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Adverse clinical outcomes associated with multidrug-resistant organisms in patients with infected pancreatic necrosis

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ABSTRACT

Background: Multidrug-resistant organisms (MDROs) is becoming a serious worldwide threat to public health. However, the impact of MDROs on the outcomes of the patients with infected pancreatic necrosis (IPN) remains unclear. This study aims to evaluate the roles of MDROs in IPN.
Methods: A prospectively maintained database of 188 patients with IPN between January 2010 and May 2019 was analyzed. The microbiology profile of organisms isolated from wall-off necrosis (WON) was specifically investigated to correlate with the outcomes of the patients.
Results: Of the 188 patients with IPN, 108 patients (57.4%) had MDROs detected in aspirates from WON. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) accounted for 43.5% of the MDROs isolated (60/138), followed by Carbapenem-resistant Acinetobacter baumanii (CRAB) (34.8%, 48/138) and *Escherichia coli* producing an extended-spectrum beta-lactamase (ESBLp) (6.5%, 9/138). MDROs infection was associated with higher mortality (35.2% vs 11.3%, $P < 0.001$), higher rate of hemorrhage (36.1% vs 11.3%, $P < 0.001$), longer intensive care unit (ICU) stay (23 vs 12 days, $P < 0.001$), longer hospital stay (68 vs 51 days, $P = 0.001$) and more hospitalization expenses (45,190 ± 31,680 vs 26,965 ± 17,167 $, $P < 0.001$). Multivariate analysis of predictors of mortality indicated that MDROs infection (OR = 2.6; 95% confidence interval [CI], 1.0–6.5; $P = 0.042$), age ≥ 50 years (OR = 2.6; 95% CI, 1.2–5.8; $P = 0.016$), severe category (OR = 2.9; 95% CI, 1.1–8.0; $P = 0.035$), bloodstream infection (OR = 3.4; 95% CI, 1.5–7.6; $P = 0.049$), step-down surgical approach (OR = 2.7; 95% CI, 1.1–6.2; $P = 0.023$) were significant factors.
Conclusions: MDROs infection was prevalent among patients with IPN and associated with adverse clinical outcomes and increased mortality.

Introduction

Infected pancreatic necrosis (IPN), a severe complication of acute necrotizing pancreatitis (ANP), is a major cause of morbidity and mortality in patients with acute pancreatitis (AP) [1]. Approximately 30% of patients with ANP will develop IPN, which carries mortality of 20–30% [2]. Due to the development of minimally invasive surgical and endoscopic techniques, much progress has been made in terms of infection source control [3]. Thus, the impact of infection on the outcomes of the patients with AP seemed to decline in high-volume centers [4,5]. Under such circumstances, the role of IPN needs to be re-evaluated.

Another important trend in recent years was the increasing proportion of infection caused by multidrug-resistant organisms (MDROs) in patients with IPN [6–8]. The main underlying reason for this change has been thought to be the overuse of broad spectrum antibiotics [7,9,10]. However, the impact of MDROs on the outcome of IPN was still lack of data and is controversial. Lee et al. found that MDROs infection in pancreatic fluid was associated with longer ICU stay, but not associated with increased mortality [6]. Whereas Jain et al. concluded that complicated IPN due to MDROs infection was one of the independent predictors of mortality in

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patients with AP [7]. Conflicting results of these studies may be due to the small sample sizes involved (46 and 108 IPN patients for Lee et al. and Jain et al. respectively) and no comparison was done between patients with or without MDROs infection. Thus, the role of MDROs in patients with IPN was still quite unclear.

The present study was undertaken in a prospectively maintained database of the patients with IPN to identify the microbiology profile from wall-off necrosis (WON) at a large Chinese tertiary hospital, with specific focus on the impact of MDROs on the outcomes of the patients.

