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Risk factors of mortality in bloodstream infections caused by *Klebsiella pneumonia*

A single-center retrospective study in China

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Abstract

The prevalence of *Klebsiella pneumonia* bloodstream infections (*KP*-BSIs) is increasing worldwide. Few study reports focus on the *KP*-BSIs published in Mainland China over the previous years. This study aimed to describe the risk factors of mortality from *KP*-BSIs.

A retrospective study was conducted in a teaching hospital in Shanghai, China, for a period of 4 years. Risk factors related to the patient mortality were analyzed using the binary logistic regression model.

Of 104 patients with *KP*-BSIs, the overall 30-day mortality rate was 25%. The logistic regression analysis revealed that thrombocytopenia (TB) (odds ratio [OR]: 1.007, 95% confidence interval [CI]: 1.002–1.013), pancreaticobiliary tract (PBT) (OR: 4.059, 95% CI: 1.398–11.78), and intra-abdominal infection (OR: 6.816, 95% CI: 1.806–25.716) were powerful risk factors leading to the mortality associated with *KP*-BSIs. Although prior antibiotic exposure, inappropriate empirical antibiotics, and inappropriate definitive antibiotics were not associated with mortality, multidrug-resistant (MDR) of *KP*-BSIs in the present study was high in both survivors and nonsurvivors (67.9% and 88.5%, respectively).

TB, PBT, and intra-abdominal infection caused significant mortality rates increase in *KP*-BSIs during the study period.

Abbreviations: ALT = cereal third transaminase, AST = glutamic-oxaloacetic transaminase, BSIs = bloodstream infections, CI = confidence interval, CRP = C-reactive protein, ESBL = extended-spectrum β-lactamase, ESBL-*KP* = extended-spectrum β-lactamase-producing *Klebsiella pneumonia*, ESR = erythrocyte sedimentation rate, *KP* = *Klebsiella pneumonia*, *KP*-BSIs = *Klebsiella pneumonia* bloodstream infections, LOS = length of stay, MDR = multidrug-resistant, MDR-*KP* = multidrug-resistant *Klebsiella pneumonia*, OR = odds ratio, PBT = pancreaticobiliary tract, PCT = procalcitonin, Scr = serum creatinine, TB = thrombocytopenia.

Keywords: bloodstream infection, *Klebsiella pneumonia*, mortality, multidrug-resistant, risk factors

1. Introduction

Klebsiella pneumonia (*KP*) has been reported as the second overall cause of gram-negative bloodstream infections (BSIs) after *Escherichia coli*.[1]*KP* is a common pathogen that causes infections of the bloodstream, urinary tract, lungs, intra-abdominal, and other sites.[2–4] Meatherall et al[5] conducted a population-based surveillance study in the Calgary Heath Region (population 1.2 million) for a period of 8 years. A total of 640 episodes of *KP*-BSIs were identified for an overall annual population incidence of 7.1 per 100,000.[5] Death was significantly more common in patients with BSIs than in patients with other infections.[6,7]

BSIs were chosen for the study to confirm that patients were truly infected, as it is rare that patients with *KP*-positive blood cultures have the negative laboratory result.[2] Multidrug-resistant (MDR) and the increase in the incidence of infections due to gram-negative bacilli producing extended-spectrum β-lactamase (ESBL) have led to the intensive use of Carbapenem.[8] Most of the reports analyzed the molecular epidemiological aspects [9,10] or focused on the special group such as ESBL-producing *K pneumonia* (ESBL-*KP*) of the isolates. Less attention has been focused on the mortality of *KP*, ESPL-*KP* as the risk factor.

