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Chronic Glucocorticoid Use is a Potential Risk Factor for Delayed Pancreatic Fistula after Laparoscopic Distal Pancreatectomy: A Retrospective Analysis

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Pancreatic fistula is a potentially morbid complication after distal pancreatectomy. Chronic glucocorticoid use is one of the risk factors for pancreatic fistula in pancreaticoduodenectomy, though it has not been reported in distal pancreatectomy. We explored whether chronic glucocorticoid use can be a risk factor for pancreatic fistula in distal pancreatectomy. We reviewed 408 consecutive patients who underwent elective distal pancreatectomy from 2011 to 2021. We evaluated two kinds of pancreatic fistula (postoperative pancreatic fistula and delayed pancreatic fistula). We defined delayed pancreatic fistula as a patient who was re-admitted for pancreatic fistula after the first discharge from the hospital. Preoperative characteristics and postoperative outcomes were analyzed. Two hundred sixty-seven patients underwent open distal pancreatectomy, while 141 patients had laparoscopic distal pancreatectomy. A comparison of patient with and without chronic glucocorticoid use showed that only patients with chronic glucocorticoid use developed delayed pancreatic fistula (0% vs. 16.7%; $p < 0.001$). In addition, delayed pancreatic fistula occurred in only laparoscopic distal pancreatectomy patients with chronic glucocorticoid use (0% vs. 25.0%; $p < 0.001$). Although sample size is small, it is reasonable to presume that chronic glucocorticoid use is a potential risk factor for delayed pancreatic fistula in laparoscopic distal pancreatectomy.

Keywords: chronic glucocorticoid use; delayed pancreatic fistula; distal pancreatectomy; laparoscopic surgery; postoperative complication
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Introduction

Distal pancreatectomy (DP) is a standard procedure for benign and malignant conditions of the body and tail of the pancreas. Postoperative pancreatic fistula (POPF) is the most frequent and a potentially morbid complication, which occurs up to 44% in DP patients (Nahm et al. 2018). When a pancreatic fistula becomes severe, it can cause an intraabdominal abscess, delayed gastric emptying, and postoperative bleeding (Fujino 2015; Sell et al. 2015). Several risk factors for the occurrence of pancreatic fistula, including smoking and open DP, have been reported (Chong et al. 2021). However, chronic glucocorticoid use has not been reported as a risk factor for POPF in DP, although it was described as one of the risk factors in pancreaticoduodenectomy (Hirono et al. 2020). On the other hand, previous studies showed that glucocorticoid can disturb wound healing and increase wound infections (Cronstein et al. 1992), and chronic glucocorticoid use was found to be relevant in the increase of surgical complications and poorer outcomes (Chouairi et al. 2019).

There is one more kind of pancreatic fistula, called delayed pancreatic fistula, which is a rare postoperative complication and limited in case reports. Previous case reports employed the terms delayed pancreatic fistula, occult pancreatic fistula and late pancreatic fistula when referring to a patient who initially did not appear to have pancreatic fistula in the perioperative period, but who

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developed it weeks to months after an operation (Veillette et al. 2008; Ito et al. 2011; Perez et al. 2016; Holsing et al. 2020; Jena et al. 2021). Because of its rarity, previous studies have not assessed delayed pancreatic fistula after DP.

In this study, we retrospectively explored whether chronic glucocorticoid use can be a risk factor for pancreatic fistulas in DP.

Methods

We reviewed 408 consecutive patients who underwent elective DP from 2011 to 2021. From the electronic database collected prospectively in our institution, preoperative characteristics and postoperative outcomes including age, sex, the postoperative complications, POPF and delayed pancreatic fistula were retrospectively analyzed. There were no specific exclusion or inclusion criteria. All surgeries were performed by trained and experienced surgeons. In terms of the closure of the pancreatic remnant, stapler closure was usually used in laparoscopic distal pancreatectomy (LDP), while a hand-sewn stump closure was employed for open DP. In LDP, if needed, we sometimes performed a hand-sewn stump closure, in cases with a hard pancreas, a thick pancreatic parenchyma at the transection line, and an additional pancreatic transection due to a positive cut of the end margin. The study protocol was approved and reviewed by the Ethics Committee of Tohoku University Hospital (approval number: 2022-1-245). As this study was a retrospective study, informed consent was waived.

