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Clinical characteristics of bacteremia caused by hypermucoviscous *Klebsiella pneumoniae* at a tertiary hospital

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ABSTRACT

This study aimed to assess the predictive factors of bacteremia due to hypermucoviscous *Klebsiella pneumoniae* (hvKP), as well as the mortality. The medical records of 114 patients with *K. pneumoniae* bacteremia who were divided into the hvKP ($n = 24$) and non-hvKP ($n = 90$) groups and were retrospectively reviewed. The male-to-female ratio, age, and underlying disease did not differ between the 2 groups. Mortality was higher among patients in the hvKP bacteremia group than in the non-hvKP bacteremia group (29.2% vs 6.7%). Multivariate analysis showed that the independent predictors associated with hvKP bacteremia were abscess ($P = 0.01$) and no antibiotic exposure ($P = 0.02$); thus, early assessment of these conditions is important. For patients with a history of abscess and no antibiotic exposure, it is necessary to administer treatment while keeping the risk of hvKP in mind.

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1. Introduction

Klebsiella pneumoniae is a common gram-negative pathogen in hospital and community infections (Podschun and Ullmann, 1998). *K. pneumoniae* causes pneumonia, urinary tract infection (UTI), and bloodstream infection (Magill et al., 2014). In recent years, a new type called hypermucoviscous *K. pneumoniae* (hvKP) has emerged, mainly in Southeast Asia. It is now becoming a global public health challenge (Struve et al., 2015). HvKP strains characteristically grow distinct sticky colonies on agar plates (Yu et al., 2007b). HvKP can cause severe infections including bacteremia, liver abscess, pneumonia, endophthalmitis, and meningitis; it is also associated with high mortality (Shon et al., 2013). In a previous study, we reported 2 serious cases of hvKP infection

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum beta-lactamase; hvKP, hypermucoviscous *Klebsiella pneumoniae*; MIC, minimum inhibitory concentration; *rmpA*, regulator of mucoid phenotype A; UTI, urinary tract infection.

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with multiple organ abscesses and endophthalmitis (Namikawa et al., 2016).

That hypermucoviscous phenotype is strongly associated with hypervirulence has long been widely accepted. Therefore, the terms hypermucoviscous and hypervirulence have often been used synonymously. However, it was proposed recently that hypermucoviscosity and hypervirulence are 2 different phenotypes that should not be used as synonyms (Catalán-Nájera et al., 2017). The hypervirulence of *K. pneumoniae* should be defined by the genomic background and not be dependent solely on the bacterial phenotype (Luo et al., 2014). In other words, hypermucoviscosity detected by the string test is inadequate to suggest a hypervirulent isolate state. However, on the other hand, we consider that clinicians cannot completely throw away the string test. First, although hypermucoviscosity and hypervirulence may not necessarily go together, the string test could give us a serious caution about whether the clinical isolation is a potential hypervirulent isolate. Secondly, facilities for genetic testing of hypervirulence are limited. From the above, we consider that the string test is still important as a way to screen for hypervirulent isolates in clinical practice.

Some studies reported that the mortality from bacteremia due to hvKP is relatively high (Ko et al., 2002; Ku et al., 2008; Togawa et al.,

2015). However, it is controversial whether the mortality following bacteremia due to hvKP is higher than that in non-hvKP. In addition, although previous studies indicate that there are various factors associated with hvKP bacteremia, these have not been extensively investigated.

The purpose of the present study was to investigate the clinical characteristics of patients with bacteremia due to hvKP at a tertiary hospital, including the risk factors and prognosis.

2. Materials and methods

The medical records of 114 patients with *K. pneumoniae* bacteremia, admitted to Osaka City University Hospital between January 2012 and April 2018, were reviewed retrospectively. The age, sex, underlying disease, clinical features, patient medication records, and prognosis were evaluated. If *K. pneumoniae* had been isolated on multiple occasions within the 6-year period in the same patient, only the first episode of *K. pneumoniae* bacteremia was reviewed.

