Nosocomial Infections Due to Multidrug-Resistant Bacteria in Cancer Patients: A Seven-Year Experience of an Oncology Center in Western China

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Abstract

Background: Bacterial infections are the most frequent complications in patients with malignancy, and the epidemiology of nosocomial infections among cancer patients has changed over time. This study aimed to evaluate characteristics, antibiotic-resistant patterns, and prognosis of nosocomial infections caused by multidrug-resistant bacteria (MDR) in cancer patients.

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

Results: Overall, 257 cancer patients developed nosocomial infections caused by MDR bacteria. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae was the most frequently isolated multidrug-resistant Gram-negative bacteria (MDRGNB), followed by ESBL-producing Klebsiella pneumonia, and Acinetobacter baumannii. Cancer patients with liver disease, received intrapleural/abdominal infusion within 30 days, length of hospitalization, hemoglobin, and albumin were independent factors for 30-day mortality in the study population. The isolated MDR bacteria were highly sensitive to amikacin, meropenem, imipenem, tigecycline, and piperacillin/tazobactam.

Conclusions: Cancer patients with prolonged hospitalization was an independent predictor of a favorable outcome. However, cancer patients with liver disease, received intrapleural/abdominal infusion within 30 days, anemia, and hypoproteinemia were independent risk factors of 30-day mortality.

Background

Bacterial infections are the most frequent complications in patients with malignancy as these patients are more likely to be immunocompromised due to malnutrition, invasive procedures, surgery, chemotherapy, radiation, and some new treatment modalities [1, 2]. There is growing evidence suggested that infection in cancer patients is associated delayed initiation of chemotherapy, reduced standard dosage, prolonged hospitalization, increased financial burden of healthcare, and raised severe morbidity and mortality [3–6]. The epidemiology of nosocomial infections among cancer patients has changed over time, and the causative organisms of nosocomial infections had shifted.
from Gram-positive pathogens to Gram-negative pathogens in the last 20 years worldwide [7].

Most of the previous studies [8-11] showed that extended-spectrum \( \beta \)-lactamase-producing Enterobacteriaceae (ESBL-PE), multidrug-resistant (MDR) Pseudomonas aeruginosa, carbapenem-resistant Enterobacteriaceae (CRE), Acinetobacter baumannii and methicillin-resistant Staphylococcus aureus (MRSA) have been increasingly identified as the predominant causative infection pathogens in cancer patients due to the phenomenon of antibiotics misuse [7, 12]. However, antibiotics management for these infections is often limited. Besides, most of the published guidelines recommend antibiotic treatment for cancer patients with neutropenia or septic shock, while there were no clearly defined empirical antibiotics treatment for highly suspected MDR bacteria caused nosocomial infection episodes in cancer patients [13-15]. Therefore, rapid and appropriate initiation of empirical antibiotic therapy is pivotal for cancer patients with MDR bacteria caused nosocomial infections [2]. We thus performed this present seven-year retrospective study to demonstrate the clinical characteristics, microbial spectrum, antibiotic resistance patterns, and prognostic factors for nosocomial infections in cancer patients caused by MDR bacteria between August 2013 and June 2019 at the First Affiliated Hospital of Xi’an Jiaotong University.

Methods

Study population and design

We conducted a single-center retrospective observational study in a 2560-bed university referral cancer center in Xi’an, China. The study included patients from August 2013 to May 2019. The electronic medical record database was reviewed to identify cancer patients with nosocomial infections caused by MDR bacteria. Patients with hematological malignancies were all excluded, and only the initial infection episode was analyzed.

Data Collection

Data in electronic medical records of all included cancer patients were extracted. The extracted clinical data included age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, primary location of the disease, existence of distant metastasis, American Joint Committee on Cancer (AJCC) TNM categories, primary sites of infection, comorbidities and severity of
underlying conditions according to the Charlson comorbidity index (CCI) [16], 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, previous antibiotics treatment within 30 days, the presence of indwelling catheters or other devices, invasive procedure within previous 30 days, empirical antibiotics treatment, effective empirical antibiotics treatment, 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), and antibiotic susceptibility tests of isolated pathogens.

Definitions

The definition of MDR infection was that an infection manifested by the presence in at least one positive for MDR pathogen clinical sample, and if clinical, laboratory, or radiology results indicated infection or there was a concrete infection diagnosis in the patient’s medical charts [7].

MDR was defined as resistance to at least one agent in each of three or more categories of antimicrobial agents, including β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam), extended-spectrum cephalosporins (ceftriaxone, ceftazidime, cefepime), carbapenems (imipenem/meropenem), monobactams, aminoglycosides (gentamicin, amikacin) and/or fluoroquinolones, regarding Enterobacteriaceae, Klebsiella pneumonia, Acinetobacter baumannii, and Pseudomonas aeruginosa [13].

