Clinical and Economic Impact of Third-Generation Cephalosporin-Resistant Infection or Colonization Caused by *Escherichia coli* and *Klebsiella pneumoniae*: A Multicenter Study in China

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**Abstract:** Quantifying economic and clinical outcomes for interventions could help to reduce third-generation cephalosporin resistance and *Escherichia coli* or *Klebsiella pneumoniae*. We aimed to compare the differences in clinical and economic burden between third-generation cephalosporin-resistant *E. coli* (3GCREC) and third-generation cephalosporin-susceptible *E. coli* (3GCSEC) cases, and between third-generation cephalosporin-resistant *K. pneumoniae* (3GCRKP) and third-generation cephalosporin-susceptible *K. pneumoniae* (3GCSKP) cases. A retrospective and multicenter study was conducted. We collected data from electronic medical records for patients who had clinical samples positive for *E. coli* or *K. pneumoniae* isolates during 2013 and 2015. Propensity score matching (PSM) was conducted to minimize the impact of potential confounding variables, including age, sex, insurance, number of diagnoses, Charlson comorbidity index, admission to intensive care unit, surgery, and comorbidities. We also repeated the PSM including length of stay (LOS) before culture. The main indicators included economic costs, LOS and hospital mortality. The proportions of 3GCREC and 3GCRKP in the sampled hospitals were 44.3% and 32.5%, respectively. In the two PSM methods, 1804 pairs and 1521 pairs were generated, and 1815 pairs and 1617 pairs were obtained, respectively. Compared with susceptible cases, those with 3GCREC and 3GCRKP were associated with significantly increased total hospital cost and excess LOS. Inpatients with 3GCRKP were significantly associated with higher hospital mortality compared with 3GCSKP cases, however, there was no significant difference between 3GCREC and 3GCSEC cases. Cost reduction and outcome improvement could be achieved through a preventative approach in terms of both antimicrobial stewardship and preventing the transmission of organisms.

**Keywords:** *Escherichia coli*; *Klebsiella pneumoniae*; third-generation cephalosporin; 3GCREC; 3GCRKP; economic cost; length of stay; hospital mortality
1. Introduction

Escherichia coli and Klebsiella pneumoniae, both species of the family Enterobacteriaceae, are the most prevalent gram-negative bacteria causing intra-abdominal infection, urinary tract infection, and bloodstream infection \[1,2\], and can be resistant to the widely used antibiotics, such as third-generation cephalosporins, namely third-generation cephalosporin-resistant E. coli (3GCREC) and third-generation cephalosporin-resistant K. pneumoniae (3GCRKP) \[3,4\]. The World Health Organization (WHO) classified 3GCREC and 3GCRKP as critical-priority bacteria \[5\]. Alvarez-Uria et al. (2018) pointed out that global resistant prevalence was 64.5% for 3GCREC and 66.9% for 3GCRKP by 2030 \[6\]. The China Antimicrobial Resistance Surveillance System reported that the average proportion of 3GCREC and 3GCRKP in 2019 was 51.9% and 31.9%, respectively \[7\], which was higher than the levels in United Kingdom (11.0% and 13.0%) and in Sweden (8.3% and 5.5%) \[8\].

Third-generation cephalosporin resistance in E. coli or K. pneumoniae is a global concern \[9,10\]. Infections caused by 3GCREC and 3GCRKP were associated with higher mortality, longer length of stay (LOS), and more economic costs compared with susceptible cases \[11-13\]. de Kraker et al. (2011) showed that 15,183 episodes of 3GCREC were associated with 2712 excess deaths, 120,065 extra LOS, and €18.1 million increased costs in 31 European countries \[13\]. It was concluded that patients with third-generation cephalosporin-resistant Enterobacteriaceae contributed to 16.1% of hospital mortality, 4.9 days of LOS, and €320 of infection cost in one study by Stewardson et al. (2016) \[14\]. In addition, colonization of E. coli and K. pneumoniae, as the reservoir for infection with these organisms, was also a risk factor for higher mortality, longer LOS, and increased hospital costs \[15,16\].

