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Risk Factors for Acquisition of Carbapenem-Resistant *Klebsiella pneumoniae* and Mortality Among Abdominal Solid Organ Transplant Recipients with *K. pneumoniae* Infections

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Background: For abdominal solid organ transplant (ASOT) recipients, infection with *Klebsiella pneumoniae*, particularly carbapenem-resistant *K. pneumoniae* (CRKP), can be life-threatening. The aims of this study were to characterize the risk factors associated with acquisition of CRKP and 90-day crude mortality among patients.

Material/Methods: In our cohort study, we retrospectively reviewed 68 *K. pneumoniae*-infected transplant recipients, studied their demographics, clinical manifestations, microbiology, and outcomes, and determined the risk factors associated with the occurrence of CRKP and crude mortality due to *K. pneumoniae* infections.

Results: Sixty-eight ASOT recipients (5.4%) experienced 78 episodes of *K. pneumoniae* infection. Among these, 20 patients (29.4%) died. The independent risk factors associated with mortality were multiple infected organs or sites (odds ratio=22.034, 95% confidence intervals=4.348-111.653, *P*=0.001) and septic shock (odds ratio=27.090, 95% confidence intervals=1.841-398.512, *P*=0.016). Risk factors associated with acquisition of CRKP were multiple infected organs or sites (odds ratio=3.056, 95% confidence intervals=1.091–8.556, *P*=0.033).

Conclusions: *K. pneumoniae* infections, especially CRKP, frequently occurred among ASOT recipients, with a high mortality rate. Multiple infected organs or sites and septic shock were predictors of crude mortality caused by *K. pneumoniae* infections, while CRKP infections were associated with multiple infected organs or sites. Greater efforts are needed towards improved antibiotic administration, early diagnosis and precise treatment, recognition of septic shock, and reduced length of hospitalization.

MeSH Keywords: **Carbapenems • Drug Resistance, Bacterial • Gram-Negative Bacterial Infections • Mortality • Risk Factors • Transplants**

Abbreviations: **SOT** – solid organ transplantation; **ASOT** – abdominal solid organ transplant; **CRKP** – carbapenem-resistant *K. pneumoniae*; **KPC** – *K. pneumoniae* carbapenemase; **CSKP** – carbapenem-susceptible *K. pneumoniae*; **MIC** – minimum inhibitory concentration; **OR** – odds ratio; **CI** – confidence intervals

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Background

Solid organ transplantation (SOT) recipients suffer from a high incidence of, and high mortality rate from, life-threatening bacterial infections [1–3]. Recent reports have demonstrated that *Klebsiella pneumoniae* infection in hospitalized patients, including bloodstream infection, urinary tract infection, pneumonia, and surgical infection, has already become a nightmare for clinicians worldwide [4,5]. The total incidence and mortality rates for *K. pneumoniae* infections vary widely among organ transplant centers, ranging from 1% to 6.9% and from 18% to 27%, respectively [6,7]. *K. pneumoniae* is of particular concern due to its limited susceptibility to antibiotics and the frequent occurrence of multidrug resistance during treatment [8, 9].

SOT recipients have become a high-risk group for infection with drug-resistant bacteria due to frequent exposure to antibiotics, prolonged hospital stays, and renal dysfunction [10]. Carbapenemase-producing *K. pneumoniae* (KPC) is widespread in Greece, Israel, South America, USA, and China. Fortunately, KPC has not been seen in western or northern Europe [5,7]. Of particular concern is drug-resistance; the growing incidence of carbapenem-resistant *K. pneumoniae* (CRKP) has led to an associated mortality rate of 82% among liver recipients [7,11,12].

So far, however, there has been little discussion among SOT recipients about the adverse effects of *K. pneumoniae* infections [11,13]. Although the presence of *K. pneumoniae*, especially CRKP, in SOT recipients has been observed in various studies, there have been few empirical investigations into the characteristics of *K. pneumoniae* among patients after abdominal solid organ transplant (ASOT) in China [12,14,15].

This study sought to obtain data which will help to address these research gaps. Specifically, our aim was to characterize the risk factors related to CRKP acquisition and 90-day crude mortality among *K. pneumoniae*-infected recipients, to shed light on appropriate prevention and treatment possibilities.

