Clinical characteristics, antibiotic-resistant patterns and prognostic factors in cancer patients with nosocomial infections caused by extended-spectrum beta-lactamase-producing Escherichia coli: a retrospective study from 2013 to 2019

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Abstract

Background: Nosocomial infections due to Extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) is increasing worldwide. This study aimed to describe the clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by ESBL-PE in cancer patients.

Methods: This retrospectively analyzed patients with nosocomial infections caused by E. coli from August 2013 to May 2019 and was conducted to investigate the risk factors, clinical features, outcomes, and antibiotic-resistant patterns of these infections.

Results: Of the 1008 nosocomial infection episodes, 265 patients suffered from infections with E. coli, and 155 episodes were caused by ESBL-PE. A multivariate analysis showed that the length of antibiotics treatment more than 6.93 days was an independent risk factor for nosocomial infections in cancer patients caused by ESBL-PE. ECOG performance status score more than 2, presence of respiratory tract infection, septic shock, lymphocytopenia, and hypoproteinemia were independent risk factors for 30-day mortality in cancer patients caused by ESBL-PE. Antimicrobial susceptibility showed that the isolated ESBL-PE were highly resistant to aztreonam and third-generation cephalosporins.

Conclusions: The length of antibiotics treatment more than 6.93 days increased the risk ratio for ESBL-PE caused nosocomial infections. However, there was no significant difference in the prognoses of patients with ESBL-PE and non-ESBL-PE caused nosocomial infections. ECOG performance status score more than 2, presence of respiratory tract infection, septic shock, lymphocytopenia, and hypoproteinemia were independent risk factors for 30-day mortality in cancer patients.
patients with nosocomial infections caused by E. coli. The isolated ESBL-PE were highly resistant to aztreonam and third-generation cephalosporins.

Background

Recently, the incidence of nosocomial infections due to Extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) is increasing worldwide. It was reported that ESBL-PE pathogens were causative of 20% of all Gram-negative nosocomial infections in patients with malignancy, and the isolation rate has been increasing over time [1]. Unfortunately, antibiotics administration for these infections are limited due to Extended-spectrum β-lactamases (ESBLs) mediates resistance to a wide variety of antibiotics [2].

Cancer patients are more susceptible to severe infection, including those caused by ESBL-PE as these patients can be immunocompromised due to malnutrition, invasive procedures, surgery, chemotherapy, radiation, and some new treatment modalities [3]. As a result, these infections became a significant therapeutic challenge for clinicians due to limited treatment strategy and are associated with delayed initiation of adequate treatment for malignancy, prolonged hospitalization, poor prognosis, increased health care costs, and high case-fatality rate [4, 5]. Therefore, rapid initiation of appropriate antibiotic therapy is pivotal for cancer patients with nosocomial infections caused by ESBL-PE, and since most empirical regimens do not adequately cover these pathogens [6]. Besides, studies have also demonstrated that inappropriate empirical antibiotic treatment is associated with worse outcomes and survival [4].

To our knowledge, most of the previous studies have only focused on bloodstream infections (BSIs), although these infections in sites other than the bloodstream are
not rare (such as the urinary tract, respiratory tract, and gastrointestinal tract). Few reports have compared the clinical, epidemiological, and microbiological characteristics of nosocomial infections caused by ESBL-PE in cancer patients. This study was therefore performed to describe the clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by ESBL-PE in cancer patients.

Methods

Study design

This retrospective observational single-center cohort study was conducted to evaluate clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by ESBL-PE in cancer patients. The electronic medical record database at the First Affiliated Hospital of Xi’an Jiaotong University, a 2560-bed medical center with a comprehensive cancer center in the northwest of China, was reviewed to identify cancer patients with nosocomial infections caused by ESBL-PE between August 2013 to May 2019. Patients with hematological malignancies were all excluded. Episodes of nosocomial infections were classified into two groups according to the status of ESBL, and the data for ESBL-producers was compared with that of non-ESBL-producers. In case of recurrence of infection after the initial hospital discharge, only the initial episode was analyzed.