POPF was identified according to the International Study Group of Pancreatic Surgery (ISGPS) definitions, that is, Grade B, a symptomatic fistula requiring therapeutic intervention such as antibiotics and percutaneous drainage; Grade C, a symptomatic fistula associated with a severe general condition of patients, sepsis, and multiorgan failure requiring aggressive treatment in an intensive care unit and surgical intervention (Bassi et al. 2017). In this study, we defined a delayed pancreatic fistula as when a patient who was re-admitted for pancreatic fistula after the first discharge from the hospital. Chronic glucocorticoid use was defined when a patient who was given glucocorticoid for comorbidities for at least one month. Data are shown as mean ± standard error of the mean (SEM). Comparisons of categorical variables were analyzed by two-tailed Student's t test and comparisons of continuous data were analyzed by either chi-square test or Wilcoxon test according to the result of Shapiro-Wilk test. Statistical significance was defined as $p < 0.05$. Statistical analyses were carried out with JMP software (SAS Institute Inc., Cary, NC, USA).

Results

Of these 408 patients, 216 were male and the mean age was 62.5 (Table 1). Two hundred sixty-seven patients underwent open DP, while 141 patients had LDP. The development rates of POPF (Grade ≧ B) and delayed pancreatic fistula were 22.8% and 0.7%, respectively. In a comparison between patients with and without chronic glucocorticoid use, there was no statistical difference in age and sex (Table 2). LDP patients were higher in chronic glucocorticoid use patient. In terms of short-term outcomes, postoperative complications (Clavien-Dindo classification ≧ III) did not occur in the patients with chronic glucocorticoid use. Although the development of POPF (Grade ≧ B) did not differ, chronic glucocorticoid use was significantly associated with delayed pancreatic fistula (0% vs. 16.7%; $p < 0.001$). Even though it has been reported that chronic glucocorticoid use is relevant to infection, the development rate of surgical site infection showed no difference.

As open DP and LDP had differences in their procedures, we further evaluated the relationship between chronic glucocorticoid use and pancreatic fistula in open DP and LDP, respectively. Patients with chronic glucocorticoid use were as follows; open DP: 6 cases (2.2%), LDP: 12 cases (8.5%). In open DP, all the valuables showed no differences. Contrary to our expectations, there were no significant difference between the groups in perioperative out-

Table 1. Patients' characteristics and postoperative outcomes.

	n = 408
Age (years, mean ± SEM)	62.5 ± 0.7
Male, n (%)	216 (52.9%)
Chronic steroid use, n (%)	18 (4.4%)
LDP, n (%)	141 (34.6%)
Stapler closure, n (%)	274 (67.2%)
Operation time (min., mean ± SEM)	356 ± 5.7
Blood loss (ml, mean ± SEM)	657 ± 43.7
Postoperative hospital stay (days, mean ± SEM)	24.3 ± 1.1
Postoperative complication (Clavien-Dindo classification ≧ III), n (%)	94 (23.0%)
POPF (Grade ≧ B), n (%)	93 (22.8%)
Delayed pancreatic fistula, n (%)	3 (0.7%)
Surgical site infection, n (%)	89 (21.9%)

LDP, laparoscopic distal pancreatectomy; POPF, postoperative pancreatic fistula.

comes, and no patient with chronic glucocorticoid use had POPF and/or delayed pancreatic fistula (Table 3). On the other hand, in the LDP group, the patients with chronic glucocorticoid use were significantly older than those without. In addition, the development of delayed pancreatic fistula was increased in the patients with chronic glucocorticoid use (0% vs. 25.0%, $p < 0.001$), although the development of POPF did not show a difference (Table 4). Therefore, only the LDP patients with chronic glucocorticoid use developed delayed pancreatic fistula.

To this end, we explored whether the amount and/or period of glucocorticoid use could affect the development of delayed pancreatic fistula (Fig. 1). Two patients received betamethasone and other patients had prednisolone. The average amount of glucocorticoid per day in the patients with delayed pancreatic fistula was not significantly different from those without delayed pancreatic fistula (Fig. 1A). Both the period of glucocorticoid use and the total amount of glucocorticoid were also comparable between the two groups (Fig. 1B, C). In addition, Fig. 1D did not show a clear relationship between delayed pancreatic fistula and chronic glucocorticoid use.