ESBL pathogens pose an increasing challenge to physicians worldwide. Studies have analyzed the relation between the rate of mortality and ESBL-producing infections due to *KP*-BSIs, which still remains controversial.[11–14] However, the clinical relevance of the mortality resistance of *KP* isolates is of great concern due to the limited therapeutic options and increased risk of treatment failure in patients infected with such strains.[15] The prevalence of multidrug-resistant *K pneumonia* (MDR-*KP*) has increased dramatically.[16,17] Patients with MDR-*KP* infection have limited treatment options. Therefore, it would be useful to determine differential risks, if any that can predict the mortality in an infected patient. Furthermore, intensive care intervention, laboratory findings, nosocomial infections, and disease severity can be used to evaluate increased mortality rates of *KP*-BSIs patients.[2–7] Few studies have investigated the mortality caused by *KP*-BSIs in mainland China.[18,19] The objective of this study was to determine the risk factors and predictors of mortality caused by *KP*-BSIs.

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2. Methods

2.1. Study design

A retrospective study of Chinese patients with *KP* bacteremia was conducted in Ren Ji Hospital affiliated to Shanghai Jiao Tong University of Medicine, an 1800-bed tertiary care university teaching hospital in Shanghai, China. The study period was between June 1, 2011, and June 30, 2015. Recurrent infections were excluded; only the first *KP* BSIs episode per patient was included in our analysis. Clinical manifestations were determined from medical charts. The study was observational in that administration of antimicrobial agents and the therapeutic managements were controlled by patient's physicians, and not by the investigators.

2.2. Definitions

2.2.1. KP-BSIs was defined as the isolation of KP in a blood culture specimen. The onset of bacteremia was defined as the date when the first positive blood culture was obtained.

The primary site of infection was determined using clinical criteria and isolation of the infecting organism from sources other than blood.[20]

MDR was defined as resistance to at least 1 member of the following 3 classes of antibiotics: aminoglycosides (amikacin, gentamicin, or netilmicin), fluoroquinolones (ofloxacin or ciprofloxacin), and cephalosporins (cefazolin, cefotaxime, cefoxitin, ceftriaxone, ceftazidime, or cefepime).

Clinical variables collected from patients with bacteremia included age, gender, underlying medical conditions (including malignancy, leukemia, chronic renal disease, and diabetes mellitus), smoking, alcohol consumption, laboratory findings (including C-reactive protein [CRP], Procalcitonin [PCT], erythrocyte sedimentation rate [ESR], leukopenia, thrombocytopenia [TB], hemoglobin, blood glucose, serum creatinine [Scr], bilirubin, albumin, cereal third transaminase [ALT], and glutamic-oxaloacetic transaminase [AST]), and insertion of invasive devices (i.e., drainage catheter, central venous catheter, mechanical ventilation, and urinary catheter). TB was defined as platelet count less than 150×10^9/L. Neutropenia was defined as a peripheral absolute neutrophil count of less than 500 cells/mL.

Bacteremia was considered as hospital acquired if the blood culture was collected less than 48 hours after admission of the patient or within hours of discharge from the hospital or an infection that existed in patients who had been admitted to another hospital in 2 weeks before the current admission.

Community-acquired infections were those in which the first positive culture was obtained in less than 48 hours after hospital admission or in more than 48 hours after discharge from the hospital.

Prior antibiotic exposure was defined as administration of an antibiotic within 30 days prior to the culture date and for a 1-day period to the culture date.

The antimicrobial therapies were classified into empirical and definitive, the former being defined as the initial therapy before the results of blood culture were available, and the latter as therapy after the result of antibiotic susceptibility tests had been received. The antimicrobial therapy was considered "appropriate" if the treatment regimen included at least 1 antimicrobial agent active in vitro against *KP*, and if the dosage and route of administration conformed to current medical standards. We considered antimicrobial therapy to be "inappropriate" if the drugs used did not have in vitro activity against the isolated strain or if the patient did not receive antimicrobial therapy.

Mortality was defined as death of any cause within 30 days from the onset of symptoms.

2.2.2. Microbiology. *KP* isolates were identified using the Vitek 2 Advanced Expert System (bioMèrieux, Marcy l'Etoile, France), and antibiotic susceptibility was tested by the Kirby-Bauer agar disk diffusion method. Antibiotic susceptibility was interpreted according to the European Committee on Antimicrobial Susceptibility Testing guidelines.[21]

Ren Ji Hospital Ethics Committee approved the study (Shanghai Jiao Tong University School of Medicine).

