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RESEARCH

Postoperative pancreatic fistula is higher in patients with necrotizing pancreatitis who develop a colon-transverse fistula

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Abstract

Background This study explores the association between the need for open necrosectomy (ON) during infected necrotizing pancreatitis (INP) treatment and the development of postoperative pancreatic fistula (POPF) following definitive surgery (DS) for transverse colonic fistulas.

Materials and methods This study was conducted at two tertiary hospitals and included patients who underwent DS for colonic fistula secondary to INP from January 2009 to December 2023. Patients were followed until hospital discharge. The primary outcome was the incidence of POPF.

Results A total of 135 patients were included. The median age was 38 years (interquartile range [IQR]: 32–44 years), with 85 (62.9%) being male. ON was required in 52 patients (38.5%), with 24 patients developing POPF post-DS. The need for ON (odds ratio [OR] = 2.78, 95% confidence interval [CI]: 1.03–7.58, $p = 0.040$) and the interval from INP resolution to DS (OR = 0.82, 95% CI: 0.68–0.92, $p = 0.011$) were associated with POPF.

Conclusion The need for ON during INP treatment is significantly associated with an increased risk of POPF following DS for transverse colonic fistulas.

Keywords Pancreatic fistula · Colon fistula · Surgery · Infected necrotizing pancreatitis · Outcomes

Introduction

Infected necrotizing pancreatitis (INP) is a severe form of acute pancreatitis characterized by inflammation and tissue necrosis, which becomes secondarily infected [1]. The development of colonic fistulas in patients with INP is a serious complication, occurring in up to 3–20% of cases [2–4]. One hypothesis posits that ischemic necrosis of the colon, resulting from mesocolon involvement, leads to the formation of colonic fistulas [5]. The mesocolon may be affected during INP due to its attachment along the long axis of the body and tail of the pancreas, allowing inflammation to spread along the mesocolon, especially in severe cases of INP [6, 7]. Chi et al. [8] demonstrated that mesocolon involvement correlates with the severity of INP.

Anatomically, there is a natural gap between the pancreas and the mesentery of the transverse colon [9]. Corrosion of the mesentery by the pancreas suggests that inflammation and necrosis have breached this gap [9]. Additionally, the transverse mesentery may contract, fuse with the pancreatic dorsal membrane, and form a scar [10]. Definitive surgery

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(DS) for transverse colonic fistula requires separating tissue contracted by prior necrosis between the colon, mesentery, and pancreas. In principle, the severity of mesenteric necrosis caused by pancreatitis directly correlates with surgical difficulty. This increased severity heightens the risk of pancreatic injury during DS for transverse colonic fistula, potentially leading to postoperative pancreatic fistula (POPF).

According to the step-up approach for INP, when puncture drainage or minimally invasive drainage fails to control the infection, open necrosectomy (ON) becomes necessary [11]. The need for ON during INP treatment suggests more extensive pancreatic necrosis and scarring, which may complicate subsequent surgeries and increase the risk of pancreatic injury during mesentery separation. Consequently, we hypothesize that patients with transverse colonic fistulas who require ON during the INP treatment are at higher risk for developing POPF after transverse colonic fistula resection.

Materials and methods

This study was conducted at two tertiary hospitals and approved by the Ethics Committee of Jinling Hospital. It adhered to the STROCSS criteria [12], and all methods were performed in accordance with relevant guidelines and regulations.

Population and grouping

From January 2009 to December 2023, patients who underwent DS for transverse colonic fistula following INP were considered eligible for inclusion. The exclusion criteria were: (1) patients younger than 18 years of age; (2) patients with an upper gastrointestinal fistula that could complicate the surgery; and (3) patients with a pre-existing pancreatic fistula. Patients were followed until hospital discharge. Postoperative pancreatic fistula (POPF) was defined according to the 2016 update of the International Study Group (ISGPS) criteria [13], as a measurable volume of drain fluid on or after postoperative day 3 with an amylase level > 3 times the upper limit of normal. Patients were divided into ON group or non-ON group based on whether ON was required. The primary outcome was POPF after DS, and the secondary outcome included postoperative morbidity, mortality, and length of hospital stay after DS.