A summary of the patients who developed delayed pancreatic fistula after DP is shown in Table 5 and Fig. 2. The duration between the presentation of delayed pancreatic fistula and the initial surgery ranged from three to five months. All the patients received conservative therapy and required a long time to be cured. Especially in Case 2, one year and eight months after admission, the patient unfortunately died due to perforation of the transvers colon related to the pancreatic fistula. Although the Case 3 patient was able to be discharged from the hospital after 28 days, he required admission twice for a relapse of the abscess.

Table 2. Comparison of patients' characteristics and postoperative outcomes between patients with and without chronic steroid use after distal pancreatectomy.

	Glucocorticoid (−)	Glucocorticoid (+)	
	n = 390	n = 18	p value
Age (years, mean ± SEM)	66.6 ± 3.5	62.3 ± 0.75	0.238
Male, n (%)	207 (53.1%)	9 (50.0%)	0.798
LDP, n (%)	129 (33.1%)	12 (66.7%)	0.0034*
Stapler closure, n (%)	268 (68.7%)	6 (33.3%)	0.0027*
Operation time (min., mean ± SEM)	356 ± 5.9	349 ± 27.5	0.799
Blood loss (ml, mean ± SEM)	669 ± 44.7	379 ± 208	0.172
Postoperative hospital stay (days, mean ± SEM)	17.6 ± 5.0	24.6 ± 1.1	0.171
Postoperative complication (Clavien-Dindo classification ≧ III), n (%)	94 (24.1%)	0 (0%)	0.018*
POPF (Grade ≧ B), n (%)	91 (23.3%)	2 (11.1%)	0.227
Delayed pancreatic fistula, n (%)	0 (0%)	3 (16.7%)	< 0.001*
Surgical site infection, n (%)	86 (21.1%)	3 (3.4%)	0.585

LDP, laparoscopic distal pancreatectomy; POPF, postoperative pancreatic fistula. *$p < 0.05$.

Table 3. Comparison of patients' characteristics and postoperative outcomes between patients with and without chronic steroid use after open distal pancreatectomy.

	Glucocorticoid (−)	Glucocorticoid (+)	
	n = 261	n = 6	p value
Age (years, mean ± SEM)	65.5 ± 0.78	64.7 ± 5.1	0.865
Male, n (%)	163 (62.5%)	4 (66.7%)	0.833
Stapler closure, n (%)	0 (0%)	0 (0%)	N/A
Operation time (min., mean ± SEM)	333 ± 5.9	317 ± 39	0.675
Blood loss (ml, mean ± SEM)	895 ± 61.1	1,050 ± 401	0.694
Postoperative hospital stay (days, mean ± SEM)	27.1 ± 1.4	17.8 ± 9	0.311
Postoperative complication (Clavien-Dindo classification ≧ III), n (%)	77 (29.5%)	0 (0%)	0.115
POPF (Grade ≧ B), n (%)	64 (24.5%)	0 (0%)	0.164
Delayed pancreatic fistula, n (%)	0 (0%)	0 (0%)	N/A
Surgical site infection, n (%)	61 (23.4%)	1 (16.7%)	0.701

POPF, postoperative pancreatic fistula; N/A, not applicable.

Table 4. Comparison of patients' characteristics and postoperative outcomes between patients with and without chronic steroid use after laparoscopic distal pancreatectomy.

	Glucocorticoid (−)	Glucocorticoid (+)	
	n = 129	n = 12	p value
Age (years, mean ± SEM)	55.8 ± 1.5	67.5 ± 4.8	0.022*
Male, n (%)	44 (34.1%)	5 (41.7%)	0.599
Stapler closure, n (%)	126 (97.8%)	12 (100%)	0.593
Operation time (min., mean ± SEM)	401 ± 12.2	373 ± 40	0.496
Blood loss (ml, mean ± SEM)	27.1 ± 1.4	17.8 ± 9	0.311
Postoperative hospital stay (days, mean ± SEM)	184 ± 20	186 ± 65.7	0.983
Postoperative complication (Clavien-Dindo classification ≧ III), n (%)	17 (13.2%)	0 (0%)	0.18
POPF (Grade ≧ B), n (%)	27 (20.9%)	2 (16.7%)	0.727
Delayed pancreatic fistula, n (%)	0 (0%)	3 (25.0%)	< 0.001*
Surgical site infection, n (%)	25 (19.3%)	2 (16.7%)	0.809

POPF, postoperative pancreatic fistula. *p < 0.05.