Material and methods

Ethics statement

The Medical Ethical Committee of Xiangya Third Hospital of Central South University endorsed the study protocol prior to data collection. No recipients or donors were coerced or paid in our study.

Study population

Our study was a retrospective analysis conducted from December 1, 2012 to July 1, 2019 at the Third Xiangya Hospital, a 1800-bed tertiary-care teaching hospital with a long-term ASOT program (annual average of 180 kidney and 35 liver transplants), located in Changsha, China. All episodes of *K. pneumoniae* infections occurring during the 7-year-period were enrolled. There were two sources of organs: living related and postcardiac death donors. Recipients with *K. pneumoniae* infection were subdivided on the basis of clinical outcomes and, separately, on the basis of drug resistance of the *K. pneumoniae* pathogen. The first group was divided into patients who died during the first 90 days after onset and those who survived beyond 90 days. The second group was divided into patients with resistant (CRKP) or carbapenem-susceptible *K. pneumoniae* (CSKP). Double or triple immunosuppression (tacrolimus or cyclosporin A, prednisone, with/without mycophenolate mofetil) was administered in all recipients enrolled, and basiliximab or antithymocyte globulin was used as an additional agent in some patients. Second- or third-generation cephalosporin, beta-lactamase inhibitors/semisynthetic penicillin, or carbapenem were prescribed 1 h before transplantation, and supplementary prescriptions were given for at least 72 h after transplantation, corresponding to the results of cultures before and after transplantation. For patients experiencing more than one episode of *K. pneumoniae* infection, only the first episode was analyzed.

Data collection and study design

This single-center retrospective study aimed to determine the independent risk factors related to acquisition of CRKP and crude mortality among *K. pneumonia*-infected recipients. Medical records for recipients infected with *K. pneumoniae* between December 1, 2012 and July 1, 2019 were collected.

The clinical and demographic characteristics included: sex, age, hallmarks of infection (white blood cell count and temperature), date and site of infection, re-operation, induction therapy, CRKP pathogen, nosocomial origin of infection, mechanical ventilation, septic shock, average duration of intensive care unit stay after transplantation, blood transfusion during the perioperative period, type of transplantation, empirical antimicrobial therapy, acute rejection within 3 months before *K. pneumoniae* infection, major infections within 3 months before *K. pneumoniae* infection, duration of antibiotic therapy within 1 month before infection, and immunosuppressive agents. Laboratory records, collected within the first 24 h after the culture was drawn, included albumin level and serum creatinine, as well as platelet and lymphocyte counts. All episodes of *K. pneumoniae* infection were collected, but further statistical analyses were conducted only for the first recorded infection. We compared clinical manifestations, demographic characteristics, and other laboratory data between the survival and death group and between the CSKP and CRKP groups. The follow-up period for all ASOT recipients was 3 months (90

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days) after the onset of *K. pneumoniae* infections. Onset of infection was defined as the combination of the first positive specimen culture and clinical manifestations.

Definitions

Throughout this paper, the onset of *K. pneumoniae* infection refers to the collection date of the first positive culture with clinical evidence of infection. According to the criteria of the centers for disease control, a patient with a positive culture from blood, sputum, urine, deep wound, skin, or abdominal cavity can be defined as infected [13]. Appropriate empirical antimicrobial therapy was indicated if administration of antibiotics *in vitro* resulted in susceptible *K. pneumoniae* within 48 h after having cultured the specimens [16]. Nosocomial infection was considered as having occurred in recipients who had been hospitalized for at least 48 hours, and early-onset infection was defined as developing within the first 2 months after ASOT [17]. CRKP was diagnosed upon a finding of non-susceptibility to at least one antimicrobial agent in the carbapenem category, which included imipenem and meropenem, in accordance with the criteria of the centers for disease control [18]. Septic shock was diagnosed in recipients with *K. pneumoniae* infection who required vasopressor therapy to maintain mean blood pressure of at least 65 mm Hg and who had a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation [19].