Methods

Patient identification and definitions

188 patients with IPN were prospectively and consecutively enrolled at Xiangya Hospital of Central South University from January 2010 to May 2019. Prospectively maintained database included clinical, radiological, microbiological, and follow-up data. All persons gave their informed consent prior to their inclusion in the study. The diagnosis and classification of AP were based on the Revised Atlanta Classification and American Gastroenterological Association guideline [11,12]. Pancreatic necrosis was diagnosed as non-enhancing areas of the pancreas on a contrast enhanced CT scan. WON was defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis which has developed a well-defined inflammatory wall. IPN was defined as a positive culture of pancreatic and/or peripancreatic necrosis or fluid obtained during the first necrosectomy or drainage. Patients with solitary fungal infections were excluded in the study. The criteria for organ failure was defined for 3 organ systems (respiratory, cardiovascular, or renal) based on the worst measurement over a 24-h period. Respiratory failure: $PaO_2/FiO_2 \leq 300$ mmHg ($\leq$40 kPa) or a need for mechanical ventilation; Cardiovascular failure: circulatory systolic blood pressure < 90 mmHg, despite adequate fluid resuscitation or need for inotropic agent; Renal failure: creatinine $\geq$ 171 μmol/L ($\geq$2.0 mg/dL) or a need for hemofiltration or hemodialysis [13]. Persistent organ failure was defined as organ failure in the same organ system for more than 48 h.

MDROs were defined as microorganisms not susceptible to at least 1 agent in at least 3 microbial categories [14]. When a species had intrinsic resistance to an antimicrobial category, that category was removed from the list before applying the criteria as per the definitions and was not included when calculating the number of categories to which the bacterial isolate was nonsusceptible. In this study, MDROs included the following microorganisms: Carbapenem-resistant Acinetobacter baumanii (CRAB), *Escherichia coli* producing an extended-spectrum beta-lactamase (ESBLp), Klebsiella oxytoca ESBLp, Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), Carbapenem-resistant Citrobacter freundii, Carbapenem-resistant *Enterobacter cloacae*, Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-resistant Coagulase-negative Staphylococci (MRCNS).

Management protocol

After admission, all patients were assessed by the multidiscipline team, which included pancreatic surgeons, ICU physicians, gastroenterology physicians and radiologists. All patients were managed according to the latest international guidelines [11,15]. Patients were admitted to the ward or ICU depending on the severity of illness proposed by the Revised Atlanta Classification [12]. In this cohort, fine-needle aspiration was never used to diagnose infected necrosis. Patients with sepsis were usually managed with empirical antibiotics initially and if failed, surgical intervention would be attempted. A step-up surgical approach consisting of percutaneous catheter drainage (PCD) [16] and if necessary, subsequent minimal access retroperitoneal necrosectomy (MARPN) [17,18] and/or open necrosectomy (OPN) [18,19] was the preferred strategy. When sepsis could not be controlled despite active minimally invasive techniques was used or severe complications (uncontrolled bleeding, intestinal leakage) occurred, OPN would be the last resort of step-up approach. OPN could also be adopted as the initial surgical procedure to remove the infected necrosis when there was no route for PCD or transluminal drainage. Multiple surgical interventions were often required to fully control the sepsis. Endoscopic drainage or debridement was seldom used in this cohort. Antimicrobial susceptibility of the cultured organisms was tested by infectious disease specialists using the standard protocol.

Ethics committee approval

The study was approved by the Ethics Committee of Xiangya Hospital, Central South University, China (reference: 201906140). Informed consent was obtained from all patients or their representative for publication of data. STROBE guidance for the reporting of data was followed [20].

Statistical analysis

Death was the primary endpoint. Continuous variables were expressed using medians with standard deviations (SD), and categorical variables were described in absolute numbers and in percentages. In the univariate analysis, the Student's t-test, the Fisher exact test, the $\chi 2$ test, and binary logistic regression analysis were used for bivariate comparisons. Significant variables were included in the multivariate analysis, which was performed using logistic regression analysis. Odds ratio (OR) with 95% confifidence interval (CI) was calculated. *P*-values < 0.05 was considered to be statistically significant. All the statistical analyses were performed using the Statistical Product and Service Solutions (SPSS) 22.0 statistical software package (IBM Analytics, Armonk, NY) in this study.

