ORIGINAL ARTICLE

Risk factors for complications and survival outcomes of *Klebsiella pneumoniae* Bacteraemia in Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia

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ABSTRACT

Introduction: Mortality of *Klebsiella pneumoniae* (*K. pneumoniae*) bacteraemia was reported to be on the rise globally. The 30-day mortality rate of *K. pneumoniae* bacteraemia ranges from 16% to 55% in Beijing, Shanghai, and Taiwan. However, there is a lack of research on the survival outcomes of *K. pneumoniae* bacteraemia in Malaysia. The objectives of this study were to determine the poor prognostic factors and predictors of 14-day in-hospital mortality from *K. pneumoniae* bacteraemia.

Methods: This was a retrospective cohort study of patients with *K. pneumoniae* bacteraemia in Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia (HCTM). We included adult patients with blood cultures positive for *K. pneumoniae* between 1 January 2016 and 31 December 2019. Those with polymicrobial bacteraemia were excluded. Medical records were reviewed to obtain the socio-demographic data, gender, underlying comorbidities, invasive procedures at presentation, sources of bacteraemia, and whether appropriate empirical and definitive antibiotics was given on time. Data regarding complications of *K. pneumoniae* bacteraemia, including liver abscess, endopthalmitis, septic shock, Quick Pitt (qPitt) bacteraemia score defined as hypothermia, hypotension, respiratory failure, cardiac arrest, and altered mental status and stay in intensive care unit (ICU) were also recorded. The main outcome measure used was the survival in 14 days. Summary of statistical analysis was done.

Results: A total of 260 patients with *K. pneumoniae* bacteraemia were included. All patients received appropriate empirical and definitive antibiotics within 24 h of the time that the sample for index blood cultures was obtained. Respiratory infection, septic shock, qPitt bacteraemia score ≥2, solid organ malignancy, stay in ICU, central venous line insertion at presentation, urinary catheterisation at presentation, and in-patient mechanical ventilation were identified as independent predictors of mortality in *K. pneumoniae* bacteraemia. The rate of complications such as liver abscess, endophthalmitis, ICU admission, and septic shock was not significantly different between survivors and non-survivors. The 14-day in-hospital mortality rate was 12.3%. The median length of hospitalisation was 11 days (IQR 6 - 19) . The predictors of poor prognosis for 14 days in-hospital mortality for *K. pneumoniae* bacteraemia were as follows: qPitt bacteraemia score ≥2, central venous line insertion, indwelling urinary catheter at presentation, and in-patient mechanical ventilation. Timing from *K. pneumoniae* bacteraemia event to death among those qPitt bacteraemia scores ≥2 was only for 9 days or less.

Conclusions: The 14-day in-hospital mortality of patients with *K. pneumoniae* bacteraemia in our setting was low. The qPitt bacteraemia score ≥2 was the strongest predictor of poor prognosis for 14-day in-hospital mortality in patients with *K. pneumoniae* bacteraemia. The qPitt bacteraemia score should be proposed to be used as a bedside screening tool for gram negative bacteraemia in our daily clinical practice, which is also useful for predicting mortality in critically ill patients.

KEYWORDS:
risk factors, hospital mortality, Klebsiella pneumoniae bacteraemia

INTRODUCTION

Gram-negative bacteraemia is a common cause of morbidity and mortality worldwide. *K. pneumoniae* was the second commonest gram-negative pathogen after *Escherichia coli*.[1] In the United States, *K. pneumoniae* causes hospital-acquired urinary tract infection, septicaemia, pneumonia, and soft tissue infection.[2] This was of great concern due to increasing antimicrobial resistance globally seen with *K. pneumoniae*. Mortality of *K. pneumoniae* bacteraemia has increased due to multifactorial reasons such as underlying comorbidities, inappropriate empirical antibiotics treatment, and invasive procedures prior to bacteraemia.[3] Delay in initiation of effective antibiotics therapy for more than 48 hours after diagnosis of *K. pneumoniae* bacteraemia was associated with more than 1.5- to 2-fold increase in morbidity and mortality risk.[4]

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Several studies that focused on *K. pneumoniae* bacteraemia found a high mortality rate in China and Europe.[5,6] However, similar large research in our geographical area was still missing. Most reports analysed the molecular epidemiological aspects of hypervirulent *K. pneumoniae*, or focused on the special group such as Extended Spectrum Beta-Lactamase (ESBL) K. pneumoniae of the isolates.[7-9] Less attention has been focused on the predictors of mortality caused by K. pneumoniae. The objectives of this study were to determine the poor prognostic factors and predictors of 14-day in-hospital mortality from *K. pneumoniae* bacteraemia.