Treatment of transverse colon fistula

The Interval from INP diagnosed to colonic fistula occurrence was 44 days (IQR:37–53days). A loop ileostomy was the first-line approach for inadequate source control in patients with colonic fistulas. During this procedure, the small intestine was extracted approximately 20 cm from the ileocecal area and fixed to the abdominal wall. If pancreatitis had not resovled and required ON, the procedure was performed in conjunction with the ileostomy. Colonic fistula resection or colostomy was not planned due to the increased risk associated with peripheral necrosis and tissue contraction during the ON process. In cases with adequate source control, the timing of DS was the main consideration for colonic fistula management (Fig. 1).

DS was scheduled at least three months after the pancreatitis resolution. Due to prior pancreatic necrosis, the mesentery of the colon often becomes corroded and fixed to the, eliminating any natural gaps. During DS, the colon was separated from the retroperitoneal tissue via blunt or sharp separation. The colonic fistula was locally resected, and the ileostomy was closed. During DS, the colon was carefully

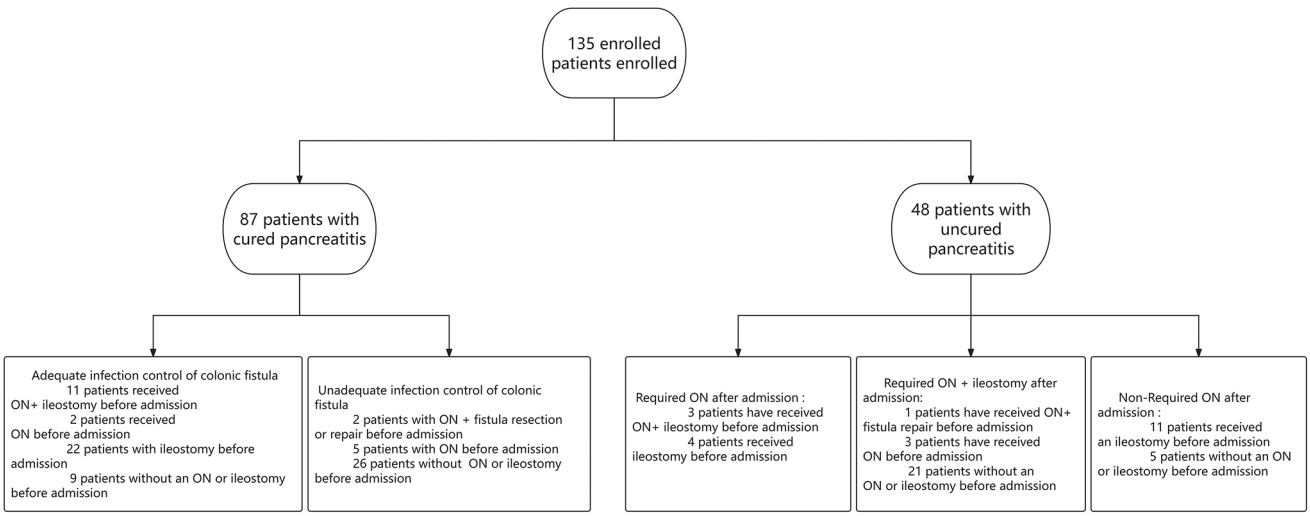

Fig. 1 The treatment process of transverse colon fistula

separated from the retroperitoneal tissue using either blunt or sharp dissection. The colonic fistula was locally excised, and the ileostomy was subsequently closed. The 10 cm segment of the colon around the fistula was isolated, and the remaining mesentery was preserved. The colon was then excised and anastomosed at least 5 cm above and below the fistula opening, on the inner side of the vascular arch. A latero-lateral end anastomosis was performed using a linear stapler (Pride Medical Inc., Jingjiang, Taizhou, Jiangsu, China) to close the colonic fistula. Hyperglycemia was defined as a blood glucose level greater than 10 mmol/L during hospitalization, necessitating short-term insulin therapy.

