American Journal of Infection Control 47 (2019) 677–682

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

# The impact of carbapenem-resistant *Pseudomonas aeruginosa* on clinical and economic outcomes in a Chinese tertiary care hospital: A propensity score–matched analysis

Zhihui Chen MBBS [a,*], Ziqin Xu MM [a], Hongmei Wu MBBS [a], Le Chen MBBS [a], Shengchun Gao MBBS [a], Yangfang Chen MBBS [b]

[a] *Department of Infection Control, Wenzhou People's Hospital, Wenzhou, China*
[b] *Laboratory of Microbiology, Wenzhou People's Hospital, Wenzhou, China*

*Key Words:*
Carbapenem resistance
*Pseudomonas aeruginosa*
Outcome
Costs
Propensity score
Infection control

***Background:*** This study aimed to estimate the impact of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) on clinical and economic outcomes in a Chinese tertiary care hospital.

***Methods:*** Patients were assigned to a carbapenem-susceptible *P aeruginosa* group or to a CRPA group and matched using propensity score matching. In-hospital mortality, length of stay (LOS), LOS after culture, total hospital costs, daily hospital cost, and 30-day readmission were comparatively analyzed. Subgroup analysis was performed to determine the associations between the subgrouping factors and in-hospital mortality in patients with CRPA isolates.

***Results:*** Within the propensity-matched cohort, in-hospital mortality (12.6% vs 7.8%; $P = .044$), LOS (median 29.0 vs 25.5 days; $P = .026$), LOS after culture (median 18.5 vs 14.0 days; $P = .029$), total hospital costs (median $6,082.0 vs $4,954.2; $P = .015$), and daily hospital cost (median $236.1 vs $223.6; $P = .045$) were significantly higher in CRPA patients than in carbapenem-susceptible *P aeruginosa* patients. Subgroup analysis revealed a significant interaction between CRPA and age ($P = .009$).

***Conclusion:*** Prevention and control of CRPA among hospitalized patients, especially among those over the age of 65 years, is a good measurement for the reduction of mortality and medical costs derived from CRPA infection or colonization.



*Pseudomonas aeruginosa* is a gram-negative bacillus that causes a variety of clinically important infections, especially in patients with underlying comorbidities.[1,2] Compared with other pathogens, *P aeruginosa* is intrinsically resistant to a range of antimicrobial agents and is capable of acquiring additional resistance through chromosomal mutations or horizontal gene transfer, which often makes it difficult to prevent and treat.[3-5] Currently, carbapenems represent the first-line therapy for severe infection by *P aeruginosa*.[6] However, the resistance of *P aeruginosa* to these drugs has become a major public health concern.[7]

Investigators have evaluated the impact of carbapenem-resistant *P aeruginosa* (CRPA) on clinical and economic outcomes in developed countries and regions.[8-12] However, the results of these studies are inconsistent.[8-12] It has been suggested that studies should adequately adjust for the impact of potential confounding factors, such as the burden of comorbidities and the appropriateness of empirical antibiotic treatment, because patients with comorbidities or inappropriate empirical antibiotic treatment are likely to have a worse clinical outcome independent of CRPA.[13,14] It remains unclear whether CRPA has a causal relationship with subsequent mortality or whether the development of CRPA simply reflects comorbidity or inappropriate empirical antibiotic treatment within a high-risk patient population. Furthermore, the impact of CRPA on the clinical and economic outcomes has not been well studied in developing countries, including China.

This study aimed to evaluate the influence of carbapenem resistance on the clinical and economic outcomes in patients infected or colonized by *P aeruginosa* in a Chinese tertiary care hospital using propensity score matching (PSM)[15] to minimize residual confounding factors.

## METHODS

### *Study design and subjects*

This was a single-center, retrospective propensity score–matched cohort study. The *P aeruginosa* isolates, which were obtained from

* Address correspondence to Zhihui Chen, MD, Department of Infection Control, Wenzhou People's Hospital, 57 Cang Hou Rd, Lucheng District, Zhejiang 325000, China.
*E-mail address:* czhdemail@126.com (Z. Chen).
Conflicts of interest: None to report.

https://doi.org/10.1016/j.ajic.2018.10.025

patients that were admitted to Wenzhou People's Hospital (a 1,500-bed tertiary care medical center in Zhejiang, China) between January 1, 2014 and March 30, 2018, were acquired from the microbiology laboratory database (Fig 1). In cases where more than one *P aeruginosa*-positive culture was obtained from a patient during the study period, only the first *P aeruginosa*–positive culture was included. Patients were excluded from the study if they were younger than 18 years old, hosted many species of microbes, or if complete information was not on record. This study included 799 patients who fulfilled the inclusion criteria (Fig 1).

### *Antibiotic susceptibility testing*

The susceptibility to each antimicrobial agent was determined by minimum inhibitory concentration (MIC), using the broth microdilution method, and interpreted according to the criteria of the Clinical and Laboratory Standards Institute.[16] In this study, CRPA was defined as isolates with imipenem and/or meropenem MICs ≥8 mg/L. The *P aeruginosa* isolates with imipenem and/or meropenem MICs <8 mg/L were identified as carbapenem-susceptible *P aeruginosa* (CSPA).

