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Epidemiology of Nosocomial Carbapenem-resistant Klebsiella Pneumonia Bloodstream Infections in South China: Factors Related to the Patient Mortality

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Abstract

Background: Carbapenem-resistant Klebsiella pneumoniae (CRKP) causing Bloodstream infection (BSI) are associated with high rates of mortality. Nevertheless, only a few studies regarding the epidemiology of CRKP BSI in south China. The purpose of this study was to describe the epidemiology, clinical characteristics, and the mortality of risk factors associated with CRKP causing bloodstream infection.

Methods: A retrospective study of patients with CRKP BSI was recruited from teaching hospital in south China from January 2016 to December 2018. Clinical data were collected from medical records.

Results: In total, 90 patients with CRKP BSI were enrolled in the study, while 57% (51/90) of the CRKP BSI were obtained from ICU. Most CRKP BSIs originated from hospitals (81; 85%), while the rest (9; 10%) were healthcare-associated. In univariate analysis, gastrointestinal hemorrhage (p=0.029), Pitt bacteremia score (P=0.045), Charlson comorbidity index (p=0.018) and Corticosteroids use (p=0.036) and Septic shock (p=0.001) were associated with the risk factors for mortality. In a multivariate analysis, septic shock (adjusted odds ratio [aOR] 5.591, 95% confidence interval [CI] 1.405-22.246, P=0.015) and Corticosteroids use (aOR 4.148, 95% CI 1.331-12.928, P=0.014) were independently predictors of mortality.

Conclusion: Our data showed that the morbidity and mortality of CRKP BSIs patient from ICU and non-ICU was no significant difference. Standardizing operation and improving nurse quality may play an important role in CRKP BSI patient in intensive care unit. Septic shock and Corticosteroids use were the independent factors of CRKP BSI patient mortality. However, the study did not show an association between invasive procedures and the development of CRKP BSI.

Background

Klebsiella pneumoniae isolates are among the most common bacteria causing hospital acquired infections, including bloodstream infections (BSIs)[1, 2]. Carbapenem-resistant K. pneumoniae (CRKP) was originally identified in 1996 and quickly became a serious health care problem in many countries, including China[3, 4]. CRKP can cause many serious infections, including, soft tissue infections, pneumonia, urinary tract infections, intra-abdominal and bloodstream infections. Bloodstream infection (BSI) with carbapenem-resistant Klebsiella pneumoniae (CRKP) is related to particularly high mortality rates[5]. The mortality rate of carbapenem-resistant Klebsiella pneumoniae (CRKP) infections were reported to be 50.06%, 46.71%, 33.24%, and 44.82% in Europe, South America, North America, and Asia respectively [6]. Indeed, all-cause mortality from critically ill patients with severe bloodstream CRKP infections is nearly 70%[7–9]. Emerging resistance to antibiotics of last resort (i.e. tigecycline or colistin) leaving very few therapeutic options have been shown in recent studies [10, 11]. Increasing antimicrobial drug resistance, especially in carbapenem-resistant Klebsiella pneumonia (CRKP), can limit the choice of antibiotics used for the treatment of infectious diseases and further poses a negative impact on patient

outcome. The high occurrence of cases and mortality, economic burden and dearth of alternative drugs makes CRKP infections an important threat to public health worldwide.

There are several risk factors associated with the development of CRKP BSI. Risk factors related to CRKP BSI include comorbidities, ICU stay, use of invasive devices, and exposure to carbapenem prior to culture[12]. Due to the extensive use of invasive surgery and the frequent use of antimicrobial agents, ICUs are described as a factory for generate, spread, and expansion of antimicrobial resistance. While regional and institutional infection control programs remain the cornerstone for reducing the risk of patient acquisition and death from MDR pathogens, additional tools are needed to facilitate patient screening, early diagnosis and timely use of appropriate antibiotic treatment regimens. The physician may consider this risk assessment when deciding whether a particular patient should receive early appropriate therapy for CRKP BSI until culture and sensitivity results are available.

To the best of our knowledge, few studies have assessed the hazard factors for mortality of CRKP bloodstream infection (BSI) in south China. In this study, we sought to evaluate the epidemiological, clinical characteristics, the risk factors for mortality of CRKP BSIs in patients admitted to a teaching hospital in Wenzhou, China.

