

Risk Factors and Mortality of Elderly Patients with Hospital-Acquired Pneumonia of Carbapenem-Resistant *Klebsiella pneumoniae* Infection

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Purpose: Hospital-acquired pneumonia (HAP) caused by carbapenem-resistant *K. pneumoniae* (CRKP), especially in elderly patients, results in high morbidity and mortality. Studies on risk factors, mortality, and antimicrobial susceptibility of CRKP pulmonary infection among elderly patients are lacking.

Patients and Methods: A retrospective case-control study was conducted from January 2019 to December 2021. The elderly inpatients (≥ 65 years) who were diagnosed with HAP caused by *K. pneumoniae* were enrolled. Clinical data were collected. Univariate and multivariate logistic regression analyses were used to identify risk factors. Propensity score matching was used to minimize the effect of potential confounding variables. Kaplan-Meier analysis was used to compare survival.

Results: A total of 115 patients with CRKP infection and 78 patients with carbapenem-susceptible *K. pneumoniae* (CSKP) infection were recruited. There were four independent risk factors for CRKP infection: history of intensive care unit (ICU) stays from hospital admission to positive respiratory specimen culture for *K. pneumoniae* (odds ratio (OR)=2.530), Charlson comorbidity index score ≥ 3 (OR = 2.420), prior exposure to carbapenems (OR = 5.280), and prior *K. pneumoniae* infection or colonization in the preceding 3 years (OR = 18.529). The all-cause 30-day mortality was 22.3%, the mortality of CRKP and CSKP infection was 28.7% and 12.8%, respectively. Independent risk factors for mortality included: older age (OR = 1.107), immunocompromised patients (OR = 8.632), severe pneumonia (OR = 51.244), quick Sepsis-related Organ Failure Assessment (qSOFA) score ≥ 2 (OR = 6.187), exposure to tigecycline before infection (OR = 24.702), and prolonged ICU stay (OR = 0.987). Thirty-day mortality was significantly lower in patients receiving ceftazidime-avibactam (CAZ-AVI) containing regimens than patients receiving polymyxin B sulfate (PB) containing regimens ($P = 0.048$). qSOFA score had a good prognostic effect [area under receiver operating characteristic curve (AUROC) of 0.838].

Conclusion: Active screening of CRKP for the high-risk populations, especially elderly patients, is significant for early detection and successful management of CRKP infection.

Keywords: elderly, hospital-acquired pneumonia, CRKP, CSKP, ceftazidime-avibactam, qSOFA

Introduction

Hospital-acquired pneumonia (HAP) is an infection of lung parenchyma caused by pathogens within the hospital environment. It is the second-most common nosocomial infection and the leading cause of death.¹ The incidence of HAP varies from 5 to more than 20 cases per 1000 hospitalized patients.² The incidence of HAP in Chinese is 1.74% to

6.4%.^{3,4} Elderly patients are more likely to develop severe pneumonia due to decreased immunity, vomiting reflex disorders, weakened fever response, and cardiopulmonary dysfunction.

The most common cause of HAP in the elderly is bacterial infection, particularly *K. pneumoniae*, a gram-negative capsulated bacterium that can cause severe pneumonia, especially in immunocompromised patients.⁵ Since carbapenems were first used to treat infections caused by *K. pneumoniae*, the emergence of CRKP has become a major concern worldwide.⁶ In 2017, the World Health Organization listed CRKP as one of the resistant pathogens in urgent need of new antimicrobial agents.⁷ The number of CRKP had increased significantly year by year. According to the China Antimicrobial Surveillance Network (CHINET, <http://www.chinets.com/>), the isolation rate of CRKP based on meropenem resistance increased significantly from 2.9% in 2005 to 27.5% in 2022.

The mortality rate of patients with CRKP pulmonary infection was high. A previous study showed that the 14-day mortality rate of patients with CRKP pulmonary infection was 23.2%, and the in-hospital mortality rate was 34.8% (73.9% of carbapenem-resistant *Enterobacterales* were CRKP).⁸ Risk factors associated with mortality of CRKP infection included older age, malignancy, high SOFA score, and inappropriate therapy.^{8–10} Additionally, several studies had demonstrated that CRKP infected patients had higher mortality and longer hospital stays than CSKP infected patients.^{11,12}

However, it is worth noting that there are few studies researching the risk factors and mortality of elderly patients with CRKP infection. The objective of this study is to identify the risk factors and mortality associated with CRKP pulmonary infection in the elderly.

Materials and Methods

Study Design

This retrospective case–control study was conducted from 1 January 2019 to 31 December 2021 at Peking University First Hospital, a tertiary hospital with 1805 beds in Beijing, China. Elderly inpatients (≥ 65 years) with confirmed with *K. pneumoniae* HAP were recruited. *K. pneumoniae* HAP was defined as a new pulmonary infiltrate confirmed by X-ray or computed tomography (occurred ≥ 48 h after admission) associated with at least one of the following: new or worsening cough with or without sputum production, fever (temperature $>37.8^{\circ}\text{C}$) or hypothermia ($<35.6^{\circ}\text{C}$), leukocytosis, left shift, or leukopenia based on local normal values, as well as isolation of *K. pneumoniae* from lower respiratory tract secretions (sputum, bronchoalveolar lavage fluid, bronchoscopic needle aspiration, or blood).¹³ The exclusion criteria were: a) age <65 years; b) incomplete medical records; c) *K. pneumoniae* colonization (did not meet the criteria for infection);¹⁴ d) outpatients or emergency patients; e) infection acquired from outside of hospital setting. Only the first episode of *K. pneumoniae* HAP was included. A total of 193 episodes were enrolled in this study.

Data Collection

The patient data were collected from the hospital's computerized microbiology laboratory database and information system. The main variables included demographic characteristics; underlying diseases; Charlson comorbidity index;¹⁵ past medical history (surgery, smoke, alcohol, exposure to antibiotics, and *K. pneumoniae* infection or colonization); sepsis/septic shock,¹⁶ Pitt bacteremia score,¹⁷ and quick Sepsis-related Organ Failure Assessment (qSOFA) score¹⁶ at infection onset; laboratory findings; co-infection with other pathogens; therapeutic processes (admission to ICU after infection, mechanical ventilation); antibiotics therapy; clinical outcomes (30-day mortality, failure rate of microbiological clearance, length of hospital stay, length of ICU stay). The events that occurred before CRKP infection were considered for analyzing risk factors. Thirty-day mortality was defined as death within 30 days from diagnosis of infection (including patients who died within 30 days, and patients who discharged within 30 days were confirmed dead by telephone follow-up). To further compare the clinical outcomes between CRKP and CSKP groups, propensity score matching was used to minimize the effect of potential confounding variables, including age, admission to ICU before infection, and Charlson comorbidity index.

