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ORIGINAL RESEARCH

Extended-Spectrum β-Lactamase-Producing *Klebsiella pneumoniae* in Southwest China: Molecular Characteristics and Risk Factors of Bloodstream Infections

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Purpose: The objective of this study was to investigate the molecular characteristics and risk factors of bloodstream infection (BSI) caused by extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* (ESBL-Kpn).

Methods: Bacterial species were identified using the matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany), while antimicrobial susceptibilities were assessed using the MicroScan WalkAway 96 Plus system (Siemens, Germany) and the microbroth dilution method. Polymerase chain reaction (PCR) was employed to detect common extended-spectrum beta-lactamase resistance genes (bla_{SHV}, bla_{TEM}, bla_{CTX-M}). Multilocus sequence typing (MLST), pulsed-field gel electrophoresis (PFGE), capsular serotyping, and serum resistance tests were utilized to analyze the molecular characteristics among the isolated strains. Additionally, a logistic regression analysis was conducted to identify the risk factors associated with BSI caused by ESBL-Kpn.

Results: A total of 371 *Klebsiella pneumoniae* (*K. pneumoniae*) strains were isolated from blood samples collected at the Affiliated Hospital of Southwest Medical University between January 2020 and June 2023, among which 45 were confirmed to produce ESBL. Twenty-eight STs were identified, with ST15 being predominant. Most strains exhibited resistance to multiple antibiotics, with $bla_{CTX-M-15}$ as the predominant ESBL resistance genes. Nine strains (n=9, 20%) of bacteria exhibited high serum resistance, and 27 strains matched capsular serotypes predominantly K17. Multivariate analysis indicated that transferred patients, prior use of cephalosporin antibiotics, and prolonged hospital stay were independent risk factors for ESBL-Kpn BSI.

Conclusion: BSI caused by ESBL-Kpn exhibit high resistance rates. The newly identified ST6835 and ST6837 indicate the emergence and spread of novel clones in Southwest China, highlighting the imperative for enhanced surveillance of ESBL-producing strains.

Keywords: *Klebsiella pneumoniae*, bloodstream infection, extended-spectrum beta-lactamase, molecular characteristics, risk factors

Introduction

Klebsiella pneumoniae (*K. pneumoniae*), a Gram-negative, capsulated bacterium, belongs to the *Enterobacteriaceae* family.[1,2] It is a member of the "ESKAPE" pathogens and can cause various infectious diseases in clinical settings, such as pneumonia, urinary tract infections, bloodstream infections (BSI) and sepsis.[3,4] According to the 2024 China Antimicrobial Surveillance Network (CHINET) report, *K. pneumoniae* ranks second in clinical isolation rates, following *Escherichia coli* (*E. coli*). This

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trend is also observed in BSI,[5,6] where *K. pneumoniae* is even showing a tendency to surpass *E. coli*.[7,8] Moreover, unlike other members of the *Enterobacteriaceae* family, *K. pneumoniae* possesses a thick polysaccharide capsule,[9] which enhances its resistance to phagocytosis, promoting its survival and increasing its pathogenicity[9,10] The rising rates of isolation and the emergence of multidrug-resistant (MDR) strains warrant increased attention.[11]

β-Lactam antibiotics (including penicillins, cephalosporins, monobactams, among others) form the therapeutic foundation for *K. pneumoniae* infections. However, with rising incidence and resistance rates of ESBL-producing *Enterobacteriaceae* (ESBL-E), the efficacy of these agents is increasingly compromised.[12,13] Extended-spectrum β-lactamases (ESBL) are bacterial enzymes that hydrolyze broad-spectrum oxyimino-cephalosporins (third- and fourth-generation) and monobactams.[14,15] The majority of ESBL are classified as class A enzymes in the Ambler classification, with prominent types including SHV, TEM, and CTX-M.[14,16] Since their discovery, ESBL have been reported globally.[17,18] In the United States, ESBL-producing bacteria are reported to cause approximately 26,000 antimicrobial-resistant infections and 1,700 associated deaths annually.[19] Moreover, ESBL-producing bacteria have been categorized as critical-priority pathogens in WHO's newly released 2024 Bacterial Priority Pathogens List.[20] Relevant studies indicate that ESBL-E are associated with higher patient mortality, prolonged hospital stays, and increased healthcare costs.[21] Due to their plasmid-mediated transmissibility, the genetic elements can facilitate the spread of resistance between humans and animals, significantly contributing to the emergence of MDR bacterial phenotypes.[22–24] Furthermore, Carbapenems remain the treatment of choice for infections caused by ESBL-producing bacteria,[25] but inappropriate empirical treatment can also lead to higher mortality rates.[26] Consequently, there is an urgent need for effective strategies to prevent and treat these infections.