Results

Patient characteristics

During the study period from January 2010 to May 2019, a total of 4920 cases of AP were admitted: 64.1% of them had mild AP, 28.6% had moderate AP, 7.3% had severe AP. The proportion of etiology were 53.8% of biliary, 27.2% of hyperlipidemic, 5.3% of alcoholic and 13.7% of other causes. Over this period, a total of 188 patients (3.8%) with IPN were enrolled prospectively. Of these, 132 patients were male (70.2%). The mean age was 46.9 ± 12.5 years old. Biliary AP was the most common cause (n = 88, 46.8%), followed by hyperlipidemic (n = 70, 37.2%), alcoholic (n = 9, 4.8%) and idiopathic (n = 21, 11.2%). 71 patients (37.8%) were classified as moderately severe and 117 patients (62.2%) were severe according to 2012 Atlanta criteria [13]. 136 patients (72.3%) were transferred from other centers after 7 days from onset of the disease.

The cohort was divided into two groups based on the culture results of the aspirates from WON: MDROs group and non-MDROs group. Table 1 shows the comparison of baseline characteristics and outcomes between two groups. There was no significant difference in baseline characteristics including age, gender and etiology. However, the rate of severe categories in MDROs group was significantly higher (75.0% vs 45.5%, $P < 0.001$). In addition, more cases with bloodstream infection (51.9% vs 20.0%, $P < 0.001$) and

Table 1
Comparison of baseline characteristics and outcomes between patients with and without MDROs.

Characteristics	Total (n = 188)	MDROs (n = 108)	Non-MDROs (n = 80)	*P* value
Age, years (mean ± SD)	46.9 ± 12.5	47.3 ± 12.1	46.3 ± 13.0	0.617
Male, n (%)	132 (70.2)	78 (72.2)	54 (67.5)	0.484
Etiology, n (%)				0.938
Biliary	88 (46.8)	51 (47.2)	37 (46.2)	
Hypertriglyceridemia	70 (37.2)	39 (36.1)	31 (38.8)	
Alcohol	9 (4.8)	6 (5.6)	3 (3.7)	
Others	21 (11.2)	12 (11.1)	9 (11.3)	
Severe AP, n (%)	117 (62.2)	81 (75.0)	36 (45.5)	0.000
Referred patient, n (%)	136 (72.3)	100 (92.6)	36 (45.0)	0.000
Time from onset to first surgical intervention, days (mean ± SD)	31.2 ± 36.3	25.8 ± 20.9	38.5 ± 49.4	0.017
Step-up surgical approach, n (%)	146 (77.7)	81 (75.0)	65 (81.3)	0.309
OPN, n(%)	52 (27.7)	34 (31.5)	18 (22.5)	0.173
Bloodstream infection, n (%)	72 (38.3)	56 (51.9)	16 (20.0)	0.000
Fungal infection, n (%)	58 (30.9)	42 (38.9)	16 (20.0)	0.006
ICU stay, days (mean ± SD)	18.3 ± 19.9	22.9 ± 21.5	12.1 ± 15.7	0.000
Hospital stay, days (mean ± SD)	60.7 ± 34.4	67.7 ± 37.8	51.2 ± 26.7	0.001
Death, n (%)	47 (25.0)	38 (35.2)	9 (11.3)	0.000
Major complications, n (%)				
Hemorrhage	48 (25.5)	39 (36.1)	9 (11.3)	0.000
Intestinal leakage	37 (19.7)	25 (23.1)	12 (15.0)	0.165
Pancreatic fistula	71 (37.8)	46(42.6)	25(31.3)	0.113
Hospitalization expenses, dollar (mean ± SD)	37,435 ± 27936	45,190 ± 31,680	26,965 ± 17,167	0.000

fungal infection (38.9% vs 20.0%, $P = 0.006$) were identified in MDROs group. Besides, the referred patients had a higher incidence of MDROs infection than those primarily admitted patients (92.6% vs 45.0%, $P < 0.001$).

Microbiology profile of organisms

Table 2 presents the microbiology profiles of organisms isolated from WON. Infection with MDROs was found in 108 (57.4%) of the 188 patients with IPN. A total of 504 microorganisms were isolated in aspirates from WON and 138 isolates (27.4%) were MDROs. The 504 isolates included 331 (65.7%) strains of Gram-negative bacteria, 112 (22.2%) strains of Gram-positive bacteria and 61 (12.1%) of fungus. *Klebsiella pneumoniae* was the most common Gram-negative bacteria (82/331, 24.8%), and Enterococcus faecium was the most common Gram-positive bacteria (59/112, 52.7%). Candida albicans was the most frequently isolated Candida species (31/61, 50.8%).