Definition of Terms

Patient conditions to be considered immunocompromised were: a) primary immune deficiency diseases; b) active malignancy or malignancy within 1 year of community-acquired pneumonia, excluding patients with localized skin cancers or early-stage

cancers; c) receiving cancer chemotherapy; d) human immunodeficiency virus infection with a CD4 T-lymphocyte count <200 cells/mL or percentage <14%; e) solid organ transplantation; f) hematopoietic stem cell transplantation; g) receiving corticosteroid therapy with a dose ≥ 20 mg prednisone or equivalent daily for ≥ 14 d or a cumulative dose >600 mg of prednisone; h) receiving biological immune modulators; i) receiving disease-modifying antirheumatic drugs or other immunosuppressive drugs (eg, cyclosporin, cyclophosphamide, hydroxychloroquine, methotrexate).¹⁸ Severe pneumonia was diagnosed if one or more major criteria (invasive mechanical ventilation or septic shock with the need for vasopressors) and/or three minor criteria [respiratory rate ≥ 30 breaths/min, PaO₂/FiO₂ ratio ≤ 250 , multilobar infiltrates, confusion/disorientation, uremia (blood urea nitrogen level ≥ 20 mg/dL), leukopenia (white blood count <4000 cells/mm³), thrombocytopenia (platelet count <100,000 cells/mm³), hypothermia (core temperature <36°C), hypotension requiring aggressive fluid resuscitation] met.¹⁹ Failure rate of microbiological clearance was defined as the persistence of positive cultures (presence of pathogens initially isolated from the site of infection).^{20,21} The definition of co-infection was defined as detection 2 or more bacteria in the same sample. Longer hospitalization time was defined as the patient's hospital stay more than 30 days after the first positive culture.

Empirical and targeted therapies were defined as antibiotics administered before and after obtaining the result of an antimicrobial susceptibility test. Appropriate therapy was defined as using at least one in vitro active agent, with or without inactive companion agents. Monotherapy was defined as only one active agent using, combination therapy was defined as more than one active agent using. Inappropriate therapy was defined as selection of agents without activity against responsible pathogens.²²

Antimicrobial Susceptibility Test

K. pneumoniae was identified by Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Microflex LT, Bremen, Germany).²³ Antibiotics susceptibility testing was completed using a Vitek 2 automated system (bio-Mérieux, France), which was performed by adopting the broth microdilution method. Gram-negative susceptibility (GNS) cards were used to determine the minimal inhibitory concentration (MIC) of strains for various antibiotics (8–64 ug/mL for amikacin, 2–32 ug/mL for aztreonam, 0.25–32 ug/mL for cefepime, 8–32 ug/mL for cefoperazone/sulbactam, 0.25–32 ug/mL for ceftazidime, 0.5–4 ug/mL for ciprofloxacin, 1–16 ug/mL for doxycycline, 1–12 ug/mL for imipenem, 0.25–8 ug/mL for levofloxacin, 0.5–12 ug/mL for meropenem, 2/4–48/8 ug/mL for piperacillin/tazobactam, 2–8 ug/mL for minocycline, 0.75–4 ug/mL for tigecycline, 8–64 ug/mL for tobramycin, 8/2–64/2 ug/mL for ticarcillin/clavulanate and 1/19–16–304 ug/mL for trimethoprim/sulfamethoxazole). Antibiotic susceptibility testing for colistin was performed using the test kit (BIO-KONT[®]), with the method of broth microdilution. Susceptibility testing results were interpreted according to the criteria recommended by the Clinical and Laboratory Standards Institute (CLSI M100 31th),²⁴ except tigecycline, which was interpreted according to the American Food and Drug Administration (FDA) standard (<https://www.fda.gov/drugs/development-resources/tigecycline-injection-products>).

Statistical Analysis

SPSS version 26.0 and *MatchIt* package in R 3.5 were used for statistical analyses. For continuous variables, patient characteristics were presented as median and IQR (interquartile range), Student's *t*-test was used to compare normally distributed variables, and Mann–Whitney *U*-test was used to compare non-normally distributed variables. For categorical variables, patient characteristics were presented with rate. Chi-square test or Fisher's exact test was used to compare categorical variables. In the multivariate logistic regression model, variables with $P < 0.01$ in the univariate analysis were analyzed. Variables whose $P < 0.05$ and OR >1 was considered as independent risk factors. Additionally, OR and the 95% confidence interval (CI) were calculated for each variable.

Results

A total of 193 patients were included in this study, including 115 patients with CRKP infection, and 78 patients with CSKP infection (Figure 1). The mean age was 76.0 years old, and the age ranged from 65 to 99 years. 66.8% (129/193) of patients were male, 33.2% (64/193) of patients were female.

