Characteristics of ST11 KPC-2-producing carbapenem-resistant hypervirulent Klebsiella pneumoniae causing nosocomial infection in a Chinese hospital

Pengwen Ouyang1 | Bin Jiang1 | Na Peng1 | Juan Wang2 | Liang Cai2 | Yi Wu1 | Jianrong Ye1 | Yiping Chen1 | Hao Yuan1 | Chaochao Tan1 | Liming Tan1 | Liangyi Xie1

1Department of Clinical Laboratory, Hunan Provincial People’s Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China
2Department of Microbiology Laboratory, Center for Disease Control and Prevention of Hunan Province, Changsha, China

Correspondence
Liangyi Xie, Department of Clinical Laboratory, Hunan Provincial People’s Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, Hunan, 410005, China. Email: lyxie78@hunnu.edu.cn

Funding information
Renshu Foundation of Hunan Provincial People’s Hospital, Changsha, China, Grant/Award Number: 2016; Research Foundation of Education of Hunan Province, China, Grant/Award Number: 20A292; Natural Science Foundation of Hunan Province, China, Grant/Award Number: 2017JJ3173

Abstract

Background: The purpose of our study is to analyze the microbiological and clinical characteristics of carbapenem-resistant hypervirulent Klebsiella pneumoniae (CR-hvKP) that causes nosocomial infection.

Methods: We collected the carbapenem-resistant K. pneumoniae (CRKP) strains that caused nosocomial infection in a hospital in China and collected the relevant clinical data. We characterized these strains for their antimicrobial and virulence-associated phenotype and genotype and analyzed the clonal relatedness. We screened hypermucoviscous strains and compared them with non-hypervirulent strains.

Results: We retrospectively analyzed 62 CRKP strains that caused nosocomial infection in a tertiary hospital within 1 year, of which 41 (41/62, 66.1%) CRKP were considered as CR-hvKP. All CR-hvKP strains were multi-drug resistance (MDR) and the vast majority of isolates (39/41, 95.1%) were ST11 KPC-2-producing strains. Two hypermucoviscous isolates and 4 capsular types were found in 41 CR-hvKP. Twenty-nine isolates (29/41, 70.7%) showed hypervirulence in Galleria mellonella infection model. PFGE showed that ST11-KL47 CR-hvKP and ST11-KL64 CR-hvKP exhibited a high degree of clonality, while non-hypervirulent strains were not significant. CR-hvKP had higher positive rates of bla_{KPC-2} and bla_{CTX-M-65} and higher levofloxacin resistance (p < 0.001, p = 0.005 and p = 0.046, respectively) when compared to the non-hypervirulent strains. There was no significant difference between the two groups in terms of in-hospital mortality (7/41, 17.1% vs 5/21, 23.8%, p = 0.743).

Conclusion: Our research finds that ST11 KPC-2-producing CR-hvKP is the main type of CRKP that caused nosocomial infection, and clonal spread has occurred. We provide more information about CR-hvKP in health care.

KEYWORDS
carbapenem resistance, hypervirulence, Klebsiella pneumoniae, nosocomial infection
INTRODUCTION

Klebsiella pneumoniae is an important opportunistic pathogen associated with bacterial infections in hospitals. Carbapenem-resistant K. pneumoniae (CRKP), which can resist almost all clinically used antibiotics and cause serious infections, poses a huge threat to global public health.\textsuperscript{1,2} K. pneumoniae sequence type (ST) 258 has contributed significantly to the dissemination of CRKP in the United States and in European countries, but ST11 is predominant in China,\textsuperscript{3} and the genomic characteristics of ST11 K. pneumoniae strains are significantly different from that of other countries.\textsuperscript{4} The most predominant carbapenemase genes of ST11 CRKP in China are \textit{bla}_{KPC-2}, \textit{bla}_{NDM-1}, \textit{bla}_{OXA-48}, and ST11 KPC-2-producing \textit{K. pneumoniae} is spreading at an alarming speed.\textsuperscript{5-7} ST11 CRKP is emerging in almost all Chinese provinces, and its prevalence in China forces us to conduct better tracing and control of such a pathogen.

