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ORIGINAL RESEARCH

Characterization of Pancreatic Infections in Patients with Severe Acute Pancreatitis: A Retrospective Study from 2019 to 2023

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Objective: This study investigated the distribution and changes in pancreatic infections among patients with acute pancreatitis (AP) from 2019 to 2023, while exploring the impact of multidrug-resistant bacterial infections on the prognosis of patients with poor outcomes.

Methods: This study included patients diagnosed with SAP between 2019 and 2023 and collected the demographic and clinical characteristics of all participants. Based on routine clinical microbiological culture results, the distribution and drug resistance of pathogens associated with pancreatic infections were analyzed. Multivariable logistic regression was used to evaluate the association between multidrug-resistant organism (MDRO) infection and poor prognosis.

Results: A total of 1586 pancreatic fluid specimens were analyzed and collected from 843 patients diagnosed with AP. The positive rate of the culture results was 81% (1280/1586), with the predominant pathogens identified as *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecium*, and *Acinetobacter baumannii* complex. Of the 843 patients, 756 met the criteria, and the proportion of MDROs in pancreatic infections was 87.57% (662/756). Multivariate logistic regression analysis revealed that septic shock, acute kidney injury, and tracheostomy were associated with a poor prognosis, whereas ICU length of stay, infected pancreatic necrosis, and tracheostomy were associated with multidrug-resistant bacterial infections in patients with severe or critical AP.

Conclusion: The proportion of MDRO infections in patients with severe or critical AP was notably high, primarily involving multidrug-resistant *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Septic shock, acute kidney injury, and tracheostomy have been identified as independent risk factors of poor prognosis in patients with severe or critical AP.

Keywords: severe acute pancreatitis, pancreatic infection, microbiological profiles, multidrug-resistant organism, risk factor

Introduction

Infected pancreatic necrosis (IPN) is a severe complication of acute pancreatitis (AP), marked by necrotic pancreatic tissue colonized by various pathogens.[1] These pathogens typically include a mix of aerobic and anaerobic bacteria,[2–4] including gram-negative bacteria, such as *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* being commonly involved. Recent studies, including those conducted by our research group, have revealed that *K. pneumoniae* now overtakes *E. coli* as the primary pathogen in pancreatic infections.[5,6] Furthermore, *K. pneumoniae* is often multi-drug-resistant, particularly carbapenems. Consequently, it is essential to investigate and analyze the pathogens responsible for pancreatic infections in patients with AP, and their drug resistance profiles. Step-up strategies, including percutaneous drainage (PCD) and minimally invasive pancreatic necrosectomy (MIPN), have demonstrated significant effectiveness in managing infected pancreatic necrosis.[7–9] However, the association between these surgeries and the occurrence of multidrug resistant organism (MDRO) infections remains limited.

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This study performed a retrospective analysis over five years to investigate the pathogens responsible for pancreatic infections in patients with AP. It employs multivariate logistic regression analysis to explore the association between MDRO infections, organ failure, and treatment modalities, thereby providing insights into their impact on SAP prognosis. This approach seeks to provide a comprehensive understanding of the disease trajectory and inform evidence-based therapeutic strategies for achieving optimal patient outcomes.

Methods

Study Design and Patients

This retrospective cohort study included patients with AP who were hospitalized at Nanjing University Jinling Hospital between 2019 and 2023. The eligibility criteria for the study required a diagnosis of AP and the collection of pancreatic fluid samples for microbial culture. These samples were obtained through percutaneous catheter drainage, fine-needle aspiration, or surgery. In some cases, multiple drainage procedures, irrigation, or removal of necrotic pancreatic tissue were necessary, resulting in the submission of several pancreatic fluid samples for culture. The IPN was managed using a step-up approach, which consisted of percutaneous drainage, if necessary, by minimally invasive pancreatic necrosectomy.[8,9] If the step-up approach failed, an open surgical necrosectomy was performed. According to the determinant-based classification of acute pancreatitis severity,[10] severe AP (SAP) was diagnosed based on the presence of either IPN or persistent organ failure. In contrast, critical AP (CAP) was characterized by the presence of both IPN and persistent organ failure. IPN was defined by the presence of at least one of the following criteria: gas bubbles within pancreatic necrosis observed on computed tomography or a positive microbial culture.