The most common MDRO was CRKP (43.5%, n = 60), followed by CRAB (34.8%, n = 48) and *Escherichia coli* ESBLp (6.5%, n = 9). Other common MDROs were CRPA (n = 7), MRCNS (n = 5), MRSA (n = 5), Carbapenem-resistant Citrobacter freundii (n = 2) and Carbapenem-resistant *Enterobacter cloacae* (n = 2). The percentages of resistance in each bacterium were as follows: 75% for *Klebsiella pneumoniae*, 73.8% for Acinetobacter baumanii, 71.4% for Coagulase-negative staphylococci, 38.5% for *Staphylococcus aureus*, 28.6% for Citrobacter freundii, 16.4% for *Escherichia coli*, 7.7% for *Enterobacter cloacae*.

Table 2
Microbiology profile of organisms in infected pancreatic necrosis.

Organisms	Total isolates (n = 504)	MDR isolates (n = 138)	Percentage of MDROs (%)
Gram negative bacteria			
Klebsiella pneumoniae	82	60	75.0
Acinetobacter baumanii	65	48	73.8
Escherichia coli	55	9	16.4
Pseudomonas aeruginosa	32	7	21.9
Enterobacter cloacae	26	2	7.7
Stenotrophomonas maltophilia	16	–	–
Proteus mirabilis	9	–	–
Citrobacter freundii	7	2	28.6
Klebsiella oxytoca	6	–	–
Burkholderia cepacia	4	–	–
Serratia marcescens	4	–	–
Bacteroides species	4	–	–
Enterobacter aerogenes	7	–	–
others	14	–	–
Gram positive bactetia			
Enterococcus faecium	59	–	–
Streptococcus	17	–	–
Staphylococcus aureus	13	5	38.5
Enterococcus faecalis	10	–	–
Coagulase-negative staphylococci	7	5	71.4
Staphylococcus haemolyticus	6	–	–
Fungus			
Candida albicans	31	–	–
Candida non-albicans species	30	–	–

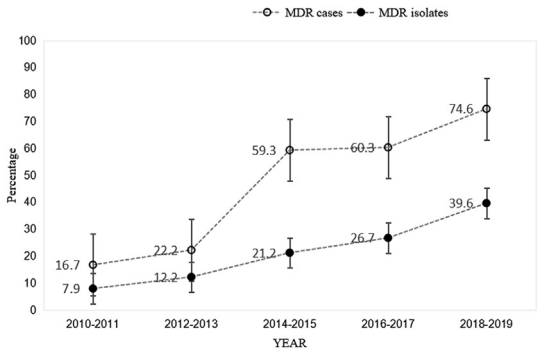

Fig. 1. Trends for percentages of MDR cases and MDR isolates in patients with IPN between 2010 and 2019. Line around the hollow point reflects the incidence rate of MDR cases by year, while the line around solid point shows the percentage of MDR isolates by year. Vertical lines around point estimates represent 95% confidence intervals estimated percentage.

Percentages of MDROs infection and their trends

From 2010 to 2019, stable increases in percentages of both MDROs strains and patients infected with MDROs were noted. The percentage of MDROs strains increased from 7.9% to 39.6% and the percentage of patients infected with MDROs increased from 16.7% to 74.6% (Fig. 1).

Outcomes

Overall mortality rate in this cohort was 25.0% (47/188). Mortality was significantly higher in patients with MDROs infection (35.2%, 38/108) compared with those without MDROs infection (11.3%, 9/80) ($P < 0.001$). In addition, patients in MDROs group had higher rate of hemorrhage (36.1% vs 11.3%, $P < 0.001$), longer hospital stay (68 vs 51days, $P = 0.001$), longer ICU stay (23 vs 12days, $P < 0.001$) and higher hospitalization expenses ($45,190 \pm 31,680$ vs $26,965 \pm 17,167$ $, $P < 0.001$) compared with those without MDROs infection. Whereas the rate of pancreatic fistula was not significantly different between two groups (42.6% vs 31.3%, $P = 0.113$).