### *Endpoints*

The primary endpoint in this study was in-hospital mortality. In-hospital mortality was defined as any death that occurred during a patient's hospital admission.

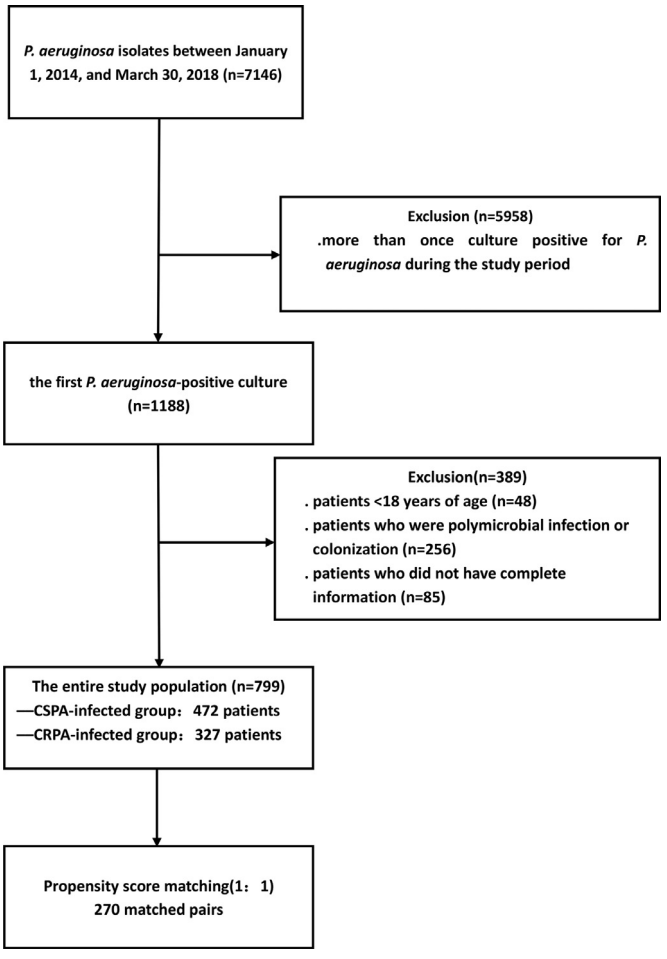


**Fig 1.** Flow chart of selection of the study cohort. CRPA, carbapenem-resistant *Pseudomonas aeruginosa;* CSPA, carbapenem-susceptible *P aeruginosa.*

Various secondary endpoints were also assessed, including length of stay (LOS), LOS after culture, total hospital costs, daily hospital cost, and 30-day readmission. Total hospital costs included the fees for integrated medical service, diagnosis, non-surgical treatment, rehabilitation care, and medication and excluded the fee for the surgeries that did not result from infection. LOS was defined as the number of days that a patient stayed in the hospital, from admission to the date that the patient was discharged, died, or was transferred to another hospital. LOS after culture was defined as the number of days that a patient stayed in the hospital from the isolation of *Pseudomonas* spp to the date that the patient was discharged, died, or was transferred to another hospital. Thirty-day readmission was defined as any repetitive admission to the same hospital within 30 days after discharge.

The data for total hospital costs and in-hospital time were extracted from the electronical medical information system of our hospital. The daily hospital cost was derived using the formula: daily hospital cost = total hospital costs/LOS. The data were collected by the first author and checked and confirmed by the coauthors.

### *Covariates*

The following covariates were included in our study: sex, source of isolates, colonization or infection of *P aeruginosa*, admission data (eg, admission to the intensive care unit [ICU], mechanical ventilation, central venous catheter, surgery, urinary catheter, hemodialysis, and hypoalbuminemia), the patient's underlying diseases (eg, chronic obstructive pulmonary disease, gastrointestinal disease, heart disease, diabetes mellitus, central nervous system disease, chronic kidney disease, solid malignancy, and acute respiratory distress syndrome), the sources of bacteremia, age, time at risk, Charlson comorbidity index, and cases of inadequate empirical antimicrobial treatment.

Colonization was defined as a positive result in culture with no indication of infection based on the symptoms, signs, or imaging results. Infection was defined as a positive result in culture in addition to symptoms, signs, and laboratory test results indicating an infectious disease. Whether a patient was colonized or infected by PA was determined by the attending physician according to the patient's condition. Hypoalbuminemia was defined as a serum albumin concentration below 3.5 g/dL.[17] Catheter-related bacteremia was defined as a blood bacterial infection that was detected at least once using peripheral vein blood culture in a patient who had used an intravascular device with no apparent alternative source of infection except the catheter. Bacteremia was classified as secondary, when the pathogen that was observed in 1 or more cultures of blood of a patient was the organism that was already identified in an infection at another site. Empirical antimicrobial therapy was considered adequate if the initial antibiotics, which were administered within 24 hours after the extraction of a sample, included at least 1 antimicrobial drug that was active in vitro. The burden of comorbidities was assessed using the Charlson comorbidity index.[18] To assess the time of exposure to the hospital environment, we used a variable termed "time at risk." For *P aeruginosa* colonization patients, time at risk was defined as the time that a patient stayed in the hospital from admission to the time when the first *P aeruginosa* sample was obtained. For *P aeruginosa* infection patients, the time at risk corresponded to the duration of the hospital stay before infection. Informed consent was not required. On extraction, the patient data were only connected with the hospital administration numbers and separated from all of the other patient identification information, such as name, identification card number, phone number, and address.