We collected patient information including demographics, underlying diseases, etiology, local complications, systemic organ dysfunction, surgical interventions such as drainage, necrotic tissue debridement, open necrosectomy, multidrug-resistant infections, antibiotic usage, ventilatory support, and clinical outcomes. Patients who were pregnant, under 18 years of age, or had negative pancreatic fluid cultures were excluded from logistic regression analysis. Additionally, influenced by traditional beliefs in Chinese culture, most critically ill patients prefer to return home before passing away. Therefore, this study does not consider death as an endpoint; instead, clinical treatment outcomes are used for assessment, categorized as either "poor" or "improved". Patients with unclear treatment outcomes were excluded from analysis. Between 2019 and 2023, 756 of 843 patients with AP were screened and met the inclusion criteria for logistic regression analysis.

Routine Microbiological Testing

All pancreatic fluid samples were inoculated onto blood, chocolate, and MH agar plates and incubated for 3 days at 35 °C in an atmosphere containing 5% CO_2. After incubation, growth on the plates was visually inspected and Gram staining was performed. Subsequently, biochemical identification and antimicrobial susceptibility testing (AST) were conducted using the VITEK®2 COMPACT system (bioMérieux, Marcyl'Étoile, France) with susceptibility cards AST-XN04, AST-N335, and AST-P639 employed for analysis. Anaerobic cultures were not performed primarily because the specimens collected through drainage or aspiration did not meet the criteria for anaerobic cultivation. Additionally, our clinical microbiology laboratories lacked the necessary conditions to conduct anaerobic cultures.

Statistical Analysis

All data were analyzed using R language (Version 4.3.3) for logistic regression to evaluate the significance of various influencing factors. The trends in the predominant pathogens responsible for pancreatic infections and their drug resistance from 2019 to 2023 were analyzed using Joinpoint Regression Analysis (Version 5.3.0).[11]

Continuous variables are presented as means and standard deviations, while categorical variables are expressed as counts and percentages. The Shapiro–Wilk test was employed to verify the normality of the variable distribution. For continuous variables that follow a normal distribution, the Student's *t*-test can be used for comparison; for continuous variables that do not follow a normal distribution, the Wilcoxon-Mann–Whitney *U*-test should be used. For the comparison of categorical variables, the chi-square test or Fisher's exact test is employed. Univariable and multivariable

regression analyses were performed with mortality or MDRO infection as the dependent variable, and sex, age, length of ICU, SAP etiology, underlying diseases and others as independent variables. Variables with a p-value less than 0.05 were included in the multivariable logistic regression analysis. Odds ratio (OR) along with the 95% confidence interval (95% CI) was calculated. Statistical significance was set at $p < 0.05$.

Results

Microbiological Profiles of Pancreatic Infection

We analyzed pancreatic fluid samples obtained from 843 hospitalized patients with AP, resulting in a total of 1586 samples collected over five years (189 cases in 2019, 298 in 2020, 416 in 2021, 247 in 2022, and 436 in 2023). Among these samples, 306 were culture-negative and 1280 were culture-positive, yielding an overall positivity rate of 81%. Positive cultures revealed 2814 pathogenic microorganisms, consisting of 2668 bacterial and 146 fungal isolates. The majority are Enterobacteriaceae and non-fermenting Gram-negative bacilli. The most frequently identified pathogenic organisms were *Klebsiella pneumoniae* (41.35%), *Pseudomonas aeruginosa* (21.75%), *Enterococcus faecium* (21.19%), *Acinetobacter baumannii* complex (18.73%), *Escherichia coli* (11.98%), and *Candida albicans* (3.85%). Importantly, the distribution of these predominant pathogens showed no significant variation across the years from 2019 to 2023, indicating a relatively stable pathogen spectrum (student's *t* test, $p > 0.05$, Figure 1; Table S1). As shown in Figure 2, the numbers of multidrug-resistant bacteria were as follows: *K. pneumoniae, E. faecium, A. baumannii* complex, *P. aeruginosa*, and *E. coli*, with rates of multidrug resistance reaching 89.98%, 95.83%, 95.96%, 62.32%, and 84.21%, respectively.

