Journal of Gastrointestinal Surgery 29 (2025) 102244

Contents lists available at ScienceDirect

Journal of Gastrointestinal Surgery

journal homepage: www.jogs.org

Original Article

The clinical and microbiological burden of gastrointestinal fistulas in patients with infected pancreatic necrosis: a retrospective study

Haosu Huang [a,b,c], Zefang Sun [c,d,e], Baiqi Liu [c,d,e], Lu Chen [c,d,e], Dingcheng Shen [c,d,e,*]

[a] Department of General Medicine, Xiangya Hospital, Central South University, Changsha, Hunan Province, China
[b] National Medical Metabolomics International Collaborative Research Center, Xiangya Hospital, Central South University, Changsha, Hunan Province, China
[c] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan Province, China
[d] Division of Pancreatic Surgery, Department of General Surgery, Xiangya Hospital, Central South University, Changsha, Hunan Province, China
[e] Division of Hernia and Abdominal Wall Surgery, Department of General Surgery, Xiangya Hospital, Central South University, Changsha, Hunan Province, China

ARTICLE INFO

Article history:
Received 30 August 2025
Received in revised form 24 September 2025
Accepted 4 October 2025
Available online 8 October 2025

Keywords:
Acute pancreatitis
Gastrointestinal fistula
Infected pancreatic necrosis
Mortality
Outcomes

ABSTRACT

Background: Gastrointestinal fistula (GIF) is a well-recognized complication of infected pancreatic necrosis (IPN). However, the evidence on the effect of GIF remains limited. This study aimed to investigate incidence, risk factors, microbiological profiles, and clinical outcomes of GIF in a large cohort of patients with IPN.
Methods: A post hoc analysis was conducted using data from a large prospective database involving 385 patients with IPN between January 2011 and April 2025. A comparative analysis of the clinical and microbiological characteristics, surgical management, and follow-up data was performed for patients with IPN with and without GIF.
Results: Of 385 patients with IPN, 62 (16.1%) developed GIF. Compared with patients without GIF, those with GIF exhibited higher rates of polymicrobial infection (59.4% vs 79.0%, respectively; P =.004), multidrug-resistant fungi (14.9% vs 27.4%, respectively; P =.016), carbapenem-resistant Enterobacteriaceae (CRE; 25.1% vs 40.3%, respectively; P =.014), carbapenem-resistant Klebsiella pneumoniae (CRKP; 32.5% vs 56.5%, respectively; P <.001), and fungal infections (23.2% vs 40.3%, respectively; P =.005). In addition, bloodstream infections from multidrug-resistant organisms and CRE were more common in patients with GIF than in those without GIF (multidrug-resistant organisms: 35.5% vs 15.5%, respectively; P <.001; CRE: 27.4% vs 6.5%, respectively; P <.001). GIF development was associated with more frequent adoption of open necrosectomy (35.5% in the GIF group vs 14.9% in the non-GIF group; P <.001), longer duration of organ failure (median: 10.5 days in the GIF group vs 3.0 days in the non-GIF group; P =.048), higher incidence of severe acute pancreatitis (69.4% in the GIF group vs 55.1% in the non-GIF group; P =.038), prolonged hospital stay (median: 96.0 days in the GIF group vs 75.5 days in the non-GIF group; P =.007), and an increased hemorrhage rate (35.5% in the GIF group vs 18.6% in the non-GIF group; P =.003). In addition, mortality was significantly higher in patients with GIF than in those without GIF (22/62 [35.5%] vs 70/323 [21.7%]; P =.019). Multivariate analysis revealed multiple organ failure (MOF) as an independent predictor of mortality in patients with GIF (odds ratio, 27.97 [95% CI, 2.35–332.89]; P =.008).
Conclusion: GIF affected 16.1% of patients with IPN and was associated with adverse outcomes. MOF predicted higher mortality for patients with IPN and GIF. CRE, particularly CRKP, is a crucial pathogen that requires urgent attention.

Introduction

Acute pancreatitis (AP) is a common gastrointestinal (GI) disease in clinical practice [1]. Of note, 10% to 30% of cases progress to acute necrotizing pancreatitis (ANP), which results in varying degrees of necrosis of the pancreatic parenchyma and/or peripancreatic tissue and severe local or systemic complications [2,3]. Patients with ANP may experience a complex, prolonged clinical course, and approximately one-third of these individuals develop infected pancreatic necrosis (IPN), resulting in elevated mortality [4].

A GI fistula (GIF) is a delayed complication secondary to necrotizing pancreatitis [5]. The fistula may involve the stomach, duodenum,

* Corresponding author.
E-mail address: shendingcheng@csu.edu.cn (D. Shen).

https://doi.org/10.1016/j.gassur.2025.102244
1091-255X/

jejunum, ileum, or colon, occurring concurrently or separately [6]. It may result from the direct erosion of digestive enzymes released by the inflamed pancreas on the adjacent GI tract or induced by vascular thrombosis–associated intestinal necrosis at an inflammation or infection site [7]. In addition, GIF may be associated with surgical interventions [8,9]. Although previous studies have suggested that fistulas of the GI tract are rare in patients with AP, IPN and operative management for IPN could increase the frequency [10].

In recent years, the prolonged use of broad-spectrum antibiotics has resulted in multidrug resistance in many bacteria, complicating the clinical management of patients with GIF. However, little data exist regarding the risk factors for this complication in IPN, and few publications have combined microbiological results for the precise and adequate prediction of the risk of GIF in patients with IPN. Therefore, early prediction of GIF and specific targeted interventions are imperative to reduce GIF-related mortality.

This study was conducted using a large prospectively maintained database of patients with IPN to identify the risk factors for GIF development at a Chinese tertiary hospital, focusing on the effect of the microbiology profile.