*Sample size determination*

After PSM, 540 participants were included in the final analysis. The proportion of CRPA in *P aeruginosa*-positive patients was estimated to be 40% in the cohort. If an odds ratio of 1.71 for CRPA patients relative to CSPA patients was to be achieved, a sample size of 226 patients in each group was needed to obtain a power of 80% for a significance level of 5%, with a 2-tailed test.

*Statistical analysis*

All analyses were performed with the use of the statistical package R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and Empower (X&Y Solutions, Inc, Boston, MA). PSM was performed by greedy matching using a caliper of 0.05 (±SD) of the logit of the propensity score to balance the baseline characteristics between the CRPA and CSPA groups. The propensity score was estimated using a nonparsimonious multivariable logistic regression model, with CRPA as the dependent variable and all the baseline characteristics that are presented in Table 1 as covariates. Standardized differences were used to assess prematch imbalances and postmatch balance for all of the baseline covariates, and the findings are presented as a Love plot.[19] A standardized difference of less than 10% suggests negligible bias.[20] Categorical data are summarized using absolute values (percentage). Normally distributed continuous data, such as age, are expressed as mean (±SD). Data with a skewed distribution, including the Charlson comorbidity index, time at risk, LOS, LOS after culture, total hospital costs, and daily hospital cost, are expressed as medians (with interquartile range). The $\chi^2$ or the Fisher exact tests were used for categorical variables, and the Student t test or the Wilcoxon test was used for continuous variables, as appropriate. Interaction and subgroup analyses were conducted according to age (<65 and ≥65 years), sex (men and women), infectious condition (*P aeruginosa* infection and *P aeruginosa* colonization), and Charlson comorbidity index (<5 and ≥5 points) using the Log likelihood ratio test. A *P* value of ≤ .05 was statistically significant. All tests were 2-tailed.

## RESULTS

*Patient characteristics*

A total of 7,146 *P aeruginosa* isolates were queried from the microbiology laboratory database, and 799 patients fulfilled the inclusion criteria. Among the included patients, 327 (40.9%) were identified as having CRPA (Fig 1). The baseline characteristics of the overall and matched