Although numerous molecular epidemiological studies on ESBL-Kpn BSI exist in China,[27–29] data from Southwest China remain scarce. This study therefore analyzes ESBL-Kpn isolates from BSI patients at the Affiliated Hospital of Southwest Medical University (Luzhou, China), characterizing their molecular profiles and identifying BSI-associated risk factors. Our findings aim to optimize hospital infection control protocols and generate evidence-based strategies for clinical management.

Materials and Methods

Bacterial Collection

From January 2020 to June 2023, a total of 371 *K. pneumoniae* strains were isolated and identified from patients with BSI at the Affiliated Hospital of Southwest Medical University. Identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany).

ESBL production was confirmed according to the Clinical and Laboratory Standards Institute (CLSI) 2023-M100.[30] Bacterial suspensions were standardized to a 0.5 McFarland turbidity using 0.9% saline, after which they were uniformly inoculated onto Mueller-Hinton (MH) agar plates with a sterile cotton swab. Antimicrobial susceptibility disks for cefotaxime, cefotaxime/clavulanic acid, ceftazidime, and cefotaxime/clavulanic acid were carefully placed on the MH agar plates, which were incubated at 37°C overnight. A test result was considered positive for ESBL production if the zone of inhibition around any of the disks increased by ≥ 5 mm following the addition of clavulanic acid.

Risk Factor Analysis

For the risk factor analysis, patients with ESBL-Kpn BSI between 2020 and 2023 were selected as the case group. During the same period, patients with non-ESBL-Kpn BSI were randomly selected as the control group at a 1:2 ratio. Comprehensive clinical data were collected, including baseline demographics, clinical antibiotic usage, invasive procedures, complications, length of hospital stay, clinical outcomes, and other relevant information.

Antimicrobial Susceptibility Testing (AST)

Antimicrobial susceptibility testing of ESBL-Kpn isolates was performed using the MicroScan WalkAway 96 Plus system (Siemens, Germany) and the microbroth dilution method. The antibiotics tested included amikacin, ampicillin, cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefepime, ciprofloxacin, gentamicin, levofloxacin, tobramycin, aztreonam, ampicillin/sulbactam, piperacillin/tazobactam, trimethoprim-sulfamethoxazole, cefoperazone/sulbactam,

cefoxitin and tigecycline. The results were interpreted according to the CLSI guidelines.[30] Tigecycline susceptibility results were interpreted following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. *E. coli* ATCC25922 served as the control strain, obtained from the China National Health Inspection Center.

Detection of Antimicrobial Resistance Genes

Genomic DNA of the strain was extracted using the boiling method.[31] Subsequently, common ESBL resistance genes, including bla_{SHV}, bla_{TEM}, and $bla_{CTX\text{-}M}$, were identified by PCR.[32] The primers used are listed in Table S1. Positive samples were then sent to Shenggong Biotechnology Co., Ltd. (Shanghai, China) for Sanger sequencing. The resulting sequencing data were analyzed using the *K. pneumoniae* database (https://bigsdb.pasteur.fr/klebsiella/).

Multilocus Sequence Typing (MLST)

The genetic correlation among all clinical ESBL-Kpn isolates was analyzed using multi-locus sequence typing (MLST).[33] The positive PCR products were subsequently sent to Shenggong Biotechnology Co., Ltd. (Shanghai, China) for Sanger sequencing. The resulting sequences were then submitted to the *K. pneumoniae* MLST database (https://bigsdb.pasteur.fr/cgi-bin/bigsdb/bigsdb.pl?db=pubmlst_klebsiella_seqdef) to determine the STs for each isolated strain. Sequences that could not be accurately matched were uploaded with the necessary information according to the website's requirements and assigned new STs as needed.

Pulsed-Field Gel Electrophoresis Analysis

The genetic homogeneity among the isolated strains was assessed using XbaI-pulsed-field gel electrophoresis (PFGE), with modifications to previously described protocols.[34] Briefly, bacterial DNA was digested with the XbaI restriction endonuclease and subjected to electrophoresis using the CHEF Mapper system (Bio-Rad, USA) for 18 hours, with fragment sizes ranging from 30 to 700 kb. After electrophoresis, the gel was stained with GoldView, and the data were analyzed using BioNumerics software. We acknowledge Shanghai Yibei Technology Co., Ltd. (Shanghai, China) for providing the software trial and technical support.

Serum Resistance Testing

The serum resistance assay was performed following a previously described method with modifications.[35] Briefly, 75 μL of healthy human mixed serum was combined with 25 μL of bacterial suspension and incubated on a shaker at 37°C (200 r) for 3 hours. Samples were collected at 0 h, 1 h, 2 h, and 3 h, serially diluted, and plated onto LB agar plates. After overnight incubation at 37°C, colony counts were conducted. Serum resistance of the strains was categorized into six levels based on colony counts.[36] *K. pneumoniae* ATCC700603 and *K. pneumoniae* ATCC2044 served as the control strain.