Materials and methods

Patients

This study included 385 patients with IPN who were admitted to the Xiangya Hospital (a large tertiary care center) between January 2011 and April 2025. We excluded pregnant women, patients with malignancy, or those with a history of chronic pancreatitis. The flowchart for patients is presented in Fig. 1. The following data were collected from the prospective institutional database of IPN [11]: clinical, radiological, and microbiological characteristics; surgical management; and follow-up data.

All study procedures adhered to the principles of the seventh revision of the Declaration of Helsinki and received ethical approval from the institutional review board of Xiangya Hospital (approval number: 201012067). Written informed consent for data publication was obtained from all participants or their representatives.

Definitions and inclusion criteria

The criteria for the diagnosis, classification, definitions, and management of AP were based on the Revised Atlanta Classification (RAC) [12] and the American Gastroenterological Association guidelines [13]. IPN was diagnosed based on computed tomography evidence of gas within pancreatic or peripancreatic necrosis and confirmed through a positive bacterial or fungal culture, Gram staining of peripancreatic/pancreatic necrosis, or fluid obtained from the first drainage procedure or necrosectomy. AP severity was defined according to RAC as follows: (i) mild AP, no organ failure or local or systemic complications; (ii) moderately severe AP, transient organ failure and/or local complications; and (iii) severe AP (SAP), persistent organ failure (> 48 h) with a score of ≥2 on the modified Marshall scoring system.

GIF was defined as a pathological connection between any part of the GI tract (stomach, duodenum, jejunum, ileum, and colon) and the pancreas and/or a peripancreatic necrotic cavity. The etiology of each GI tract perforation or fistula was categorized as follows: (i) spontaneous, resulting from ischemia/necrosis or diagnosed without any previous invasive intervention; (ii) iatrogenic, caused by an inadvertent perforation during endoscopic intervention, percutaneous catheter drainage (PCD), or surgical procedure; and (iii) unknown, when the distinction between spontaneous and iatrogenic could not be determined or a combination was possible. No distinction was made between perforation and fistula, as these entities are not always clinically distinguishable. Intentionally created iatrogenic fistulas resulting from endoscopic drainage were excluded from the definition of GI tract perforation or fistula because of their deliberate nature [7,14].

For the surgical management of IPN, a step-up approach using PCD or endoscopic transluminal drainage serves as the initial step. If clinical improvement was inadequate after drainage, additional drainage or minimal access retroperitoneal pancreatic necrosectomy (MARPN) was performed as the second step in the surgical step-up strategy. Open pancreatic necrosectomy (OPN) was consistently reserved as the final treatment option for patients with uncontrolled infections or severe complications after MARPN. Detailed surgical management protocols have been described in our previous studies [15–18]. In contrast, OPN could be adopted as the initial surgical procedure to remove the infected necrosis when there is no route for PCD or transluminal drainage. If indicated, PCD or MARPN could be a subsequent adjuvant procedure to control the infection, which is also known as the step-down approach [11]. The aforementioned treatment plans meet the current international guidelines [2,4].

Microbial culture specimens were obtained from pancreatic necrosis or fluid during the first necrosectomy or drainage, and blood

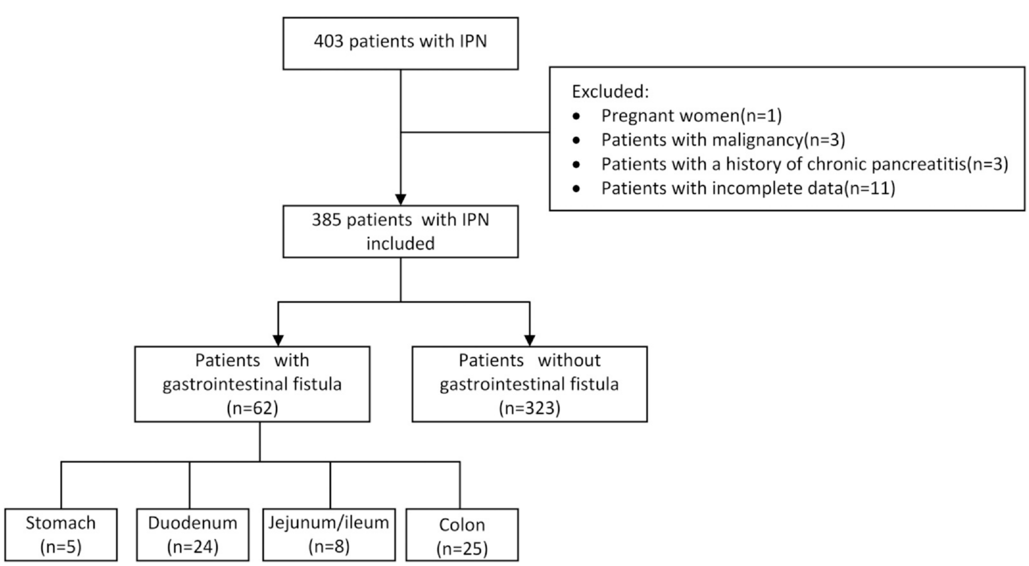

Figure 1. Inclusion flowchart. IPN, infected pancreatic necrosis.

cultures were collected during fever (≥38.5 °C) in patients with IPN. The multidrug-resistant organisms (MDROs) were defined as organisms resistant to at least 1 antimicrobial agent in ≥3 antimicrobial categories [19].

Using the modified Marshall scoring system (as detailed in the RAC [12]), organ failure was defined as a score of ≥2 affecting the respiratory, cardiovascular, or renal organ system. Multiple organ failure (MOF) is characterized by the failure of ≥2 organ systems [20].

Hemorrhages related to AP included GI, intraperitoneal, or retroperitoneal bleeding. Pancreatic fistulas were confirmed by elevated drain amylase levels (ie, > 3 times the upper limit of normal serum amylase concentration) in peripancreatic fluid collected during debridement or drainage [21].

