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CASE REPORT

Case Study and Genomic Analysis of a Hypervirulent ST25 *Klebsiella pneumoniae* Strain in a Liver Cirrhosis Patient

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Abstract: Bloodstream infections (BSIs) caused by *Klebsiella pneumoniae* (*K. pneumoniae*) are associated with high morbidity and mortality rates. This study presents a sequence type 25 (ST25) strain of hypermucoid *K. pneumoniae* A1 isolated from the blood of a patient with liver cirrhosis (LC) who succumbed to severe infections. We performed whole-genome sequencing of *K. pneumoniae* A1, which revealed virulence factors and antibiotic resistance genes. The strain harbors virulence genes encoding aerobactin, salmochelin, yersiniabactin, enterobactin, and rmpA. Additionally, the strain possessed five drug resistance genes: blaSHV-110, blaSHV-81, fosA6, OqxA, and OqxB. We further constructed a phylogenetic tree using 98 ST25 *K. pneumoniae* strains downloaded from NCBI together with *K. pneumoniae* A1. Phylogenetic analysis revealed that our isolated strain was closely related to a highly virulent strain isolated from a neonate in our region, differing by only 123 single nucleotide polymorphisms (SNPs). *K. pneumoniae* A1 is highly suspected to be Hypervirulent *Klebsiella pneumoniae* (hvKp). This study provided the first in-depth genomic analysis of ST25 *K. pneumoniae* in a patient with LC in China, highlighting the urgent need for early identification and diagnosis to combat this emerging threat.

Keywords: sequence type 25, *Klebsiella pneumoniae*, hypervirulent, bloodstream infections, liver cirrhosis

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a common gastrointestinal commensal in humans, but is also an opportunistic pathogen capable of causing moderate to severe infections, including pneumonia, intra-abdominal infections, urinary tract infections, and bloodstream infections (BSIs).[1,2] Based on its virulence, *K. pneumoniae* can be categorized into classic (cKp) and hypervirulent (hvKp) strains. HvKp exhibits increased virulence, rapid dissemination, and metastasis potential compared to cKp.[3] BSIs caused by hvKp, particularly sequence type 25 (ST25), have emerged as a significant global threat,[4] with cases reported in Spain,[5] England,[6] Australia,[7] Argentina,[8] and Italy.[9]

It is well-documented that liver cirrhosis (LC), a prevalent end-stage hepatic condition, increases the risk of bacterial infections in patients, particularly those caused by *K. pneumoniae*.[10,11] Several reports have documented BSIs caused by *K. pneumoniae* in LC patients, exhibiting clinical features reminiscent of hvKp, including rapid dissemination and metastasis spread. For instance, Khatri A et al[12] reported a case of osteomyelitis in a patient infected with a mucoid strain of *K. pneumoniae*, whose condition subsequently rapidly deteriorated, resulting in sepsis, cellulitis, liver cysts, renal failure, and ascites. Shah A et al[13] described a metastatic *K. pneumoniae* infection with pulmonary septic emboli, ascites, renal abscess, pyomyositis, and septic arthritis. Shih HI et al[14] presented a cirrhotic patient who rapidly developed fatal *K. pneumoniae* meningitis and an emphysematous brain abscess, despite receiving appropriate antimicrobial therapy. Park CH et al[15] reported a cirrhotic patient with spontaneous bacterial arthritis and spontaneous bacterial peritonitis attributed to *K. pneumoniae*. However, despite these clinical similarities to hvKp, definitive genomic characterization to conclusively confirm the presence of hvKp in these cases remains lacking.

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This study presents a comprehensive whole-genome analysis of an ST25 putative hvKp strain isolated from a LC patient in China. The objectives are to characterize its virulence factors and antibiotic resistance mechanisms and to elucidate the molecular epidemiology of ST25 *K. pneumoniae* through phylogenetic analysis.