Patients And Methods

Study design and patients

From January 2016 to December 2018, we retrospectively analyzed clinical data in the First Affiliated Hospital of Wenzhou Medical University, a tertiary university hospital with 4,100 beds in Zhejiang, southern China. We included all adult patients (age of day ≥ 18 years) hospitalized in the First Affiliated Hospital of Wenzhou Medical University in south China. BSI onset was defined as the collection date of a positive blood culture. Only the first CRKP BSI was included, and patients with polymicrobial BSI were excluded. All criteria are graded within 48 hours before or on the day of first positive blood culture. Laboratory examination included lymphocytes (10*9/L). The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Because the retrospective study did not cause harm to the patient, informed consent was waived.

Data collection and definitions

The data of the clinical microbiology laboratory collected included information regarding demographic characteristics, comorbidities, intravascular catheter use, recent (30 days) surgical procedures, the use of Corticosteroids (use Corticosteroids during bloodstream infections), carbapenem exposure (exposure to carbapenems during the 30 days preceding admission to the ICU) and patient outcomes were also collected(Table 1). BSIs patients were further classified into death group (n = 60) and survivor group (n = 30) according to clinical outcome of antimicrobial treatment. BSIs were defined as hospital-acquired if the positive blood culture results more than 48 h after the admission of patient to the hospital and no symptoms of infection had been noted at admission. If blood culture samples had been collected within

48 h after hospital admission, the isolate was defined as Community-acquired or healthcare-associated [13]. Septic shock was defined as sepsis associated with organ dysfunction and persistent hypotension despite volume replacement[14]. Comorbidities were calculated according to the Charlson's score[15], and the Pitt bacteremia score (PBS) was used to assess disease severity at the time of positive blood culture [16].

Table 1
Demographic and clinical characteristics of patients with bloodstream infections due to carbapenem-resistant Klebsiella pneumonia

Characteristics	All patients (N = 90)	Survivor group (n = 30)	Death group (n = 60)	P-value
Demographics				
Age (years), median(IOR)	68(58–74)	63(55–69)	70(61–75)	0.599
Male sex	64(67)	24(77)	19(32)	0.123
Hospital-acquired	81(85)	27(90)	54(83)	0.963
Healthcare-associated	9(10)	3(10)	6(9)	0.342
Lymphocyte 0.56(0.22–0.85)		0.68(0.39–0.90)	0.51(0.21–0.82)	0.702
Comorbidities				
Respiratory disease	6(7)	1(3)	5(9)	0.482
Intracranial disease	27(30)	10(32)	17(29)	0.950
Cardiovascular disease 4(4)		2(6)	2(3)	0.442
Diabetes mellitus	24(27)	8(26)	16(27)	0.836
Previous Surgery [a]	40(44)	17(55)	23(39)	0.063
Gastrointestinal hemorrhage 19(20)		2(7)	17(29)	0.003
Chronic kidney disease [b] 15(17)		3(10)	12(20)	0.246
Liver disease	14(16)	4(13)	10(17)	0.513
Malignancy	28(31)	7(33)	21(36)	0.106
Organ transplantation	3(3)	1(3)	2(3)	0.673
Immunosuppressive therapy[c] 12(13)		5(16)	7(12)	0.608
CCI, median (IQR) 4(3–5)		3(2–5)	4(3–6)	0.172
Invasive Procedures				
Indwelled Urinary catheter 69(77)		22(71)	47(80)	0.753
Indwelled central venous catheter 72(80)		22(71)	50(85)	0.328
Mechanically ventilated 45(50)		15(48)	30(51)	0.876
Surgical drainage 27(19)		5(16)	12(20)	0.568
Renal replacement therapy 14(16)		4(13)	10(17)	0.673

Characteristics	All patients (N = 90)	Survivor group (n = 30)	Death group (n = 60)	P-value
Gstrointestinal decompression	63(70)	20(65)	43(73)	0.741
Severity of Illness				
Septic shock	34(38)	3(10)	31(53)	0.000
PBS, median(IQR)	3(2–6)	2(1–4)	3(2–8)	0.128
Treatments administered				
Corticosteroids use	35(39)	9(29)	26(44)	0.003
Chemotherapy, radiotherapy	12(13)	4(13)	8(14)	0.102
Length of hospitalization	36(19–56)	52(36–64)	27(16–48)	0.047

Microbiological methods

We processed bacterial cultures in the clinical microbiology laboratory. Initially, Vitek2 system (BioMèrieux, France) was used to determine bacterial identification and the antimicrobial susceptibility. Then, the isolates were stored in frozen condition at − 80◦C with 30% glycerol. The minimum inhibitory concentration (MIC) values for tested antimicrobial agents were determined by an automated broth dilution method and interpreted by the recommendation of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2015).