2.2.3. Statistical analysis. Student's *t* test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables. A stepwise logistic regression model was used to identify independent risk factors for 30-day mortality. Risk factors with a *P* value less than .10 in the univariate analysis for 30-day mortality were included in the initial model, and forward stepwise selection was performed to develop the final model. A *P* value less than .05 were considered statistically significant. All data were analyzed using the IBM SPSS Statistics for Windows (version 19.0). Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association.

3. Results

A total of 104 *KP* blood isolates were identified during the study period. Patient demographics, clinical characteristics, type of infections, and prior antibiotic exposures for both survivors and nonsurvivors of *KP*-BSIs are shown in Table 1. The median age of patients was 56.5 years (range 15–96 years) and 39 (37.5%) were women. Of the 104 patients, 78 (75%) survived and 26 (25%) died within 30 days of onset.

When co-morbid conditions of the 2 groups were compared by univariate analysis, the non-survivor group was significantly more likely to have diabetes mellitus ($P = .014$) and leukemia/lymphoma ($P = .001$) than controls. The rate of mortality was higher in the ESBL-producing *KP* cases ($P = .028$). The non-survivor group was also more frequently intubated (a Foley catheter ventilation). The nonsurvivor group had higher incidence of leukopenia and higher blood platelet and bilirubin levels than the survival group ($P = .007$, .030, and .001, respectively). MDR in nonsurvivor and survivor groups was serious (88.5% and 67.9%, respectively). No difference was found in the prior antibiotic exposure between the 2 groups.

The results of multivariate logistic regression analysis of risk factors for mortality are shown in Table 1. TB (OR, 1.007; 95% CI, 1.002–1.013; $P = .011$), and bilirubin remained as independent risk factors for mortality caused by *KP*-BSI. An association between mortality and implanted Foley catheter was observed (OR, 4.520; 95% CI, 0.957–21.341; $P = .057$).

The most common source of BSI was pulmonary (39%). Liver abscess, primary bacteremia, and biliary tract infection were also frequent sources of infection (Table 2). Nonsurvivors had a higher rate of biliary tract (34.6%) and intra-abdominal infections (26.9%) caused by *KP*. Pulmonary infection was more common in survivors than in nonsurvivors. Only biliary tract and intra-abdominal infections were found to be associated with mortality on multivariate logistic regression analysis (Table 2).

Table 1

Risk factors associated with 30-day mortality in patients with *KP*-BSI (univariate analysis)*.

