Infection and Drug Resistance

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ORIGINAL RESEARCH

Epidemiology, Drug Resistance, and Risk Factors for Mortality Among Hematopoietic Stem Cell Transplantation Recipients with Hospital-Acquired *Klebsiella pneumoniae* Infections: A Single-Center Retrospective Study from China

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Objective: Infection is the most common complication and cause of death after hematopoietic stem cell transplantation (HSCT). Our study aims to investigate the clinical characteristics and risk factors for death of *Klebsiella pneumoniae* infections in HSCT recipients, so as to provide evidence for guiding antibiotic use and improving prognosis in the future.

Methods: The epidemiology, clinical manifestations and drug resistance rate with *K. pneumoniae* infections among HSCT recipients between January 1, 2012 and September 30, 2021 were retrospectively reviewed. Logistic regression model and Cox regression model were respectively used to determine the risk factors for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) acquisition and death.

Results: Fifty-nine HSCT recipients suffered from *K. pneumoniae* infections, with a mortality rate of 42.4%. The most common site was lung, followed by blood stream. The resistance rate of *K. pneumoniae* to various clinically common antibiotics was high, especially CRKP, which was only sensitive to amikacin and tigecycline. Independent risk factor for CPKP acquisition was a previous infection within 3 months before transplantation (OR=10.981, 95% CI 1.474–81.809, *P*=0.019). Independent risk factors for mortality included interval from diagnosis to transplantation > 180 days (HR=3.963, 95% CI 1.25–12.561, *P*=0.019), engraftment period > 20 days (HR=8.015, 95% CI 2.355–27.279, *P*=0.001), non-use of anti-CMV immunoglobulin/rituximab after transplantation (HR=10.720, 95% CI 2.390–48.089, *P*=0.002), and PCT > 5 μg/L (HR=5.906, 95% CI 1.623–21.500, *P*=0.007).

Conclusion: *K. pneumoniae* infection has become a serious threat for HSCT recipients, which reminds us to pay enough attention and actively seek new strategies.

Keywords: *Klebsiella pneumoniae*, carbapenems, drug resistance, hematopoietic stem cell transplantation, mortality, risk factors

Introduction

Hematopoietic stem cell transplantation (HSCT) is an important treatment for many malignant and refractory blood diseases, and even the only way to cure some hematological tumor.[1] Although the efficacy of HSCT is getting better and better as the technology continues to mature, infections remain one of the most common complications and causes of death.[2,3]

With the increasing number of reports around the world, *Klebsiella pneumoniae* has become an urgent global public health problem in recent years.[4] Among them, carbapenem-resistant *K. pneumoniae* (CRKP) is more likely to results in poor prognosis due to severe symptoms, high incidence of septic shock, and low drug sensitivity. For example, Micozzi et al found that the mortality rate caused by CRKP bacteremia in patients with acute myeloid leukemia was

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as high as 71%.[5] Kalpoe et al reported the mortality rate of CRKP infection in patients after liver transplantation also exceeded 70%.[6] In China, the prevalence of CRPK increased rapidly from 2.9% in 2005 to 13.4% in 2014 and 25% in 2018. The prevalence also varies among different provinces, with the lowest in the northeast region and the highest in the eastern coastal region.[7,8] HSCT recipients are at high risk for hospital-acquired *K. pneumoniae* infections because of their long hospital stay, large-dose chemotherapy/radiotherapy/immunosuppressant/broad-spectrum antibiotics, as well as catheter implantation, intravenous hyperalimentation, and delayed hematopoietic reconstruction.[9]

Although some studies have been carried out on *K. pneumoniae* or CRKP infections, few investigations have focused on the epidemiology, antibiotic resistance, risk factors, and clinical outcomes of HSCT recipients with hospital-acquired *K. pneumoniae* infections in China. This study aims to answer these questions and provide evidence for guiding antibiotic selection and improving patient prognosis in the future.

Materials and Methods

Study Design and Data Collection

This study was performed at Xiangya Hospital of Central South University, an 3500-bed tertiary care teaching hospital with the largest hematology transplant ward in Central-South China. Medical records for HSCT recipients infected with *K. pneumoniae* between January 1, 2012 and September 30, 2021 were collected.

The diagnosis of acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplastic syndrome, aplastic anemia, and lymphoma were made according to relevant guidelines.[10–14] Patients < 14 years or > 65 years were excluded.