Statistical analysis

Statistical analysis was carried out by SPSS for Windows, version 21.0 (IBM, Armonk, NY, USA).

The mean and standard deviation (SD), median and interquartile range (IQR) were used to compare the continuous variables of normally and non-normally distributed, respectively. Students't test (normal distribution) and Mann-Whitney U-test (non-normal distribution) were used to analyze and compare continuous variables. Categorical variables are represented by numbers and percentages. The categorical variables were analyzed by Fisher's exact test. Logistic regression analysis was used to determine the risk factors of death in each variable. In univariate analysis, the significant variables with $P < 0.05$ were included in multivariate analysis, in which we evaluated the risk factors for CRKP BSI-related mortality. A p value < 0.05 was considered to statistically significant.

Results

Characteristics of patients

Overall, 90 patients with CRKP BSI met the inclusion criteria. Ultimately, according to the inclusion and exclusion the unique episodes were included in the analysis (Fig. 1). The demographic and clinical

characteristics of patients with CRKP-BSIs are presented in Table 1. CRKP-BSI cases mainly occurred in subjects aged over 60 years (72%). The median patient age was 68 years (interquartile range 21–93 years), and 64 of 90 patients (67%) were males. All episodes of CPKP BSIs were either hospital acquired (85%) or healthcare associated (10%), while none was community acquired.

The most common disease was diabetes (27%), Previous Surgery (44%) or intracranial disease (30%), gastrointestinal hemorrhage (20%), chronic kidney disease (17%), cardiovascular disease (4%) and solid tumors (15%). There were 3(3%) cases involving solid organ transplantation and 12(13%) receiving chemotherapy. Overall, 39% of patients underwent Corticosteroids use. 12 (13%) patients received immunosuppressive therapy (cyclosporine or leflunomide) to treat systemic lupus erythematosus (Fig. 2). The median Charlton comorbidity index (CCI) and Pitt bacteremia score at onset were 4 (interquartile range3-5) and 3 (interquartile range 2.0–6.0), respectively. The invasive Procedures was indwelled Urinary catheter (69%), indwelled central venous catheter (72%), mechanically ventilated (45%), gastrointestinal decompression (63%), renal replacement therapy (14%) (Fig. 2).

Increased rates of CRKP-BSIs, including ICU and Non-ICU patients

In our study, 90 unique episodes of CRKP-BSI were included, 57% (51/90) of the CRKP isolates were came from ICU and 43% (39/90) of the CRKP BSI patients were came from non-ICU. We discovered that the occurrence of bloodstream infection causing nosocomial carbapenem-resistant Klebsiella pneumonia is increasing since 2016, and the rates of infections are much higher than the national average in the hospital included in this study. The percent of CRKP-BSI mortality in this study are presented in Fig. 3. The percentage of overall mortality increased from 60% in 2016 to 65% in 2017, with the highest rate obtained in 2018, up to 69% of CRKP BSI patients in our hospital. A similar trend, the rates of CRKP BSI mortality acquired from our Hospital in intensive care unit, rising from 60% in 2016 to 66.7% in 2017 and 78.9% in 2018. Simultaneously, the rates of CRKP BSI mortality acquired from our Hospital in non-ICU, rising from 61.5% in 2016 to 62.5% in 2017, descending 58.8% in 2018(Fig. 3).