Postoperative drainage tube and amylase

A drainage tube was placed below the colonic anastomosis, and amylase levels in the drainage fluid were measured 48 h after DS. At this time, the absence of intestinal fluid in the drainage tube was noted. Elevated amylase content in the drainage fluid was considered indicative of POPF. If amylase levels exceeded three times the normal value, they were measured weekly. The drainage tube was removed when amylase levels fell below three times the normal value, drainage volume was less than 50 ml/day, and colonic anastomotic leakage was excluded via postoperative colonography. Continuous amylase measurement was not performed in cases with postoperative anastomotic leakage, as the presence of amylase in intestinal contents could complicate the diagnosis and monitoring of pancreatic fistula.

Data analysis

Baseline data included patient demographics (sex, BMI, age) and laboratory test results (hemoglobin and albumin) collected upon admission. The location of the fistula was determined using colonography, while computed tomography (CT) was employed to assess the location and proximity of the anastomosis. Colonic patency was evaluated using colonoscopy, with endoscopic colonic stenosis defined as the inability to pass the colonoscope through the colon. Laboratory tests were performed daily for seven days following DS, and results were analyzed. Statistical analyses were performed using SPSS 26.0 software (IBM, Analytics, Armonk, NY, USA). The Mann–Whitney U-test was used to compare continuous variables across groups, while Fisher's exact test was used to compare categorical variables. Multivariate logistics regression was employed to analyze confounding variables. A p-value of <0.05 was considered statistically significant.

Table 1 ON in the 52 patients

Surgical process before admission, No.(%)	Total NO.	Surgical process after admission, No		
		ON	ileostomy	ON + ileostomy
ON				
Colonic fistula detected prior to ON				
ON + fistula resection or repair	3		2	1
ON + ileostomy	5	1		
Colonic fistulas detected after ON				
ON + subsequent ileostomy	9	2		
ON	10		5	3
Ileostomy	4	4		
None	21			21

Results

Population and treatment process before DS

The study initially identified 179 patients with transverse colon fistula following INP who underwent DS.After applying exclusion criteria, 135 patients were included in the final analysis. Exclusions comprised 4 patients under 18 years of age, 21 patients with duodenal fistula, and 19 patients with pancreatic fistula before DS. Of the 135 patients, 87 had resolved pancreatitis prior to admission. Among these, 54 did not require surgical intervention before DS, while 33 underwent an ileostomy. Of the 48 patients with unresolved pancreatitis on admission, 7 underwent ON, and 25 received ON with ileostomy post-admission.

In total, 52 patients who required ON, either before or after admission, were allocated to the ON group, with the remaining 83 forming the non-ON group. Table 1 provides a detailed breakdown of surgical procedures for the ON group. Of the 27 patients who underwent ON before admission, 8 developed colonic fistula prior to ON: 5 required an additional ileostomy, and 3 underwent fistula resection or repair during ON, resulting in subsequent recurrent fistulas. In 19 patients, colonic fistula was detected post-ON, with 9 receiving subsequent ileostomy. Among the 27 patients with pre-admission ON, 4 underwent additional ON, 7 received ileostomy, and 4 had ON with ileostomy after admission. Of the 25 patients without prior ON, 4 had ileostomy upon admission, followed by ON. The remaining 21 patients, who had not undergone any surgical procedures before admission, received both ON and ileostomy post-admission.

Characteristics

The median age of participants was 38 years (interquartile range [IQR]: 32–44 years), with a median BMI of 22.6 kg/m² (IQR: 21.3–24.1 kg/m²). Males constituted 62.9% ($n=85$)

of the study population. The etiology of INP included cholelithiasis ($n=68$), hyperlipidemia ($n=59$), and alcoholism ($n=8$). Fistulas were primarily located in the left transverse colon fistula ($n=118$ [87.4%], Table 2). Patients requiring ON had longer intervals from INP resolution to DS, longer DS durations, greater blood loss during DS, and higher amounts of albumin infused during and within 48 h after DS (Table 2).