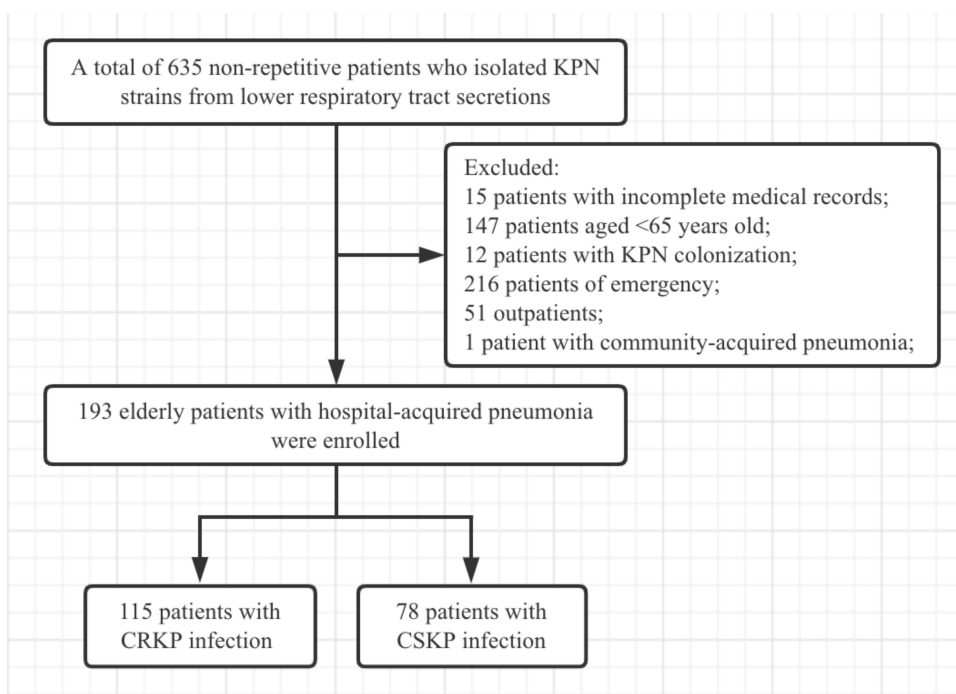


Figure 1 Flowchart outlining of the patients included in this study.

Results of *K. pneumoniae* Susceptibility Test

Detailed findings for susceptibilities of CRKP and CSKP are shown in Figure 2. In vitro antimicrobial susceptibility test showed that CRKP strains were significantly resistant to ciprofloxacin, piperacillin-tazobactam, aztreonam, ceftazidime, levofloxacin, cefoperazone, cefepime, minocycline, doxycycline, tobramycin, and amikacin, the resistance rate was 50%–100%. The proportion of CRKP resistant to tigecycline and colistin was 5.9% and 14.8%, respectively. CSKP strains were sensitive to most antibiotics.

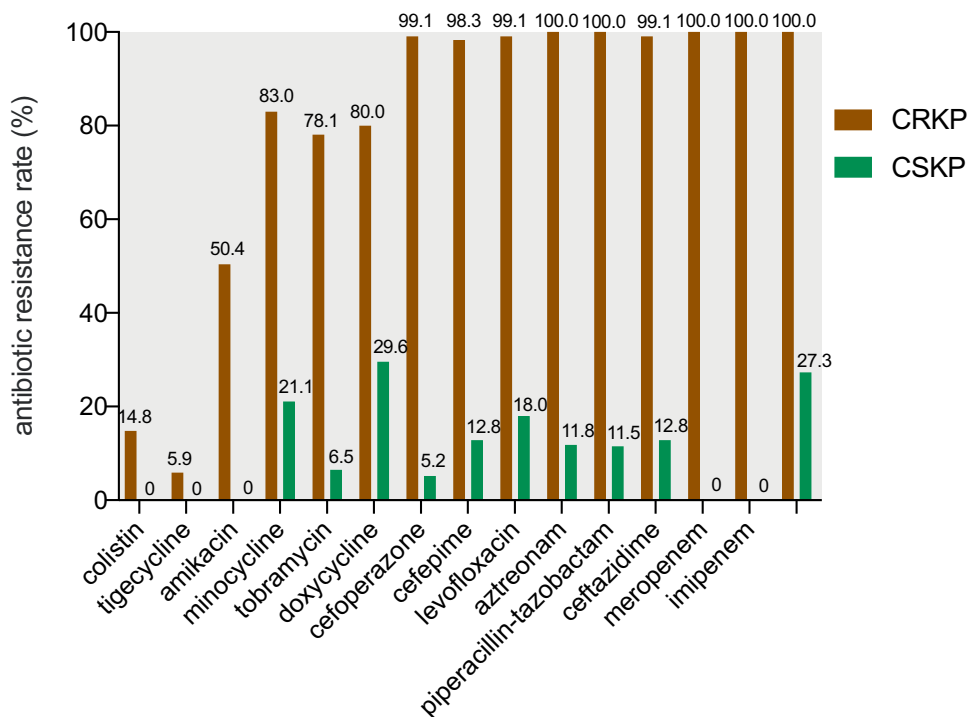


Figure 2 The results of antimicrobial susceptibility test of *K. pneumoniae* strains.

The Risk Factors for CRKP Infection

The demographic and clinical characteristics of patients are summarized in Table 1. The majority of patients infected with CRKP (77/115, 67.0%) and CSKP (52/78, 66.7%) were male. Patients with CRKP infection (median age = 79.0 years) were older than patients with CSKP infection (median age = 73.0 years). Patients with history of ICU stays from hospital admission to positive respiratory specimen culture for *K. pneumoniae*, Charlson comorbidity index score ≥ 3 , long hospital stay before infection, prior *K. pneumoniae* infection or colonization in the preceding 3 years, exposure to carbapenems or tigecycline within 3 months before a positive culture were more likely to be infected with CRKP.

Multivariate logistic regression analysis showed that independent risk factors for CRKP infection were history of ICU stays from hospital admission to positive respiratory specimen culture for *K. pneumoniae* (OR = 2.530, 95% CI: 1.195–5.356; $P=0.015$), Charlson comorbidity index score ≥ 3 (OR = 2.420, 95% CI: 1.097–5.338; $P=0.029$), prior exposure to carbapenems (OR = 5.280, 95% CI: 2.330–11.966; $P<0.001$), and prior *K. pneumoniae* infection or colonization in the preceding 3 years (OR = 18.529, 95% CI: 3.801–90.336; $P<0.001$) (Table 2).