Microbiology

For blood culture, each blood sample was aseptically injected into each of a set of aerobic and anaerobic blood culture bottles before processing by the BACTEC 9120 blood culture system (Becton Dickinson, Cockeysville, MD, USA) in the microbiology laboratory. For other cultures, specimens were obtained for routine bacterial culture. Bacterial species identification was performed using the Vitek-2 system (bioMérieux, Marcyl'Etoile, France).The minimum inhibitory concentration (MIC) was measured by agar dilution, and susceptibility was determined by the Kerby-Bauer disk diffusion method [20]. A strain was considered carbapenem-susceptible when the MIC of meropenem or imipenem was ≤1 mg/L [21]. Intermediate susceptibility to the antibiotics was considered as resistance.

Statistical analysis

Data are listed as mean (±SD) and median (1^{st}–3^{rd} quartile) for continuous variables with normal and skewed distributions, respectively. Categorical variables were compared with the χ^2 test or Fisher exact test. Univariate analysis was applied to inspect the association between demographic/clinical variables and acquisition of CRKP infections and crude mortality caused by *K. pneumoniae* infections. All the variables with $P<0.05$ in the univariate analysis entered into the multivariate logistic regression analysis to determine independent risk factors. A forward stepwise logistic regression approach was adopted to obtain the final result. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to assess associations. Kaplan-Meier curves were used to describe the survival distribution. Log rank test was used to compare survival time with some risk factors. Statistical significance was defined as $P<0.05$ (two-tailed). All analyses were performed using SPSS 24.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, United States).

Results

A total of 1249 ASOT recipients, including 1039 kidney and 210 liver recipients, at the Third Xiangya Hospital, were eventually enrolled in this 7-year cohort study. Sixty-eight ASOT recipients with a mean age of 44.4, with 2 and 66 grafts from living related donors and cardiac death donors, respectively, experienced 78 episodes of *K. pneumoniae* infections, resulting in 20 deaths within 90 days following *K. pneumoniae* infections. The average infection prevalence rate among recipients was 5.4% (68/1249), with a rate of 4.8% (50/1039) in kidney recipients and 8.6% (18/210) in liver recipients. The demographic, laboratory, and clinical characteristics of the 68 recipients are shown in Table 1. Of these 68 patients, 60.3% (41 of 68) had *K. pneumoniae* infections of nosocomial origin and 56% (38 of 68) suffered from CRKP infections. Thirty-seven patients (55.4%) did not receive rational antibiotic treatment within 48 h after *K. pneumoniae* infection diagnosis. Thirteen (19.1%) patients required mechanical ventilation support as a treatment for *K. pneumoniae* infection, seven (10.3%) developed septic shock at the onset of infection, and 28 (41.2%) suffered from multiple organ or site infections. The predominant primary site of infection was the bloodstream (n=24, 35.3%), followed by the lung (n=13, 19.1%), urinary tract (n=12, 17.6%), deep wound/skin (n=11, 16.2%), and abdominal cavity (n=8, 11.8%). Forty-six patients (67.6%) developed early-onset infections.

Table 2 shows that in the univariate analysis, mechanical ventilation was needed more frequently in the mortality group, although this difference did not reach statistical significance ($P=0.07$). Inappropriate empirical antibiotics ($P=0.006$), septic shock ($P=0.003$), *K. pneumoniae* bacteremia ($P=0.001$), nosocomial infection ($P=0.007$), and multiple infected organs or sites ($P<0.001$) were related to crude mortality. These five risk factors of P values <0.05 in the univariate analysis were introduced into the multivariate analysis, and multiple infected organs or sites (OR=22.034, 95% CI=4.348–111.653, $P=0.001$) as well as septic shock (OR=27.090, 95% CI=1.841–398.512, $P=0.016$) remained a significant association with crude mortality in the final multivariate analysis.

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Table 1. Clinical characteristic and demographic, laboratory of 68 *K. pneumoniae* infections recipients.