**Table 1**
Demographic and clinical characteristics before and after PSM

| | Full cohort (n = 799) | | | Propensity score–matched cohort (n = 540) | | |
|---|---|---|---|---|---|---|
| Characteristic | CRPA n = 327 | CSPA n = 472 | Stand diff, % | CRPA n = 270 | CSPA n = 270 | Stand diff, % |
| Male, n (%) | 233 (71.3) | 283 (60.0) | 24.0 | 190 (70.3) | 185 (68.5) | 4.0 |
| Microbiological finding, n (%) | | | | | | |
| Sputum | 274 (83.8) | 285 (60.4) | 54.0 | 222 (82.2) | 196 (72.6) | 6.0 |
| Urine | 20 (6.1) | 97 (20.6) | 43.6 | 18 (6.7) | 37 (13.7) | 4.1 |
| Pus/wound | 6 (1.8) | 52 (11.0) | 38.3 | 6 (2.2) | 15 (5.6) | 5.4 |
| Blood | 18 (5.5) | 23 (4.9) | 2.7 | 15 (5.6) | 18 (6.7) | 4.6 |
| Catheter | 2 (0.6) | 4 (0.8) | 27.2 | 2 (0.7) | 2 (0.7) | 0.0 |
| Others | 7 (2.1) | 11 (2.3) | 1.4 | 7 (2.6) | 2 (0.7) | 7.4 |
| *Pseudomonas aeruginosa* infection, n (%) | 84 (25.7) | 93 (19.7) | 14.4 | 46 (17) | 46 (17) | 0.0 |
| Admission data, n (%) | | | | | | |
| Admitted to ICU | 86 (26.3) | 86 (18.3) | 19.3 | 60 (22.2) | 56 (20.7) | 3.6 |
| Mechanic ventilation | 126 (38.5) | 87 (18.4) | 45.7 | 85 (31.5) | 76 (28.1) | 7.3 |
| Central venous catheter | 167 (51.1) | 131 (27.8) | 49.1 | 115 (42.6) | 110 (40.7) | 3.8 |
| Surgery | 134 (41.0) | 164 (34.7) | 13.0 | 100 (37.0) | 95 (35.2) | 3.9 |
| Urinary catheter | 168 (51.4) | 187 (39.6) | 23.9 | 121 (44.8) | 116 (43.0) | 3.7 |
| Hemodialysis | 4 (1.2) | 8 (1.7) | 4.2 | 4 (1.5) | 3 (1.1) | 3.5 |
| Hypoalbuminemia | 67 (20.5) | 83 (17.6) | 7.4 | 51 (18.9) | 42 (15.6) | 8.8 |
| Underlying disease, n (%) | | | | | | |
| COPD | 16.0 | 40 (8.5) | 25.1 | 37 (13.7) | 38 (14.1) | 1.1 |
| Gastrointestinal disease | 64 (18.3) | 79 (16.7) | 4.2 | 58 (21.5) | 57 (21.1) | 0.9 |
| Heart disease | 75 (22.9) | 80 (16.9) | 15.1 | 60 (22.2) | 58 (21.5) | 1.8 |
| Diabetes mellitus | 84 (25.7) | 107 (22.7) | 7.0 | 66 (24.4) | 71 (26.3) | 4.3 |
| CNS disease | 151 (46.2) | 155 (32.8) | 15.7 | 114 (42.2) | 103 (38.1) | 8.3 |
| Chronic kidney disease | 88 (26.9) | 146 (30.9) | 8.8 | 72 (26.7) | 76 (28.1) | 3.3 |
| Solid malignancy | 49 (15.0) | 62 (13.1) | 5.5 | 38 (14.1) | 41 (15.2) | 3.1 |
| ARDS | 18 (5.5) | 14 (3.0) | 12.4 | 9 (3.3) | 9 (3.3) | 0.0 |
| Primary bacteremia | | | | | | |
| Central line catheter related | 3 (0.9) | 4 (0.8) | 1.1 | 3 (1.1) | 4 (1.5) | 3.3 |
| Unknown | 10 (3.1) | 12 (2.5) | 3.6 | 8 (3.0) | 9 (3.3) | 1.7 |
| Secondary bacteremia | | | | | | |
| Respiratory tract | 3 (0.9) | 4 (0.8) | 1.1 | 2 (0.7) | 3 (1.1) | 4.2 |
| Urinary tract | 1 (0.3) | 2 (0.4) | 1.7 | 1 (0.4) | 1 (0.4) | 0.0 |
| Others | 1 (0.3) | 1 (0.2) | 2.0 | 1 (0.4) | 1 (0.4) | 0.0 |
| Inadequate empirical therapy | 26 (8.0) | 71 (15.0) | 22.1 | 25 (9.3) | 24 (8.9) | 1.3 |
| Continuous variables | | | | | | |
| Age (y, mean ± SD) | 69.3 ± 16.4 | 68.6 ± 16.5 | 4.3 | 69.7 ± 16.4 | 70.0 ± 14.9 | 2.0 |
| Time at risk* (median [IQR]) | 7.0 (1.0-19.0) | 3.0 (1.0-11.0) | 22.5 | 6.0 (2.0-16.0) | 6.0 (1.0-17.0) | 5.3 |
| Charlson comorbidity index (median [IQR]) | 5.0 (3.0-7.0) | 4.0 (3.0-6.0) | 19.2 | 5.0 (3.0~7.0) | 5.0 (3.0~6.0) | 3.1 |

NOTE. Data are presented as number (%) of patients or mean ± SD or median (IQR).
*ARDS*, acute respiratory distress syndrome; *CNS*, central nervous system; *COPD*, chronic obstructive pulmonary disease; *CRPA*, carbapenem-resistant *P aeruginosa*; *CSPA*, carbapenem-susceptible *P aeruginosa*; *ICU*, intensive care unit; *IQR*, interquartile range; *PSM*, propensity score matching; *Stand diff*, standardized difference.
*Adjusted for time at risk, which was defined as the time that a patient stayed in the hospital from admission to the time when the first *P aeruginosa* sample was obtained, for *P aeruginosa* colonization patients, or as the duration of hospital stay before infection, for *P aeruginosa* infection patients.

