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

Yan-Feng Liu¹,², Ya Liu¹, Xuefeng Chen³, Yan Jia¹

¹Department of Hematology, Xiangya Hospital, Central South University, Changsha, Hunan, People’s Republic of China; ²National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, People’s Republic of China; ³Department of Hematology, The Third Xiangya Hospital of Central South University, Changsha, Hunan, People’s Republic of China

Correspondence: Yan Jia, Department of Hematology, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, People’s Republic of China, Tel/Fax +86-731-89753730, Email jiayan1992@outlook.com

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.⁰ 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...
as high as 71%. Kalpoe et al reported the mortality rate of CRKP infection in patients after liver transplantation also exceeded 70%. In China, the prevalence of CRKP 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. 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.

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 hematologic 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. 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. 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. Prophylactic antibacterial therapy: levofloxacin (at a dose of 500 mg/24 hours) was administered when a nonfebrile patient became agranulocytosis (an absolute neutrophil count < 0.5×10⁹/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. 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. 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. 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 Mann-Whitney 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. In addition, with the widespread use of broad-spectrum antibiotics, the
| 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 ballyximab.*

**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.
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. 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. 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 Gavrilaki et al, 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 bloodstream, contrary to previous reports that bloodstream was the primary route of infections. The mortality rate we calculated here was 42.4%, obviously higher than 23.3% reported by Higashino et al. 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 < 0.5×10⁹/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.
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. 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. 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. 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.

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, 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. 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%). 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

| Variable                                | Univariate Analysis | Multivariate Analysis |
|-----------------------------------------|---------------------|------------------------|
| **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*                 |
| **HLA non-identical**                   | 1.664 (0.665–4.168) | 0.277                  |
| **Engraftment period > 20 days**        | 3.26 (1.358–7.827)  | 0.008*                 |
| **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*                 |
| **Inappropriate empiric antimicrobial treatment** | 1.625 (0.740–3.566) | 0.226                  |
| **Indicators within 24 hours of infection** |                       |                        |
| Neutrophil count < 1.5 × 10⁹/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*                 |
| 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.
high activity in carbapenem-resistant Enterobacteriaceae (CRE) infections. In particular, MV has good efficacy on a variety of CRKP strains, including CAZ-AVI resistance. 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. 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. 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 antibiotics.

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=0.003).

Abbreviations: CMV, cytomegalovirus; HR, hazard ratio.
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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References
1. Narinx J, Servais S, Baron F, Beguin Y, Willems E. Allogeneic hematopoietic stem cell transplantation: general principles and recent progress. Rev Med Liege. 2021;76(5–6):464–469.
2. Sahin U, Toprak SK, Atilla PA, et al. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. J Infect Chemother. 2016;22(8):305–314. doi:10.1016/j.jiac.2016.05.006
3. Omrani AS, Almaghrabi RS. Complications of hematopoietic stem cell transplantation: bacterial infections. Hematol Oncol Stem Cell Ther. 2017;10(4):228–232. doi:10.1016/j.hemonc.2017.05.018
4. Effah CY, Sun T, Liu S, et al. Klebsiella pneumoniae: an increasing threat to public health. Ann Clin Microbiol Antimicrob. 2020;19(1):1–9. doi:10.1186/s12941-019-0343-8
5. Miccozzi A, Gentile G, Minotti C, et al. Carbapenem-resistant Klebsiella pneumoniae in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem-resistant Klebsiella pneumoniae bacteremias. BMC Infect Dis. 2017;17(1):1–12. doi:10.1186/s12879-017-2297-9
6. Kalpoe JS, Sonnenberg E, Factor SH, et al. Mortality associated with carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. Liver Transpl. 2012;18(4):468–474. doi:10.1002/lt.23374
7. Zheng B, Dai Y, Liu Y, et al. Molecular epidemiology and risk factors of carbapenem-resistant Klebsiella pneumoniae infections in Eastern China. Front Microbiol. 2017;8:1061. doi:10.3389/fmicb.2017.01061
8. Hu Y, Liu C, Shen Z, et al. Prevalence, risk factors and molecular epidemiology of carbapenem-resistant Klebsiella pneumoniae in patients from Zhejiang, China, 2008–2018. Emerg Microbes Infect. 2020;9(1):1771–1779. doi:10.1080/22221751.2020.1799721
9. Asai S, Ohshima T, Iwashita H, et al. Carbapenem-resistant Klebsiella pneumoniae in a febrile neutropenia patient with acute myelogenous leukemia after hematopoietic stem cell transplantation. Infect Dis Clin Pract. 2018;26(5):e38–e39. doi:10.1097/IPC.0000000000000633
10. Hematology Oncology Committee, Chinese Anti-Cancer Association, Leukemia & Lymphoma Group, Chinese Society of Hematology. Chinese guidelines for diagnosis and treatment of adult acute lymphoblastic leukemia (2021). Chin J Hematol. 2021;42(9):705–716.
11. Leukemia & Lymphoma Group, Chinese Society of Hematology, Chinese Medical Association. Chinese guidelines for the diagnosis and treatment of adult acute myeloid leukemia (not AML) (2021). Chin J Hematol. 2021;42(8):617–623.
12. Chinese Society of Hematology, Chinese Medical Association. Chinese guidelines for diagnosis and treatment of myelodysplastic syndromes (2019). Chin J Hematol. 2019;40(2):89–97.
13. Red Blood Cell Disease (Anemia) Group, Chinese Society of Hematology, Chinese Medical Association. Chinese expert consensus on the diagnosis and treatment of aplastic anemia (2017). Chin J Hematol. 2017;38(1):1–5.