Case Presentation

A 50-year-old male LC patient presented to our hospital with symptoms of progressively worsening abdominal distension and oliguria over a four-day period. Upon admission, the patient manifested chills and a fever of 38.4°C. His medical history was intricate, encompassing esophageal varices, recurrent hepatic encephalopathy, spontaneous bacterial peritonitis, type 2 diabetes mellitus, and gastric ulcers. Notably, the patient had experienced multiple hospitalizations for hepatic encephalopathy and *K. pneumoniae*-induced spontaneous bacterial peritonitis, each time showing improvement after treatment. Despite rigorous follow-up and strict adherence to the prescribed medication regimen, the patient's condition unexpectedly deteriorated upon hospital admission. Physical examination revealed mild jaundice of the skin and sclerae, spider nevi on the neck and trunk, clear heart and lung sounds, distended abdomen without visible veins, significant abdominal tenderness with rebound pain, nonpalpable liver and spleen, negative liver percussion pain, normal liver dullness, positive shifting dullness, and mild edema in both lower extremities.

Table 1 shows the laboratory data upon admission. Two sets of blood cultures were obtained prior to antibiotic administration. Given the patient's symptoms and laboratory results, abdominal paracentesis was performed, and peritoneal fluid was sent for laboratory testing. The peritoneal fluid was yellow and turbid in appearance, with a positive Rivalta test (+++), nucleated cell count of 19,330/μL, lactate dehydrogenase (LDH) of 615 U/L, and Gram staining showing gram-negative bacilli. Based on these findings, the patient was promptly treated with piperacillin-tazobactam 4.5 g IV q8h. Additionally, ornithine aspartate was administered to reduce blood ammonia alongside supportive treatments, including liver protection, jaundice reduction, diuretics, antiviral therapy, albumin supplementation, sodium correction, and potassium reduction.

Owing to the rapid progression of the disease, the antibiotic regimen was changed to meropenem 1.00 g IV q8h. The patient was diagnosed with acute liver failure, acute kidney failure, metabolic acidosis, hyponatremia, and severe septicemia. The patient was transferred to the ICU for advanced life support and continued antibiotics and supportive care. Despite aggressive treatment, the patient's condition continued to deteriorate rapidly. On February 16, the peritoneal fluid culture results showed *Klebsiella pneumoniae*, with sensitivity matching to those of the blood culture obtained on February 17 (Table 2). Unfortunately, the patient died despite aggressive treatment. The disease process is illustrated in Figure 1.

The isolate, *K. pneumoniae* A1, was identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) (bioMérieux, France). Antimicrobial susceptibility testing of the isolates was

Table 1 Laboratory Data Upon Admission

Test	Result	Normal Range of Value
White blood cell count (WBC)	12.4	3.9 ~ 9.5×10^9/L
Neutrophil percentage	92.0	40.0 ~75.0%
Platelets count	46	125 ~ 350×10^9/L
Total bilirubin	88.0	0.0 ~ 21.0μmol/L
Direct bilirubin	48.2	0.0 ~ 4.0μmol/L
Albumin	20.7	40.0 ~ 55.0 g/L
Potassium	5.74	3.50 ~ 5.30 mmol/L
Sodium	115.4	137.0 ~ 147.0 mmol/L
Chloride	86.9	99.0 ~ 110.0 mmol/L
Creatinine	118	53 ~ 97μmol/L
C-reactive protein (CRP)	91.1	0.0 ~ 5.0 mg/L
Ammonia	28	18 ~ 72μmol/L
Procalcitonin	5.80	< 0.50 ng/mL
Lactic acid	8.6	0.5 ~ 1.6 mmol/L

