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Effect of Hypervirulent Strains, Antibiotic Resistance, and Host Characteristics on Mortality of *Klebsiella pneumoniae* Bacteremia Patients at a Tertiary Referral Hospital in Denpasar, Indonesia

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Abstract

Klebsiella pneumoniae bacteremia is one of the leading causes of sepsis that has a high mortality rate. The effect of multidrug resistance and different virulence of *Klebsiella pneumoniae* on mortality is still controversial. This study aimed to determine the impact of hypervirulent K. pneumoniae (hvKp), MDR, and clinical characteristics on mortality of *K. pneumoniae* bacteremia patients. A retrospective cross-sectional study was conducted on *K. pneumoniae* bacteremia cases of patients hospitalized at Professor dr. I.G.N.G Ngoerah General Hospital from December 1, 2020, to May 31, 2021. A positive PCR of *rmpA, iucA* genes, and/or a positive string test was identified as hvKp. The mortality rate of 51 K. pneumoniae bacteremia patients samples (aged 0–74 years) was 72.5%, in which 9.8% (5/51) of them were hvKp and 51% of the isolates (26/51) produced the Extended Spectrum Beta Lactamase (ESBL). Furthermore, 9.8% (5/51) of the cases were carbapenem-resistant. Thus, hvKp, MDR, gender characteristics, and comorbidities do not significantly affect the mortality of *K. pneumoniae* bacteremia patients. Multivariate logistic regression analysis showed that sepsis (odds ratio (OR) 4.29; p=0.038) and adult age group (mean 50 years) (OR 3.75; p=0.039) are independent predictors with a significant effect on mortality of *K. pneumoniae* bacteremia patients. Careful and integrated management of *K. pneumoniae* bacteremia patients is essential for better outcomes, especially in sepsis and elderly patients. Although hvKp prevalence is low, emerging MDR-hvKp in health facilities is a severe concern for further actions and research.

Keywords: Bacteremia, *Klebsiella pneumoniae*, mortality, multidrug resistance, sepsis

Introduction

Sepsis is a significant cause of death from infectious diseases, especially if it is not detected early or appropriately treated.[1] *Klebsiella pneumoniae* bacteremia is one of the main etiologies of sepsis and is highly prevalent in Asia and the Middle East.[2] According to a preliminary study by Professor dr. I.G.N.G. Ngoerah Hospital In 2019, there were 177 cases of sepsis with a mortality rate of 74.57%, where *K. pneumoniae* was the most isolated gram-negative bacteria, with 18.54% of all blood culture results (*unpublished data*).

Klebsiella pneumoniae is an opportunistic pathogen and often causes bacteremia and sepsis, both obtained from hospitals and the community, and also has been associated with some common underlying conditions such as elderly patients, patients with diabetes, malignancy, end-stage renal failure, and suppression of the immune system.[3,4] *Klebsiella pneumoniae* has many virulence factors such as capsules, lipopolysaccharide, fimbriae, and siderophores and also its ability to produce an Extended Spectrum of Beta-Lactamase (ESBL) enzyme that causes resistance to many antibiotics, especially third-generation cephalosporins,

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and monobactams.[4] Hypercapsular virulence factors and siderophore aerobactin biosynthesis of hypervirulent *Klebsiella pneumoniae* (hvKp) have an essential role in the pathogenesis of *K. pneumoniae* invasive bacteremia infection and have an impact on patient outcomes.[5]
The presence of hypermucoviscosity (*rmpA*) and aerobactin (*iucA*) genes are closely related to morbidity and mortality as well as an accurate molecular marker of hvKp infection both epidemiologically and clinically experimentally and in murine sepsis models.[5] A study in China showed that several cases of Multidrug-resistant (MDR) hvKp bacteremia patients, including carbapenems, had poor clinical outcomes in septic shock and death.[6,7]

The increasing numbers of hvKp bloodstream infections and the high rate of MDR *K. pneumoniae* in Asia are concerns about the impact, including in Indonesia. Until now, the study of hvKp bacteremia in Indonesia is limited. This study aimed to determine the prevalence of hvKp and analyze the effect of hypervirulent strains, MDR *K. pneumoniae*, demographic characteristics, and patient comorbidities on mortality of *K. pneumoniae* bacteremia patients.