Predictors of mortality

Table 3 lists the potential predictive factors of mortality in patients with IPN. In the univariate analysis, age ≥50 years, severe category, MDROs infection, bloodstream infection, OPN, step-down surgical approach were associated with increased mortality. In the multivariate analysis, age ≥50 years (OR = 2.6; 95% CI, 1.2–5.8; $P = 0.016$), severe category (OR = 2.9; 95% CI, 1.1–8.0; $P = 0.035$), MDROs infection (OR = 2.6; 95% CI, 1.0–6.5; $P = 0.042$), bloodstream infection (OR = 3.4; 95% CI, 1.5–7.6; $P = 0.049$), step-down surgical approach (OR = 2.7; 95% CI, 1.1–6.2; $P = 0.023$) were identified as independent predictors associated with higher mortality in IPN patients.

Discussion

To the best of our knowledge, this is the largest prospective study ever conducted in a tertiary hospital in China that specifically evaluates the impact of MDROs on outcomes of patients with IPN. We found that the percentages of both MDROs strains and patients infected with MDROs increased significantly over the past 10 years. MDROs infection was associated with adverse outcomes, including higher mortality and morbidity, longer ICU and hospital stay, and higher hospitalization expenses as well. Clinically, these results suggested that MDROs has become a major obstacle in battling against the infectious complications of AP in China.

Antibiotic resistance has become one of the leading public threats worldwide [21], with antimicrobial overuse thought to be the main culprit, thus creating a dilemma surrounding selection of appropriate antibiotics. Selection pressure from antimicrobial overuse was thought to be the main culprit. In patients with AP, antibiotic overuse was quite common. In many instances, clinicians initiated antibiotic therapy only based on increased white blood cells and/or elevated CRP, lipase and amylase levels, which has been proven to have no association with infections in AP [22]. No consensus has been reached on the indication of prophylactic antibiotic therapy. Controversies existed even among the guidelines. Guidelines from Western countries or societies did not recommend routine antibiotic prophylaxis for patients with AP [11,15,23,24], whereas Asian countries or societies like Japan recommended that although the prophylactic administration of antibiotics was not necessary in mild AP, the antibiotic prophylaxis was encouraged in SAP and necrotizing pancreatitis [25]. In population-based studies, 14–30% of patients with AP received prophylactic antibiotics in Europe and America, in contrast with alarming high percentages of 74–81% in Asian countries [26–30]. The differences of antibiotic usage might explain the differences of percentages of MDRO in patients with IPN between the districts. MDROs were isolated from 12.3% (15/122) of patients in Silvia et al.'s report from Germany [31] and 6.7% (5/75) in Sahar et al.'s report from the USA [32]. In contrast, 86.8% (164/189) and 63% (29/46) of patients were found to have MDROs infection in India and Korea, both of which were from Asia [6,33]. In this cohort, 57.4% (108/188) of patients with IPN were found to have MDROs infection. Moreover, both the percentages of MDROs isolated and patients infected with MDROs increased almost 5-fold over the past 10 years. MDROs have become a major threat to patients with IPN in our institute. Whereas a high frequency of gram-positive organisms might have been anticipated in previous studies [6,32,34], our results were noteworthy of the high frequency of gram-negative organisms, with CRKP and CRAB the most common MDROs. In this study, only a few cases had multidrug-resistant gram-positive organisms. No

Table 3
Predictors of mortality in IPN patients.

Variables	Non-survivors (n = 47)	Survivors (n = 141)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
Male, n (%)	36(76.6)	96(68.1)	1.5(0.7–3.3)	0.269	–	–
Age≥50 years, n (%)	29 (61.7)	59 (41.8)	2.2(1.1–4.4)	0.018	2.6 (1.2–5.8)	0.016
Severe category, n (%)	40 (85.1)	77 (54.6)	4.8 (2.0–11.3)	0.000	2.9 (1.1–8.0)	0.035
MDROs infection, n (%)	38 (80.9)	70 (49.6)	4.3 (1.9–9.5)	0.000	2.6 (1.0–6.5)	0.042
Bloodstream infection, n (%)	33 (70.2)	39 (27.7)	6.2(3.0–12.7)	0.000	3.4 (1.5–7.6)	0.002
Fungal infection, n (%)	13 (27.7)	45 (31.9)	0.8(0.4–1.7)	0.584	–	–
OPN, n (%)	19 (40.4)	33 (23.4)	2.2(1.1–4.5)	0.024	1.6(0.5–5.6)	0.419
Step-down surgical approach, n (%)	17 (36.2)	26 (18.4)	2.5(1.2–5.2)	0.012	2.7(1.1–6.2)	0.023