Statistical analysis

Statistical analyses were conducted using SPSS software (version 26.0; SPSS Inc). Continuous variables were presented as mean ± SD or median (IQR), based on distribution normality assessed by the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. For group comparisons, categorical variables were analyzed using the chi-square test, whereas continuous variables were assessed with either the Student *t* test or the Mann-Whitney *U* test, depending on their distribution. Variables showing significant associations were subsequently included in the multivariate logistic regression analysis. Results are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was set at $P < .05$.

Results

Clinical characteristics of patients with IPN

This study included 385 patients treated for IPN between 2011 and 2025, of whom 62 (16.1%) developed GIF at a median of 48 days (IQR, 25–78) after disease onset. In 47 patients (75.8%) with GIF, an invasive intervention was performed before the diagnosis of GIF. There was a median of 23 days (IQR, 8–47) between the first intervention and diagnosis of the GIF. The cohort was further divided into the GIF and non-GIF groups. Fig. 2 presents the GIF distribution. The colon (40.2%) was the most common GIF location in patients with IPN, followed by the duodenum (38.71%), jejunum/ileum (12.9%), and stomach (8.06%). Table 1 presents the comparison of the baseline and clinical characteristics between the 2 groups. The GIF group had 49 men (79%) with a mean age of 44.9 ± 12 years, and the most prevalent etiology was hyperlipidemia (45.2%), followed by biliary (30.6%), others (16.1%), alcoholic (6.5%), and iatrogenic (1.6%). There were no significant differences in the baseline characteristics, including age, sex (male/female), etiology, or occurrence of diabetes mellitus, between the 2 groups. However, the SAP rate in the GIF group was significantly higher than that in the non-GIF group (69.4% vs 55.1%, respectively; $P = .038$).

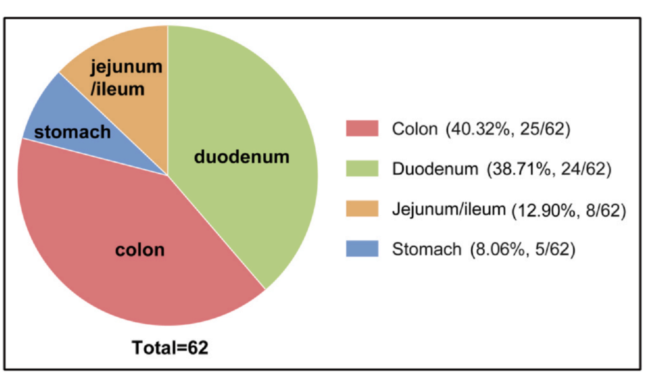

Figure 2. Distribution sites of gastrointestinal fistula in patients with infected pancreatic necrosis.

The culture results of the drainage fluid showed that polymicrobial infection exhibited a higher prevalence in patients with GIF than in those without GIF (79% vs 59.4%, respectively; $P = .004$). The occurrence of MDRO infection in the drainage fluid was not significantly different between the 2 groups, whereas the occurrence of carbapenem-resistant *Enterobacteriaceae* (CRE) and multidrug-resistant fungal infections were more frequently in the GIF group than in the non-GIF group (CRE: 40.3% vs 25.1%, respectively; $P = .014$; multidrug-resistant fungal infection: 27.4% vs 14.9%, respectively; $P = .016$, respectively). Among the 62 patients with GIF, the dominant pathogens were Gram-negative bacilli, including *Klebsiella pneumoniae* (56.5%), *Escherichia coli* (33.9%), *Acinetobacter baumannii* (33.9%), and *Pseudomonas aeruginosa* (12.9%). The microorganisms identified in the 62 patients are presented in Fig. 3. The prevalence rates of 7 multidrug-resistant pathogens, carbapenem-resistant *Klebsiella pneumoniae* (CRKP), carbapenem-resistant *Acinetobacter baumanii* (CRAB), *Escherichia coli* producing an extended-spectrum beta-lactamase (ESBLp), *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Staphylococcus epidermidis*, and *Candida tropicalis*, are presented in Fig. 3.

Patients with IPN and GIF had higher rates of *Klebsiella pneumoniae* and fungal infections than those without GIF (*Klebsiella pneumoniae* infection: 56.5% vs 32.5%, respectively; $P < .001$; fungal infection: 40.3% vs 23.2%, respectively; $P = .005$).

In the bloodstream culture results, MDRO and CRE infections were higher in patients with GIF than in those without GIF (MDRO: 35.5% vs 15.5%, respectively; $P < .001$; CRE: 27.4% vs 6.5%, respectively; $P < .001$).

Surgical interventions and outcomes between patients with GIF and those without GIF

Table 2 presents the surgical interventions, major complications, and outcomes. There were no significant differences in the number of surgical interventions, number of PCDs, number of MARPNs, rate of MOF, ICU admission, length of ICU stay, or rate of pancreatic fistula between patients with IPN complicated by GIF and those without GIF. The overall mortality rate was 23.9% (92/385). Mortality was significantly higher in patients with GIF (22/62 [35.5%]) than in those without GIF (70/323 [21.7%]) ($P = .019$). In addition, compared with patients without GIF, those with IPN and GIF had a higher open necrosectomy rate (14.9% vs 35.5%, respectively; $P < .001$), longer duration of organ failure (median: 3.0 vs 10.5 days, respectively; $P = .048$), longer hospital stay (median: 75.5 vs 96.0, days, respectively; $P = .007$), and higher hemorrhage rates (18.6% vs 35.5%, respectively; $P = .003$).

Predictors of mortality in patients with IPN and GIF

The overall mortality rate of patients with IPN and GIF was 35.5% (22/62). Table 3 presents the potential risk factors for mortality in patients with IPN and GIF. In the univariate analysis, SAP ($P = .013$), MOF ($P < .001$), step-down surgical interventions ($P = .039$), hemorrhage ($P = .005$), drainage fluid with MDRO infection ($P = .018$), bloodstream infections ($P = .01$), and bloodstream with MDRO infection ($P = .023$) were associated with increased mortality. In the multivariate analysis, MOF (OR, 27.973 [95% CI, 2.351–332.886]; $P = .008$) was identified as an independent predictor of higher mortality in patients with IPN and GIF.