Table 1 Univariate Analysis of Risk Factors for CRKP Infection

Variables	Total (n=193)	CRKP (n=115)	CSKP (n=78)	P value
Demographics				
Sex, male	129 (66.8%)	77 (67.0%)	52 (66.7%)	0.967
Age, median (IQR)	76.0 (69.0–84.0)	79.0 (71.0–85.0)	73.0 (68.0–80.3)	0.001
History of ICU stays (from hospital admission to positive respiratory specimen culture for <i>K. pneumoniae</i>)	95 (49.2%)	72 (62.6%)	23 (29.5%)	<0.001
Underlying conditions				
Charlson comorbidity index ≥ 3	130 (67.4%)	89 (77.4%)	41 (52.6%)	<0.001
Immunocompromised	52 (26.9%)	35 (30.4%)	17 (21.8%)	0.184
Chronic lung diseases	85 (44.0%)	59 (51.3%)	26 (33.3%)	0.014
Chronic renal diseases	41 (21.2%)	35 (30.4%)	6 (7.7%)	<0.001
Chronic liver diseases	15 (7.8%)	11 (9.6%)	4 (5.1%)	0.392
Myocardial infarction	43 (22.3%)	25 (21.7%)	18 (23.1%)	0.827
Peripheral vascular diseases	65 (33.7%)	58 (50.4%)	7 (9.0%)	<0.001
Heart failure	36 (18.7%)	27 (23.5%)	9 (11.5%)	0.037
Cerebrovascular diseases	96 (49.7%)	60 (52.2%)	36 (46.2%)	0.412
Connective tissue diseases	19 (9.8%)	13 (11.3%)	6 (7.7%)	0.408
Peptic ulcer	15 (7.8%)	10 (8.7%)	5 (6.4%)	0.561
Hematological malignancy	7 (3.6%)	4 (3.5%)	3 (3.8%)	1.000
Carcinoma	51 (26.4%)	29 (25.2%)	22 (28.2%)	0.644
Diabetes mellitus	73 (37.8%)	48 (41.7%)	25 (32.1%)	0.173
Hypertension	128 (66.3%)	79 (68.7%)	49 (62.8%)	0.397
History				
Surgical history within 3 months	117 (60.6%)	68 (59.1%)	49 (62.8%)	0.607
Previous smoking history	87 (45.1%)	51 (44.3%)	36 (46.2%)	0.805
Previous drinking history	43 (22.3%)	24 (20.9%)	19 (24.4%)	0.568
Antibiotics (within 3 months before a positive culture)				
Carbapenems	177 (91.7%)	110 (95.7%)	67 (85.9%)	0.016
Cephalosporins	70 (36.3%)	55 (47.8%)	15 (19.2%)	<0.001
Tigecycline	32 (16.6%)	11 (9.6%)	21 (26.9%)	0.001
β lactam/ β lactam inhibitors	24 (12.4%)	20 (17.4%)	4 (5.1%)	0.014
Quinolones	58 (30.1%)	36 (31.3%)	22 (28.2%)	0.645
Quinolones	20 (10.4%)	12 (10.4%)	8 (10.3%)	0.968
Prior <i>K. pneumoniae</i> infection or colonization in the preceding 3 years	40 (20.7%)	38 (33.0%)	2 (2.6%)	<0.001
Length of stay before infection	14 (5.0–33.0)	16 (6.0–51.0)	11.0 (4.0–25.0)	0.038

Abbreviations: IQR, interquartile range; ICU, intensive care unit.

Table 2 Multivariate Analysis of Risk Factors for CRKP Infection

Variables	Univariate		Multivariate	
	P	OR (95% CI)	P value	OR (95% CI)
Age, median (IQR)	0.001	0.941 (0.907–0.976)	0.167	0.969 (0.926–1.013)
History of ICU stays (from hospital admission to positive respiratory specimen culture for <i>K. pneumoniae</i>)	<0.001	4.004 (2.162–7.414)	0.015	2.530 (1.195–5.356)
Charlson comorbidity index ≥ 3	<0.001	3.089 (1.656–5.761)	0.029	2.420 (1.097–5.338)
Exposure to carbapenems	<0.001	3.850 (1.967–7.535)	<0.001	5.280 (2.330–11.966)
Exposure to cephalosporins	0.001	0.287 (0.129–0.638)	0.661	1.257 (0.452–3.491)
Exposure to tigecycline	0.014	3.895 (1.276–11.886)	0.054	3.388 (0.977–11.747)
Prior <i>K. pneumoniae</i> infection or colonization in the preceding 3 years	<0.001	18.753 (4.369–80.492)	<0.001	18.529 (3.801–90.336)
Length of stay before infection	0.038	0.998 (0.996–1.000)	0.499	1.001 (0.999–1.003)

Abbreviations: IQR, interquartile range; ICU, intensive care unit.

The Clinical Outcomes Between CRKP and CSKP Infected Patients

The all-cause 30-day mortality was 22.3% (43/193) in all patients, the 30-day mortality of CRKP infection was 28.7% (33/115), and the 30-day mortality of CSKP infection was 12.8% (10/78). The all cause in-hospital mortality was 41.5% (80/193) in all patients, the in-hospital mortality of CRKP infection was 53.9% (62/115), and the in-hospital mortality of CSKP infection was 23.1% (18/78). Patients with CRKP infection had higher mortality than patients with CSKP infection ($P=0.009$). Compared with patients with CSKP infection, patients with CRKP infection were more likely to have sepsis/septic shock (29/78 vs 8/73, $P<0.001$), severe pneumonia (31/78 vs 12/78 $P=0.001$), and long hospital stay (40/78 vs 20/78, $P<0.001$). In addition, CRKP strains were more difficult to clear up than CSKP strains (49/78 vs 16/78 $P<0.001$) (Figure 3).

The Risk Factors for All-Cause 30-Day Mortality

In univariate analysis, the following factors were associated with 30-day mortality, including history of ICU stays from hospital admission to positive respiratory specimen culture for *K. pneumoniae*, immunocompromised patients, exposure to carbapenems or tigecycline within 3 months prior to a positive culture, Pitt bacteremia score ≥ 3 , qSOFA ≥ 2 , received mechanical ventilation treatment, sepsis/septic shock occurred, ICU admission after infection, severe pneumonia, CRKP infection, and prolonged ICU stay. Some laboratory variables, such as high procalcitonin, sensitivity C-reactive protein, D-dimer, neutrophils, and low lymphocytes, were also associated with mortality (Table 3).