Hypervirulent \textit{K. pneumoniae} (hvKP) is a more virulent variant of \textit{K. pneumoniae}, known for causing invasive infections among young and relatively healthy individuals. This phenomenon is first observed in community infections and mainly occurs in the Asian Pacific Rim.\textsuperscript{8} However, infections caused by hvKP are increasingly being reported worldwide in recent years.\textsuperscript{9,10} Researches find that the genetic determinants of hypervirulence of hvKP are generally on a typical ~200 kb virulence plasmid, as well as integrative conjugal elements.\textsuperscript{8,11} Alarminglv, hvKP can continuously increase antibiotic resistance by acquiring resistance elements.\textsuperscript{12} Convergence of hypervirulent and resistance make hvKP a global pathogen of current concern.\textsuperscript{13}

In the past years, reports on carbapenem-resistant hypervirulent \textit{K. pneumoniae} (CR-hvKP) infection were increasing, even a fatal outbreak caused by CR-hvKP in a Chinese hospital had been observed.\textsuperscript{14} Worryingly, ST11 CRKP with both hypervirulence and high drug resistance demonstrated limited adaptive cost and enhanced environmental survival,\textsuperscript{10,13,15} which might cause CR-hvKP to spread more quickly and widely, particularly in the hospital environment.

However, our knowledge of CR-hvKP is still very limited so far, and more monitoring and research results are urgently needed to fight this pathogen, particularly the pheno- and genotypic characteristics of prevalent strains from continually survey in hospitals. This study analyzed the presence of CR-hvKP among CRKP which caused nosocomial infection in hospitalized patients, and studied the phenotypes and genotypes of the strains, as well as clinical characteristics of the associated patients, which provided more information on understanding CR-hvKP.

METHOD

2.1 Study design and definition

A one-year retrospective study was conducted in Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University. This study was approved by the ethics committee of Hunan Provincial People's Hospital. The hospital is located in Changsha, Hunan Province, China. It is a large-scale comprehensive tertiary hospital with nearly 4000 beds. We used VITEK 2 Compact system (bioMérieux, Marcy-l’Étoile, France) conducting identification and antimicrobial susceptibility test of all strains isolated in Clinical Microbiology Laboratory from January to December 2018. The results of the antimicrobial susceptibility test were interpreted according to the rules provided by the CLSI guidelines.\textsuperscript{16} Strains identified as \textit{K. pneumoniae} and resistant to imipenem and/or meropenem (defined as CRKP in this study) were collected. Strains isolated from the same part of the same patient were excluded. Identification results were reconfirmed through VITEK MS (bioMérieux, Marcy-l’Étoile, France). For strains resistant to imipenem or meropenem, the E test method was used to verify their susceptibility. The antimicrobial susceptibility tests of tigecycline and colistin were carried out by the micro-broth dilution method. The interpretation of the results was carried out according to the FDA guidelines and EUCAST guidelines, respectively.\textsuperscript{17,18} Multi-drug resistance (MDR) was defined as resistance to three or more different antimicrobial classes. Disease-related data of all patients with CRKP infection were collected from medical records, including demographic characteristics, underlying diseases, invasive treatments, infection sites, length of stay, and infection outcome. Nosocomial infection was defined as a new infection which developed 48 h after patient admission. Only patients with a complete hospitalization history and who developed CRKP nosocomial infection were included in the study. CR-hvKP was defined by the presence of virulence gene \textit{iucA}, \textit{iroN}, \textit{frmpA}, or \textit{rmpA}, in CRKP.\textsuperscript{14}

2.2 Carbapenem-resistant phenotype and hypurmucoviscous phenotype detection

The carbapenem-resistant phenotype of strains was detected by CLSI recommended modified carbapenem inactivation method (mCIM).\textsuperscript{19} And, the hypurmucoviscous phenotype was detected by string test.\textsuperscript{14}

2.3 Resistance genes, virulence genes, and capsular type genes dection

We detected resistance genes by PCR amplification, including genes encoding carbapenemases (\textit{bla}_{KPC}, \textit{bla}_{NDM}, \textit{bla}_{IMP}, \textit{bla}_{VIM}, and \textit{bla}_{OXA-48}) and genes encoding other β-lactamasases (\textit{bla}_{CTX-M}, \textit{bla}_{SHV}, and \textit{bla}_{TEM}).\textsuperscript{20} We detected virulence genes by PCR amplification, including siderophores (\textit{entB}, \textit{irp}-1, and \textit{irp}-2), fimbriae biosynthesis (\textit{fimH} and \textit{mrkD}), lipopolysaccharide biosynthesis (\textit{wabG}), fucose synthesis (\textit{wcaG}), allantoin metabolism (\textit{allS}), and putative transporter (\textit{peg}-344).\textsuperscript{21-24} The positive amplification products after agarose gel electrophoresis were sequenced and compared on the NCBI BLAST website (https://blast.ncbi.nlm.nih.gov/blast.cgi). We genotyped the capsular polysaccharide
synthesis (cps) gene of strains by amplifying and sequencing the \emph{wzi} gene, as previously described.\textsuperscript{25} All primers used in this study are provided in Appendix S1.