14. Hoppe RT, Advani RH, Ai WZ, et al. Hodgkin lymphoma, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020;18(6):755–781. doi:10.6004/jnccn.2020.0026

15. Cao Z, Yue C, Kong Q, et al. Risk factors for a hospital-acquired carbapenem-resistant Klebsiella pneumoniae bloodstream infection: a five-year retrospective study. Infect Drug Resist. 2022;15:641–654. doi:10.2147/IDR.S342103

16. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):757–786. doi:10.1001/jama.2016.0289

17. Stem Cell Application Group, Chinese Society of Hematology, Chinese Medical Association. Chinese consensus of allogeneic hematopoietic stem cell transplantation for hematological disease (III)-acute graft-versus-host disease (2020). Zhonghua Xueyexue Zazhi. 2020;41(7):529–536. doi:10.3760/cma.j.issn.0253-2727.2020.07.001

18. Wan Q, Liu H, Ye S, et al. Confirmed transmission of bacterial or fungal infection to kidney transplant recipients from donated after cardiac death (DCD) donors in China: a single-center analysis. Med Sci Monit. 2017;23:3770–3779. doi:10.12659/MSM.901884

19. Di W, Chen CM, Liu TH, et al. Risk factors for acquisition of carbapenem-resistant Klebsiella pneumoniae and mortality among abdominal solid organ transplant recipients with K. pneumoniae infections. Med Sci Monit. 2020;26:e92296. doi:10.12659/MSM.922996

20. Diekema DJ, Hsueh PR, Mendes RE, et al. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrob Agents Chemother. 2019;63(7):e00555–19. doi:10.1128/AAC.00555-19

21. Tian L, Sun Z, Zhang Z. Antimicrobial resistance of pathogens causing nosocomial bloodstream infection in Hubei Province, China, from 2014 to 2016: a multicenter retrospective study. BMC Public Health. 2018;18(1):1121. doi:10.1186/s12889-018-6013-5

22. Mohd Asri NA, Ahmad S, Mohamud R, et al. Global prevalence of nosocomial multidrug-resistant Klebsiella pneumoniae: a systematic review and meta-analysis. Antibiotics. 2021;10(12):1508. doi:10.3390/antibiotics10121508

23. Iosifidis E, Chorafa E, Agakidou E, et al. Use of ceftazidime-avibactam for the treatment of extensively drug-resistant or pan drug-resistant Klebsiella pneumoniae in neonates and children< 5 years of age. Pediatr Infect Dis J. 2019;38(8):812–815. doi:10.1097/INF.0000000000002344

24. Higashino HR, Marchi AP, Martins RCR, et al. Carbapenem-resistant Klebsiella pneumoniae colonization and infection is associated with lower overall survival in a cohort of haematopoietic stem-cell transplantation patients: mechanism of resistance and virulence by whole-genome sequencing. J Med Microbiol. 2021;70(10):1422. doi:10.1099/jmm.0.004122

25. Gavriilaki E, Sakellari I, Chatzikonstantinou T, et al. Risk factors and outcomes of Klebsiella pneumoniae infection before and after allogeneic hematopoietic cell transplantation. Front Med. 2020;7:608165. doi:10.3389/fmed.2020.608165

26. Forcina A, Baldan R, Marasco V, et al. Control of infectious mortality due to Carbapenemase-producing Klebsiella pneumoniae in hematopoietic stem cell transplantation. Bone Marrow Transplant. 2017;52(1):114–119. doi:10.1038/bmt.2016.234

27. Han QZ, Chen Y, Yang H, et al. Incidence of blood stream infections of 1265 patients with hematopoietic stem cell transplantation and analysis of pathogenic bacteria. Zhonghua Xue Xue Za Zhi. 2017;38(11):930–933. doi:10.3760/cma.j.issn.0253-2727.2017.11.005

28. Lou W, Venkataraman S, Zhong G, et al. Antimicrobial polymers as therapeutics for treatment of multidrug-resistant Klebsiella pneumoniae lung infection. Acta Biomater. 2018;78:78–88. doi:10.1016/j.actbio.2018.07.038

29. Hu F, Zhu D, Wang F, et al. Current status and trends of antibacterial resistance in China. Clin Infect Dis. 2018;67(suppl_2):S128–134. doi:10.1093/cid/ciy657

30. Wu D, Huang X, Jia C, et al. Clinical manifestation, distribution, and drug resistance of pathogens among abdominal solid organ transplant recipients with Klebsiella pneumoniae infections. Transplant Proc. 2020;52(1):289–294. doi:10.1016/j.transproceed.2019.11.023