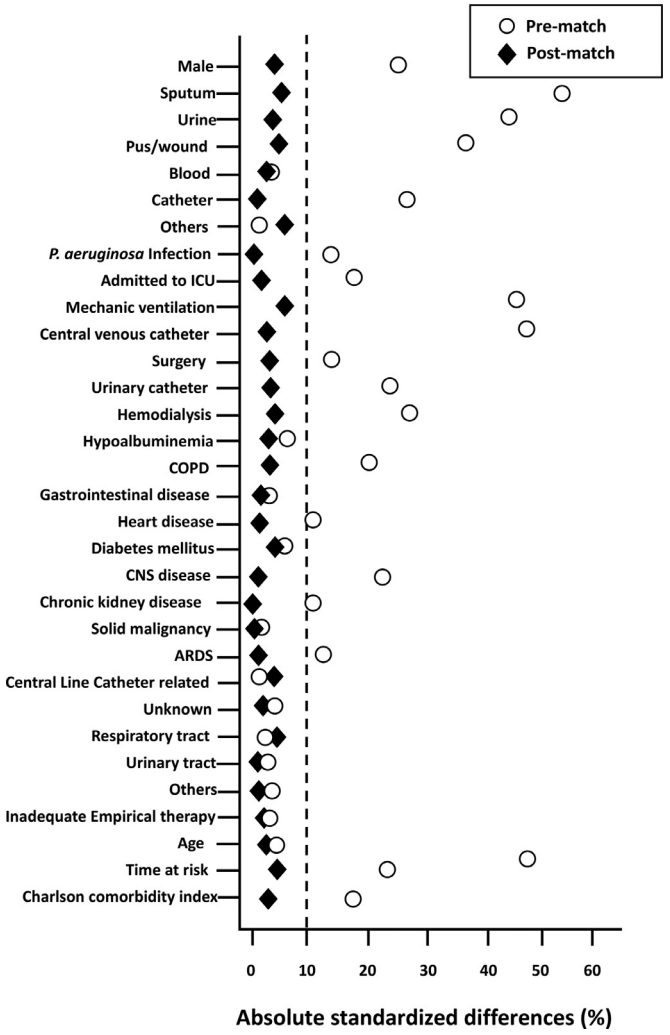


**Fig 2.** Love plots for the absolute standardized differences in variables before and after propensity score matching. *ARDS*, acute respiratory distress syndrome; *CNS*, central nervous system; *COPD*, chronic obstructive pulmonary disease; *ICU*, intensive care unit.

cohorts are listed in Table 1. Before PSM, several differences were observed between the 2 groups. The rates of *P aeruginosa* infection, chronic obstructive pulmonary disease, heart disease, central nervous system disease, acute respiratory distress syndrome, inadequate empirical therapy, and invasive procedures were higher in the CRPA patients than in the CSPA patients. Conversely, the likelihood of isolates from urine was lower in the CRPA patients than in the CSPA patients. Furthermore, patients with CRPA were more frequently admitted to the ICU than patients with CSPA, particularly in male and elderly patients. Patients with CRPA also had a higher Charlson comorbidity index and a longer time at risk than patients with CSPA (Table 1). After PSM, all the baseline characteristics were similar between the groups. The standardized differences of all the covariates were less than 10% (Fig 2).

### *Clinical outcomes and costs*

Table 2 shows that overall, patients with CRPA isolates were significantly more likely to die during their hospital stay than patients with CSPA isolates (15.6% vs 6.4%; $P < .001$). Similarly, both the LOS and the LOS after culture were longer in patients with CRPA isolates than in patients with CSPA isolates (median 29.0 vs 21.0 days; $P < .001$ and median 17.0 vs 13.0 days; $P = .005$, respectively). Furthermore, patients with CRPA isolates had a significantly higher total hospital cost (median $6,483.7 vs $3,378.9; $P < .001$) and a significantly higher daily hospital cost (median $249.6 vs $187.2; $P < .001$) than patients with CSPA isolates (Table 2).

In the matched samples, in-hospital mortality (12.6% vs 7.8%; $P = .044$), LOS (median 29.0 vs 25.5 days; $P = .026$), LOS after culture (median 18.5 vs 14.0 days; $P = .029$), total hospital costs (median $6,082.0 vs $4,954.2; $P = .015$), and daily hospital cost (median $236.1 vs $223.6; $P = .045$) were significantly higher in patients with CRPA isolates than in patients with CSPA isolates. Table 2 demonstrates that no difference was observed in the 30-day readmission rate between the 2 groups.

Subgroup analysis did not show a significant interaction between carbapenem resistance or any of the subgrouping factors, except age ($P = .009$). Carbapenem resistance was associated with a higher risk of in-hospital mortality among patients 65 years of age or older (odds ratio, 3.8; 95% confidence interval, 1.8-8.0), but not among patients younger than 65 years old (odds ratio, 0.6; 95% confidence interval, 0.2-2.0 [Fig 3]).

## DISCUSSION

One of the key findings of this study was that in the propensity score–matched cohort, the risk of in-hospital mortality was higher in the CRPA patients than in the CSPA patients. Hospital resource utilization was also found to be greater for patients with CRPA, as evidenced by a longer LOS (including LOS and LOS after culture) and higher costs (including total hospital costs and daily hospital cost). The 30-day readmission rate did not differ between the CRPA and the CSPA patients.

**Table 2**
Primary and secondary outcomes before and after PSM

| | Unadjusted | | | PSM adjusted | | |
|---|---|---|---|---|---|---|
| Outcome | CRPA n = 327 | CSPA n = 472 | *P* value | CRPA n = 270 | CSPA n = 270 | *P* value |
| In-hospital mortality, n (%) | 51 (15.6) | 30 (6.4) | < .001 | 34 (12.6) | 21 (7.8) | .044 |
| LOS (d), median (IQR) | 29.0 (17.0, 44.0) | 21.0 (11.0, 34.0) | < .001 | 29.0 (17.0, 42.3) | 25.5 (13.8, 41.3) | .026 |
| LOS after culture*, median (IQR) | 17.0 (8.0, 32.0) | 13.0 (7.0, 25.0) | .005 | 18.5 (8.0, 30.0) | 14.0 (7.0, 28.0) | .029 |
| Total hospital costs†, median (IQR) | 6,483.7 (3,420.8, 14,591.7) | 3,378.9 (1,969.5, 7,744.0) | < .001 | 6,082.0 (3,333.1, 12,662.6) | 4,954.2 (2,755.9, 10,162.1) | .015 |
| Daily hospital cost, median (IQR) | 249.6 (182.8, 399.4) | 187.2 (133.4, 264.6) | < .001 | 236.1 (163.3, 397.0) | 223.6 (152.4, 311.8) | .045 |
| 30-d readmission, n (%) | 47 (14.4) | 55 (11.7) | .257 | 33 (12.2) | 38 (14.1) | .524 |