Variables

Clinical and demographic characteristics included: gender, age, primary disease type, HLA matching degree between donors and recipients, umbilical cord blood stem cell and mesenchymal stem cell infusion, acute graft-versus-host disease (GVHD), time of granulocyte and platelet engraftment, infection sites, use of antibiotics and special immunosuppressants, mechanical ventilation, ICU admission, sepsis shock, hospitalization time, and so on. The neutrophil, lymphocyte, platelet counts, and serum creatinine, albumin, total bilirubin, procalcitonin (PCT) levels were recorded within 24 hours after culture extraction.

Definitions

Hospital-acquired *K. Pneumoniae* infections referred to the appearance of inflammatory response symptoms more than 48 hours after hospital admission, and isolation of pathogenic microorganisms from blood or other usually sterile sites.[15] Onset of *K. pneumoniae* infection was defined as the collection date of the first positive culture with clinical evidence. Septic shock was defined as persistent hypotension despite adequate volume resuscitation, vasoconstrictor drugs were still required to maintain mean arterial pressure (MAP) ≥ 65mmHg, and serum lactate levels > 2 mmol/L.[16] Prophylactic antibacterial therapy: levofloxacin (at a dose of 500 mg/24 hours) was administered when a nonfebrile patient became agranulocytosis (an absolute neutrophil count < 0.5×10^9/L) and when > 7 days of neutropenia was expected during pretreatment chemotherapy. Acute GVHD was defined as an inflammatory response in the skin, gastrointestinal tract and liver that occurred within 100 days after transplantation.[17] Appropriate empirical antimicrobial treatment was defined as prescription of antibiotics to which the organism was susceptible in vitro within 48 hours after the specimen was obtained.[18] Mortality was defined as death within 90 days from infections.

Microbiology

All isolates identification and antibiotic susceptibility tests were performed using the same VITEK 2 compact automatic system (bioMérieux, Marcy-l'Étoile, France). When *K. pneumoniae* was repeatedly detected in the same patient, only the data of the first positive result was recorded for statistical analysis. CRKP was determined by measuring the minimum inhibitory concentration (MIC) using E-test strips (AB Biodisk, Solna, Sweden). Carbapenem resistance was defined as an ertapenem MIC ≥ 2 μg/mL and meropenem and/or imipenem MIC ≥ 4 μg/mL.[19] Intermediate susceptibility was classified as resistant.

Statistical Analysis

Data of continuous variables were presented as mean ± standard deviation (normal distribution) or quartile (skewed distribution), and comparison between groups was performed by Student's *t*-test or ManneWhitney *U*-test. Data of categorical variables were expressed as absolute value or percentage, and comparison between groups was performed by Fisher's exact test or Chi-squared test. Logistic regression and Cox regression analyses were used to assess associations between variables and CRKP acquisition and mortality, respectively. Survival curves were drawn by Kaplan-Meier method, survival rates of independent risk factors were compared by Log rank test. All statistical analysis was carried out using SPSS version 24.0, and *P*-value < 0.05 was considered statistically significant.

Results

Over the 9-year period, *K. pneumoniae* infections occurred in 59 of 1269 (4.6%) HSCT recipients, including 41 males (69.5%) and 18 females (30.5%), with a mortality of 42.4% (25/59). According to disease types, 17 patients with acute lymphoblastic leukemia, 14 with acute myeloid leukemia, 10 with myelodysplastic syndrome, 7 with severe aplastic anemia, 3 with lymphoma, and 8 with other types. The most common infection sites were lungs (64.4%), followed by blood stream (30.5%). Thirty-two (54.2%) patients had multiple times/sites or polymicrobial infections, and 24 (40.7%) patients were not given appropriate empirical antimicrobial treatment. The incidence of CRKP infections and septic shock was 18.6% and 20.3%, respectively. Of these 59 patients, 6.8% required mechanical ventilation to treat respiratory failure caused by infections. Demographic and clinical data of enrolled patients are detailed in Table 1.