Data collection

The following clinical data were collected from electronic medical records: age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, primary location of the disease, existence of distant metastasis, AJCC TNM
categories, primary sites of infection, comorbidities and severity of underlying conditions according to the Charlson comorbidity index [7], existence of fever, types of cancer therapy within 30 days (surgery, chemotherapy, radiotherapy or concurrent chemoradiotherapy), corticosteroid treatment within previous 30 days, prior infection before hospital admission, Granulocyte colony-stimulating factor (G-CSF) use within 30 days, empirical antibiotics use within 30 days, the presence of indwelling catheters or other devices, invasive procedure within previous 30 days, length of antibiotics treatment, intensive care unit (ICU) admission during hospitalization, existence of septic shock, mechanical ventilation, outcome of the analyzed infection episode (death or discharged), the worst values of laboratory parameters before infection diagnosis including blood routine test, serum albumin, procalcitonin (PCT), antibiotic susceptibility tests of ESBL-negative E. coli and ESBL-positive E. coli.

Definitions

E. coli infection was defined as an infection manifested by the presence in at least one positive clinical sample for the same pathogen. Fever was defined as an axillary temperature of 38.3 °C on one occasion or a temperature of > 38.0 °C on two or more occasions during 12 h [8]. Nosocomial infection was defined as signs or symptoms of infection started > 48 h after hospital admission or < 48 h after hospital discharge. Otherwise, the case was considered community onset [9].

Study outcomes

We aimed to describe the clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by ESBL-PE in cancer patients and to present 30-day mortality and its associated risk factors
Statistical Analysis

All statistical analyses were performed by the SPSS software version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Means ± standard deviation was used for continuous quantitative variables, which were parametric (with normal distribution, checked by Shapiro test, boxplots, and histograms), while median and interquartile ranges were used for non-parametric continuous variables. The chi-square or Fisher's exact tests were used for categorical data analyses. Variables that were associated with ESBL in the univariate analysis (P ≤ 0.1) were entered into a multivariate logistic regression analysis using stepwise selection. We used univariate and multivariate logistic regression analyses to identify the risk factors and independent risk factors for 30-day mortality of cancer patients with nosocomial infections caused by ESBL-PE as described above. All variables in the univariate analysis (P ≤ 0.1) and variables with clinical significance were entered into a multivariable model.

Results

Essential characteristics of the study population

During the seven years, there were 14695 patients admitted to the oncology center of the First Affiliated Hospital of Xi'an Jiaotong University and received systemic treatment. In total, 1008 cancer patients developed nosocomial infection, and E. coli caused 265 episodes. These patients were classed into ESBL-PE infection group (n = 155, 58.5%) and non-ESBL-PE infection group (n = 110, 41.5%) (Fig. 1). It shows that the prevalence of ESBL-PE infection has been increased dramatically from 2013 to 2019, and the majority of patients had ESBL-PE caused nosocomial
infections that were detected throughout the year with a peak in June and August (Fig. 2). The demographic and clinical characteristics of included patients are summarized in Table 1. There were no significant differences in age and gender between the two groups (59.74 ± 12.41 vs. 58.17 ± 11.20, P = 0.286; male, 33 vs. 46, P = 0.955). Diabetes mellitus, renal disease, and liver disease were found in 18 (6.8%), 16 (6.0%), and 13 (4.9%) patients, respectively. Of the primary infection sites of the 265 nosocomial infection episodes caused by E. coli, urinary tract infection was the major reason for nosocomial infections, accounting for 59.2% of the cases, followed by bloodstream infections (18.9%) and abdominal cavity infections (7.5%). The most frequent diagnoses were gynecological cancer in 99 (37.4%), colon and rectal cancer in 39 (14.7%), and breast cancer in 26 (9.8%) patients.

Risk factors for nosocomial infections in cancer patients caused by ESBL-PE

A univariate analysis (Table 1) showed that risk factors for nosocomial infections in cancer patients caused by ESBL-PE included presence of urinary tract infection (P = 0.025), presence of abdominal cavity infection (P = 0.003), presence of indwelling urinary catheters (P = 0.011), presence of drains postoperation (P = 0.008), presence of nasogastric tube (P = 0.005), length of antibiotics treatment (P = 0.003), and intensive care unit admission (P = 0.014). The results of multivariate analysis showed that the length of antibiotics treatment more than 6.93 days (OR = 1.80, P = 0.049) was an independent risk factor for nosocomial infections in cancer patients caused by ESBL-PE.

Risk factors for 30-day mortality in cancer patients with nosocomial
infections caused by E. coli

The cancer patients with nosocomial infections caused by E. coli were classified into survivor and non-survivor groups based on the outcome at 30 days. The overall case-fatality rate of the 265 patients was 10.2% (27/265), and the overall case-fatality caused by ESBL-PE was 6.8% (18/265). A survival curve analysis (Fig. 3) showed that the 30-day mortality among cancer patients with nosocomial infections caused by ESBL-PE group was higher than non-ESBL-PE group (11.6% vs. 8.2%, $\chi^2 = 0.381$, $P = 0.537$), and the difference was not statistically significant. Furthermore, the patients were divided into bloodstream infection group/non- bloodstream infection group and septic shock group/non-septic shock group according to primary infection sites and the presence of septic shock. There was no significant difference in the mortalities between these groups among patients with nosocomial infections, as detailed in Fig. S1 (Supplementary Material).