2.1. Definition of bacteremia and its source

Bacteremia was defined as when 1 or more positive blood cultures were observed in patients with clinical signs of infection (such as fever, shaking chills, and sweats), with or without local signs and symptoms (Yamada et al., 2011). A patient was diagnosed with *K. pneumoniae* UTI when the clinical and diagnostic findings included 2 or more of the following: 1) *K. pneumoniae* confirmed in a urine specimen, 2) clinical manifestations suggestive of UTI, and 3) imaging findings suggestive of pyelonephritis. Symptoms and urinary findings (including dysuria, suprapubic pain, hematuria, flank pain, costovertebral-angle tenderness, nausea or vomiting, and pyuria or bacteriuria) are characteristic of UTI (Hooton, 2012). Furthermore, the imaging findings (including perinephric stranding, renal swelling, thickening of Gerota's fascia, and a poor segmental enhancement region) are characteristic of pyelonephritis (Hammond et al., 2012). The diagnosis of *K. pneumoniae* biliary tract infection was made when the clinical and diagnostic findings included 3 or more of the following: 1) fever and/or chills, 2) laboratory evidence of an inflammatory response, 3) jaundice or abnormal liver chemistries, 4) biliary dilation or evidence of an etiology observed on imaging, and 5) *K. pneumoniae* isolated from a bile specimen. Pneumonia was diagnosed when new or persistent pulmonary infiltrates, not otherwise explained, appear on the chest radiograph, along with purulent respiratory secretions and systemic signs of inflammatory response (Magret et al., 2011). *K. pneumoniae* catheter-related bloodstream infection was diagnosed based on clinical and diagnostic findings, including 1 or more of the following: 1) *K. pneumoniae* growth in at least 1 percutaneous blood and catheter tip culture and 2) *K. pneumoniae* growth in a blood sample drawn from a catheter hub at least 2 h before the growth of *K. pneumoniae* was detected in a peripheral vein blood sample (Mermel et al., 2009).

2.2. Assessment of laboratory data

If the initial blood culture was positive, then the leukocyte count, C-reactive protein levels, and albumin levels were assessed within 2 days of the culture. The present study applied the 2016 Sepsis-3 criteria (Singer et al., 2016).

2.3. Identification of bacteria

All *K. pneumoniae* isolates were identified via colony morphologic analysis and gram staining. Isolate identification and antimicrobial susceptibility were confirmed using the MicroScan WalkAway-96 SI (Beckman Coulter, Inc., Brea, CA). The minimum inhibitory concentrations (MICs) were also determined using the MicroScan WalkAway-96

SI. The results were interpreted according to the 2017 Clinical and Laboratory Standards Institute (CLSI) breakpoints. The production of extended-spectrum beta-lactamase (ESBL) was screened by measuring the MICs of cefotaxime, ceftazidime, and aztreonam. Confirmational testing was performed using an Ambler class C & ESBL Identification Set (Kanto Chemical Co., Inc., Tokyo, Japan). All plates were incubated at 35 °C for 24 h. The string test was performed on all isolates. A positive string test was defined as bacterial colonies on an agar plate stretching for >5 mm using an inoculation loop. *K. pneumoniae* strains with a positive string test were designated as hvKP.

2.4. Antimicrobial treatments

The attending physician determined the appropriate initial antimicrobial treatment regimen. Antimicrobial treatment administered within 5 days after bacteremia onset was defined as empirical therapy, and that administered afterward, as definitive therapy (Lee et al., 2013). Appropriate antibiotic therapy was defined as therapy (with antibiotics) that matches the in vitro susceptibility, according to the CLSI criteria.

2.5. Capsular polysaccharide typing and detection of virulence factor

K1 and K2 capsular serotypes and regulator of mucoid phenotype A (*rmpA*) were identified by polymerase chain reaction using primers

Table 1
Clinical characteristics and laboratory findings of hvKP and non-hvKP bacteremia.