Characteristics	Value
Age, mean years ±SD	44.4±10.4
Sex, no. of male (%)	43 (63.2)
Median body temperature of °C at the onset (IQR)	37.3 (36.8~38.1)
Temperature of 39°C or greater, n (%)	4 (5.9)
Nosocomial origin, n (%)	41 (60.3)
Inappropriate empirical antimicrobial use, n (%)	37 (54.4)
Carbapenem-resistant *K. pneumoniae*, n (%)	38 (55.9)
Duration of ICU stays after surgery (IQR)	6 (5~8)
Intraoperative blooding, ml (IQR)	200 (100~900)
RBC transfusion during the perioperative period, unit (IQR)	2 (0~16.38)
Dialysis within 1 month after transplantation, n (%)	14 (20.6)
Creatinine >1.5 mg/dL within 1 week after transplantation, n (%)	36 (52.9)
Mechanical ventilation, n (%)	13 (19.1)
Septic shock, n (%)	7 (10.3)
Acute rejection within 3 months before infection, n (%)	2 (2.9)
Other infections within 3 months before infection, n (%)	9 (13.2)
Re-operation, n (%)	8 (11.8)
Induction therapy, n (%)	
Basiliximab	18 (26.5)
Antithymocyte globulin	35 (51.5)
Use of wide-spectrum antibiotics for 5 days or more within 1 month before infection, n (%)	30 (44.1)
Use of meropenem for 3 days or more within 1 month before infection, n (%)	30 (44.1)
Multiple infected organisms or sites, n (%)	28 (41.2)
Organ resource, no. of cases (%)	
DCD	66 (97.1)
Living-related	2 (2.9)
Type of infections, no. of cases (%)	
Bacteremia	24 (35.3)
Pulmonary infection	13 (19.1)
Urinary tract infection	12 (17.6)
Deep wound and Skin infection	11 (16.2)
Abdominal cavity infection	8 (11.8)
Patient immunosuppressant treatment, no. of cases (%)	
Cyclosporine A	8 (11.8)
Tacrolimus	57 (83.8)
No use of calcineurin inhibitor	3 (4.4)

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Table 1 continued. Clinical characteristic and demographic, laboratory of 68 *K. pneumoniae* infections recipients.

Characteristics	Value
Type of transplantation, no. of cases (%)	
Kidney	50 (73.5)
Liver	18 (26.5)
Laboratory variables from blood, no. of cases (%)	
Lymphocyte count <300/mm^3	25 (36.8)
Albumin <30 g/L	9 (13.2)
WBC count >15,000/mm^3	15 (22.1)
Platelet count <50,000/mm^3	11 (16.2)
Creatinine >1.5 mg/dL	38 (55.9)
Time of infection onset, no. of cases (%)	
<2 months posttransplant	46 (67.6)
≥2 months posttransplant	22 (32.4)
Mortality, no. of cases (%)	20 (29.4)

SD – standard deviation; ASOT – abdominal solid organ transplant; RBC – red blood cells; WBC – white blood cells; IQR – interquartile range; ICU – Intensive Care Unit; DCD – donation after cardiac death.

Compared with CSKP infections, the factors associated with CRKP infections in univariate analysis were multiple infected organs or sites (P=0.031) and the use of meropenem at least 3 days within 1 month before *K. pneumoniae* infection (P=0.037). Multiple infected organs or sites (OR=3.056, 95% CI=1.091–8.556, P=0.033) was the only independent risk factor related to CRKP infections in multivariate analysis (Table 3).

Figure 1 shows the survival time of patients with certain risk factors. Compared with the single infected organ or site group, the mortality was significantly higher in the multiple infected organs or sites group (P<0.001). For the outcome of patients with different predominant sites of infection (bloodstream versus non-bloodstream), mortality in the bloodstream group was clearly higher (P<0.001). Mortality in the CRKP-infected patients was higher than in the CSKP-infected patients, but this result was not statistically significant (P=0.283). However, mortality was significantly higher in the hospital-acquired infections group compared with the community-acquired infections group (P=0.022).

Discussion

Infection is a life-threatening complication among SOT recipients. *K. pneumoniae* is an important cause of bacterial infections among SOT recipients, who are notably vulnerable to severe infections due to numerous hospitalizations, preexisting and posttransplant immunosuppression, surgical interventions, invasive procedures, and frequent antibiotic treatments. These infections result in significant morbidity and mortality with limited therapeutic options.

We observed that *K. pneumoniae* infections frequently occurred in our cohort of ASOT recipients, with an incidence rate of 5.4%, in accordance with a previous study [22]. In line with previous research, we also found that *K. pneumoniae* infections resulted in a mortality rate as high as 29.4% among ASOT recipients, a high proportion of which were nosocomial infections (60.3%) and CRKP infections (55.9%) [12,15,22,23].