In this study, we used a stepwise logistics regression model to identify the prognostic significance of the clinical data for cancer patients with nosocomial infections caused by ESBL-PE and non-ESBL-PE. The results of the univariate analyses demonstrated that existence of distant metastasis, stage of cancer, primary sites of infection (respiratory tract infection, urinary tract infection, and bloodstream infection), presence of liver disease, received chemotherapy or concurrent chemoradiotherapy within 30 days, corticosteroid therapy within 30 days, prior G-CSF use within 30 days, presence of percutaneous pleural drainage tube, mechanical ventilation, septic shock, laboratory examination results including hemoglobin, lymphocytes count, and albumin were significantly variables (Table 2). Results of the multivariate stepwise logistic regression analyses identified ECOG performance status, presence of respiratory tract infection, septic shock,
lymphocytes count, and albumin as independent factors for 30-day mortality in the study population (Table 2).

**Antimicrobial susceptibility for cancer patients with nosocomial infections caused by E. coli**

We then investigated the antimicrobial sensitivity of the isolated ESBL-PE and non-ESBL-PE to commonly used antibiotics. The results showed that both ESBL-PE and non-ESBL-PE were highly sensitive to meropenem (100.0% vs. 100.0%), imipenem (100.0% vs. 100.0%), amikacin (92.9% vs. 99.1%), tigecycline (89.3% vs. 100.0%), and piperacillin/tazobactam (88.3% vs. 99.1%). Compared with non-ESBL-PE, the isolated ESBL-PE were highly resistant to ceftriaxone (98.1% vs. 9.2%), ceftazidime (48.1% vs. 3.6%), cefepime (38.8% vs. 1.8%), aztreonam (77.3% vs. 6.4%), ciprofloxacin (76.5% vs. 54.5%), and levofloxacin (73.4% vs. 52.7%) (Fig. 4).

