ORIGINAL ARTICLE

Clinical Characteristics and Outcomes of Klebsiella Pneumonia Bacteraemia in Adult

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ABSTRACT

INTRODUCTION: Klebsiella pneumonia (K. pneumonia) bacteremia is one of the leading causes of hospital morbidity and mortality. Our study aimed to evaluate the clinical characteristics, risk factors and outcomes of K. pneumonia bacteremia in a Malaysian public hospital. **MATERIALS AND METHODS**: A retrospective cross-sectional study of adults with K. pneumonia bacteremia was conducted in a hospital in Johor, Malaysia. Demographics, medical comorbidities, source of infections and the mortality rate was reviewed and analyzed. **RESULTS:** A total of 185 cases of K. pneumonia bacteremia were included for analysis. The mean age for this study was 54.9 (SD 15.4), with 56.8% males and 46.5% in-hospital mortality. Extended-spectrum Beta Lactamase (ESBL) producing and Carbapenem-resistant K. pneumonia contributed to 37.3% and 1.1% of K. pneumonia bacteremia, respectively. Among those who contracted K. pneumonia bacteremia, three most frequent sources were primary bloodstream infections (n=75, 40.5%), pneumonia (n=44, 23.8%) and urinary tract infections (n=28, 15.1%) "or" the most frequent sources were primary bloodstream infections (n=75, 40.5%), pneumonia (n=44, 23.8%) and urinary tract infections (n=28, 15.1%). There was statistically significant associations found between diabetes mellitus (AOR 1.46, 95% CI 1.02-2.08), cancer (AOR 2.02, 95% CI 1.33-3.05) and alcohol use disorder (AOR 7.73,95% CI 1.38-43.21) with K. pneumonia bacteremia. In-hospital mortality was higher in older patients by 1.03 odds (p=0.003). **CONCLUSION:** Diabetes mellitus, cancer, and alcohol use disorder were independent risk factors associated with K. pneumonia bacteremia. Patients with advanced age had a higher mortality rate.

Keywords
Klebsiella pneumonia, bacteremia, mortality

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INTRODUCTION

Bloodstream infections are one of the leading causes of morbidity and mortality worldwide.[1] These infections are linked to a greater risk of hospitalization, increased healthcare costs, and mortality.[2-3] *K. pneumonia* bacteremia ranks second to *Escherichia Coli (E. coli)* as the common cause of gram-negative bloodstream infection globally .[4-5]

The burden of *K. pneumonia* bacteremia is well documented in many countries, with population-based incidence ranging from 7.8 to 11.6 per 100,000 person-years.[6] The United States National Nosocomial Infection Surveillance (NNIS) System reported that 18% of gram-negative bacteremia and 4.2% of all bacteremia in 2003 were caused by *K. pneumoniae*.[7] In Asia, *K. pneumonia* is an important pathogen causing pneumonia, urinary tract infections, intra-abdominal infections, primary bacteremia, and invasive syndromes. A worldwide collaborative study across different continents showed that the clinical patterns and sources of *K. pneumonia* bacteremia were geographically distinctive, possibly due to interactions between bacterial and host variables, socio-economic factors, and racial genetic susceptibility.[8]

A retrospective analysis of *K. pneumonia* bacteremia in Canada showed that 70% were nosocomial and healthcare -associated, while 30% were community-acquired.[4] Risk factors for acquiring *K. pneumonia* bacteremia and hospital mortality include elderly gentlemen, patients undergoing

dialysis, solid organ transplantation, and those with chronic liver disorders or malignancy.[4] Compared to community-acquired infections, hospital-acquired *K. pneumonia* bacteremia was associated with more serious manifestations of the illness, including septic shock, respiratory failure, and mortality.[9]

The emergence of hypervirulent strains has widened the group of people susceptible to these infections, encompassing both immunocompetent and immunocompromised hosts. In countries outside of Asia, reports of invasive *K. pneumonia* liver abscesses are on the rise.[10-12] There have been numerous reports describing extrahepatic metastatic complications caused by bacterial dissemination, including endophthalmitis, meningitis, and necrotizing fasciitis.[13-16] The emergence of multi-resistant ESBL-producing *K. pneumonia* and Carbapenem hydrolyzing beta-lactamase strains tremendously impacts antimicrobial agent choice, healthcare costs and clinical outcomes.[16]

Despite being a major health concern, relatively scarce literature has been published on *K. pneumonia* bacteremia in Malaysia. Consequently, we conducted a single-center study to assess clinical characteristics, risk factors, and outcomes of *K. pneumonia* bacteremia in Malaysian adults.