Discussion

GIF is a well-recognized complication that occurs in the late phase of AP [22]. However, the clinical relevance of GIF in patients

Table 1
Baseline and clinical characteristics of patients with infected pancreatic necrosis.

Characteristics	Total (N = 385)	With GIF (n = 62)	Without GIF (n = 323)	*P* value
Age (y), mean ± SD	46.9 ± 12.8	44.9 ± 12	47.3 ± 12.9	.176
Male sex, n (%)		49 (79.0)	233 (72.1)	.261
Etiology, n (%)				.558
Biliary	151	19 (30.6)	132 (40.9)	
Hypertriglyceridemia	162	28 (45.2)	134 (41.5)	
Alcoholic	18	4 (6.5)	14 (4.3)	
ERCP	7	1 (1.6)	6 (1.9)	
Others	47	10 (16.1)	37 (11.5)	
Revised Atlanta classification, n (%)				.038
MSAP	164	19 (30.6)	145 (44.9)	
SAP	221	43 (69.4)	178 (55.1)	
Diabetes mellitus	75	12 (19.4)	63 (19.5)	.978
Infection, n (%)				
Drainage fluid infection, n (%)				
With polymicrobial infection	241	49 (79.0)	192 (59.4)	.004
With CRE infection	106	25 (40.3)	81 (25.1)	.014
With MDROs infection	213	38 (61.3)	175 (54.2)	.302
With multidrug-resistant fungal infection	65	17 (27.4)	48 (14.9)	.016
Microbiology profile of organisms, n (%)				
Escherichia coli	98	21 (33.9)	77 (23.8)	.097
Klebsiella pneumoniae	140	35 (56.5)	105 (32.5)	< .001
Acinetobacter baumannii	102	21 (33.9)	81 (25.1)	.151
Pseudomonas aeruginosa	47	8 (12.9)	39 (12.8)	.855
Fungal infection	100	25 (40.3)	75 (23.2)	.005
Bloodstream infection, n (%)	118	31 (50.0)	87 (26.9)	< .001
With MDRO infection	72	22 (35.5)	50 (15.5)	< .001
With CRE infection	38	17 (27.4)	21 (6.5)	< .001

CRE, carbapenem-resistant *Enterobacteriaceae*; ERCP, endoscopic retrograde cholangiopancreatography; GIF, gastrointestinal fistula; MDRO, multidrug-resistant organism; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; SD, standard deviation.

with IPN, based on microbiological characteristics, has rarely been studied. This prospective cohort of IPN, one of the largest cohorts worldwide, revealed a 16.1% incidence rate of GIF among patients with IPN and demonstrated that patients with IPN complicated by GIF exhibited a significantly higher prevalence of polymicrobial infections, higher rates of CRE and *Klebsiella pneumoniae* infections,

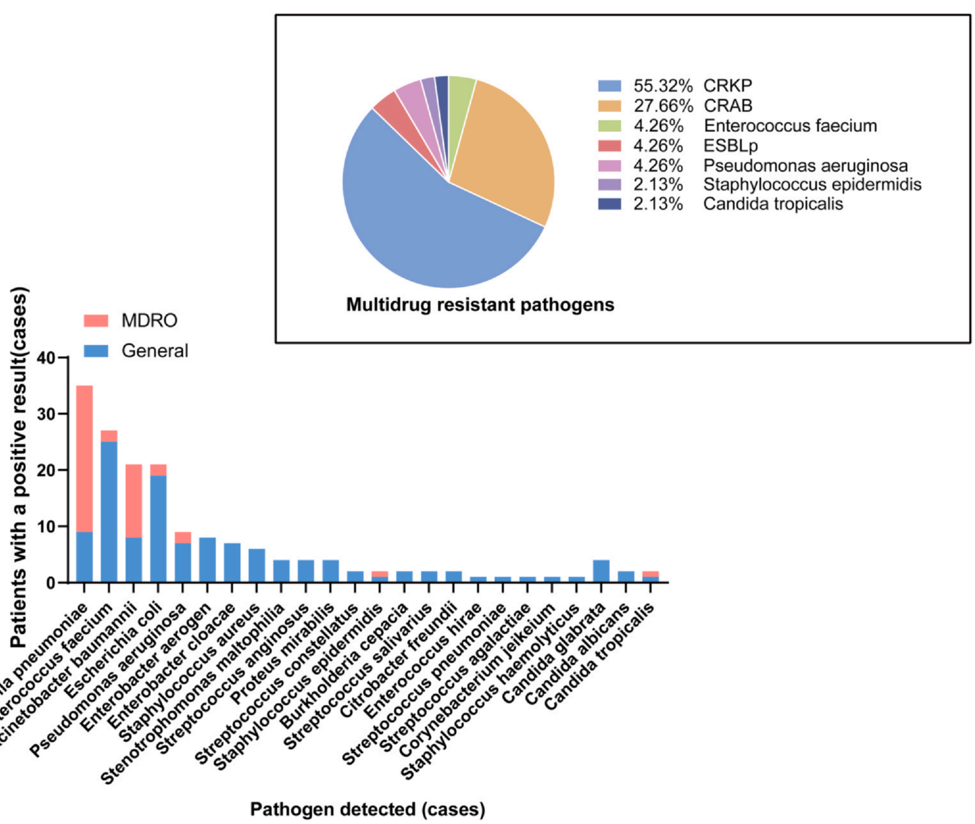

Figure 3. The microbiology profiles of organisms isolated from wall-off necrosis and the prevalence rates of 7 multidrug-resistant pathogens in patients with infected pancreatic necrosis. CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBLp, *Escherichia coli* producing an extended-spectrum beta-lactamase; MDRO, multidrug-resistant organism.