The main revelation of our study was that multiple infected organs or sites were strongly associated with the occurrence of CRKP infections, as well as crude mortality due to *K. pneumoniae* infections. The presence of multiple infected organs or sites indicated the complexity of these patients, with severe infections and inadequate antimicrobial therapies, similar to our previous study. In line with other studies, patients suffering from multiple infected organs or sites were treated with different categories of antibiotics, including carbapenem, which contributed to further emergence of CRKP infections [24–26]. In addition, polymicrobial infections were associated with a high mortality rate, while the ability of the microbes to acquire and disseminate drug-resistance amplified the cascade of multiple infections [27]. Due to the lack of information on immunity in our present study, further research should be undertaken to

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Table 2. Univariate and multivariate analysis of risk factors related to crude mortality in *K. pneumoniae* infection recipients.

Characteristics	Mortality	Survival	P	OR (95% CI)
Total, n (%)	20 (29.4)	48 (70.6)		
Univariate analysis, n (%)				
Age ≥40 years	13 (65)	32 (66.7)	0.895	
Male sex	10 (50)	33 (68.8)	0.144	
Temperature ≥39°C	2 (10)	2 (4.2)	0.714	
Inappropriate empirical antibiotics	16 (80)	21 (43.8)	0.006*	
Nosocomial infection	17 (85)	24 (50)	0.007*	
Liver transplantation	6 (30)	12 (25)	0.670	
K. pneumoniae bacteremia	13 (65)	11 (22.9)	0.001*	
Early-onset infection	15 (75)	31 (64.6)	0.581	
Re-operation	4 (20)	4 (8.3)	0.343	
Multiple infected organisms or sites	17 (85)	11 (22.9)	<0.001*	
Mechanical ventilation	7 (35)	6 (12.5)	0.070	
The use of antithymocyte globulin	8 (40)	27 (56.3)	0.222	
The use of tacrolimus	15 (75)	42 (87.5)	0.361	
Septic shock	6 (30)	1 (2.1)	0.003*	
Platelet count <50,000/mm^3	6 (30)	5 (10.4)	0.102	
Lymphocyte count <300/mm^3	10 (50)	15 (31.3)	0.144	
Albumin <30 g/L	5 (25)	4 (8.3)	0.146	
WBC count >15,000/mm^3	7 (35)	8 (16.7)	0.180	
Creatinine >1.5 mg/dL	12 (60)	26 (54.2)	0.659	
Carbapenem-resistant *K. pneumoniae*	13 (65)	25 (52.1)	0.328	
Multivariate analysis				
Multiple infected organisms or sites			0.001*	22.034 (4.348–111.653)
Septic shock			0.016*	27.090 (1.841–398.512)

P-value from Pearson's χ^2 test or Fisher's exact test in univariate analysis and from multiple logistic regression in multivariate analysis.
* The *P*-values are statistically significant. OR – odds ratio; CI – confidence interval; WBC – white blood cells.

investigate whether multiple infected organs or sites affected patient mortality via decreased immune function of ASOT recipients. Our finding, while preliminary, suggested that clinicians should pay more attention to early diagnosis and precise treatment for various infections.

We also revealed that the most common positive cultures of *K. pneumoniae* were obtained from the bloodstream (35.3%). This contrasts with studies reporting the urinary tract as the most common site of infections [11,12]. This discrepancy can be partially explained by our larger sample size. Previous research has associated bacteremia, particularly accompanied by septic shock, with high mortality among ASOT recipients [6,28,29]. In line with our previous study, an interesting result of survival analysis was that *K. pneumoniae* bacteremia that was not successful as a non-bloodstream infection had a significant adverse impact on the outcome of ASOT recipients [24]. As a consequence of this *K. pneumoniae* bacteremia, patients required increased hospitalization with longer hospital stays, accompanied by treatment difficulty as well as a high risk of death. These results corroborated our previous studies demonstrating that septic shock, which is associated with more severe disease, more hospital care, more invasive device use and/or greater difficulty in diagnosis and treatment, was an

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Table 3. Univariate and multivariate analysis of risk factors associated with the occurrence of CRKP among *K. pneumoniae* infection recipients.