MATERIALS AND METHODS

A retrospective, cohort study was conducted at Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia (HCTM), which is a 1084-bed teaching hospital located in an urban setting. The study period was from 1 January 2016 to 31 December 2019. All patient aged over 13 years, who developed monomicrobial blood culture positive for *K. pneumoniae* during the study period were included. Relevant data were retrieved from patients' medical records and electronic microbiologic database. Patient demographics, gender, underlying comorbidities, invasive procedures at presentation, and sources of bacteraemia were collected. The severity of illness was calculated by qPitt bacteraemia score. The main outcome measure used was the 14-day in-hospital mortality rate.

K. pneumoniae bacteraemia was defined as an infection confirmed by blood culture positive for *K. pneumoniae*. Patients with further positive blood cultures taken within 14 days from the first specimen and positive for the same organism were considered the same episode of bacteraemia. However, it was considered as a non-related, independent episode, if more than one episode occurred within more than a 2-week interval in the same patient who had been properly treated and clinically cured. Bacteraemia was classified as primary when the patient had a positive *K. pneumoniae* cultured from one or more blood cultures, and the organism cultured from blood was not related to an infection at another site.[10] Bacteraemia was considered secondary when the patient had a positive *K. pneumoniae* cultured from one or more blood cultures and the organism cultured from blood was related to an infection at another site.[10]

Appropriateness of empirical therapy was defined as therapy (with at least one agent, if more than one agent was used), given within 24h of time that the sample for index culture was obtained, to which the isolate was found to be susceptible on the final antimicrobial susceptibility report and the doses used were appropriate for the end organs function of the patients.[11] Appropriate definitive antimicrobial therapy was defined as therapy given after antimicrobial susceptibility was reported, which ranged from 2-4 days from onset of bacteraemia, and the treatment administered was susceptible to the *K. pneumoniae* strain.[11] Liver abscess was defined by the coexistence of blood culture positive for *K. pneumoniae* and evidence of an intrahepatic abscess cavity by ultrasonography or computed tomography.[12] Endophthalmitis was defined as decreased visual acuity, pain, hypopyon, or severe anterior uveitis in a patient with concurrent *K. pneumoniae* bacteraemia.[12]

Survivors were defined as those who survive beyond 14-day in-hospital setting. Non-survivors were defined as those who passed away within 14-day in-hospital. Septic shock was defined as sepsis associated with evidence of organ hypoperfusion and either a systolic blood pressure of <90 or 30mmHg less than the baseline value or a requirement for the use of vasopressor to maintain blood pressure.[13] The severity of bacteraemia was calculated using the qPitt bacteraemia score, each of the following contributes to 1 point: evidence of hypothermia (temperature<36°c), hypotension (systolic BP<90mmHg or vasopressor use), respiratory failure (respiratory rate ≥25 breaths per min or need for mechanical ventilation), cardiac arrest, and altered mental status.[12] A qPitt bacteraemia score ≥2 was associated with higher mortality risks.[12]

Community-acquired infection was defined as a gram-negative bacteraemia detected within 48 hours of hospital admission, and the patient had not received healthcare in either the community or hospital in the previous 28 days.[14] Hospital-acquired infection was defined as infection that occurred more than 48 hours after hospital admission.[14]

Data analysis was carried out on Statistical Package for Social Science (SPSS) software version 23. At 95% confidence interval (95%CI), $p<0.05$ was considered to be significant. Categorical variables were expressed as frequency and percentage (%), and general associations between categorical variables were examined using Chi-square test. Finally, Kaplan–Meier analysis was used to estimate the survival function (hazard ratio, HR) of *K. pneumoniae* bacteraemia at a respective time interval. Hazard ratio is defined as the hazard rate comparing the rate of event in one group versus the other over time. Multivariate cox regression analysis was then used to determine predictors of 14-day in-hospital mortality from *K. pneumoniae* bacteraemia.