Figure 1 shows the susceptibility of *K. pneumoniae* to 12 antibiotics commonly used in clinical practice: the drug resistance rates to amoxicillin-clavulanic acid (AMC), ceftriaxone (CTRX), aztreonam (AZT), gentamicin (GEN), ciprofloxacin (CPFX), levofloxacin (LVF) and cotrimoxazole (SMZ-TMP) were close to or over 60% (Figure 1A). CRKP had a higher drug resistance rate, only sensitive to amikacin (AN) and tigecycline (TGC) (resistance rate was 11.8% and 27.3% respectively) (Figure 1B). Took these CRKP isolates into two groups according to time span to further compare the change trend of drug resistance: 33 strains were detected before 2018 and 34 strains were detected after 2018. The drug resistance rates to TZP, AMC, AMK, LVF, TGC, MEM, IPM and SMZ-TMP were 23.3%, 50.0%, 13.3%, 50.0%, 20.0%, 13.3%, 10.0%, 73.3% (before 2018) and 31.0%, 65.5%, 13.8%, 75.9%, 20.7%, 20.7%, 17.2%, 82.8% (after 2018), respectively (Figure 1C). This indicates that although resistance rates of *K. pneumoniae* to most antibiotics are at a high level, fortunately, they have not risen further in recent years, except for LVF.

Table 2 shows in Logistic univariate analysis, factors associated with CRKP acquisition included infections occurred within 3 months before transplantation (*P*=0.013), urethral catheterization (*P*=0.007), and creatinine > 177 μmol/L (*P*=0.047). However, in Logistic multivariate analysis, the occurrence of infection within 3 months prior to transplantation was the only independent risk factor (OR=10.981, 95% CI 1.474–81.809, *P*=0.019).

In Cox univariate analysis, age > 50 years (*P*=0.047), interval from diagnosis to transplantation > 180 days (*P*=0.002), engraftment period > 20 days (*P*=0.008), non-use of anti-CMV immunoglobulin/rituximab (*P*=0.010), PCT > 5 μg/L (*P*=0.000), total bilirubin > 34.2 μmol/L (*P*=0.004), creatinine > 177 μmol/L (*P*=0.027), septic shock (*P*=0.000), and mechanical ventilation (*P*=0.000) were statistically different between the death group and the survival group. In Cox multivariable analysis, interval from diagnosis to transplantation > 180 days (HR=3.963, 95% CI 1.25–12.561, *P*=0.019), engraftment period > 20 days (HR=8.015, 95% CI 2.355–27.279, *P*=0.001), non-use of anti-CMV immunoglobulin/rituximab after transplantation (HR=10.720, 95% CI 2.390–48.089, *P*=0.002), and PCT > 5 μg/L (HR=5.906, 95% CI 1.623–21.500, *P*=0.007) were 4 independent risk factors associated with mortality (Table 3). The Kaplan-Meier curves of each independent risk factor are shown in Figure 2. Patients with interval from diagnosis to transplantation > 180 days (34.5% vs 80.0% *P*=0.001), engraftment period > 20 days (37.9% vs 76.7%, *P*=0.005), non-use of anti-CMV immunoglobulin/rituximab after transplantation (43.2% vs 81.8%, *P*=0.005), and PCT > 5 μg/L (12.5% vs 64.7%, *P*<0.001) had significantly lower survival rates.

Discussion

K. pneumoniae is an important opportunistic pathogen causing hospital-acquired infections. In China, the isolation rate of it ranks second among gram-negative bacilli.[20,21] In addition, with the widespread use of broad-spectrum antibiotics, the

Table 1 Clinical Characteristics and Laboratory Data of 59 HSCT Recipients with *K. pneumoniae* Infections