Nosocomial infection was defined as signs or symptoms of infection that occurred > 48 hours after hospital admission or < 48 hours after hospital discharge. Otherwise, the case was considered community-onset [17].

Fever was considered 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 hours [18].

Empirical antibiotics treatment was considered as the initiation of antimicrobial agents before the
results of microbiology and communicated to clinicians [7]. Empirical antibiotics treatment was considered effective once the antibiotics could suppress the activity of the isolated MDR pathogens according to the results of antimicrobial susceptibility tests [7].

Study Outcomes

This study aimed to describe the clinical characteristics, microbial spectrum, antibiotic resistance patterns, and prognostic factors of all cancer patients with MDR bacteria caused nosocomial infections and to present 30-day mortality and its associated risk factors during the seven-year study period.

Statistical Analysis

The extracted clinical data were recorded in a standardized form and compared based on the patient's survival status within 30 days after infection. Parametric continuous quantitative variables were described as means and standard deviation, while median and interquartile ranges were used for non-parametric continuous variables. Categorical data were analyzed by the chi-square or Fisher's exact tests. Univariate and multivariate logistic regression analyses were used to investigate risk factors for 30-day mortality of cancer patients with nosocomial infections caused by MDR bacteria. Variables with a p-value of < 0.10 from univariate analysis and variables with clinical significance were included in a multivariate logistic regression analysis using stepwise selection. All statistical analyses were performed by the SPSS software version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

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 infections, and MDR bacteria caused 257 infection episodes (Fig. 1). Among the study subjects, there were 117 (45.5%) males and 140 (54.5%) females, with an average age of 59.6 ± 11.5 years. Diabetes mellitus, renal disease, and liver disease accounted for 20 (7.8%), 15 (5.8%), and 11 (4.3%), respectively. The most frequent diagnoses were esophago-gastrointestinal cancer in 74 (28.8%) cases, gynecological cancer in 63 (24.5%) cases, colon and rectal cancer in 34
(13.2%) cases, and breast cancer in 21 (8.2%) cases. Overall, 183 (71.2%) had a performance status
greater than 2, 66 (25.7%) had distant metastasis, 109 (42.4%) had received surgery within 30 days,
90 (35.0%) had received chemotherapy within 30 days, 34 (13.2%) had received radiotherapy within
30 days, and 37 (14.4%) had received concurrent chemoradiotherapy within 30 days. Eighty-nine
(34.6%) patients had a drain post-operation, 86 (33.5%) had an indwelling urinary catheter, and 67
(26.1%) had a nasogastric tube.

We reviewed all of the clinical data of MDR bacteria caused nosocomial infections in cancer patients.
In our study, approximately 13 (5.1%) patients had a prior infection history within 30 days, and
12(4.7%) patients had received antibiotics therapy within 30 days. Urinary tract infection was the
leading cause of nosocomial infections, accounting for 38.1% of the cases, followed by respiratory
tract infection (26.8%) and bloodstream infections (BSIs) (12.5%). Besides, there were 33 (12.8%)
patients had admitted to the ICU, and 18 (7.0%) patients had received mechanical ventilation
(Table 1).

Comparison of clinical characteristics in the study population based on the patient’s survival status
within 30 days

We used 30-day mortality to evaluate the primary clinical outcomes of MDR bacteria caused
nosocomial infections in cancer patients. Among the study subjects, the overall case-fatality rate was
10.9% (28/257). We also analyzed the relationship between prognosis and clinical characteristics of
these infections in cancer patients. The results showed that smoking history, ECOG performance
status, existence of distant metastasis, primary sites of infection (respiratory tract infection, urinary
tract infection, and bloodstream infection), presence of liver disease, CCI, existence of fever,
underwent surgery or chemotherapy within 30 days, received intrapleural/abdominal infusion within
30 days, presence of indwelling catheters or other devices (indwelling urinary catheters and drains
post-operation), length of hospitalization, and septic shock significantly differed between survivors
and non-survivors (P < 0.05; Table 1). Additionally, hemoglobin, platelet count, lymphocytes count,
and albumin in laboratory tests have also differed between survivors and non-survivors (P < 0.05;
Table 1).
Bacterial Characteristics

