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ORIGINAL RESEARCH

Clinical Characteristics, Virulence Profile, and Molecular Epidemiology of *Klebsiella pneumoniae* Infections in Kidney Transplant Recipients

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Background: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections may increase the potential for mortality in kidney transplant (KT) recipients. This study aimed to investigate the clinical features, molecular epidemiology, virulence, and antimicrobial resistance of KP strains from KT patients.

Methods: Strains isolated from KT patients were collected, and antimicrobial susceptibility analysis was verified *via* the Vitek2 compact instrument and the disc diffusion method. In gene expression analysis, carbapenemase genes (KPC-2, OXA-48, IMP, VIM, NDM), capsular genes (K1, K2, K5, K20, K54, K57), and virulence genes (rmpA, rmpA2, aerobactin, peg344) were identified *via* polymerase chain reaction (PCR). Molecular epidemiology was analyzed using multilocus sequence typing (MLST) and minimal spanning trees (MST).

Results: A total of 43 KP isolates were collected from KT patients in this study, and 24 of them were identified as CRKP (55.81%). KPC-2 genes were detected in all of the CRKP strains (100%), and other carbapenemase genes were not detected. Twenty-two strains (91.67%) of CRKP strains were identified as ST11, while 2 (8.33%) were ST15-typing. Finally, two highly virulent *K. pneumoniae* strains (both K20-ST268 type) were identified. In addition, the group of CRKP showed a higher deceased kidney donor ratio ($p = 0.011$), a higher proportion of post-transplant transfers to the ICU ($p = 0.037$), a higher proportion of late-onset infections (3 months post-transplantation acceptance) ($p = 0.007$), and high positive rates for the virulence gene *rmpA2* ($p = 0.01$) when comparing the group of carbapenem-sensitive KP.

Conclusion: The resistance rate to carbapenem of KP from KT patients exceeded the regional average with predominant ST typing of ST11. Clinical data were analyzed to derive some high-risk factors for CRKP infection. Therefore, we recommend early prophylactic isolation of transplant patients with high-risk factors for CRKP infection to improve the quality of nosocomial control.

Keywords: kidney transplant, *Klebsiella pneumoniae*, virulence gene, multilocus sequence typing

Introduction

Kidney transplant (KT) is the most effective treatment for end-stage renal disease, which can significantly improve the quality of patient survival and prolong life expectancy.[1] Globally, more than 100,000 patients with end-stage renal disease undergo kidney transplantation each year. Of these, approximately 10,000 were completed in China.[2] Bacterial infection is the second most common cause of graft loss in transplant recipients.[3] *Klebsiella pneumoniae* (KP) is the most clinically significant opportunistic pathogen. In patients with urinary tract infections complicated by kidney transplant, KP is the second most frequently isolated pathogen, compared to *Escherichia coli*.[4] In a five-year-long single-center study, of all KT patients infected by pathogenic organisms, KP led all gram-negative bacterial infections with a prevalence of 20.1%.[5] Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection poses a significant problem to KT patients' clinical management and prognosis. Statistical data showed that the mortality rate of KT patients infected with CRKP is nearly 40% (3–5 times) higher than that of patients infected with carbapenem-susceptible *Klebsiella*

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pneumoniae (CSKP).[6] Recently, hypervirulent *Klebsiella pneumoniae* (hvKP) has gradually received widespread clinical attention, and the number and type of virulence genes significantly increase the pathogenicity of strains.[7] Acquisition of drug-resistance genes by the hvKP strain or hypervirulence by the CRKP strain characterizes the emergence of both hypervirulent and multiresistant Klebsiella pneumoniae.[8,9] Therefore, epidemiologic statistics on KP strains are essential. However, there is a lack of molecular epidemiologic analysis of KP strains isolated from patients with KT. This study was designed to systematically investigate the clinical characteristics of KP infections in renal transplantation patients in our hospital. Moreover, this study identified the antibiotic resistance, virulence, and molecular epidemiology of the infected KP strains to provide a theoretical basis for controlling nosocomial infections.

Materials and Methods

Strains Collection and Antimicrobial Susceptibility Analysis

KP strains isolated from the kidney transplantation ward between January 2021 and May 2023 were screened from the laboratory's strain bank, duplicates were excluded. The strains were confirmed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS), while their antimicrobial susceptibility analysis was assessed with the Vitek2 compact instrument and the disc diffusion method.