MATERIALS AND METHODS

Study Design and Patient Selection

We conducted a retrospective observational study at Sultan Ismail Hospital, a public tertiary hospital in the southern state of Peninsular Malaysia. Study subjects were patients aged 18 years and older admitted from 1st January to 31st December 2016 and had *K. pneumonia* bacteremia. An ethics approval was obtained from the Medical Research and Ethics Committee (NMRR-18-2446-42720) and the local hospital authority. The WHONET programme database was reviewed for positive blood cultures from 1stJanuary to 31stDecember 2016. The demographic data, medical co-morbidities, source of infection, type of acquisition, and clinical outcomes were reviewed and extracted from electronic medical records.

Definitions

A bacteremia *K. pneumonia* infection was established based on isolation from one or more blood culture specimens. Infections were defined as the first new detection of *K. pneumonia* from the blood; subsequent isolations within 365 days after the first isolation were considered the same infection. *K. pneumonia* bacteremia was further sub-categorized into community-acquired (CA), healthcare-associated (HCA) and nosocomial infections. Positive cultures obtained within 48 hours of hospital admission or 48 hours after discharge from the hospital constitutes community-acquired infections. Bloodstream infections acquired after 48 hours of hospital admission are referred to as nosocomial bloodstream infections.

Patients with healthcare-associated infections included those who attended the emergency department or hospital clinic within the previous 5 to 30 days before acquiring bloodstream infection and were admitted to the hospital for two or more days within the last 90 days before a positive culture. Clinical history, imaging evidence, and blood culture criteria were used to determine the source of the infection. It was assumed that the culture was aseptically obtained unless otherwise contaminated.

Bacteriology

Blood culture bottles were processed with BACTEC 9240 Automated Blood Culture System (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). Disk diffusion method was used to determine the antimicrobial susceptibility, in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines.[17]

Data Collection and Analysis

We analyzed the data using Statistical Package for Social Sciences (SPSS) for Windows, Version 18. A mean and standard deviation were used to express normally distributed data, whereas a relative frequency and percentage were used to express categorical data. The median with interquartile range (IQR) of non-normally distributed variables was calculated. A Chi-squared test or Fisher's Exact Test was used for categorical data. Logistic

regression was used to identify risk factors influencing *K. pneumonia* acquisition and mortality. A univariate analysis with a significant level of 0.25 was initially used to determine suitable factors to be included in the multiple logistic regressions. Afterwards a multiple logistic regression with enter method was used to determine the risk factors for both *K. pneumonia* infection and its mortality. Gender, cancer, alcohol use disorder, kidney disease and hypertension were included in the multiple logistic regressions for risk factors of K. *pneumonia* infection whereas age, gender, race, cancer, stroke and kidney disease was included in a multiple logistic regression for risk of *K. pneumonia* infection mortality. Although diabetes mellitus does not meet the criteria, it was included in the analysis as it is a well-known risk for K. *pneumonia* infection. A p-value of <0.05 was considered statistically significant.

RESULTS

Study Population and Clinical Characteristics

A total of 5,714 blood culture samples were collected from 24,143 adult admissions over a-year period of which 1,124 (19.7%) were positive cultures. As shown in figure 1, 825 blood culture samples met eligibility criteria; 299 samples were excluded as clinically insignificant or contaminated.