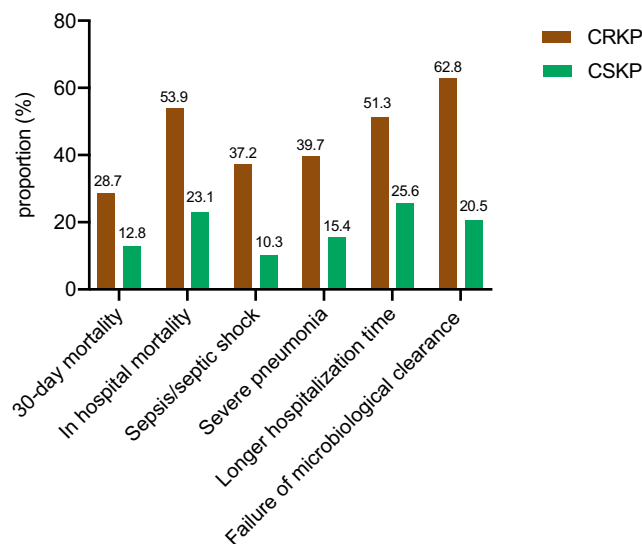


Figure 3 The clinical outcomes of patients with CRKP and CSKP infection.

Table 3 Univariate Analysis of Risk Factors for 30-Day Mortality

Variables	Total (n=193)	Death (n=43)	Survive (n=150)	P value
Demographics				
Sex, male	129 (66.8%)	30 (69.8%)	99 (66.0%)	0.644
Age, median (IQR)	76.0 (69.0–84.0)	79.0 (71.0–86.0)	75.0 (69.0–84.0)	0.207
History of ICU stays (from hospital admission to positive respiratory specimen culture for <i>K. pneumoniae</i>)	95 (49.2%)	33 (76.7%)	62 (41.3%)	<0.001
Underlying conditions				
Charlson comorbidity index ≥ 3	130 (67.4%)	32 (74.4%)	98 (65.3%)	0.263
Immunocompromised	52 (26.9%)	22 (51.2%)	30 (20.0%)	<0.001
Chronic lung diseases	85 (44.0%)	22 (51.2%)	63 (42.0%)	0.286
Chronic renal diseases	41 (21.2%)	13 (30.2%)	28 (18.7%)	0.102
Chronic liver diseases	15 (7.8%)	4 (9.3%)	11 (7.3%)	0.919
Myocardial infarction	43 (22.3%)	9 (20.9%)	34 (22.7%)	0.809
Peripheral vascular diseases	65 (33.7%)	21 (48.8%)	44 (29.3%)	0.017
Heart failure	36 (18.7%)	11 (25.6%)	25 (16.7%)	0.186
Cerebrovascular diseases	96 (49.7%)	20 (46.5%)	76 (50.7%)	0.631
Connective tissue diseases	19 (9.8%)	5 (11.6%)	14 (9.3%)	0.656
Peptic ulcer	15 (7.8%)	3 (7.0%)	12 (8.0%)	1.000
Hematological malignancy	7 (3.6%)	2 (4.7%)	5 (3.3%)	1.000
Carcinoma	51 (26.4%)	9 (20.9%)	42 (28.0%)	0.354
Diabetes mellitus	73 (37.8%)	14 (32.6%)	59 (39.3%)	0.419
Hypertension	128 (66.3%)	30 (69.8%)	98 (65.3%)	0.588
History				
Surgical history within 3 months	117 (60.6%)	29 (67.4%)	88 (58.7%)	0.299
Previous smoking history	87 (45.1%)	19 (44.2%)	68 (45.3%)	0.894
Previous drinking history	43 (22.3%)	9 (20.9%)	34 (22.7%)	0.809
Antibiotics (within 3 months before a positive culture)				
Exposure to carbapenems	177 (91.7%)	43 (100%)	134 (89.3%)	0.025
Exposure to tigecycline	70 (36.3%)	22 (51.2%)	48 (32.0%)	0.021
Exposure to tigeicycline	24 (12.4%)	12 (27.9%)	12 (8.0%)	<0.001
Clinical severity at infection onset				
Pitt bacteremia score ≥ 3	74 (38.3%)	34 (79.1%)	40 (26.7%)	<0.001
qSOFA ≥ 2	78 (40.4%)	37 (86.0%)	41 (27.3%)	<0.001
Sepsis/septic shock	51 (26.4%)	33 (76.7%)	18 (12.0%)	<0.001
Severe pneumonia	62 (32.1%)	39 (90.7%)	23 (15.3%)	<0.001
Clinical biochemical indexes				
PCT (ng/mL)	0.4 (0.1–1.1)	0.9 (0.4–2.4)	0.2 (0.1–0.8)	0.017
HR-CRP (mg/L)	57.6 (27.1–122.1)	127.0 (42.3–154.8)	48.7 (24.8–89.6)	<0.001
D-dimer (mg/L)	0.8 (0.4–2.0)	1.3 (0.7–3.4)	0.7 (0.4–1.5)	0.099
WBC ($10^9/L$)	9.9 (7.0–13.5)	10.8 (6.0–16.1)	9.7 (7.1–12.4)	0.247
NEU ($10^9/L$)	8.0 (5.1–11.4)	9.1 (5.2–14.1)	7.5 (5.1–10.8)	0.280
LYM ($10^9/L$)	0.8 (0.5–1.3)	0.6 (0.3–1.0)	0.9 (0.5–1.3)	0.211
NEU (%)	82.8 (74.7–89.8)	88.7 (83.1–91.6)	80.5 (73.9–87.5)	0.025
LYM (%)	8.1 (5.2–15.2)	5.4 (4.2–7.1)	9.5 (5.5–15.8)	0.011
Bacteria				
CRKP infection	115 (59.6%)	33 (76.7%)	82 (54.7%)	0.009
Failure of microbiological clearance	85 (44.0%)	21 (48.8%)	64 (42.7%)	0.472
Length of stay before infection	14.0 (5.0–33.0)	12.0 (6.0–22.0)	14.0 (4.8–36.5)	0.244
Co-infection	24 (12.4%)	8 (18.6%)	16 (10.7%)	0.164
Prior <i>K. pneumoniae</i> infection or colonization in the preceding 3 years	40 (20.7%)	6 (16.3%)	33 (23.0%)	0.415

(Continued)

Table 3 (Continued).