**Discussion**

*Escherichia coli* is one of the most common bacteria which producing extended-spectrum β-lactamase (ESBL) and is also one of the most common pathogens in clinical infections. In the past ten years, the prevalence of ESBL-PE colonization and infection has continued to increase dramatically worldwide [10], and these pathogens generally associated with delayed initiation of appropriate antimicrobial therapy and extra medical costs, hence leading to worse clinical outcomes [4]. Patients with malignancy are predisposed to developing infections caused by these resistant pathogens since cancer patients are easily immunocompromised due to frequently exposed to cytotoxic agents, surgery, radiation, malnutrition, and malignancy itself [3]. Therefore, timely and appropriate antibiotic therapy plays an essential role in cancer patients developed nosocomial infections caused by these
pathogens. Thus, we conducted this seven years period retrospective study to investigate the clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by ESBL-PE in cancer patients. In the present study, the prevalence of ESBL-PE infection is 15.4% (155/1008) among cancer patients. This finding was comparable with the studies conducted in Germany (17.5%) [11] and the Czech Republic (11.3%) [12] among patients with malignancy. Previous studies reported high colonization rates of ESBL-PE among cancer patients in Asia [13–15]. This could be explained by the fact that the prevalence of nosocomial infections among cancer patients varies widely from region to region. Our study demonstrated that ESBL-PE was primarily derived from urinary tract infections, followed by the bloodstream and abdominal cavity infections, which is consistent with the findings of many previous studies [16–19]. The results of this study suggested that the length of antibiotics treatment more than 6.93 days was independent risk factor for nosocomial infections in cancer patients caused by ESBL-PE. Biehl LM et al. [4] reported that nosocomial acquisition, recent antimicrobial use, ICU care, and prolonged hospitalizations were associated with increased ESBL-PE BSI risk in patients with malignancy. Besides, cancer patients constitute a population that is intrinsically vulnerable to developing FN since they frequently underwent radiation and chemotherapy. Therefore, beta-lactams with beta-lactamase inhibitors and carbapenems are widely considered the first-choice treatment option for infections caused by ESBL-PE in our hospital, and generally, the length of antibiotics treatment at least more than one week. Nosocomial infections in cancer patients have been associated with increased mortality in this patient population [4]. Several studies [14, 15, 20] reported that the overall case-fatality was significantly higher in the ESBL-positive group.
compared with ESBL-negative group. Conversely, there was no significant difference in the 30-day mortality between patients with nosocomial infections caused by ESBL-PE and those infected with non-ESBL-PE in this study, similar to the findings of some previous studies [19, 21, 22]. This may be attributed to the use of many broad-spectrum antibiotics in the clinic due to the current high prevalence of ESBL-PE. In multivariate analysis, we found that ECOG performance status score more than 2 is an independent risk factor for 30-day mortality in cancer patients with nosocomial infections caused by ESBL-PE, which is consistent with the previous study [19]. An interesting finding of our study is that the presence of respiratory tract infection is an independent risk factor for 30-day mortality in these patients as well despite its small proportion in our cohort. This may have been due to respiratory tract infection is a strong independent predictor of chemotherapy interruption, which in turn impacts disease control [23]. Our analysis demonstrated that septic shock is also an independent risk factor for 30-day mortality in patients with ESBL-PE caused nosocomial infections, which is also similar to previous studies [14–16]. We also found that low lymphocytes count and serum albumin are independent risk factors for 30-day mortality in cancer patients with nosocomial infections caused by ESBL-PE. Lymphocytes count level is a standard indicator for assessing a patient’s immune status. Lymphocytopenia has been identified as a prognostic factor in several solid tumors since it was associated with a condition of cancer-induced immunodeficiency, which can limit tumor control following radiation and chemotherapy [24]. Several studies have shown that patients with hypoproteinemia were correlated with worse prognosis in hospitalized patients, and serum albumin level is generally used to evaluating patients’ nutritional status, organ function, and comorbidity [19, 25].
In this retrospective study, we observed that E. coli was highly sensitive to carbapenems, beta-lactams with beta-lactamase inhibitors, amikacin, and tigecycline, regardless of ESBL status. Compared with non-ESBL-PE, the isolated ESBL-PE were highly resistant to aztreonam and third-generation cephalosporins. We also observed that both ESBL-PE and non-ESBL-PE were associated with slightly increased resistance to fluoroquinolones. These observations are consistent with previous studies [26]. Thus, piperacillin/tazobactam or carbapenem should be used for the initial empirical treatment of cancer patients with nosocomial infections caused by ESBL-PE [4]. To our knowledge, this is the first study evaluated clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by ESBL-PE among cancer patients in China. However, our study has several limitations. First, there might be hidden biases in the analyses of the relationship in this retrospective study. Besides, this study was conducted from data at a single center. Therefore, it needs to be further validated in a prospective multicenter study. Moreover, we should perform more precise drug resistance gene detection to better understand the drug resistance patterns and the appropriate treatment options.

Conclusions

In summary, the length of antibiotics treatment more than 6.93 days was independent risk factor for nosocomial infections in cancer patients caused by ESBL-PE. However, there was no significant difference in the prognoses of patients with ESBL-PE and non-ESBL-PE caused nosocomial infections. ECOG performance status score more than 2, presence of respiratory tract infection, septic shock, lymphocytopenia, and hypoproteinemia were independent risk factors for 30-day
mortality in cancer patients with nosocomial infections caused by E. coli. The isolated E. coli were highly sensitive to carbapenems, beta-lactams with beta-lactamase inhibitors, amikacin, and tigecycline, regardless of ESBL status. Compared with non-ESBL-PE, the isolated ESBL-PE were highly resistant to aztreonam and third-generation cephalosporins.

Abbreviations

ESBL: extended-spectrum beta-lactamase; ESBL-PE: Extended-spectrum β-lactamase-producing Enterobacteriaceae; BSIs: bloodstream infections; ECOG: Eastern Cooperative Oncology Group; G-CSF: granulocyte colony-stimulating factor; PICC: peripherally inserted central catheter; CVC: central venous catheter; ICU: Intensive care unit; PCT: procalcitonin.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the First Affiliated Hospital of Xi’an Jiaotong University. Waiving of informed consent was obtained due to the retrospective noninterventional study design.

Consent for publication

Not applicable.

Availability of data and material

Please contact author for data requests.