Collection of Clinical Data

Clinical data from patients was obtained from the electronic medical record system, which involved sex, age, duration of hospitalization, donor source type of the transplanted kidney, use of carbapenem antibiotics in the perioperative period, transfer to the intensive care unit (ICU) after transplantation, time of infection (was it within three months of transplantation), was it the first infection with KP, were there any other bacterial infections and fungal infections before the current infection, diabetes mellitus, and hypertension, graft loss after kidney transplantation (such as death, transplanted nephrectomy, and transplanted renal insufficiency necessitating dialysis) and hemoglobin level during the infection period (the results at the time of identification of the infection), and the presence or absence of invasive syndromes.

Definitions

According to experts' consensus, CRKP was characterized by the production of carbapenemases or resistance to any carbapenem antibiotics, including imipenem, meropenem, and ertapenem.[10] Furthermore, hvKP was screened using a positive string test according to the previous reference.[11]

String Test

After rewarming, the KP strains were inoculated in Colombian blood agar. The strains were then grown in a 37°C constant incubator for 16 to 18 h. The aseptic inoculation ring was dipped in a single colony and then gently lifted, and a positive string test was determined as a pulling length >5 mm.

Detection of Capsular Genes, Virulence Genes, and Carbapenemase Genes

DNA templates of KP strains were extracted and then amplified using polymerase chain reaction (PCR) for the detection of capsular genes, virulence genes, and carbapenemase genes. The primers were obtained from Sangon Biotech (Shanghai) Co. (Supplemental Table 1). The amplification cycling process was as follows: denaturation at 95°C for 30s, annealing at 50–56°C for 30s, extension at 72°C for 1 min in 35 cycles, followed by final extension at 72°C for 10 min. The products were confirmed by 1.5% agarose gel electrophoresis, and results were detected via a UV gel imager (BIO-RAD, USA).

Multilocus Sequence Typing (MLST)

Primer sequences for housekeeping genes were obtained from the MLST database of *K. pneumoniae* (https://bigsdb.pasteur.fr/klebsiella/primers-used/), as detailed in Supplemental Table 2. The conditions of amplification cycles were as follows: initial denaturation at 95°C for 30 sec, followed by annealing at 50°C (gapA at 60°C/tonB at 45°C) for 30 sec,

and extension at 72°C for 1 min, repeated for 35 cycles, with a final extension at 72°C for 10 min. The products were transferred to Nanjing Sangong Biological Company for sequencing, and sequencing results were submitted to the MLST database. The sequencing results were compared at the MLST database website (https://bigsdb.pasteur.fr/klebsiella/). The respective allelotypes and typing results were also obtained. The typing results were analyzed by PHYLOViZ online (https://online.phyloviz.net/index) for affinity analysis using minimal spanning trees (MST).

Statistical Analysis

Data was statistically analyzed via IBM SPSS 25 software. The antibiotic susceptibility test results were examined using the WHONET 5.6 software. Continuous variables were checked for normality by the Kolmogorov–Smirnov normality test. Normally distributed data were expressed as mean ± standard deviation ($\overline{x} \pm SD$) and compared between two groups using the *t*-test. Skewed data were expressed as median (interquartile spacing) [M (P25, P75)] and compared between two groups via the Mann–Whitney *U*-test. Categorical variables were represented as sample size (%) [n (%)] and compared between the two groups using the chi-square test. A bilateral p-value <0.05 was regarded as statistically significant.

Ethical Approval

The study received ethical approval from the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (Approval Number PJ 2024–12-54). In the cases covered by this study, all kidneys were donated voluntarily with written informed consent, and these were conducted in accordance with the Declaration of Istanbul. The clinical isolates used in our study were obtained from patients as part of routine hospital procedures. All clinical data and isolates in this experiment were kept strictly confidential, and the recovered strains were autoclaved and sterilized after completion. Due to the retrospective nature of the study, informed consent was waived. Our study complies with the Declaration of Helsinki.

Results

Strain Information and Antimicrobial Susceptibility Analysis

A total of 43 non-repeat KP strains were isolated. The strain was isolated from 21 (48.84%) urine, 7 (16.28%) ascites, 6 (13.95%) sputum, 5 (11.63%) blood, and 4 (9.30%) postoperative drainage fluid. The results of the antimicrobial susceptibility analysis showed that of the 43 KP strains, 24 were resistant to carbapenem antibiotics and 19 were susceptible.