Variables	hvKP (n = 24)	Non-hvKP (n = 90)	P value
Male sex	17 (70.8%)	53 (58.9%)	0.35 ^a
Age ≥ 65 years	16 (66.7%)	53 (58.9%)	0.64 ^a
Underlying disease ^b			
Malignancy	9 (39.1%)	56 (62.2%)	0.06 ^a
Immunosuppressive drug or corticosteroid use	4 (17.4%)	14 (15.6%)	0.76 ^a
Diabetes mellitus	6 (26.1%)	32 (35.6%)	0.47 ^a
Chronic obstructive pulmonary disease	4 (17.4%)	10 (11.1%)	0.48 ^a
Chronic kidney disease	4 (17.4%)	18 (20.0%)	1.00 ^a
Lower gastrointestinal disease	0 (0%)	6 (6.7%)	0.34 ^a
Charlson score ^{b,c}	3.1 ± 2.7	3.4 ± 2.5	0.31 ^d
No antibiotic exposure ^{b,e}	16 (70.0%)	39 (43.3%)	0.03 ^a
Leukocyte count ≥12,000 (/μL)	10 (41.7%)	36 (40.0%)	1.00 ^a
C-reactive protein ≥10 (mg/dL)	17 (70.8%)	34 (37.8%)	0.01 ^a
Albumin ≤2.5 (g/dL)	6 (25.0%)	22 (24.4%)	1.00 ^a
Community-acquired infection	16 (66.7%)	34 (37.8%)	0.01 ^a
Operation within 30 days ^b	2 (8.7%)	11 (12.2%)	1.00 ^a
Hospitalization within 90 days ^b	7 (30.4%)	33 (36.7%)	0.63 ^a
Infection site			
Urinary tract	6 (25.0%)	10 (15.6%)	0.36 ^a
Biliary tract	5 (20.8%)	29 (32.2%)	0.33 ^a
Lung	4 (16.7%)	6 (6.7%)	0.21 ^a
Intravascular device	1 (4.2%)	5 (5.6%)	1.00 ^a
Others	1 (4.2%)	3 (3.3%)	1.00 ^a
Unknown	7 (29.2%)	33 (36.7%)	0.63 ^a
Abscess ^b	6 (26.1%)	7 (7.9%)	0.03 ^a
Liver	3 (13%)	5 (5.6%)	0.36 ^a
Drainage	2 (8.7%)	1 (1.1%)	0.11 ^a
Eye	2 (8.7%)	0 (0%)	0.04 ^a
Brain	1 (4.3%)	0 (0%)	0.21 ^a
Lung	2 (8.7%)	1 (1.1%)	0.11 ^a
Kidney	1 (4.3%)	0 (0%)	0.21 ^a
Prostate	1 (4.3%)	0 (0%)	0.21 ^a
ESBL-producing strain	0 (0%)	8 (8.9%)	0.20 ^a
Sepsis	13 (54.2%)	23 (25.6%)	0.01 ^a
Mortality	7 (29.2%)	6 (6.7%)	0.01 ^a

ESBL = extended spectrum beta-lactamase; hvKP = hypermucoviscous *Klebsiella pneumoniae*; SD = standard deviation.

^a Fisher analysis.

^b The details about 1 patient among hvKP bacteremia group were unknown.

^c Data are presented as mean ± SD.

^d Mann-Whitney *U* test.

^e Sixty days prior to isolation.