Primary outcome

POPF was detected in 42 patients (24 among patients with ON [46.2%] and 18 among patients without ON [21.7%]). Unadjusted regression analysis for POPF is presented in Table 3. Patients who developed POPF after DS had a higher rate of previous ON implementation (57.1% vs. 30.1%, $p=0.003$), a longer duration of INP (17 weeks [IQR: 12–23] vs. 15 weeks [IQR: 12–22], $p=0.04$), significantly greater intraoperative blood loss (1700 mL [IQR: 1200–1800] vs. 1400 mL [IQR: 1100–1600], $p=0.02$), and received more albumin (80 g [IQR: 60–110] vs. 70 g [IQR: 50–90], $p=0.003$) both during and within 48 h after DS. Adjusted logistic regression revealed that ON (odds ratio [OR] = 2.78, 95% confidence interval [CI]: 1.03–7.58, $p=0.04$, Table 4) was associated with POPF after DS. Another significant factor was the interval from INP resolution to DS (OR = 0.82, 95% CI: 0.68–0.92, $p=0.01$, Table 4).

Monitoring of POPF

Among the 42 patients with POPF, only 4 patients received pancreatic duct stent implantation due to POPF connecting with the Wirsung duct, as identified by endoscopic retrograde cholangiopancreatography (ERCP). The 90.5% patients ($n=38$) showed no sign of contrast agent overflowing from the pancreatic duct.

Drainage fluid amylase levels (2828 U/L [IQR: 1914–2993 U/L] vs. 1501 U/L [IQR: 870–2200 U/L] vs. 900 U/L [IQR: 296–1430 U/L]; $p<0.001$) and drainage fluid volume (400 mL [IQR: 300–450 mL] vs. 200 mL [IQR: 150–200 mL] vs. 80 mL [IQR: 50–100 mL]; $p<0.001$) among the 42

Table 2 Baseline characteristics of enrolled patients

	Total ($n=135$)	ON ($n=52$)	None ON ($n=83$)	p
Male, No.(%)	85 (62.9)	32 (61.5)	53 (63.9)	0.78
Age, year; (median, IQR)	38 (32–44)	38 (32–46)	39 (33–44)	0.79
Preoperative BMI, kg/m2,(median, IQR)	22.6 (21.3–24.1)	22.3 (21.1–24.2)	22.4 (21.5–23.9)	0.68
Etiology of INP, No.(%)				0.59
Cholelithiasis	68 (50.4)	29 (55.8)	39 (47)	
Hyperlipidemic	59 (43.7)	20 (38.4)	39 (47)	
Alcoholic	8 (5.9)	3 (5.8)	5 (6)	
Endoscopic colonic stenosis around fistula, No.(%)	28 (20.7)	14 (26.9)	14 (16.9)	0.16
Location, No.(%)				0.18
Left transverse colon fistula	112 (82.9)	46 (88.5)	66 (79.5)	
Right transverse colon fistula	23 (17.1)	6 (11.5)	17 (20.5)	
Duration of treatment of INP, weeks, (median, IQR)	16 (12–23)	19 (14–27)	15 (11–22)	0.02
Interval from INP diagnosed to fistula occurrence, days, (median, IQR)	44 (37–53)	41 (35–53)	46 (37–54)	0.27
Interval from INP cured to DS, weeks, (median, IQR)	11 (9–13)	11 (10–14)	10 (9–13)	0.02
Preoperative albumin, g/L, (median, IQR)	38 (36–41)	39 (36–41)	38 (37–40)	0.42
Preoperative hemoglobin, g/L, (median, IQR)	127 (121–135)	125 (119–132)	127 (122–135)	0.34
Blood loss during DS, ml, (median, IQR)	1500 (1100–1700)	1600 (1200–2000)	1400 (1100–1800)	0.02
Duration of DS, min, (median, IQR)	210 (170–240)	220 (170–250)	200 (160–240)	0.03
The amount of red blood cells infused during and within48 hours after DS*,Unit, (median, IQR)	7 (6–9)	8 (6–10)	7 (6–9)	0.14
The amount of albumin infused during and within48 hours after DS**, g.(median, IQR)	80 (60–90)	90 (70–100)	70 (60–90)	<0.001
Comorbidity, No.(%)				
Hypertension	4 (2.9)	2 (3.8)	2 (2.4)	0.63
Hyperglycemia	58 (42.9)	26 (50)	32 (38.6)	0.19