During the seven years, there were 257 cultures isolated from different clinical specimens. It showed that the MDR bacteria caused nosocomial infection episodes have been declined gradually from 2015 to 2019, although fewer episodes were counted in 2013 and 2019 (Fig. 2a). Besides, it also showed that the majority of patients had MDR bacteria caused nosocomial infections that were detected with a peak during August and September of each year (Fig. 2b). The causative pathogens of nosocomial infection episodes are compared by survival status within 30 days in Table 2. Overall, ESBL-PE was the most frequently isolated multidrug-resistant Gram-negative bacteria (MDRGNB) (60.3%), followed by ESBL-producing Klebsiella pneumonia (12.1%), Acinetobacter baumannii (11.7%), Stenotrophomonas maltophilia (6.2%), MDR Pseudomonas aeruginosa (5.1%), Carbapenem-resistant Enterobacteriaceae (1.6%), and ESBL-producing Enterobacter aerogenes (0.4%). MRSA was the only isolated multidrug-resistant Gram-positive bacteria, accounting for 2.7%. However, there was no significant difference in causative pathogen distribution (P > 0.05) between the survivor and non-survivor groups (Table 2).

Risk factors for 30-day mortality in cancer patients with nosocomial infections caused by MDR bacteria

In this study, the univariate analysis demonstrated that smoking history, ECOG performance status, existence of distant metastasis, primary sites of infection (respiratory tract infection, urinary tract infection, and bloodstream infection), presence of liver disease, CCI, existence of fever, underwent surgery or chemotherapy within 30 days, received intrapleural/abdominal infusion within 30 days, presence of indwelling catheters or other devices (indwelling urinary catheters and drains post-operation), length of hospitalization, septic shock, hemoglobin, platelet count, lymphocytes count, and albumin were significant variables (Table 3). The multivariate analysis identified that the presence of liver disease, received intrapleural/abdominal infusion within 30 days, length of hospitalization, hemoglobin, and albumin were independent prognostic factors for 30-day mortality in cancer patients with nosocomial infections caused by MDR bacteria (Table 3).

Antimicrobial Susceptibility Analysis
The antimicrobial sensitivity of commonly used antibiotics showed that the isolated MDRGNB was highly sensitive to piperacillin/tazobactam, meropenem, imipenem, amikacin, and tigecycline, while they were highly resistant to ceftriaxone, aztreonam, and ciprofloxacin. MRSA was the only isolated MDR Gram-positive bacteria, and the drug sensitivity analysis showed that these strains were highly sensitive to vancomycin, linezolid, moxifloxacin, levofloxacin, and tigecycline (Fig. 3).

**Discussion**

In this retrospective study, we found the prevalence of MDR bacteria caused nosocomial infections in cancer patients was 25.5%, which was consistent with the recent study conducted in Spain (25.5%) [19]. However, in the Spain study, the subjects were cancer patients with FN, and all of the organisms were isolated from blood culture. At the same time, a prospective observational study conducted in Turkey showed that MDR bacteria isolated from all cultures caused 36.3% of nosocomial infection episodes, while 17.1% of cases were identified as nosocomial infection episodes if only blood cultures were included. This suggests that we should pay more attention to other sites of infections (such as urinary tract infection, respiratory tract infection, and gastrointestinal tract infection) rather than focusing merely on BSIs, even though BSIs are more worrisome and are related with high mortality.

In this study, we found that ESBL-producing Enterobacteriaceae was the most frequent organism caused nosocomial infection episodes in cancer patients, accounting for 60.3%, followed by ESBL-producing Klebsiella pneumoniae (12.1%), and Acinetobacter baumannii (11.7%). Compared with Gram-negative bacteria, MRSA was the only isolated MDR bacteria in Gram-positive bacteria, accounting for 2.7%. Biehl LM et al. [20] reported that ESBL-producing Enterobacteriaceae is emerging as a new threat to both nosocomial and community infections worldwide, and ESBL-producing Enterobacteriaceae caused approximately 1 in 10 nosocomial infection episodes in patients with malignancy. At the same time, ESBL-producing Enterobacteriaceae caused nosocomial infections was more worrisome due to the increased mortality in these patients [20]. Therefore, rapid initiation of appropriate and adequate antibiotic therapy is pivotal for nosocomial infection episodes caused by ESBL-producing Enterobacteriaceae, and since most empirical regimens do not adequately cover these pathogens [1].
Among the study subjects, a considerable overall case-fatality rate of 10.9% was observed in our study, which was lower compared with most of the previous studies conducted in other countries [7, 21-24]. According to a retrospective conducted in Brazil, Freire MP et al. reported that the overall case-fatality rate of carbapenem-resistant K. pneumoniae caused nosocomial infection reached 57.8% in patients with solid tumor as well despite its small sample size in this cohort (83 infection episodes) [21]. In a case-control study, including 204 cancer patients admitted to ICU, Nazer LH et al. reported that 30-day mortality exceed 70% for cancer patients with Acinetobacter baumannii caused nosocomial infection [23]. At the same time, Moghnieh R et al. reported that the case-fatality rates of MDR bacteria caused nosocomial infection up to 57.1% in cancer patients with FN [24]. Recently, in a five years period retrospective study including 73 patients with solid tumors, Perdikouri EIA et al. reported that 30% of cases were died due to MDR bacteria-caused infection [7]. This may have been due to the majority of patients in this study who were at an advanced stage and have distant metastasis.