2.4 | \textbf{Galleria mellonella infection model}

Further virulence assessment for CR-hvKP was conducted by \textit{in vivo} G. \textit{mellonella} infection model.\textsuperscript{14} Healthy G. \textit{mellonella} larvae weighing 250–350 mg were obtained from Huiyude Biotech Company (Huiyude Biotech Company, Tianjin, China). Setting up each strain as an experimental group, each experimental group contained 10 larvae. The mid-log phase culture was diluted with PBS into a bacterial suspension with a concentration of $10^6$ cfu/ml, and 10 μl of the bacterial suspension was injected with a microsyringe into the left forefoot of each larva. After injection, the larvae were kept at 37°C in dark to observe the 72-h mortality. Strain which the pathogenicity was similar or stronger than the positive control was assessed respectively.

2.5 | \textbf{Multilocus sequence typing (MLST) and pulsed field gel electrophoresis (PFGE)}

We conducted MLST by amplifying and sequencing 7 housekeeping genes (\emph{gapA, infB, mdh, pgi, phoE, rpoB,} and \emph{tonB}).\textsuperscript{26} The allele types and STs were confirmed based on the database provided on the Institut Pasteur website (https://bigsdb.pasteur.fr/). Genetic correlations among the CRKP strains were subsequently analyzed by PFGE.\textsuperscript{27} The PFGE banding pattern was clustered by BioNumerics software version 5.1 (Applied Maths, Kortrijk, Belgium). Isolates with 100% similarity were considered the same PFGE cluster.

2.6 | \textbf{Statistic analysis}

Statistical analysis was performed using SPSS 19.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables were assessed by Student’s t tests. The comparison of the categorical variables was calculated by Chi-square test or Fisher’s exact test. \emph{p} value <0.05 was considered to be statistically significant.

3 | \textbf{RESULTS}

3.1 | \textbf{Strain and patient information}

In this study, a total of 1743 \emph{K. pneumoniae} strains from Hunan Provincial People’s Hospital were collected between January 1 and December 31, 2018, by routine monitoring, among which 125 cases, 1 (1.6%) reproductive tract case, and 1 (1.6%) urine case. No pyogenic liver abscess or metastatic infection was reported in the 62 CRKP-infected patients.

More than half of the 62 (41/62, 66.1%) CRKP were CR-hvKP. The positive rates of \emph{lucA, iroN, rmpA}, and \emph{rmpA2} in 41 CR-hvKP were 40/41 (97.6%), 30/41 (73.2%), 3/41 (7.3%), and 19/41 (46.3%), respectively, among which 3 isolates had all four virulence genes (Figure 2). CR-hvKP mainly came from respiratory tract specimens (41/41, 34.2%). Males were mostly infected (30/41, 73.2%). Surgery department and ICU were the main epidemic departments (25/41, 61.0% and 12/41, 29.3%, respectively). Only 7 cases of CR-hvKP infection caused fatal outcomes (7/41, 17.1% mortality rate) (Table 1). We compared the clinical features between CR-hvKP and carbapenem-resistant non-hypervirulent \emph{K. pneumoniae} (CR-nhvKP). Through our analysis, there were no significant differences between the two groups in terms of age, gender, underlying diseases, invasive treatments, infection sites, length of hospital stay, and in-hospital mortality (Table 2).

3.2 | \textbf{Antibiotic resistance characteristics of CR-hvKP compared to CR-nhvKP in nosocomial infection}

All 62 CRKP were MDR. The 62 CRKP had high drug resistance rates for most of the antibacterial drugs that were tested, except for colistin and tigecycline. For CR-hvKP, the resistance levels for cefepime, ceftazidime, imipenem, meropenem, and piperacillin/
tazobactam were all 100%, followed by levofloxacin (97.6%), trimethoprim/sulfamethoxazole (51.2%), amikacin (41.5%), colistin (0%), and tigecycline (0%) (Figure 2, Table 3). In terms of resistance rate for levofloxacin from the CR-hvKP group, it was significantly higher than those from the CR-nhvKP group (97.6% vs 52.4%, \( p < 0.001 \)) (Table 3).