Table 2
Comparison of patient outcomes between 2 groups.

Characteristics	Total (N = 385)	With GIF (n = 62)	Without GIF (n = 323)	*P* value
Surgical interventions				
Time from onset to first surgical intervention (d), median (IQR)	22.0 (13.0–32.0)	22.5 (11.5–34.0)	21.0 (13.8–32.0)	.931
Number of surgical interventions, median (IQR)	3 (2–5)	4 (2–5)	3 (2–5)	.050
Step-up surgical interventions, n (%)	325	44 (71.0)	281 (87.0)	.001
PCD alone, n (%)	66	6 (9.7)	60 (18.6)	.089
Number of PCD	1 (1–2)	1 (1–2)	1 (1–2)	.651
Number of MARPNs	1 (0–3)	1 (0–3)	1 (0–3)	.842
Open necrosectomy, n (%)	70	22 (35.5)	48 (14.9)	< .001
Number of OPNs	0 (0–1)	1 (0–1)	0 (0–0)	< .001
Duration of the organ failure	4.0 (0.0–23.0)	10.5 (0.0–31.0)	3.0 (0.0–22.3)	.048
Multiple organ failure (vs single organ failure), n (%)	132	25 (40.3)	107 (33.1)	.274
ICU admission, n (%)	273	47 (75.8)	226 (70.0)	.354
Length of ICU stay (d), median (IQR)	10.0 (0.0–21.8)	12.0 (1.5–29.3)	10.0 (0.0–21)	.165
Hospital stay (d), median (IQR)	76.0 (57.0–110.5)	96.0 (65.8–135.8)	75.5 (56.0–102.5)	.007
Major complications, n (%)				
Hemorrhage	82	22 (35.5)	60 (18.6)	.003
Pancreatic fistula	156	28 (45.2)	128 (39.6)	.308
Mortality, n (%)	92 (23.9)	22 (35.5)	70 (21.7)	.019

GIF, gastrointestinal fistula; ICU, intensive care unit; IQR, interquartile range; MARPN, minimal access retroperitoneal pancreatic necrosectomy; OPN, open pancreatic necrosectomy; PCD, percutaneous catheter drainage.

and higher rates of fungal and multidrug-resistant fungal infections in the drainage fluid. Similarly, we found higher rates of MDRO and CRE bloodstream infections in patients with IPN complicated by GIF than in those without GIF. CRE members, particularly CRKP, are emerging as a crucial concern requiring substantial attention. Furthermore, our data suggested that combined IPN and GIF were associated with a high open necrosectomy rate, long duration of organ failure, prolonged hospital stays, and high hemorrhage rates. Finally, this study revealed that MOF was an independent predictor of high mortality in patients with IPN and GIF. Here, we specifically focused on the association between GIF risk in patients with IPN and microbial culture results, which may help clinicians identify and stratify patients based on microbial culture results.

GIF, a delayed complication of necrotizing pancreatitis, typically develops after the first month of onset [7,23]. Pancreatic necrosis directly exposes the adjacent GI tract to necrotic material and pancreatic enzymes, resulting in its deterioration and the failure of the intestinal barrier. Concurrently, a severe regional inflammatory response induces thrombosis and ischemia in affected segments [14,24], culminating in focal transmural necrosis and fistulous tract formation communicating with pancreatic or peripancreatic necrotic collections or the peritoneal space [25]. The reported incidences (3%–67%) of perforation or fistula of the GI tract vary largely [5,7,10,14,26], and the incidence of GIF in our study (16.1%) was comparable with that reported by Timmerhuis et al. [14] (16.0%) but slightly lower than that reported in other studies. These discrepancies could be explained by the different study populations and the limited number of patients included in previously published studies.

GIF could involve the stomach, duodenum, jejunum, ileum, or colon, occurring concurrently or separately [5]. Similar to other studies [22,27], colonic fistula was the most common form in this study, which was found in 40.32% of patients, followed by duodenal fistula (38.71%). The underlying mechanism of this phenomenon may be that the colon is more prone to ischemia due to a low-flow state or the hemodynamic response to sepsis than the stomach, jejunum, and ileum [27,28].

Previous studies have confirmed that the microbial pathogens responsible for IPN in necrotizing pancreatitis are predominantly gut derived [29–31]. Within the first 1 to 2 weeks, a transition occurs from a proinflammatory response to an anti-inflammatory response. During this period, intestinal barrier failure places patients at risk of translocation of intestinal flora, followed by the development of consequent IPN and fluid collections. These complications are associated with a severe local inflammatory response, which may directly erode blood vessels, induce vasospasm, promote thrombosis, and reduce capillary perfusion, particularly when secondary infection occurs [32–34]. Furthermore, the inflammation or infected necrosis, combined with enzyme-rich fluid, exacerbates GI tract injury. This facilitates the formation of edema, thrombosis, ischemia, and necrosis, ultimately resulting in fistula formation [35].

This study showed that the prevalence of polymicrobial infection was significantly higher in patients with IPN and GIF than in those without GIF, possibly because GIF created direct communication between the peripancreatic necrotic areas and the intestinal lumen, allowing abundant aerobic and anaerobic bacteria from the gut to invade the originally sterile pancreatic and surrounding necrotic tissues through the fistula tract. Although the occurrence of MDRO infections in the drainage fluid was not significantly different between the groups with and without GIF, CRE and multidrug-resistant fungal infections occurred more frequently in the GIF group than in the non-GIF group. Among the 62 patients with GIF, the most

Table 3
Predictors of mortality in patients with infected pancreatic necrosis and gastrointestinal fistula.