Basic Clinical Data

Among the 43 KT patients, 31 (72.10%) were male and 12 (17.90%) were female, aged 19–69 years, with a mean of 39.95±10.18 years. The patient's hospitalization duration was 36.00 [19.00, 60.00] days. The patients received kidneys from deceased donors in 26 cases (60.46%) and from relatives in 17 cases (39.54%). Twenty-six (60.46%) patients were treated with carbapenem antibiotics to prevent infections in the perioperative period, 14 (32.56%) were patients who were transferred to ICU for treatment after transplantation, 24 (55.81%) cases of infections occurred within three months after transplantation, 32 (74.42%) cases were first time infected with KP, 20 (46.51%) cases had other bacterial infections and 13 (30.23%) cases had fungal infections before the current infection, 7 (16.28%) patients had diabetes mellitus, and 33 (76.74%) had hypertension. In 29 cases (67.44%), transplanted kidneys were still functional as of December 31, 2023, while in 14 cases (32.56%) had failed. Furthermore, the mean hemoglobin level of the patients during the infection was 87.26±17.05 g/L.

Carbapenemase Genes of KP Strains

24 CRKP strains were KPC-2-producing, and none were identified with the carbapenemase gene of NDM, VIM, IMP, and OXA-48. The gel imaging results of the representative positive strains are depicted in Figure 1.

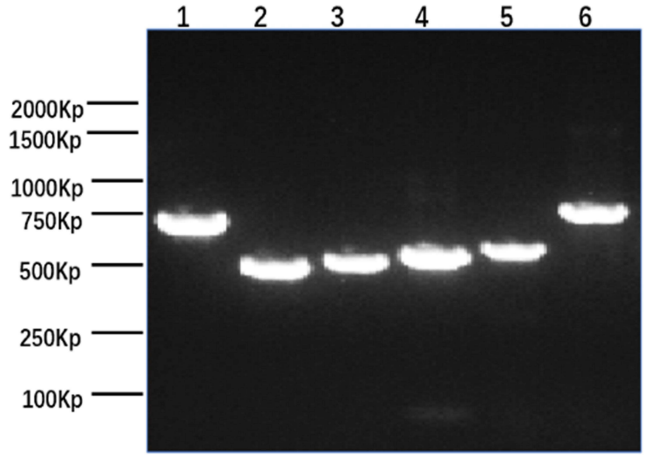

Figure 1 Representative gel imaging of positive genes.
Notes: Positive genes corresponding to 1–6 are for K20, Peg344, rmpA, aerobactin, rmpA2, and KPC-2, respectively.

Detection of String Test, Capsular Genes, and Virulence Genes

Two strains (4.65%) of the 43 KP strains were positive for the string test. Furthermore, all 2 (4.56%) strains were identified with the K20 capsular gene type, while the *K1, K2, K5, K54*, and *K57* capsular types were not identified. There were 20 (46.51%) rmpA2-positive, 8 (18.60%) peg344-positive, 7 (16.28%) rmpA-positive, and 2 (4.65%) aerobactin-positive strains detected in the virulence gene testing results. Gel imaging results for the representative positive strains are illustrated in Figure 1.

Comparison of Clinical Features and Virulence Gene Between the Groups of CRKP and CSKP

Based on the antibiotic susceptibility results, the strains were further divided into the CRKP (n = 24) and the CSKP (n = 19) groups. The results were then statistically analyzed for the clinical characteristics of the patients in each group (Table 1). Overall findings showed that the CRKP group had 19 deceased donors (79.17%), significantly higher than the CSKP group (36.84%). The difference was statistically significant ($p = 0.011$), at the same time, the CRKP group possessed a higher rate of

Table 1 Comparison of Clinical Data Between the Groups of CRKP and CSKP from KT Patients