Quantifying clinical and economic outcomes would facilitate strategies towards the containment of third-generation cephalosporin resistance and E. coli or K. pneumoniae. Resistance to third-generation cephalosporins by E. coli or K. pneumoniae, which represented the major mechanism of antimicrobial resistance, had been reported as independently associated with a poor outcome and increased use of healthcare resources \[12,17\]. However, no significant difference in hospital mortality between 3GCREC and third-generation cephalosporin-susceptible E. coli (3GCSEC) was reported \[13,18\]. In China, there was only one study exploring longer LOS and higher hospital costs attributable to extended spectrum beta-lactamase (ESBL)-positive intra-abdominal infection caused by E. coli or K. pneumoniae \[19\]. The clinical and economic outcomes of 3GCREC and 3GCRKP remained largely uninvestigated in China. In this study, we aimed to compare the clinical and economic difference between 3GCREC and 3GCSEC, and between 3GCRKP and third-generation cephalosporin-susceptible K. pneumoniae (3GCSSK), in China.

2. Materials and Methods

2.1. Study Site

We conducted this study in four tertiary hospitals in China; three in Zhejiang Province (Site 1, Site 3, and Site 4) are a general provincial hospital, general county hospital, and combined traditional Chinese and Western medicine provincial hospital, respectively, and one in Shandong Province (Site 2) is a general provincial hospital. There are 3200, 3500, 1727, 2100 of hospital beds and 170,000, 160,000, 80,000, 50,000 inpatients per year in these four hospitals, respectively.

2.2. Study Design and Patients

A retrospective and multicenter study was conducted. We collected data from electronic medical records (EMR) for patients who had clinical samples positive for E. coli or K. pneumoniae isolates, that were detected in any specimens (e.g., blood, stool, cervical, and urethral sources) between 2013 and 2015 \[20\]. Patients were defined as 3GCREC/3GCRKP cases if patients infected or colonized by E. coli or K. pneumoniae were resistant or intermediate to any third-generation cephalosporin or as 3GCSEC/3GCSSK cases if they were susceptible to all third-generation cephalosporins according to the Clinical and Laboratory Standards Institute (CLSI) definitions \[15,21\]. We only included the first
episode for each patient to avoid duplication. The study was approved by the institutional review board of Zhejiang University School of Public Health, who waived the need for informed consent. All inpatients data were anonymized prior to analysis.

2.3. Data Collection

We collected patient characteristics from EMR. The data for each patient included demographics (age, sex, and insurance), comorbidities (disease diagnosis, and Charlson comorbidity index (CCI), hospital events (admitting service, surgical services, and date of hospital and intensive care unit (ICU) admission or discharge), microbiological data, clinical outcomes (discharged alive or death during hospitalization), and economic costs.

2.4. Propensity Score Matching

To minimize the impact of potential confounding variables, we performed propensity score matching (PSM) with 1:1 nearest-neighbor matching. PSM, widely used to control for confounding in observational studies, is a powerful statistical matching technique for reducing a set of confounding variables to a single propensity score in order to effectively control for all observed confounding bias [22]. There were two step-by-step rounds of PSM. First, we employed a logistic regression model with third-generation cephalosporin-resistant or-susceptible as dependent variables, and with age, sex, insurance, number of diagnoses, CCI, admission to ICU, surgery, and comorbidities as independent variables. Second, because LOS is the major contributor to additional economic cost, we repeated the PSM including LOS before culture as a potential confounding variable. The generated pairs matched with potential confounding variables were subjected to further analyses of economic costs, LOS and hospital mortality.

2.5. Indicators and Statistical Analyses

The main indicators included economic costs, LOS and hospital mortality. The economic costs comprised total hospital cost, medication cost (antibiotic cost), diagnostic cost, treatment cost, material cost, and other costs, and they covered out-of-pocket payment by patients themselves and payments by health insurers. All economic costs were presented in 2015 United States (US) dollars values according to purchasing power parities and the consumer price index of China [23,24].

The Wilcoxon rank-sum test and $\chi^2$ test were conducted to compare the main indicators between 3GCREC and 3GCSEC and between 3GCRKP and 3GCSKP for the quantitative and qualitative variables, respectively. Statistical analyses were performed using STATA. All $p$-values were two-tailed, and those less than 0.05 were considered statistically significant.