Variables	Total (n=193)	Death (n=43)	Survive (n=150)	P value
Antimicrobial therapy				
Inappropriate empirical therapy	92 (47.7%)	19 (44.2%)	73 (49.7%)	0.604
Inappropriate targeted therapy	71 (36.8%)	12 (27.9%)	59 (39.3%)	0.171
Treatment process				
Mechanical ventilation	75 (38.9%)	29 (67.4%)	46 (30.7%)	<0.001
Admission to ICU after infection	127 (65.8%)	38 (88.4%)	89 (59.3%)	<0.001
Length of hospital stay	21 (10.0–51.5)	10 (5.0–14.0)	32.5 (14.0–61.0)	<0.001
Length of ICU stay	8 (0–25.5)	16 (12.0–25.0)	4 (0–27.3)	0.002

Abbreviations: IQR, interquartile range; ICU, intensive care unit; PCT, procalcitonin; HR-CRP, hypersensitive C-reactive protein; WBC, white blood cell count; NEU, neutrophil count; LYM, lymphocyte count.

Multivariate logistic regression showed that older age (OR = 1.107; 95% CI: 1.016–1.206; $P=0.020$), immunocompromised status (OR = 8.632; 95% CI: 1.926–38.680; $P=0.005$), severe pneumonia (OR = 51.244; 95% CI, 10.181–257.918; $P<0.001$), qSOFA score ≥ 2 (OR = 6.187; 95% CI, 1.445–26.481; $P=0.014$), exposure to tigecycline before infection (OR = 24.702; 95% CI, 2.418–252.408; $P=0.007$), and prolonged ICU stay (OR = 0.987; 95% CI, 0.977–0.997; $P=0.013$) were independent risk factors for 30-day mortality (Table 4). Kaplan–Meier analyses also confirmed that 30-day mortality was higher in patients with CRKP infection than patients with CSKP infection (Figure 4A). The patients with severe pneumonia had higher 30-day mortality than patients without severe pneumonia ($P<0.001$) (Figure 4B). The 30-day mortality of elderly patients with severe pneumonia was 62.9%. In addition, immunocompromised patients had higher 30-day mortality than immunocompetent patients ($P<0.001$) (Figure 4C). The 30-day mortality of patients with immunocompromised pneumonia was 42.3%.

Antimicrobial Therapy

Among 193 patients included, 122 patients received appropriate targeted therapy. Among those received appropriate targeted therapy, 102 patients received monotherapy, 20 patients received combination therapy. Tigecycline and carbapenems were the most commonly used monotherapy options for patients with CRKP and CSKP infection, respectively. In combination therapy, amikacin combined with tigecycline, and PB combined with tigecycline were

Table 4 Multivariate Analysis of Risk Factors for 30-Day Mortality

Variables	Univariate		Multivariate	
	P value	OR (95% CI)	P value	OR (95% CI)
Age	0.207	1.025 (0.986–1.066)	0.020	1.107 (1.016–1.206)
Gender	0.644	1.189 (0.571–2.457)	0.824	1.151 (0.332–3.994)
History of ICU stays (from hospital admission to positive respiratory specimen culture for <i>K. pneumoniae</i>)	<0.001	4.684 (2.150–10.203)	0.182	3.718 (0.540–25.621)
Immunocompromised	<0.001	4.190 (2.041–8.604)	0.005	8.632 (1.926–38.680)
CRKP infection	0.009	2.737 (1.258–5.953)	0.051	0.152 (0.023–1.011)
Severe pneumonia	<0.001	53.837 (17.552–165.130)	<0.001	51.244 (10.181–257.918)
qSOFA ≥ 2	<0.001	16.394 (6.440–41.733)	0.014	6.187 (1.445–26.481)
Admission to ICU after infection	<0.001	5.209 (1.940–13.986)	0.470	1.758 (0.381–8.104)
Exposure to tigecycline	<0.001	4.452 (1.828–10.840)	0.007	24.702 (2.418–252.402)
Inappropriate empirical therapy	0.604	0.835 (0.422–1.651)	0.295	2.806 (0.406–19.382)
Inappropriate targeted therapy	0.171	0.597 (0.284–1.255)	0.874	0.867 (0.149–5.044)
Length of ICU stay	0.002	0.999 (0.996–1.001)	0.013	0.987 (0.977–0.997)

Abbreviations: ICU, intensive care unit; qSOFA, quick Sepsis Related Organ Failure Assessment; CRKP, Carbapenem-resistant *Klebsiella pneumoniae*.