The mCIM tests of all 62 CRKP strains were positive. Two families of carbapenemase genes were identified from 62 CRKP strains: \( \text{bla}_{KPC-2} \) (49/62, 79.0%) and \( \text{bla}_{IMP-4} \) (1/62, 1.6%). Most (39/41, 95.1%) CR-hvKP harbored \( \text{bla}_{KPC-2} \) and 1 (1/41, 2.4%) harbored \( \text{bla}_{IMP-4} \). 1 CR-hvKP isolate did not carry \( \text{bla}_{KPC} \), \( \text{bla}_{NDM} \), \( \text{bla}_{IMP} \), \( \text{bla}_{VIM} \) or \( \text{bla}_{OXA-48} \) but the mCIM phenotype test was positive, indicating that it might harbor other carbapenem resistance genes. Other \( \beta \)-lactamase genes were detected in CR-hvKP strains, including \( \text{bla}_{CTX-M-3} \), \( \text{bla}_{CTX-M-15} \), \( \text{bla}_{CTX-M-65} \), \( \text{bla}_{SHV-11} \), \( \text{bla}_{SHV-12} \) and \( \text{bla}_{TEM-1} \). The positive rates of \( \text{bla}_{KPC-2} \) and \( \text{bla}_{CTX-M-65} \) in CR-hvKP group were both higher than that of CR-nhvKP group \( (p < 0.001 \) and \( p = 0.046 \), respectively) (Table 3).
TABLE 1  Clinical characteristics of 41 CR-hvKP strains

| Strain ID | Source | Department | Collection date | Outcome | mCIM | Antibiotic resistance genes | String test | Capsular type | ST |
|-----------|--------|------------|----------------|---------|------|-----------------------------|-------------|--------------|----|
| KP1       | Reproductive tract | SSD       | 2018/3/7       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP5       | Blood  | GSD        | 2018/3/1       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP13      | Sputum | RD         | 2018/3/12      | Death    | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP25      | Ascites| GSD        | 2018/1/5       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP26      | Wound  | SSD        | 2018/1/6       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP32      | Blood  | GSD        | 2018/3/7       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-12}}\) |             | KL64(wzi64) | 11 |
| KP145     | Bile   | GSD        | 2018/3/31      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP178     | Blood  | ICU        | 2018/5/14      | Death    | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP213     | Blood  | ICU        | 2018/4/17      | Death    | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP219     | Blood  | GSD        | 2018/4/8       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP238     | Ascites| HSD        | 2018/4/17      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP241     | Sputum | ICU        | 2018/4/19      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-12}}\) |             | KL64(wzi64) | 11 |
| KP292     | Ascites| GSD        | 2018/4/25      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-12}}\) |             | KL64(wzi64) | 11 |
| KP343     | Ascites| HSD        | 2018/5/8       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP497     | Sputum | GSD        | 2018/6/11      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-12}}\) |       | Untypable    | 11 |
| KP648     | Urine  | ICU        | 2018/6/26      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-12}}\) |             | KL64(wzi64) | 11 |
| KP669     | Sputum | ICU        | 2018/6/26      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP688     | Bile   | HSD        | 2018/6/29      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP1027    | Blood  | HSD        | 2018/8/2       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP1079    | Bile   | HSD        | 2018/8/4       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-12}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP1224    | Sputum | ICU        | 2018/8/14      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-11}}\) |             | KL47(wzi209) | 11 |
| KP1235    | Sputum | RD         | 2018/8/15      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL54(wzi115) | 2928 |
| KP1243    | Sputum | ICU        | 2018/8/15      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL47(wzi209) | 11 |
| KP1259    | Blood  | HSD        | 2018/8/19      | Death    | +    | \(\text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP1325    | Ascites| HSD        | 2018/8/25      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-12}}\) |             | KL64(wzi64) | 11 |
| KP1326    | Sputum | HSD        | 2018/8/26      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{TEM-1}}\) |             | KL64(wzi64) | 11 |
| KP1367    | Pus    | GSD        | 2018/8/29      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL47(wzi209) | 11 |
| KP1398    | Sputum | NSD        | 2018/8/14      | Death    | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}, \text{bla}_{\text{TEM-1}}\) |             | KL47(wzi209) | 11 |
| KP1537    | Wound  | GSD        | 2018/9/5       | Death    | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-11}}\) |             | KL47(wzi209) | 11 |
| KP1570    | Ascites| HSD        | 2018/9/6       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-11}}\) |             | KL47(wzi209) | 11 |
| KP1590    | Pus    | HSD        | 2018/9/9       | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP1640    | Sputum | ICU        | 2018/9/13      | Survived | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{SHV-11}}\) |             | KL64(wzi64) | 11 |
| KP1687    | Sputum | NSD        | 2018/9/16      | Death    | +    | \(\text{bla}_{\text{KPC-2}}, \text{bla}_{\text{CTX-M-65}}, \text{bla}_{\text{SHV-11}}\) |             | KL47(wzi209) | 11 |

(Continues)
3.3 Virulence-related characteristics of CR-hvKP compared with CR-nhvKP in nosocomial infection