vancomycin-resistant enterococcus (VRE) infection was noted. One explanation for this phenomenon was the fact that almost all the patients in our institute were administered with carbapenems or the third-generation cephalosporins either prophylactically or therapeutically. In contrast, vancomycin was never used prophylactically and unless when the culture and sensitivity results indicated its usage.

Abundant cases of MDROs infection in Asian countries provided a good opportunity to investigate the burden and the impact of MDROs. Lim et al. collected patient records including microbiological and laboratory data from nine hospitals in northeast Thailand from 2004 to 2010 and linked these with the national death registry to obtain the 30-day mortality outcome. They estimated that an extra 19,000 deaths were caused by MDROs in Thailand each year [21]. Similar situation also occurred in India [35]. Critically ill patients with prior antimicrobial exposure or comorbidities were particularly vulnerable to infection with MDROs, which might increase mortality and medical costs [36,37]. However, its role in IPN were still lacking in data and is controversial. Lee et al. found that MDROs infection in pancreatic fluid was associated with longer ICU stay, but not associated with increased mortality [6]. However, the cohort study was quite small ($n = 46$). Moka et al. investigated the microbiological profile in pancreatic and extrapancreatic sites in patients with AP and found that infection with multidrug-resistant bacteria increased mortality [33]. However, the bacteria were from multiple sites including blood, endotracheal aspirate/sputum or WON. No conclusions could be drawn on the association of MDROs in WON and the outcomes of patients with IPN. Recently, a growing number of studies using multivariate analysis have identified MDROs infection as independent predictor of mortality in patients with AP [7] and IPN [31]. Previous study in our institute also demonstrated that MDROs infection was one of the independent death predictors in patients with critical AP [38], which was the most severe category of AP in determinant-based classification [39]. However, studies mentioned above were either retrospective or only involved a small cohort made up of patients with IPN. A prospective study involving more patients with IPN were urgently needed to address questions that existed regarding the impact of MDROs on the clinical outcomes of IPN. In this prospective, single-center observational cohort study involving 188 cases of IPN, MDROs infection was associated with higher mortality, higher rate of hemorrhage, longer ICU stay and hospital stay and more medical costs, compared with susceptible organism infection. Multivariate analysis of predictors of mortality indicated that MDROs infection was one of the significant factors in patients with IPN.

Our findings have important implications for the management of patients with IPN, especially in low- and middle-income countries, where MDROs are prevalent. In patients with IPN, empirical antibiotic usage was always the initial therapy. However, nearly 75% of the patients had MDROs, which means that antibiotics alone will fail in most of the cases. New antibiotics are eagerly called for [40]. However, slowness can't meet hasty demand. Antibiotics represent a limited health care resource. More efforts should be focused on how to control the infection source using surgical and/or endoscopic techniques [3].

Given significantly higher death risk and higher possibility of treatment failure observed in patients with IPN caused by MDROs, renewed efforts and effective strategies to prevent against MDROs infection are urgently required. Prevention is better than cure. Empirical antibiotic therapy should be modified based on the existing evidence in each and individual medical center, as well as susceptibility results. Meanwhile, culture and sensitivity results of acquired samples should be regularly reviewed to adjust prescribing and monitor for emergence of MDROs.

This study has several limitations. As the case with large tertiary center in China, most of the patients with IPN were transferred from other centers. The lack of complete clinical data precluded us from capturing potentially important variables, including precise data on the use of antibiotics, duration of antibiotic exposure, time to effective therapy, details before referral, all of which are associated with MDROs infection. Additionally, the data on extrapancreatic infections involving blood, bile, urine, sputum, etc were insufficient, thereby producing bias due to unmeasured confounders. Lastly, the results of the present study which derived from a single-center could not be generalized to other hospitals indiscriminately. Further multicenter, prospective original studies would provide more precise data to reduce potential confounding results.

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