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Author Contributions

YY and TT conceived the study. AMJ and XS were involved in data collecting, statistical analysis, and drafting the manuscript. NL carried out the data collection and analysis and provided the critical revision. ZPR and XL participated in the study design and manuscript revision. XQZ and XF participated in the study design and helped with the data collection. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Clinical and demographic characteristics of cancer patients with nosocomial infections caused by E. coli

| Demographic data                  | ESBL-negative (n =110) | ESBL-positive (n =155) | P-value | Multivariate analysis |
|-----------------------------------|------------------------|------------------------|---------|-----------------------|
| Sex (male)                        | 33(30.0)               | 46(29.7)               | 0.955   |                       |
| Age (years)                       | 59.74±12.41            | 58.17±11.20            | 0.286   |                       |
| Smoking history                   |                        |                        |         |                       |
| Never smoker                      | 91(82.7)               | 122(78.7)              | 0.707   |                       |
| Former smoker                     | 11(10.0)               | 20(12.9)               |         |                       |
| Current smoker                    | 8(7.3)                 | 13(8.4)                |         |                       |
| ECOG performance status           |                        |                        | 0.271   |                       |
| 0,1                               | 88(80.0)               | 115(74.2)              |         |                       |
| 2,3,4                             | 22(20.0)               | 40(25.8)               |         |                       |
| Underlying cancer type            |                        |                        |         |                       |
| Head and neck cancer              | 2(1.8)                 | 2(1.3)                 | 1.000   |                       |
| Lung cancer                       | 2(1.8)                 | 8(5.2)                 | 0.280   |                       |
| Esophagus cancer                  | 7(5.4)                 | 13(8.4)                | 0.539   |                       |
| Gastric cancer                    | 7(5.4)                 | 8(5.2)                 | 0.676   |                       |
| Gastroesophageal junction cancer  | 1(0.9)                 | 4(2.6)                 | 0.598   |                       |
| Pancreatic cancer                 | 5(4.5)                 | 1(0.6)                 | 0.092   | 0.12(0.01-1.13)       |
| Hepatobiliary                     | 5(4.5)                 | 6(3.9)                 | 1.000   |                       |
| Breast cancer                     | 14(12.7)               | 12(7.7)                | 0.179   |                       |
| Colon and rectal cancer           | 14(12.7)               | 25(16.1)               | 0.441   |                       |
| Genitourinary cancer              | 5(4.5)                 | 9(5.8)                 | 0.651   |                       |
| Gynecological cancer              | 44(40.0)               | 55(35.5)               | 0.454   |                       |
| Lymphoma                          | 1(0.9)                 | 3(1.9)                 | 0.870   |                       |
| Metastatic disease                | 1(0.9)                 | 1(0.6)                 | 1.000   |                       |
| Othersa                           | 2(1.8)                 | 8(5.2)                 | 0.280   |                       |
| Existence of distant metastasis   |                        |                        | 0.284   |                       |
| None                              | 69(62.7)               | 107(69.0)              |         |                       |
| Yes                               | 41(37.3)               | 48(31.0)               |         |                       |
| Stage of cancer                   |                        |                        | 0.376   |                       |
| Stage I                           | 12(10.9)               | 25(16.1)               |         |                       |
| Stage II                          | 30(27.3)               | 44(28.4)               |         |                       |
| Stage III                         | 20(18.2)               | 33(21.3)               |         |                       |
| Stage IV                          | 48(43.6)               | 53(34.2)               |         |                       |
## Primary sites of infection

| Site                     | Cases | Controls | Odds Ratio | 95% CI       |
|--------------------------|-------|----------|------------|--------------|
| Respiratory tract        | 4     | 12       | 0.167      | 0.23-1.61    |
| Gastrointestinal         | 0     | 1        | 1.000      |              |
| Urinary tract            | 74(67.3) | 83(53.5) | 0.025      |              |
| Hepatobiliary            | 3     | 0        | 1.139      |              |
| Skin and soft tissue     | 4     | 8        | 0.773      |              |

### Comorbidities

| Condition                   | Cases | Controls | Odds Ratio | 95% CI       |
|-----------------------------|-------|----------|------------|--------------|
| Myocardial infarction       | 3     | 0        | 0.139      |              |
| Cerebrovascular disease     | 1     | 3        | 0.870      |              |
| Liver disease               | 4     | 9        | 0.420      |              |
| Diabetes                    | 8     | 10       | 0.794      |              |
| Renal disease               | 6     | 10       | 0.737      |              |

### Charlson Co-morbidity Index score

| Score | Cases   | Controls | Odds Ratio | 95% CI       |
|-------|---------|----------|------------|--------------|
| 0     | 91(82.7)| 122(78.7)|            |              |
| 1-2   | 15(13.6)| 30(19.4) |            |              |
| ≥3    | 4(3.6)  | 3(1.9)   |            |              |