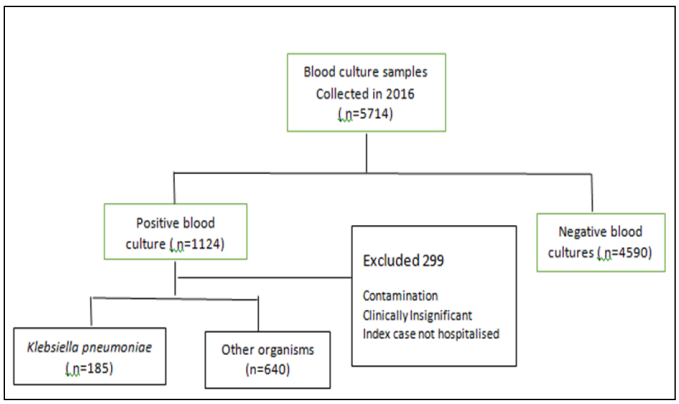

Figure 1: Blood Cultures Collected in 2016

Gram-negative bacteremia accounted for 69.2% of positive blood cultures in our cohort. As shown in figure 2, *K. pneumonia* was the most prevalent pathogen (n=185, 22.4%), followed by *E.coli* (n=179, 21.7%) and Staphylococcus aureus (n=153, 18.4%).

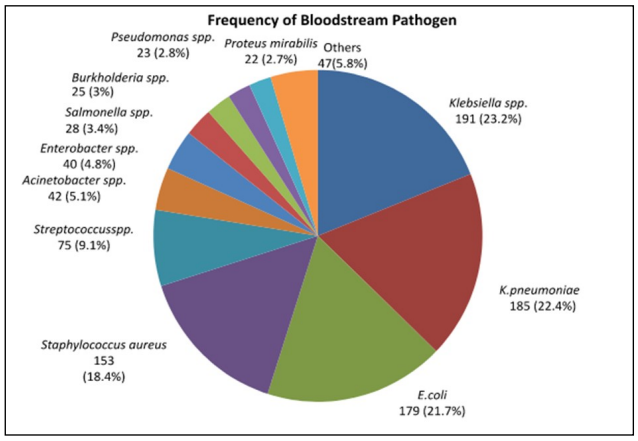

Figure 2: Frequency of Bloodstream Pathogens

Table I summarizes the demographics and clinical characteristics of K. pneumonia bacteremia. Overall, 185 patients with K. pneumonia bacteremia were included for analysis 79 (42.7%), 65 (35.1%), and 41 (22.1%) presented with nosocomial infections, HCA and CA, respectively. This study had a 56.8% male predominance, with a mean age of 54.9 (SD±15.4) years. More than half of the population was Malay (n=120, 64.9%), followed by Chinese (n=35, 18.9%) and Indian (n=21, 11.4%). Sources of infection identified were primary bloodstream infections (n=75, 40.5%), pneumonia (n=44, 23.8%), urinary tract infections (n=28, 15.1%) and liver abscesses (n=16, 8.6%). Diabetes mellitus (n=95, 51.4%) was the commonest medical co-morbidity identified, followed by hypertension (n=53, 28.6%), cancer (n=45, 24.3%), and chronic kidney disease and end-stage renal disease (n=25, 13.5%).

Table II shows the co-morbidities and sources of infection among CA, HCA, and nosocomial infection patients. Primary bacteremia was observed predominantly in nosocomial acquired infections (57%). Conversely, community-acquired infections caused significantly more urinary tract infections and liver abscesses. Infections acquired in hospitals were common among cancer patients and kidney diseases patients.

Analysis of logistic regression indicated that diabetes mellitus (AOR 1.46, 95% CI 1.02-2.08), cancer (AOR 2.02, 95% CI 1.33-3.05) and alcohol use disorder (AOR 7.73, 95% CI 1.38-43.21) as independent risk factors for K. pneumonia bacteremia, as illustrated in Table III.

Table I: Demographic and Clinical Characteristics of *K. pneumonia* Bacteremia Infection

Variables	Frequency and Percentage (n=185)
Age (years)	54.9±15.42
Gender	105(56.8%)
Male	80(43.2%)
Female	
Race	
Malay	120(64.9%)
Chinese	35(18.9%)
Indian	21(11.4%)
Others	9(4.9%)
Acquisition	65(35.1%)
Community	41(22.1%)
Healthcare	79(42.7%)
Nosocomial	
Comorbidities	95(51.4%)
Diabetes Mellitus	53(28.6%)
Hypertension Cancer	45(24.3%)
Kidney Disease (CKD and ESRD)	25(13.5%)
Heart Disease	23(12.4%)
Alcohol Use Disorder	4(2.1%)
Others	44(25.9%)
Source of Infection	
Primary Bloodstream Infection	75(40.5%)
Pneumonia	44(23.8%)
Urinary Tract Infection	28(15.1%)
Liver Abscess	12(6.5%)
Skin and Soft Tissue Infection	8(4.3%)
Others	18(9.8%)