Risk factors for mortality of CRKP BSI patients

Overall in-hospital crude mortality was 65% (59/90), similar to the previous studies[17]. Our results indicate that the invasive Procedures was indwelled Urinary catheter (69%), indwelled central venous catheter (72%), mechanically ventilated (45%), gastrointestinal decompression (63%), renal replacement therapy (14%) (Table 1). Previous studies have evaluated several risk factors for the mortality associated with CRKP BSI, including use of indwelled Urinary catheter, indwelled central venous catheter, mechanically ventilated and exposure to carbapenems. However, in our analysis, gastrointestinal hemorrhage ($p = 0.029$), Pitt bacteremia score ($P = 0.045$), Charlton comorbidity index ($p = 0.018$) and Corticosteroids therapy ($p = 0.036$) and Septic shock ($p = 0.001$) were associated with risk factors for mortality (Fig. 4). In univariate analyses, variables significant at $p < 0.05$ were included in the multivariate analysis. On multivariate analyses, septic shock (adjusted odds ratio [aOR] 5.591, 95% confidence interval

[CI] 1.405–22.246, P = 0.015) and Corticosteroids therapy (aOR 4.148, 95% CI 1.331–12.928, P = 0.014) were independently associated with a risk effect on mortality (Table 2).

Table 2
Univariate and multivariate logistic regression analysis of predictors of in-hospital mortality in patients with CRKP bacteremia

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio(OR)(95%CI)	P-value	Odds ratio(OR)(95%CI)	P-value
PBS	1.588(1.003–1.394)	**0.045**	1.071(0849 – 1.350)	0.563
CCI	1.314(1.047–1.650)	**0.018**	1.248(0.943–1.651)	0.122
Gastrointestinal hemorrhage 5.535(1.186–25.832)		**0.029**	3.763(0.672–21.058)	0.131
Septic shock 9.621(2.633–35.154)		**0.001**	5.591(1.405–22.246)	**0.015**
Corticosteroids use 2.875(1.072–7.710)		**0.036**	4.148(1.331–12.928)	**0.014**

Therapeutic characteristics

As defined in Materials and methods, 53 patients (58.8%) received early appropriate therapy, and 37 patients who received inappropriate therapy. Fifty-there patients received at least one active antibiotic, including 45 patients who received Tigecycline-based therapy (84.7%, 45/53), one patient who received Polymyxin B -based therapy and 7 who received Tigecycline combine Polymyxin B (13.2%, 7/53). The clinical characteristics of patients who underwent Tigecycline-based therapy, Polymyxin B -based therapy and Tigecycline combine Polymyxin B were summarized in Fig. 4.

Discussion:

In recent years, carbapenem-resistant Klebsiella pneumoniae (CRKP) associated bacterial infections have spread worldwide becoming a serious global public health problem in a number of countries, including China. Surveillance of antibiotic resistance by the China CHINET reported that the rate of carbapenem-resistant Klebsiella pneumoniae isolates increased from 2.4% in 2005 to 13.4% in 2014[18]. The studies were to demonstrate the epidemiological, clinical characteristics and the risk factors for predictors of mortality in south china. While our study has been collected in a single medical center, the samples were date from the First Affiliated Hospital of Wenzhou Medical University, which is one of the largest integrated teaching hospitals, clinical practice and scientific research.

CRKP-BSI cases mainly occurred in aged over 60 years (72%) and more frequently in males (67%) than in females. Confirmation of this finding is also available in the European Centers for Disease Control and Prevention database, where the higher proportion of carbapenem-resistant K. pneumoniae in males is particularly evident in countries at high prevalence of carbapenem resistance such as Italy and Romania. The reason for the higher incidence of CRKP-BSI in males than in females is not clear, but it is worth noting that the higher incidence of sepsis in males is associated with genetic susceptibility [19]. In our

study, we observed an increase in CRKP-BSI with age. This increase, especially for patients 60 years of age and older, may be associated with the high vulnerability in the elderly[20], which may determine higher frequencies and longer hospital stays than younger patients.

The patient population affected by CPKP BSI had several evident characteristics; all episodes of BSIs were either hospital or health care associated. The data showed that the rate of hospital-acquired infections was 66%, however, 75% of the patients who died had hospital-acquired infection from the CRE Epicenter of the United States[21]. Our data showed that the rate of 90% CRKP BSI patients had hospital-acquired infection, while none was community acquired. It is important for physician to control hospital infection as soon as possible.