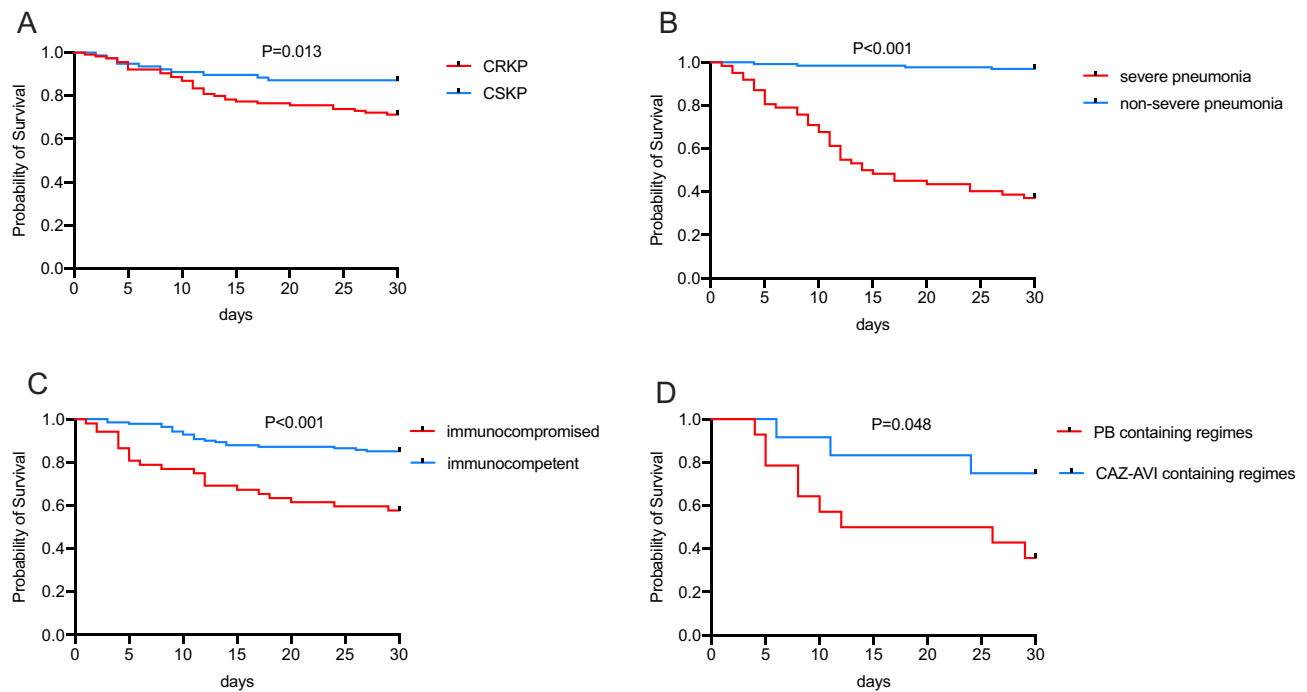


Figure 4 Kaplan–Meier analysis was used to compare the 30-day survival rate for (A) CRKP vs CSKP infection; (B) severe pneumonia vs non-severe pneumonia; (C) immunocompromised vs immunocompetent patients, and (D) patients receiving CAZ-AVI containing regimens vs polymyxin B sulfate (PB) containing regimens. The data were analyzed using SPSS 26 to obtain p-values (SPSS 26_analyze_survival_Kaplan-Meier_log-rank_p value), and the drawing was made using Prism 8 app.

common treatment options (Supplemental Table 1). In particular, 30-day mortality was significantly lower in patients received CAZ-AVI containing regimens than in patients received PB containing regimens (25.0% vs 64.3%, $P=0.048$) (Figure 4D).

Relationship Between qSOFA Score and the Prognosis of Patients

The distribution of qSOFA score and its relationship with 30-day mortality are shown in Figure 5. When qSOFA score was 0 point, the 30-day mortality rate of patients was 3.0% (2/65), qSOFA score was 1 point, the 30-day mortality of

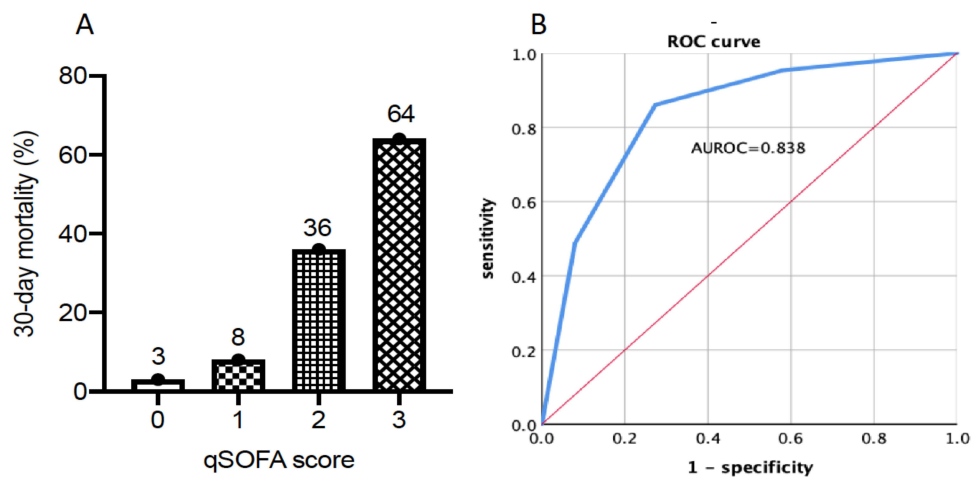


Figure 5 Distribution and mortality of patients by qSOFA score. (A) Distribution of qSOFA score (0–3) and its association with 30-day mortality (the x axis indicated the specific value of the qSOFA score when the patient developed *K. pneumoniae* infection) (B) the area under receiver operating characteristic curve (AUROC) predicted the prognosis of patients using qSOFA score. The (A) was made using Prism 8 app., the (B) was made using SPSS 26 analysis (SPSS 26_analyze_category_ROC curve).

patients was 8.0% (4/50), qSOFA score ≥ 2 , the 30-day mortality of patients was 47.4% (37/78). Among the died, 86.0% of patients had a qSOFA ≥ 2 , the AUROC was 0.838.

Discussion

HAP caused by CRKP infection was commonly reported to be associated with higher mortality,²⁵ but data regarding risk factors and clinical outcomes for CRKP pulmonary infection in the older patients was still limited. Therefore, this purpose of this study was to systematically review HAP caused by CRKP infection, especially the risk factors of morbidity and mortality and clinical outcomes, so as to provide clinical value for the treatment and control of CRKP infection.

Early identification of people at high-risk of CRKP infection is important. Previous studies demonstrated that prior central venous catheter use, sputum suction, continuous renal replacement therapy, exposure to fluoroquinolones,²⁶ hypertension, exposure to carbapenems, ICU stay,²⁷ hematologic malignancies, ICU acquired infection,²⁸ β -lactam/ β -lactamase inhibitor combinations exposure, solid organ transplantation,²⁹ liver cirrhosis, and length of hospital stay over the previous 14 days³⁰ were independent risk factors for the morbidity of CRKP infection. In this study, we found that history of ICU stays from hospital admission to positive respiratory specimen culture for *K. pneumoniae*, Charlson comorbidity index score ≥ 3 , prior exposure to carbapenems, and prior *K. pneumoniae* infection or colonization in the preceding 3 years were independent risk factors for CRKP infection.

ICU patients were more likely to undergo invasive procedures, which may hinder airway clearance, increase the risk of CRKP colonization. In addition, such invasive measures exposed ICU patients to pathogens carried by roommates or presented in the hospital environment. Therefore, the use of invasive devices should be minimized for the elderly. In humans, *K. pneumoniae* often colonizes at various mucosal surfaces, including the upper respiratory tract and the gut. In hospitalized patients, colonization rates in the nasopharynx rise to 19%, while it can be as high as 77% in the gastrointestinal tract.^{31,32} Gastrointestinal colonization serves as a major reservoir for transmission and infection to other sites. Previous study found that 16% of the patients colonized with *K. pneumoniae* were found to be infected, compared to only 3% in the non-carriers, whole-genome sequencing revealed that the patients were infected with the same strain they carried in the form of colonization.³³ This indicated that *K. pneumoniae* colonization in high-risk units (such as intensive care, transplant surgery, hematology oncology wards) at admission should be actively monitored and continuously monitored during subsequent hospitalization.