Factors	Survivors (n = 78)	Nonsurvivors (n = 26)	P
Demographic data			
Male sex	45 (57.7%)	20 (76.9%)	.079
Age	57.55±15.58	52.77 ± 14.79	.173
Underlying diseases			
Congestive heart failure	5 (6.4%)	2 (7.7%)	.561
Chronic liver disease	14 (18.2%)	8 (32%)	.121
Chronic renal failure	9 (11.5%)	3 (11.5%)	.653
Solid tumor	12 (15.4%)	11 (42.3%)	.006
Diabetes mellitus	6 (7.7%)	8 (32.2%)	.014
Leukemia/lymphoma	2 (2.5%)	9 (33.3%)	.001
Hypoproteinemia	31 (39.7%)	16 (61.5%)	.053
Alcoholism	9 (11.5%)	0 (0.0%)	.159
Smoke	13 (16.7%)	0 (0.0%)	.06
ESBL-producing	26 (33.3%)	15 (57.7%)	.028
Site of hospitalization			.406
Stay in medical ward/surgical ward	63 (80.8%)	19 (73.1%)	
Stay in ICU	15 (19.2%)	7 (26.9%)	
Septic shock	10 (12.8%)	13 (54.2%)	.001
Source of infection			.364
Community-acquired	44 (56.4%)	12 (46.2%)	
Hospital-acquired	34 (43.6%)	14 (53.8%)	
Invasive device			
Foley catheter	16 (20.5%)	17 (65.4%)	<.001
Nasogastric feeding tube	16 (20.5%)	7 (26.9%)	.495
Central venous catheter	35 (44.9%)	16 (61.5%)	.141
Ventilation	10 (12.8%)	11 (44.0%)	.001
Lab finding			
Thrombocytopaenia	23 (29.5%)	14 (53.8%)	.023
Leukopenia	21 (26.9%)	4 (15.4%)	.178
CRP, mg/L	101.35±79.14	115.8±91.34	.649
PCT, ng/mL	7.29±20.19	10.83±22.24	.084
ESR	69.13±36.3	47.25±30.02	.249
Hemoglobin, g/L	100.64±44.14	110.46±50.07	.323
Blood glucose, mmol/L	7.09±2.95	6.89±2.31	.99
Serum creatine, μmol/L	81.53±66.8	85.28±69.09	.62
Bilirubin, μmol/L	27.56±42.73	71.43±115.41	.001
Albumin, g/L	31.03±7.89	29.79±6.25	.474
ALT, U/L	50.05±49.81	51.06±68.22	.287
AST, U/L	56.26±78.39	56.99±69.48	.749
MDR	53 (67.9%)	23 (88.5%)	.041
Prior antibiotic exposure			
Cephalosporins	27 (34.6%)	7 (26.9%)	.469
Quinolones	16 (20.5%)	1 (3.8%)	.064
Beta-lactam/lactamase inhibitors	2 (2.6%)	0 (0.0%)	1
Carbapenems	5 (6.4%)	1 (3.8%)	1
Inappropriate empirical antibiotics	18 (51.4%)	7 (77.8%)	.148
Inappropriate definitive antibiotics	27 (34.6%)	11 (42.3%)	.316
Source of blood stream infections			
Primary	21 (26.9%)	2 (7.7%)	.041
Pulmonary	28 (35.9%)	13 (50.0%)	.203
Liver abscess	15 (19.2%)	2 (7.7%)	.284
Pancreaticobiliary tract infection	11 (14.1%)	9 (34.6%)	.026
Urinary tract infection	5 (6.4%)	4 (15.4%)	.314
Intra-abdominal infection	5 (6.4%)	7 (26.9%)	.009
Intestinal infection	4 (5.1%)	0 (0.0%)	.57
Muscle abscess	1 (1.3%)	0 (0.0%)	1
Skin infection	2 (2.6%)	0 (0.0%)	1
Other	0 (0.0%)	1 (3.8%)	1

ALT = cereal third transaminase, AST = glutamic-oxaloacetic transaminase, CRP = C-reactive protein, ESBL-*KP* = extended-spectrum β-lactamase-producing *Klebsiella pneumonia*, ESBL-producing = extended-spectrum β-lactamase enzyme-producing, ESR = erythrocyte sedimentation rate, ICU = intensive care unit, MDR = multidrug-resistant, PCT = procalcitonin.

* Data are number (%) of patients or mean ± standard deviation.

Table 2

Multivariate logistic regression analysis of risk factors for mortality.

Factors	OR (95%CI)	P
Thrombocytopaenia	1.007 (1.002–1.013)	.011
Bilirubin	1.015 (1.005–1.025)	.005
Foley catheter	4.52 (0.957–21.341)	.057
Biliary tract infection	4.059 (1.398–11.780)	.01
Intra-abdominal infection	6.816 (1.806–25.716)	.005

95%CI = 95% confidence interval, OR = odds ratio.