Characteristic	Value
Age, years, median (IQR)	29 (23.5, 49)
Sex, no. of males (%)	41 (69.5%)
Primary disease, n (%)	
Acute lymphocytic leukemia	17 (28.8%)
Acute myelogenous leukemia	14 (23.7%)
Myelodysplastic syndrome	10 (16.9%)
Severe aplastic anemia	7 (11.9%)
Lymphoma	3 (5.1%)
Others	8 (13.6%)
Infection sites, n (%)	
Lung	38 (64.4%)
Bloodstream	18 (30.5%)
Others	3 (5.1%)
CRKP infections	11 (18.6%)
ESBL infections	41(69.5%)
Time between diagnosis and transplantation, days, median (IQR)	190 (140, 363)
History of relapse/refractory state, n (%)	11 (18.6%)
Identical match, n (%)	19 (32.2%)
Time of engraftment	
Granulocyte, days, median (IQR)	14 (11.5, 16)
Platelets, days, median (IQR)	19 (13.5, 26.5)
Umbilical cord blood stem cell infusion, n (%)	13 (22.0)
Mesenchymal stem cell infusion, n (%)	11 (18.6)
Urethral catheterization, n (%)	6 (10.2%)
Acute GVHD (grade I–II), n (%)	36 (61%)
Time from HSCT and infection, days, median (IQR)	30 (14.5, 48)
Multiple times/sites/polymicrobial infections, n (%)	32 (54.2%)
Use of broad-spectrum antibiotics > 5 days one month prior to infection, n (%)	56 (94.9%)
Use of carbapenems > 3 days one month prior to infection, n (%)	41 (69.5%)
Inappropriate empiric antimicrobial treatment, n (%)	24 (40.7%)
Non-use of anti-CMV gamma globulin/rituximab, n (%)	37 (62.7%)
Use of special immunosuppressants[#], n (%)	23(39.0%)
Indicators within 24 hours of infection	
Neutrophil count, 10^9/L, median (IQR)	2 (0.1, 3.55)
Lymphocyte count, 10^9/L, median (IQR)	0.3 (0.1, 0.55)
Platelet count, 10^9/L, median (IQR)	34 (14, 63)
PCT, μg/L, median (IQR)	0.3 (0.165, 0.865)
Albumin, g/L, median (IQR)	32.3 (28.85, 37.3)
Total bilirubin, μmol/L, median (IQR)	12.4 (7.55, 20.4)
Creatinine, μmol/L, median (IQR)	63 (49.95, 84.05)
Septic shock, n (%)	12 (20.3%)
Admission to ICU after transplantation, n (%)	15 (25.4%)
Mechanical ventilation, n (%)	4 (6.8%)
Hospital stay, days, median (IQR)	50 (33, 69.5)
Mortality, n (%)	25 (42.4%)

Note: [#]Special immunosuppressants here mainly refer to ruxolitinib, tacrolimus and balliximab.

Abbreviations: HSCT, hematopoietic stem cell transplantation; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL, extended-spectrum beta-lactamase; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; CMV, cytomegalovirus; PCT, procalcitonin; ICU, intensive care unit; IQR, interquartile range.

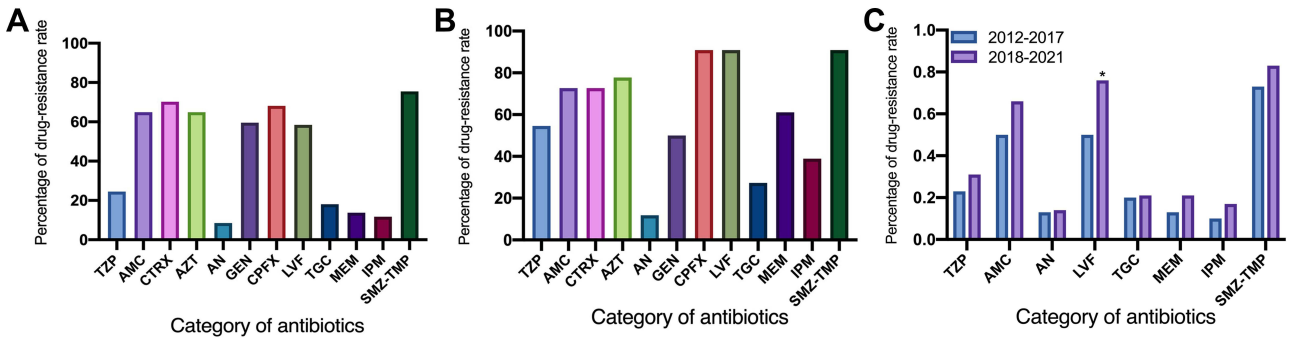

Figure 1 Susceptibility of *K. pneumoniae* to clinically common antibiotics. (**A**) Drug resistance rates of *K. pneumoniae* to twelve antibiotics; (**B**) drug resistance rates of carbapenem-resistant *Klebsiella pneumoniae* to twelve antibiotics; (**C**) comparison of drug resistance rates of *K. pneumoniae* in two time periods (before 2018 vs after 2018).
Note: **P* < 0.05.
Abbreviations: TZP, piperacillin-tazobactam; AMC, amoxicillin-clavulanic acid; CTRX, ceftriaxone; AZT, aztreonam; AN, amikacin; GEN, gentamicin; CPFX, ciprofloxacin; LVF, levofloxacin; TGC, tigecycline; MEM, meropenem; IPM, imipenem; SMZ-TMP, cotrimoxazole.

drug resistance of *K. pneumoniae* has gradually enhanced, resulting in the emergence of a large number of multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan drug-resistant (PDR) strains.[22,23] In this environment, HSCT recipients are more prone to *K. pneumoniae* infections due to long hospital stay, low immunity and frequent invasive operation. Worse, the vast majority of them have a poor prognosis.[24] This is the longest time span retrospective cohort study to characterize the epidemiology, risk factors, antibiotic sensitivity, and clinical outcomes of hospital-acquired *K. pneumoniae* infections among HSCT recipients in China to date.