RESULTS

A total of 260 *K. pneumoniae* bacteraemia cases were extracted from our database. Out of 260 cases, there were 229 patients with 1 episode, 11 patients with 2 episodes, and 3 patients with 3 episodes of *K. pneumoniae* bacteraemia. All 260 cases were included in the study. There were a total of 139 males and 121 females in the study. The mean age of the patients who died was 68 while the mean age of those who survived was 64. There were a total of 131 Malay patients (50.4%), 101 Chinese patients (38.8%), 25 Indian patients (9.6%), and 3 foreigners (1.2%) in the study. There were a total of 46 patients with primary bacteraemia while there were 221 patients with a secondary source of bacteraemia (Table I).

There was no significant difference in survival outcomes between males and females. There was no significant difference in mortality among patients who had diabetes (p=0.073) or hypertension (p=0.421) compared to those without. Likewise, there were no significant differences between patients who survived or died for the following comorbidities ischaemic heart disease (p=0.631), end stage renal failure (p=0.481), liver cirrhosis (p=0.685), chronic lung disease (p=0.764), haematological disease (p=0.596), and immunodeficiency (p=0.097). Patients who had organ

Table I: Comparison of clinical characteristics and survival outcomes of K. pneumoniae bacteraemia

Characteristics	Total (n=260) n (%)	Death (n=32) n (%)	Alive (n=228) n (%)	p value
Demographic data				
Age, years (mean)		68 (SD 12)	64 (SD 15)	
Gender				
Male	139 (53.5)	19 (59.4)	120 (52.6)	0.474
Female	121 (46.5)	13 (40.6)	108 (47.4)	
Ethnicity				
Malay	131 (50.4)	15 (46.9)	116 (50.8)	
Chinese	101 (38.8)	12 (37.5)	89 (39)	0.454
Indian	25 (9.6)	4 (12.5)	21 (9.3)	
Foreigner	3 (1.2)	1 (3.1)	2 (0.9)	
Underlying disease				
Diabetic mellitus	144 (55.4)	13 (40.6)	131 (57.5)	0.073
Hypertension	163 (62.7)	18 (56.3)	145 (63.6)	0.421
Ischaemic heart disease	72 (27.7)	10 (31.3)	62 (27.2)	0.631
End stage renal failure	30 (11.5)	2 (6.3)	28 (12.3)	0.481
Liver cirrhosis	9 (3.5)	2 (6.3)	7 (3.1)	0.685
Chronic lung disease	6 (2.3)	0 (0.0)	6 (2.6)	0.764
Solid organ malignancy	45 (17.3)	12 (37.5)	33 (14.5)	0.001
Haematology malignancy	8 (3.1)	0 (0.0)	8 (3.5)	0.596
Immunodeficiency	24 (9.2)	6 (18.8)	18 (7.9)	0.097
Complications				
Liver abscess	29 (11.2)	1 (3.1)	28 (12.3)	0.123
Endophthalmitis	1 (0.4)	0 (0.0)	1 (0.4)	0.707
Septic shock	52 (20.0)	20 (62.5)	32 (14.0)	<0.001
QPitt bacteraemia score ≥2 high	40 (15.4)	27 (84.4)	13 (5.7)	<0.001
Stay in ICU	17 (6.5)	10 (31.3)	7 (3.1)	<0.001
Invasive procedures				
Central venous line	28 (10.8)	8 (25.0)	20 (8.8)	0.014
Urinary catheterisation	49 (18.8)	15 (46.9)	34 (14.9)	<0.001
Mechanical ventilation	13 (5.0)	10 (31.3)	3 (1.3)	<0.001
Surgical intervention	54 (20.8)	6 (18.8)	48 (21.1)	0.764
Source of bacteraemia				
Primary	46 (17.7)	9 (28.1)	37 (16.2)	0.099
Secondary				
Respiratory tract infection	64 (24.6)	16 (50.0)	48 (21.1)	<0.001
Urinary tract infection	53 (20.4)	3 (9.4)	50 (22.0)	0.099
Intra-abdominal infection	67 (25.8)	5 (15.6)	62 (27.2)	0.161
Skin infection	18 (6.9)	0 (0.0)	18 (7.9)	0.099
Catheter-related bloodstream infection	19 (7.3)	0 (0.0)	19 (8.3)	0.09
Antibiotics				
Amoxicillin–clavulanate	174 (66.9)			
Cefuroxime	49 (18.8)			
Piperacillin–tazobactam	22 (8.5)			
Ceftriaxone	15 (5.8)			
Time from admission to positive blood culture				
48hours or less, community-acquired infection	255 (98)	32 (100)	223 (98)	
more than 48 hours, hospital-acquired infection	5 (2)	0 (0.0)	5 (2)	
Duration of antibiotics use, days		14 (SD 19)	16 (SD 21)	
Time of first antibiotic administration	24 hours			