### Existence of fever

| Type               | Cases   | Controls | Odds Ratio | 95% CI       |
|--------------------|---------|----------|------------|--------------|
| Surgery (within 30 days) | 39(35.5) | 60(38.7) | 0.589      |              |

### Chemotherapy (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 54(49.1)| 81(52.3) |            |              |
| Neoadjuvant               | 1(0.9)  | 0(0.0)   |            |              |
| Adjuvant                  | 17(15.5)| 17(11.0) |            |              |
| 1st line                  | 6(5.5)  | 4(2.6)   |            |              |
| 2nd line                  | 4(3.6)  | 5(3.2)   |            |              |
| ≥3rd line                 | 28(25.5)| 48(31.0) |            |              |

### Radiotherapy (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 23(20.9)| 23(14.8) |            |              |

### Concurrent chemoradiotherapy (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 29(26.4)| 32(20.6) |            |              |

### Corticosteroid therapy (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 80(72.7)| 96(61.9) | 0.067      |              |

### Prior infection (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 4(3.6)  | 8(5.2)   | 0.773      |              |

### Prior G-CSF use (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 63(57.3)| 70(45.2) | 0.052      |              |

### Prior antibiotics (within 30 days)

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| None                      | 6(5.5)  | 7(4.5)   | 0.727      |              |

### Presence of indwelling catheters or other devices

| Type                      | Cases   | Controls | Odds Ratio | 95% CI       |
|---------------------------|---------|----------|------------|--------------|
| Biliary stent             | 3(2.7)  | 1(0.6)   | 0.391      |              |

### Length of antibiotics treatment (days)

| Length                   | Cases   | Controls | Odds Ratio | 95% CI       |
|--------------------------|---------|----------|------------|--------------|
| <6.93                    | 67(60.9)| 66(42.6) | 1.80       |              |
| ≥6.93                    | 43(39.1)| 89(57.4) | 1.80       |              |
| Demographic data       | Survivor (n = 238) | Non-survivor (n = 27) | P-value | Multivariate analysis OR (95% CI) |
|------------------------|--------------------|-----------------------|---------|----------------------------------|
| Sex (male)             | 68(28.6)           | 11(40.7)              | 0.190   |                                  |
| Age (years)            | 58.71±11.66        | 59.81±12.42           | 0.643   |                                  |
| Smoking history        |                    |                       |         |                                  |
| Never smoker           | 193(81.1)          | 20(74.1)              | 0.180   |                                  |
| Former smoker          | 25(10.5)           | 6(22.2)               |         |                                  |
| Current smoker         | 20(8.4)            | 1(3.7)                |         |                                  |
| ECOG performance status |                    |                       | 0.077   |                                  |
| 0,1                    | 186(78.2)          | 17(63.0)              |         | REF (1.00)                       |
| 2,3,4                  | 52(21.8)           | 10(37.0)              |         | 2.85(1.80-4.52)                  |
| Underlying cancer type |                    |                       |         |                                  |
| Head and neck cancer   | 2(0.8)             | 2(7.4)                | 0.053   | 2.57(0.93-7.10)                  |
| Lung cancer            | 8(3.4)             | 2(7.4)                | 0.608   |                                  |
| Esophagus cancer       | 15(6.3)            | 5(18.5)               | 0.058   | 0.74(0.38-1.45)                  |
| Gastric cancer         | 14(5.9)            | 1(3.7)                | 0.980   |                                  |
| Gastroesophageal junction cancer | 3(1.3)   | 2(7.4)                | 0.083   | 0.67(0.14-3.16)                  |
| Pancreatic cancer      | 4(1.7)             | 2(7.4)                | 0.116   |                                  |
| Hepatobiliary cancer   | 10(4.2)            | 1(3.7)                | 1.000   |                                  |
| Breast cancer          | 24(10.1)           | 2(7.4)                | 0.919   |                                  |
| Colon and rectal cancer | 36(15.1)          | 3(11.1)               | 0.786   |                                  |
| Genitourinary cancer   | 14(5.9)            | 0(0.0)                | 0.400   |                                  |
| Gynecological cancer   | 93(39.1)           | 6(22.2)               | 0.086   | 0.50(0.20-1.21)                  |
| Lymphoma               | 4(1.7)             | 0(0.0)                | 1.000   |                                  |
| Others<sup>a</sup>     | 9(3.8)             | 1(3.7)                | 1.000   |                                  |
| Existence of distant metastasis |            |                       | 0.011   |                                  |
| None                   | 164(68.9)          | 12(44.4)              |         | REF (1.00)                       |
| Yes                    | 74(31.1)           | 15(55.6)              |         | 2.36(0.92-6.05)                  |

Abbreviations: ESBL, extended-spectrum beta-lactamase; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; PICC, peripherally inserted central catheter; CVC, central venous catheter; ICU, Intensive care unit; PCT, procalcitonin.