Methods

This research was conducted with 51 consecutive cases of *K. pneumoniae* bacteremia between December 1, 2020, and May 31, 2021, collected from patients hospitalized at Professor dr. I.G.N.G. Ngoerah Hospital, a tertiary teaching hospital in Denpasar, Bali, Indonesia. This retrospective cross-sectional study included only the first bacteremia episode for each patient. Patient characteristics, including age, sex, underlying disease (comorbidity), clinical features, and outcome, were evaluated. The study was approved by the Ethical Research of Udayana University, Indonesia (Number 1236/UN14.2.2.VII.14/LT/2021). The need for written informed consent was waived owing to the study's retrospective nature.

Klebsiella pneumoniae bacteremia was defined as one or more positive blood cultures of *K. pneumoniae* in patients with clinical signs of infection, such as fever, shaking chills, and sweats, with or without local signs and symptoms.[8] Multidrug-resistant (MDR) *K. pneumoniae* was defined as the resistance of *K. pneumoniae* to at least one of three different classes of antibiotics or more as seen from the results of antibiotic sensitivity tests.[9] Comorbidities were underlying diseases that have been diagnosed in patients other than bloodstream infections (bacteremia) in this case centered on critical illnesses in the central nervous system, cardiovascular, respiratory, digestive, urogenital, endocrine, musculoskeletal, malignancies and immune system disorders. Sepsis was defined as organ dysfunction characterized by more than or same as 2 of Sequential Organ Failure Assessment (SOFA) scores or more than or same as 7 of PELOD-2 scores (0–18 years old patients) or clinically and laboratory diagnosed sepsis recorded in the patient's medical record, as a result of bloodstream infection (bacteremia) *K. pneumoniae.* The medical record data for SOFA/PELOD-2 scores and the diagnosis of sepsis used were between 48 hours before and after taking blood culture specimens identified as *K. pneumoniae.* The thirty-day mortality rate was defined as the clinical outcome of dying from *K. pneumoniae* bacteremia patients in the care of patients at Professor dr. I.G.N.G. Ngoerah Hospital within a period of up to 30 days from the day of taking positive blood culture specimens reviewed from the patient's medical record.[10]
Identification and antimicrobial susceptibility testing of *Klebsiella pneumoniae* blood isolates were performed by using Vitek 2 Compact system (bioMerieux, Marcy l'Etoile, France). MICs results were interpreted according to the 2020 Clinical and Laboratory Standards Institute (CLSI, M100-S27) breakpoints. The production of ESBL was screened by measuring the MICs of cefotaxime, ceftazidime, and aztreonam that were automatically defined by the Vitex 2 Compact system. Carbapenem-resistant *K. pneumoniae* was described as being resistant to meropenem or ertapenem. All *K. pneumoniae* isolates were cultured on blood agar plates, incubated for 24 hours at 37°C, and subjected to a string test. Using an inoculation loop, a positive string test was defined as bacterial colonies on a blood agar plate stretching for >5 mp.[11] DNA was extracted from bacterial colonies using a plasmid DNA extraction kit (QIAprep® Spin Miniprep Kit, Qiagen, Gmbh) following the manufacturer's instructions. Uniplex PCR was performed to detect hypervirulent *K. pneumoniae* (hvKp) biomarker genotypes such as *p-rmpA* and *iucA* genes with primer sets, as shown in Table 1.

The final concentration of the primer set was ten µM each. PCR cycles of *p-rmpA* consisted of pre-denaturation at 94°C for 4 minutes; 30 cycles of denaturation at 94°C for 30 seconds, primer annealing at 50°C for 40 seconds, and extension at 72°C for 1 minute; and a final extension at 72°C

Table 1 Primer Sets Used for Identification of hvKp

PCR Target	Primer Sequence (5'- 3')	Size (bp)	Reference
$_p$rmpA	F: ACTGGGCTACCTCTGCTTCA	366	12
	R: CAGTAGGCATTGCAGCA		
iucA	F: CGCTTCACTTCTTTCACTGACAGG	239	5
	R: AATCAATGGCTATTCCCGCTG		