The results of the multivariate analysis identified that liver disease is an independent risk factor for 30-day mortality in cancer patients with MDR bacteria caused nosocomial infections, similar to a retrospective study conducted in China [8]. It can be explained by the fact that bacterial infection is the leading cause of death in patients with severe liver disease [25]. Our study demonstrated that prolonged hospitalization was an independent factor for a favorable outcome in these patients. On the contrary, Perdikouri EIA et al. reported that prolonged hospitalization was associated with an increased fatality rate in cancer patients [7]. On the one hand, it may be attributed to the majority of cases in this study suffered from metastasis disease, and received invasive procedures during hospitalization. On the other hand, we used 30-day mortality to evaluate the clinical outcomes of infection episodes in our study, and the average length of hospitalization is 22.42 days in our study, which is less than 30 days obviously. Therefore, it needs to be further validated before drawn conclusions. We also found that cancer patients who received intrapleural/abdominal infusion within 30 days was associated with high case-fatality rate in our cases, possibly suggesting that these patients are more likely to exposure MDR bacterial infection, catheter-related infection, and can be
easily immunocompromised [2]. Besides, anemia and hypoproteinemia were also found to be independent risk factors for 30-day mortality in cancer patients with MDR bacteria caused nosocomial infections. Zhang LN et al. reported that pretreatment anemia-induced tissue hypoxia may directly reduce the overall survival of cancer patients [26]. Several studies have shown that cancer patients with hypoproteinemia were correlated with worse prognosis, and serum albumin level is generally used to evaluating patients’ nutritional status, organ function, and comorbidity [8, 27].

The antimicrobial susceptibility showed that the isolated MDRGNB were highly sensitive to piperacillin/tazobactam, meropenem, imipenem, amikacin, and tigecycline, while they were highly resistant to aztreonam, cephalosporins (third or fourth generation), and fluoroquinolone. MRSA was the only isolated MDR Gram-positive bacteria, and the drug sensitivity analysis showed that these strains were highly sensitive to vancomycin, linezolid, moxifloxacin, levofloxacin, and tigecycline, which was comparable with previous studies [28, 29]. The phenomenon of MDR can be attributed to the overuse of antibiotics in China. There is an urgent need to execute and implement policies on the control of antibiotics misuse to avoid the evolution of newer generations of highly resistant pathogens. Besides, the entire microbial spectrum should be taken into consideration when initiating empirical antibiotic treatment [28]. As far as we know, this is the first study evaluated clinical characteristics, microbial spectrum, antibiotic resistance patterns, and prognostic factors among cancer patients with MDR bacteria caused nosocomial infections in China, and one of the advantages of our study is that we have studied the vital number of risk factors. However, our study has several limitations. First, it is hard to collect some variables (e.g., concrete chemotherapeutic or radiation dosage, concrete antibiotics treatment before admission, and some laboratory examination results) in this retrospective study. Thus, there might be hidden biases in the analysis of the relationship. In addition, our study was a single-center retrospective study. Therefore, a prospective multicenter study is needed for further validation.

Conclusions
In conclusion, the overall case-fatality rate in cancer patients with MDR bacteria caused nosocomial infections was 10.9%. The most frequently isolated pathogens were ESBL-PE, ESBL-producing
Klebsiella pneumonia, and Acinetobacter baumannii. Prolonged hospitalization was an independent predictor of favorable outcomes. However, cancer patients with liver disease, received intrapleural/abdominal infusion within 30 days, anemia, and hypoproteinemia were independent risk factors for 30-day mortality in the study subjects. The isolated MDR bacteria were highly sensitive to piperacillin/tazobactam, meropenem, imipenem, amikacin, and tigecycline.

**Abbreviations**

MDR: multidrug-resistant bacteria; ESBL: Extended-spectrum β-lactamase; MDRGNB: multidrug-resistant Gram-negative bacteria; CRE: carbapenem-resistant Enterobacteriaceae; MRSA: methicillin-resistant Staphylococcus aureus; ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer; CCI: Charlson comorbidity index; G-CSF: granulocyte colony-stimulating factor; ICU: intensive care unit; PCT: procalcitonin; FN: febrile neutropenia; CVC: central venous catheter; PICC: peripherally inserted central catheter; OR: odds ratio; CI: confidence interval.

