Infection and Drug Resistance

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ORIGINAL RESEARCH

Gram-Negative Bacteria Bloodstream Infections in Patients with Hematological Malignancies – The Impact of Pathogen Type and Patterns of Antibiotic Resistance: A Retrospective Cohort Study

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Background: *Enterobacteriaceae* (EB) and non-fermentative bacteria (NFB) are the main pathogens responsible for gram-negative bloodstream infections (GN-BSI) in patients with hematological malignancies (HMs). These two pathogen types have heterogeneous resistance mechanisms to antibiotics. However, the impact of pathogen species and pattern of antibiotic resistance on the outcomes of patients with HMs remains unclear.

Methods: We retrospectively collected clinical data of patients with HMs at three comprehensive hospitals in Hunan Province, China, between January 2010 and May 2018. The data analyzed the impact that different species and patterns of antibiotic resistance had on the outcome of patients with HMs.

Results: The majority of the 835 monomicrobial isolates collected from patients with HMs and GN-BSIs were *Enterobacteriaceae* (75.7%). While detections of MDR pathogens in BSIs as a whole are decreasing, sub-analysis shows that detections of extended spectrum β-lactamase-producing (ESBL) *Enterobacteriaceae* and carbapenem-resistant pathogens in BISs are rising. Comparing different species, the early mortality rate associated with infections caused by NFB was significantly higher than infections caused by *Enterobacteriaceae* (22.6% vs 9.7%, $p < 0.001$). Across different multidrug-resistant (MDR) patterns, ESBL bacteria did not have a significant impact on health outcomes. Carbapenem-resistant bacteria, on the other hand, were observed to significantly affect early mortality rate, such as carbapenem-resistant *Klebsiella pneumoniae* (36.0% vs 7.6%, $P < 0.001$) and carbapenem-resistant non-fermentative bacteria (44.7% vs 16.5%, $P < 0.001$).

Conclusion: Our findings suggest that both species and patterns of antibiotic resistance can affect the early mortality of patients with HMs during BSI.

Keywords: multidrug-resistant patterns, hematological malignancies, gram-negative bloodstream infections, carbapenem-resistant bacteria

Introduction

In the past few decades, gram-negative bacteria (GNB) have become the main pathogens responsible for bloodstream infections (BSI) in patients with hematological malignancies (HMs), accounting for 50–75% of all BSI cases.[1–4] GNB are mainly composed of *Enterobacteriaceae (*ie, *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae*, and non-fermentative bacteria (NFB) (ie, *Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*) with

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associated infections resulting in mortality rates ranging from 15% to 42%.[3–8] Although the use of broad-spectrum antibiotics and appropriate administration of antimicrobial therapies has led to a decrease in patient mortality, at the same time, the proportion of multidrug-resistant (MDR) bacteria has steadily increased as an unfortunate consequence.

MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[9] MDR pathogens can display increased resistance to clinical antibiotics and may result in treatment failure. Among multidrug-resistant GNB, *Enterobacteriaceae* with an extended spectrum β-lactamase (ESBL) phenotype and carbapenem-resistant (CRE) isolates in particular have become an increasing concern in the medical and health sectors.[8,10] Patients with HMs who have disease-related immunosuppression and long-term exposure to broad-spectrum antibiotics are especially at risk.[34]

Whether pathogen type or patterns of antibiotic resistance affect the prognosis of patients with HMs remains debatable.[3,8,10–12] Our previous studies showed that endogenous (host-related factors, such as disease status, organ functions, and nutritional status) factors or exogenous (treatment-related factors, such as inappropriate initial antimicrobial therapy (IIAT)) factors had impact on patient prognoses.[13,14] However, bacterial-related factors such as pathogen species or patterns of antibiotic resistance may also act as risk factors leading to poorer health outcomes in HM patients, but prior literature focusing on these bacterial-related factors is limited and inconsistent. One study showed that the 21-day prognosis of multidrug-resistant gram-negative bacteria (MDR-GN) BSI was worse compared to BSIs of drug-sensitive gram-negative bacilli,[8,10] while other studies have shown opposing findings.[11,12] In addition, the influence of bacterial pathogen type in BSI on prognosis of patients is also an area requiring further research. Studies have shown that the prognosis of patients with non-fermentative bacterial BSIs was worse compared to *Enterobacteriaceae* induced BSIs, emphasizing the heterogeneity of different pathogens in GNB-BSI.[13,14] Given the state of current literature, there is a need to increase our understanding of whether BSI pathogen type or patterns of antibiotic resistance can affect the outcomes of HM patients, which can hold important clinical implications and inform policies concerning antimicrobial stewardship and infection control surveillance.