Clinical Characteristics	Overall (n=43)	CRKP Group (n = 24)	CSKP Group (n = 19)	$\chi 2/t$ Values	*P* Values
Age (years)	39.95±10.18	39.75±12.2o	40.21±7.15	−0.146	0.885
Duration of Hospitalization (days)	36.00 (19.00, 60.00)	36.00 (17.50, 64.75)	36.0 (21.0, 60.0)	−0.061	0.951
Sex	31 (72.10)	18 (75.00)	13 (68.42)	0.228	0.738
Deceased donation	26 (60.46)	19 (79.17)	7 (36.84)	7.947	0.011
Graft loss	14 (32.56)	8 (33.33)	6 (31.58)	0.150	0.583
Fungal infection	13(30.23)	8(33.33)	5(26.32)	0.248	0.619
Other bacterial infections	20(46.51)	13(54.17)	7(46.51)	1.279	0.258
Recent infection (<3 months post-transplant)	24(55.81)	9(37.50)	15(78.95)	7.387	0.007
First infection with KP	32(74.42)	14(58.33)	18(94.74)	7.382	0.007
Perioperative Transfer to ICU	14(32.56)	11(45.83)	3(15.79)	4.359	0.037
Perioperative use of carbapenem antibiotics	26 (60.46)	19 (79.17)	7 (36.84)	7.947	0.011
Diabetes	7(16.28)	4(16.67)	3(15.79)	0	1.0
Hypertension	33(76.74)	20(83.33)	13(64.42)	0.618	0.432
Haemoglobin (g/L)	87.26±17.05	84.38±16.42	90.89±17.58	0.978	0.217

Notes: Data are $\bar{x} \pm SD$ or median (interquartile range) or n (%). *p* values were calculated by *t*-test, Mann–Whitney *U*-test, $\chi 2$ test, or Fisher's exact test, as appropriate.
Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; ICU, intensive care unit; SD, standard deviation.

postoperative ICU transfers (45.83%) (p = 0.037) and use of carbapenems antimicrobials (79.17%) (p = 0.011) in the perioperative period. However, more patients in the CSKP group had their first KP infection after transplantation (94.74%) (p =0.007) or an early infection that occurred within 3 months of surgery (78.95%) (p = 0.007).

As shown in Table 2, we also compared the positivity rates of virulence genes between the CRKP and CSKP groups. In contrast to the CSKP group, the CRKP group showed an increase in the positivity rate of rmpA2 (p = 0.01).

MLST

The MLST results of the 43 KP strains are presented in Table 3. Twenty-two strains (51.16%) were predominantly ST11. The remaining strains were identified as ST273, ST15, ST17, ST184, ST268, ST165, ST45, ST3368, and 1 untyped strain was also found (Figure 2A). Two ST types were detected in the CRKP group, ST11 and ST15, and the MST of the strains showed that ST11 and ST15 were relatively close to each other (Figure 2B). The results of MLST and genes are shown in Table 3. The detection rate of rmpA2 was significantly higher at 77.27% among the 22 ST11 CRKPs.

Table 2 Comparison of Positivity Rates of Virulence Genes Between the Groups of CRKP and CSKP

Virulence Genes	Total (n=43)	CRKP Group (n=24)	CSKP Group (n=19)	$\chi 2$	*P*
RmpA2	20 (46.51)	17 (70.83)	3 (15.79)	12.915	0.010
Peg344	8 (18.60)	6 (25.00)	2 (10.53)	0.667	0.414
RmpA	7 (16.28)	5 (20.83)	2 (10.53)	0.243	0.437
Aerobactin	2 (4.65)	0	2 (10.53)	–	0.189

Notes: Data are n (%). *p* values were calculated by $\chi 2$ test, or Fisher's exact test, as appropriate.
Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*.

Table 3 Carbapenemase Genes, Virulence Genes, and Sequence Typing of KP Strains

MLST	Housekeeping Genes							Carbapenemase Genes	Capsular Serotypes and Virulence Genes	Amount
	Gapa	*Infb*	*Mdh*	*Pgi*	*Phoe*	*rpob*	*tonb*			
ST11	3	3	1	1	1	1	4	KPC-2	*RmpA2*	12
	3	3	1	1	1	1	4	KPC-2	*Peg334, rmpA, rmpA2*	4
	3	3	1	1	1	1	4	KPC-2		4
	3	3	1	1	1	1	4	KPC-2	*Peg334, rmpA*	1
	3	3	1	1	1	1	4	KPC-2	*Peg334, rmpA2*	1
ST15	1	1	1	1	1	1	1	KPC-2		2
ST17	2	1	1	1	4	4	4			2
ST45	2	1	1	6	7	1	12			1
ST184	3	1	1	4	7	4	66			2
ST268	2	1	2	1	7	1	81		K20, *aerobactin, peg334, rmpA, rmpA2*	2
ST273	3	4	6	1	7	4	4			4
ST469	2	1	2	1	10	1	4			1
ST685	2	1	2	1	3	4	25			1
ST1715	2	1	1	3	8	25	15			2
ST2370	2	9	1	1	13	1	16			2
ST3368	4	1	2	1	1	1	7		*RmpA2*	1
Not typed	2	9	6	1	13	1	4			1
Total										43

Abbreviations: MLST, multilocus sequence typing; KP, *Klebsiella pneumoniae*.