*QPitt: quick Pitt, ICU: intensive care unit

Table II: 14-day in-hospital mortality predictors of K. pneumoniae bacteraemia

	Crude			Adjusted		
	HR*	95% CI	p value	HR	95% CI	p value
Respiratory tract infection	3.38	1.49–7.66	0.004	1.63	0.60–4.41	0.334
Septic shock	7.78	3.30–18.35	<0.001	0.65	0.23–1.79	0.399
QPitt bacteraemia score ≥2	45.48	13.50–153.25	<0.001	37.5	10.78–130.38	<0.001
Solid organ malignancy	1.66	0.65–4.21	0.286	2.2	0.72–6.75	0.166
Stay in ICU	5.53	2.18–14.04	<0.001	3.55	0.60–21.00	0.163
Central venous line	1.67	0.57–4.90	0.354	5.62	1.18–26.76	0.03
Urinary catheterisation	4.84	2.13–10.99	<0.001	3.38	1.10–10.44	0.034
Mechanical ventilation	11.38	4.67–27.76	<0.001	5.98	1.26–28.29	0.024

*HR: Hazard ratio, defined as the hazard rate of event in one group versus the other over time

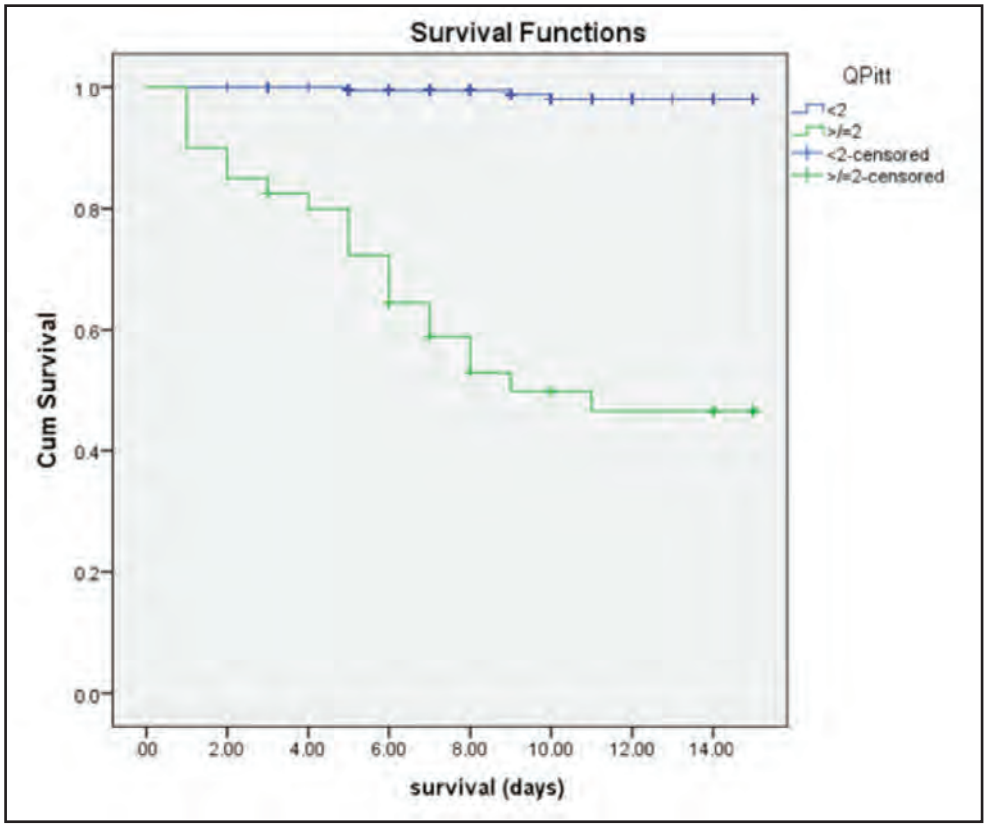

Fig. 1: Kaplan–Meier survival curve of *K. pneumoniae* bacteraemia in QPitt bacteraemia scores ≥2

QPitt bacteraemia scores	Median time effect (death, days)	95% CI	Log Rank test (df)	*p value*
<2	No event			
≥2	9	5.72–12.28	112.9	<0.001

malignancy were likelier to die than those who did not (p=0.001) (Table I).

K. pneumoniae bacteraemia was associated with the respiratory source of infection (p<0.001). Primary bacteraemia, urinary tract infection, intra-abdominal infection, skin infection, and catheter-related bloodstream infection did not show a significant difference in mortality. There were no significant differences in liver abscess and endophthalmitis between survivors and non-survivors, p=0.123 and p=0.707, respectively. Septic shock, ICU stay, and a raised qPitt bacteraemia score ≥2 were associated with significantly higher mortality rate, respectively (p<0.001). There were 52 patients had septic shock but only 17 (32%) patients were admitted to ICU. Furthermore, 61% (32/52) of patients with septic shock survived (Table 1).

Table I illustrated patients who had invasive procedures like CVL insertion (p=0.014), urinary catheter insertion (p<0.001), and mechanical ventilation (p<0.001) had significantly higher mortality rates. None of the cases received inappropriate empirical or definitive antibiotic therapy. The 14-day in-hospital mortality was 12.3% (32/260).