CKD: Chronic kidney disease
ESRD: End-stage renal disease

Table II: Relationship between co-morbidities, source of infection & method of acquisition

Variable	Method of Acquisition			P-value
	Health-Acquired n=41	Nosocomial-Acquired n=79	Community-Acquired n=65	
Co-morbidities				
Diabetes Mellitus	24(58.5%)	33(41.8%)	38(58.5%)	
Cancer	18(43.9%)	18(22.8%)	9(13.8%)	0.002
Hypertension	16(39.0%)	18(22.8%)	19(29.2%)	0.174
Heart Disease	8(19.5%)	8(10.1%)	7(10.8%)	0.295
Kidney Disease	8(19.5%)	14(17.7%)	3(4.6%)	0.032
Chronic Liver Disease	0(0.0%)	3(3.8%)	3(4.6%)	
Stroke	4(9.8%)	5(6.3%)	7(10.8%)	0.615
Chronic Obstructive Pulmonary Disease	1(2.4%)	1(1.3%)	2(3.1%)	0.826
Systemic Lupus Erythematosus	1(2.4%)	1(1.3%)	1(1.5%)	0.222*
Rheumatoid Arthritis	1(2.4%)	0(0.0%)	0(0.0%)	1.000
Alcohol Use Disorder	1(2.4%)	2(2.5%)	1(1.5%)	1.000
Hepatitis B	1(2.4%)	0(0.0%)	1(1.5%)	0.327
Hepatitis C	0(0.0%)	3(3.8%)	0(0.0%)	0.242
Source of Infection				
Bloodstream	14(34.1%)	45(57.0%)	16(24.6%)	<0.00
Pneumonia	11(26.8%)	20(25.3%)	13(20.0%)	0.662
Urinary Tract	11(26.8%)	6(7.6%)	11(16.9%)	0.018
Skin and Soft Tissue	2(4.9%)	3(3.8%)	3(4.6%)	1.000
Biliary Tract	1(2.4%)	0(0.0%)	3(4.6%)	0.155
Liver Abscess	2(4.9%)	0(0.0%)	10(15.4%)	0.001
Pancreas	0(0.0%)	0(0.0%)	1(1.5%)	0.573
Intra-abdominal Sepsis	0(0.0%)	3(3.8%)	2(3.1%)	0.723
Gastro-intestinal Tract	0(0.0%)	0(0.0%)	3(4.6%)	0.052
Reproductive	0(0.0%)	0(0.0%)	1(1.5%)	0.573
Bone and Joint	0(0.0%)	2(2.5%)	2(3.1%)	0.684

**Fisher's Exact Test*

The study found Extended-Spectrum β-Lactamase (ESBL) producing and Carbapenem-resistant K. pneumonia is attributed to 37.3% and 1.1% of cases, respectively. Most ESBL K. pneumonia bacteremia were nosocomial in origin (71.0%, n=49), followed by healthcare-related (26.1%, n=18) and community acquired (2.9%, n=2) (p<0.001). The case fatality rate for K. pneumonia bacteremia was higher than other bacteremia (46.5% versus 37%) (p=0.02). ESBL-producing K. pneumonia bacteremia carried a higher mortality rate of 50.7% compared to 44.7% in Non-ESBL K. pneumonia bacteremia, although it was not statistically significant. Older patients have an odd of 1.03 for in-hospital mortality (p=0.003). The mean age of mortality was 58.3±13.60 years old.

DISCUSSION

The incidence of bloodstream infection is comparable to the magnitude of acute myocardial infarction, stroke, and major trauma.[2] Gram-negative bacilli cause approximately a quarter to a half of all bloodstream infections and are a predominant culprit of septic shock amongst critically ill patients.[18] The epidemiology and microbiology of bloodstream infections are changing with a shift in population demographics, healthcare delivery models, and medical advances, such as increased utilization of immunosuppressive agents and intravascular devices.[19] A study conducted two decades ago in Kuala Lumpur reported that 56.7% of the blood cultures were gram-positive, and 38.4% were gram-negative.[20] In contrast, 69.2% of bloodstream infections were from gram-negative organisms in our cohort. *K. pneumonia* and *E. coli* were the predominant pathogens.