PCR=polymerase chain reaction; bp = base pairs; hvKp = hypervirulent *k. pneumoniae*

for 10 minutes.[12] PCR cycles of *iucA* consisted of pre-denaturation at 95°C for 2 minutes; 30 cycles of denaturation at 95°C for 30 seconds, primer annealing at 55°C for 43 seconds, and extension at 72°C for 1 minute; and a final extension at 72°C for 10 minutes (MiniAmp™ thermal cycler, Applied Biosystems™).[5] Hypervirulent *K. pneumoniae* (hvKp) was defined by biomarker that contain at least 2 of 3 phenotypic and genotypic markers, including positive string test, detectable hypervirulent *rmpA* and *iucA* gene.

Data were input and processed using Microsoft Excel 2019, and descriptive statistics were calculated. Data analysis used SPSS statistic 25.0 (USA, IBM analytics). The bivariate chi-square or Fisher's exact test assessed significant associations and effects between two categorical variables. Multivariate logistic regression was used to identify risk factors for *K. pneumoniae* sepsis and independent predictors of 30-day mortality. All variables were included in the multivariate model in a forward stepwise approach using the likelihood-ratio test. The chi-square test showed that the association measure was an odds ratio (OR) while the logistic regression was an adjusted odd ratio (OR). The inference process based on a 95% Confidence Interval of OR and *p-value* < 0.05 were considered statistically significant.

Results

During the study period, 51 patients were identified as *K. pneumoniae* bacteremia, and 5 of 51 *K. pneumoniae* isolates (9.8%) were identified as hvKp strains. All hvKp isolates positive for *rmpA* and/or *iucA* genes have positive string tests. The general characteristics of *K. pneumoniae* bacteremia patients are shown in Table 2. The adult group (>18 years old) was dominant in this study (58.8%), and diabetes and gastrointestinal abnormality were the most frequent underlying diseases. The proportion was no significant difference in sex, age group, comorbidity, incidence of sepsis, and mortality in the different strains of *K. pneumoniae.* In this study, it was found that all hvKP isolates were not ESBL-producer. In addition, no MDR or carbapenem-resistant were found in the hvKP

Table 2 General Characteristics of *Klebsiella pneumoniae* Bacteremia Patients

Variable	n (%) (n=51)
Age groups	
0–1 years old	17 (33.4)
1–18 years old	4 (7.8)
>18 years old	30 (58.8)
Male	25 (49)
Female	26 (51)
Comorbidities	37 (72.5)
Low birth weight and preterm infants	10 (19.6)
Diabetes	9 (17.6)
Gastrointestinal abnormality	7 (13.7)
Cardiovascular disease	4 (7.8)
Malignancy	3 (5.9)
Chronic kidney disease	2 (3.9)
Immunocompromise (AIDS)	2 (3.9)
hvKp	5 (9.8)
cKp	46 (90.2)
MDR-*K. pneumoniae*	31 (60.8)
ESBL *producer K. pneumoniae*	26 (51)
Carbapenem-resistant *K. pneumoniae*	5 (9.8)
Sepsis/shock septic	37 (72.5)
Mortality	37 (72.5)

n=total sample; hvKp=Hypervirulent *K. pneumoniae;* cKp =Classical *K. pneumoniae*

Table 3 Patient Characteristics of Hipervirulent *Klebsiella pneumoniae* bacteremia

Characteristics	hvKp (n=5)	cKp (n=46)	p-value
Sex			
Male	3 (60%)	22 (47.8%)	0.668
Female	2 (40%)	24 (52.2%)	
Age			
More than 18 years old	5 (100%)	25 (54.3%)	0.069
0-18 years old	0 (0%)	21 (45.7%)	
With comorbidities	4 (80%)	33 (71.7%)	1.000
Antibiotics resistance			
ESBL	0 (0%)	26 (56.5%)	0.023*
MDR	0 (0%)	31 (67.4%)	0.007*
Carbapenem resistant	0 (0%)	5 (10.9%)	1.000
Sepsis/Septic shock in infection onset	4 (80%)	33 (71.7%)	1.000
30-day mortality	5 (100%)	32 (69.6%)	0.305

*Statistically significant, p<0.05; hvKp-BSI=hypervirulent *k. pneumoniae*-bloodstream infection; cKp-BSI=classical *k. pneumoniae*-bloodstream infection; ESBL=extended spectrum beta-lactamase; MDR=multidrug-resistant

of males and females was mostly similar, with 49% and 51%, respectively. Most of the isolates were classical strains of *K. pneumoniae* (cKp) (90.2%), which tended to have ESBL-producing (51%) and carbapenem-resistant *K. pneumoniae* (9.8%) compared to hvKp strains.