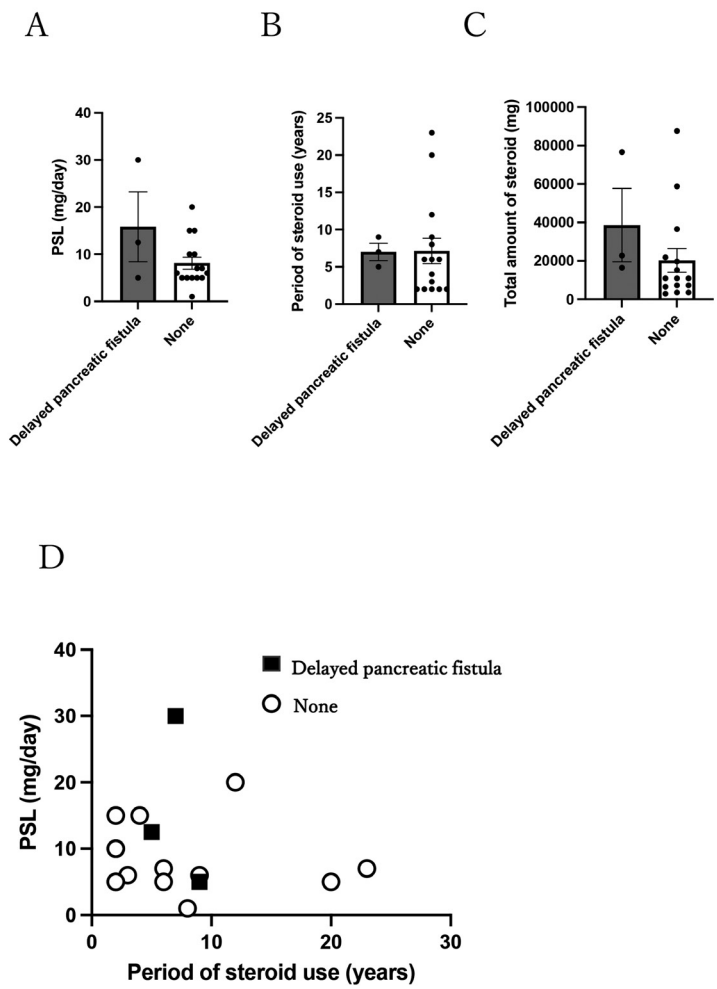

Fig. 1. Comparison between the patients with and without delayed pancreatic fistula in the chronic glucocorticoid use group. (A) Comparison of daily amount of glucocorticoid. (B) Comparison of period of glucocorticoid use. (C) Comparison of total amount of glucocorticoid. Each dot represents data of each patient in (A), (B) and (C). Data in bar graphs are shown as mean ± standard error of the mean (SEM). (D) Evaluation of amount of daily glucocorticoid use and period of glucocorticoid use according to the patients with and without delayed pancreatic fistula. Glucocorticoid was converted to predonisolone by calculation. PSL, predonisolone.

Table 5. Summary of the three cases that developed delayed pancreatic fistula.

	Case 1	Case 2	Case 3
Age	63	70	73
Sex	Female	Female	Male
Disease	IPMN	IPMN	PDAC
Comorbidity for glucocorticoid use	Myelodysplastic syndrome	Adult-onset Still's disease	Rheumatoid arthritis
Period of glucocorticoid use (years)	7	5	9
Duration between presentation of delayed pancreatic fistula and initial surgery (months)	3	4	5
CT findings	Pleural effusiton	Intraabdominal fluid collection	Retroperitoneal abscess
Treatment	Drainage + ENBD + octreotide	Drainage + antibiotics	Drainage + antibiotics
Hospital stay (days)	155	171	28
Outcomes	Alive	Dead	Alive

IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; ENBD, endoscopic nasobilliary drainage.

Discussion

In the present study, we investigated the influence of chronic glucocorticoid use on postoperative outcomes after DP and showed two remarkable findings. First, chronic glucocorticoid use showed an impact on delayed pancreatic fistula, but not on POPF. Second, delayed pancreatic fistula occurred only in patients who underwent LDP. There has been no previous report concerning delayed pancreatic fistula after DP, therefore, this is the first report showing that chronic glucocorticoid use is potentially associated with delayed pancreatic fistula after LDP.