NOTE. Data are presented as number (%) of patients or median (IQR).
*CRPA*, carbapenem-resistant *Pseudomonas aeruginosa*; *CSPA*, carbapenem-susceptible *P aeruginosa*; *IQR*, interquartile range; *LOS*, length of stay; *PSM*, propensity score matching.
*LOS after culture was defined as the number of days that a patient stayed in the hospital from isolation of *Pseudomonas* to the date that the patient was discharged, died, or transferred to another hospital.
†Total hospital costs included the fees for integrated medical service, diagnosis, nonsurgical treatment, rehabilitation care, and medication with exclusion of the fee for the surgeries that did not result from infection.

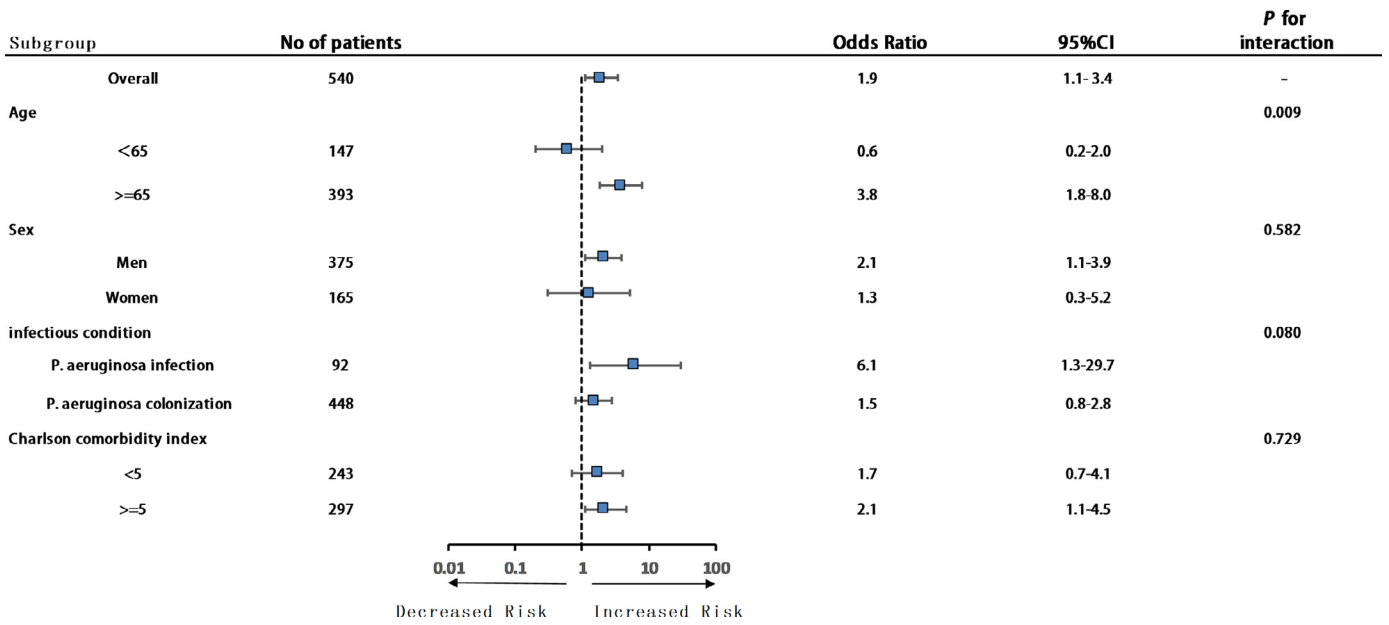


**Fig 3.** Relationship between carbapenem-susceptible *Pseudomonas aeruginosa* and in-hospital mortality in the subgroups of the patients. *CI*, confidence interval.