Carbapenem-resistant Klebsiella pneumoniae (CRKP) Bloodstream infections(BSI) are becoming an crisis of global dimensions, including ICU and Non-ICU patients, due to high morbidity and mortality[22]. In our study, 57% (51/90) of the CRKP isolates were came from ICU and 43% (39/90) of the CRKP BSI patients were came from non-ICU. The overall mortality obviously increased from 60% in 2016 to 65% in 2017, with the highest rate obtained in 2018, up to 69%. This discrepancy probably caused by Zhejiang Province is one of the highest CRKP infections prevalence's region in China[18]. It is a major clinical finding that the morbidity and mortality of CRKP BSIs patient in ICU and non-ICU was no significant difference. A possible explanation may be that standardizing operation and improving nurse quality is vital key to the critically CRKP BSI patient in intensive care unit. Furthermore, characterized by advanced technology to care for severely patients and early appropriate therapy in intensive care unit, which may lead to the difference from previous data[23]. It is a monocentric study that our data may be different from other centers. Therefore, further multi-centric studies are needed to confirm our findings.

Bloodstream infections causing by Carbapenem-resistant Klebsiella pneumoniae (CRKP) clinical characteristics have been attributed to the various aspects. In previous study, it is more frequent among patients associated with CRKP BSIs with severe chronic comorbidities, but chronic comorbidities were not risk factors for CRKP BSI[24]. As consistently shown in our studies, comorbidities were not independent risk factors for CRKP BSI. Furthermore, our studies show that indwelling central venous catheter and urinary catheter were not independent risk factors for CRKP BSI, which is different with previous studies. The reason for this might associated with the small number of CRKP BSI cases in the study. All the patient peripheral blood lymphocytes before bloodstream infection were decreased in CRKP in this study. It may help physicians pay more attention to the patients who have a higher risk of bloodstream infection when the lymphocytes decreased.

The mortality rates associated with CRKP BSI have been widely reported and they range from 40–70%[25, 26]. Overall, the rate of mortality in our patients with CRKP BSI was higher (65%) compared to the findings of previously studies [27]. Previous studies have evaluated several risk factors for the mortality associated with CRKP BSI, including use of corticosteroid, use of invasive devices, septic shock and exposure to carbapenems[27–29]. Fig-4 shows that CRKP BSI was related to gastrointestinal hemorrhage, Pitt bacteremia score, Charlton comorbidity index and Corticosteroids use and Septic shock.

Septic shock and Corticosteroids use were independent risk factors for CRKP BSI, which is different with previous reported. The reason for this might provide an explanation that the regional differences and effective Hospital Infection-Control of CRKP BSI in our study. Corticosteroid should be added to septic shock patients according to the Surviving Sepsis Campaign guidelines[30]. In our study, an alarming finding is that the use of corticosteroids as adjunctive therapy in CRKP infections has deleterious effects. The most important risk factor for mortality in our study was septic shock at CRKP BSI onset; not surprisingly, this variable had been found to be associated with mortality in several previous studies performed on general population patients with CRKP BSI[8, 31].

There were several limitations associated with this study. First, the current study was a retrospective, single-center study including 90 patients with clinical analysis. Second, Clinical data were obtained retrospectively from medical records, and there may be some differences in physician practices or accuracy of information. Finally, prospective and further multi-centric studies are needed to confirm our findings.

Conclusion

There was no significant difference in CRKP BSIs patient morbidity and mortality between ICU and non-ICU. Standardizing operation and improving nurse quality may play an important role in CRKP BSI patient in intensive care unit. Septic shock and Corticosteroids therapy were independent risk factor related to the patient mortality. However, the present study did not show an association between invasive procedures and the development of CRKP BSI, which is different with previous studies reported. The regional differences and effective Hospital Infection-Control of CRKP BSI in our study might be the reason.

Declarations

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the First Affiliated Hospital of Wenzhou Medical University Ethics Committee. Informed consent was not needed due to the retrospective nature of the study; additionally, the patient data accessed inthis research was anonymous. Therefore, the First Affiliated Hospital of Wenzhou Medical University Ethics Committee waived the need for consent.