By string test, only 2/62 (3.2%) CRKP strains were hypermucoviscous (both were CR-hvKP). wzi sequencing revealed 11 capsular types in 62 CRKP (28 KL64, 17 KL47, 2 KL28, 1 KL54, 1 KL136, 1 KL38, 1 KL19, 1 KL17, 1 KL123, 1 KL23, and 1 KL25, with 7 untypable). The vast majority of CR-hvKP belonged to KL64 and KL47, and KL64 was the dominant capsular type (27/41 KL64, 10/41 KL47, 2/41 KL28, and 1/41 KL54, with 1 untypable), while in the CR-nhvKP group more diverse capsular types were found. Capsule type KL64 (27/41 vs 1/21, p < 0.001) was significantly associated with the CR-hvKP group when compared to the CR-nhvKP group (Table 4). For virulence background genes in 62 CRKP strains, the positive rates of fimH, wabG, entB, mrkD, irp-1, peg-344, irp-2, wcaG, and allS were 96.8%, 95.2%, 93.5%, 93.5%, 77.4%, 58.1%, 0%, 0%, and 0%, respectively. Virulence genes irp-1 (37/41 vs 11/21, p = 0.003) and peg-344 (30/41 vs 6/21, p=0.001) were significantly associated with the CR-hvKP group when compared to the CR-nhvKP group (Table 4). By G. mellonella infection model, we found that 29/41 (70.7%) CR-hvKP strains showed hypervirulence in vivo (Figure 2).

3.4 Phylogenetic characteristics of CR-hvKP isolates

A total of 13 STs among 62 CRKP were identified in the study. ST11 was the most prevalent ST (49/62), followed by ST571 (2/62), ST15 (1/62), ST37 (1/62), ST170 (1/62), ST101 (1/62), ST414 (1/62), ST515 (1/62), ST1040 (1/62), ST1779 (1/62), ST1933 (1/62), ST2928 (1/62), and new ST (1/62). The majority of CR-hvKP belonged to ST11 (40/41, 97.6%) and 1 belonged to ST2928 (Table 1). More scattered clones were observed in the CR-nhvKP group. ST11 (40/41 vs 9/21, p < 0.001) was strongly associated with CR-hvKP when compared to CR-nhvKP (Table 4).

In the PFGE test, 1 CRKP strain had no complete bands despite several repeats. 61 CRKP strains displayed 36 PFGE clusters (Appendix S2). Clusters 10, 15, and 18 were the three main clusters, which all consisting of CR-hvKP strains. Cluster 10 included 7 strains that all belonged to ST11-KL47, cluster 15 included 11 strains that all belonged to ST11-KL64, and cluster 18 included 8 strains that all belonged to ST11, among which 7 were KL64. Notably, all 7 CR-hvKP strains in cluster 10 shared the same virulence genes and resistance genes, as well as high lethality in the G. mellonella infection model and resistance pattern. The 7 strains were all isolated between June and September 2018, suggesting clonal transmission. For CR-nhvKP, the homology of isolates was more diverse; only one cluster included 2 strains with 100% similarity was found.

4 DISCUSSION

Hypervirulent K. pneumoniae is originally known for community infections and has become a global clinical problem. This study analyzed the CR-hvKP that caused nosocomial infection during a specific period in a Chinese hospital, and we provided more medical institution related data about the “superbug.”

By detecting virulence genes highly related to hypervirulence, we found 66.1% CR-hvKP from 62 CRKP strains. We further investigated the virulence genetic background of these strains, and we found 70.7% CR-hvKP showed hypervirulence in G. mellonella infection model. Our data showed that the hypervirulent K. pneumoniae with carbapenem resistance was the main member of the CRKP that caused nosocomial infection in hospitalized patients and clonal spread of this pathogen had occurred. To date, reports on nosocomial infection CR-hvKP are very limited. Liu et al28 found 45.3% hypervirulent K. pneumoniae strains from 117 cases
of nosocomial *K. pneumoniae* infection, reporting a substantial change in the epidemiology of hypervirulent *K. pneumoniae*. Yang et al. found that CRKP strains harbored a virulence-encoding plasmid accounted for 58% of 784 *bla*KPC-2-bearing CRKP strains in a recently published study in China.\textsuperscript{29} Our data partially supported this trend. These CR-hvKP were mainly isolated from respiratory tract specimens, and most of the cases occurred in surgical department and ICU. These findings were partly consistent with the results of previous studies.\textsuperscript{10} Zhao et al.\textsuperscript{30} found that hypervirulent *K. pneumoniae* strains were prevalent in surgical site infections, with an infection rate as high as 46.0%, suggesting surgical patients should be considered to take more stringent infection prevention measures. In previous studies on hypervirulent *K. pneumoniae* infection, it was found that males were more commonly infected, and those in the fifth and sixth decades of life were of the highest risk.\textsuperscript{8} In our study, we did not find similar results. It is worth noting that we had observed CRKP infections in hospitalized infants. Although the strains were non-hypervirulent, it releases a danger signal, as Wang et al.\textsuperscript{31} reported. Metastatic spreading or pyogenic liver abscess are typical