4. Discussion

This study aimed to determine differential risk factors, if any, which could predict the mortality of *KP*-BSIs. The 30-day mortality rate was 25% in the present study. Few population-based reports have recorded the mortality rate of *KP*. A report from Canada identified an overall annual population incidence of 1.3 per 100,000. The crude mortality rate reported in previous studies was within the range 23% to 46%.[8] Hospital-acquired infection carried a higher mortality rate compared with community-acquired infection in these studies, which was consistent with the present study findings.[4,18,22–24] A study of Korean population found the mortality rate of hospital-acquired and community-acquired infections to be 22% and 11%, respectively. A study of patients in Hong Kong found the mortality rate of hospital-acquired and community-acquired infections to be 43% and 20.2%, respectively.[4,22] Similar studies reported the crude mortality rate to be 20% to 45% in European and North American populations [8,23] and 26% in China.[18] The high range might be related to the population studied and the source of infection.

ESBL-producing *KP* isolates have been increasing worldwide. The prevalence of these isolates varied from 2% to 50% in prior investigations.[24,25] It was observed that nonsurvivors had a higher rate of ESBL-producing isolates (57.7%) than survivors (33%), and this difference was not found to be statistically significant by multivariate logistic regression analysis. Previous studies showed that *KP*-BSIs did not increase mortality due to ESBL-producing.[9–11,26] A case–control study lasted10 years in Mexico and attributed the irrelevance to small number of isolates; the appropriate and prompt definitive therapy almost always included a β-lactam and an amino-glycoside.[24] Gürntke et al[27] believed that studies on the impact of ESBL production on the mortality of *KP*-BSIs could not prove that ESBL-related increased mortality was directly attributable to ESBL-producing infections. The authors found the effect of length of stay (LOS) before BSI onset on mortality. The present study did not evaluate the effect of LOS before and after BSI onset. However, it supported the conclusion by Gürntke et al that ESBL-*KP* bacteremia was not associated with a worse clinical outcome. No correlation was found between MDR and the mortality caused by KP-BSIs. China had a high rate of overall antibiotic use. The rate of MDR was 88.5% and 67% in the nonsurvivors and survivors, respectively. No significant difference was observed in the prior antibiotic exposure and mortality. This might be due to a low number of patients included in this study.

The presence of indwelling catheters had been previously reported as a significant risk factor for *KP*-BSIs.[28–30] The role of invasive devices had been implicated in colonization and infection by destroying the continuum of the skin or mucosa.[31]

An association between mortality and implanted Foley catheter was observed in the present study.

PBT infection has been considered as a factor leading to a good outcome. The mortality was significantly higher in patients having PBT BSI in the present study, which might be attributed to the underlying disease. Of 9 patients with PBT infection in this study, 5 (55.6%) were taking immunosuppressants after liver transplantation and 4 (44.4%) had septic shock onset. The mortality rate in PBT patients in the present study was 34.6% compared with other studies in which PBT was rare (4–21%).[4,8,32]

A low platelet count is a common laboratory abnormality in critically ill patients. Thrombocytopenia was found to be an independent risk factor for mortality in the present study, which was confirmed by several other studies.[33,34] The rate of thrombocytopenia (TB) in patients with bacteremia was 79.6%. The rate of mortality was higher in patients with bacteremia. The mechanism by which TB occurs in patients with infection is not clear. The most common cause of TB is severe infection and/or inflammation.[35] Other related causes of TB are thrombotic microangiopathy, disseminated intravascular coagulation, massive blood loss, and drug-induced thrombocytopenia.[35–38]

The present study had several limitations, including its retrospective design. BSIs were chosen for the study to confirm that patients were truly infected. However, patients who had bacteremia but did not have blood samples for culture were missed. Another limitation was that study pathogens were not collected. Therefore, data pertaining to strain genotype were not available. Finally, this study was performed in a single metropolitan area, including only 104 patients. Therefore, risk factors and bacterial population might have been different at other institutions.

The present study considered ESBL-*KP*, MDR, and laboratory findings as the risk factors for mortality caused by *KP*-BSIs. In conclusion, the study demonstrated that PBT, intra-abdominal infection, and TB represent strong risk factors for the mortality caused by *KP*-BSIs.

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