Characteristics	CSKP	CRKP	*P*-value	OR (95% CI)
Total, n (%)	30 (44.1)	38 (55.9)		
Univariate analysis, n (%)				
Male sex	17 (56.7)	26 (68.4)	0.318	
Age ≥40 years	23 (76.7)	22 (57.9)	0.104	
Nosocomial infection	16 (53.3)	25 (65.8)	0.297	
Duration of ICU stay >7 days after transplantation	9 (30)	10 (26.3)	0.737	
RBC transfusion >10 units during perioperative period	8 (26.7)	16 (42.1)	0.186	
Dialysis	4 (13.3)	10 (26.3)	0.189	
Mechanical ventilation	8 (26.7)	5 (13.2)	0.160	
Septic shock	2 (6.7)	5 (13.2)	0.636	
Acute rejection within 3 months before infection	1 (3.3)	1 (2.6)	0.865	
Other infections within 3 months before *K. pneumoniae* infection	3 (10)	6 (15.8)	0.734	
Re-operation	2 (6.7)	6 (4.5)	0.435	
The use of antithymocyte globulin	15 (50)	20 (52.6)	0.829	
Use of meropenem for 3 days or more within 1 month before infection	9 (30)	21 (55.3)	0.037*	
Multiple infected organisms or sites	8 (26.7)	20 (52.6)	0.031*	
Use of wide-spectrum antibiotics for 5 days or more within 1 month before infection	15 (50)	15 (39.5)	0.385	
Liver transplantation	7 (23.3)	11 (28.9)	0.602	
K. pneumoniae bacteremia	8 (26.7)	16 (42.1)	0.186	
Early-onset infection	20 (66.7)	26 (68.4)	0.878	
The use of tacrolimus	26 (86.7)	31 (81.6)	0.815	
Platelet count <50,000/mm^3	4 (13.3)	7 (18.4)	0.815	
Lymphocyte count <300/mm^3	11 (36.7)	14 (36.8)	0.988	
Albumin <30 g/L	8 (21.1)	1 (3.3)	0.075	
WBC count >15,000/mm^3	7 (23.3)	8 (21.1)	0.822	
Creatinine >1.5 mg/dL	16 (53.3)	22 (57.9)	0.707	
Multivariate analysis				
Multiple infected organisms or sites			0.033*	3.056 (1.091–8.556)

P-value from Pearson's χ^2 test or Fisher's exact test in univariate analysis and from multiple logistic regression in multivariate analysis.
* The *P*-values are statistically significant. OR – odds ratio; CI – confidence interval; WBC – white blood cells; ICU – Intensive Care Unit; RBC – red blood cells.