**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**

TT and YY conceived the study. AMJ and XS were involved in data collecting, statistical analysis, and drafting the manuscript. NL, HG, and MDR carried out the data collection and analysis and provided
the critical revision. XQZ and XF participated in the study design and helped with the data collection. XL and ZPR participated in the study design and manuscript revision. 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 characteristics of cancer patients who survived or died within 30 days of nosocomial infections caused by MDR bacteriaa | All (n =257) | Survivor (n =229) | Non-survivor (n = 28) | P-value |
|-----------------|-------------|------------------|----------------------|---------|
| **Demographic data** |             |                  |                      |         |
| Sex (male)      | 117(45.5)   | 103(45.0)        | 14(50.0)             | 0.614   |
| Age (years)     | 59.6±11.5   | 59.1±11.4        | 63.6±12.2            | 0.052   |
| Smoking history |             |                  |                      |         |
| Never smoker    | 171(66.5)   | 153(66.8)        | 18(64.3)             | 0.039   |
| Former smoker   | 46(17.9)    | 37(16.2)         | 9(32.1)              |         |
| Current smoker  | 40(15.6)    | 39(17.0)         | 1(3.6)               |         |
| **ECOG performance status** |         |                  |                      | 0.002   |
| 0,1             | 183(71.2)   | 170(74.2)        | 13(46.4)             |         |
| 2,3,4           | 74(28.8)    | 59(25.8)         | 15(53.6)             |         |
| **Underlying cancer type** |         |                  |                      |         |
| Head and neck cancer | 4(1.6)     | 3(1.3)           | 1(3.6)               | 0.371   |
| Lung cancer     | 19(7.4)     | 17(7.4)          | 2(7.1)               | 1.000   |
| Esophago-       | 74(28.8)    | 65(28.4)         | 9(32.1)              | 0.678   |
| Diagnosis                           | Count 1 | Count 2 | Count 3 | p-value |
|------------------------------------|---------|---------|---------|---------|
| Colon and rectal cancer            | 34(13.2)| 30(13.1)| 4(14.3) | 1.000   |
| Hepatobiliary and pancreatic cancer| 10(3.9) | 8(3.5)  | 2(7.1)  | 0.671   |
| Breast cancer                      | 21(8.2) | 18(7.9) | 3(10.7) | 0.877   |
| Genitourinary cancer               | 15(5.8) | 14(6.1) | 1(3.6)  | 0.909   |
| Gynecological cancer               | 63(24.5)| 59(25.8)| 4(14.3) | 0.183   |
| Lymphoma                           | 4(1.6)  | 3(1.3)  | 1(3.6)  | 0.371   |
| Others b                           | 13(5.1) | 12(5.2) | 1(3.6)  | 1.000   |
| **Existence of distant metastasis**|         |         |         | **0.008**|
| None                               | 191(74.3)| 176(76.9)| 15(53.6)|         |
| Yes                                | 66(25.7) | 53(23.1)| 13(46.4)|         |
| **Stage of cancer**                |         |         |         | **0.143**|
| Stage I                            | 48(18.7)| 44(19.2)| 4(14.3) |         |
| Stage II                           | 76(29.6)| 71(31.0)| 6(21.4) |         |
| Stage III                          | 60(23.3)| 54(23.6)| 5(17.9) |         |
| Stage IV                           | 73(28.4)| 60(26.2)| 13(46.4)|         |
| **Primary sites of infection**     |         |         |         |         |
| Respiratory tract                  | 69(26.8)| 56(24.5)| 13(46.4)| **0.013**|
| Urinary tract                      | 98(38.1)| 94(41.0)| 4(14.3) | **0.006**|
| Skin and soft tissue               | 19(7.4) | 18(7.9) | 1(3.6)  | 0.663   |
| Thoracic cavity                    | 9(3.5)  | 9(3.9)  | 0(0.0)  | 0.603   |
| Abdominal cavity                   | 24(9.3) | 22(9.6) | 2(7.1)  | 0.937   |
| Catheter related                   | 2(0.8)  | 2(0.9)  | 0(0.0)  | 1.000   |
| Endogenous source                  | 32(12.5)| 24(10.5)| 8(28.6) | **0.015**|
| **Comorbidities**                  |         |         |         |         |
| Cerebrovascular disease            | 6(2.3)  | 4(1.7)  | 2(7.1)  | 0.130   |
| Liver disease                      | 11(4.3) | 7(3.1)  | 4(14.3) | **0.023**|
| Diabetes                           | 20(7.8) | 17(7.4) | 3(10.7) | 0.810   |
| Renal disease                      | 15(5.8) | 11(4.8) | 4(14.3) | 0.111   |
| **CCI**                            |         |         |         | **0.005**|
| 0                                  | 203(79.0)| 187(81.7)| 16(57.1)|         |
| 1-2                                | 49(19.1)| 39(17.0)| 10(35.7)|         |
| ≥3                                 | 5(1.9)  | 3(1.3)  | 2(7.1)  |         |
| **Existence of fever**             |         |         |         | **0.003**|
| Surgery (within 30 days)           |         |         |         |         |
| None                               | 148(57.6)| 124(54.1)| 24(85.7)|         |
| Curative surgery                   | 93(36.2)| 91(39.7)| 2(7.1)  |         |
| Palliative surgery                 | 16(6.2) | 14(6.1) | 2(7.1)  |         |
| **Chemotherapy (within 30 days)**  |         |         |         | **0.026**|
| None                               | 167(65.0)| 146(63.8)| 21(75.0)|         |
| Neoadjuvant                        | 1(0.4)  | 1(0.4)  | 0(0.0)  |         |
| Adjuvant                           | 57(22.2)| 54(23.6)| 3(10.7) |         |
| 1st line                           | 20(7.8) | 20(8.7) | 0(0.0)  |         |
| 2nd line                           | 7(2.7)  | 4(1.7)  | 3(10.7) |         |
| ≥3rd line                          | 5(1.9)  | 4(1.7)  | 1(3.6)  |         |
| **Radiotherapy (within 30 days)**  |         |         |         |         |
| 34(13.2)                           | 31(13.5)| 3(10.7) | 0.904   |
| Concurrent chemoradiotherapy (within 30 days) | 37(14.4)| 36(15.7)| 1(3.6)  | 0.149   |
| **Intrapleural/abdominal infusion (within 30 days)** | 10(3.9) | 5(2.2)  | 5(17.9) | <0.001 |
| **Corticosteroid therapy (within 30 days)** | 125(48.6)| 112(48.9)| 13(46.4)| 0.804   |
| **Prior infection (within 30 days)** | 13(5.1) | 10(4.4) | 3(10.7) | 0.322   |
| Prior G-CSF use (within 30 days)    | 90(35.0)| 84(36.7)| 6(21.4) | 0.110   |
| Prior antibiotics (within 30 days)  | 12(4.7) | 11(4.8) | 1(3.6)  | 1.000   |