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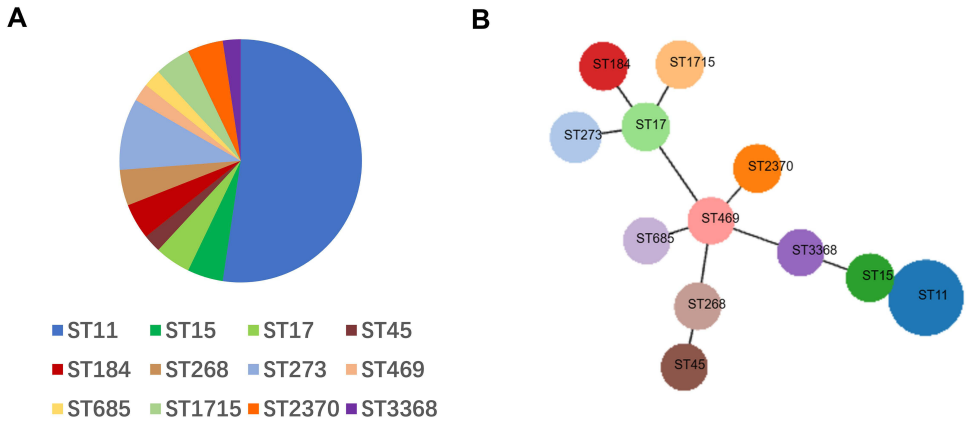

Figure 2 ST typing distribution and minimum development tree diagram of KP strains. (**A**) Distribution of ST typing. (**B**) Illustrates a minimum development tree derived from MLST typing.
Notes: Each circle denotes a specific ST type. The size of each circle correlates with the number of strains, while the length of the lines connecting the circles reflects the genetic relationship distance between the isolates.

Discussions

The clinical management of KT patients is significantly impacted by their susceptibility to KP infections, primarily CRKP infections, which increase the risk of kidney graft rejection and raise patient mortality rates. This study investigates the clinical characteristics of KT patients infected with KP strains, antibiotic resistance, virulence, and molecular epidemiological characteristics of those KP strains. We found a significant prevalence of carbapenem resistance rates in KP strains isolated from KT patients. Patients in the CRKP group had a higher percentage of kidneys from deceased donors and higher positivity for the virulence gene *rmpA2* than the CSKP group. Analysis of clinical data revealed that CRKP infections were more likely to occur in patients with a history of ICU residency, the time of infection was more likely to occur farther post-transplantation, and infections were more likely to recur. The CRKP group identified two distinct ST types, ST11 and ST15. Notably, as we know, we reported the first detection of the hvKP strain K20-ST268 in patients with KT. The above results may provide valid information on KP strains' clinical and molecular characteristics in KT patients.

The detection rate of CRKP in KT patients is much higher than the national average for drug resistance of KP in 2022 (10.0%).[12] This is close to the results from other centers in China.[5,13] Such elevated rates are frequently attributed to nosocomial transmissions and antimicrobial selection pressures. Then the results of MLST revealed that the CRKPs were primarily ST11 strains that produced KPC-2, consistent with the prevalent CRKP strains in China.[14–17] Furthermore, the MST results indicated close relationships among the ST typing of CRKPs, suggesting clonal dissemination of multidrug-resistant bacteria within the same wards. These results highlight the urgent need for improving care, isolation protocols for patients with CRKP in kidney transplants, and enhancing infection control measures in renal transplant units.

The comparison of clinical characteristics showed a higher proportion of kidneys from deceased donors in the CRKP group. This means patients receiving deceased donor kidney transplants are more susceptible to CRKP infection, and this phenomenon may be elucidated by the donor's transmission of CRKP or the selective pressure from carbapenem antibiotics during their lifetime. There are no relevant studies that have counted the difference in the rate of CRKP infection in kidney transplants from different donor types, but many studies have shown that donor-derived infection (DDI) is one of the important factors of CRKP infection in KT patients,[18,19] which mainly occurs in deceased donor kidney transplantation. Zhang F et al found that the incidence of death or graft loss was significantly higher in transplanted kidney preservation fluid culture CRKP-positive patients (30.0%) than in CRKP-negative patients (8.1%).[20] However, the acute organ shortage has resulted in a continued increase in the use of organs from marginal donors.[21] Overall, it is crucial to consistently monitor DDI in clinical renal transplant patients during the perioperative period.