The patient characteristics with hvKp and cKp bacteremia are shown in Table 3. There

Table 4 Antibiotic Susceptibility of *K. Pneumoniae* Bacteremia Isolates

Antimicrobial Agents	hvKp (n=5)	cKp (n=46)	p-value
Ampicillin-sulbactam	5 (100%)	14 (30.4%)	0.005*
Piperacillin-tazobactam	5 (100%)	32 (69.6%)	0.305
Cefazolin	5 (100%)	13 (28.3%	0.004*
Cefuroxime	5 (100%)	15 (32.6%)	0.007*
Ceftriaxone	5 (100%)	16 (34.8%)	0.009*
Ceftazidime	5 (100%)	17 (37%)	0.011*
Cefepime	5 (100%)	30 (65.2%)	0.167
Cefoperazone	5 (100%)	15 (32.6%)	0.007*
Cefoperazone-sulbactam	5 (100%)	15 (32.6%)	0.007*
Aztreonam	5 (100%)	16 (34.8%)	0.009*
Ertapenem	5 (100%)	41 (89.1%)	1
Meropenem	5 (100%)	41 (89.1%)	1
Gentamicin	5 (100%)	27 (58.7%)	0.143
Amikacin	5 (100%)	33 (71.7%)	0.311
Levofloxacin	4 (80%)	18 (39.1%)	0.152
Ciprofloxacin	4 (80%)	16 (34.8%)	0.071
Trimethoprim-sulfamethoxazole	5 (100%)	20 (43.5%)	0.023*

*Statistically significant, *p*<0.05; hvKp=Hypervirulent *K. pneumoniae;* cKp=Classical *K. pneumoniae*

Table 5 Clinical and Microbiological Characteristics Associated with 30-Day Mortality of Klebsiella pneumoniae Bacteremia Patients

Variable	Mortality		OR (95% CI)	p-value
	Death (n=37)	Survivors (n=14)		
Sex				
Male	21 (56.8%)	4 (28.6%)	3.281 (0.868–12.400)	0.072
Female	16 (43.2%)	10 (71.4%)		
Age groups				
>18 years old	25 (67.6%)	5 (35.7%)	3.750 (1.030–13.648)	0.039*
0–18 years old	12 (32.4%)	9 (64.3%)		
Comorbidities				
Present	27 (73%)	10 (71.4%)	1.080 (0.275–4.241)	1.000
Absent	10 (27%)	4 (28.6%)		
K. pneumoniae strain				
hvKp	5 (13.5%)	0 (0%)	-	0.305
cKp	32 (86.5%)	14 (100%)		
Antibiotic resistance				
ESBL	18 (48.6%)	8 (57.1%)	0.711 (0.206–2.454)	0.588
MDR	21 (56.8%)	10 (71.4%)	0.525 (0.139–1.984)	0.338
Carbapenem-resistant	3 (8.1%)	2 (14.3%)	0.529 (0.079–4.562)	0.606
Sepsis/septic shock	30 (81,1%)	7 (50%)	4.286 (1.131–16.238)	0.038*

*Statistically significant, $p<0.05$; OR (95% CI)=Odd Ratio (95% Confidence Interval); hvKp=Hypervirulent *K. pneumoniae;* cKp=Classical *K. pneumoniae;* ESBL=Extended Spectrum Beta Lactamase; MDR=Multidrug-Resistant

isolate. ESBL-producing and MDR *K. pneumoniae* were significantly identified in more cKp isolates (26/46, 56.5%) than in hvKp isolates (0%) (p<0.05). The incidence of sepsis in hvKP bacteremia was found to be 80% (4/5) with a 100% (5/5) mortality rate, but this was not statistically significant if compared with cKP-BSI (p=0.305) (Table 3).