Antimicrobial Resistance Analysis

The antimicrobial resistance of *K. pneumoniae, E. coli, P. mirabilis, A. baumannii, P. aeruginosa*, and *E. faecium* was analyzed (Figure 3). Our findings indicate that *K. pneumoniae* exhibited sensitivity rates of 14.24% for imipenem and 14.53% for meropenem, whereas *E. coli* demonstrated significantly higher sensitivity rates of 71.12% for imipenem and 71.96% for meropenem (student's *t* test, $p < 0.05$). In contrast, *A. baumannii* complex showed markedly lower sensitivity rates of 1.4% and 0.85% for carbapenems, respectively. *P. aeruginosa* had sensitivity rates of 12.54% and 15.04% for carbapenems. Additionally, *E. faecium* exhibited a sensitivity of approximately 77.51% for vancomycin. Notably, from 2019 to 2023, the sensitivity and resistance profiles of these six pathogens remain largely stable, with no significant increase or decrease observed (student's *t* test, $p > 0.05$), highlighting the consistency of their resistance patterns over this period. However, using Joinpoint Regression Analysis, we found that the resistance of *A. baumannii* and *K. pneumoniae*

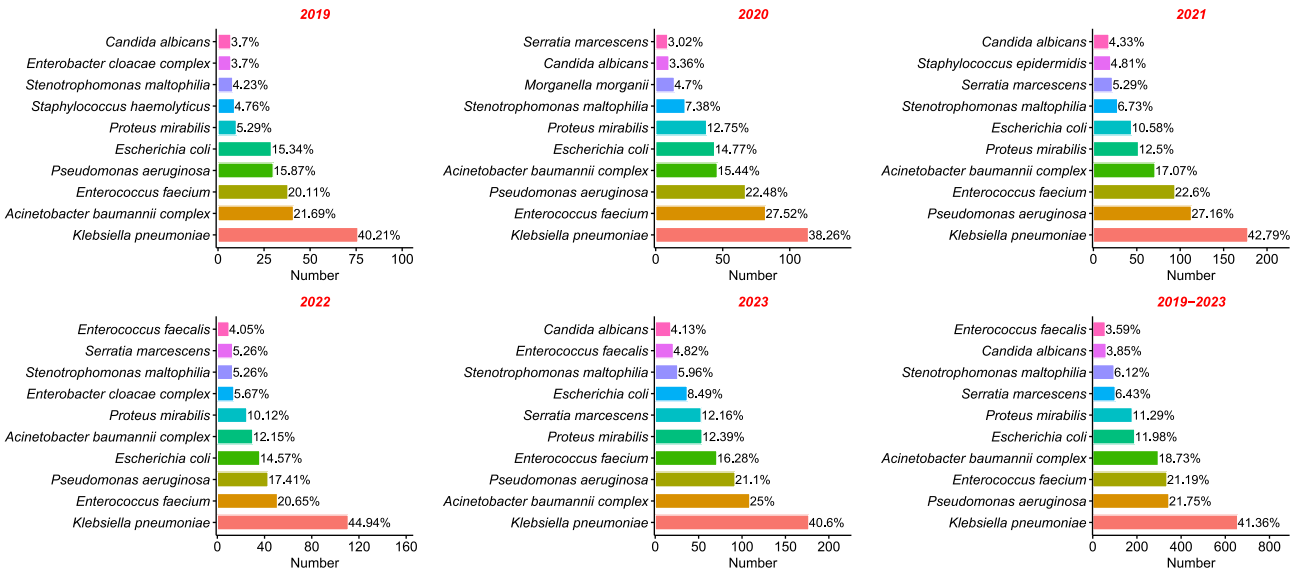

Figure 1 Quantity and proportion of microbes isolated from the pancreatic fluid of SAP patients between 2019 and 2023. The percentages in the bar chart represent the detection rates in pancreatic fluid samples.