3. Results

The proportions of 3GCREC and 3GCRKP in the sampled hospitals were 44.3% and 32.5%, respectively. A total of 2056 inpatients infected or colonized with 3GCREC and 2588 with 3GCSEC, 1679 with 3GCRKP and 3485 with 3GCSKP were included during the study period. There were significant differences in sex, admission to ICU, surgery, and some comorbidities between the 3GCREC and 3GCSEC groups, and in age, number of diagnoses, admission to ICU, surgery, and some comorbidities between the 3GCRKP and 3GCSKP groups before PSM. Therefore, we conducted PSM to minimize the influencing of variables in two steps. First, excluding LOS before culture as a potential confounding variable, we obtained 1815 pairs and 1617 pairs, respectively. In addition, 1804 pairs and 1521 pairs were generated, respectively, after PSM for potential confounding variables including LOS before culture. There were no differences in patients’ characteristics between the two groups after PSM (Table 1).
Table 1. Characteristics of patients with 3GCREC and 3GCSEC and with 3GCRKP and 3GCSKP before PSM and after PSM.

| Baseline Characteristics       | Before PSM | After PSM for Potential Confounding Variables Excluding LOS Before Culture | After PSM for Potential Confounding Variables Including LOS Before Culture |
|-------------------------------|------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
|                               | 3GCS EC    | 3GCS REC                                                                  | 3GCS KP                                                                    | 3GCR KP                                                                  |
|                               | p Value    | p Value                                                                   | p Value                                                                   | p Value                                                                   |
| Number of inpatients, n       | 2588       | 2056                                                                      | 3485                                                                      | 1679                                                                     |
| Age in years, median (range)  | 73 (0–100) | 72 (0–100)                                                                | 72 (0–100)                                                                | 72 (0–100)                                                               |
| Sex male, n (%)               | 1174       | 600                                                                       | <0.000                                                                    | 0.233                                                                    |
| Surgery, n (%)                | <0.000     | 0.917                                                                     | 0.917                                                                     | 0.917                                                                    |
| Myocardial infarction, n (%)  | 0.000      | 0.741                                                                     | 0.43                                                                      | 0.914                                                                    |
| Congestive heart failure, n (%)| 0.000     | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Peripheral vascular disease, n (%)| 0.000      | 0.83                                                                       | 0.83                                                                       | 0.847                                                                    |
| Cerebrovascular diseases, n (%)| 0.000     | 0.017                                                                     | 0.017                                                                     | 0.316                                                                    |
| Dementia, n (%)               | 0.000      | 0.879                                                                     | 0.879                                                                     | 0.302                                                                    |
| Chronic pulmonary disease, n (%)| 0.000     | 0.741                                                                     | 0.741                                                                     | 0.323                                                                    |
| Connective tissue disease, n (%)| 0.000     | 0.064                                                                     | 0.064                                                                     | 0.358                                                                    |
| Mild liver disease, n (%)     | 0.000      | 0.179                                                                     | 0.179                                                                     | 0.057                                                                    |
| Peptic ulcer disease, n (%)   | 0.000      | 0.42                                                                       | 0.42                                                                       | 0.266                                                                    |

Excluding LOS Before Culture

|                               | 3GCR EC    | 3GCR KP                                                                  | 3GCS KP                                                                    | 3GCS KP                                                                  |
|                               | p Value    | p Value                                                                   | p Value                                                                   | p Value                                                                   |
| Number of diagnoses, median (range) | 5 (1–29) | 6 (1–37)                                                                | 0.95                                                                      | 0.722                                                                    |
| Charlson comorbidity index, median (range) | 6 (1–29) | 6 (1–37)                                                                | 0.95                                                                      | 0.722                                                                    |
| Admission to ICU, n (%)       | 175        | <0.000                                                                    | 0.000                                                                     | 0.938                                                                    |
| Surgery, n (%)                | 770        | <0.000                                                                    | 0.000                                                                     | 0.938                                                                    |
| Myocardial infarction, n (%)  | 63         | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Congestive heart failure, n (%)| 439       | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Peripheral vascular disease, n (%)| 19        | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Cerebrovascular diseases, n (%)| 1077      | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Dementia, n (%)               | 96         | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Chronic pulmonary disease, n (%)| 442       | <0.000                                                                    | 0.000                                                                     | 0.65                                                                     |
| Connective tissue disease, n (%)| 84         | 0.064                                                                     | 0.064                                                                     | 0.65                                                                     |
| Mild liver disease, n (%)     | 86         | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Peptic ulcer disease, n (%)   | 2.40       | 0.42                                                                       | 0.42                                                                       | 0.266                                                                    |