Hypervirulent *K. pneumoniae* isolates were significantly susceptible to ampicillin-sulbactam, cefazolin, cefuroxime, ceftriaxone, ceftazidime, cefoperazone, cefoperazone-sulbactam, aztreonam, and trimethoprim-sulfamethoxazole than cKp (Table 4).

Table 5 showed that gender and host comorbidities, hypervirulent strains, and antibiotic resistance of *K. pneumoniae* did not show a statistically significant relationship or effect on mortality in *K. pneumoniae* bacteremia patients (p >0.05).

The variables of the adult age group and the incidence of sepsis showed a significant relationship and effect on the mortality of *K. pneumoniae* bacteremia patients (p<0.05).

Table 6 Multivariate Logistic Regression Analysis of Predictive Factors that Influence 30-day Mortality of *Klebsiella pneumoniae* Bacteremia Patients

Outcome	Variable	Adjusted OR 95% CI	P value
Sepsis/septic shock	Male sex	1.592 (0.441–5.747)	0.478
	Comorbidity present	1.919 (0.488–7.548)	0.351
30-day mortality	>18 years old group	4.272 (1.060–17.224)	0.041*
	Sepsis/septic shock	4.901 (1.164–20.635)	0.030*

*Statistically significant, $p<0.05$; OR=Odd Ratio; CI=Confidence Interval

Multivariate analysis further demonstrated that the adult group (>18 years old patients) (OR=4.272) and sepsis/septic shock (OR=4.901) at infection onset were independent predictors for 30-day mortality in patients with *K. pneumoniae* bacteremia (Table 6).

Discussion

Sepsis is a life-threatening organ dysfunction caused by the failure of the patient's response to an infection characterized by severe systemic inflammation in response to the spread of infectious pathogens.[1]morphology, cell biology, biochemistry, immunology, and circulation The mortality and incidence of sepsis in *K. pneumoniae* bacteremia in this study was relatively high compared to previous studies, which were 15-48%.[10,13] To reduce the high incidence of sepsis and mortality of *K. pneumoniae* bacteremia at Professor dr. I.G.N.G. Ngoerah Hospital, adequate management of bacteremia patients is required, starting from diagnostics, appropriate empirical and definitive antibiotic therapy, and preventing the spread of MDR *K. pneumoniae* and hvKp strain.

The hvKp bacteremia prevalence in this study was lower than in other studies from Asian countries such as China (46%), Korea (42.2%), and Taiwan (41.9%).[14,15] However, the prevalence of this study was not much different from that in Algeria (9.2%) and Spain (10.7%).[12,16] Several previous studies showed the endemic spread of hvKp infection in East Asian countries, especially in Taiwan, Korea, and China, which have the same geographical and ethnic characteristics. Hence, the prevalence of hvKp is higher than that in this study. In addition, the research conducted in these East Asian countries has a large and multicenter sample size compared to this study. At the same time, the similarity of the prevalence rates of this study with the prevalence in Algeria and Spain could be due to the similarity of the population of the study samples, which were both carried out in tertiary referral hospitals which did not reflect community infection. Nonetheless, in several case reports in Western countries, hvKp infection often occurs in Asian ethnicities. This data suggests that Asians may be more susceptible to hvKP infection than other ethnic groups.[14]

This study found that hvKp strains tend to be sensitive to many antibiotics and do not produce ESBL and Carbapenemase. These findings were not much different from other studies.[3,17]This is because of majorly hvKp in community infection that tends to less exposure to multiple antibiotics and hospital care. According to the genomic study of Lam et al. in 2018, it was speculated that hvKp is a hypercapsular expression that acts as a barrier to the transformation and conjugation of antibiotic resistance genes and also the CRISPR/Cas system that blocks foreign DNA from entering hvKp cells.[18] However, in the study by Zhang et al. in 2016, it was shown that there were Carbapenem-resistant hvKp strains of 7.4% of all patient specimens in two hospitals in China with poor outcomes.[6]Based on the study of a hospital in China, Shen et al. in 2019 also showed that MDR-hvKp was carrying the blaCTX-M ESBL resistance gene and hypervirulence gene (*rmpA* and *rmpA2*) on the same hybrid plasmid, plasmid p11492-vir-CTXM, in *K. pneumoniae* bacteremia patients with pancreatic abscess with sepsis and death outcome.[7] This indicates that emerging MDR-hvKp in tertiary referral hospitals is becoming a concern that requires vigilance and further elucidation.