The in-hospital mortality was higher in the CRPA group than in the CSPA group. This finding is consistent with previous observations that the in-hospital mortality is higher in patients with CRPA isolates than in patients with CSPA isolates.[11,12] It has been proposed that this association is likely the result of inadequate therapy and may be related to the degree of severity of the underlying disease.[8,21] This postulation is supported by our observation that the underlying diseases were more severe in the CRPA patients than in the CSPA patients before PSM. However, even after the severity of underlying diseases and the rate of inadequate empirical therapy were matched between groups using PSM, the in-hospital mortality was still higher in the CRPA patients than in the CSPA patients. This indicates that there are more factors that mediate the observed increased rate of in-hospital mortality in CRPA patients, in addition to the severity of the underlying illness and inadequate empirical therapy. Moreover, the existence of increased virulence in the resistant microorganisms, which might cause the negative influence on clinical outcomes, has not been confirmed.[14,15] In fact, it has been reported that antibiotic resistance generally confers a reduction in the fitness of microorganisms, decreasing the possibility of deleterious inflammatory responses being triggered in the host.[16] Nevertheless, the cause of the observed elevated mortality in CRPA patients is still not clear. Many factors, including the bacterium biofilm formation ability and the health status of the host, are likely to be involved.[22]

Of interest in this study is the observed associated between CRPA and the increased in-hospital mortality among patients aged 65 years or older, but not among the younger patients. This difference may be a result of the senescent immune system.[23,24] This suggests that action should be taken to prevent and control the spread of CRPA among elderly patients.

To our knowledge, this is the first study that has addressed the economic burden of CRPA patients in mainland China. We observed the medical costs as well as the length of hospital stay were higher in patients carrying CRPA than in patients carrying CSPA. This finding is in agreement with the observations of Lautenbach et al,[12] who observed that the LOS and total hospital cost were substantially higher for patients carrying CRPA than in other patients, even after adjusting for confounding factors, such as the duration of hospitalization, transfer from another health care facility, and patient location in an ICU. Additionally, the present study found that the economic burden of both the total hospital cost and the daily hospital cost was larger in the CRPA patients than in the CSPA patients. No significant difference was observed in the risk of 30-day readmission between the 2 study groups. This indicates that there was no difference in the quality of the hospital care among the patients with PA isolates. However, the sample size, as well as the data for 30-day hospital readmissions, was limited to our hospital. Thus, some caution should be taken in the interpretation of these results.

Because CRPA is linked to worse outcomes and a higher economic burden on hospitals, it is imperative to take effective infection prevention and control interventions to reduce the transmission of CRPA among hospitalized patients. Active culture surveillance,[25,26] hand hygiene compliance,[27,28] provision of a single room, and application of contact precautions for multidrug-resistant gram-negative bacteria patients should be enforced to prevent the spread of CRPA in hospitals.[28,29] Furthermore, hospital cleaning and disinfection should also be enhanced to control the spread of CRPA in the endemic setting.[30,31] Meanwhile, medical care centers should be properly monitored to prevent the domination of CRPA, due to the massive and long-term usage of carbapenem in the microenvironment. Antimicrobial stewardship programs should be established to preserve the utility and to devise the most rational treatment paradigms for new broad-spectrum antibiotics.[32,33] When it is not affordable to provide single rooms to all CRPA patients, such as in some developing countries, priority may be given to patients aged 65 years and older to achieve a cost-effective reduction in mortality, because our data suggest that the mortality rate is higher in elderly patients with CRPA.

## CONCLUSIONS

Our study has several limitations. First, selection bias may be an issue, as our study was performed at a single institution. Conditions vary among hospitals and regions, and thus, caution should be taken in extrapolating the results of this study. Second, although this study used the PSM method to reduce the biases that are inherent in observational studies, hidden bias is inevitable because the PSM cannot rule out residual confounding factors from unknown or unmeasured variables. Third, compared with the total hospital costs, hospitalization costs after culture may be a more suitable indicator of economic burden. However, we could not obtain this indicator, due to limited

data access methods. Finally, the sample size in this study may still be too small to have enough power to detect the significance of the difference between the subgroups. Additional larger longitudinal multicenter studies are required to clarify this association.

Our findings suggest that effective action should be taken to prevent and control CRPA among hospitalized patients, especially among patients aged 65 years and older, to reduce the mortality rate and medical costs derived from CRPA infection or colonization.