**Presence of**
| Indwelling Catheters or Other Devices                  | No. (%)                      | Yes. (%)                     | p-Value |
|-----------------------------------------------------|------------------------------|------------------------------|---------|
| Biliary stent                                       | 2(0.8)                       | 2(0.9)                       | 1.000   |
| Ureteral stent                                       | 15(5.8)                      | 15(6.6)                      | 0.333   |
| Indwelling urinary catheters                        | 86(33.5)                     | 82(35.8)                     | 0.023   |
| CVC (port-a-cath or PICC)                           | 35(13.6)                     | 31(13.5)                     | 1.000   |
| Percutaneous pleural drainage tube                  | 55(21.4)                     | 51(22.3)                     | 0.331   |
| Percutaneous abdomen drainage tube                  | 6(2.3)                       | 4(1.7)                       | 0.130   |
| Drains post-operation                               | 89(34.6)                     | 85(37.1)                     | 0.017   |
| Nasogastric tube                                    | 67(26.1)                     | 62(27.1)                     | 0.294   |
| **Invasive procedure (within 30 days)**             | 157(61.1)                    | 142(62.0)                    | 0.387   |
| **Length of hospitalization**                       |                               |                              | **<0.001** |
| <22.42                                              | 147(57.2)                    | 122(53.3)                    | 25(89.3) |
| ≥22.42                                              | 110(42.8)                    | 107(46.7)                    | 3(10.7)  |
| **Empirical antibiotics treatment**                 | 91(35.4)                     | 81(35.4)                     | 1035.7) |
| **Effective empirical antibiotics treatment**       | 133(51.8)                    | 117(51.1)                    | 16(57.1) |
| **Length of antibiotics treatment (days)**          |                               |                              | 0.143   |
| <8.86                                               | 141(54.9)                    | 122(53.3)                    | 19(67.9) |
| ≥8.86                                               | 116(45.1)                    | 107(46.7)                    | 9(32.1)  |
| **ICU admission**                                   | 33(12.8)                     | 30(13.1)                     | 3(10.7)  |
| **Mechanical ventilation**                          | 18(7.0)                      | 14(6.1)                      | 4(14.3)  |
| **Septic shock**                                    |                               |                              | **<0.001** |
| None                                                | 219(85.2)                    | 202(88.2)                    | 17(60.7) |
| Yes                                                 | 38(14.8)                     | 27(11.8)                     | 11(39.3) |
| **Laboratory examination results**                  |                               |                              |         |
| Hemoglobin (g/L)                                    | 105.5±18.7                   | 18.3±1.2                     | 18.9±3.6 |
| Platelet count (×10^9/L)                            | 218.4±114.2                  | 110.1±7.3                    | 134.5±25.4 |
| White-cell count (×10^9/L)                          | 8.1±5.2                      | 5.3±0.3                      | 4.5±0.9 |
| Neutrophils count (×10^9/L)                         | 6.5±4.8                      | 4.9±0.3                      | 4.0±0.8 |
| Lymphocytes count (×10^9/L)                         | 1.0±0.7                      | 0.7±0.4                      | 0.6±0.1 |
| PCT (ng/mL)                                         | 4.6±20.3                     | 18.2±1.2                     | 31.8±6.0 |
| Albumin (g/L)                                       | 34.5±5.6                     | 5.5±0.4                      | 5.0±0.9 |