Table 2 MIC Values (μg/Ml) of K. Pneumoniae A1

Antibiotics	MIC (μg/mL)	Sensitivity
Amoxicillin-clavulanate	=4.0	S
Piperacillin-tazobactam	<=4.0	S
Cefoperazone-sulbactam	<=8.0	S
Cefotaxime	<=0.12	S
Cefuroxime	=2.0	S
Ceftriaxone	<=0.25	S
Cefepime	<=0.12	S
Cefoxitin	<=4.0	S
Imipenem	<=1.0	S
Ertapenem	<=0.12	S
Levofloxacin	<=0.12	S
Trimethoprim-sulfamethoxazole	<=20.0	S
Tigecycline	<=0.5	S
Amikacin	<=2.0	S
β-lactamase	Negative	-

performed using the VITEK2 Compact system (bioMérieux, France) and the results were interpreted according to the recommendations of the CLSI M100-S33 guidelines (version 2023). Whole-genome sequencing of *K. pneumoniae* A1 was performed using the Illumina HiSeq 4000 platform (Illumina Inc., USA). The genome assembly of *K. pneumoniae* A1 was conducted using Unicycler v0.5.0, and subsequent genome annotation was performed using Prokka v1.14.6. Antimicrobial resistance genes (ARGs) were predicted using resfinder v4.5.0. Virulence factors were annotated by blasting against the VFDB database. Additionally, the sequence type (ST) and capsular types were detected using the online database BIGSdb-Pasteur. We downloaded the whole-genome sequences of 98 ST25 *K. pneumoniae* strains from the NCBI database and subsequently uploaded their sequence files along with *K. pneumoniae* A1 to the Prokka server for annotation. The annotated files were uploaded to Roary v3.13.0 for pan-genome analysis. Fast tree v2.1.11 was used to construct a maximum likelihood tree based on the alignment of core genes, and the online tool iTOL was employed to

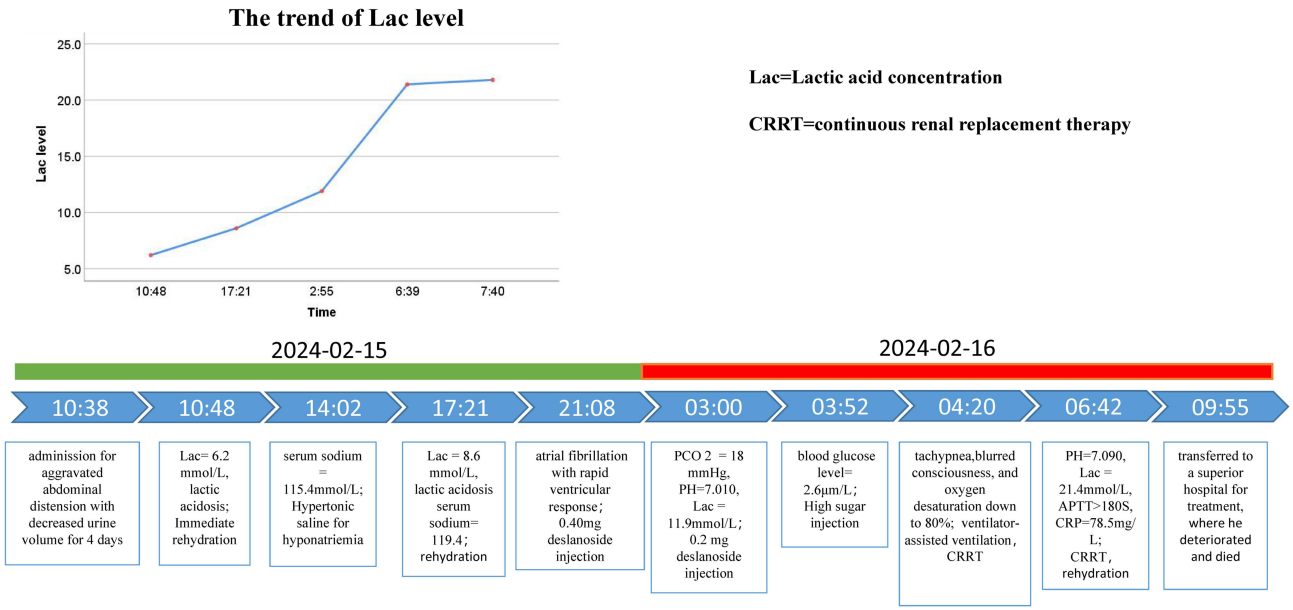

Figure 1 Disease progression of bloodstream infections in the liver cirrhotic patient.