In this study, we retrospectively analyzed multi-center clinical data of patients with HMs complicated with GNB-BSI over a 9 year timeframe, with the purpose of exploring the influence of different pathogen type and antibiotic resistance patterns on prognosis of patients.

Patients and Methods

Setting and Study Design

We identified all episodes of GN-BSIs in patients (age ≥16 years) with hematologic malignancies at three university-affiliated hospitals in Hunan Province, China, from January 2010 to May 2018. The following characteristics were collected for each patient: demographic information, malignancy characteristics, comorbidities, laboratory data, antibiotic agents, and the outcome of infection. For each bacterial isolate, the antimicrobial susceptibility was determined and analyzed. In patients who had multiple positive cultures with the same specificity and sensitivity, only the first culture was included for analysis. Blood culture samples which detected different bacterial strains within 48h were defined as polymicrobial bacteremia and excluded from this study due to the limited sample size and possible confounding effects. Anti-infection therapies were performed according to pre-defined guidelines.[6,15] The primary outcome was all-cause mortality within 7-days after BSI onset.

Definitions

The following terms were defined before data analysis. BSI was defined by the isolation of infectious organisms from blood culture specimens in patients with compatible clinical signs and symptoms.[16] Neutropenia and profound neutropenia were defined as an absolute neutrophil count (ANC) of <500 cells/mm3 and <100 cells/mm3, respectively.[15] Pitt bacteremia score was calculated at the time of fever onset.[17] The date of BSI onset was represented by the collection date of the first positive blood culture (index culture). BSIs were classified as nosocomial if the index blood culture was drawn more than 48h after hospital admission.[6] MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories.[9]

Carbapenem-resistant Enterobacteriaceae (CRE) was defined as *Enterobacteriaceae* isolates demonstrating resistance to any carbapenem (ertapenem, meropenem, imipenem, and/or doripenem), based on antimicrobial susceptibility testing (AST).[18] Disease status was assessed by

the most recently available bone marrow biopsy and categorized as remission, relapsed, or uncontrolled malignancy, as previously defined.[19] According to our population characteristics and cutoff value, sustained neutropenia exceeding 21 days was defined as prolonged neutropenia. Acute respiratory failure and acute renal failure were described in Tang et al.[19] Antibiotic exposure was defined as any antimicrobial therapy lasting more than 48h in the previous one month.[20] Inappropriate initial antimicrobial therapy (IIAT) refers to antibiotic regimens prescribed and administered during the first 72h after suspecting BSI, and was not active against the pathogen identified by culture and in vitro susceptibility testing.[19,21]

Antibiotic Susceptibility Test

Bloodstream isolate identification and antibiotic susceptibility tests were performed on VITEK 2 Compact (bioMe´rieux SA, Marcy l'Etoile, France). VITEK 2 Compact was used to screen ESBL positive *E. coli* or *K. pneumoniae*. According to the CLSI guidelines, phenotypic confirmatory test for ESBL was performed using both disk containing 30 μg ceftazidime and disk containing 30 μg cefotaxime, alone and in combination with 10 μg clavulanic acid (Becton–Dickinson, Franklin Lakes, NJ, USA). Strains producing ESBL were confirmed as a ≥5mm increment in a zone diameter for either combination treatment versus corresponding monotreatment. CRE was defined as Enterobacteriaceae isolates demonstrating resistance to any carbapenem (ertapenem, meropenem, imipenem, and/or doripenem), based on antimicrobial susceptibility testing (AST). Carbapenem resistance was defined as an ertapenem MIC ≥2 μg/mL and meropenem and/or imipenem MIC ≥4 μg/mL.[18]

Statistical Analysis

Statistical analysis was performed with SPSS version 19.0 for Windows. Categorical variables were compared using chi square tests. Variables with $P \leq 0.1$ (two tailed) in the bivariate analysis were taken as candidates for multivariate analysis. Logistic regression was used for multivariate analysis to identify independent risk factors for 7-day mortality. Cutoff value means the diagnostic threshold, it represents the clinical decision point. The cutoff values for continuous variables were set according to clinical practice or laboratory references by using the receiver operating characteristic curve (ROC). In cases where less than 5% of data were missing, missing values for continuous variables were replaced via mean imputation; missing categorical variable values were replaced via mode imputation. All p values were two sided, and $p \leq 0.05$ was considered significant.

Results

Pathogens and the Trend of Antibiotics Resistance Over the Years

In the present study, a total of 835 strains of GNB were detected, 633 strains (75.7%) were *Enterobacteriaceae* bacteria and 177 strains (21.2%) were non-fermentative bacteria. The majority (53.6%) of *Enterobacteriaceae* bacteria were *Escherichia coli*, while the majority (61.6%) of non-fermentative bacteria consisted of *Pseudomonas aeruginosa* (Table 1).