Including LOS Before Culture

|                               | 3GCS EC    | 3GCS KP                                                                  | 3GCR KP                                                                  | 3GCR KP                                                                  |
|                               | p Value    | p Value                                                                   | p Value                                                                   | p Value                                                                   |
| Number of diagnoses, median (range) | 5 (1–29) | 6 (1–37)                                                                | 0.95                                                                      | 0.722                                                                    |
| Charlson comorbidity index, median (range) | 6 (1–29) | 6 (1–37)                                                                | 0.95                                                                      | 0.722                                                                    |
| Admission to ICU, n (%)       | 175        | <0.000                                                                    | 0.000                                                                     | 0.938                                                                    |
| Surgery, n (%)                | 770        | <0.000                                                                    | 0.000                                                                     | 0.938                                                                    |
| Myocardial infarction, n (%)  | 63         | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Congestive heart failure, n (%)| 439       | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Peripheral vascular disease, n (%)| 19        | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Cerebrovascular diseases, n (%)| 1077      | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Dementia, n (%)               | 96         | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Chronic pulmonary disease, n (%)| 442       | <0.000                                                                    | 0.000                                                                     | 0.65                                                                     |
| Connective tissue disease, n (%)| 84         | 0.064                                                                     | 0.064                                                                     | 0.65                                                                     |
| Mild liver disease, n (%)     | 86         | 0.017                                                                     | 0.017                                                                     | 0.65                                                                     |
| Peptic ulcer disease, n (%)   | 2.40       | 0.42                                                                       | 0.42                                                                       | 0.266                                                                    |
Table 1. Cont.

| Baseline Characteristics                  | 3GCS EC | 3GCREC | p Value | 3GCS KP | 3GCR KP | p Value | 3GCS EC | 3GCREC | p Value | 3GCS KP | 3GCR KP | p Value | 3GCS EC | 3GCREC | p Value | 3GCS KP | 3GCR KP | p Value |
|-------------------------------------------|---------|--------|---------|---------|---------|---------|---------|--------|---------|---------|---------|---------|---------|---------|--------|---------|---------|---------|---------|---------|
| Diabetes mellitus, n (%)                  | 894     | 3G     | 0.884   | 706     | 3G     | 0.631   | 952     | 3G     | 0.631   | 448     | 3G     | 0.631   | 628     | 3G     | 0.944   | 630     | 3G     | 0.185   | 401     | 3G     | 0.185   | 434     | 3G     | 0.185   | 633     | 3G     | 0.78    | 625     | 3G     | 0.78    | 411     | 3G     | 0.78    | 409     | 3G     | 0.78    | 0.935   | 0.935   |
| Diabetes mellitus with chronic complications, n (%) | 132     | 3G     | 0.007   | 167     | 3G     | 0.404   | 115     | 3G     | 0.404   | 63     | 3G     | 0.404   | 119     | 3G     | 0.066   | 93      | 3G     | 0.852   | 61      | 3G     | 0.852   | 59      | 3G     | 0.852   | 97      | 3G     | 0.094   | 121     | 3G     | 0.094   | 57      | 3G     | 0.094   | 0.847   | 0.847   |
| Moderate to severe chronic kidney disease, n (%) | 232     | 3G     | 0.832   | 188     | 3G     | 0.012   | 235     | 3G     | 0.012   | 189    | 3G     | 0.012   | 171     | 3G     | 0.775   | 166     | 3G     | 0.529   | 165     | 3G     | 0.529   | 176     | 3G     | 0.529   | 166     | 3G     | 0.529   | 167     | 3G     | 0.529   | 153     | 3G     | 0.529   | 0.477   | 0.477   |
| Hemiplegia, n (%)                          | 33      | 3G     | 0.521   | 22      | 3G     | 0.026   | 24      | 3G     | 0.026   | 22     | 3G     | 0.026   | 18      | 3G     | 0.629   | 21      | 3G     | 0.544   | 20      | 3G     | 0.544   | 24      | 3G     | 0.544   | 20      | 3G     | 0.544   | 18      | 3G     | 0.544   | 20      | 3G     | 0.544   | 0.744   | 0.744   |
| Solid tumor without metastases, n (%)      | 316     | 3G     | 0.119   | 207     | 3G     | 0.019   | 224     | 3G     | 0.019   | 126    | 3G     | 0.019   | 198     | 3G     | 0.751   | 204     | 3G     | 0.793   | 128     | 3G     | 0.793   | 124     | 3G     | 0.793   | 206     | 3G     | 0.793   | 121     | 3G     | 0.793   | 126     | 3G     | 0.793   | 0.474   | 0.474   |
| Leukemia, n (%)                            | 40      | 3G     | 0.191   | 21      | 3G     | 0.084   | 51      | 3G     | 0.084   | 40     | 3G     | 0.084   | 22      | 3G     | 0.878   | 21      | 3G     | 0.574   | 38      | 3G     | 0.574   | 43      | 3G     | 0.574   | 38      | 3G     | 0.574   | 38      | 3G     | 0.574   | 35      | 3G     | 0.574   | 39      | 3G     | 0.574   | 0.638   | 0.638   |
| Malignant lymphoma, n (%)                  | 34      | 3G     | 0.013   | 12      | 3G     | 0.025   | 33      | 3G     | 0.025   | 28     | 3G     | 0.025   | 8       | 3G     | 0.37    | 12      | 3G     | 0.78    | 25      | 3G     | 0.78    | 25      | 3G     | 0.78    | 25      | 3G     | 0.78    | 32      | 3G     | 0.841   | 24      | 3G     | 0.841   | 0.41    | 0.41    |
| Severe liver disease, n (%)                | 52      | 3G     | 0.37    | 33      | 3G     | 0.457   | 43      | 3G     | 0.457   | 26     | 3G     | 0.457   | 29      | 3G     | 0.698   | 32      | 3G     | 0.89    | 26      | 3G     | 0.89    | 27      | 3G     | 0.89    | 26      | 3G     | 0.89    | 27      | 3G     | 0.89    | 26      | 3G     | 0.89    | 0.41    | 0.41    |
| Metastatic tumor, n (%)                    | 129     | 3G     | 0.48    | 112     | 3G     | 0.000   | 206     | 3G     | 0.000   | 59     | 3G     | 0.000   | 99      | 3G     | 0.409   | 88      | 3G     | 0.323   | 59      | 3G     | 0.323   | 70      | 3G     | 0.323   | 59      | 3G     | 0.323   | 70      | 3G     | 0.323   | 59      | 3G     | 0.323   | 35      | 3G     | 0.323   | 0.653   | 0.653   |