visualize this tree. The core genome single-nucleotide polymorphisms (SNPs) differences between each pair of strains were analyzed using Snp-dists v0.8.2 (https://github.com/tseemann/snp-dists).

The genome of *K. pneumoniae* A1 consists of 5,309,824 base pairs and exhibits a G+C content of 57.36%. The strain was predicted to contain 130 contigs, 4906 coding sequences (CDSs), and 78 RNA genes (72 tRNA, 2 5S rRNA, 2 16S rRNA, and 2 23S rRNA genes).

K. pneumoniae A1 displayed a complex resistance profile encompassing two blaSHV subvariants (blaSHV-110 and blaSHV-81), efflux pump genes (oqxA and oqxB), and fosA6. However, *K. pneumoniae* A1 is sensitive to various antibiotics including levofloxacin, ceftriaxone, amoxicillin-clavulanate, ertapenem, imipenem, cefuroxime, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, cefoxitin, cefepime, amikacin, tigecycline, and trimethoprim-sulfamethoxazole. Furthermore, it was negative for extended-spectrum beta-lactamases (ESBL) (Table 2). This may be attributed to the fact that although these genes encode resistance enzymes that exhibit some level of resistance to fluoroquinolones and β-lactam antibiotics, such as penicillins and cephalosporins, they are not sufficient to significantly affect the sensitivity of the strain to these common antibiotics. The presence of fosA6 in all 99 ST25 *K. pneumoniae* isolates indicated resistance to fosfomycin, warranting caution in its use against ST25 *Klebsiella pneumoniae*. Furthermore, caution should be exercised regarding ESBL, as our study revealed significant findings: among the 99 ST25 *K. pneumoniae* strains analyzed, the detection rate of the ESBL gene CTX-M-15 was particularly high, with a rate of 44.44% specifically in ST25 strains.

String tests for *K. pneumoniae* A1 were positive, with strings > 5 mm in length (Figure 2). Using the VFDB database, we identified a substantial number of virulence factors harbored by *K. pneumoniae* A1. These included genes encoding aerobactin (iutA), salmochelin (iroBCDEN), yersiniabactin (fyuA, irp1, irp2, and ybtAEPQSTUX), enterobactin (entABCDEFS, fepABCDG, and fes), capsule (rmpA), type 1 fimbriae (fimABCDEFGHIK), and type 3 fimbriae (mrkABCDFHIJ), among others (Table 3).

Phylogenetic tree analysis of 99 ST25 *K. pneumoniae* strains revealed an extensive distribution worldwide (Figure 3). The isolates were primarily distributed in Norway (30.30%). In comparison, China reported only two isolates, GCA_021441845.1, and *K. pneumoniae* A1. Further analysis revealed that the two ST25 *K. pneumoniae* strains, specifically GCF_024495515.1 and GCF_024495065.1, harboring OXA-181, and one strain, GCA_021441845.1,

Figure 2 String tests of colonies from the culture media were positive, with strings exceeding 5 mm in length.