Capsule Serotyping by PCR and Sequencing

Capsule serotyping was performed as previously described, with minor modifications.[37] PCR amplification was conducted using wzi primers, and the positive products were sequenced by Shenggong Biotechnology Co., Ltd. (Shanghai, China). The sequences were then compared on the pasteur website (https://bigsdb.pasteur.fr/) to determine the capsule serotype. The relevant primers are listed in Table S2.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 (IBM, USA) Chi-square tests or Fisher's exact tests were used to analyze categorical variables. For continuous variables, independent sample t-tests or non-parametric rank sum tests were employed. Variables with a univariate analysis $P < 0.10$ and clinical relevance were included in a multivariable binary logistic regression model to identify independent risk factors. Results included calculation of P values, 95% confidence intervals (CIs), and odds ratios (ORs). A significance level of $P < 0.05$ (two-tailed) was considered statistically significant.

Results

Basic Characteristics of the ESBL-Kpn Strains

From January 2020 to June 2023, a total of 45 strains of ESBL-Kpn associated with BSI were collected at the Affiliated Hospital of Southwest Medical University (Luzhou, China). As shown in Figure 1A, the strains were isolated from various departments: the hematology department (n = 7, 15.6%), intensive care unit (n = 5, 11.1%), urology ward (n = 4, 8.9%), neonatology ward (n = 4, 8.9%), vascular surgery (n = 3, 6.7%), and other departments.

The study population consisted of 26 males (57.8%) and 19 females (42.2%). The ages of the patients ranged from 11 days to 76 years, with a mean age of 45 ± 3.73 years. Specifically, females had a mean age of 41.6 ± 5.5 years, while males averaged 47.5 ± 5.1 years. Although males were generally older than females, the difference was not statistically significant ($P > 0.05$), as shown in Figure 1B.

Antimicrobial Susceptibility Profiles

Most isolated strains exhibited resistance to most antibiotics. As shown in Table 1, resistance rates were 100% for ampicillin, ceftriaxone, cefotaxime, cefazolin, and cefuroxime, and over 90% for ampicillin/sulbactam. Resistance rates exceeded 80% for trimethoprim-sulfamethoxazole, aztreonam, and cefepime. High resistance was also observed for