| Variables                        | Total (n = 62) | CR-hvKP (n=41) | CR-nhvKP (n=21) | $\chi^2$ | p value |
|----------------------------------|---------------|----------------|-----------------|---------|---------|
| Demographics                     |               |                |                 |         |         |
| Age (mean ± SD)                  | 56.9 ± 19.9   | 57.07 ± 18.14  | 56.86 ± 23.50   | NA\textsuperscript{a} | 0.923   |
| Age (<1)                         | 2 (3.2%)      | 0 (0%)         | 2 (9.5%)        | 0.69\textsuperscript{b} | 0.403   |
| Age (1–49)                       | 17 (27.4%)    | 14 (34.1%)     | 3 (14.3%)       |         |         |
| Age (≥50)                        | 43 (69.4%)    | 27 (65.9%)     | 16 (76.2%)      |         |         |
| Male                             | 41 (66.1%)    | 30 (73.2%)     | 11 (52.4%)      | 2.680   | 0.102   |
| Underlying diseases              |               |                |                 |         |         |
| Diabetes mellitus                | 8 (12.9%)     | 7 (17.1%)      | 1 (4.8%)        | NA      | 0.247   |
| Chronic cardiovascular system    | 6 (9.7%)      | 2 (4.9%)       | 4 (19.0%)       | NA      | 0.167   |
| Chronic respiratory system       | 4 (6.5%)      | 1 (2.4%)       | 3 (14.3%)       | NA      | 0.108   |
| Tumor                            | 7 (11.3%)     | 3 (7.3%)       | 4 (19.0%)       | NA      | 0.214   |
| Chronic kidney diseases          | 1 (1.6%)      | 1 (2.4%)       | 0 (0%)          | NA      | 1.000   |
| Chronic Hepatitis/cirrhosis      | 4 (6.5%)      | 3 (7.3%)       | 1 (4.8%)        | NA      | 1.000   |
| Invasive treatments              |               |                |                 |         |         |
| Puncture or venous catheterization | 30 (48.4%)  | 19 (46.3%)     | 11 (52.4%)      | 0.203   | 0.652   |
| Mechanical Ventilation           | 18 (29.0%)    | 13 (31.7%)     | 5 (23.8%)       | 0.420   | 0.517   |
| History of surgery               | 38 (61.3%)    | 27 (65.9%)     | 11 (52.4%)      | 1.062   | 0.303   |
| Infection sites                  |               |                |                 |         |         |
| Respiratory tract                | 25 (40.3%)    | 14 (34.2%)     | 11 (52.4%)      | 1.919   | 0.166   |
| Biliary tract                    | 11 (17.7%)    | 5 (12.2%)      | 6 (28.6%)       | NA      | 0.160   |
| Abdomen                          | 9 (14.5%)     | 8 (19.5%)      | 1 (4.8%)        | NA      | 0.150   |
| Blood                            | 8 (12.9%)     | 7 (17.1%)      | 1 (4.8%)        | NA      | 0.247   |
| Wound                            | 4 (6.5%)      | 3 (7.3%)       | 1 (4.8%)        | NA      | 1.000   |
| Pus                              | 3 (4.9%)      | 2 (4.9%)       | 1 (4.8%)        | NA      | 1.000   |
| Urinary tract                    | 1 (1.6%)      | 1 (2.4%)       | 0 (0%)          | NA      | 1.000   |
| Reproductive tract               | 1 (1.6%)      | 1 (2.4%)       | 0 (0%)          | NA      | 1.000   |
| Hospitalization                  |               |                |                 |         |         |
| <30 days                         | 51 (82.3%)    | 31 (75.6%)     | 20 (95.2%)      | 1.052   | 0.305   |
| ≥30 days                         | 11 (17.7%)    | 10 (24.4%)     | 1 (4.8%)        | NA      | 0.080   |
| Outcome                          |               |                |                 |         |         |
| In-hospital mortality            | 12 (19.4%)    | 7 (17.1%)      | 5 (23.8%)       | 0.404   | 0.525   |