<sup>a</sup> Others: primitive neuroectodermal tumor (3 patients), thymic carcinoma and duodenal carcinoma two patients each, carcinoid cancer of appendix, and malignant pleural mesothelioma one patient each.

Bolded values indicate statistical significance.

Table 2 Analysis of risk factors for 30-day Mortality in cancer patients with nosocomial infections caused by E. coli.
| **Stage of cancer** | **Stage I** | **Stage II** | **Stage III** | **Stage IV** | **0.017** | **REF (1.00)** |
|---------------------|-------------|--------------|---------------|--------------|---------|---------------|
|                     | 36(15.1)    | 71(29.8)     | 47(19.7)      | 84(35.3)     |         | 1.00(0.44-2.28) |
| **Primary sites of infection** |             |              |               |              |         | 1.07(0.48-2.39) |
| Respiratory tract   | 9(3.8)      | 150(63.0)    | 2(0.8)        | 11(4.6)      | <0.001 | 2.90(1.50-5.60) |
| Urinary tract       | 7(25.9)     | 7(25.9)      | 1(3.7)        | 1(3.7)       | 0.277  | 1.50(0.64-3.53) |
| Skin and soft tissue| 19(8.0)     | 40(16.8)     | 11(4.6)       |             | 1.000  |               |
| Abdominal cavity    | 1(3.7)      | 10(37.0)     |               |              | 0.111  | 1.09(0.41-2.94) |
| Endogenous source   |             |              |               |              |         |               |
| **Comorbidities**   |             |              |               |              |         |               |
| Liver disease       | 9(3.8)      | 16(6.7)      | 13(5.5)       | 40(16.8)     |         | 0.041         |
| Diabetes            | 14(18.4)    | 7(27.4)      | 3(11.1)       |              | 1.000  | 1.97(0.92-4.23) |
| Renal disease       | 6(22.2)     | 2(7.4)       |               |              | 0.458  |               |
| **Charlson Co-morbidity Index score** | 0 | 194(81.5) | 19(70.4) | 1.000 |
|                     | 1-2 | 39(16.4) | 6(22.2) | 0.277 |
|                     | ≥3  | 5(2.1)  | 2(7.4)  |               |
| **Existence of fever** | Surgery (within 30 days) | None | 176(73.9) | 24(88.9) | 0.100 |
|                     |   | Curative surgery | 50(21.0) | 2(7.4) | 0.006 |
|                     |   | Palliative surgery | 12(5.0) | 1(3.7) |               |
| **Chemotherapy**    | (within 30 days) | None | 115(48.3) | 20(74.1) | 1.87(0.71-4.94) |
|                     |   | Neoadjuvant | 1(0.4) | 0(0.0) | 1.86(0.20-17.30) |
|                     |   | Adjuvant | 73(30.7) | 3(11.1) | 1.27(0.53-3.07) |
|                     |   | 1st line | 34(14.3) | 0(0.0) | 0.33(0.13-0.87) |
|                     |   | 2nd line | 8(3.4) | 2(7.4) | 1.13(0.39-3.28) |
|                     |   | ≥3rd line | 7(2.9) | 2(7.4) | 1.97(0.92-4.23) |
| **Radiotherapy (within 30 days)** | 43(18.1) | 3(11.1) | 0.525 |
| **Concurrent chemoradiotherapy (within 30 days)** | 59(24.8) | 2(7.4) | 0.042 |
| **Chemotherapy**    | (within 30 days) | Corticosteroid | 164(68.9) | 12(44.4) | 0.72(0.33-1.57) |
|                     |   | therapy (within 30 days) | | | |
| **Prior infection (within 30 days)** | 11(4.6) | 1(3.7) | 1.000 |
| **Prior G-CSF use (within 30 days)** | 127(53.4) | 6(22.2) | 0.002 |
| **Prior antibiotics (within 30 days)** | 13(5.5) | 0(0.0) | 0.438 |
| **Presence of indwelling catheters or other devices** | | | |
| Billary stent       | 2(0.8) | 2(7.4) | 0.053 |
| Ureteral stent      | 16(6.7) | 0(0.0) | 0.335 |
| Indwelling urinary catheters | 42(17.6) | 3(11.1) | 0.557 |
| PICC                | 18(7.6) | 2(7.4) | 1.000 |
| Venous port         | 5(2.1) | 0(0.0) | 1.000 |
| CVC                 | 7(2.9) | 1(3.7) | 0.582 |
| Percutaneous pleural drainage tube | 12(5.0) | 6(22.2) | 0.003 |
| Drains              | 43(18.1) | 3(11.1) | 0.525 |
| **postoperation**   | Nasogastric tube | 25(10.5) | 4(14.8) | 0.723 |
| Invasive procedure (within 30 days) | 107(45.0) | 14(51.9) | 0.496 |
| **Length of antibiotics treatment (days)** | | | 0.320 |
| <6.93               | 117(49.2) | 16(59.3) | | |
| ≥6.93               | 121(50.8) | 11(40.7) | | |
| ICU admission       | 20(8.4) | 3(11.1) | 0.910 |
| Mechanical ventilation | 7(2.9) | 4(14.8) | 0.015 |
| Septic shock        | None | | 2.02(0.95-4.31) |
|                     | 200(84.0) | 15(55.6) | REF (1.00) |
|                              | Yes       | 12(44.4) | 0.363 |
|------------------------------|-----------|----------|-------|
| ESBL status                  | Negative  | 101(42.4)| 9(33.3)| 4.73(2.17-10.28) |
|                              | Positive  | 137(57.6)| 18(66.7)| |