In the present study, we revealed the incidence of *K. pneumoniae* infections in HSCT recipients was 4.6%, lower than 15.6% reported by Gavriilaki et al,[25] which may be related to the differences in age, disease type and intensity of pretreatment chemotherapy of enrolled patients. Further analysis showed that lungs were the most common infection sites, followed by blood stream, contrary to previous reports that bloodstream was the primary route of infections.[26,27] The mortality rate we calculated here was 42.4%, obviously higher than 23.3% reported by Higashino et al.[24] Meanwhile, we noticed that more than half of patients in this cohort were complicated with multiple times/sites or polymicrobial infections, and most received broad-spectrum antibiotics within one month prior to infection. In addition, more than 18% of patients had relapsed or refractory state before transplantation. This reflects the complexity and severity of patients' condition, which is speculated to be one of the reasons for poor efficacy and high mortality.

Table 2 Univariate and Multivariate Analysis of Risk Factors Associated with CRKP Acquisition Among HSCT Recipients

Variable	Univariate Analysis			Multivariable Analysis	
	CRKP (-)	CRKP (+)	*P*	OR (95% CI)	*P*
Age > 50 years, n (%)	7 (14.6%)	4 (36.4%)	0.106		
Male, n (%)	34 (70.8%)	7 (63.6%)	0.641		
Interval from diagnosis to transplantation > 180 days, n (%)	21 (43.8%)	8 (72.7%)	0.095		
An infection 3 months before transplant, n (%)	3 (6.2%)	4 (36.4%)	0.013*	10.981(1.474, 81.809)	0.019*
Use of carbapenems > 3 days 1 month prior to infection, n (%)	34 (70.8%)	7 (63.6%)	0.641		
Urethral catheterization, n (%)	2 (4.2%)	4 (36.4%)	0.007*	5.819(0.674, 50.271)	0.109
Use of special immunosuppressants, n (%)	19 (39.6%)	4 (36.4%)	0.844		
Indicators within 24 hours of infection, n (%)					
Neutrophil count < 0.5×10^9/L	12 (25.0%)	4 (36.4%)	0.448		
PCT > 5 μg/L	6 (12.5%)	2 (18.2%)	0.622		
Creatinine > 177 μmol/L	8 (16.7%)	5 (45.5%)	0.047*	4.225(0.694, 25.726)	0.118

Note: **P* values are statistically significant.
Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; HSCT, hematopoietic stem cell transplantation; CMV, cytomegalovirus; PCT, procalcitonin; OR, odd ratio; CI, confidence interval.

Table 3 Univariate and Multivariate Analysis of Risk Factors Associated with Mortality of *K. pneumoniae* Infection in HSCT Recipients

Variable	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age > 50 years	0.132 (0.018–0.974)	0.047*		
Interval from diagnosis to transplantation > 180 days	4.276 (1.699–10.761)	0.002*	3.963(1.25–12.561)	0.019*
HLA non-identical	1.664 (0.665–4.168)	0.277		
Engraftment period > 20 days	3.26 (1.358–7.827)	0.008*	8.015 (2.355–27.279)	0.001*
CRKP infections	2.613 (1.122–6.082)	0.026*		
Non-use of anti-CMV gamma globulin/rituximab	4.051 (1.389–11.821)	0.010*	10.720 (2.390–48.089)	0.002*
Inappropriate empiric antimicrobial treatment	1.625 (0.740–3.566)	0.226		
Indicators within 24 hours of infection				
Neutrophil count < 1.5×10^9/L	1.885 (0.855–4.159)	0.116		
Albumin < 30 g/L	1.31 (0.578–2.967)	0.518		
Total bilirubin > 34.2 μmol/L	3.98 (1.571–10.080)	0.004*		
Creatinine > 177 μmol/L	2.525 (1.112–5.735)	0.027*		
PCT > 5 μg/L	6.589 (2.665–16.291)	0.000*	5.906 (1.623–21.500)	0.007*
Mechanical ventilation	11.743 (3.542–38.932)	0.000*		
Septic shock	6.741 (2.945–15.429)	0.000*		

Note: *P values are statistically significant.
Abbreviations: HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen; CMV, cytomegalovirus; PCT, procalcitonin; HR, hazard ratio; CI, confidence interval.