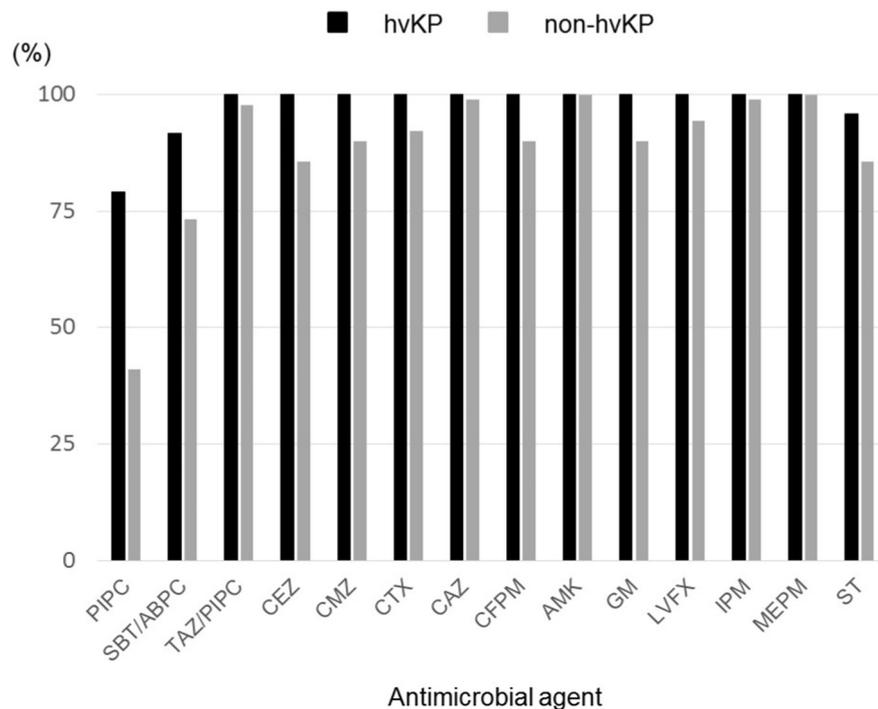


Fig. 1. Various antimicrobial susceptibility rate data against hvKP and non-hvKP. AMK = amikacin; CAZ = ceftazidime; CEZ = cefazolin; CFPM = ceftipime; CMZ = cefmetazole; CTX = cefotaxime; GEM = gentamicin; hvKP = hypermucoviscous *Klebsiella pneumoniae*; IPM = imipenem; LVFX = levofloxacin; MEPM = meropenem; PIPC = piperacillin; SBT/ABPC = sulbactam/ampicillin; ST = sulfamethoxazole/trimethoprim; TAZ/PIPC = tazobactam/piperacillin.

documented previously (Compain et al., 2014; Fang et al., 2004; Yu et al., 2007a, 2007b).

2.6. Statistical analysis

Patient characteristics, blood examination data, treatments, and outcomes were compared between the hvKP bacteremia patients and non-hvKP bacteremia patients.

The Fisher's exact test and Mann–Whitney *U* test were used for univariate comparison of categorical data. Gender, age, and variables with a *P* value <0.1 in the univariate analyses were considered for inclusion in the backward, stepwise, multivariate logistic regressions using EZR (version 1.37; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (version 3.4.1; The R Foundation for Statistical Computing, Vienna, Austria), to determine the independent predictors of hvKP bacteremia. *P* values <0.05 indicated a statistically significant difference.

3. Results

3.1. Patient clinical characteristics, laboratory findings, treatments, and outcomes

The clinical characteristics and laboratory findings of patients with hvKP or non-hvKP bacteremia are summarized in Table 1. The 24 patients with hvKP bacteremia included 17 men and 7 women with a mean age of 67.8 years. The 90 patients with non-hvKP bacteremia included 53 men and 37 women with a mean age of 65.6 years. Of the patients with hvKP bacteremia, 9 (39.1%) had malignancy, 6 (26.1%) had diabetes mellitus, 16 (70.0%) had not received antibiotics, and 16 (66.7%) had community-acquired bacteremia. In comparison, of the 90 patients with non-hvKP bacteremia, 56 (62.2%) had malignancy, 32 (35.6%) had diabetes mellitus, 39 (43.3%) had not received antibiotics, and 34 (37.8%) had community-acquired bacteremia. Charlson score did not differ between hvKP and non-hvKP groups (3.1 ± 2.7 vs. 3.4 ± 2.5 , *P* = 0.31). The occurrence of abscess was higher in patients

with bacteremia due to hvKP than that in patients with bacteremia due to non-hvKP (26.1% vs. 7.9%, *P* = 0.03). Furthermore, sepsis and the 30-day mortality rates were higher among patients in the hvKP bacteremia group than in patients in the non-hvKP bacteremia group (sepsis: 54.2% vs 25.6%, *P* = 0.01, 30-day mortality: 29.2% vs 6.7%, *P* = 0.01).

3.2. Antimicrobial susceptibility

Data on various antimicrobial susceptibility rates against hvKP and non-hvKP are shown in Fig. 1. Notably, the resistance rate of almost all antimicrobial agents for non-hvKP was higher than that of the hvKP. Although 8 (8.9%) non-hvKP isolates were found to be ESBL-producing strains and 1 (1.1%) non-hvKP isolate was resistant to imipenem, there was no ESBL-producing or imipenem-resistant strain in hvKP.

3.3. Treatment

The empirical and definitive therapies against hvKP and non-hvKP bacteremia are summarized in Table 2. The utilization rates of carbapenems against hvKP or non-hvKP bacteremia as both an empirical and definitive therapy were significantly higher than for other antimicrobial agents. The proportions of appropriate empirical or definitive therapy did not differ between the bacteremia groups (empirical: 100% vs. 93.3%, *P* = 0.34, definitive: 100% vs 95.3%, *P* = 1.0).

3.4. Molecular characteristics

Molecular characteristics of hvKP and non-hvKP are shown in Table 3. Notably, the rates of capsular serotype K2 and the *rmpA* gene in the hvKP group were higher than those in the non-hvKP (K2: 20.8% vs. 5.6%, *P* = 0.03, *rmpA*: 50.0% vs. 2.2%, *P* < 0.001).