Note: NA: Data not applicable.
\textsuperscript{a}Assessed by Student’s t tests.
\textsuperscript{b}For the number of patients younger than 1 year old is too small, it is combined with "Age (1–49)" in statistical analysis.
enemase genes detected, gene KPC-2 showed the highest de-
bla tors, which reduced their pathogenicity to host. 
Secondly, these hypervirulent strains might lose some virulence fac-
timely intervention, the infections were prevented from worsening.
explained from the following two aspects. Firstly, patients were in the
the serious impact of hypervirulence. These results could be ex-
ning diseases, invasive treatments, infection sites, hospitalization
of CR-hvKP in this study. Two hypermucoviscous strains
were from blood and sputum; both showed high lethality in the
phenotype of CR-hvKP in this study. Two hypermucoviscous strains
necessary. 
Obviously, we reported a lower incidence of hypermucoviscosity
No significant differences were found in age, gender, underly-
ing diseases, invasive treatments, infection sites, hospitalization
time, and mortality rates between hypervirulent group and non-
hypervirulent group. From these existing data, it is difficult to find
the serious impact of hypervirulence. These results could be ex-
period of medical observation when the infection occurred. Due to
timely intervention, the infections were prevented from worsening.
Secondly, these hypervirulent strains might lose some virulence fac-
tors, which reduced their pathogenicity to host.

All CR-hvKP strains were MDR in this study. Of all carbap-
enemase genes detected, gene bla_kpc-2 showed the highest de-
tection rate, which is the most common type of carbapenemase
gene carried by ST11 CR-hvKP in China. 10,14,32 And, we found that
bla_kpc-2 and bla_CTX-M-65 tended to exist in hypervirulent strains.
Hypervirulent strains were more resistant to levofloxacin, which
may result from the co-transfer of bla_kpc and quinolone resistance
factors. For bla_kpc is usually carried by plasmid, the plasmid often
simultaneously carries other drug resistance genes. 11 In addition,
all strains in this research showed a high level of susceptibility to
colistin and tigecycline. Continuous resistance screening is still
necessary.

Clinical features of hypervirulent K. pneumoniae infection, but in our
research, we did not find such performances.

TABLE 3 Comparison of resistance features between CR-hvKP and CR-nhvKP

| Variables          | Total (n = 62) | CR-hvKP (n = 41) | CR-nhvKP (n = 21) | χ²  | P value |
|--------------------|---------------|-----------------|------------------|-----|---------|
| Antibiotic resistance rates |               |                 |                  |     |         |
| AMK                | 24 (38.7%)    | 17 (41.5%)      | 7 (33.3%)        | 0.387 | 0.534   |
| SXT                | 34 (54.8%)    | 21 (51.2%)      | 13 (61.9%)       | 0.640 | 0.424   |
| FEP                | 62 (100.0%)   | 41 (100.0%)     | 21 (100.0%)      | NA   | NA      |
| CAZ                | 62 (100.0%)   | 41 (100.0%)     | 21 (100.0%)      | NA   | NA      |
| IPM                | 62 (100.0%)   | 41 (100.0%)     | 21 (100.0%)      | NA   | NA      |
| MEM                | 62 (100.0%)   | 41 (100.0%)     | 21 (100.0%)      | NA   | NA      |
| TZP                | 61 (98.4%)    | 41 (100.0%)     | 20 (95.2%)       | NA   | 0.339   |
| LVX                | 52 (83.9%)    | 40 (97.6%)      | 11 (52.4%)       | NA   | <0.001  |
| COL                | 0 (0%)        | 0 (0%)          | 0 (0%)           | NA   | NA      |
| TGC                | 0 (0%)        | 0 (0%)          | 0 (0%)           | NA   | NA      |

| Antibiotic-resistant genes |               |                 |                  |     |         |
|--------------------------|---------------|-----------------|-----------------|-----|---------|
| bla_kpc-2                | 49 (79.0%)    | 39 (95.1%)      | 10 (47.6%)      | NA  | <0.001  |
| bla_4                    | 1 (1.6%)      | 1 (2.4%)        | 0 (0%)          | NA  | 1.000   |
| bla_CTX-M-3              | 3 (4.8%)      | 1 (2.4%)        | 2 (9.5%)        | NA  | 0.263   |
| bla_CTX-M-14             | 1 (1.6%)      | 0 (0%)          | 1 (4.8%)        | NA  | 0.339   |
| bla_CTX-M-15             | 1 (1.6%)      | 0 (0%)          | 1 (4.8%)        | NA  | 0.339   |
| bla_CTX-M-65             | 19 (30.6%)    | 16 (39.0%)      | 3 (14.3%)       | 3.999 | 0.046   |
| bla_SHV-V1               | 2 (3.2%)      | 0 (0%)          | 2 (9.5%)        | NA  | 0.111   |
| bla_SHV-V11              | 40 (64.5%)    | 29 (70.7%)      | 11 (52.4%)      | 2.043 | 0.153   |
| bla_SHV-V12              | 11 (17.7%)    | 10 (24.4%)      | 1 (4.8%)        | NA  | 0.080   |
| bla_SHV-V28              | 1 (1.6%)      | 0 (0%)          | 1 (4.8%)        | NA  | 0.339   |
| bla_SHV-V187             | 1 (1.6%)      | 1 (2.4%)        | 0 (0%)          | NA  | 1.000   |
| bla_TEM-1                | 17 (27.4%)    | 8 (19.5%)       | 9 (42.9%)       | 3.803 | 0.051   |