Carbapenems, a subclass of β-lactam antibiotics, are considered as the first-line therapy for *K. pneumoniae* due to their wide antibacterial spectrum and good antibacterial activity.[28] However, with the increase of medication frequency, drug resistance becomes more and more serious. According to the Statistics of China Antimicrobial Resistance Surveillance System (CARSS), *K. pneumoniae*'s resistance rates to IPM and MEM increased from 3.0% and 2.9% in 2005 to 25.0% and 26.3% in 2018, respectively, and this proportion was even higher in CRKP.[29] Notably, our data showed CRKP-infected HSCT recipients had significantly lower resistance rates to IPM than MEM. Therefore, we believe that use of IPM may be more advisable than MEM until the results of drug sensitivity testing (DST) are available. Although this different from the recommendation that MEM was preferred for CRKP-infected solid organ transplant recipients.[30] Of course, this conclusion needs more data to further support. Consistent with previous studies, TGC showed excellent efficacy against all *K. pneumoniae* including CRKP, and drug resistance rate did not increase significantly in recent years. So, it remains a good option for patients. Whereas, this may be related to the relatively small number of bloodstream infections in our study. It is well known that TGC has a low plasma concentration, so it is less effective against bacteremia when used in conventional doses or alone, but more effective for lung, abdominal and soft tissue infections.[31,32] AN belongs to the class of aminoglycosides and is also the most sensitive antibiotic of *K. pneumoniae* in our study. Although its safety has been generally recognized,[33] it should be noted that, unlike ordinary patients, HSCT recipients were usually accompanied by fungal infections in addition to bacterial infections due to severe immunosuppression. Therefore, they often need to receive antifungal drugs such as caspofungin, amphotericin B, and voriconazole, which increased the potential risk of renal impairment. In view of this, AN should be used in HSCT recipients under the premise of close monitoring of renal function changes. It is important to emphasize that due to the actual medical conditions in different regions (time to market and price of drugs, health insurance policy, drug susceptibility test means, etc.), we are temporarily unable to make detailed comparisons with the efficacy of some new antibiotics. For example, several studies have shown that ceftazidime avibactam (CAZ-AVI) has high clinical success, survival and safety in the treatment of CRKP infections after organ transplantation.[34–36] Han et al also reported that the antimicrobial activity of CAZ-AVI against CRKP in vitro was significantly higher than that of TGC (resistance rate 7.8% vs 35.5%).[37] Meropenem-vaborbactam (MV) is a combination of meropenem and a novel β-lactamase inhibitor. In August 2017, the FDA approved it for the treatment of complex urinary tract infections and confirmed its