3GCREC: third-generation cephalosporin-resistant *Escherichia coli*; 3GSEC: third-generation cephalosporin-susceptible *E. coli*; 3GCRKP: third-generation cephalosporin-resistant *Klebsiella pneumoniae*; PSM: propensity score matching; LOS: length of stay; ICU: intensive care unit.
After PSM for potential confounding variables excluding LOS before culture, inpatients with third-generation cephalosporin resistance were significantly associated with higher economic costs and LOS than susceptible cases. The median differences (95% certainty interval (CI)) in total hospital cost, antibiotic cost, medication cost, diagnostic cost, treatment cost, and material cost were $1366 ($1179–$1453), $152 ($146–$168), $627 ($577–$715), $81 ($57–$79), $363 ($324–$393), and $134 ($129–$143), respectively, for inpatients with 3GCREC (Table 2), and were $7671 ($7419–$7932), $881 ($809–$982), $4461 ($4168–$4658), $620 ($566–$708), $1612 ($1501–$1756), and $583 ($535–$641), respectively, for inpatients with 3GCRKP (Table 3). The median LOS of inpatients with 3GCREC and 3GCRKP were longer than those with 3GCSEC and 3GCSKP, with a difference of 4 days and 11 days, respectively (Table 4). In addition, there was no significant difference in hospital mortality between the 3GCREC and 3GCSEC groups (\( p = 0.281 \)), however, a significant difference with 3.09% (2.78–3.39%) of hospital mortality was found between the 3GCRKP and 3GCSKP groups (\( p < 0.000 \)) (Table 5).