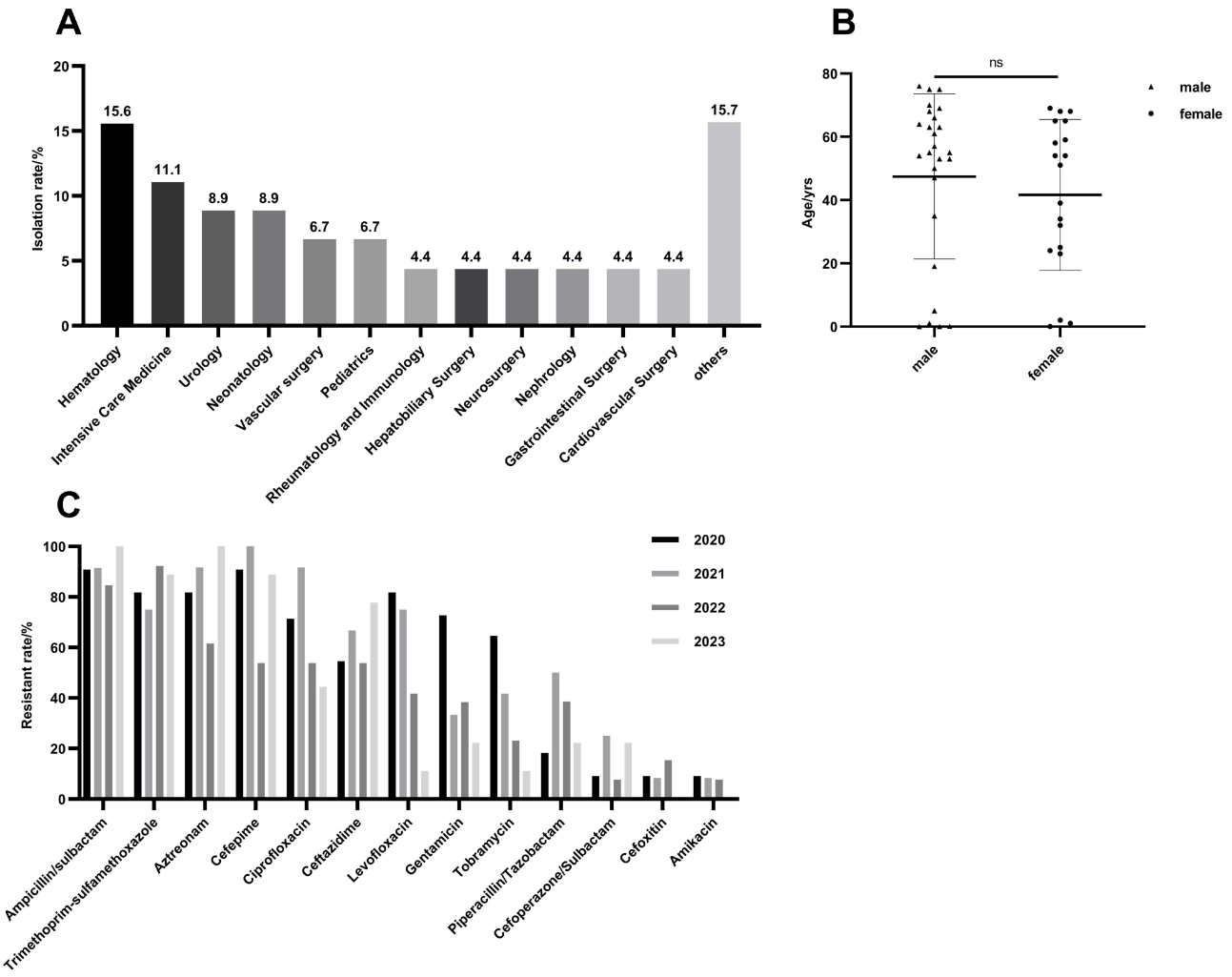

Figure 1 Basic characteristics of 45 ESBL-Kpn. (**A**) Department distribution of 45 isolates; (**B**) comparison of age distribution in infected patients of different genders; (**C**) trends in the distribution of antibiotic resistance rates of 45 strains to commonly used antibiotics.
Abbreviation: ns, no statistical difference.

Table 1 Antimicrobial Susceptibility Profiles of 45 Clinical ESBL-Producing *Klebsiella Pneumoniae* Strains

Antimicrobial Agent	No.	%R	No.	%I	No.	%S
Ampicillin	45	100	0	0	0	0
Ceftriaxone	45	100	0	0	0	0
Cefotaxime	45	100	0	0	0	0
Cefazolin	45	100	0	0	0	0
Cefuroxime	45	100	0	0	0	0
Ampicillin/Sulbactam	41	91.1	3	6.7	1	2.2
Trimethoprim-sulfamethoxazole	38	84.4	0	0	7	15.6
Aztreonam	37	82.2	3	6.7	5	11.1
Cefepime	37	82.2	6	13.4	2	4.4
Ciprofloxacin	32	71.1	1	2.2	12	26.7
Ceftazidime	28	62.2	4	8.9	13	28.9
Levofloxacin	24	53.3	0	0	21	46.7
Gentamicin	19	42.3	2	4.4	24	53.3
Tobramycin	16	35.5	4	8.9	25	55.6
Piperacillin/tazobactam	15	33.4	2	4.4	28	62.2
Cefoperazone/sulbactam	7	15.6	10	22.2	28	62.2
Cefoxitin	4	8.9	4	8.9	37	82.2
Amikacin	3	6.7	0	0	42	93.3
Tigecycline	2	4.4	2	4.4	41	91.2

Abbreviations: S, susceptible; I, intermediate; R, resistant.

ciprofloxacin, ceftazidime, levofloxacin, gentamicin, tobramycin, cefoperazone/sulbactam and piperacillin/tazobactam. However, resistance rates were below 10% for cefoxitin, amikacin, and tigecycline.

Antibiotic resistance rate analysis reveals fluctuating trends as follows: ampicillin/sulbactam (84.6–100%), trimethoprim-sulfamethoxazole (75.0–92.3%), aztreonam (61.5–100%), cefepime (53.8–100%), ceftazidime (53.8–77.8%), and other antibiotics show generally high resistance rates with a tendency to fluctuate and rise. Ciprofloxacin (44.4–91.7%), levofloxacin (11.1–81.8%), gentamicin (22.2–72.7%), tobramycin (11.1–64.6%), piperacillin/tazobactam (18.2%-50.5%) exhibit a slight overall decrease in resistance rates. Furthermore, resistance rates are relatively low for cefoperazone/sulbactam (9.1–25.0%), cefoxitin (9.1–15.4%), and amikacin (0–9.1%). Specific trends in resistance rates are depicted in Figure 1C.

Phenotype and Genotype Analysis

All 45 strains were confirmed to produce ESBL through verification experiments following CLSI guidelines. Three types of ESBL resistance genes, bla_{TEM}, bla_{SHV}, and $bla_{\text{CTX-M}}$, were detected. As shown in Figure 2, PCR experiments revealed that 23 strains carried bla_{TEM}, 37 strains carried bla_{SHV}, and 36 strains carried $bla_{\text{CTX-M}}$. Furthermore, 15 strains harbored all three resistance genes simultaneously. The predominant resistance genes identified were $bla_{\text{CTX-M-15}}$ (n = 14).