Amoxicillin–clavulanate was the most commonly used empirical agent (66.9%, 174/260) and 18.8% (49/260) of cases that received cefuroxime. Piperacillin–tazobactam was used in 8.5% (22/260) of patients. Ceftriaxone was administered to 5.8% (15/260). There were a total of 255 patients with community-acquired infection (98%) while there were 5 patients with hospital-acquired infection (2%). The median duration of antibiotics for those alive was 16 days while the median duration of antibiotic for those dead was 14 days. All patients received antibiotics within 24 hours on admission or blood culture being taken (Table I).

Figure 1 illustrated the median overall survival for patients with high qPitt bacteraemia score ≥2 is 9 days (95%CI: 5.72, 12.28).

Table II illustrates that the most significant predictors related to 14-day in-hospital mortality was qPitt bacteraemia score with Hazard Ratio, HR=37.50 (95%CI: 10.78, 130.38). This is followed by mechanical ventilation (HR 5.98, 95%CI: 1.26, 28.29), central venous line insertion (HR 5.62, 95%CI: 1.18, 26.76), and indwelling urinary catheter (HR 3.38, 95%CI: 1.10, 10.44).

DISCUSSION

This study shows a low mortality rate of 12.3% in HCTM compared to other regional centres that range from 16% to 55% in Beijing, Shanghai, and Taiwan.[3,15,16] The difference in mortality rates across the different studies is most likely due to the differences in the population studied. The mortality rate in Beijing was 16% which is closest to our study. The mortality rate in Shanghai was high at 25%, and this is most likely due to inappropriate use of empirical antibiotics in as high as 77% of patients. The mortality rate in Taiwan was 55%, and this reflects their study population with a higher mean age of 73 and almost 50% of patients have chronic lung disease.

The most common sources of infections in the present cohort were respiratory infection, intra-abdominal infection, and urinary tract infection, similar to previously identified sources of *K. pneumoniae* bacteraemia.[17] Intra-abdominal infections in our study comprised gastrointestinal sepsis, hepatobiliary sepsis, cholangitis, cholecystitis, peritonitis or spontaneous bacterial peritonitis, and intra-abdominal abscesses (excluding liver abscess). In view of this, imaging should be considered accordingly.