After PSM for potential confounding variables including LOS before culture, the differences in economic costs, LOS and hospital mortality for inpatients with 3GCREC and 3GCRKP were lower than the results after PSM for variables excluding LOS before culture. The differences in total hospital cost, antibiotic cost, medication cost, diagnostic cost, treatment cost, and material cost between the 3GCREC and 3GCSEC groups and between the 3GCRKP and 3GCSKP groups were statistically significant, with median differences of $1140 ($942–$1227), $127 ($127–$147), $515 ($456–$592), $67 ($61–$85), $271 ($245–$296), and $107 ($101–$114), respectively, for inpatients with 3GCREC (Table 2), and with median differences of $4763 ($4340–$5024), $729 ($655–$814), $2998 ($2695–$3310), $445 ($380–$460), $952 ($989–$1015), and $340 ($299–$383), respectively, for inpatients with 3GCRKP (Table 3). The LOS of inpatients with 3GCREC or 3GCRKP was significantly longer than that of inpatients with 3GCSEC or 3GCSKP, with a median difference of 2.5 days and 7 days, respectively (Table 4). In addition, no significant difference in hospital mortality between the 3GCREC and 3GCSEC groups was found (\( p = 0.508 \)), but significant difference existed between the 3GCRKP and 3GCSKP groups (\( p = 0.001 \)) (Table 5).
Table 2. Economic costs of patients with 3GCREC and 3GCSEC for potential confounding variables.

| Confounding Variables | Hospital Cost ($) | 3GCREC | 3GCSEC | Difference | p Value |
|-----------------------|-------------------|--------|--------|------------|---------|
|                       | Median 95% CI     | Median 95% CI | Median 95% CI | Median 95% CI |   |
| Excluding LOS before culture | | | | | |
| Total hospital cost    | 3867 3558 4185 | 5233 4737 5638 | 366 1179 1453 | <0.000 |
| Antibiotic cost        | 126 99 143 | 278 246 311 | 152 146 168 | <0.000 |
| Medication cost        | 1418 1286 1563 | 2045 1863 2279 | 627 577 715 | <0.000 |
| Diagnostic cost        | 873 844 914 | 955 801 992 | 81 57 79 | <0.000 |
| Treatment cost         | 778 719 858 | 1142 1043 1250 | 363 324 393 | <0.000 |
| Material cost          | 187 160 225 | 321 289 368 | 134 129 143 | <0.000 |
| Other costs            | 8 8 9 | 8 8 10 | 0 1 1 | <0.000 |
| Including LOS before culture | | | | | |
| Total hospital cost    | 4057 3791 4435 | 5197 4733 5662 | 1140 942 1227 | <0.000 |
| Antibiotic cost        | 132 108 150 | 260 235 297 | 127 127 147 | <0.000 |
| Medication cost        | 1522 1385 1669 | 2037 1840 2281 | 515 456 592 | <0.000 |
| Diagnostic cost        | 886 848 916 | 953 909 1022 | 67 61 85 | <0.000 |
| Treatment cost         | 841 773 934 | 1111 1018 1207 | 271 245 296 | <0.000 |
| Material cost          | 199 172 238 | 306 273 352 | 107 101 114 | <0.000 |
| Other costs            | 8 7 9 | 8 8 10 | 1 1 1 | <0.000 |

3GCREC: third-generation cephalosporin-resistant *Escherichia coli*; 3GCSEC: third-generation cephalosporin-susceptible *E. coli*; LOS: length of stay; CI: certainty interval.

Table 3. Economic costs of patients with 3GCRKP and 3GCSKP for potential confounding variables.

| Potential Confounding Variables | Hospital Cost ($) | 3GCSKP | 3GCRKP | Difference | p Value |
|--------------------------------|-------------------|--------|--------|------------|---------|
|                                | Median 95% CI     | Median 95% CI | Median 95% CI | Median 95% CI |   |
| Excluding LOS before culture   | | | | | |
| Total hospital cost            | 8084 7380 9029 | 15,754 14,799 16,961 | 7671 7419 7932 | <0.000 |
| Medication cost                | 490 430 538 | 1372 1239 1521 | 881 809 982 | <0.000 |
| Diagnostic cost                | 3461 3122 3781 | 7923 7290 8439 | 4461 4168 4658 | <0.000 |
| Treatment cost                 | 1397 1332 1472 | 2017 1898 2180 | 620 566 708 | <0.000 |
| Material cost                  | 1637 1491 1768 | 3249 2992 3524 | 1612 1501 1756 | <0.000 |
| Other costs                    | 472 419 536 | 1055 954 1177 | 583 535 641 | <0.000 |
|                                | 14 12 16 | 17 15 20 | 3 3 4 | <0.000 |
| Including LOS before culture   | | | | | |
| Total hospital cost            | 9699 9089 10,537 | 14,463 13,428 15,561 | 4763 4340 5025 | <0.000 |
| Antibiotic cost                | 526 467 590 | 1255 1122 1404 | 729 655 814 | <0.000 |
| Medication cost                | 4166 3811 4571 | 7164 6506 7881 | 2998 2695 3310 | <0.000 |
| Diagnostic cost                | 1452 1380 1554 | 1896 1761 2014 | 445 380 460 | <0.000 |
| Treatment cost                 | 2043 1831 2240 | 2995 2852 3255 | 952 989 1015 | <0.000 |
| Material cost                  | 623 566 689 | 963 866 1071 | 340 299 383 | <0.000 |
| Other costs                    | 16 14 18 | 16 14 19 | 0 1 1 | 0 0.4680 |