Abbreviations: AMK, amikacin; SXT, trimethoprim/sulfamethoxazole; FEP, cefepime; CAZ, ceftazidime; IPM, imipenem; MEM, meropenem; TZP, piperacillin/tazobactam; LVX, levofloxacin; COL, colistin; TGC, tigecycline; NA, Data not applicable.
series might have formed. This was confirmed by PFGE analysis. ST11-KL47 CR-hvKP which from the PFGE cluster 10 shared the same virulence and resistance characteristics and all isolated from a short period of time, suggested that clonal spread had occurred in our hospital. Interestingly, among ST11-KL64 CR-hvKP in PFGE cluster 15 and 18, no consistent characteristics were observed. This might result from the rapid reshaping and diversification of the genome pool of ST11-KL64 CR-hvKP.

Moreover, we found 2 ST11-KL28 KPC-2-producing CR-hvKP and 1 ST2928-KL54 IMP-4-producing CR-hvKP. As far as we know, hvKP of these types had not been reported, suggesting the diversity of CR-hvKP evolution.

In this study, only 3 strains with all the four virulence genes positive were detected; the three all showed high lethality in the G. mellonella infection model, suggesting complete pLVPK plasmid harboring. Interestingly, KP13, KP145, KP669, and KP1590 shared the same drug resistance type and genotype with KP178, KP213, KP238, and KP1640, but they showed opposite results in the G. mellonella infection model. This might be caused by the presence of undetected virulence factors. In addition, we also found that virulence genes irp-1 and peg-344 mainly existed in hypervirulent strains, indicating that these two genes may contribute to the virulence. In future research, the mechanism of hypervirulence is still worthy of attention.

This study only analyzed CRKP isolated from one hospital in China in one year. The sample size is very limited, and larger-scale or multi-center research results are needed to support the above results. In addition, the condition for screening hypervirulent strains in this study is the presence of one or more of virulence gene markers, rather than virulence plasmid, which may cause an overestimation of CR-hvKP. And, we cannot provide data related to plasmid analysis. Given the excellent ability of K. pneumoniae to obtain exogenous genes encoding resistance and virulence, we need to arouse sufficient vigilance over CR-hvKP.

### 5 | CONCLUSION

ST11 KPC-2-producing CR-hvKP is widespread in our hospital, and two significant lineages of ST11-KL64 and ST11-KL47 have emerged and clonal transmission occurred. It is urgent to develop novel rapid
and convenient methods to accurately distinguish hypervirulent K. pneumoniae and classical K. pneumoniae in order to perform precise treatment and deal with the spread of CR-hvKP.

**AUTHOR CONTRIBUTIONS**

LX and PO conceived and designed the study. PO, BJ, NP, and JW contributed to data collection and experiments implementation. PO, LC, YW, JY, YC, HY, CT, and LT contributed to data analysis and data interpretation. PO and LX contributed to writing the report and revising the report. All authors read and approved the final version of the manuscript.

**ACKNOWLEDGMENTS**

This work was funded by Natural Science Foundation of Hunan Province, China (grant number: 2017JJ3173), Research Foundation of Education of Hunan Province, China (grant number: 20A292), and Renshu Foundation of Hunan Provincial People's Hospital, Changsha, China (grant number: 2016).

**CONFLICT OF INTEREST**

All authors—none to declare.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**ORCID**

Liangyi Xie https://orcid.org/0000-0003-1861-1267

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SUPPORTING INFORMATION

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**How to cite this article:** Ouyang P, Jiang B, Peng N, et al. Characteristics of ST11 KPC-2-producing carbapenem-resistant hypervirulent *Klebsiella pneumoniae* causing nosocomial infection in a Chinese hospital. *J Clin Lab Anal*. 2022;36:e24476. doi:10.1002/jcla.24476