Homology Analysis Results of Clinical Isolates

A total of 26 known STs were identified, with ST15 (n = 5, 11.1%), ST37 (n = 4, 8.9%), ST101 (n = 4, 8.9%), ST23 (n = 3, 6.7%), and ST485 (n = 3, 6.7%) being the most prevalent. Additionally, ST17, ST45, and ST967 were each found in two isolates, while ST14, ST86, ST147, ST193, ST225, ST307, ST340, ST353, ST437, ST502, ST534, ST678, ST1540, ST1798, ST1825, ST1834, ST2004, and ST4065 were each found in one isolate. Two new STs, ST6835 and ST6837, were also discovered.

Further analysis using PFGE experiments revealed that for the majority of strains with the same STs, there was a high similarity in their fingerprint patterns, indicating a high degree of homology and close isolation dates. As shown in Figure 2.

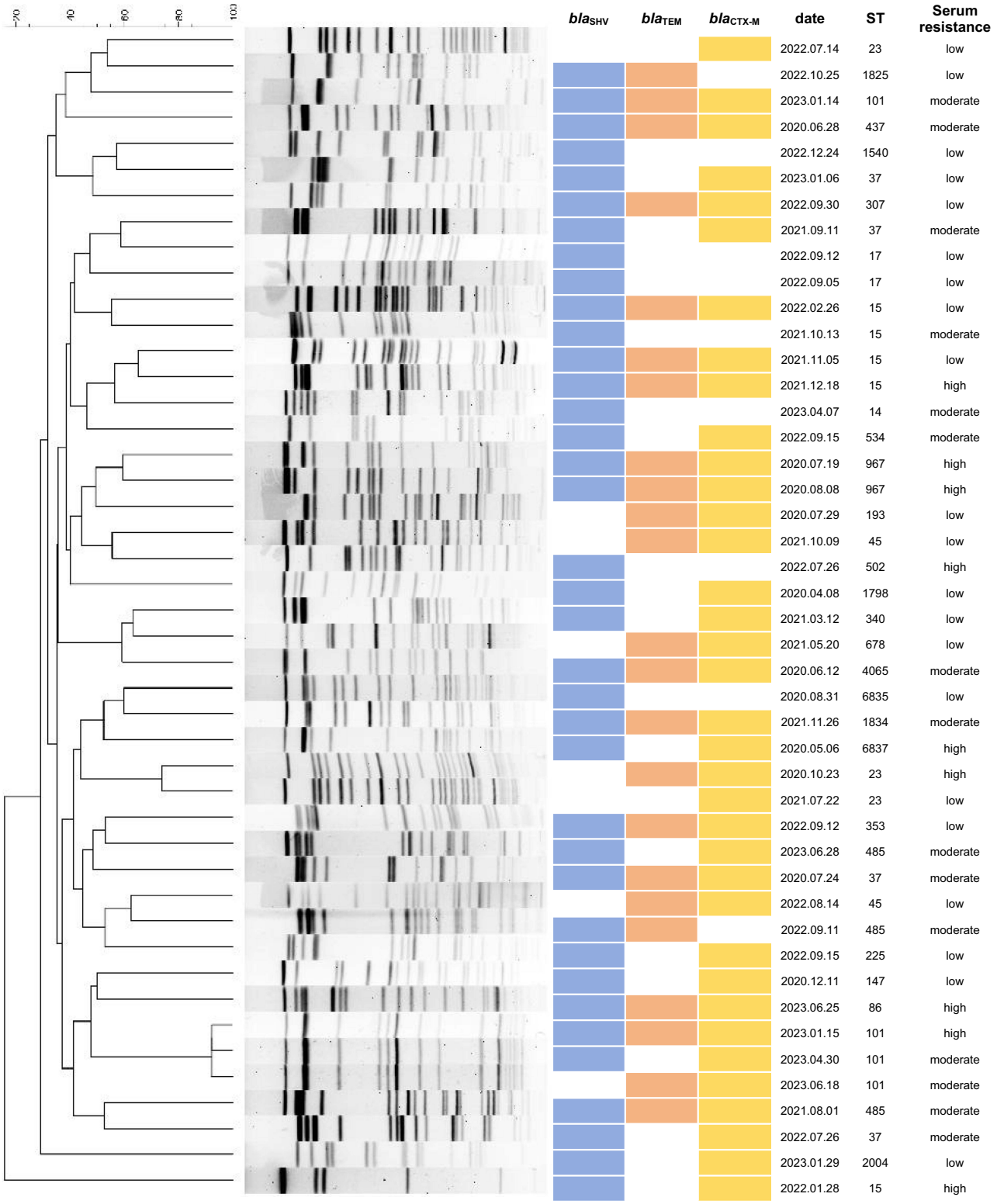

Figure 2 Molecular characteristics and homology analysis of ESBL-Kpn.