Table III: Risk Factors for *K. pneumonia* Bacteremia

Variables	Crude OR	P-value	Adjusted OR	P-value
Cancer	1.99 (1.33-3.00)	0.001	2.02 (1.33-3.05)	0.001
Diabetes Mellitus	1.12 (0.81-1.56)	0.485	1.46 (1.02-2.08)	0.038
Alcohol Use Disorder	7.05 (1.28-38.80)	0.025	7.73 (1.38-43.21)	0.020
Hypertension	0.63 (0.44-0.90)	0.011	0.59 (0.40-0.86)	0.006

Table IV: Risk Factors for Mortality in *K. pneumonia* Bacteremia

Variables	Crude OR	P-value	Adjusted OR	P-value
Age	1.03 (1.01-1.05)	0.006	1.03 (1.01-1.05)	0.003
Cancer	0.49 (0.24 –1.00)	0.044	0.43 (0.21-0.88)	0.022

K. pneumonia is a highly resilient bacterium that readily colonizes human mucosal surfaces, such as the skin, digestive tract, and oropharynx. Subsequently, the organism gains entry to other tissues and causes localized or disseminated infections in the hosts. A study by Ling et al. in Singapore found that the Chinese population had a high colonization rate of 66.0% compared to Malay (14.3%), Indian (7.9%), and other nationals (11.8%).[21] *K. pneumonia* has long been regarded as an opportunistic pathogen that causes infections in hospitalized or immunocompromised hosts. In recent years, Asia has witnessed an increase in community-acquired infections.[8,22] Numerous established virulence factors, including capsular serotype, hypermucoviscosity phenotype, lipopolysaccharides, siderophores, and pili, have potentiated *K. pneumonia* pathogenicity.[23] Furthermore, hypervirulent strains resist phagocytosis and intracellular killing by neutrophils and bactericidal complements.[23] *K. pneumonia* can overcome mechanical barriers and invade the host's humoral and adaptive immune system.

Nosocomial and healthcare-associated *K. pneumonia* bacteremia was 64.9% (n=120) compared to community-acquired bacteremia, 35.1% (n=65), in agreement with a retrospective study conducted in Canada (70% versus 30%).[4] Primary *K. pneumonia* bacteremia contributed to 40.5% (n=75) of total cases, with a higher prevalence in nosocomial acquired infections (57% versus 24.6%). A source of infection was identified in the remaining 59.5% of cases (n=110). Pneumonia (23.8%, n=44), urinary tract infection (15.1%, n=28) and liver abscesses (8.6%, n=16) were the common sources of infections. The growing evidence suggests that bacteremia *K. pneumonia* liver abscesses are almost exclusively associated with community-acquired infections.[24-25] Cancer, diabetes mellitus, and alcohol use were independent risk factors. There were studies reported that neoplastic diseases were common in patients with nosocomial bacteremia.[4,9] Invasive procedures, chemotherapy, and antibiotics therapy are common in patients with malignancy, predisposing them to serious infections. Abnormal phagocytic function and other immune deficits resulting from neutropenia increase their susceptibility to infections.[26] Patients with cancers are ten times more at risk for acquiring sepsis than the general population and have a two-fold risk of dying from sepsis.[27]

Large population-based studies in western countries have reported a 2-4 times higher risk of infection in diabetes mellitus.[28] Numerous studies have suggested that diabetes mellitus is associated with higher Klebsiella infections.[8,29] Several aspects of immunity are altered in patients with diabetes, including neutrophil dysfunction, depression of the antioxidant system,and humoral immunity.[30] More than half of our subjects had underlying diabetes mellitus (51.4%, n=95), comparatively higher than the reported prevalence of 34–36% of cases of *K. pneumonia* bacteremia in other studies in Asia, reflecting a higher prevalence of diabetes in Malaysia.[2-3,31]