31. Hasan MJ, Nizhlu LN, Rabbani R. Bloodstream infection with pandrug-resistant Alcaligenes faecalis treated with double-dose of tigecycline. IDCases. 2019;18:660. doi:10.1160/j.ijc.2019.060600

32. Chinese Society Of Hematology, Chinese Medical Association, Chinese Medical Doctor Association. Management of Carbapenem-resistant Enterobacteriaceae (CRE) infection in patients with hematological malignancies: Chinese consensus (2020). Zhonghua Xue Xue Za Zhi. 2020;41(11):881–889. doi:10.3760/cma.j.issn.0253-2727.2020.11.001

33. Freire MP, de Oliveira GD, Cury AP, et al. The role of therapy with aminoglycoside in the outcomes of kidney transplant recipients infected with polymyxin-and carbapenem-resistant Enterobacteriaceae. Eur J Clin Microbiol Infect Dis. 2019;38(4):755–765. doi:10.1007/s10096-019-03468-4

34. Zhang F, Zhong J, Ding H, et al. Efficacy of Ceftazidime-Avibactam in the treatment of Carbapenem-resistant Klebsiella pneumoniae infection after kidney transplantation. Infect Drug Resist. 2021;14:5165. doi:10.2147/IDR.S343505

35. Chen W, Sun L, Guo L, et al. Clinical outcomes of ceftazidime-avibactam in lung transplant recipients with infections caused by extensively drug-resistant gram-negative bacilli. Ann Transl Med. 2020;8(3):39. doi:10.21037/atm.2019.10.40

36. Chen F, Zhong H, Yang T, et al. Ceftazidime-avibactam as salvage treatment for infections due to Carbapenem-resistant Klebsiella pneumoniae. J Natl Compr Canc Netw. 2020;18(5):105833. doi:10.1016/j.jncn.2019.10.014

37. Tofas P, Skiada A, Angelopoulou M, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections in neutropenic patients with haematological malignancies or aplastic anaemia: analysis of 50 cases. Int J Antimicrob Agents. 2016;47(4):335–339. doi:10.1016/j.ijantimicag.2016.01.011

38. Luo X, Chen S, Zhang J, et al. Procalcitonin as a marker of Gram-negative bloodstream infections in hematological patients with febrile neutropenia. Leuk Lymphoma. 2019;60(10):2441–2448. doi:10.1080/10428194.2019.1581928
44. Schuetz P, Christ-Crain M, Muller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections—hope for hype? *Swiss Med Wkly*. 2009;139(23–24):318–326.

45. Self WH, Wunderink RG, Jain S, et al. Procalcitonin as a marker of etiology in adults hospitalized with community-acquired pneumonia. *Clin Infect Dis*. 2018;66(10):1640–1641. doi:10.1093/cid/cix1090

46. Kim H, Roh YH, Yoon SH. Blood procalcitonin level as a diagnostic marker of pediatric bacterial meningitis: a systematic review and meta-analysis. *Diagnóstics*. 2021;11(5):846. doi:10.3390/diagnostics11050846

47. Wang S, Chen D. The correlation between procalcitonin, C-reactive protein and severity scores in patients with sepsis and their value in assessment of prognosis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2015;27(2):97–101. doi:10.3760/cma.j.issn.2095-4352.2015.02.004

48. Gregoriano C, Heilmann E, Molitor A, et al. Role of procalcitonin use in the management of sepsis. *J Thorac Dis*. 2020;12(Suppl 1):S5–S15. doi:10.21037/jtd.2019.11.63

49. Styczynski J. Who is the patient at risk of CMV recurrence: a review of the current scientific evidence with a focus on hematopoietic cell transplantation. *Infect Dis Ther*. 2018;7(1):1–16. doi:10.1007/s40121-017-0180-z

50. Griffiths P. The direct and indirect consequences of cytomegalovirus infection and potential benefits of vaccination. *Antiviral Res*. 2020;176:104732. doi:10.1016/j.antiviral.2020.104732

51. Charlotte R, François P, Jonathan M, et al. Use of anti-CMV immunoglobulins in lung transplant recipients: the French experience. *Transpl Infect Dis*. 2021;23(6):e13754. doi:10.1111/tid.13754

52. Burns DM, Rana S, Martin E, et al. Greatly reduced risk of EBV reactivation in rituximab-experienced recipients of alemtuzumab-conditioned allogeneic HSCT. *Bone Marrow Transplant*. 2016;51(6):825–832. doi:10.1038/bmt.2016.19

53. Trecarichi EM, Pagano L, Martino B, et al. Bloodstream infections caused by Klebsiella pneumoniae in one-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey. *Am J Hematol*. 2016;91(11):1076–1081. doi:10.1002/ajh.24489

54. Mario T, Maria TE, Giuseppe DRF, et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. *J Antimicrob Chemother*. 2015;70(7):2133–2143. doi:10.1093/jac/dkv086

55. Petrosillo N, Taglietti F, Granata G. Treatment options for colistin resistant Klebsiella pneumoniae: present and future. *J Clin Med*. 2019;8(7):934. doi:10.3390/jcm8070934