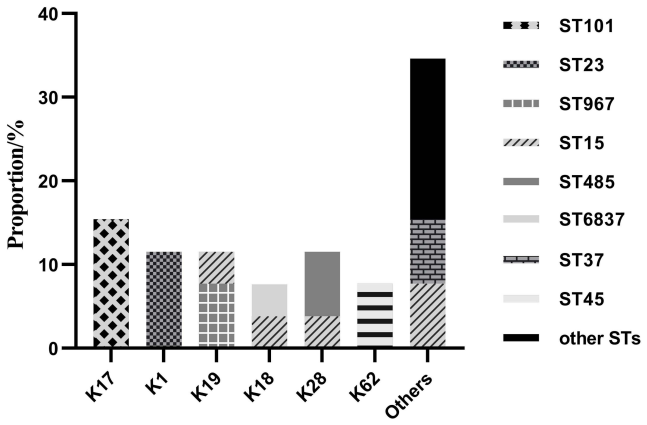

Figure 3 Distribution of capsular serotypes of ESBL-Kpn and their correspondence with STs.

Serum Resistance Test

Nine strains (n = 9, 20%) exhibited high serum resistance, demonstrating unrestricted growth when exposed to healthy human serum, and were categorized as grades 5 and 6. Fifteen strains (n = 15, 33.33%) showed moderate serum resistance, classified as grades 3 and 4. Twenty-one strains (n = 21, 46.67%) were serum-sensitive, being rapidly killed when exposed to healthy human serum, classified as grades 1 and 2, as illustrated in Figure 2.

Capsular Serotyping Profiles

Among the 45 strains, a total of 15 capsular serotypes were identified, with varying distributions. The most prevalent capsular serotypes were K17 (n = 4), K1 (n = 3), K19 (n = 3), K18 (n = 2), K28 (n = 3), and K62 (n = 2). Additionally, 18 strains did not match any known capsular serotype. Among the 27 strains with identified capsular serotypes, an analysis of the relationship between capsular serotypes and STs revealed the following associations: all K17 strains (n = 4) belonged to ST101, all K1 strains (n = 3) belonged to ST23, K19 strains (n = 3) were predominantly associated with ST967 and ST15, K18 strains (n = 2) corresponded to ST6837 and ST15, K28 strains (n = 3) corresponded to ST485 and ST15, and K62 strains (n = 2) all corresponded to ST45. The distribution of capsular serotypes among the 26 ESBL-Kpn strains with identified capsular serotypes and their corresponding STs is shown in Figure 3.

Risk Factors and Multivariate Analysis of ESBL-Kpn BSI

Single-factor statistical analysis identified several key risk factors for BSI caused by ESBL-Kpn, including transferred patient ($P = 0.001$), gastrointestinal diseases ($P = 0.022$), history of surgery within the past six months ($P = 0.004$), use of cephalosporin antibiotics ($P = 0.004$), and prolonged total hospital stay ($P < 0.001$). Multivariable analysis further revealed that transferred patient (OR = 2.520, 95% CI 1.071–5.931, $P = 0.034$), use of cephalosporin antibiotics (OR = 2.761, 95% CI 1.112–6.856, $P = 0.029$), and prolonged hospital stay (OR = 1.029, 95% CI 1.006–1.052, $P = 0.013$) were independent risk factors for BSI caused by ESBL-Kpn. The relevant results are shown in Table 2.

Discussion

K. pneumoniae poses an increasingly serious threat to clinical antimicrobial therapy. Bacteremia caused by ESBL-Kpn is associated with higher mortality.[38] This study characterizes the molecular epidemiology and identifies risk factors for 45 ESBL-Kpn isolates from BSI, collected over a three-year period at a teaching hospital in Southwest China. These isolates accounted for 16.7% of all *K. pneumoniae* BSI, a prevalence lower than reported in other Chinese studies.[39] Notably, global prevalence rates vary markedly across regions. A global study by Tsepo Ramatla et al reported an ESBL-Kpn prevalence of 32.7%.[40] This significant disparity highlights the urgent need to strengthen infection control measures for preventing ESBL-Kpn BSI.

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Table 2 Clinical Characteristics of ESBL and Non-ESBL Strains