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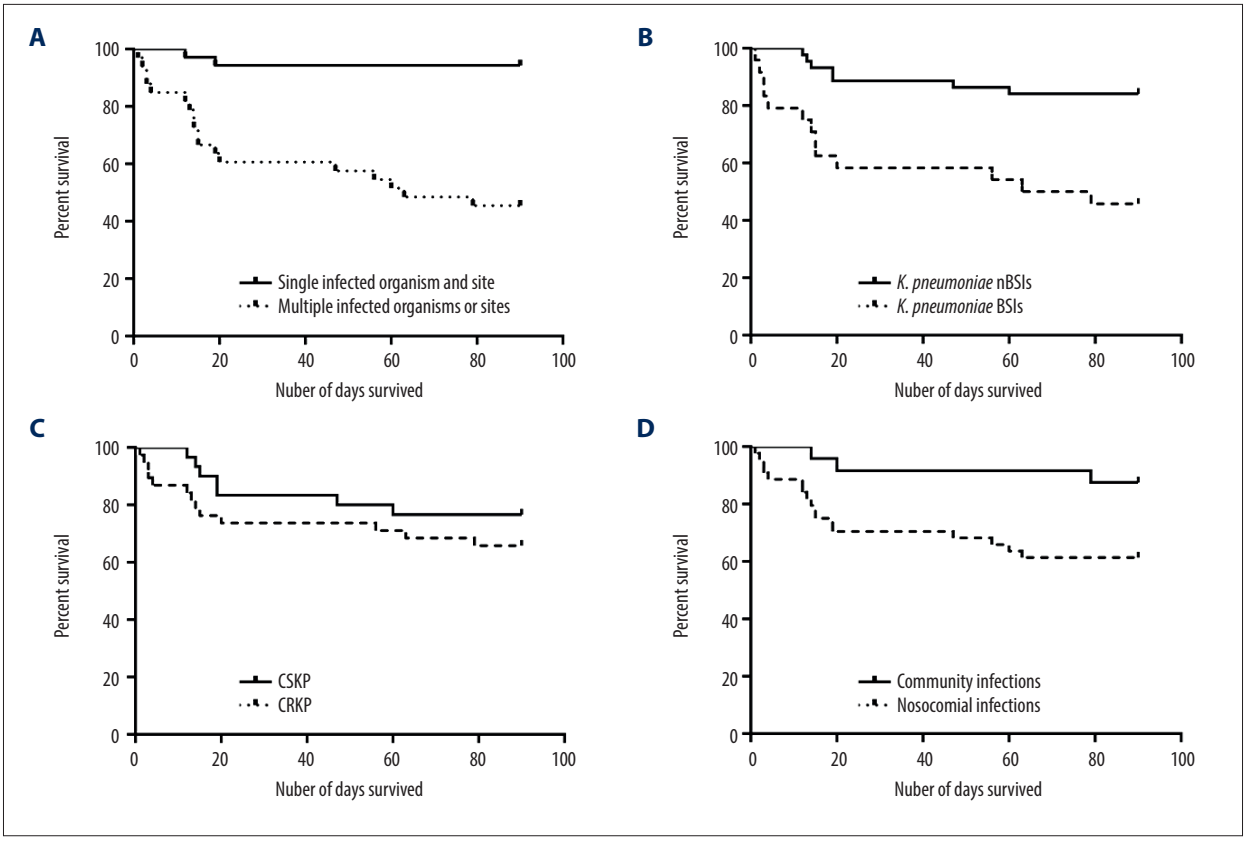

Figure 1. Kaplan-Meier survival curves estimating the outcome of *K. pneumoniae* infection recipients. (**A**) Recipients with infections caused by single *vs.* multiple infected organs or sites ($P<0.001$); (**B**) recipients with infections originating in the bloodstream (BSIs) *vs.* non-bloodstream sites (nBSIs) ($P<0.001$); (**C**) recipients with infections caused by carbapenem-susceptible *Klebsiella pneumoniae* (CSKP) *vs.* carbapenem-resistant *Klebsiella pneumoniae* (CRKP) ($P=0.283$); (**D**) recipients with nosocomial infections *vs.* those with community infections $P=0.022$).

independent risk factor influencing mortality among ASOT recipients [24,30]. It can therefore be assumed that the recognition and treatment of septic shock can have a critical influence on the outcome of *K. pneumoniae* infection in ASOT patients.

Nosocomial infection is a great threat among ASOT recipients. In previous studies, Shendi et al. and Lee et al. found that high resistance to antibacterial agents among ASOT recipients was associated with a high rate of nosocomial origins [31,32]. In accordance with our previous study based on ASOT recipients with drug-resistant gram-negative infections, we observed that in the present cohort, based on survival analysis, nosocomial infection induced a significant increase in mortality [24]. Notably, several empirical antibiotics may be prescribed to treat the nosocomial infection, leading to severe drug resistance which could make the choice of antibiotics and the subsequent anti-infective treatments more difficult.

CRKP was widespread in patients in the current study, in line with previous studies revealing that CRKP has spread rapidly and emerged as a great threat to ASOT patients in the last decade [33,34]. ASOT *per se* is an important risk factor for infections and has been strongly associated with CRKP infections. However, in our study, CRKP was not a determinant factor associated with mortality among ASOT recipients. This finding differed from another study that found CRKP bacteremia to be associated with greater mortality than CSKP bacteremia among ASOT recipients. This could be due in part to the small number of bacteremia cases in our study; only 35% of all the cases in our cohort were patients with bacteremia [22].

Previous antibiotic exposure might prevent some infections; however, it has induced an increasing number of CRKP infections among ASOT recipients [7]. We found that the prescription of meropenem for at least 3 days within 1 month prior to *K. pneumoniae* infection was associated with the occurrence of CRKP infections in the univariate analysis. However, this variable no longer remained significant in the multivariate analysis. This finding may serve as a warning to physicians to recognize the importance of normative treatment including avoiding overuse of antibiotics, especially carbapenem.