In the present study, hvKp did not have a significant relationship and influence on the incidence of sepsis and mortality in *K. pneumoniae* bacteremia patients. The different results obtained from the multivariate analysis of research by Togawa et al. in 2015 showed that hvKp had 15 times more effect on the risk of sepsis compared to cKp (OR=15.92) but had no effect on mortality,[19] as found in this study. Meanwhile, research by Harada et al. in 2019 showed that hvKp strain was a risk factor for the incidence of sepsis (RR=1.55) and mortality (RR=1.25).[20] The effect of hypervirulent strain from these studies is still controversial on the outcome of sepsis and mortality. Previous studies reported that other comorbid cofactors were more influential in mortality than hvKp in bacteremia.[8,21] Similar findings were also observed in this study that bacteremia events were dominantly found with comorbidities. The sample of patients with hvKp bacteremia in this study had an average age of 49 years, one of which was without comorbidities. All of them had sepsis and death, but due to the prevalence of hvKp bacteremia being low compared to cKp, it did not show a statistically significant effect on the incidence of sepsis and mortality.

The overproduction of polysaccharide capsules (hypermucoviscosity) in hvKp strains plays a role in the resistance mechanism to complement and anti-phagocytosis against neutrophils and macrophages.[4] Furthermore, the virulence factor siderophore aerobactin

also has a role in the pathogenesis of bacteria to cause more severe bacteremia. Aerobactin siderophore, which has a greater affinity for iron than host transport proteins, can take up free iron in host plasma and make it easier to multiply and spread.[15] Therefore, hvKp has a high invasive tendency from foci of infection, including rapidly causing bacteremia, multiple organ abscesses, metastatic infections such as endophthalmitis, meningitis, and pneumonia, which are associated with high mortality and consequently challenging to approach therapy.[4,11] The higher mortality in bacteremia by hvKp strains compared to cKp is related to bacterial virulence factors, including capsule strain K2 and the presence of the *rmpA* gene compared to comorbid host factors.[8]

Due to the limited choice of antibiotics that effectively manage MDR *K. pneumoniae* infections, such infections have a higher morbidity and mortality rate than non-MDR bacterial infections.[4] According to Xu et al., adult patients (>18 years) showed that carbapenem-resistant *K. pneumoniae* bacteremia provided a significant mortality risk of 2 times compared to carbapenem-sensitive ones.[17] Whereas, in the pediatric and neonatal patient population, patients with sepsis caused by MDR had a significantly higher risk than non-MDR.[22] However, different things were found in this study. There was no difference in the proportion and significant effect of antibiotic resistance (ESBL and carbapenem resistance) on the incidence of sepsis and mortality. This study is not much different from the results of research by Namikawa et al., where there was no significant difference and effect between ESBL-producing *K. pneumoniae*, AmpC, and carbapenemase on the mortality of *K. pneumoniae* bacteremia patients.[13] This could be due to the influence of other variables such as comorbidity, suitability, and appropriateness of empirical antibiotic administration in *K. pneumoniae* bacteremia patients.

Neonates and the elderly have a higher risk of *K. pneumoniae* infections than other age groups.[4] It is not much different from this study that the proportion of *K. pneumoniae* bacteremia was more prevalent in the adult patient group (>18 years) aged 26–74 years. This finding showed that the older age has a higher risk of bacteremia. The study of Namikawa et al. (2019) also showed that the risk of death from *K. pneumoniae* bacteremia in the elderly (median age 66.5 years) was significantly higher than in other age groups.[13] It was also shown in this study that the predominant adult age group was the elderly, which significantly affected the mortality of *K. pneumoniae* bacteremia patients. In older people, there is a decrease in the differentiation and repopulation of lineage cells of the immune system, such as dendritic cells, natural killer (NK) cells, neutrophils, macrophages, and lymphocytes. Increasing age also decreases the function of adaptive immune cells of B lymphocytes and T lymphocytes. B lymphocyte cells experience a decrease in the number and function of antibody secretion, IL-2, and class switch recombination of antibodies. Meanwhile, T lymphocytes decreased lymphopoiesis, naive T cells, mitogen-associated proliferation, signal transduction, CD28 expression on CD8+ T cells, and decreased membrane receptors. In older people, there is also an increase in the level of pro-inflammatory cytokines such as IL-6 and TNF-α, acute phase reactants such as CRP, and clotting factors, referred to as inflammatory. Manifestations of a decrease in the immune system can facilitate the occurrence of severe infections such as bacteremia from opportunistic pathogenic bacteria such as cKp, which is dominant in this study. The effect of inflammatory aging is closely related to the risk of mortality in elderly patients.[23]