**Abbreviations:** MDR, multidrug-resistant; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index score; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; CVC, central venous catheter; PICC, peripherally inserted central catheter; ICU, intensive care unit; PCT, procalcitonin.

a Data are no. (%) of patients unless otherwise stated.

b Others: primitive neuroectodermal tumor (4 patients), duodenal carcinoma three patients, thymic carcinoma, carcinoid cancer of appendix, and sarcoma two patients each.

Bolded values indicate statistical significance.
Table 2 Causative agents of all nosocomial infection episodes caused by MDR bacteria in cancer patients

| Causative organisms                  | All (n = 257) | Survivor (n = 229) | Non-survivor (n = 28) | P-value |
|-------------------------------------|---------------|-------------------|----------------------|---------|
| MRSA                               | 7(2.7)        | 5(2.2)            | 2(7.1)               | 0.171   |
| ESBL-producing Enterobacteriaceae  | 155(60.3)     | 137(59.8)         | 18(64.3)             | 0.649   |
| MDR Pseudomonas aeruginosa         | 13(5.1)       | 13(5.7)           | 0(0.0)               | 0.403   |
| Acinetobacter baumannii            | 30(11.7)      | 27(11.8)          | 3(10.7)              | 1.000   |
| Stenotrophomonas maltophilia       | 16(6.2)       | 13(5.7)           | 3(10.7)              | 0.531   |
| ESBL-producing Klebsiella pneumonia| 31(12.1)      | 29(12.7)          | 2(7.1)               | 0.590   |
| Carbapenem-resistant Enterobacteriaceae | 4(1.6)  | 4(1.7)             | 0(0.0)               | 1.000   |
| ESBL-producing Enterobacter aerogenes | 1(0.4)  | 1(0.4)             | 0(0.0)               | 1.000   |

Abbreviations: MDR multidrug-resistant; MRSA, Oxacillin-resistant Staphylococcus aureus; ESBL, extended-spectrum β-lactamase.

* Data are no. (%) of patients unless otherwise stated.

Table 3 Risk factors for 30-day mortality in cancer patients with nosocomial infections caused by MDR bacteria