Comparing with CSKP infected patients, CRKP infected patients had higher mortality. Regarding risk factors for mortality, different populations, regions and types of infection could contribute to different results. Previous studies showed that treatment failure for infection,²⁶ CRKP infection and isolation in ICU,²⁷ severe sepsis or septic shock incidents, inadequate empirical antimicrobial therapy, corticosteroids use,²⁸ CRKP bloodstream infections, mechanical ventilation >96 hours, and platelet counts $<100 \times 10^9/L$ ²⁹ were independent risk factors for mortality of CRKP infection. In this study, we found that the independent risk factors for mortality included older age, immunocompromised status, severe pneumonia, qSOFA score ≥ 2 , empirical use of tigecycline, and prolonged ICU stay.

It has been demonstrated that age ≥ 65 years was an independent risk factor for hospital mortality of patients with pneumonia.³⁴ The incidence of pneumonia increased rapidly with age and peaked between 60 and 79 years of age.³⁵ Immunocompromised patients were prone to acquire pneumonia with high mortality. Different from the general immunocompetent population, the etiologies of lung infection in immunocompromised patients were more diverse, and the possibility of co-infection should be considered. Due to the failure to implement early and rapid diagnosis, many patients were initially treated with inappropriate antibiotics, which may cause several serious comorbidities such as respiratory failure and infectious shock, further increasing mortality.³⁶ In this study, empirical use of tigecycline before infection was associated with death. This is probably because the standard dose of tigecycline (50 mg of tigecycline every 12 h after a 100-mg loading dose) was absolutely insufficient to eradicate strains with tigecycline MIC >0.5 mg/L.³⁷ In this study, the tigecycline MIC >0.5 mg/L in 71.3% of the strains. With suboptimal pharmacokinetics properties in certain sites of infection increased potential for toxicity. High doses of tigecycline (received 100 mg of tigecycline every 12 h after a 200-mg loading dose) and combination therapy can be considered for HAP caused by multidrug-resistant bacterial infections, but caution is needed for its side effects, such as gastrointestinal.³⁸

In addition, treatment options against CRKP infections are very limited. Clinicians are compelled to use last-resort antimicrobials, like CAZ-AVI and PB. In this study, we found that the 30-day mortality was significantly lower in patients received CAV-AZI containing regimens than patients received PB containing regimens, providing encouraging results. More recently, several new agents with activity against carbapenem-resistant pathogens have been approved for clinical use or are reaching late-stage clinical development, they include β -lactam- β -lactamase inhibitor combinations (ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam), plazomicin, eravacycline, and cefiderocol. Clinicians appear to generally favor newer agent over previous best available therapy.³⁹

The knowledge of the exact mechanism of CRKP was crucial for the selection of the most appropriate antimicrobial.^{39,40} For example, ceftazidime/avibactam was not active against strains producing class B metallo- β -lactamases (MBLs), the combination of aztreonam-ceftazidime/avibactam had a treating effect against 86% of MBLs producing members of *Enterobacteriaceae* family.⁴¹ In addition, the antibiotic resistance and virulence factors could co-exist in CRKP isolates.⁴² Antibiotic resistance and virulence genes can be transmitted horizontally through plasmids, which lead to the accelerated spread of multidrug resistance among different populations of pathogens.⁴³ Understanding the direct relationship between the frequency of the genes involved in the development of virulence and resistance, which could provide a highly effective model for physicians to prescribe suitable antibiotics.⁴⁴ Determining genetic diversity for the identification of dominant species and complete knowledge of biofilm formation were necessary to stop the spread of infections in hospitals and to control and manage associated infections.⁴⁵ The information on genetic resistance profile is not reported in this article, we have collected all strains, and will further study the genetic resistance profile of strains in the future.

qSOFA has been proposed as a screening and prognostic tool in patients with suspected infection, sepsis, or septic shock, it can be used to predict the prognosis of patients.¹⁶ In this study, we found that qSOFA score ≥ 2 could predict the mortality of patients with HAP infected with *K. pneumoniae*. Previous study had shown that the accuracy of qSOFA score in predicting in-hospital mortality of elderly hospitalized patients with suspected infection was low (AUROC = 0.680).⁴⁶ One plausible reason for this difference may be that this study only focused on older patients with HAP who were infected with *K. pneumoniae*. The accuracy of qSOFA score in predicting the prognosis of patients with HAP needs to be further verified by more studies in the future.

The present work has several limitations: first, the number of cases were relatively small; second, this study mainly focused on HAP caused by *K. pneumoniae*, and lacked analysis of *K. pneumoniae* infections in other sites; third, due to the limited data available in retrospective studies, some predictors may be missing from the data analysis.

Conclusion

In summary, history of ICU stays from hospital admission to positive respiratory specimen culture for *K. pneumoniae*, Charlson comorbidity index score ≥ 3 , prior exposure to carbapenems, and prior *K. pneumoniae* infection or colonization in the preceding 3 years were associated with the development of CRKP pulmonary infection. We also found a high mortality caused by *K. pneumoniae* pulmonary infection in elderly patients with older age, immunocompromised status, severe pneumonia, qSOFA ≥ 2 , exposure to tigecycline, and prolonged ICU stays. Ceftazidime-avibactam-based regimens were associated with better outcomes. Active screening of CRKP for high-risk groups, especially for elderly patients, is conducive to the early identification, treatment and control of CRKP infections, so as to achieve the successful management.

Data Sharing Statement

The data for this study may be available by contacting the corresponding author (Lei Huang) upon reasonable request.

Ethics Approval and Consent to Participate

The Ethics Committee of Peking University First Hospital, Beijing, China, provided ethical approval for this research (2022-yan-498). As it was an observational study, informed consent was waived.

Acknowledgments

We thank Home for Researchers editorial team for language editing service.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Key R&D Program of China Research on the Precision Diagnosis, Treatment, and Integrated Prevention, Control for the elderly with common infectious disease (2020YFC2005401), Youth Clinical Research Project of Peking University First Hospital (2018CR27), National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital) (2023IR46).

Disclosure

The authors report no conflicts of interest in this work.

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