## References


1. Fernández-Barat L, Ferrer M, De RF, Gabarrús A, Esperatti M, Terraneo S, et al. Intensive care unit-acquired pneumonia due to *Pseudomonas aeruginosa* with and without multidrug resistance. J Infect 2016;74:142-52.
2. Li Z, Kosorok M, Farrell P, Laxova A, West S, Green C, et al. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. JAMA 2005;293:581-8.
3. Castanheira M, Deshpande LM, Costello A, Davies TA, Jones RN. Epidemiology and carbapenem resistance mechanisms of carbapenem-non-susceptible *Pseudomonas aeruginosa* collected during 2009–11 in 14 European and Mediterranean countries. J Antimicrob Chemother 2014;69:1804-14.
4. Tam VH, Chang KT, Larocco MT. Prevalence, mechanisms, and risk factors of carbapenem resistance in bloodstream isolates of *Pseudomonas aeruginosa*. Diagn Microbiol Infect Dis 2007;58:309-14.
5. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. Clin Infect Dis 2006;43(Suppl 2):49-56.
6. Rahal JJ. The role of carbapenems in initial therapy for serious Gram-negative infections. Crit Care 2008;12:1-7.
7. Buehrle DJ, Shields RK, Clarke LG, Potoski BA, Clancy CJ, Nguyen MH. Carbapenem-resistant *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and microbiologic treatment failure. Antimicrob Agents Chemother 2016;61:e01243-16.
8. Liu Q, Li X, Li W, Du X, He JQ, Tao C, et al. Influence of carbapenem resistance on mortality of patients with *Pseudomonas aeruginosa* infection: a meta-analysis. Sci Rep 2015;5:11715.
9. Lin KY, Lauderdale TL, Wang JT, Chang SC. Carbapenem-resistant *Pseudomonas aeruginosa* in Taiwan: prevalence, risk factors, and impact on outcome of infections. J Microbiol Immunol Infect 2014;49:52-9.
10. Dantas RC, Ferreira ML, Gontijo-Filho PP, Ribas RM. *Pseudomonas aeruginosa* bacteraemia: independent risk factors for mortality and impact of resistance on outcome. J Med Microbiol 2014;63:1679-87.
11. Joo EJ, Kang CI, Ha YE, Kang SJ, Park SY, Chung DR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. Microb Drug Resist 2011;17:305-12.
12. Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, et al. Imipenem resistance in *Pseudomonas aeruginosa*: emergence, epidemiology, and impact on clinical and economic outcomes. Infect Control Hosp Epidemiol 2010;31:47-53.
13. Pena C, Suarez C, Gozalo M, Murillas J, Almirante B, Pomar V, et al. Prospective multicenter study of the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bloodstream infections. Antimicrob Agents Chemother 2012;56:1265-72.
14. Harbarth S, Nobre V, Pittet D. Does antibiotic selection impact patient outcome? Clin Infect Dis 2007;44:87-93.
15. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.
16. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty-second informational supplement. CLSI document M02-A11–M07-A9]. Wayne(PA): Clinical and Laboratory Standards Institute; 2012.
17. Merriel SW, Carroll R, Hamilton F, Hamilton W. Association between unexplained hypoalbuminaemia and new cancer diagnoses in UK primary care patients. Fam Pract 2016;33:449-52.
18. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-83.
19. Ekundayo OJ, Adamopoulos C, Ahmed MI, Pitt B, Young JB, Fleg JL, et al. Oral potassium supplement use and outcomes in chronic heart failure: a propensity-matched study. Int J Cardiol 2010;141:167-74.
20. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. N Engl J Med 2015;372:1213-22.
21. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis 2006;42(Suppl 2):82-9.
22. Su JJ, Sang SY, Bae IK, Jeong SH, Kim JM, Lee K. Risk factors for mortality in patients with bloodstream infections caused by carbapenem-resistant *Pseudomonas aeruginosa*: clinical impact of bacterial virulence and strains on outcome. Diagn Microbiol Infect Dis 2014;80:130-5.
23. Tariq MA, Hazeldine J, Lord JM. Innate immunosenescence and its impact on health in old age. Basel(Switzerland): Springer International Publishing; 2017.
24. Dewan SK, Zheng SB, Xia SJ, Bill K. Senescent remodeling of the immune system and its contribution to the predisposition of the elderly to infections. Chin Med J (Engl) 2012;125:3325-31.
25. Derde L, Cooper BS, Goossens H, Malhotrakumar S, Willems R, Gniadkowski M, et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect Dis 2014;14:31-9.
26. Landman D, Babu E, Shah N, Kelly P, Olawole O, Bäcker M, et al. Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration. J Antimicrob Chemother 2012;67:1427-31.
27. Geladari A, Karampatakis T, Antachopoulos C, Iosifidis E, Tsiatsiou O, Politi L, et al. Epidemiological surveillance of multidrug–resistant gram–negative bacteria in a solid organ transplantation department. Transpl Infect Dis 2017;19:e12686.
28. Tacconelli E, Cataldo MA, Dancer SJ, De AG, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect 2014;20:1-55.
29. Eveillard M, Eb F, Tramier B, Schmit JL, Lescure FX, Biendo M, et al. Evaluation of the contribution of isolation precautions in prevention and control of multi-resistant bacteria in a teaching hospital. J Hosp Infect 2001;47:116-24.
30. Otter JA, Yezli S, French GL. The role of contaminated surfaces in the transmission of nosocomial pathogens. Basel(Switzerland): Springer International Publishing; 2014.
31. Passaretti CL, Otter JA, Reich NG, Myers J, Shepard J, Ross T, et al. An evaluation of environmental decontamination with hydrogen peroxide vapor for reducing the risk of patient acquisition of multidrug-resistant organisms. Clin Infect Dis 2013;56:27-35.
32. Zi L, Cheng B, Zhang K, Xie G, Wang Y, Hou J, et al. Pharmacist-driven antimicrobial stewardship in intensive care units in East China: a multicenter prospective cohort study. Am J Infect Control 2017;45:983-9.
33. Malani AN, Richards PG, Kapila S, Otto MH, Czerwinski J, Singal B. Clinical and economic outcomes from a community hospital's antimicrobial stewardship program. Am J Infect Control 2013;41:145-8.