly associated with the NLR. The NLR is one of several factors that reflect a patient's inflammatory and nutritional status. These findings suggested that improving patients' inflammatory and nutritional status might shorten the healing time of POPF that occurs after DP.

DISCLOSURE

Conflict of Interest: Authors had no conflict of interests for this article.

Ethical Approval: This study has a retrospective design and is approved by the Institutional Ethics Review Committee (Certificate Number 20466). After an extensive dialogue with the Institutional Ethics Review Committee, patient consent for participation was obtained through an opt-out method.

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