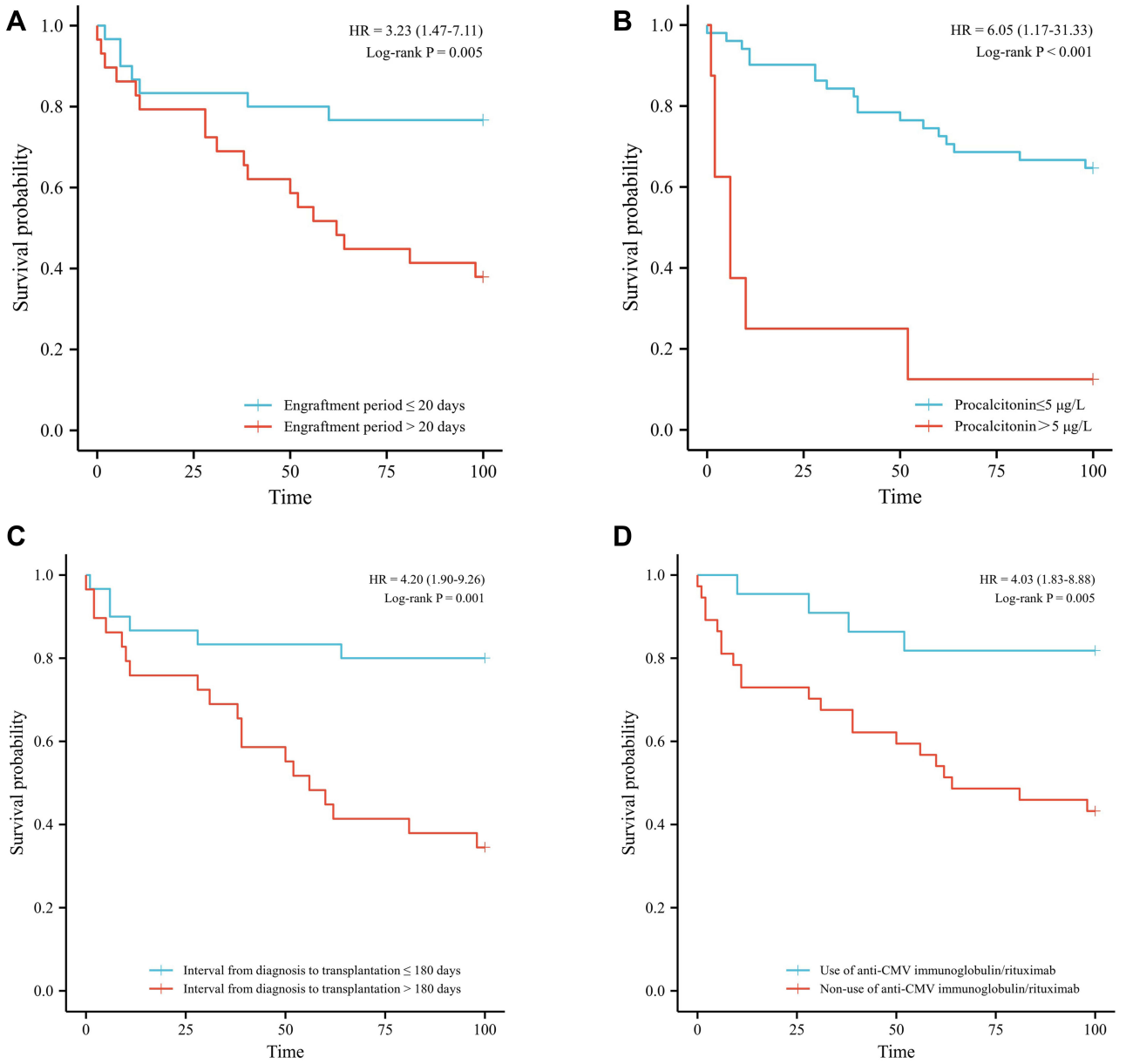

Figure 2 Survival comparison of patients with independent risk factors (Kaplan-Meier curve). (**A**) Engraftment period > 20 days vs ≤ 20 days (37.9% vs 76.7%, *P*=0.005); (**B**) procalcitonin > 5 μg/L vs ≤ 5 μg/L (12.5% vs 64.7%, *P*<0.001); (**C**) interval from diagnosis to transplantation > 180 days vs ≤ 180 days (34.5% vs 80.0% *P*=0.001) (**D**) non-use of anti-CMV immunoglobulin/rituximab vs use of (43.2% vs 81.8%, *P*=0.005).
Abbreviations: CMV, cytomegalovirus; HR, hazard ratio.

high activity in carbapenem-resistant Enterobacteriaceae (CRE) infections.[38] In particular, MV has good efficacy on a variety of CRKP strains, including CAZ-AVI resistance.[39] A Greek study published in 2022 tested the efficacy of several current novel antibiotics against CRKP, of which plazomicin inhibited 94% of the isolates, imipenem-relebactam (I/R), CAZ/AVI and MV also inhibited more than 98.5% of KPC and OXA-48 strains, while the inhibition rates of eravacycline on NDM and VIM strains were 61.3% and 66.7% respectively. These newly approved drugs are expected to fight CRKP. However, the emergence of some resistance also reminds the need to monitor antimicrobial activity and strengthen management.[40] Moreover, for the efficacy evaluation of some "classical" antibiotics, a meta-analysis showed that the resistance rates of CRKP to colistin, polymyxin B, gentamicin and fosfomycin were 31.1%, 9.8%, 35.7% and 47.3%, respectively.[41] That, in addition to newer agents, some relatively "old" drugs still retain a certain (or even good) effect on CRKP infections. Therefore, medical institutions in different regions should comprehensively select CRKP

treatment strategies based on local epidemiology and medical resources. Especially in the current situation where the development of new drugs is slow and expensive, re-introducing affordable old drugs to replace new antibiotics will not only conducive to maintaining a good environment for antibiotic application, but also help to alleviate the economic burden of patients.

Interval from diagnosis to transplantation > 180 days, engraftment period > 20 days, non-use of anti-CMV immunoglobulin/rituximab after transplantation, and PCT > 5 μg/L were independent risk factors associated with death from *K. pneumoniae* infections. The big time span from diagnosis to transplantation indicates a longer duration of disease status, more times of chemotherapy, and weaker body status, which is not conducive to rapid recovery after HSCT.