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Figures

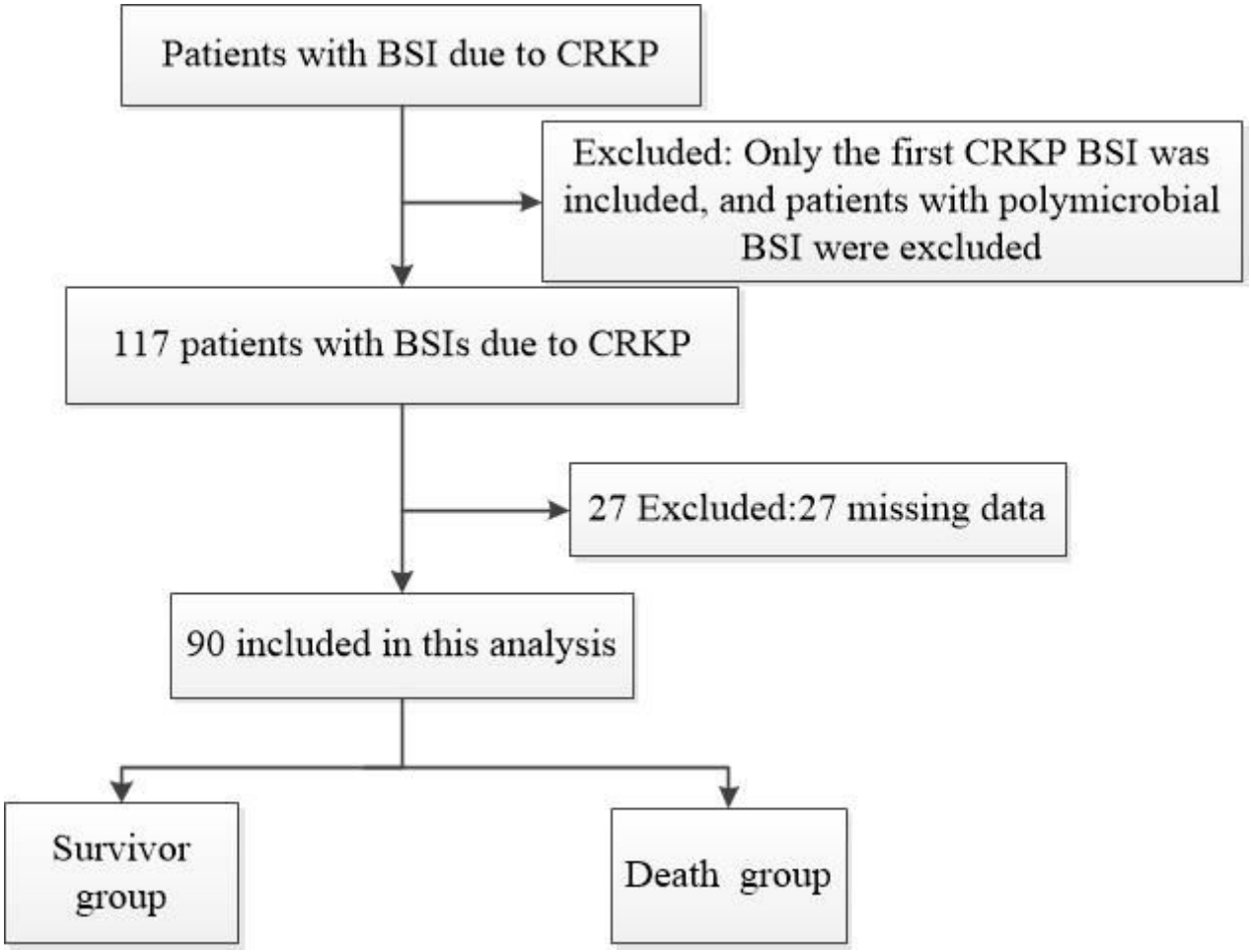


Figure 1

Flowchart of the included patients with BSIs due to CRKP

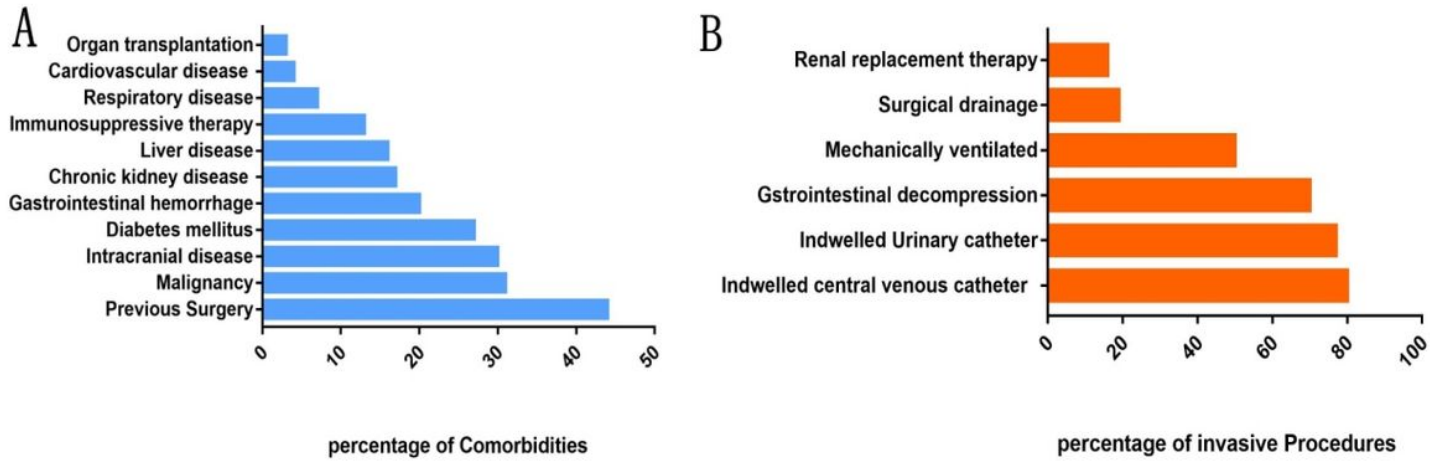


Figure 2

The percentage of CRKP BSIs patients from January 2016 to December 2018. A: percentage of CRKP BSIs patients' comorbidities; B: percentage of CRKP BSIs patients invasive Procedures