POPF is a critical complication that confers a statistical increase in morbidity and mortality. Many studies had been conducted to identify the risk factors of POPF and how to prevent POPF (Jiang et al. 2016; Kawaida et al. 2019; Iseki et al. 2021; Chong et al. 2021). In contrast, delayed pancreatic fistula is a rare postoperative complication in pancreatic resection, which has been limited to individual case reports. Almost all cases developed delayed pancreatic fistula after pancreaticoduodenectomy. So far, there is only one report showing delayed pancreatic fistula after DP in the setting of acute pancreatitis (Holsing et al. 2020). Because of its rarity, the duration between presentation of delayed pancreatic fistula and initial surgery has yet to be elucidated. Veillette et al. (2008) reported 13 cases of delayed pancreatic fistula after pancreaticoduodenectomy that occurred within 90 days after surgery. On the other hand, in a case reported by Faraj et al. (2010), the interval was seven years, which is the longest. In our cases, the interval ranged from three to five months.

Since it has been reported that chronic glucocorticoid use is one of the risk factors for POPF in pancreaticoduodenectomy (Hirono et al. 2020), we expected chronic glucocorticoid use could have an effect on both POPF and delayed pancreatic fistula in DP. Although chronic glucocorticoid use did not increase the development of POPF and severe postoperative complications (Clavien-Dindo classification $\geqq$ III), only the patients with chronic glucocorticoid use developed delayed pancreatic fistula. These results suggest that chronic glucocorticoid use can affect only long-term outcomes in DP. Previous case reports described that pancreatic duct obstruction, recurrent pancreatitis, ischemia and fibrosis may lead to delayed pancreatic fistula (Faraj et al. 2010). Barreto et al. (2008) discussed how a small initial amount of pancreatic juice that goes unnoticed may become aggravated by infection, which could be the reason for the delayed pancreatic fistula. In Case 1 and 2, the computed tomography (CT) scan before discharge from the hospital showed fluid collection around the pancreatic stump (Fig. 2). Since chronic glucocorticoid use impairs wound healing, as time goes by, the amount of pancreatic juice would be increased. Then, it may get aggravated by infection because glucocorticoid increases the risk of infection. A plausible explanation for the repeated abscess formation in Case 3 would be chronic glucocorticoid use, as well.

As LDP and open DP involve different procedures, we next explored the relation between chronic glucocorticoid use and delayed pancreatic fistula in open DP and LDP, respectively. Regarding the difference between LDP and open DP, there are two kinds of differences. The first one is the closure of the pancreatic stump and the second one is that laparoscopic surgery can reduce the adhesion of intrabdominal structure (Krielen et al. 2020). Although previous studies have shown that stapler closure is not inferior in POPF to a hand-sewn closure (Kleeff et al. 2007; Diener et al. 2011; Ban et al. 2012), they did not assess the long-term outcomes such as delayed pancreatic fistula. Therefore, we can speculate that stapler closure could increase the delayed pancreatic fistula. Since it is well known that pancreatic injury while stapling can lead to POPF, pancreatic injury may occur easily in the patients with chronic glucocorticoid use. In addition, there is a second speculation about the