Broadly speaking, the proportion of BSI attributable to MDR-GNB showed a downward trend from 75.7% in 2010–2011 to 63.0% in 2016–2018 (Figure 1A, refer to Supplementary Table 1and 1a). Sub-analysis also revealed that the proportion of MDR *Enterobacteriaceae* in all Enterobacteriaceae decreased over the years; however, the MDR rates of non-fermentative bacteria in all non-fermentative bacteria showed an upward tendency with detection rates of non-fermentative bacteria increasing from 46.7% in 2010–2012 to 79.5% in 2016–2018 (Figure1B, refer to Supplementary Table 1 and 1b). ESBL-producing rate increased from 31.1% in 2010–2014 to 50.5% (Figure 1C, Supplementary Table 1 and 1c) in 2015–2018 in *Enterobacteriaceae*. The percentage of carbapenem-resistant strains in both *Enterobacteriaceae* and GN-bacteria increased significantly, from 0.0% in 2010 to 13.1% in 2018 among *Enterobacteriaceae* and from 3.0% in 2010 to 15.8% in 2018 among GN-bacteria (excluding *Stenotrophomonas maltophilia*) (Figure 1D, Supplementary Table 1 and 1d).

Table 1 Composition of GN-Bacteria Isolated from Bloodstream Infection in Patients with HMs

GN-Bacteria	n=835
Enterobacteriaceae	632 (75.7%)
Escherichia coli	339 (53.6%)
Klebsiella pneumoniae	197 (31.2%)
Enterobacter cloacae	33 (5.2%)
Others Enterobacteriaceae	63 (10.0%)
Non-fermentative bacteria	177 (21.2%)
Pseudomonas aeruginosa	109 (61.6%)
Acinetobacter baumannii	25 (14.1%)
Stenotrophomonas maltophilia	20 (11.3%)
Other Non-fermentative bacteria	23 (13.0%)
Other GN-bacteria	26 (3.1%)