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Appropriate antibiotic therapy, administered at the initial stage of infection, influences the outcome of patients with severe bacterial infections. Empiric therapy must not merely be activated as if *in vitro* against the pathogen but also must be prescribed in a well-timed pattern. ASOT recipients with CRKP infections may be treated with appropriate antibiotics only after lengthy delays, due to missed identification and drug-resistance testing of CRKP strains, costing up to 3 days. In line with previous studies, inappropriate empirical antibiotics use was a risk factor associated with crude mortality as *K. pneumoniae* infections were related to high prevalence of drug-resistance [35–38]. Therapies for patients with drug-resistant infections were reported to be limited due to severe deficiency of effective antibiotics [39]. The optimal drugs for CRKP-infected ASOT recipients, according to retrospective studies, were recommended as polymyxin E, amikacin. and tigecycline [40,41]. In addition, carbapenems remained a component of effective treatments for CRKP infections due to the relatively low number of pathogens with *in-vitro* resistance, according to MIC. The effectiveness of carbapenem treatments for CRKP infections, such as high-dose or double-carbapenem treatment, needs to be determined among ASOT recipients in further studies. Further prospective studies are therefore recommended to focus on drug-resistance of *K. pneumoniae* in organ recipients and to guide prescription of appropriate empiric regimens in the face of rising carbapenem resistance.

Mechanical ventilation, a vital medical treatment for assisted spontaneous breathing, is a cruel source of hospital-acquired pneumonia and a surrogate marker of clinical severity. In our present study, the application of mechanical ventilation was more frequent in the mortality group than in the survival group; however, it was not a predictor of mortality (P=0.07) among *K. pneumoniae* infection recipients. This finding requires further investigations, but nevertheless may be taken as cause to alert clinicians to limit and shorten the use of mechanical ventilation.

Contrary to previous studies that found that CRKP infections frequently occurred in the early period after ASOT, early-onset infection was not found to be a significant risk factor for CRKP infections in our study [21,32]. The value of enhancing prevention within the first two months after transplantation is not clear.

Several limitations need to be indicated in our study. Firstly, our study is limited by its retrospective monocentric study design, the nature of which includes the potential for incorrect written records, deficient data, or selection biases. Prospective studies, adopted to fill this gap, are required to verify our findings. These should be designed to address the role of surveillance of CRKP and management of both CRKP-colonized ASOT donors and their recipients, especially in the current era of donor deficiencies. Secondly, the study should collect more clinical records from different time points in the course of antibiotic therapy, so that the transformation to drug resistant strains of pathogens during ongoing treatment may be understood. Thirdly, the high OR scores have a potential negative predictive value due to the limited sample size of our study. Multicenter, even nationwide, research studies are needed to minimize this bias. Finally, there were also some variables we did not collect, such as Sequential Organ Failure Assessment score, the production of carbapenemase, donor transmission of infection, and so on, which may be risk factors associated with *K. pneumoniae* infections among ASOT recipients. Despite the limitations mentioned above, all of our reported findings should be taken into account attentively. This 7-year period monocentric study set in China can be beneficial for its universally applicable research findings and should be validated by more investigators in future studies.

Conclusions

This is the first study to specifically focus on the determination of risk factors related to mortality of *K. pneumoniae*-infected ASOT recipients and the acquisition of CRKP infection among Chinese ASOT recipients. This research showed a high prevalence of and mortality rate from *K. pneumoniae* infections among Chinese ASOT recipients. Multiple infected organs or sites and septic shock were independent risk factors related to the crude mortality caused by *K. pneumoniae* infections. Multiple infected organs or sites was also an independent risk factor associated with CRKP infections. More strategies based on our present study findings are required to lower the prevalence of CRKP and *K. pneumoniae* infection among ASOT recipients and to reduce the effect of *K. pneumoniae* infections on outcomes of grafts and patients. These could include early diagnosis, precise treatment, improvement of the administration of antibiotics, recognition of septic shock, and shortening of the length of hospitalization. Physicians need clinical characteristics and epidemiology in order to be able to rapidly confirm *K. pneumoniae* infections and minimize the spread of CRKP pathogens.

Conflicts of interest

None.

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