Variables	n (%)		Univariate analysis		Multivariate analysis	
	Died (n = 22)	Survived (n = 40)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
SAP	20 (90.9)	23 (57.5)	7.391 (1.518–35.991)	.013	1.535 (0.111–21.243)	.749
Multiple organ failure (vs single organ failure)	18 (81.8)	7 (17.5)	21.214 (5.466–82.332)	< .001	27.973 (2.351–332.886)	.008
Step-down surgical interventions	10 (45.5)	8 (20.0)	3.333 (1.064–10.445)	.039	2.420 (0.294–19.913)	.411
Hemorrhage	13 (59.1)	9 (22.5)	4.975 (1.610–15.376)	.005	4.214 (0.763–23.288)	.099
Drainage fluid with MDRO infection	18 (81.8)	20 (50.0)	4.500 (1.292–15.678)	.018	5.383 (0.355–81.601)	.225
Bloodstream infection	16 (72.7)	15 (37.5)	4.444 (1.427–13.839)	.010	3.892 (0.288–52.555)	.306
Bloodstream with MDRO infection	12 (54.5)	10 (25.0)	3.600 (1.195–10.847)	.023	0.313 (0.023–4.189)	.380
Drainage fluid with *Acinetobacter baumannii* infection	11 (50.0)	10 (25.0)	3.000 (0.998–9.015)	.050	0.699 (0.089–5.491)	.734

CIs, confidence intervals; MDRO, multidrug-resistant organism; OR, odds ratio; SAP, severe acute pancreatitis.

common pathogens were *Klebsiella pneumoniae* and *Escherichia coli*, similar to our previous findings in the entire IPN cohort. *Klebsiella pneumoniae* was the most common pathogen and Gram-negative bacterium in patients with IPN, and *Escherichia coli* and *Acinetobacter baumannii* also constituted a large proportion [24,31]. In addition, the most common MDRO in patients with IPN and GIF in this study was CRKP, followed by CRAB and ESBLp, similar to the findings of previous studies on the entire IPN cohort [24]. Carbapenem resistance has been recently linked to high mortality rates and has emerged as a global concern, increasing the treatment burden for infection control. *Klebsiella pneumoniae* has surpassed *Escherichia coli* as the most prevalent strain, exhibiting the highest proportion of resistance mechanisms, consistent with previous research [36]. This trend necessitates significant clinical attention. *Klebsiella pneumoniae* was the most prevalent pathogen in the microbial culture results of drainage fluid from patients with IPN complicated by GIF [9], explaining why the occurrence of GIF in patients with IPN was associated with a high infection rate of *Klebsiella pneumoniae* in this study.

Furthermore, our study showed that the occurrence of GIF in patients with IPN was associated with a high rate of fungal and multidrug-resistant fungal infections in the drainage fluid. The detection of fungal infections is clinically challenging, and delays in antifungal treatment, prolonged use of antifungal medications, and pronounced side effects pose significant challenges in managing fungal infections associated with GIF [37,38].

Moreover, it was found that patients with IPN and GIF had a higher rate of CRE infection in the drainage fluid and blood flow cultures than those without GIF. This study highlighted that patients with IPN and GIF predominantly presented with multidrug-resistant Gram-negative bacteria, particularly CRE, with *Klebsiella pneumoniae* emerging as a crucial concern that requires substantial attention.

Here, mortality was significantly higher in patients with IPN and GIF than in those without GIF (35.5% vs 21.7%, respectively), and patients with GIF had a more severe disease course and suffered more organ failure. In addition, previous studies have indicated that GIF might cause clinical consequences, such as GI hemorrhage and sepsis, leading to death [27]. Interestingly, several previous studies have suggested that GIF did not increase mortality because it could benefit patients by draining the IPN into the GI tract, particularly when the IPN, wall-off necrosis, or pseudocyst communicates with the gut [5,7,10,39], which seemed to contradict our study's findings. However, previous studies have reported that MOF, prolonged organ failure (≥5 days), and open necrosectomy performed outside a step-up approach were associated with high mortality rates in patients with IPN [11,40]. Timmerhuis et al. [14] reported that patients with necrotizing pancreatitis who developed a GIF had a higher rate of organ failure and longer lengths of hospital and ICU stays. Our results were consistent with those of previous studies demonstrating that, compared with patients without GIF, those with IPN and GIF demonstrated significantly higher rates of open necrosectomy (14.9% vs 35.5%, respectively), longer median duration of organ failure (3.0 vs 10.5 days, respectively), higher incidence of SAP (55.1% vs 69.4%, respectively), longer hospital stays (median: 75.5 vs 96.0 days, respectively), and higher hemorrhage rates (18.6% vs 35.5%, respectively). More importantly, the higher incidence of SAP and longer duration of organ failure in patients with IPN and GIF suggested that GIF might serve as a marker of disease severity, whereas SAP and organ failure were the primary drivers of increased mortality, potentially explaining the increased mortality rate observed among patients with IPN and GIF in this study.

Previous studies have revealed multiple clinical risk factors predictive of mortality in patients with IPN, including SAP, MDRO infection, candidemia, step-down surgical approach, history of uncontrolled arterial hypertension, renal failure, and hemodynamic failure [24,40,41]. Consistent with these findings, our investigation demonstrated that, even in patients with IPN complicated by GIF, several factors, including SAP, MOF, step-down surgical interventions, hemorrhage, and MDRO infection, remained significantly associated with elevated mortality rates. In addition, MOF was identified as an independent predictor of higher mortality in patients with IPN and GIF. Formulating and implementing appropriate surgical intervention strategies are crucial for improving the prognosis of patients with IPN. The primary interventions for IPN include the endoscopic or surgical step-up approach and open surgery. Although the endoscopic step-up approach has demonstrated outcomes comparable with the surgical step-up approach in reducing major complications and mortality, the surgical step-up strategy remains the standard treatment cornerstone for IPN in most hospitals [42]. Typically, PCD is used as the initial intervention, followed by minimally invasive surgery or OPN [43]. Based on our experience, the MARPN procedure serves as the cornerstone of the step-up treatment strategy. However, if MARPN fails to control infection or if complications, such as intra-abdominal bleeding or intestinal fistula arise, prompt conversion to open surgery is essential [18].

