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Clinical characteristics and risk factors associated with secondary bloodstream infection in patients with intensive care unit-acquired pneumonia due to carbapenem-resistant *Klebsiella pneumoniae*

Xin-Yun Zhu[1], Hong-Bin Wang[2], Ye-Han Zhu[1], Yan-Bin Chen[1], Bei-Lei Zhang[1], Cheng Chen[1]

[1]Department of Respiratory and Critical Medicine, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China;
[2]Institute of Respiratory Diseases, Soochow University, Suzhou, Jiangsu 215006, China.

The global spread of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has become a major healthcare burden because of the limited therapeutic options and poor prognosis, and this situation gets worse among patients admitted to intensive care unit (ICU).[1] CRKP can cause a range of infections, including pneumonia, urinary tract infection (UTI), and bloodstream infection (BSI). BSI is one of the most serious infections caused by CRKP and associated with high mortality ranging from 39% to 82%.[2] BSI due to CRKP could be primary infection or secondary infection that originated from primary infections in the lungs or bladder, and 50% of CRKP-BSIs originated from primary infections in the lungs.[3] Although previous studies have explored several risk factors for CRKP infections, the association between CRKP pneumonia and the development of secondary CRKP-BSI was not fully revealed thus far. The aim of this study was to predict risk factors of 28-day mortality and the development of secondary CRKP-BSI in ICU-acquired pneumonia caused by CRKP.

This retrospective study was conducted at the respiratory intensive care unit of the First Affiliated Hospital of Soochow University in China between January 2017 and September 2019. Clinical information was collected from the electronic medical records. Data regarding antimicrobial susceptibilities and bacterial isolates were identified by the clinical microbiology laboratory. We enrolled all cases with at least two positive cultures of CRKP obtained from lower respiratory tract specimens (qualified sputum, endotracheal aspirate, and bronchoalveolar lavage fluid) after ICU admission. Two incomplete cases and six colonization cases were excluded. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (No. 2021-019).

The data collected include demographics, ICU exposure and invasive procedures within 30 days, the count of leukocytes, neutrophils, lymphocytes, platelets and C-reactive protein (CRP), procalcitonin (PCT) at infection onset, treatment, and outcome. Furthermore, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and sequential organ failure assessment (SOFA) score at infection onset were recorded for assessment of severe infection. The outcome was measured by mortality within 28 days of the first positive culture. Survivors and non-survivors were analyzed to identify risk factors for 28-day mortality in ICU-acquired CRKP pneumonia. To investigate predictive factors of the development of secondary CRKP-BSI in ICU-acquired CRKP pneumonia, BSI group and non-BSI group were compared with only the first episode of BSI in each case being included.

CRKP was defined as a minimum inhibitory concentration for meropenem or imipenem ≥4 μg/mL, or for ertapenem ≥2 μg/mL. ICU-acquired pneumonia was defined as pneumonia present in patients at least 48 h after ICU admission. Colonization was defined as a positive culture with absence of clinical or laboratory evidence of systemic inflammation. BSI was diagnosed when patients showed clinical symptoms or signs of bacteremia and a positive culture was obtained from blood samples. All BSIs were secondary BSIs which resulted from respiratory tract infections in this study. Patients received colistin treatment with a dose of 500,000 units every 12 h.

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Xin-Yun Zhu and Hong-Bin Wang contributed equally to this work.

Correspondence to: Prof. Cheng Chen, Department of Respiratory and Critical Medicine, The First Affiliated Hospital of Soochow University, 899 Pinghai Road, Suzhou, Jiangsu 215006, China
E-Mail: chencheng@suda.edu.cn

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Categorical variables were presented as frequencies and percentages and were evaluated by Pearson Chi-squared test or Fisher exact tests. Continuous variables with abnormal distribution were presented as median (Q_1, Q_3) and were evaluated by Mann-Whitney *U* test. Binary logistic regression was performed to identify risk factors for the development of secondary CRKP-BSI and 28-day mortality in patients with ICU-acquired CRKP pneumonia, respectively. Survival analyses were conducted by using Kaplan-Meier method and the survival curves were compared by log-rank test. *P* value of <0.05 was considered as indicative of statistical significance. All statistical analyses were performed with SPSS 24.0 software (SPSS Inc., Chicago, IL, USA).