A review of transplant patients' medical records revealed differences in perioperative prophylactic use of antimicrobials between patients receiving deceased donor and living kidney transplants, with meropenem routinely used in the former and melphalan-sulbactam predominantly in the latter. The use of carbapenem antibiotic makes patients more

susceptible to CRKP infection.[22,23] In addition, the medical records showed that more patients in the CRKP group were transferred to the ICU for post-transplantation treatment compared to the CSKP group, which is an endemic area of CRKP.[22,24] Also, according to the results of the analysis of the clinical data, infections at a later stage after transplantation (>3 months) and patients with multiple KP infections are high-risk factors for CRKP. A study of urinary tract infections in KT patients due to KP also reached consistent conclusions.[25] Therefore, we need to be highly vigilant about the possibility of CRKP infection in patients with the above risk factors.

K1/K2 hvKP was not detected in our isolates. However, current studies have shown that serotype (K1/K2), rmpA and aerobactin are important predictors of hvKP.[26,27] In our experiment, two K20-ST268 hvKP were determined, and they were sensitive to most antibiotics except ampicillin. To the best of our knowledge, our study was the first to report the detection of a K20-ST268 type KP strain in KT patients. In recent years, carbapenemase-sensitive and carbapenemase-resistant K20-ST268 hvKPs have been successively detected.[28,29] Research has demonstrated that K20-ST268 has the potential to be highly virulent and multi-drug resistant, which could pose a future clinical challenge.[27] Given the above, the detection of carbapenemase-negative K20-ST268 KP in our hospital deserves to be noticed. The prevalence of this strain in KT patients needs to be clarified by multicenter studies with larger sample sizes.

Moreover, in this study, the positivity rate of *rmpA2* in the CRKP group was significantly higher than in the CSKP group, and further analysis revealed that the ST11 CRKP strains showed a higher *rmpA2* positivity rate. In a previous study focused on rapidly detecting rmpA2-carrying hvKP, 28 *rmpA2*-positive KP strains were all ST11.[30] Similarly, other studies have shown that ST11 KP strains have a higher rate of rmpA2 positivity.[31,32] *RmpA/rmpA2* genes have been shown to regulate capsular polysaccharides (CPS) biosynthesis, and *rmpA2* is present in plasmids as *p-rmpA2*.[33] A previous study showed that in different strains, the length of *p-rmpA2 was variable, and* the effects of the *p-rmpA2* gene on CPS regulation and virulence could be different.[34] *p-rmpA2* in NTUH-K2044 inhibited CPS,[34] however, in KP CG43, it is an activator of CPS and important for virulence in mice.[35] Thus, we surmised that *p-rmpA2* in ST-11 KP may repress the expression of CPS and propagate through plasmids, which is consistent with the results of our experiments. More studies are needed to confirm the function of *p-rmpA2* in ST11 KP.

Our study has some limitations. First, the design of this retrospective study may help explain the bias of the results. Second, the treatment of patients included in this study could not be evaluated. Finally, the interpretation of our findings might be limited by the sample size.

Conclusion

This study was the first retrospective analysis of the epidemiological characteristics of KP strains in KT patients at our center. Based on the high detection rate of CRKP in KT patients and the close affinity of these CRKP strains, the current status of CRKP infections in KT patients is not favorable. It highlights the importance of strengthening nosocomial infections in preventing and controlling CRKP in KT patients. The analysis of the clinical data yielded some high-risk factors associated with CRKP infection, these high-risk factors include a deceased donor, transfer to the ICU, use of carbapenem antibiotics, infection in the later post-transplantation period, or multiple recurrent infections. Therefore, we recommend early prophylactic isolation measures for transplant patients with high-risk factors for CRKP infection. Moreover, the detection of K20-ST268 hvKP suggests that we need to be wary of the emergence of KP strains that are both multi-resistant and hypervirulent.

Disclosure

The authors report no conflicts of interest in this work.

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