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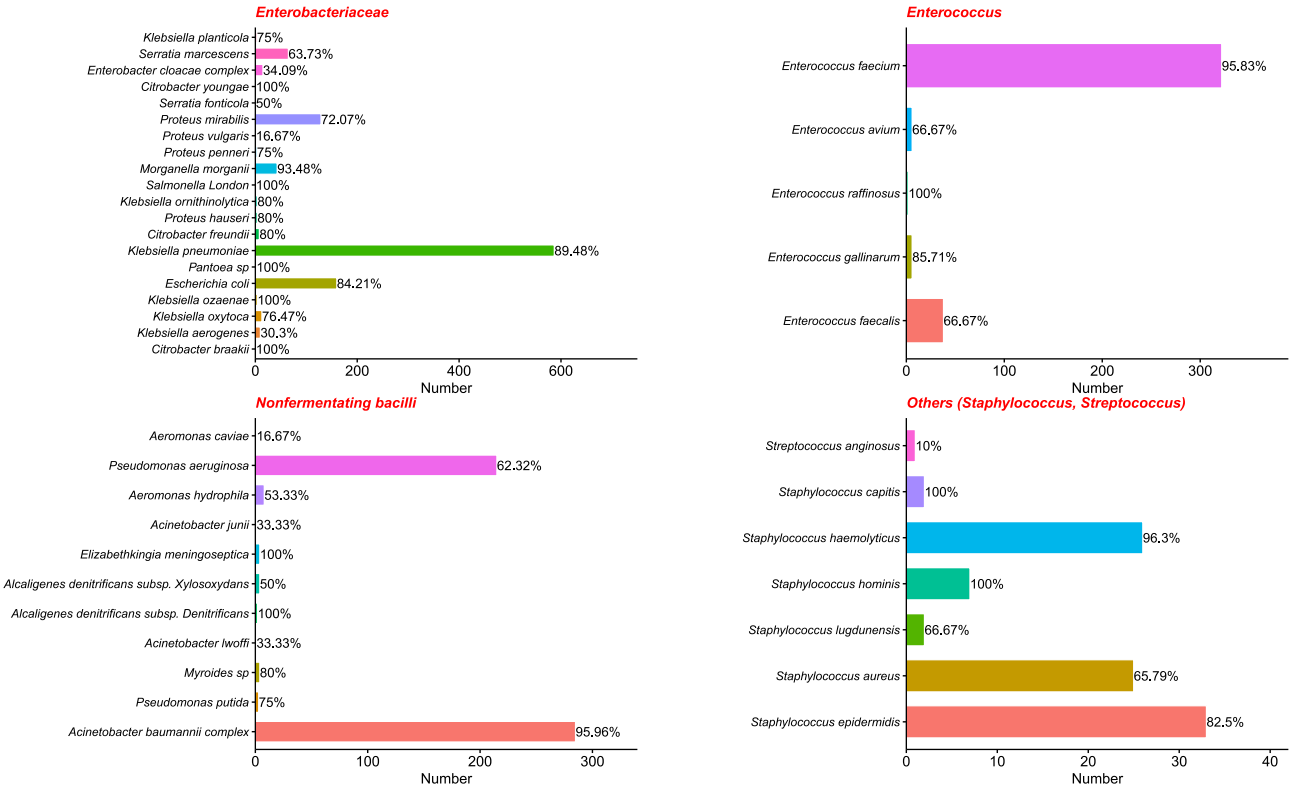

Figure 2 Distribution and quantity of multidrug-resistant bacteria. Multidrug-resistant bacteria are defined as those resistant to three different classes of antibiotics. The percentages in the bar chart represent the rates of multidrug resistance.