Table 3 Major Virulence Factors for K. Pneumoniae A1

Category	Virulence Factors	Virulence Genes
Biological adhesion	Type 1 fimbrial Type 3 fimbrial	fimA, fimB, fimC, fimD, fimE, fimF, fimG, fimH, fimI, fimK mrkA, mrkB, mrkC, mrkD, mrkF mrkH, mrkI, mrkJ
Secretory system	T6SS T2SS	tssA, tssB, tssC, tssD, tssE, tssF, tssG, tssH, tssI, tssJ, tssK, tssL, icmF, tle1, tli1, vgrG, clpV, ompA, VipA, VipB, Hcp gspB, gspD, gspE, gspF, gspG gspH, gspI, gspJ, gspK, gspL
Siderophores	Yersiniabactin	ybtP, ybtX, ybtQ, ybtU, ybtE, ybtA, ybtS, ybtT, irp1, irp2, fyuA
	Aerobactin	iutA
	Enterobactin	entA, entB, entC, entD, entE entF, entS, fepA, fepB, fepC fepD, fepG, fes
	Salmochelin	iroB, iroC, iroD, iroE, iroN

carrying NDM-1, were the closest relatives to the *K. pneumoniae* A1 strain. The virulence and resistance genes present in *K. pneumoniae* A1 and the other 98 strains are shown in Supplementary Materials 1 and 2, respectively.

Discussion

HvKp is an emerging pathotype with significantly higher virulence compared to cKp. While infections with hvKp have been more prevalent in the Asia-Pacific region, they are increasingly being observed worldwide.[16] However, despite its increasing recognition, the hvKp lacks a universal definition with varying terminology. In this study, we adhered to the