Excessive alcohol consumption affects pro-inflammatory cytokine production and generates reactive oxygen species, leading to multiorgan dysfunctions. It is well known that alcohol perturbs the normal intestinal microbiota (alcohol–mediated dysbiosis) and increases intestinal permeability and bacterial translocation, thus making the host more susceptible to infection.[32] Alcohol use disorders have historically been linked to community-acquired *K. pneumonia* pneumonia and poorer clinical outcomes. A study found that patients with alcohol use disorders who contracted bacteremia *K. pneumonia* pneumonia (BKPP) experienced almost double the mortality rate of alcohol use disorders patients infected with other pathogens.[33] Considering that less than 5% of our cohort had alcohol use, no conclusion could be drawn regarding alcohol-related mortality.

K. pneumonia has become increasingly important as an invasive pathogen with broad antimicrobial resistance, especially in strains that produce Extended-spectrum β-lactamase (ESBL).[34] A systematic review of bloodstream infections (BSIs) due to ESBL Enterobacteriaceae demonstrates an increased risk of attributable mortality

and extended length of hospital stay even after adjustment for inappropriate empirical therapy.[35] A study in 1999 of 570 clinical isolates from medical centers in Malaysia and Singapore showed a prevalence of ESBL-producing *K. pneumonia* at between 36.7% and 38%.[36] In our study, ESBL-producing *K. pneumonia* accounted for 37.3% of total *K. pneumonia* bacteremia. The likelihood of acquiring ESBL. *Pneumonia* bacteremia is twice higher nosocomial infections than community-acquired infections (62%, n=49 versus 3.1%, n=2) ($p<0.001$). ESBL colonization and infections were associated with prior antibiotic treatment, prolonged hospitalization, prolonged ICU stay, mechanical ventilation, increased instrumentation, and catheter placement.[37]

The reported crude mortalities in *K. pneumonia* bacteremia ranged from 22.8% to 55.3%.[5,38-40] Overall, our cohort's hospital mortality rate of 46.5% was considerably higher than the 20-26% quoted in Singapore and Taiwan.[38,40] ESBL-producing *K. pneumonia* bacteremia had a higher mortality rate than its counterpart of Non-ESBL *K. pneumonia* bacteremia. The major risk factor for in-hospital mortality in our study was advanced age. One study found that advanced age was strongly associated with a greater risk of sepsis and adverse clinical outcomes.[42] The elderly were susceptible to various serious infections due to impaired physiology, substantial changes in immune responses, and multiple co-morbidities. There are age-related functional impairments in cell-mediated immunity and humoral immune responses, often termed immunosenescence.[43] Among the common age-related comorbidities that increase the risk of infection are diabetes mellitus, chronic kidney disease, heart failure, chronic obstructive pulmonary disease, and stroke. Presence of sepsis shock, intensive care unit admission, kidney failure, meropenem resistance, invasive instruments usage, and pneumonia was associated with higher mortality in nosocomial *K. pneumonia* bacteraemia.[44] It is interesting to find from our sample that patients with hypertension were at less risk of getting *K. pneumonia* infection. As this result was unexpected, and since this study was done retrospectively, this could have occurred by chance.

LIMITATION

This retrospective observational study was subject to a few potential confounding factors. The number of primary bacteremia may be overestimated as this is a retrospective analysis. The source of infection and other potential risk factors for acquisition were not assessed clinically at study time. There are some limitations on the completeness of electronic medical records, particularly relating to risk factors and sources of infections. Our study did not evaluate the Pitt bacteremia score, virulence factors, antimicrobial sensitivity, and appropriateness of antimicrobial therapy, which could contribute significantly to patients' outcomes. Further studies are required to elucidate factors contributing to higher mortality in our cohort.

CONCLUSION

K. pneumonia bacteremia represents a serious public health concern and burden. Primary bloodstream infection, pneumonia, and urinary tract infection accounted for most cases of *K. pneumonia* bacteremia. Diabetes mellitus, cancer, and alcohol use disorders were major risk factors, while advanced age strongly predicts in-hospital mortality. Multidrug-resistant *K. pneumonia* bacteremia is a growing health threat. A better understanding of the epidemiology and microbiology of the *K. pneumonia* organism is crucial to developing effective strategies to improve patient outcomes.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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