Table 2
Empirical and definitive therapy against hvKP and non-hvKP bacteremia.

Variables	Empirical therapy		Definitive therapy	
	hvKP (n = 24)	Non-hvKP (n = 90)	hvKP (n = 20) ^a	Non-hvKP (n = 86) ^b
Carbapenems	14 (58.3%)	30 (33.3%)	5 (25.0%)	22 (25.6%)
Tazobactam/piperacillin	2 (8.3%)	13 (14.4%)	2 (10.0%)	13 (15.1%)
Quinolones	2 (8.3%)	5 (5.6%)	3 (15.0%)	8 (9.3%)
Fourth-generation cephalosporins	3 (12.5%)	8 (8.9%)	3 (15.0%)	5 (5.8%)
Third-generation cephalosporins	2 (8.3%)	16 (17.8%)	2 (10.0%)	16 (18.6%)
Sulbactam/ampicillin	0 (0%)	8 (8.9%)	2 (10.0%)	8 (9.3%)
Second-generation cephalosporins	1 (4.2%)	8 (8.9%)	1 (5.0%)	5 (5.8%)
First-generation cephalosporins	0 (0%)	2 (2.2%)	2 (10.0%)	9 (10.5%)
Appropriate therapy	24 (100%)	84 (93.3%)	20 (100.0%)	81 (94.2%)

hvKP = hypermucoviscous *Klebsiella pneumoniae*.

^a Four patients died before definitive therapy.

^b Three patients died and 1 patient was transferred to a different hospital before definitive therapy.

3.5. Predictive factors of hvKP bacteremia

The independent predictors associated with hvKP bacteremia in the multivariate analysis included abscess [odds ratio (OR), 5.54; $P = 0.01$] and no antibiotic exposure (OR, 3.31; $P = 0.02$) (Table 4).

4. Discussion

The results of our study revealed the following. First, hvKP bacteremia showed a tendency of increasing severity of disease and a higher mortality than that of non-hvKP bacteremia. Second, abscess and no antibiotic exposure were independent predictors of hvKP bacteremia.

Some studies reported that the mortality was higher among patients in the hvKP bacteremia group than in patients in the non-hvKP bacteremia group (Ko et al., 2002; Ku et al., 2008; Togawa et al., 2015). In contrast, other previous studies indicated that the mortality did not differ between patients in the hvKP bacteremia and non-hvKP bacteremia groups (Cubero et al., 2016; Lee et al., 2006; Liu et al., 2014). It was therefore controversial whether the mortality in bacteremia due to hvKP was higher than that of non-hvKP. Previous report documented that the presence of morbidity cofactors could themselves influence mortality (Yu et al., 2017). However, in our study, Charlson score did not differ between hvKP and non-hvKP groups. HvKP has the feature of a thick capsule for reducing the antiphagocytic effect against macrophages and neutrophils (Fung et al., 2011; Yeh et al., 2010). HvKP also has a high tendency of causing bacteremia; multiple organ abscesses including liver; and metastatic infections such as endophthalmitis, meningitis, and pneumonia, which are associated with a remarkably high mortality (Shon et al., 2013). Furthermore, aerobactin and the mucoid phenotype A (*rmpA*) genes regulator, as critical virulence factors, are more prevalent in hvKP than in non-hvKP (Kim et al., 2017). The isolates of K1 or K2 capsular serotype demonstrated a more significant phagocytic resistance and virulence than non-K1/K2 strains (Yeh et al., 2007). In addition, in the present study, the incidence of sepsis was higher in patients with bacteremia due to hvKP than in non-hvKP bacteremia patients (54.2% vs. 25.6%, $P = 0.01$). A previous report has shown that mortality rates after sepsis are extremely high (Huggan et al., 2017). These findings support the fact that hvKP bacteremia showed

a tendency of increasing severity, with mortality higher than that for non-hvKP bacteremia, and the high mortality in hvKP was related to the bacterial virulence factors including K2 and the *rmpA* gene rather than to multiple and serious comorbidities.

Previous studies showed abscess to be an independent predictor of hvKP bacteremia (Guo et al., 2017; Yu et al., 2006). The mechanism for hvKP infection is considered to be through the leakage of *K. pneumoniae* from patients' intestinal epithelium, and bacterial translocation into the liver via the portal circulation, and then result in liver abscess and bacteremic dissemination (Siu et al., 2012). Yu et al. (2006) reported that hypermucoviscosity and *rmpA* were strongly associated with abscess formation among *K. pneumoniae* bacteremia patients. Further, the mucoviscosity-associated gene A, which is related to the expression of the hypermucoviscous phenotype, is associated with septic metastatic complications (Fang et al., 2007). These findings suggest that the abscess formation is strongly associated with hvKP bacteremia.