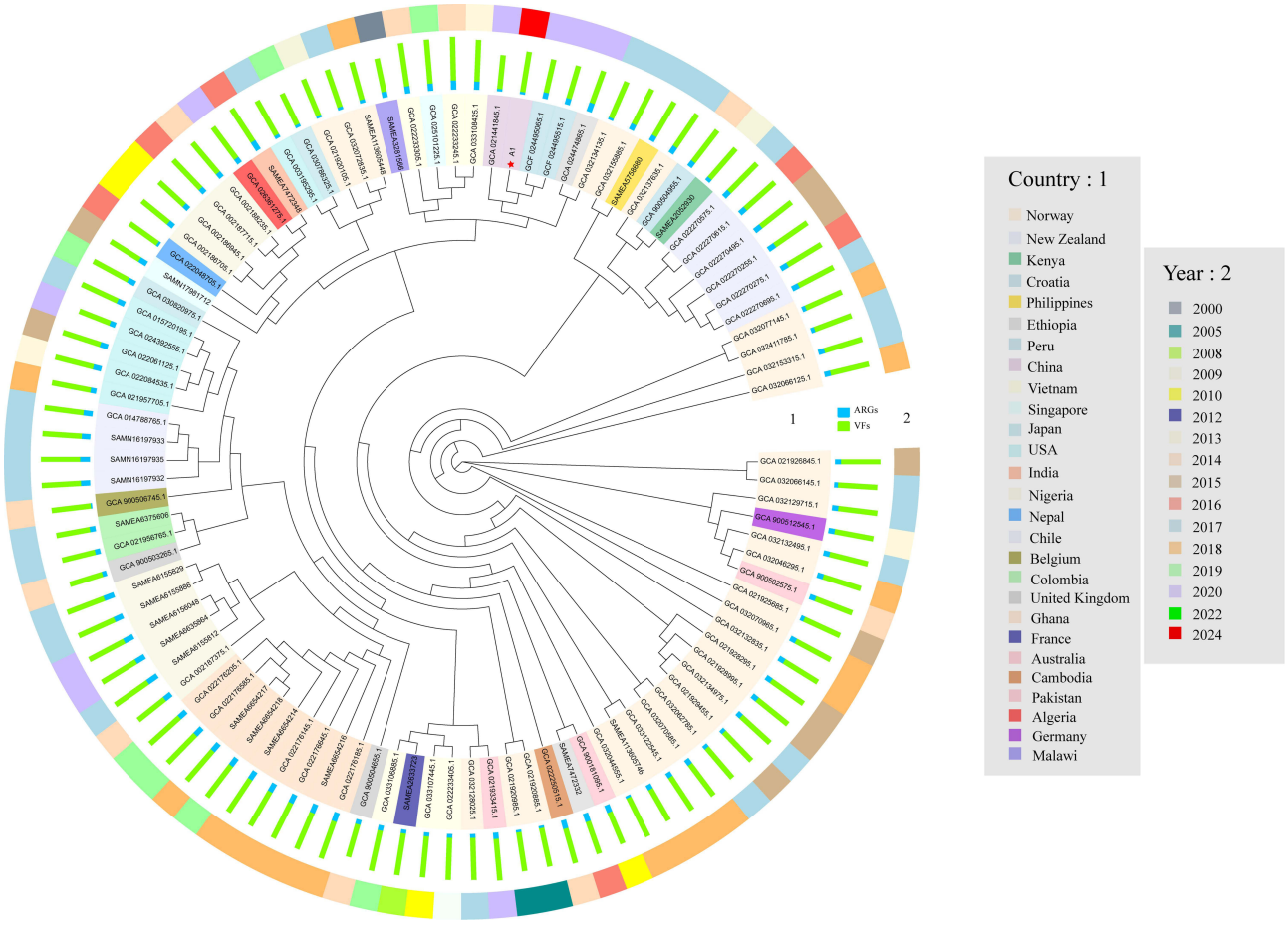

Figure 3 Recombination-filtered core genome phylogeny for a total of 99 *K. pneumoniae* isolates worldwide deposited in the NCBI database. The isolation date, host, source, country, virulence genes numbers and antibiotic resistance genes numbers are represented by squares of different colors. The isolate recovered by this study was marked with a red five-pointed star.

classical definition, classifying it as *K. pneumoniae* strains harboring two or more of the key virulence genes: rmpA, rmpA2, iucA, iroB, and peg-344.[17] Compared to cKp, hvKp exhibits distinct characteristics in terms of bacterial dissemination, and bacterial phenotypic features: (1) Its infections are migratory and invasive, capable of disseminating to cause meningitis, osteomyelitis, endophthalmitis, etc.; (2) hvKp colonies exhibit high mucoid characteristics.[3,16]

In our case, the patient had a history of long-term LC, which is an independent risk factor for hvKp infection, owing to increased mucosal permeability, bacterial translocation, and compromised immune capacity.[18–21] This patient was admitted to the hospital at 10:38 on February 15, 2024, and subsequently experienced BSIs and intra-abdominal infections caused by hypervirulent *K. pneumoniae*. The infection demonstrated rapid migration and invasion, leading to multiple organ failure. Despite resuscitation efforts, the patient succumbed to the infection at 11:39 on February 16. On the same day, peritoneal fluid culture results confirmed the presence of *K. pneumoniae*, and the subsequent blood culture results, obtained on February 17, revealed the presence of the same bacterium. Additionally, a recent case of septicemia in a neonate with purulent meningitis highlighted the high virulence of the ST25 *K. pneumoniae* strain (GCF_021441845.1), which differed by only 123 SNPs from *K. pneumoniae* A1(see Supplementary Material 3) and was confirmed in a mouse model.[22]

The *K. pneumoniae* A1 strain harbors 84 virulence genes within its genome. These virulence genes encode a series of factors that potentially underlie the pathogenicity of hvKp, including the capsule, siderophores, fimbriae, and secretion systems. The capsule often exhibits a hypermucoviscous phenotype, enabling evasion from complement-mediated killing and phagocytosis by neutrophils and macrophages, thus promoting infection spread.[23] Siderophores are small molecules synthesized intracellularly and secreted extracellularly. They have a high affinity for iron, allowing hvKp to acquire this essential element, which promotes their growth and reproduction.[24] Fimbriae are crucial for mediating adhesion, promoting invasion, and facilitating biofilm formation.[25] These secretion systems, particularly the T6SS, function as nanosyringes, injecting effector proteins into target cells to destroy eukaryotic cells or contend against other prokaryotes.[26] When the treatment for hvKp proves ineffective, the virulence factors it harbors escalate in their deadly potential, particularly when there is a coexistence of hypervirulent agents and multidrug-resistant elements.[27] Colistin, the last resort for combating carbapenem-resistant *K. pneumoniae* (CRkp), has come under scrutiny. Shein AMS et al found that colistin-resistant *K. pneumoniae* (ColRkp) can enhance their virulence, potentially leading to colistin-resistant hvKp.[28] This combination poses a formidable challenge to healthcare systems, as it significantly hinders treatment options and underscores the need for innovative therapeutic strategies.