*In order to maintain the Hemoglobin > 100 g/L within 48 h after surgery

**In order to maintain the Albumin > 30 g/L within 48 h after surgery

Table 3 unadjusted analysis for POPF

	POPF ($n=42$)	Non POPF ($n=93$)	p
ON during the process of pancreatitis, No.(%)	24 (57.1)	28 (30.1)	0.003
Male, No.(%)	28 (66.7)	57 (61.3)	0.55
Age, year; (median, IQR)	40 (35–44)	37 (32–44)	0.17
Preoperative BMI, kg/m2,(median, IQR)	22.7 (21.1–24.7)	22.6 (21.4–24.1)	0.73
Etiology of INP, No.(%)			0.50
Cholelithiasis	22 (52.4)	46 (49.5)	
Hyperlipidemic	19 (45.2)	40 (43)	
Alcoholic	1 (2.3)	7 (7.5)	
Endoscopic colonic stenosis around fistula, No.(%)	12 (28.6)	16 (17.2)	0.13
Location, No.(%)			0.12
Left transverse colon fistula	38 (90.5)	74 (79.6)	
Right transverse colon fistula	4 (9.5)	19 (20.4)	
Duration of INP, weeks, (median, IQR)	15 (12–23)	16 (12–22)	0.14
Interval from INP diagnosed to fistula occurrence, days, (median, IQR)	41 (34–53)	47 (38–54)	0.21
Interval from INP cured to DS, weeks, (median, IQR)	10 (9–12)	11 (9–14)	0.04
Preoperative albumin, g/L, (median, IQR)	39 (37–41)	38 (36–40)	0.35
Preoperative hemoglobin, g/L, (median, IQR)	128 (120–135)	127 (121–134)	0.81
Blood loss during DS, ml, (median, IQR)	1700 (1200–1800)	1400 (1100–1600)	0.001
Duration of DS, min, (median, IQR)	220 (180–240)	210 (170–240)	0.27
The amount of red blood cells infused during and within48 hours after DS*,Unit,.(median, IQR)	8 (6–9)	7 (6–9)	0.15
The amount of albumin infused during and within48 hours after DS**, g.(median, IQR)	80 (60–110)	70 (50–90)	0.003
Comorbidity, No.(%)			
Hypertension	2 (4.7)	2 (2.2)	0.41
Hyperglycemia	22 (52.3)	36 (38.7)	0.14

*In order to maintain the Hemoglobin > 100 g/L within 48 h after surgery

**In order to maintain the Albumin > 30 g/L within 48 h after surgery

Table 4 Adjusted logistic regression for POPF

	OR	95% CI	p	Variance inflation factor
ON during the process of pancreatitis	2.78	1.03–7.58	0.04	1.67
Interval from INP cured to DS	0.82	0.68–0.92	0.01	1.15
Blood loss during DS	1.00	0.99–1.00	0.48	1.74
The amount of albumin infused during and within48 hours after DS*	1.01	0.99–1.03	0.14	1.29

*In order to maintain the Albumin > 30 g/L within 48 h after surgery

patients decreased on the 3rd, 7th, and 14th day after DS, respectively (Fig. 2A and B).

Secondary outcomes

Twenty-one (50%) of the 42 POPF patients experienced colonic anastomotic leakage, which was also present in an additional 7 patients without POPF. Among the remaining 21 patients who developed POPF associated with colonic anastomotic leakage, 8 underwent ileostomy post- DS, with successful closure of colonic leakage observed in 6 of these cases (the rest 2 received another DS). Spontaneous closure of colonic leakage was observed in 3 out of the remaining 13 patients (10 patients received another DS, and the remaining 3 patients received a colostomy). Of the 7 patients without a POPF who experienced colonic anastomotic leakage, 4 received an ileostomy with successful closure of colonic leakage in all cases, 2 had a spontaneous closure, and 1 patient received a colostomy.