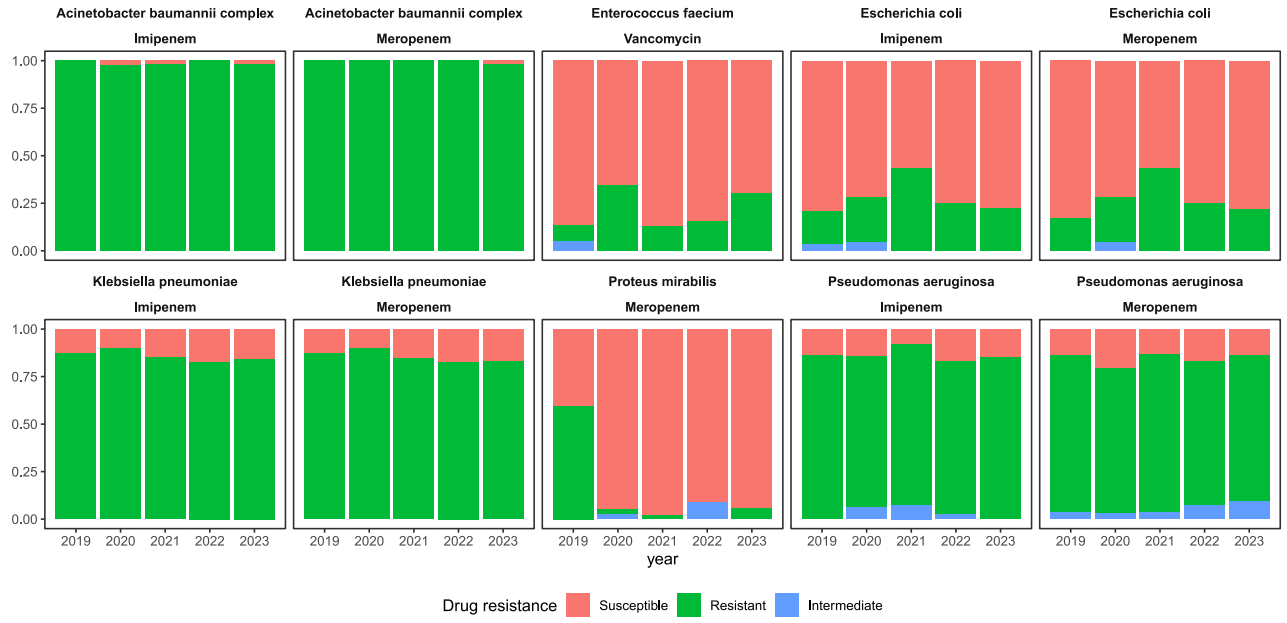

Figure 3 Analysis of antibiotic resistance in predominant pathogens from 2019 to 2023. The resistance of *A. baumannii* complex, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis* to carbapenem antibiotics, imipenem and meropenem; the percentage of vancomycin resistance in *E. faecium*.

to meropenem exhibited a significant decreasing trend (Table S2, $p < 0.05$). Overall, *A. baumannii* displays virtually complete resistance to carbapenems, whereas over 80% of *K. pneumoniae* and *P. aeruginosa* strains are resistant to these drugs.

Risk Factor Analysis

All cohort data are shown in Table 1. Multivariate logistic regression revealed that the risk factors for poor clinical prognosis in patients with AP and pancreatic infection included septic shock, acute kidney injury, and tracheostomy (Figure 4A). The risk factors for infections caused by multi-drug resistant bacteria included length of stay in the ICU, IPN, and tracheostomy (Figure 4B).

Table 1 Demographic and Clinical Characteristics

Characteristics[a]		Clinical Outcome		*p*-value[b]
		Poor (N=138)	Improved (N=618)	
Gender	Female	38 (27.5%)	167 (27%)	0.987
	Male	100 (72.5%)	451 (73%)	
Age	Mean ± SD	51.9 ± 12.3	43.9 ± 12.8	<0.001
ICU days	Mean ± SD	32.3 ± 22.7	37.5 ± 27.4	0.018
Severity of SAP[c]	Moderate	0 (0%)	14 (2.3%)	<0.001
	Severe	34 (24.6%)	396 (64.1%)	
	Critical	104 (75.4%)	208 (33.7%)	
Etiology	Alcoholic	3 (2.2%)	5 (0.8%)	0.009
	Biliary	69 (50%)	251 (40.6%)	
	ERCP	0 (0%)	5 (0.8%)	
	Hyperlipidemia	48 (34.8%)	306 (49.5%)	
	Others	18 (13%)	51 (8.3%)	
Referred patient	Yes	127 (92%)	574 (92.9%)	0.867
	No	11 (8%)	44 (7.1%)	
Coagulation disorders	Yes	11 (8%)	8 (1.3%)	<0.001
	No	127 (92%)	610 (98.7%)	
Infected ascites	Yes	37 (26.8%)	122 (19.7%)	0.084
	No	101 (73.2%)	496 (80.3%)	
Septic shock	Yes	119 (86.2%)	126 (20.4%)	<0.001
	No	19 (13.8%)	492 (79.6%)	
ALI	Yes	16 (11.6%)	21 (3.4%)	<0.001
	No	122 (88.4%)	597 (96.6%)	
AKI	Yes	109 (79%)	218 (35.3%)	<0.001
	No	29 (21%)	400 (64.7%)	
ARDS	Yes	102 (73.9%)	223 (36.1%)	<0.001
	No	36 (26.1%)	395 (63.9%)	
Pneumonia	Yes	20 (14.5%)	72 (11.7%)	0.436
	No	118 (85.5%)	546 (88.3%)	
Cholecystitis	Yes	48 (34.8%)	168 (27.2%)	0.093
	No	90 (65.2%)	450 (72.8%)	
PVT	Yes	4 (2.9%)	12 (1.9%)	0.705
	No	134 (97.1%)	606 (98.1%)	

(*Continued*)

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Table 1 (Continued).