In this study, 61% of patients with septic shock survived in non-ICU setting. Only a small percentage of patient gained access to ICU. This was because all patients received timely and appropriate empirical and definite antibiotics like amoxicillin–clavulanate, ceftriaxone, and cefuroxime following the local national antimicrobial guideline, and this potentially contributed to the lower mortality rates. A large number of studies found that septic shock and ICU admission were independent risk factors for mortality in patients with *K. pneumoniae* bacteraemia, and inappropriate antibiotics led to increased mortality.[18,19] Thus, the administration of appropriate antibiotic treatment can improve patient survival outcomes.

Battle et al.,[12] derived the qPitt bacteraemia score and determined that a score of 2 or more carries higher mortality. Our study used the same cut-off value and arrived at the same conclusion that qPitt bacteraemia of two or more carries higher mortality.

The presence of indwelling urinary catheterisation, central venous line, and mechanical ventilation had been previously reported as a significant risk factor for *K. pneumoniae* bacteraemia.[2,3] The role of invasive devices has been implicated in colonisation and infection by destroying the continuum of the skin or mucosa.[3]

There were fewer cases of liver abscess and endophthalmitis found in this series when compared to studies from China, New York, and Taiwan.[3,7,15] It is still controversial whether all patients diagnosed with *K. pneumoniae* bacteraemia needed an ultrasound to rule out a liver abscess. The incidence of liver abscess in *K. pneumoniae* bacteraemia was as low as 2% to as high as 18% in countries like Taiwan.[20,21] The majority of cases were caused by ascending infection from a biliary tract pathology rather than primary bacteraemia.[21]

Future studies should look at the proportion of patients with *K. pneumoniae* who are being screened for endophthalmitis and liver abscess. These factors might have directly influenced the mortality outcome as seen in the Taiwan study that the presence of endopthalmitis and liver abscess did carry a devastating mortality.[7,22] The worst outcome of endogenous endophthalmitis was irreversible blindness if there was a delay in the diagnosis and antibiotic treatment.[23] Thus, patients with *K. pneumoniae* bacteraemia in HCTM should be considered to undergo ophthalmologic screening routinely.

The present study had several limitations. Clinical data were obtained retrospectively from medical records, and therefore, some differences in physician practices will affect the accuracy of information. Only cases of *K. pneumoniae* infection associated with positive blood culture were included in the study. Patients with significant infections which may have been bacteraemia but who did not have blood cultures were not included in the study. This was a single-centre study, including 260 cases with detailed clinical analysis, and further multi-centric, a prospective design to allow exploration of a number of important data. Researchers could look at the genotype strain analysis of K. pneumoniae which at the time of study was not available in HCTM.

This study is a first in Malaysia and is of paramount importance as it lays the groundwork for future studies.

CONCLUSION

The 14-day in-hospital mortality of patients with *K. pneumoniae* bacteraemia in our setting was low. The qPitt bacteraemia score ≥2 was the strongest predictor of poor prognosis for 14-day in-hospital mortality in patients with *K. pneumoniae* bacteraemia. The qPitt bacteraemia score should be proposed to be used as a bedside screening tool for gram-negative bacteraemia in our daily clinical practice, which is also useful for predicting mortality in critically ill patients.

AUTHOR CONTRIBUTIONS

(1) concept of design: ASH, PP, SAS, RR, NK, CLL, (2) Acquisition of data: ASH, PP, RR, (3) Analysis or interpretation of data: ASH, PP, SAS, (4) Drafting of article: ASH, PP, (5) Critical revision for important intellectual content: PP, SAS, RR, NK, CLL

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

CONFLICTS OF INTEREST

All authors have disclosed no conflicts of interest.

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ETHICS APPROVAL
This research was approved by the Health Research Ethical Committee of the University Kebangsaan Malaysia Teaching Hospital with the approval project code FF-2020-136. This is a study involving data collection through medical records, therefore informed consent from patients is not required.

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