A total of 84 cases with positive respiratory cultures for CRKP were identified during the period. After excluding six colonization cases and two incomplete records, 76 patients finally met the inclusion criteria. Among these 76 cases with ICU-acquired CRKP pneumonia, 18 cases were identified as developing secondary CRKP-BSI. At infection onset [Supplementary Table 1, http://links.lww.com/CM9/A504], 100% (18/18), 83.3% (15/18), and 44.4% (8/18) of patients with secondary CRKP-BSI had fever, septic shock, and CRKP UTI, which were significantly more than those of patients without secondary CRKP-BSI (77.6% [45/58], 46.6% [27/58], 6.9% [4/58]; all $P < 0.05$). The median APACHE II score (25.50 [17.75, 31.00] *vs.* 13.00 [10.00, 18.00], $U = 136.00$, $P < 0.001$) and SOFA score (9.50 [6.75, 12.00] *vs.* 4.00 [3.00, 7.00], $U = 219.00$, $P < 0.001$) were significantly higher in patients with secondary CRKP-BSI. Furthermore, the median PCT and CRP in patients with secondary CRKP-BSI were 2.72 ng/mL and 131.50 mg/L, which were significantly higher than 0.39 ng/mL and 94.15 mg/L in patients without secondary CRKP-BSI ($U = 288.50$, $P = 0.011$; $U = 326.00$, $P = 0.025$). Additionally, the counts of lymphocytes (0.37 [0.16, 0.77] $\times 10^9$/L *vs.* 0.71 [0.35, 1.04] $\times 10^9$/L, $U = 340.50$, $P = 0.027$) and platelets (57.50 [21.50, 93.50] $\times 10^9$/L *vs.* 159.00 [96.25, 209.75] $\times 10^9$/L, $U = 178.00$, $P < 0.001$) were significantly lower in patients with secondary CRKP-BSI.

The univariate analyses showed that the potential risk factors for 28-day mortality of ICU-acquired CRKP pneumonia included septic shock (odds ratio [OR], 13.778, 95% confidence interval [CI]: 3.632–52.270, $P < 0.001$), secondary CRKP-BSI (OR, 12.115, 95% CI: 3.399–43.187, $P < 0.001$), lymphopenia (OR, 0.064, 95% CI: 0.013–0.303, $P = 0.001$), thrombocytopenia (OR, 0.989, 95% CI: 0.982–0.996, $P = 0.002$), APACHE II score (OR, 1.143, 95% CI: 1.059–1.234, $P = 0.001$) and SOFA score (OR, 1.276, 95% CI: 1.108–1.470, $P = 0.001$). Further, the multivariate analysis showed that associations between 28-day mortality and septic shock (OR, 7.955, 95% CI: 1.406–45.000, $P = 0.019$), secondary CRKP-BSI (OR, 10.308, 95% CI: 1.339–79.381, $P = 0.025$) and lymphopenia (OR, 0.071, 95% CI: 0.008–0.625, $P = 0.017$) remained statistically significant [Supplementary Table 2, http://links.lww.com/CM9/A504]. In addition, patients with secondary CRKP-BSI (22.2% *vs.* 77.6%, $P < 0.001$) and septic shock (42.9% *vs.* 91.2%, $P < 0.001$) had worse 28-day survival according to Kaplan-Meier survival curves [Supplementary Figure 1A and 1B, http://links.lww.com/CM9/A504].

The univariate analyses showed that the variables associated with the development of secondary CRKP BSI included septic shock (OR, 5.741, 95% CI: 1.499–21.983, $P = 0.011$), UTI (OR, 10.800, 95% CI: 2.726–42.796, $P = 0.001$), bronchoscopy within 30 days (OR, 4.063, 95% CI: 1.060–15.566, $P = 0.041$), lymphopenia (OR, 0.227, 95% CI: 0.054–0.954, $P = 0.043$), thrombocytopenia (OR, 0.980, 95% CI: 0.970–0.991, $P < 0.001$), APACHE II score (OR, 1.201, 95% CI: 1.095–1.318, $P < 0.001$) and SOFA score (OR, 1.200, 95% CI: 1.053–1.369, $P = 0.006$). Further, the multivariate analysis showed that the independent risk factors for developing secondary CRKP BSI were thrombocytopenia (OR, 0.984, 95% CI: 0.970–0.998, $P = 0.028$) and APACHE II score (OR, 1.185, 95% CI: 1.024–1.373, $P = 0.023$) [Table 1].

In terms of outcome [Supplementary Figure 1C and 1D, http://links.lww.com/CM9/A504], among patients without

Table 1: Univariate and multivariate analysis of risk factors for secondary CRKP-BSI among patients with ICU-acquired CRKP pneumonia.