In contrast to hvKp strains which can cause a primary infection in patients, cKp strains can cause serious infections such as pneumonia, bacteremia, or meningitis in immunocompromised individuals, including people suffering from diabetes or malignancies.[4] Bacteremia infection in this study was caused mainly by cKp infection (90.2%), most of whom had comorbidities (72.5%). The bivariate chi-square test did not show a statistically significant difference in influencing the incidence of sepsis and patient mortality. However, the multivariate analysis with logistic regression found a tendency for the influence of comorbid variables on the incidence of sepsis, although not statistically significant. This is because the dependent variable of sepsis is the outcome variable of infection, where all patient samples have homogeneous characteristics, namely bacteremia infection. Patients with diabetes mellitus and malignancy have innate immune system reduction.[4] Failure of the defense function against bacteria, including decreased production of chemokines and cytokines, decreased response, and phagocytic ability of neutrophils, occurs in patients with comorbid diabetes mellitus. This condition is caused by changes in glucose metabolism and oxidative stress in patients with diabetes mellitus.[24] Decreased

function of the natural immune system in patients with malignancy can be caused by chemotherapy's cytotoxic effect, killing immune cell division rapidly and causing neutropenia conditions.[4] In the neonates, especially in premature infants, the risk of an immature immune system, the absence of gastrointestinal microbiota, and an increase in the permeability of the gastrointestinal mucosa facilitate the spread of gastrointestinal pathogenic microbes such as cKp.[25]

Patients with *K. pneumoniae* bacteremia who had fallen into sepsis had a higher mortality risk of 4.9 times than those without sepsis (adjusted OR=4.901) in this study. This study is in line with previous studies where sepsis was a risk factor for mortality in *K. pneumoniae* bacteremia patients.[10,13,17,19] Sepsis in bacteremia is a severe systemic inflammation in response to the spread of infection and pathogenic virulence factors and or an uncontrolled hyperinflammatory response mediated by the release of various pro-inflammatory mediators due to host factors. Sepsis, characterized by organ failure due to endothelial dysfunction and global tissue hypoxia, presents a very high mortality risk.[1]

This study had several limitations. First, this study had a relatively narrow population in only one tertiary referral hospital, thus providing a selection bias where in this study, most of the cKp strains were MDR. Second, this study was conducted on a population of all ages, from neonates to the elderly, with heterogeneous characteristics that cannot be generalized. Third, this study design was a retrospective cross-sectional study with a limited number of variables analyzed and is not longitudinal, so the number of samples that can be reached is only the minimum number of statistical calculations required. The limitations of retrospective data collection in this study include several things, including firstly, the large number of patient samples that were not subjected to culture other than blood cultures, so it is complicated to determine the source of invasive infection or metastasis from hvKp strains; the second is the existence of operational biases such as confounding variables that cannot be controlled due to data limitations such as the severity of sepsis (SOFA/PELOD-2 and APACHE scores) that affect the results of data analysis, especially the effect of comorbidities on sepsis and mortality. Further prospective research with an appropriate and longitudinal research design is needed to validate the results of this study.

In conclusion, using a retrospective single-center study of patients with *K. pneumoniae* bacteremia, our study demonstrated that the adult age group (>18 years old) with elderly dominance and sepsis/shock septic were independent risk factors associated with *K. pneumoniae* bacteremia mortality. Although hvKp strain was not significantly impacting 30-day mortality in this study because of the low prevalence, finding and high mortality of hvKp strain in tertiary hospital settings with high MDR prevalence is a severe concern for further action and research.

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