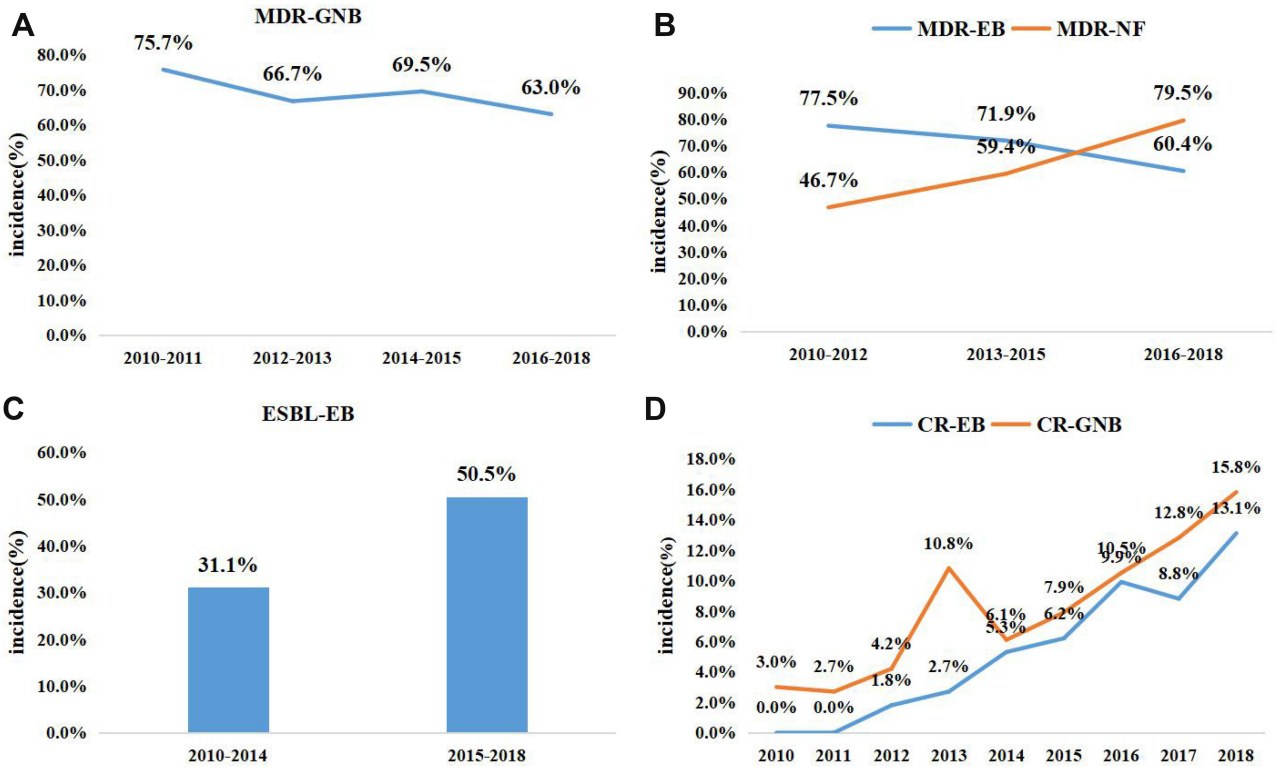

Figure 1 Proportion of BSI based on pathogen resistance phenotype from 2010–2018. The X-axes represents years. (**A**) The change in percentages of MDR detection rate in all GN-bacteria over the study period. (**B**) The change in percentages of MDR detection rate in EB and NF isolates over the study period. (**C**) The change in the detection rate of ESBL producing Enterobacteriaceae. (**D**) The change in carbapenem-resistant bacteria detection rate from Jan 2010–May 2018 in EB and NF strains.
Abbreviations: MDR-GNB, multidrug resistance-gram negative bacteria; MDR-EB, multidrug resistance –Enterobacteriaceae; MDR-NF, multidrug resistance-non fermentative bacteria; ESBL-EB, extended-spectrum β-lactamases producing-Enterobacteriaceae; CR-EB, carbapenem resistant-Enterobacteriaceae; CR-GNB carbapenem resistant-Gram negative bacteria.

Impact of Pathogen Type on Mortality—Non-Fermentative Bacterial BSI is an Independent Risk Factor for Early Mortality

In terms of bacterial species, the early mortality rate of patients with non-fermentative bacteria associated BSIs was significantly higher than that of patients with *Enterobacteriaceae* associated BSIs (22.6% vs 9.7%, 2.733 (1.760–4.244), p < 0.001) (Figure 2A and Supplementary Table 2). BSI due to *Acinetobacter baumannii* demonstrated the highest early mortality rate (64.0%, 16/25), followed by infections resulting from *Stenotrophomonas maltophilia* (35.0%,7/20) and *Pseudomonas aeruginosa* (13.8%,15/109) (Figure 2B and Supplementary Table 2). The early mortality rate of infections due to *Escherichia coli* and *Klebsiella pneumoniae* was similar (11.2% vs 11.2%) (Figure 2).