Characteristics[a]		Clinical Outcome		*p*-value[b]
		Poor (N=138)	Improved (N=618)	
Underlying disease				
Hypoproteinemia	Yes	45 (32.6%)	163 (26.4%)	0.168
	No	93 (67.4%)	455 (73.6%)	
Diabetes	Yes	34 (24.6%)	158 (25.6%)	0.906
	No	104 (75.4%)	460 (74.4%)	
Hypertension	Yes	13 (9.4%)	53 (8.6%)	0.88
	No	125 (90.6%)	565 (91.4%)	
Fatty Liver	Yes	28 (20.3%)	214 (34.6%)	0.002
	No	110 (79.7%)	404 (65.4%)	
Gallbladder stones	Yes	52 (37.7%)	148 (23.9%)	0.001
	No	86 (62.3%)	470 (76.1%)	
MV	Yes	15 (10.9%)	12 (1.9%)	<0.001
	No	123 (89.1%)	606 (98.1%)	
Intervention for pancreatic necrosis				
PCD	0	68 (49.3%)	290 (46.9%)	0.707
	1–2	62 (44.9%)	299 (48.4%)	
	≥3	8 (5.8%)	29 (4.7%)	
MIPN	0	107 (77.5%)	456 (73.8%)	0.654
	1–2	30 (21.7%)	156 (25.2%)	
	≥3	1 (0.7%)	6 (1%)	
ON	No	123 (89.1%)	596 (96.4%)	<0.001
	Yes	15 (10.9%)	22 (3.6%)	
MDR organism				
	Non-MDRO	13 (9.4%)	81 (13.1%)	0.297
	MDRO	125 (90.6%)	537 (86.9%)	
Fungi infection	Yes	66 (10.7%)	24 (17.4%)	0.040
	No	552 (89.3%)	114 (82.6%)	

Notes: [a]APFC, acute peripancreatic fluid collection; ANC, acute necrotic collection; PPC, pancreatic pseudocyst; WON, walled-off necrosis; IPN, infected pancreatic necrosis; PVT, portal vein thrombosis; NIV, non-invasive ventilation; MV, mechanical ventilation; ETI, endotracheal intubation; PCD percutaneous catheter drainage; MIPN, minimally invasive pancreatic necrosectomy; ON, open necrosectomy; AKI, acute kidney injury; ALI, acute liver Injury; ARDS, acute respiratory distress syndrome; ERCP, endoscopic retrograde cholangiopancreatography. [b]p-values are derived from Student's *t*-test, chi-square test, or Fisher's exact test. [c]Classification of acute pancreatitis severity is based on the actual local and systemic determinants of severity.[5]

Discussion

We conducted a single-center retrospective analysis of the microbial spectrum of pancreatic infections in patients with AP from 2019 to 2023, and analyzed the factors associated with the prognosis and risk of multidrug-resistant infections. The results showed that *K. pneumoniae, P. aeruginosa, A. baumannii*, and *E. faecium* were the most common pathogens associated with pancreatic infections, and most of these pathogens were classified as multidrug-resistant. Multivariate logistic regression analysis identified septic shock, acute kidney injury, and tracheostomy as independent risk factors of poor prognosis in patients with SAP or CAP.

In this study, over 90% of the patients with AP were referred, with approximately 40% classified as CAP. This indicates that most patients progressed to a severe or critically ill status owing to ineffective early treatment. Additionally, likely influenced by prior antimicrobial therapy, routine microbial cultures of 1586 pancreatic fluid samples revealed over 40% isolated *K. pneumoniae*, a significant increase compared to the previously reported rate of 10–30% in SAP,[3,12–14] although this remains lower than the results obtained through next-generation sequencing (NGS) in our previous study.[5] Notably, nearly 90% of *K. pneumoniae* strains are multidrug-resistant. The positive culture rate for non-