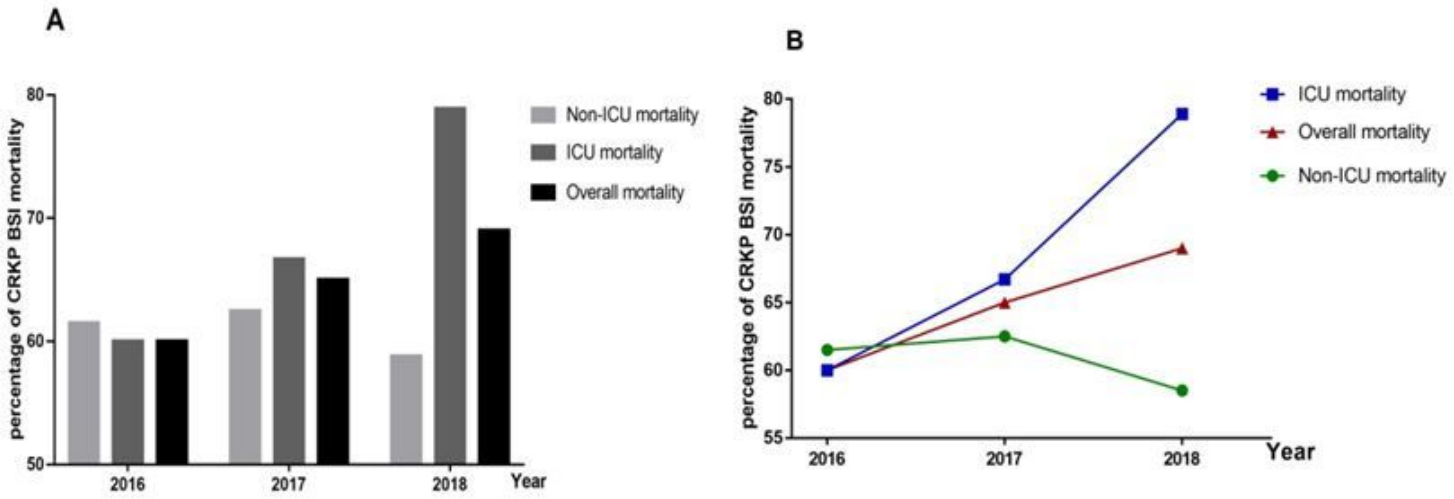


Figure 3

The percentage of CRKP BSIs mortality from January 2016 to December 2018. A: LightGray bar, percentage of CRKP-BSI mortality in our Hospital in Non-ICU; dark grey bar, percentage of CRKP-BSI mortality in our Hospital in intensive care unit; Black bar, percentage of CRKP-BSI overall mortality in our Hospital; B: Blue line, percentage