A multivariate analysis was conducted to determine whether pathogen type affected the prognosis of patients. Results show that non-fermentative bacteria BSI is an independent risk factor for the 7-day mortality of patients (Tables 2, 2.093 (1.077–4.067), p=0.029). Other patient characteristics which contributed to worse mortality outcomes were disease state, presence of acute respiratory failure, use of vasopressors, and inadequate treatment (Table 2).

Table 3 shows demographic and clinical characteristic differences between *Enterobacteriaceae* BSI patients and non-fermentative bacteria BSI patients. The incidence of respiratory failure, rate of urine tube placement, and 72 h IIAT are significantly higher in the non-fermentative bacteria BSI patient group compared to the *Enterobacteriaceae* BSI patient group. Most other variables (such as age, gender, disease status, etc.) showed no significant differences.

Patterns of Antibiotics Resistance Impact Mortality—BSI Associated with Carbapenem Resistant GN-Bacteria Has Poorer Prognosis for Patients

We did not find a significant association between MDR pathogens and patient prognosis in our study. Additionally,

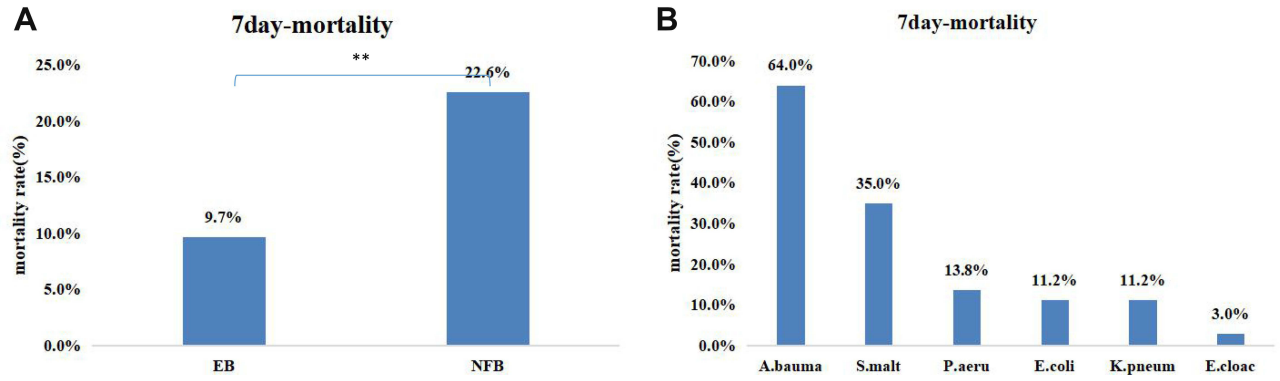

Figure 2 7 day mortality rate of patients with BSI: *Enterobacteriaceae* vs non-fermenting bacteria BSI. (**A**) 7 day mortality rate of Enterobacteriaceae and Non fermentative bacteria; (**B**) 7 day mortality rate of different strains. **P<0.001.