Patients who underwent ON had a longer length of stay compared to those without ON (19 days [IQR: 14–34 days] vs. 16 days [IQR: 16–19 days], $P=0.003$).

Discharge within 30 days after surgery was detected in 106 patients (72 in non - ON group, and 34 in the ON group). Adjusted Cox regression analysis revealed that ON was a risk factor for delayed discharge within 30 days after

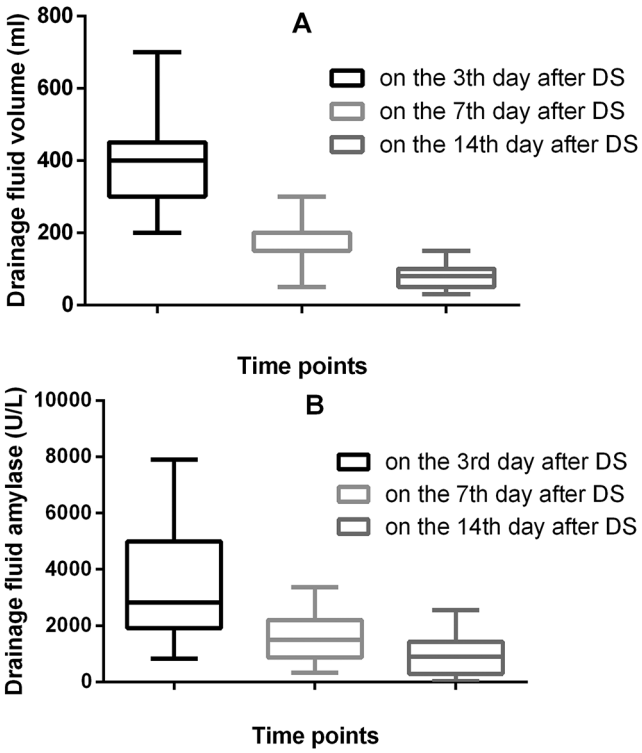

Fig. 2 **A**. Drainage fluid volume at different time point. **B**. Drainage fluid amylase at different time point

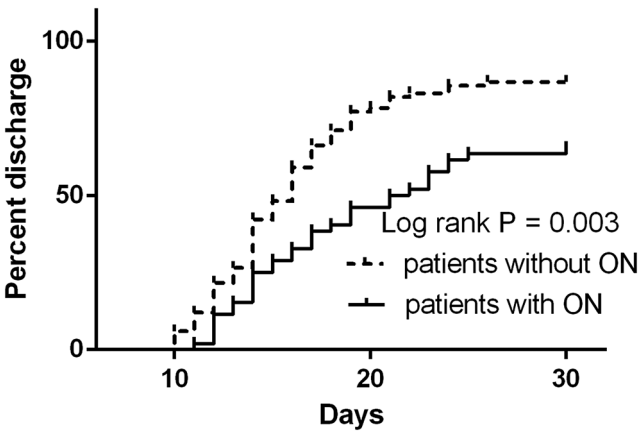

Fig. 3 The length of stay after DS

DS (Hazard ratio[HR] = 0.62; 95% CI: 0.46–0.92; $P = 0.003$, Fig. 3).

Discussion

This study investigated the risk factors associated with POPF following DS for transverse colonic fistulas caused by INP. Our primary finding was that patients who underwent ON as a part of INP treatment were significantly more likely to develop POPF after DS. Additionally, a longer interval between INP resolution and colonic fistula resection was associated with a reduced risk of developing POPF. These findings highlight the complexity of managing colonic complications in patients with severe INP and underscore the influence of surgical approaches and timing on postoperative outcomes.