of CRKP-BSI mortality in our Hospital in intensive care unit; Red line, percentage of CRKP-BSI overall mortality in our Hospital; Green line, percentage of CRKP-BSI mortality in our Hospital in Non-ICU.

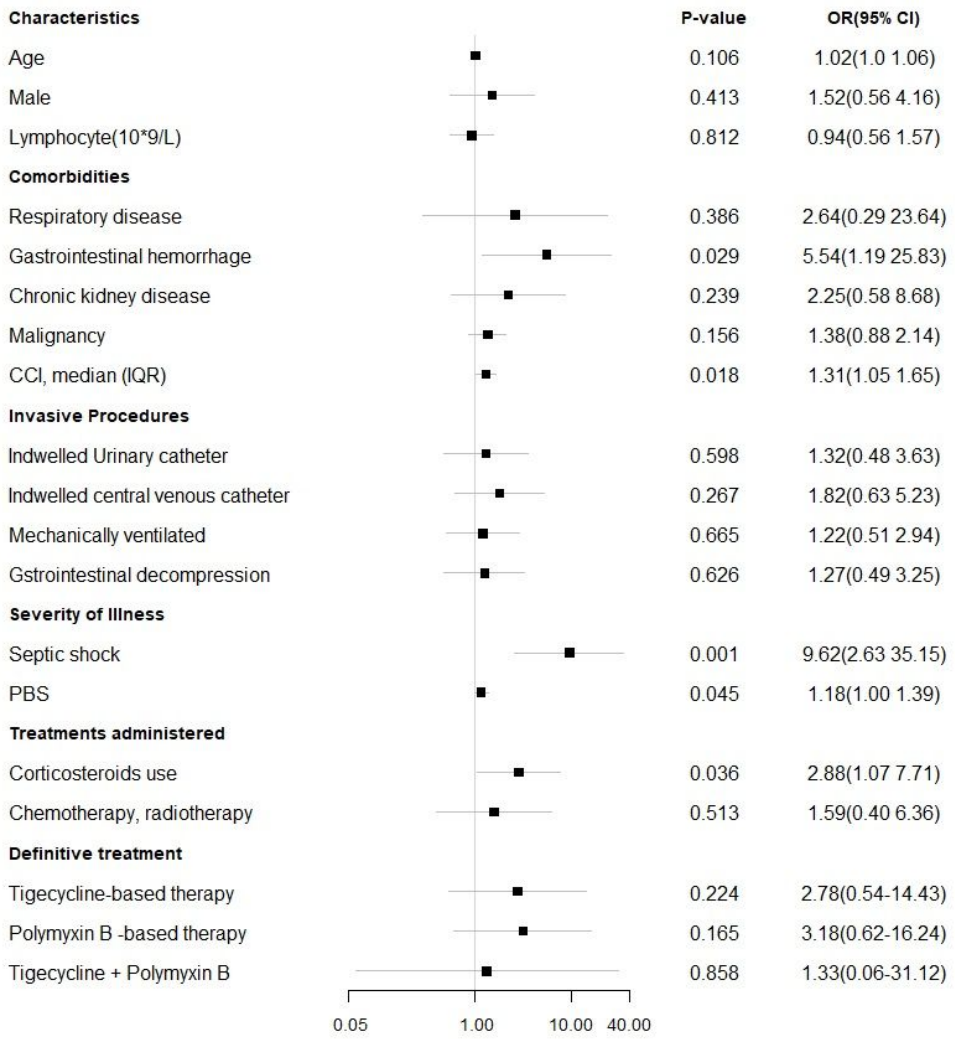


Figure 4

Crude odds ratio (OR) for the association mortality of patients with carbapenem-resistant Klebsiella pneumonia bloodstream infections