Abbreviations: EB, Enterobacteriaceae; NFB, non fermentative bacteria; *A. bauma*, *Acinetobacter baumannii*; *S. malt*, *Stenotrophomonas maltophilia*; *P. aeru*, *Pseudomonas aeruginosa*; *E. coli*, *Escherichia coli*; *K.pneum*, *Klebsiella pneumoniae*; *E. cloac*, *Enterobacter cloacae*.

ESBL-production isolates had no significant impact on the early prognosis of patients with HMs (P > 0.05) (Figure 3A and B, Supplementary Table 3). In Carbapenem-resistance Gram-negative strains, the early mortality of patients was significantly higher than carbapenem-sensitive strains, especially in carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) strains (36.0% vs 7.6%, 6.880 (2.548–18.576), P < 0.001) and non-fermentative bacteria (44.7% vs 16.5%, P < 0.001) (Figure 3C and D, Supplementary Table 3).

Discussion

Our study data show that both pathogen type and pattern of antibiotic resistance can affect early outcomes of HM patients with GNB-BSI. To our knowledge, this is the first study evaluating the effect of bacteriological factors on the prognosis of patients with HMs. These findings have important implications for managing the increasingly common problem of bacteremia associated with non-fermentative and carbapenem-resistant bacteria in immunocompromised patients.

Previous studies conducted in patients with HMs have shown that *Enterobacter* are responsible for 55–70% of GN-bacteria BSI in patients with HMs, while non-fermenting bacteria are responsible for 20–40% of BSI worldwide.[2,22] In comparison, the rate of *Enterobacter* related BSI is reported to be about 70–75% in China,[4,7,23] consistent with our present study. Although the overall prognosis of patients with bacterial infections has improved with the continuous administration of broad-spectrum antibiotics, antibiotic resistance has also become progressively more severe. According to the United States Centers for Disease Control and Prevention (CDC), antibiotic resistant GN-bacteria is becoming increasingly widespread, and the prevalence of BSI associated with carbapenem-resistant GN-bacteria is also rising over time; the prevalence of CR-KP BSI was lower than 1% in 2000 but has since grown to 21% in 2018.[24] This upward pattern has also been identified in other countries.[24,25] Our study identifies a similar trend gathered from 9-years of data. Carbapenem-resistant *Enterobacter* related BSIs that were not detected in 2010 have increased to a prevalence of 13.1% in 2018.

It is well documented that the type of pathogenic bacteria can affect the prognoses of patients with HMs suffering from BSI. A study surveying 575 patients with HMs revealed that the 21-day mortality rate of patients with GN-BSI was significantly higher than the mortality rate of patients with bacteremia associated with Gram-positive bacteria (16.9% vs 5.6%, p < 0.001).[3] Among different GN-bacteria species, the mortality of patients with *Pneumocystis, Aeruginosa*, and *Baumannii* related BSI was remarkably higher than that of patients with other pathogen related BSIs (p < 0.05),[1,3,26,27] suggesting the heterogeneity of bacteria could influence the prognosis of patients. In our present study, the patients with BSI caused by non-fermentative bacteria had a significantly higher early mortality rate compared to patients with *Enterobacter* caused BSI (22.6% vs 9.7%, p < 0.001), with *Acinetobacter baumannii*- associated BSI patients having the highest mortality rate (64.0%). Furthermore, the incidence of respiratory failure, rates of urinary catheter placement, and 72h IIAT were significantly higher in patients with non-fermentative bacteria BSI compared to patients with *Enterobacteriaceae* BSI, demonstrating the need for prudent administration

Table 2 Univariate Analysis and Multivariable Analysis of Variables Associated with 7-Day Mortality