Variable	ESBL Group(n=45)	Non ESBL Group(n=90)	*P*-value
Demographic, n (%) or IQR			
Age (≥60)	16(35.5%)	31(34.4%)	0.898
Sex (male)	26(57.8%)	56(62.2%)	0.618
Length of hospital stay	27 (15–44)	14.5 (6.75–52.25)	**<0.001**
Surgical ward	16(35.6%)	27(30%)	0.514
Transferred patient	23(51.1%)	21(23.3%)	**0.001**
Adminssion to ICU	14(31.1%)	23(25.6%)	0.495
Co-morbidity, n (%)			
Malignant disease	10(22.2%)	18(20%)	0.764
Hypertension	13(28.9%)	37(41.1%)	0.166
Cardiovascular diseases	22(48.9%)	33(36.7%)	0.173
Hepatobiliary disease	25(55.6%)	63(70%)	0.097
Respiratory disease	31(68.9%)	67(74.4%)	0.495
Renal disease	26(57.8%)	46(51.1%)	0.464
Urinary tract infection	10(22.2%)	11(12.2%)	0.131
Respiratory infection	25(55.6%)	51(56.7%)	0.902
Gastrointestinal disease	16(35.6%)	16(17.7%)	**0.022**
Nervous system disease	13(28.9%)	39(43.3%)	0.104
Endocrine disease	18(40%)	46(51.1%)	0.223
Hypoproteinemia	30(66.7%)	54(60%)	0.451
Leukopenia	11(24.4%)	17(18.9%)	0.453
Trauma and invasive procedures			
Bronchoscope	3(6.7%)	3(3.3%)	0.400
Surgery	24(53.3%)	25(27.8%)	**0.004**
Mechanical ventilation	11(24.4%)	19(21.1%)	0.661
Drainage tube	6(13.3%)	14(15.6%)	0.732
Urinary duct	19(42.2%)	25(27.8%)	0.091
Tracheal intubation	10(22.2%)	16(17.8%)	0.537
Nasal catheter	5(11.1%)	5(5.6%)	0.300
Gastric tube	7(15.6%)	18(20%)	0.531
Central vein catheterization	11(24.4%)	12(13.3%)	0.106

(*Continued*)

Table 2 (Continued).

Variable	ESBL Group(n=45)	Non ESBL Group(n=90)	*P*-value
Antibiotic treatment, n (%)			
Penicillins	7(15.6%)	13(14.4%)	0.864
Cephalosporins	35(77.8%)	47(52.2%)	**0.004**
Aminoglycosides	3(6.7%)	1(1.1%)	0.108
Quinolones	11(24.4%)	22(24.4%)	1.000
Carbapenems	33(73.3%)	55(61.1%)	0.160
Clinical outcomes, n (%)			
Patient outcome: mortality	3(6.7%)	6(6.7%)	1.000

Note: The bolded values indicate $P < 0.05$.
Abbreviations: ESBL, extended-spectrum beta-lactamases; IQR, interquartile range; ICU, intensive care unit.

Bacterial antibiotic resistance is mechanistically mediated through four primary pathways: hydrolase production, antibiotic target modification, reduced membrane permeability, and efflux pump overexpression.[41] Among these, hydrolase production represents the most prevalent mechanism. Current studies predominantly identify CTX-M as the most prevalent resistance-conferring hydrolase in ESBL-Kpn. First identified in 1990, this β-lactamase demonstrates enhanced cefotaxime-hydrolyzing activity.[42,43] CTX-M are primarily categorized into several subfamilies: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25 groups.[44,45] Among the isolates analyzed in this study, three CTX-M-type β-lactamases genes were identified: $bla_{\text{CTX-M-15}}$ (n = 14), $bla_{\text{CTX-M-3}}$ (n = 12), and $bla_{\text{CTX-M-14}}$ (n = 10). Notably, $bla_{\text{CTX-M-15}}$ emerged as the predominant variant among *K. pneumoniae* isolates from BSI patients at our hospital over the three-year study period. This distribution pattern aligns with global surveillance reports on ESBL genotype epidemiology.[31,46,47] Recent reports indicate that *K. pneumoniae* harboring $bla_{\text{CTX-M-15}}$ is frequently associated with carbapenem-resistant phenotypes (CRKP) and exhibits hypervirulent traits, raising significant concerns for clinical therapy.[48–50] Research by Chien-Ming Chao et al revealed $bla_{\text{CTX-M-3}}$ and $bla_{\text{CTX-M-14}}$ as the predominant ESBL genotypes in Taiwan, China, with evidence suggesting their clonal dissemination both within and between healthcare institutions.[51] Furthermore, $bla_{\text{CTX-M-3}}$ contributes significantly to distinctive resistance phenotypes in *K. pneumoniae*, where the IncFII plasmid harboring $bla_{\text{CTX-M-3}}$ serves as the primary transmission vector.[52] Furthermore, recent studies identify $bla_{\text{CTX-M-14}}$ and $bla_{\text{CTX-M-55}}$ as the predominant ESBL in Asia, whereas $bla_{\text{CTX-M-1}}$ dominates in Europe,[53] demonstrating marked geographical variation in $bla_{\text{CTX-M}}$ distribution. These findings highlight the critical necessity for enhanced surveillance of plasmid-mediated clonal transmission in hospital settings.