This study has some limitations. First, in the case of a large tertiary center in China, most patients with IPN were transferred from other centers. The lack of complete clinical data precluded the capture of potentially significant variables, including precise data on the use of antibiotics, duration of antibiotic exposure, time to effective therapy, and details before referral, which are associated with MDROs, particularly CRE. Moreover, the results were derived from a single center. Thus, they cannot be indiscriminately generalized to other hospitals. Further multicenter, prospective, original studies would provide more precise data to reduce potential confounding results. Furthermore, the small sample size led to wide CIs for some variables in the multivariate analysis, suggesting unstable estimates that required cautious interpretation. Finally, the long study period and the evolution of surgical/endoscopic practices over 14 years may have been significant confounders that compromised the uniformity of the results.

Conclusion

The incidence of GIF in patients with IPN was 16.1%. This study revealed that patients with IPN and GIF had significantly higher risks of polymicrobial infections and multidrug-resistant pathogens than those without GIF, including an increased prevalence of CRE and *Klebsiella pneumoniae* infections and elevated rates of fungal infections, particularly multidrug-resistant fungal strains in the drainage fluid. In addition, we found high frequencies of bloodstream infections caused by MDROs and CRE in patients with IPN and GIF. CRE, particularly CRKP, have emerged as crucial pathogens requiring urgent clinical attention. GIF was associated with poor clinical outcomes and increased mortality in patients with IPN. Finally, MOF was the most significant predictor of mortality in patients with IPN and GIF.

Author contributions

H Huang conceived the study and drafted the manuscript; H Huang and D Shen participated in the study design and performed the statistical analyses; Z Sun, B Liu, and L Chen collected the data; and D Shen edited and checked the manuscript. All the authors have read and approved the final manuscript.

Funding

This study was supported financially by the Natural Science Foundation of Hunan Province (grant number: 2024JJ6653), the National Natural Science Foundation of China (grant number: 82403227), the Hunan Youth Talent Program (Science and

Technology Innovation Category; grant number: 2025RC3051), the China Postdoctoral Science Foundation (grant number: 2024M763715), and the Youth Science Foundation of Xiangya Hospital (grant number: 2023Q13).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgments

The authors thank the staff members of Xiangya Hospital of Central South University for their support in the data collection.