Among these virulence factors, capsule and siderophores play pivotal roles in the hypervirulence of hvKp. The capsule, a polysaccharide matrix surrounding bacterial cells, is crucial for *K. pneumoniae* virulence, and its synthesis is regulated by the transcriptional activator rmpA. Capsule types K1, K2, and K5 have been identified as virulence factors associated with pathogenicity in both humans and mouse models,[29] and are classically recognized as being at high risk for invasive infections.[17] Our study found that all ST25 *K. pneumoniae* isolates associated with BSIs exclusively carried K2 (94/99) or K5 (5/99). Specifically, *K. pneumoniae* A1 was K2 and harbored rmpA.

In iron-poor environments, many bacteria secrete iron-complexing agents known as siderophores to meet their iron requirements.[30,31] HvKp exhibits variable capabilities for producing four siderophores: enterobactin, salmochelin, yersiniabactin, and aerobactin. Molecular epidemiologic studies have revealed that salmochelin, yersiniabactin, and aerobactin are more prevalent in hvKp strains compared to cKp strains.[16,32,33] The genes involved in siderophores, namely iroB (salmochelin), irp2 (yersiniabactin), and iucA\iutA (aerobactin), have demonstrated effectiveness in identifying hvKp.[17] Given that *K. pneumoniae* A1 possesses the hallmark virulence genes rmpA, iroB, and iutA, the isolate *K. pneumoniae* A1 meets the classical definition of hvKp. According to the classical definition of hvKp, 13.13% (13/99) of 99 ST25 *K. pneumoniae* strains were identified as hvKp.

Most hvKp strains are sensitive to commonly used antibiotics other than ampicillin compared to cKp strains.[34] However, carbapenem-resistant hvKps (CR-hvKp) have been increasingly reported globally.[34–36] Among the three ST25 *K. pneumoniae* strains most closely related to the *K. pneumoniae* A1 strain, two carried the OXA-181 gene, and one carried the NDM-1 gene. The acquisition of these genes severely limits the range of clinical antibiotic options, potentially leading to a dire situation in which no effective treatment is available. This study highlights the need for monitoring and limiting the spread of high-risk genes in this region.

Conclusions

Our report underscores the grave threat posed by ST25 hvKp in rapidly progressing BSIs in LC patients. Gene-based screening followed by phenotype validation was effective in identifying hvKp. To effectively curb outbreaks caused by hvKp strains, it is crucial to implement rigorous surveillance and strict infection control strategies. Our study has some limitations. These include the inability to conduct animal model validation for the high virulence of *K. pneumoniae* A1 and the lack of comprehensive CT imaging data across multiple organs due to rapid disease progression in cirrhotic patient, which hinders a full understanding of *K. pneumoniae* infections.

Data Sharing Statement

The data that support the findings of this study are openly available in SRA at https://trace.ncbi.nlm.nih.gov/Traces/index.html?view=run_browser&acc=SRR29184303&display=metadata.

Ethics Statement

The study received approval from the Ethics Committee of Sanmen People's Hospital, Taizhou, China, with the ethical approval number: 2024-132.

Patient Consent for Publication

The patient provided written informed consent for the publication of case details and accompanying images.

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Disclosure

The author declares no potential conflicts of interest relevant to this article.

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