3GCRKP: third-generation cephalosporin-resistant *Klebsiella pneumoniae*; 3GCSKP: third-generation cephalosporin-susceptible *K. pneumoniae*; LOS: length of stay; CI: certainty interval.
Table 4. Length of stay of patients with 3GCREC and 3GCSEC and with 3GCRKP and 3GCSKP for potential confounding variables.

| Potential Confounding Variables | LOS (Days) | Third-Generation Cephalosporins-Susceptible | Third-Generation Cephalosporins-Resistant | Difference | p Value |
|--------------------------------|------------|---------------------------------------------|------------------------------------------|------------|---------|
|                                |            | Median | 95% CI | Median | 95% CI | Median | 95% CI |
| Excluding LOS before culture   | 3GCREC vs. 3GCSEC | 16     | 16-17 | 20     | 19-21 | 4      | 3-4   | <0.000 |
|                                | 3GCRKP vs. 3GCSKP | 20     | 19-21 | 31     | 30-32 | 11     | 11-11 | <0.000 |
| Including LOS before culture   | 3GCREC vs. 3GCSEC | 17     | 16-17 | 19.5   | 18-21 | 2.5    | 2-4   | <0.000 |
|                                | 3GCRKP vs. 3GCSKP | 23     | 22-24 | 30     | 29-31 | 7      | 7-7   | <0.000 |

3GCREC: third-generation cephalosporin-resistant *Escherichia coli*; 3GCSEC: third-generation cephalosporin-susceptible *E. coli*; 3GCRKP: third-generation cephalosporin-resistant *Klebsiella pneumoniae*; 3GCSKP: third-generation cephalosporin-susceptible *K. pneumoniae*; LOS: length of stay; CI: certainty interval.

Table 5. Hospital mortality of patients with 3GCREC and 3GCSEC and with 3GCRKP and 3GCSKP for potential confounding variables.

| Potential Confounding Variables | Mortality Rate (%) | Third-Generation Cephalosporins-Susceptible | Third-Generation Cephalosporins-Resistant | Difference | p Value |
|--------------------------------|--------------------|---------------------------------------------|------------------------------------------|------------|---------|
|                                |                    | Rate | 95% CI | Rate | 95% CI | Rate | 95% CI |
| Excluding LOS before culture   | 3GCREC vs. 3GCSEC  | 2.15 | 1.58-2.93 | 2.7  | 2.05-3.55 | 0.55  | 0.47-0.62 | 0.281 |
|                                | 3GCRKP vs. 3GCSKP | 3.65 | 2.84-4.68 | 6.74 | 5.62-8.07 | 3.09  | 2.78-3.39 | <0.000 |
| Including LOS before culture   | 3GCREC vs. 3GCSEC | 2.36 | 1.58-2.94 | 2.49 | 1.87-3.32 | 0.33  | 0.29-0.38 | 0.508 |
|                                | 3GCRKP vs. 3GCSKP | 3.81 | 2.86-4.89 | 6.51 | 5.35-7.9  | 2.7   | 2.39-3.01 | 0.001 |

3GCREC: third-generation cephalosporin-resistant *Escherichia coli*; 3GCSEC: third-generation cephalosporin-susceptible *E. coli*; 3GCRKP: third-generation cephalosporin-resistant *Klebsiella pneumoniae*; 3GCSKP: third-generation cephalosporin-susceptible *K. pneumoniae*; LOS: length of stay; CI: certainty interval.
4. Discussion

Previous studies mainly focused on antibiotic utilization and resistance mechanisms and the clinical and economic outcomes of 3GCREC and 3GCRKP in China remained largely uninvestigated. To the best of our knowledge, this is the first study to quantify the clinical and economic outcome of 3GCREC and 3GCRKP in mainland China using the PSM method with large sample size and multiple hospital settings. We focused on *E. coli* or *K. pneumoniae*, avoiding non-specific effects from a combination of bacteria [14,25]. In this study, we found that compared with third-generation cephalosporin-susceptible cases, those with 3GCREC and 3GCRKP were associated with significantly increased total hospital cost and excess LOS. In addition, inpatients with 3GCRKP were significantly associated with higher hospital mortality compared with 3GCSPK cases, however, there was no significant difference between the 3GCREC and 3GCSEC groups.