|                                | Univariate Model |                | Multivariate Model |                |
|--------------------------------|------------------|----------------|-------------------|----------------|
|                                | OR (95% CI)      | P-value        | OR (95% CI)       | P-value        |
| Age                            | 1.04(1.00-1.08)  | 0.054          | 1.03(0.96-1.10)   | 0.413          |
| Smoking history                |                  |                |                   |                |
| Never smoker                   | REF (1.00)       | 0.064          | REF (1.00)        | 0.082          |
| Former smoker                  | 2.07(0.86-4.97)  | 0.105          | 5.41(1.04-28.04)  | 0.044          |
| Current smoker                 | 0.22(0.03-1.68)  | 0.144          | 0.44(0.03-7.25)   | 0.567          |
| ECOG performance status        |                  |                |                   |                |
| 0,1                            | REF (1.00)       | 0.003          | REF (1.00)        | 0.003          |
| 2,3,4                          | 3.33(1.50-7.40)  |                | 3.57(0.83-15.36)  | 0.088          |
| Existence of distant metastasis|                  |                |                   |                |
| Primary sites of infection     | 2.88(1.29-6.43)  | 0.010          | 1.51(0.29-7.87)   | 0.625          |
| Respiratory tract              | 2.68(1.20-5.97)  | 0.016          | 5.36 (0.43-66.55) | 0.191          |
| Urinary tract                  | 0.24(0.08-0.71)  | 0.010          | 0.58 (0.04-8.21)  | 0.686          |
| Endogenous source              | 3.42(1.36-8.60)  | 0.009          | 4.02 (0.18-89.40) | 0.379          |
| Comorbidities                  |                  |                |                   |                |
| Liver disease                  | 5.29(1.44-19.37) | 0.012          | 28.12(1.72-460.45)| 0.019          |
| CCI                            | 0.009            |                |                   | 0.917          |
| 0                              | REF (1.00)       |                | REF (1.00)        |                |
| 1-2                            | 3.00(1.27-7.10)  | 0.013          | 0.73 (0.14-3.77)  | 0.709          |
| ≥3                             | 7.79(1.21-50.08) | 0.031          | 1.08 (0.02-58.19)| 0.968          |
| Surgery (within 30 days)       |                  |                |                   |                |
| None                           | REF (1.00)       |                | REF (1.00)        |                |
| Curative surgery               | 0.11(0.03-0.49)  | 0.004          | 0.01(0.00-0.53)   | 0.024          |
| Palliative surgery             | 0.74(0.16-3.46)  | 0.700          | 0.36(0.02-6.02)   | 0.479          |
| Chemotherapy (within 30 days)  |                  |                |                   |                |
| None                           | REF (1.00)       |                | REF (1.00)        |                |
| Neoadjuvant                    | 0.00             | 1.000          | 0.000             | 1.000          |
| Adjuvant                       | 0.00             | 0.998          | 0.000             | 0.998          |
| 1st line                       | 5.21(1.09-24.95) | 0.039          | 3.11(0.22-44.84)  | 0.405          |
| 2nd line                       | 1.74(0.19-16.30) | 0.628          | 0.05(0.00-12.95)  | 0.285          |
| ≥3rd line                      | 0.39(0.11-1.35)  | 0.136          | 0.74(0.08-7.02)   | 0.796          |

Presence of
| Indwelling catheters or other devices | Indwelling urinary catheters | 0.30 (0.10-0.89) | 0.030 | 13.51 (0.70-262.79) | 0.086 |
|--------------------------------------|-----------------------------|------------------|--------|-------------------|--------|
| Drains post-operation                | 0.28 (0.10-0.84)            | 0.023            | 1.43 (0.06-37.43) | 0.829 |
| **Length of hospitalization (days)** |                             |                  |        |                   |        |
| <22.42                               | REF (1.00)                  |                  |        |                   |        |
| ≥22.42                               | 0.14 (0.04-0.47)            | **0.001**        | 0.10 (0.02-0.62) | **0.013** |
| **Intrapleural/abdominal infusion (within 30 days)** | 9.74 (2.62-36.16) | **0.001** | 23.92 (2.16-264.29) | **0.010** |
| Mechanical ventilation               | 2.56 (0.78-8.40)            | 0.121            | 4.29 (0.41-44.57) | 0.223 |
| Septic shock                         |                             |                  |        |                   |        |
| No                                   | REF (1.00)                  |                  |        |                   |        |
| Yes                                  | 4.84 (2.05-11.42)           | **<0.001**       | 1.27 (0.17-9.48) | 0.814 |
| **Laboratory examination results**   |                             |                  |        |                   |        |
| Hemoglobin (g/L)                     | 0.96 (0.94-0.99)            | **0.001**        | 0.95 (0.91-0.99) | **0.025** |
| Platelet count (×10⁹/L)              | 0.99 (0.99-1.00)            | **0.009**        | 1.00 (0.99-1.01) | 0.801 |
| Lymphocytes count (×10⁹/L)           | 0.32 (0.13-0.79)            | **0.013**        | 1.00 (0.24-3.87) | 0.958 |
| Albumin (g/L)                        | 0.87 (0.80-0.94)            | **0.001**        | 0.85 (0.73-0.99) | **0.031** |

**Abbreviation:** OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Co-morbidity Index score; PCT, procalcitonin. Bolded values indicate statistical significance.

Figures
Figure 1

Flow chart of clinical characteristics, antibiotic-resistant patterns, and prognostic factors associated with nosocomial infections caused by MDR bacteria in cancer patients treated at the First Affiliated Hospital of Xi’an Jiaotong University between August 2013 to May 2019.
Figure 2

Trend in the etiology of nosocomial infections in cancer patients caused by MDR bacteria treated at the First Affiliated Hospital of Xi’an Jiaotong University between August 2013 to May 2019. (a) The annual distribution of MDR bacteria caused nosocomial infections in cancer patients. (b) The seasonal distribution of MDR bacteria caused nosocomial infections in cancer patients.
Figure 3

Antimicrobial susceptibility comparison among cancer patients with nosocomial infections caused by MDR bacteria. (a) The isolated MDRGNB. (b) The isolated MRSA.