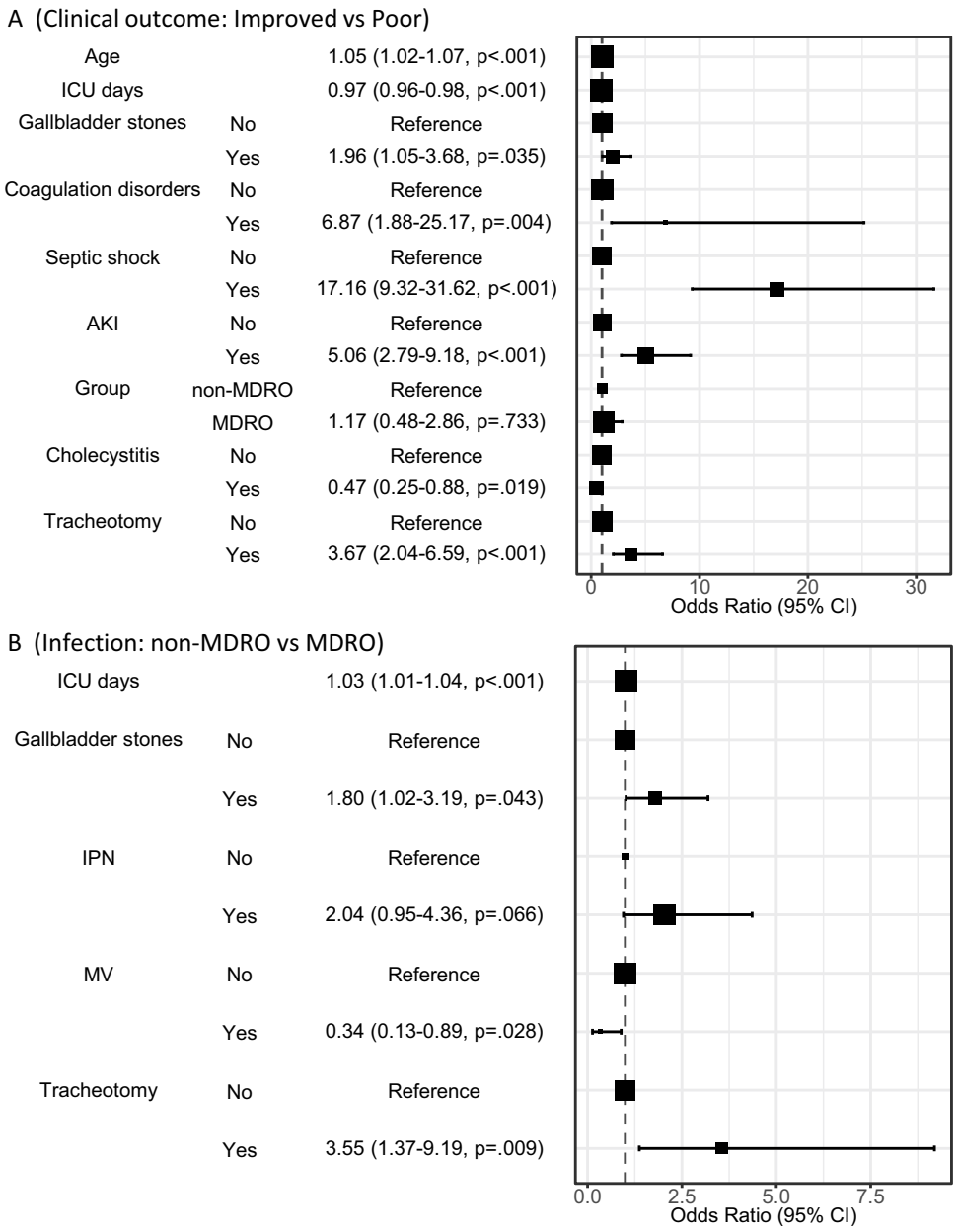

Figure 4 Multivariate logistic regression analysis of risk factors for clinical outcome (**A**) and multiple drug-resistant organism (MDRO) infection (**B**) in SAP patients.
Abbreviations: ICU, intensive care unit; AKI, acute kidney injury; MV, mechanical ventilation; IPN, infected pancreatic necrosis.

fermenting bacteria, including *P. aeruginosa* and *A. baumannii* complex, was approximately 20%, with over 90% of *A. baumannii* and 60% of *P. aeruginosa* identified as multidrug-resistant.[15] Due to the favorable penetration and drug concentration of carbapenems in the pancreas,[16] as well as their resistance to β-lactamases, they have shown good efficacy against MDRO and are widely used in the antimicrobial treatment of patients with SAP. However, both *K. pneumoniae* and *A. baumannii* have high rates of carbapenem resistance, suggesting that a combination of multiple antibiotics may be necessary. Another important pathogen identified was *E. faecium*, with a positive culture rate of approximately 20%. Approximately 95% of the strains were classified as multidrug-resistant, with vancomycin resistance exceeding 10%. Overall, from 2019 to 2023, there were no significant changes in the types of pathogens causing pancreatic infections, and while the resistance rates of pathogens fluctuated between years, there was no clear trend of increase or decrease.