Colonic fistulas in INP patients represent a serious complication, reflecting the severity of the condition [14]. Colon ischemic necrosis, secondary to mesocolon involvement, leads to colonic fistulas formation [5]. Chi et al. [8] demonstrated that mesocolon involvement correlates with the severity of INP. Histologically and embryologically, the transverse colon and pancreas develop from distinct distinct origins. The transverse colon originates from the midgut, while the pancreas arises from the foregut, and a natural fusion gap exists between them. When pancreatic necrosis during INP invades the mesentery of the colon, it disrupts the blood supply to the transverse colon, indicating severe pancreatic necrosis and rapid disease progression. After extensive local necrosis and inflammatory response associated with INP, fibrous tissue forms thick and distorted scars around the pancreas [15]. The transverse colon mesentery may also contract following corrosion and necrosis. The destruction of the fusion fascia during INP leads to scar formation in the mesentery of the transverse colon, causing it to adhere to surrounding tissues and resulting in a lack of normal tissue space fixation.

In the context of the step-up approach for INP, when ON is necessary, it indicates more severe and widespread pancreatic tissue necrosis [16]. During DS for colonic fistulas, the adhesions between the colonic mesentery and pancreatic tissue are more severe, with the dorsal pancreas potentially merging with the colonic mesentery or even the colonic serosa. Separating the colon from these adhesions often damages the pancreas, leading to the development of postoperative POPF. Several mechanisms explain why ON increases the risk of POPF. First, ON involves the removal of necrotic pancreatic tissue, which exacerbates local inflammation. As noted by Trikudanathan et al. [17], aggressive surgical debridement in severe acute pancreatitis often results in significant postoperative complications. Brunschot et al. [18] showed that extensive necrosectomy can lead to considerable tissue damage and complications, supporting this hypothesis. Bugiantella et al. [19] also emphasized the challenges in surgically managing pancreatic and peripancreatic necrosis. Additionally, severe scarring and fibrosis following ON result in dense adhesions between the pancreas, mesocolon, and surrounding tissues. These adhesions complicate the safely separation the colon from the pancreas during DS for colonic fistulas, increasing the risk of pancreatic injury and subsequent POPF.

The protective effect of a longer interval between INP resolution to DS can be attributed to reduced inflammation and stabilization of necrotic tissues over time. Allowing sufficient time for inflammation to subside and tissues to heal minimizes intraoperative injury and complications. The World Society of Emergency Surgery guidelines [20] recommend delaying surgical intervention until inflammation has subsided, which leads to better outcomes and fewer complications.

One key limitation of this study is its relatively small sample size, which may limit the generalizability of the results. A larger sample would provide more statistical power and enable more nuanced analyses. Additionally, the participants were young adults with a median age of 36 years, so the results may not be applicable of other age groups. Future research should include more diverse populations. Another limitation is the retrospective design, which prevents the determination of causal relationships or the examination of changes over time. A longitudinal design would provide more insight into the dynamic relationships between the factors studied. Moreover, the study did not control for potential confounding variables, such as socioeconomic status, education level, or prior mental health history, which could influence the observed relationships. Controlling for these factors would help isolate the effects of key variables. Furthermore, the lack of sufficient follow-up made it difficult to assess long-term outcomes. However, given the constraints of retrospective research, addressing this issue is challenging. Further studies are needed to corroborate and expand upon these findings. Another significant limitation is failure to outline the anatomical situation of the pancreatic bed. Meanwhile, notablely, there is no "normal" pancreatic tissue in the affected area. This makes it extremely challenging to fully distinguish and separate the tissues surrounding the pancreas. Consequently, identifying the precise anatomical arrangement of the residual pancreas becomes difficult.

Conclusion

This study identifies significant risk factors for POPF following DS for transverse colonic fistulas in INP patients, highlighting the impact of severe mesocolon involvement and the necessity of ON on postoperative outcomes. The findings underscore the importance of strategic surgical planning and timing in managing these complex cases to minimize complications.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All experimental protocols were approved by Ethics Committee of Jinling Hospital.

Informed consent informed consent was waived by the ethics committee of Jinling Hospital.

Competing interests The authors declare no competing interests.

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