Although previous studies indicated that there are various factors associated with hvKP bacteremia, its particular association with no antibiotic exposure that we observed at multivariate analysis is an unusual finding. It has been previously reported that an exposure to ampicillin and/or amoxicillin within the past 30 days was associated with *K. pneumoniae* liver abscess (Lin et al., 2013). With regards to the discrepancy between the result of the previous study and ours, we consider the following reasons. First, the case settings differ. That is, in the previous study, the patients with a pyogenic liver abscess formed the case group; however, in our study, the patients with hvKP bacteremia formed the case group. Secondly, no proven causative microorganism of liver abscess was reported in the previous study. From the above, strictly speaking, we consider that an exposure to ampicillin and/or amoxicillin within the past 30 days cannot be a risk factor of *K. pneumoniae* liver abscess. By the way, hvKP was more resistant to complement and neutrophil-mediated bactericidal activity than non-hvKP; therefore, hvKP easily causes serious infection even in normal hosts (Pomakova et al., 2012). On the other hand, a previous report has shown that in some of the antimicrobial agents, excessive exposure reduces the virulence of hvKP (Choi and Ko, 2015). Moreover, the antimicrobial resistance rate of hvKP was significantly lower than that of non-hvKP strains (Zhang et al., 2016). Thus, these findings suggest that no antibiotic exposure may be associated with an increased risk of hvKP bacteremia.

Table 3
Molecular characteristics of hvKP and non-hvKP.

Variables	hvKP (n = 24)	Non-hvKP (n = 90)	P value ^a
K1	9 (37.5%)	48 (53.3%)	0.25
K2	5 (20.8%)	5 (5.6%)	0.03
Non-K1/K2	10 (41.7%)	37 (41.1%)	1.00
<i>rmpA</i>	12 (50.0%)	2 (2.2%)	<0.001

hvKP = hypermucoviscous *Klebsiella pneumoniae*, *rmpA* = regulator of mucoid phenotype A.

^a Fisher's analysis.

Table 4
Multivariate analysis of predictive factors associated with hvKP bacteremia.

Predictive factor	OR (95% CI)	P value
Abscess	5.54 (1.49–20.6)	0.01
No antibiotic exposure	3.31 (1.18–9.93)	0.02

CI = confidence interval; hvKP = hypermucoviscous *Klebsiella pneumoniae*; OR = odds ratio.

In the present study, the proportions of appropriate empirical or definitive therapy did not differ between the 2 groups. Nevertheless, the frequency of severe cases or mortality rate was higher among patients in the hvKP bacteremia than in the non-hvKP bacteremia patients. Therefore, considering that the incidence of abscess was higher in patients with bacteremia due to hvKP than with non-hvKP bacteremia patients, we consider that it is important to implement not only antimicrobial treatment approach but also multidisciplinary treatment approaches including adequate abscess drainage and adjuvant therapy such as steroids or vasopressors if the patients with hvKP bacteremia develop septic shock.

Our study had several limitations. First, this study had a relatively small study population because it was conducted in patients in 1 tertiary hospital only; thus, there was selection bias. We will need to collect and analyze data on more patients with bacteremia caused by *K. pneumoniae* in both community and tertiary hospital settings. Second, the string test is merely a quantitative method; it lacks the precision to evaluate hvKP mucoviscosity. Moreover, hvKP may be affecting the string test because there is the possibility of a challenge with the preservation of hvKP due to the use of some old *K. pneumoniae* strains. We need to identify a more appropriate method to more accurately evaluate hvKP mucoviscosity instead of the string test. Third, we conducted this retrospective study primarily with the aim of investigating the predictive factors of bacteremia caused by hvKP. There is need for a prospective study including genetic testing.

5. Conclusion

In conclusion, the results of our study showed higher mortality among hvKP bacteremia patients than the non-hvKP bacteremia patients. Abscess and no antibiotic exposure were independent predictors of hvKP bacteremia. For patients with a history of such predictors, it is necessary to administer treatment while keeping the risk of hvKP in mind.

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Declarations of interest

None.

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