Analysis of the 45 ESBL-Kpn isolates identified 26 distinct STs; ST15 was the most prevalent. ST15 is recognized as a high-risk *K. pneumoniae* clone,[54,55] with studies confirming its frequent production of ESBL or carbapenemases, often associated with nosocomial outbreaks.[56,57] This study found that 80% of ST15 ESBL-Kpn isolates produced $bla_{\text{CTX-M}}$. Similarly, a study by Hang Zhao et al reported significant carriage of $bla_{\text{CTX-M-15}}$ in ST15 CRKP strains.[58] Min Wang et al also observed this prevalence of $bla_{\text{CTX-M-15}}$ in ST15 isolates.[59] In contrast, Carla Rodrigues et al found that ESBL-encoding genes were primarily observed in clonal group (CG) CG14-I, while CTX-M-15 was particularly prevalent in CG15 and CG15-IIB.[60] In addition, the high-risk clone ST101 is associated with enhanced virulence and antimicrobial resistance in *K. pneumoniae*. Infections caused by ST101 strains show an 11% higher mortality rate compared to non-ST101 infections,[61] with most isolates belonging to the K17 capsular serotype.[62] Our findings are consistent with these reports, further confirming the clinical significance of this epidemic lineage. However, no statistically significant increase in mortality was observed among ST101-infected patients in our study. This discrepancy may reflect the limited sample size in our cohort. Moreover, ST23 *K. pneumoniae* belongs to the CG23 clonal group, which is the most virulent clonal group of *K. pneumoniae*.[63] ST23 *K. pneumoniae* has been widely reported in Asia and is significantly associated with the K1 capsule serotype, which is consistent with the findings of this study.[64] This study identified high-level and moderate serum resistance in 24

K. pneumoniae isolates. Serum resistance in *K. pneumoniae* is mediated by multiple factors, including complement, peptidoglycan-associated lipoprotein and murein lipoprotein.[65–67] The prevalence of serum-resistant isolates in our research (53.3%) was lower than rates reported elsewhere.[68] This discrepancy may reflect distinct virulence profiles of circulating strains, suggesting that bloodstream isolates in Southwest China exhibit comparatively reduced serum resistance. Notably, ST6385 (18-22-26-59-154-37-49) and ST6387 (25-10-1-1-20-1-929) are novel STs identified in this study. Enhanced vigilance and control measures are warranted to prevent the spread of these emerging clones in Southwest China.

BSI caused by MDR *K. pneumoniae* in hospital settings are associated with multiple factors, including patient health status, healthcare environment, microbial infections, and treatment-related variables.[69] Currently, studies specifically addressing the risk factors for BSI caused by ESBL-producing non-CRKP remain limited. This study identified patient transfer, prior use of cephalosporin antibiotics, and prolonged hospitalization as independent risk factors for BSI caused by ESBL-Kpn. Recently, a study found that recent antimicrobial use was an independent risk factor for BSI caused by ESBL-E, which is consistent with the findings of this study.[70] Although carbapenems are widely considered effective for the treatment of ESBL-producing pathogens, their use in specific clinical contexts remains controversial. The indiscriminate application of carbapenems for treating ESBL-Kpn infections, without considering individual circumstances, may exacerbate the ongoing antibiotic resistance crisis.[71] Furthermore, ESBL-associated resistance genes are often located on plasmids, which are transferable, facilitating horizontal transfer during patient transitions between healthcare facilities. These findings highlight the importance of rational antibiotic use and the prevention of MDR infections.[72] Prognostically, most ESBL-Kpn BSI patients achieved clinical recovery with discharge, while 3 (6.7%) died. This mortality rate is lower than the global average.[40] The deceased patients were predominantly elderly individuals and children with severe underlying comorbidities, who are more susceptible to critical illnesses and have a poorer prognosis. These findings provide valuable insights for optimizing clinical patient management, guiding rational antimicrobial use, and preventing the emergence of MDR organisms.

This study has several limitations. First, the sample size of included strains was relatively limited; future studies should expand strain collection and perform phylogenetic analyses of STs using larger cohorts. Second, as a single-center investigation, this study lacks generalizability. Multicenter studies are therefore warranted to enhance molecular epidemiological surveillance of ESBL-Kpn in Southwest China. Such efforts are crucial for comprehensively characterizing resistant strain prevalence and informing evidence-based infection control strategies.

Conclusion

This study demonstrated a high prevalence of BSI caused by ESBL-Kpn, with ST15 as the predominant STs. Notably, the novel sequence types ST6835 and ST6837 identified in this work represent, to our knowledge, the first reported instances of these STs. Furthermore, the presence of antibiotic resistance genes was a key contributing factor to the observed high-level resistance phenotypes. Hospital transfer, prior cephalosporin use, and prolonged hospitalization were identified as independent risk factors for ESBL-Kpn BSI. These findings highlight the critical need for appropriate antibiotic use and effective infection control measures to prevent ESBL-Kpn BSI and reduce their transmission within healthcare settings.

Data Sharing Statement

The data used or analyzed in this study can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The research was approved by the Institutional Ethics Committee at the Affiliated Hospital of Southwest Medical University (KY2022267). This ethical review process strictly followed the fundamental principles established in the Declaration of Helsinki. In addition, all patients participated by providing written informed consent; for minors, written informed consent was obtained from their legal guardians.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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