Prolonged engraftment time means patients had to experience longer period of agranulocytosis, during which their immunity was extremely low, giving *K. pneumoniae* more opportunity to invade. Meanwhile, patients were forced to receive different classes of antibiotics more frequently, which likely to cause the emergence of CRKP.[9,42]

PCT is a stable marker of infections unaffected by neutropenia, immune deficiency and glucocorticoid application.[43,44] It is expressed at very low (< 0.05 μg/L) or even undetectable levels in healthy individuals.[45] When the body is infected, PCT can be rapidly produced and released into blood under the action of inflammatory factors or bacterial toxins.[46] PCT is strongly associated with APACHE II and SOFA, two important scoring systems for assessing the severity of a patient's condition. That is, the more severe the disease, the higher the APACHE II and sofa scores, the greater the PCT value, and vice versa.[47] Besides, serum PCT level also has good sensitivity and specificity for the early diagnosis of sepsis patient.[48]

Crucially, we propose for the first time that use of anti-CMV immunoglobulin or rituximab can help reduce the risk of death in *K. pneumoniae* infected HSCT recipients. China is a country with high incidence of CMV infection, and the positive rate of CMV IgG in bone marrow and organ donors can be as high as 92%. After HSCT, about 50% of latent CMV infection will occur CMV reactivation, while about 30% of patients without CMV infection will develop primary infection.[49] CMV infection can trigger a variety of direct and indirect effects, among which the direct effect is that virus replication enters the active phase through new infection or reactivation, which further develops into CMV syndrome or end-organ disease. The indirect effect is to increase the risk of other pathogens (bacteria, fungi and other viruses) infections and GVHD and drug toxicity exposure by affecting bone marrow hematopoiesis or immune function.[50] Studies have shown that anti-CMV immunoglobulin can significantly reduce the load of CMV in the prevention and preemptive treatment, thereby decrease the occurrence and severity of infection.[51] Based on the above, we speculate that anti-CMV immunoglobulin may improve the prognosis of *K.pneumoniae* infections in HSCT recipients by double inhibiting the direct and indirect effects of CMV. Using rituximab before (or shortly after) HSCT was found to significantly reduce the risk of EBV reactivation after transplantation, especially in high-risk patients such as the elderly, GVHD, and antithymocyte globulin. The mechanism may be related to delayed B cell reconstitution and reduced EBV load.[52] Although our findings are preliminary, clinicians are still advised to pay more attention to post-transplant CMV/EBV infections and treat them promptly.

Unlike previous reports that septic shock, acute respiratory failure, HLA matching degree, GVHD, and CRKP increased the risk of mortality in HSCT patients with *K. pneumoniae* infections,[4,26,53,54] we found no statistical differences in these factors between survival and death groups.

Of course, there are some limitations to our study. First, this is a single-center retrospective cohort study, so the results may differ from those in other regions due to sample size, accuracy of medical records, data integrity, selection bias. Combining multi-center data or conducting prospective studies will help remedy the above deficiencies, which is also the focus of our next work. Secondly, polymyxin and ceftazidime-avibactam have been widely used in the treatment of *K. pneumoniae* infections at present,[55] but our hospital did not carry out DST for it until nearly 2 years, so this part of data is missing. Thirdly, there are some variables not covered in this study, such as CRKP colonization, inflammatory factor level, combined use of antibiotics, and donor infection transmission, which may be other risk factors associated with *K. pneumoniae* infections acquisition or death in HSCT recipients.

Conclusions

K. pneumoniae infections have become the serious threat with high mortality in HSCT recipients. Interval from diagnosis to transplantation > 180 days, Engraftment period > 20 days, non-use of anti-CMV immunoglobulin/rituximab after transplantation and PCT > 5 μg/L were 4 independent risk factors associated with mortality. In addition, the general resistance of *K. pneumoniae* deserves our further attention. When microbial culture results suggest CRKP, it is recommended to use TGC, or use AN under the premise of strict renal function monitoring. Of course, different regions need to make comprehensive judgments based on local epidemiology and actual medical resources.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This was a retrospective cohort analysis and all data were obtained through an electronic medical record information system. The institutional review board of Xiangya Hospital endorsed this project and approved the waiver of informed consent from patients (no. 2019030162). This study was in compliance with the Declaration of Helsinki. As a privacy statement, authors guarantee the confidentiality of patient information.

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Disclosure

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