Variables	Total (n=835)	Survivors (n=729)	Non-Survivors (n=106)	Univariate Analysis		Multivariate Analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Age >60 years	88(10.5)	66(9.1)	22(20.8)	2.631(1.544–4.484)	<0.001	1.817(0.822–4.016)	0.140
Male sex	462(55.3)	401(55.0)	61(57.5)	1.109(0.734–1.674)	0.623	1.145(0.637–2.057)	0.650
Relapsed or uncontrolled malignancy	588(70.4)	491(67.4)	97(91.5)	5.224(2.594–10.523)	<0.001	4.480(1.894–10.597)	0.001
MASCC score<21	643(77.0)	543(74.5)	100(94.3)	5.709(2.463–13.230)	<0.001	2.469(0.848–7.189)	0.097
Urine tube	41(4.9)	20(2.7)	21(19.8)	8.758(4.561–16.817)	<0.001	2.094(0.805–5.444)	0.129
Use of vasopressors	180(21.6)	111(15.2)	69(65.1)	10.383(6.636–16.244)	<0.001	3.805(2.083–6.949)	<0.001
Acute respiratory failure	143(17.1)	70(9.6)	73(68.9)	20.826(12.895–33.632)	<0.001	3.052(2.275–4.094)	<0.001
Renal insufficiency	18(2.2)	13(1.8)	5(4.7)	2.727(0.952–7.809)	0.052	0.975(0.453–2.099)	0.949
Prior antimicrobial exposure	455(54.5)	384(52.7)	71(67.0)	1.823(1.185–2.802)	0.006	1.048(0.582–1.888)	0.876
CR-GNB	78(9.3)	51(7.0)	27(25.5)	4.544(2.697–7.537)	<0.001	1.430(0.625–3.271)	0.397
NFB	177(21.2)	137(18.8)	40(37.7)	2.619(1.696–4.044)	<0.001	2.093(1.077–4.067)	0.029
Inadequate antibiotic treatment	69(13.2)	66(9.1)	40(37.7)	5.530(3.484–8.778)	<0.001	3.572(1.722–7.046)	0.001
Hemoglobin <70g/Dl	679(81.3)	580(79.6)	99(93.4)	3.633(1.653–7.985)	0.001	1.437(0.544–3.794)	0.464
Platelet $<10\times10^{3}mm^{-3}$	518(62.0)	435(59.7)	83(78.3)	2.439(1.502–3.961)	<0.001	1.639(0.862–3.117)	0.132
Albumin <30g/L	444(53.2)	369(50.6)	75(70.8)	2.360(1.516–3.676)	<0.001	1.414(0.758–2.637)	0.276
AST >120U/L	80(9.6)	64(8.8)	16(15.1)	1.847(1.024–3.334)	0.039	1.072(0.441–2.604)	0.878
TBil >34.2μmol/L	114(13.7)	87(11.9)	27(25.5)	2.522(1.544–4.121)	<0.001	1.000(0.477–2.094)	0.999
PT >14s	205(24.6)	151(20.7)	54(50.9)	3.975(2.610–6.055)	<0.001	1.524(0.826–2.812)	0.178

Abbreviations: CI, confidence interval; OR, ratio; CR-GNB, carbapenem-resistance gram negative bacteria; NFB, non fermentative bacteria; AST, aspartate transaminase; TBil, total bilirubin; PT, prothrombin time.

Table 3 Demographic and Clinical Characteristics of EB and NF Associated BSI Patients

Variables	EB (%) n=632	NF (%) n=177	OR (95% CI)	P
Demographic information				
Age >60 years	64(10.1)	22(12.4)	1.260(0.752–2.110)	0.380
Male sex	349(55.2)	96(54.2)	0.961(0.688–1.343)	0.816
Underlying malignancies				
Acute myeloid leukemia	315(49.8)	91(51.4)	1.065(0.763–1.486)	0.712
Acute lymphoblastic leukemia	223(35.3)	55(35.1)	0.827(0.578–1.182)	0.297
Lymphoma	38(6.0)	12(6.8)	1.137(0.581–2.225)	0.708
Disease status				
Remission	188(29.7)	54(30.5)	1.037(0.722–1.490)	0.845
Relapsed or uncontrolled	444(70.3)	123(69.5)	0.964(0.671–1.386)	0.845
Risk factors				
Charlson Comorbidity index ≥4	103(16.3)	32(18.1)	1.133(0.732–1.755)	0.574
Pitt bacteremia score≥4	153(24.2)	45(25.4)	1.067(0.727–1.567)	0.740
MASCC score<21	491(77.7)	134(75.7)	0.895(0.605–1.323)	0.578
Neutropenia				
Profound neutropenia	556(88.0)	148(83.6)	0.698(0.438–1.110)	0.127
Prolonged neutropenia	221(35.0)	49(27.7)	0.712(0.493–1.028)	0.069
Previous chemotherapeutics	575(91.0)	152(85.9)	0.603(0.364–0.997)	0.047
Urine tube	22(3.5)	18(10.2)	3.139(1.644–5.994)	<0.001
CVC	258(40.8)	78(44.1)	1.142(0.816–1.599)	0.439
Dysfunctional organ systems				
Use of vasopressors	130(20.6)	45(25.4)	1.316(0.892–1.943)	0.166
Acute respiratory failure	95(15.0)	44(24.9)	1.870(1.248–2.803)	0.002
Renal insufficiency	11(1.7)	7(4.0)	2.325(0.888–6.088)	0.078
Antibiotic therapy				
Prior antimicrobial exposure	353(55.9)	91(51.4)	0.836(0.599–1.168)	0.294
Nosocomial bacteremia	568(89.9)	153(86.4)	0.776(0.424–1.420)	0.195
72h-IIAT	158(25.0)	68(38.4)	1.872(1.316–2.662)	<0.001
Patterns of pathogen resistance				
MDR bacteria	429(67.9)	116(65.5)	0.900(0.633–1.280)	0.557
CR-GNB	40(6.3)	38(21.5)	4.046(2.501–6.545)	<0.001
Laboratory parameters				
Hemoglobin <70g/dL	527(83.4)	136(76.8)	0.661(0.440–0.993)	0.045
Platelet $<10\times10^3mm^{-3}$	403(63.8)	105(59.3)	0.829(0.589–1.165)	0.280
Albumin <30g/L	339(53.6)	93(52.5)	0.957(0.685–1.336)	0.796
AST >120U/L	63(10.0)	14(7.9)	0.776(0.424–1.420)	0.409
TBil >34.2μmol/L	84(13.3)	26(14.7)	1.123(0.698–1.807)	0.631
PT >14s	157(24.8)	41(23.2)	0.912(0.616–1.351)	0.646
7-day mortality	61(9.7)	40(22.6)	2.733(1.760–4.244)	<0.001