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	0.990	0.304–3.227	0.987			
Septic shock	5.741	1.499–21.983	0.011	2.160	0.235–19.855	0.496
Urinary tract infection	10.800	2.726–42.796	0.001	6.979	0.889–54.766	0.065
Artificial airway	1.575	0.455–5.457	0.474			
Central venous catheter	4.435	0.535–36.744	0.167			
Bronchoscopy	4.063	1.060–15.566	0.041	2.074	0.281–15.285	0.474
Urethral catheter	1.872	0.374–9.366	0.445			
Leukocyte	1.029	0.984–1.077	0.214			
Neutrophil	1.034	0.985–1.086	0.181			
Lymphocyte	0.227	0.054–0.954	0.043	1.505	0.188–12.066	0.700
Platelet	0.980	0.970–0.991	<0.001	0.984	0.970–0.998	0.028
PCT	1.027	0.992–1.063	0.137			
APACHE II score	1.201	1.095–1.318	<0.001	1.185	1.024–1.373	0.023
SOFA score	1.200	1.053–1.369	0.006	0.913	0.730–1.142	0.426

APACHE II: Acute physiology and chronic health evaluation II; BSI: Bloodstream infection; CI: Confidence interval; CRKP: Carbapenem-resistant *Klebsiella pneumoniae*; ICU: Intensive care unit; OR: Odds ratio; PCT: Procalcitonin; SOFA: Sequential organ failure assessment.

secondary CRKP-BSI ($n = 58$), the 28-day mortality in colistin-included therapy subgroup was comparable to that in colistin-excluded therapy subgroup (29.4% *vs.* 19.5%, $P = 0.546$). Interestingly, among patients with secondary CRKP-BSI ($n = 18$), the 28-day mortality in colistin-included therapy subgroup was 66.67%, which was significantly lower than that in colistin-excluded therapy subgroup (100%, $P < 0.001$).

We identified that secondary CRKP-BSI and septic shock were independent risk factors for the 28-day mortality in patients with ICU-acquired CRKP pneumonia. Patients with CRKP-BSI and septic shock were usually of older ages and critically ill, had more comorbidities and underwent more invasive procedures. All of these factors could increase mortality. Similarly, a study showed that BSI and septic shock were strong prognostic factors associated with 14-day mortality among patients with CRKP infections.[4] We also found that lymphocytopenia was associated with the higher 28-day mortality. Lymphocytopenia due to inflammation was related to serious infection and poor outcome and has been suggested to diagnose the infection-related sepsis which has become the major cause of death in ICU.

Our study confirmed a high incidence of developing secondary CRKP-BSI in patients with ICU-acquired CRKP pneumonia (23.7%). We found that APACHE II score and thrombocytopenia were independent risk factors for the development of secondary CRKP-BSI among patients with ICU-acquired CRKP pneumonia. As a clinical characteristic, APACHE II score can describe the severity of the illness and make predictions about the prognosis. Further, patients with CRKP-BSI are usually severely ill and associated with higher APACHE II scores. Although various etiologies can cause a low platelet count, thrombocytopenia is essentially the result of reduced production, increased consumption or destruction, and abnormal sequestration. Thrombocytopenia is always associated with direct bone marrow suppression, which increases the risk for infections. Further, CRKP-BSI can increase the peripheral consumption which might reduce the platelet count.

The rapid spread of CRKP has posed a great challenge for physicians due to the limited effective and safe treatment. Treatment options for CRKP infections had been limited to regimens such as colistin and tigecycline in combination with other antibiotics. Our study found that colistin-included therapy was associated with higher 28-day survival rate in BSI group. However, the similar association was not shown in non-BSI group. Patients without secondary CRKP-BSI are usually in better conditions with lower APACHE II scores than patients with secondary CRKP-BSI. Thus, patients in non-BSI group might not benefit from colistin-included therapy as much as patients did in BSI group. Further, patients without secondary CRKP-BSI may have better long-term survival with colistin-included therapy. Fortunately, several new agents with activity against CRKP have been approved to be used clinically or are in late-stage clinical development, including ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, plazomicin, eravacycline, and cefiderocol.[5] These new agents will provide more treatment options and are expected to improve the outcome of patients with CRKP-BSI.

In summary, septic shock, secondary CRKP-BSI, and lymphopenia were independent predictors for 28-day mortality of ICU-acquired CRKP pneumonia. Further, thrombocytopenia and APACHE II score at infection onset were independently associated with the development of secondary CRKP-BSI among patients with ICU-acquired CRKP pneumonia. Additionally, patients with secondary CRKP-BSI treated with colistin-included therapy had a better survival. However, our study was limited because the study was retrospective and conducted in a single-center, including 76 patients. Prospective and multi-center studies with large populations are needed to validate our findings.

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Conflicts of interest

None.

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