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The clinical course of patients with SAP is generally divided into two mortality.[17] The first peak occurs within the first two weeks after onset, primarily due to a systemic inflammatory response leading to multiple organ dysfunction. Pancreatic infections are relatively rare in their early stages. The second peak is associated with late deterioration due to organ failure, primarily resulting from IPN and sepsis.[18] In this study, the poor prognosis rate of SAP or CAP was 18.25% (138/756). Notably, the poor prognosis rate for patients with IPN was 23.83%, which is consistent with recent reports.[4,19] Hyperlipidemia has emerged as the leading etiology, whereas patients with gallstone-related SAP or CAP display a higher rate of poor prognosis. With advancements in the management of IPN,[7] there has been a shift from direct open surgical necrosectomy to a step-up treatment approach incorporating antibiotics, PCD, and MINV. Although the IPN is still an important determinant associated with the clinical outcome of patients with SAP or CAP, it was not an independent risk factor for poor prognosis in patients with SAP or CAP in the present study, which is consistent with several previous studies.[4,19,20] Similar to the findings of Lee et al,[21] multidrug-resistant bacterial infections were not identified as independent risk factors for poor prognosis in patients with SAP or CAP. This may be attributed to the close relationship between multidrug-resistant infections and IPN; changes in management strategies for IPN may have mitigated the negative impact of both on the prognosis of patients with SAP or CAP. Open necrosectomy was not an independent risk factor for overall prognosis, although it showed significant differences in the univariate analysis. This can be explained by the fact that open necrosectomy is performed after PCD and/or MINV for debridement, which significantly improves the prognosis of patients with SAP or CAP. Septic shock and acute kidney injury were major risk factors for poor treatment outcomes in SAP or CAP, which aligns with previous study.[4,19,22] Furthermore, tracheostomy, typically performed on patients requiring prolonged mechanical ventilation, is associated with high mortality rates, challenging rehabilitation processes, and decreased quality of life.[23] Notably, the emergence of MDROs (multidrug-resistant organisms) is also linked to invasive mechanical ventilation measures.[24] Therefore, in assessing patient prognosis, besides tracheostomy, which stands out as an important predictor, septic shock, and acute kidney injury should also be considered as crucial factors.

The limitations of this study include the inherent nature of retrospective research, which inevitably presents missing variables and data imbalances; in particular, a significant number of patients were transferred from other facilities, and the pre-admission treatment strategies, medication regimens, and interventions all significantly influence patient prognosis and infection status. Second, MDRO infections could potentially be linked to infection control issues at our hospital. Owing to constraints, we also lacked data on anaerobic culture results related to pancreatic infections. Finally, a prospective study is needed to investigate the factors associated with the prognosis of severe pancreatitis to better guide clinical intervention.

In conclusion, this study analyzed the pathogen infection status of patients with SAP or CAP over the past five years while assessing the risk factors influencing patient prognosis. Our findings indicate that *K. pneumoniae, P. aeruginosa, A. baumannii* complex, and *E. faecium* are the predominant pathogens, all showing a high prevalence of multidrug resistance in pancreatic infections. Moreover, organ failure, such as septic shock and acute kidney injury, has been identified as an independent risk factor for a poor prognosis in patients with SAP.

Ethics Statement

This study was approved by the Human Use Ethics Committee of the Jinling Hospital (2024DZGJJ-121). All experimental procedures adhered to the ethical standards of Jinling Hospital in China as well as the 1964 helsinki Declaration and its later amendments or comparable ethical standards. Owing to the retrospective nature of this cohort study, the Jinling Hospital Ethics Review Committee waived the requirement for direct patient enrollment and informed consent. Information was collected anonymously from the electronic medical system, and all authors ensured confidentiality of patient data.

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Disclosure

The authors report no conflicts of interest in this work.

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