Abbreviations: CVC, centre vein catheter; 72h-IIAT, 72h-initial inappropriate antibiotic treatment; CR-GNB, carbapenem-resistance gram negative bacteria; MDR bacteria, multidrug resistance bacteria; AST, aspartate transaminase; TBil, total bilirubin; PT, prothrombin time.

of invasive operations and initial treatment of appropriate antibiotics.

The influence of different antibiotic resistance mechanisms on the prognosis of patients with BSI has been a highly debated topic.[1,4–6,9,21,28,29] An Italian study investigating HM patients with *Pseudomonas aeruginosa* BSI reported that the 21-day mortality of patients infected with MDR bacteria was significantly worse than that of patients infected with non-MDR bacteria (42.4% vs 12.5%, p = 0.03).[28] However, another study conducted by Scheich et al reported that the two kinds

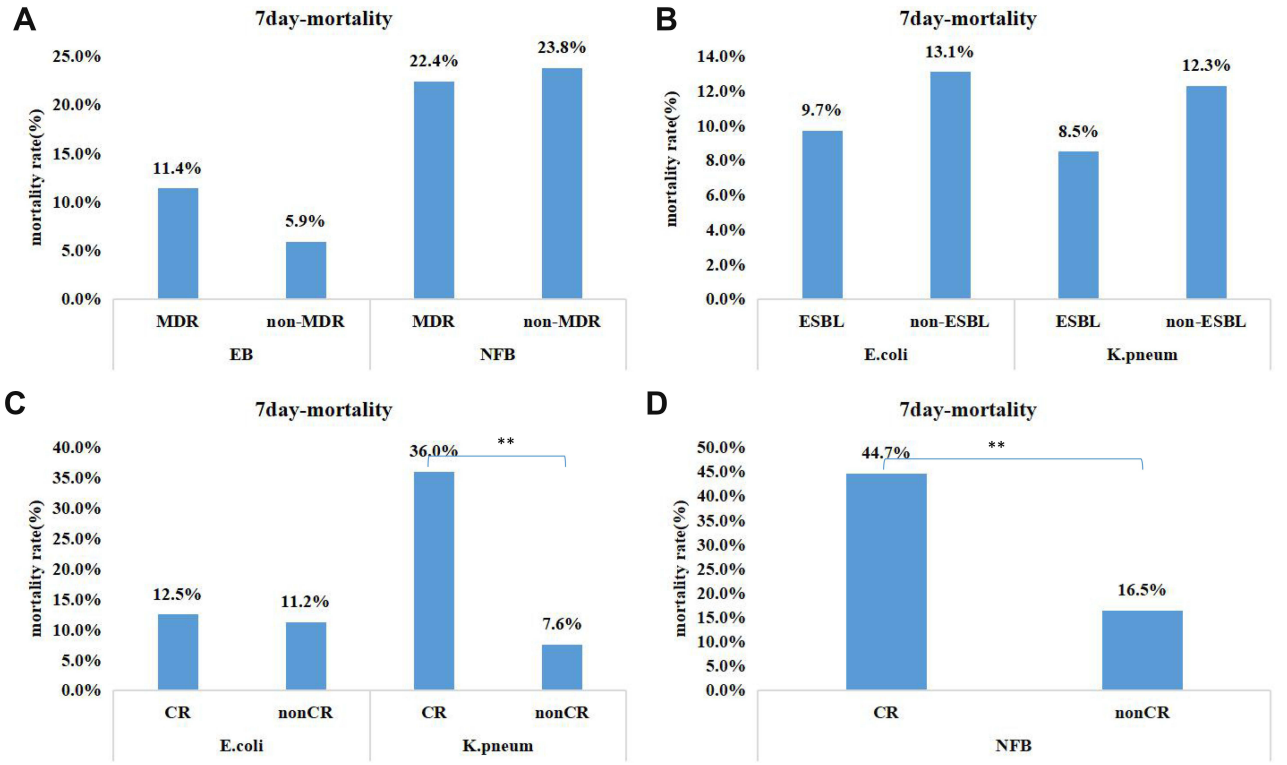

Figure 3 Impact of pathogen antibiotic resistance profile on 7 day-mortality of patients with BSI. (**A**) Multidrug resistance on prognosis of Enterobacteriaceae and Non-fermentative bacteria; (**B**) ESBL production on prognosis of Escherichia coli and *Klebsiella pneumoniae*; (**C**) Carbapenem resistance on prognosis of Escherichia coli and *Klebsiella pneumoniae*; (**D**) Carbapenem resistance on prognosis of Non fermenting bacteria. **P<0.001.

Abbreviations: EB, Enterobacteriaceae; NFB, non fermentative bacteria; MDR, multi-drug resistance; ESBL, extended-spectrum β-lactamase; CR, carbapenem-resistant; *E. coli*, *Escherichia coli*; *K. pneum*, *Klebsiella pneumoniae*.

of antibiotic resistance mechanisms had an equivalent effect on patient outcomes.[5] Our results showed that although the early mortality of patients with HMs who had *Enterobacter* MDR BSI is higher compared to patients with non-MDR bacteria BSI, the difference was not statistically significant. This may be related to the initial use of appropriate antibiotics in more than 75% of patients (Table 3). Additionally, whether ESBL affects the prognosis of patients is also debatable A South Korean study showed that pathogens with ESBL production could impair the prognosis of patients with HMs,[29] while other trials have indicated conflicting results.[12,30] The results of our study showed that ESBL production of *E. coli* and *K. pneumoniae* had little effect on the early mortality of patients ($P > 0.05$). However, these contradictory results may be a result of insufficient sample size and different initial medications. Of note, the majority of studies have consistently reported that the existence of carbapenem resistance in bacteria could significantly impact the prognosis of patients.[18,26,31,32] Compared with carbapenem-sensitive bacteria-related BSI, patients who were infected with carbapenem-resistant bacteria had more unfavorable outcomes. CR- *Klebsiella Pneumoniae* infected patients were particularly vulnerable, which may be due to the highly resistant features of CR- *Klebsiella Pneumoniae* against common antibiotics. Our study draws the same conclusion that infections related to CR- *Klebsiella Pneumoniae* puts patients with HMs at greater disadvantage. Given the huge impact of CR bacteria on the prognosis of patients, antibiotic prophylaxis and decolonization should be considered for patients who are at high-risk for infection and have positive CRE screening.

To our knowledge, this is the first study to investigate the influence of bacteriological factors on the prognosis of patients with HMs who had BSI. However, this study has several limitations. First, as a retrospective research, we could not obtain bacterial samples for homology analysis and determine the distribution of drug-resistant genotypes, it cannot be analyzed from a deeper level, while the genotypes of *E. coli* in China are mostly NDM, while those of Klebsiella pneumoniae are mostly KPC.[33] Second, our study relied on inpatient records, and we could only analyze objective and easily measurable outcomes, such as patients' all-cause 7-day mortality. More well-designed prospective studies based on bacterial genotypes are needed in the future.

Conclusion

In conclusion, GNB antibiotic resistance, particularly CR-GNB, has become an increasingly notable problem for patients with HMs. Both pathogen type and patterns of antibiotic resistance can affect the early outcome of patients. Clinical attention should be paid in particular to infections related to non-fermentative bacteria and carbapenem-resistant bacteria.

Ethical Statement

This study was approved by the ethics committee of the Third Xiangya Hospital, Central South. Our study was a retrospective study, this study would not do harm to rights, benefits, and health of the subjects, no personally identifiable information was collected in this study. So the requirement for informed consent from patients was also waived, and we guarantee the covering patient data confidentiality. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors meet the ICMJE authorship criteria. All authors made substantial contributions to the work, Xin Li for conception and design, Yishu Tang for analysis and interpretation of data and took part in drafting the article, Cong Xu, Han Xiao, Qian Cheng acquisition of data and Liwen Wang for checking the English version of the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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