References

[1] Liu B, Zhang X, Li J, Sun Z, Lin C, Ning C, et al. The global, regional, and national burden of pancreatitis in 204 countries and territories, 1990-2021: a systematic analysis for the global burden of disease study 2021. Dig Dis Sci 2025;70(7):2328–39.
[2] Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology 2022;162(1):122–34.
[3] Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association clinical practice update: management of pancreatic necrosis. Gastroenterology 2020;158(1):67–75. e1.
[4] Tenner S, Vege SS, Sheth SG, Sauer B, Yang A, Conwell DL, et al. American College of Gastroenterology guidelines: management of acute pancreatitis. Am J Gastroenterol 2024;119(3):419–37.
[5] Kochhar R, Jain K, Gupta V, Singhal M, Kochhar S, Poornachandra KS, et al. Fistulization in the GI tract in acute pancreatitis. Gastrointest Endosc 2012;75(2):436–40.
[6] Maatman TK, Roch AM, Ceppa EP, Easler JJ, Gromski MA, House MG, et al. The continuum of complications in survivors of necrotizing pancreatitis. Surgery 2020;168(6):1032–40.
[7] Liu Z, Ke H, Xiong Y, Liu H, Yue M, Liu P. Gastrointestinal fistulas in necrotizing pancreatitis receiving a step-up approach incidence, risk factors, outcomes and treatment. J Inflamm Res 2023;16:5531–43.
[8] Yin M, Zheng H, Xu L, Jin R, Wang X, Man Y, et al. Development a risk prediction nomogram for multidrug-resistant bacterial and fungal infection in gastrointestinal fistula patients during the perioperative period. Front Cell Infect Microbiol 2024;14:1502529.
[9] Podda M, Pacella D, Pellino G, Coccolini F, Giordano A, Di Saverio S, et al. coMpliAnce with evideNce-based cliniCal guidelines in the managemenT of acute biliaRy pancreAtitis: the MANCTRA-1 international audit. Pancreatology 2022;22(7):902–16.
[10] Jiang W, Tong Z, Yang D, Ke L, Shen X, Zhou J, et al. Gastrointestinal fistulas in acute pancreatitis with infected pancreatic or peripancreatic necrosis: a 4-year single-center experience. Medicine 2016;95(14):e3318.
[11] Shen D, Wang D, Ning C, Lin C, Cao X, Liu Z, et al. Prognostic factors of critical acute pancreatitis: a prospective cohort study. Dig Liver Dis 2019;51(11):1580–5.
[12] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102–11.
[13] Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association institute guideline on initial management of acute pancreatitis. Gastroenterology 2018;154(4):1096–101.
[14] Timmerhuis HC, van Dijk SM, Hollemans RA, Umans DS, Sperna Weiland CJ, Besselink MG, et al. Perforation and fistula of the gastrointestinal tract in patients with necrotizing pancreatitis: a nationwide prospective cohort. Ann Surg 2023;278(2):e284–92.
[15] Ning C, Ouyang H, Xiao J, Wu D, Sun Z, Liu B, et al. Development and validation of an explainable machine learning model for mortality prediction among patients with infected pancreatic necrosis. eClinicalMedicine 2025;80:103074.
[16] Ning C, Ouyang H, Shen D, Sun Z, Liu B, Hong X, et al. Prediction of survival in patients with infected pancreatic necrosis: a prospective cohort study. Int J Surg 2024;110(2):777–87.
[17] Ning C, Sun Z, Shen D, Lin C, Li J, Wei Q, et al. Is contemporary open pancreatic necrosectomy still useful in the minimally invasive era? Surgery 2024;175(5):1394–401.
[18] Zhu S, Ning C, Sun Z, Liu B, Hong X, Lin C, et al. Minimal access retroperitoneal pancreatic necrosectomy for infected pancreatic necrosis: a single-center of 15 years' experience. Surgery 2025;183:109392.
[19] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268–81.
[20] Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 2019;68(6):1044–51.
[21] Arvanitakis M, Dumonceau JM, Albert J, Badaoui A, Bali MA, Barthet M, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy 2018;50(5):524–46.
[22] Hua Z, Su Y, Huang X, Zhang K, Yin Z, Wang X, et al. Analysis of risk factors related to gastrointestinal fistula in patients with severe acute pancreatitis: a retrospective study of 344 cases in a single Chinese center. BMC Gastroenterol 2017;17(1):29.
[23] Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245(5):674–83.
[24] Ning C, Huang G, Shen D, Bonsu AAFK, Ji L, Lin C, et al. Adverse clinical outcomes associated with multidrug-resistant organisms in patients with infected pancreatic necrosis. Pancreatology 2019;19(7):935–40.
[25] Yang D, Yue L, Tan B, Hu W, Li M, Lu H. Comprehensive management of gastrointestinal fistulas in necrotizing pancreatitis: a review of diagnostic and therapeutic approaches. Expert Rev Gastroenterol Hepatol 2025. Epub ahead of print.
[26] Doctor N, Philip S, Gandhi V, Hussain M, Barreto SG. Analysis of the delayed approach to the management of infected pancreatic necrosis. World J Gastroenterol 2011;17(3):366–71.
[27] Mohamed SR, Siriwardena AK. Understanding the colonic complications of pancreatitis. Pancreatology 2008;8(2):153–8.
[28] Huang H, Wang H, Long Z, Wang M, Ding J, Peng J. Factors influencing hospital stay duration for patients with mild ischemic colitis: a retrospective study. Eur J Med Res 2022;27(1):36.
[29] Huang H, Peng J, Ning C, Wei Q, Li J, Lin C, et al. Escherichia coli infection indicates favorable outcomes in patients with infected pancreatic necrosis. Front Cell Infect Microbiol 2023;13:1107326.
[30] Li J, Lin C, Ning C, Wei Q, Chen L, Zhu S, et al. Early-onset emphysematous pancreatitis indicates poor outcomes in patients with infected pancreatic necrosis. Dig Liver Dis 2022;54(11):1527–32.
[31] Besselink MG, van Santvoort HC, Boermeester MA, Nieuwenhuijs VB, Van Goor H, Dejong CH, et al. Timing and impact of infections in acute pancreatitis. Br J Surg 2009;96(3):267–73.
[32] Doerken S, Metsini A, Buyet S, Wolfensberger A, Zingg W, Wolkewitz M. Estimating incidence and attributable length of stay of healthcare-associated infections-modeling the Swiss point-prevalence survey. Infect Control Hosp Epidemiol 2022;43(8):1022–31.
[33] Noor MT, Radhakrishna Y, Kochhar R, Ray P, Wig JD, Sinha SK, et al. Bacteriology of infection in severe acute pancreatitis. JOP 2011;12(1):19–25.
[34] Sunkara T, Etienne D, Caughey ME, Gaduputi V. Small bowel obstruction secondary to acute pancreatitis. Gastroenterol Res 2017;10(1):42–4.
[35] Van Minnen LP, Besselink MG, Bosscha K, Van Leeuwen MS, Schipper ME, Gooszen HG. Colonic involvement in acute pancreatitis. A retrospective study of 16 patients. Dig Surg 2004;21(1):33–8. discussion 39-40.
[36] Liu Q, Ren J, Wu X, Wang G, Wang Z, Wu J, et al. Shifting trends in bacteriology and antimicrobial resistance among gastrointestinal fistula patients in China: an eight-year review in a tertiary-care hospital. BMC Infect Dis 2017;17(1):637.
[37] Schwender BJ, Gordon SR, Gardner TB. Risk factors for the development of intra-abdominal fungal infections in acute pancreatitis. Pancreas 2015;44(5):805–7.
[38] Horibe M, Sanui M, Sasaki M, Honda H, Ogura Y, Namiki S, et al. Impact of antimicrobial prophylaxis for severe acute pancreatitis on the development of invasive candidiasis: a large retrospective multicenter cohort study. Pancreas 2019;48(4):537–43.
[39] Levy I, Ariche A. Complete recovery after spontaneous drainage of pancreatic abscess into the stomach. Scand J Gastroenterol 1999;34(9):939–41.
[40] Podda M, Pellino G, Di Saverio S, Coccolini F, Pacella D, Cioffi SPB, et al. Infected pancreatic necrosis: outcomes and clinical predictors of mortality. A post hoc analysis of the MANCTRA-1 international study. Update Surg 2023;75(3):493–522.
[41] Ning C, Zhu S, Wei Q, Liu Z, Lin C, Li J, et al. Candidemia indicates poor outcome in patients with infected pancreatic necrosis. Mycoses 2021;64(6):684–90.
[42] Morató O, Poves I, Ilzarbe L, Radosevic A, Vázquez-Sánchez A, Sánchez-Parrilla J, et al. Minimally invasive surgery in the era of step-up approach for treatment of severe acute pancreatitis. Int J Surg 2018;51:164–9.
[43] Shen D, Ning C, Huang G, Liu Z. Outcomes of infected pancreatic necrosis complicated with duodenal fistula in the era of minimally invasive techniques. Scand J Gastroenterol 2019;54(6):766–72.