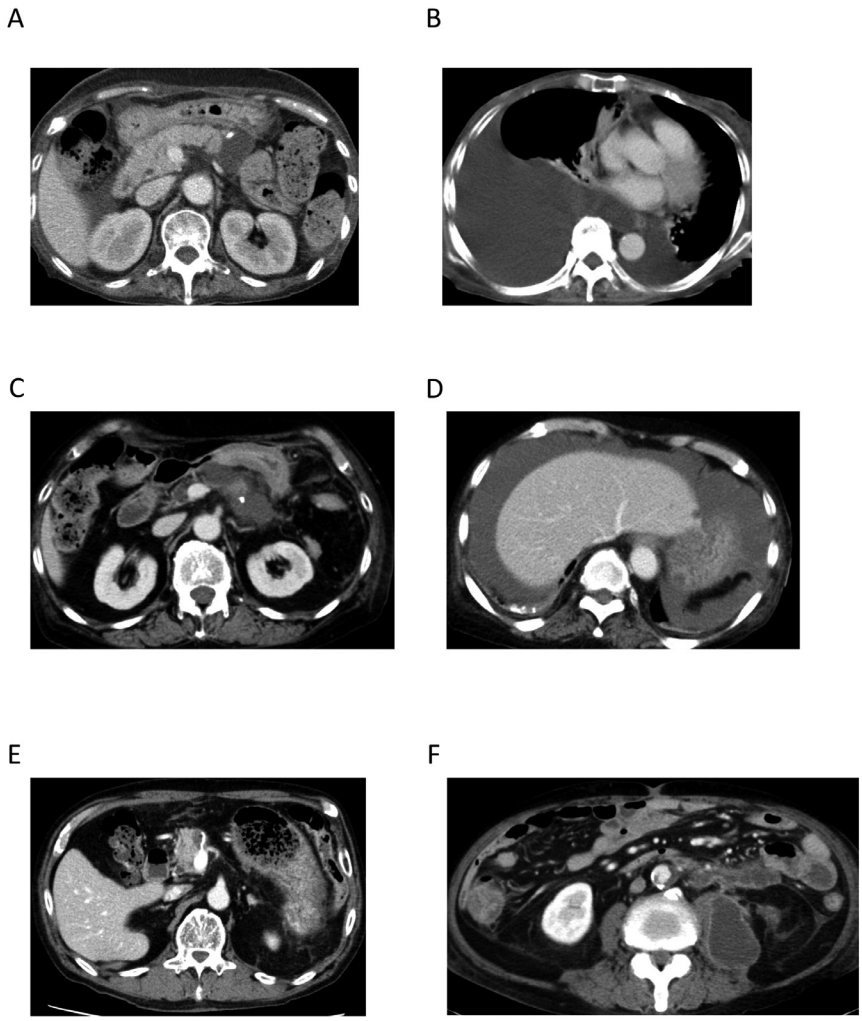

Fig. 2. CT scan before discharge hospital and at the onset of delayed pancreatic fistula.
(A) Case 1, before hospital discharge. Fluid collection around pancreatic stump was detected. (B) Case 1, onset of delayed pancreatic fistula. Massive pleural effusion was detected. (C) Case 2, before hospital discharge. Fluid collection around pancreatic stump was detected. (D) Case 2, onset of delayed pancreatic fistula. Massive ascites was identified. (E) Case 3, before hospital discharge. POPF was cured before hospital discharge. (F) Case 3, onset of delayed pancreatic fistula. Retroperitoneal abscess was developed.

reason why only LDP developed delayed pancreatic fistula. As laparoscopic surgery can reduce the adhesion of the intrabdominal structure, an LDP patient may not be able to form an adhesion, which likely prevents pancreatic juice from spreading. This may be one of the reasons why pancreatic juice can easily increase.

Glucocorticoid impairs wound healing through the delayed appearance of inflammatory cells, fibroblasts, collagen, regenerating capillaries and epithelial migration (Harvey et al. 1974; Fauci et al. 1976; Furst et al. 1994). In an animal model, it has been reported that glucocorticoid significantly impaired colonic anastomosis in a dose-dependent manner (Dostal and Gamelli 1990). In addition, Iguchi et al. (2013) showed that a high dose of glucocorticoid increased the development of postoperative complications. Therefore, we next explored the relationship between the amount of glucocorticoid and delayed pancreatic fistula. However, we were not able to find a clear relationship between the amount of glucocorticoid and delayed pancreatic fistula. As we have only three cases that developed delayed pancreatic fistula, further investigation with larger number of cases is required.

In terms of the treatment, conservative therapy was employed in most case reports. In our cases, we chose conservative treatment as well, but a long term was needed for recovering. Especially, in Case 2, the patient developed a transverse colon fistula that we could not rescue. Although we offered surgical treatment, the family refused because she had severe dementia and her general condition was not good due to a long hospital stay. As she had a massive intraabdominal fluid collection at admission, we should have chosen surgical drainage to rescue. We should keep in mind that delayed pancreatic fistula with chronic glucocorticoid use is hard to control.

This study has some limitations. Firstly, our study was retrospective and had a relatively small sample size. Secondly, there might be several confounding factors in this study because we mainly analyzed correlations between chronic glucocorticoid use and pancreatic fistula. In addition, a selection bias existed. Although we analyzed the data statistically, the population of delayed pancreatic fistula is very small and we need a further investigation with larger data.

Despite the above limitations, it is reasonable to presume chronic glucocorticoid use is a potential risk factor for delayed pancreatic fistula in LDP. If a patient with chronic glucocorticoid use develops delayed pancreatic fistula, a prompt response is required, which may prevent worse complications. We should note that a delayed pancreatic fistula is difficult to cure with conservative therapy and we need to choose other treatment options such as surgical drainage if it does not work.

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Conflict of Interest

The authors declare no conflict of interest.

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