Laboratory examination results

|                          | Hemoglobin(g/L) | Platelet |    |    |
|--------------------------|-----------------|----------|----|----|
| Hemoglobin(g/L)          | 104.76±18.90    | 90.04±18.28 | <0.001 | 1.00(0.99-1.01) |
| Platelet                 | 207.71±109.77   | 176.70±137.42 | 0.177 |

Hematological count (×10^9/L)

|                          |    |    |    |    |
|--------------------------|---|---|---|---|
| White-cell count         | 7.14±4.71 | 7.09±5.01 | 0.957 |
| Neutrophils count        | 5.62±4.44 | 5.96±4.69 | 0.714 |
| Lymphocytes              | 1.00±0.62 | 0.70±0.48 | 0.015 |
| Neutrophils count        | 5.62±4.44 | 5.96±4.69 | 0.714 |
| Lymphocytes              | 1.00±0.62 | 0.70±0.48 | 0.015 |

PCT (ng/mL)

|                          | 7.18±22.79 | 26.87±52.01 | 0.121 |

Albumin(g/L)

|                          | 36.62±5.93 | 30.42±5.96 | <0.001 |

| Abbreviations: ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; PICC, peripherally inserted central catheter; CVC, central venous catheter; ESBL, extended-spectrum beta-lactamase; ICU, Intensive care unit; PCT, procalcitonin. |
| Others: primitive neuroectodermal tumor (3 patients), thymic carcinoma and duodenal carcinoma, two patients each; carcinoid cancer of appendix, and malignant pleural mesothelioma one patient each. |
| Bolded values indicate statistical significance. |

**Figures**
Patients admitted to the oncology center of the First Affiliated Hospital of Xi’an Jiaotong University and received systematic treatment between August 2013 to May 2019 (n=14695).

Exclusion (n=13687)
1. Not infection episodes (n=13612)
2. Missing clinical data (n=10)
3. Not cancer episodes (n=65)
   - Lung transplant (n=15)
   - Lung abscess (n=12)
   - Bronchiectasis (n=12)
   - Pulmonary tuberculosis (n=11)
   - Pulmonary fibrosis (n=10)
   - Others (n=5)

Infection episodes (n=1008)

Nosocomial infection episodes caused by E. coli (n=265)

ESBL-PE infection (n=155)
non-ESBL-PE infection (n=110)

Figure 1

Flow chart of clinical characteristics, antibiotic resistant patterns and prognostic
Figure 2

Trend in etiology of nosocomial infections in cancer patients caused by E. coli tre
Figure 3

Kaplan-Meier 30-day survival estimates among cancer patients with nosocomial infections caused by ESBL-PE and non-ESBL-PE.
Antimicrobial susceptibility comparison among cancer patients with nosocomial infections caused by ESBL-PE and non-ESBL-PE.

Figure 4

(a) Susceptible rate of isolated E. coli

(b) Resistant rate of isolated E. coli
Supplementary Files

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