Conducting economic and clinical evaluation for interventions could help to reduce the transmission of 3GCREC or 3GCRKP in hospital settings [26]. It was demonstrated that third-generation cephalosporin resistance increased the economic costs and prolonged the LOS among inpatients with *E. coli* and *K. pneumoniae* [11–15,18,19,25,27–32]. For example, Hu et al. (2010) showed that ESBL-positive intra-abdominal infection led to attributable hospital costs and excess hospital stay in China [19]. MacVane et al. (2018) reported that urinary tract infection caused by ESBL-producing *E. coli* or *K. pneumoniae* was associated with significant hospital cost and hospital stay in the United States [31]. Meanwhile, one study explored the possibility that colonization with ESBL producing *E. coli* was associated with longer LOS and higher hospital costs as well [16].

In addition, inpatients with 3GCRKP were significantly associated with higher hospital mortality compared with those with 3GCSPK, which was consistent with other studies [2,32]. However, there was no significant difference in hospital mortality between 3GCREC and 3GCSEC in our study, which was different compared to other studies conducted in European countries [13,18]. Meanwhile, some studies also found there was no difference in hospital mortality between ESBL-producing *E. coli* cases and non-ESBL-producing cases [16,33]. Different conclusions might be associated with different study design, sample size, geography, resistant pattern, etc. Therefore, this finding needs to be further explored in the future. In addition, the manners in which the use of beta-lactams might affect prevalence of third-generation cephalosporin resistance remained to be fully elucidated [27].

LOS could increase daily bed cost, and might contribute to more treatment service and diagnostic service, therefore, LOS was the major contributor to economic costs [34]. In this study, we applied the PSM method using two step-by-step rounds [29,30,35]. Although the inclusion of LOS before culture as an independent variable in PSM could attenuate the effect of 3GCREC or 3GCRKP on economic costs, LOS and hospital mortality, the conclusion was unchanged when LOS before culture was excluded between the two groups.

This study is not without limitations. First, due to the retrospective nature of our study, it was difficult to distinguish infection or colonization. It was necessary to explore the burden of 3GCREC and 3GCRKP, either infection or colonization, because colonization was an important reservoir for organisms of infection. Prospective studies among patients with infections need to be conducted in the future. Second, PSM was used to balance potential confounding factors, however, some unmeasured variables might still be there. Third, as we had data from between 2013 and 2015 only, we were able to analyze only data corresponding to this study period. Although the study period did not influence the conclusions, future studies with updated data are warranted.

5. Conclusions

Third-generation cephalosporin resistance increased economic costs and prolonged LOS among inpatients with *E. coli* and *K. pneumoniae*. In addition, inpatients with 3GCRKP were significantly associated with higher hospital mortality compared with 3GCSPK cases, however, there was no significant difference in hospital mortality between the 3GCREC and 3GCSEC groups. Given the clinical and economic burden associated with 3GCREC and 3GCRKP that we have demonstrated,
efforts to control the development and spread of third-generation cephalosporin resistance and *E. coli* and *K. pneumoniae* should be a priority. Cost reduction and outcome improvement could be achieved through a preventative approach in terms of both antimicrobial stewardship and preventing the transmission of organisms. In addition, proper assessment before the empirical use of third-generation cephalosporins is recommended to mitigate costs.

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**Conflicts of Interest:** The authors declare no conflict of interest.

**Abbreviations**

3GCREC: third-generation cephalosporin-resistant *Escherichia coli*; 3GCRKP: third-generation cephalosporin-resistant *Klebsiella pneumoniae*; WHO: World Health Organization; LOS: length of stay; 3GCSEC: third-generation cephalosporin-susceptible *E. coli*; ESBL: extended spectrum beta-lactamase; 3GCSKP: third-generation cephalosporin-susceptible *K. pneumoniae*; EMR: electronic medical record; CLSI: Clinical and Laboratory Standards Institute; CCI: Charlson comorbidity index; ICU: intensive care unit; PSM: propensity score matching; CI: certainty interval.

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