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Impact of multidrug resistance in cancer patients with bloodstream infections caused by Gram-negative bacilli: results from a multicentre study

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Objective: To evaluate the impact of multidrug resistance (MDR) on the mortality of cancer patients with bloodstream infection (BSI) by Gram-negative bacilli (GNB).

Patients and methods: This was a prospective observational multicentre study including cancer patients with BSI caused by GNB (June 2018–January 2020). The primary outcome was 30-day mortality. The secondary outcome was mortality attributable to MDR organisms, including extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant (CR) Enterobacterales and CR non-fermenting GNB (CR-NFGNB). A multivariable regression analysis identified factors associated with 30-day mortality. Adjusted odds ratio (aOR) with 95% confidence intervals (95% CI) were calculated. Attributable mortality was estimated according to DRIVE-AB Consortium's formula.

Results: Of 347 cancer patients, 232 (66.9%) had BSI caused by MDR-GNB. Thirty-day mortality was 27.2% in patients with BSI caused by MDR organisms compared to 7% in those with BSI by susceptible GNB ($P<0.001$). In the multivariable analysis, MDR-GNB including ESBL-producing Enterobacterales (aOR 8.734, 95% CI 1.411–54.077, $P=0.02$), KPC-producing Enterobacterales (aOR 8.548, 95% CI 1.296–56.411, $P=0.026$), metallo-β-lactamases (MBL)-producing Enterobacterales (aOR 15.802, 95% CI 1.408–68.667, $P=0.022$) and CR-NFGNB (aOR 53.373, 95% CI 5.104–89.146, $P<0.001$) as compared to susceptible GNB were independently associated with 30-day mortality. Mortality attributable to MDR-GNB was 43%. According to causative pathogens, attributable mortality was 33% in ESBL, 32% in KPC, 47% in MBL and 73% in CR-NFGNB.

Conclusions: In cancer patients, BSIs due to MDR-GNB are associated with excess mortality compared to BSI by susceptible GNB. Strategies to reduce the spread of MDR-GNB and to promote optimal management of affected patients are urgently needed.

Introduction

Antimicrobial resistance (AMR) is one of the greatest public health threats worldwide. Deaths attributable to AMR are growing each year.[1] AMR was associated with 4.95 million deaths in 2019 and 1.27 million people died as a direct result of drug-resistant infections.[2] It has been estimated that this number could reach 10 million by 2050, when AMR may become the leading cause of death, overcoming cancer as a leading fatal disease.[3] In the last decade, the spread of multidrug-resistant (MDR) Gram-negative bacilli (GNB), including extended-spectrum β-lactamases (ESBL)- and carbapenamases-producing GNB, drew the attention of the scientific community and represents a great challenge for clinicians.[4–7] Patients with cancer are vulnerable to infection by GNB as a result of oncological treatments, neutropenia, immune dysfunction, mucositis and use of intravascular devices.[8] A recently published study showed that most (60.4%) of bloodstream infections (BSIs) among solid cancer patients were caused by GNB with MDR-GNB accounting for 84.8% of GNB-related BSI.[9] The occurrence of infections by MDR-GNB represents a challenge in the management of patients with cancer, increasing the morbidity and mortality of the disease. AMR has several implications for these patients: it escalates the cost of cancer care, may determine temporary discontinuation of anticancer treatments, exacerbates health disparities in patients living in countries with limited access to antibiotics and eventually increased mortality. However, limited data are available about the role of AMR in the natural history of patients with cancer.

This study aimed to evaluate the impact of MDR in patients with cancer who developed a bloodstream infection (BSI) by GNB.

Methods

This is a secondary analysis of a prospective observational study including patients with BSI caused by GNB in 19 hospitals belonging to the ALARICO Network (June 2018 to January 2020).[5] We selected all patients with active cancer who had been hospitalized with a BSI by GNB included in the ALARICO Study. The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The study was approved by the Internal Review Board (IRB) of the promoter centre (approval number 954/17) and by local ethical committees of participating centres. Written informed consent was obtained from study participants. This study is reported according to the STROBE statement.

Study outcomes

The primary objective was to describe the clinical characteristics and outcome of cancer patients with BSI caused by GNB. The primary outcome measure was 30-day mortality.

The secondary objective was to quantify the excess mortality of patients with BSI by MDR-GNB compared to those with BSI due to susceptible GNB. Excess mortality (or attributable mortality) was defined as previously reported.[5]

Study design and definitions

The ALARICO Study was a prospective observational study including hospitalized adults (>18 years old) with BSI caused by GNB from 19 hospitals in Italy. Study procedures were described previously. Data were collected in a pre-formed clinical report form (CRF) using Castor EDC. The CRF included demographics, comorbidities, clinical characteristics at BSI onset, microbiological data and outcome. BSI episodes were categorized as BSI caused by susceptible GNB and those caused by MDR-GNB. MDR-GNB were defined as extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and carbapenem-resistant non-fermenting GNB (CR-NFGNB), including both CR *Pseudomonas aeruginosa* (CRPA) and CR *Acinetobacter baumannii* (CRAB). ESBL-producing Enterobacterales were selected according to phenotype (ceftriaxone-non-susceptible Enterobacterales).[10] CRE were selected according to both phenotype (carbapenem resistance) and genotype using molecular detection of *bla* genes involved in carbapenem resistance by using the GeneXpert® System (Xpert-CARBA test, Cepheid, Sunnyvale, CA, USA). Patients with polymicrobial BSI were excluded. Day 1 was defined as the day of index blood culture collection. Active cancer was defined as cancer diagnosed within the previous six months, or recurrent, regionally advanced or metastatic cancer, or cancer for which treatment had been administered within 6 months.[11] Receipt of steroids was defined as the use of prednisone at a daily dose of 20 mg (or equivalent) for a minimum of 2 weeks within the previous 30 days.

Patients were followed up until 30 days from day 1. Thirty-day mortality was defined as death occurring within 30 days from day 1.

Statistical analysis

Continuous variables were reported as median with interquartile ranges (IQRs) and categorical variables as numbers and percentages. Continuous variables were compared by Student's *t*-test and the Mann–Whitney *U*-test as appropriate. Categorical variables were evaluated using χ^2 or the two-tailed Fisher's exact test, as appropriate.

A multivariable regression analysis was performed to identify factors independently associated with 30-day mortality. Variables with statistical significance in the univariate analysis ($P<0.05$) were entered in the multivariable model. To adjust for the time from BSI onset to active antibiotic

therapy, we included in the model the variable 'active antibiotic therapy within 24 hours from infection onset'. The variance inflation factor (VIF) value was calculated to control the influence of collinearity. We assumed a lack of multicollinearity if all variables had a VIF value <2. The multivariate model was built using a forward stepwise procedure. The validity of the final model was assessed by estimating the goodness of fit with the Hosmer and Lemeshow test. Results are expressed as adjusted odds ratio (aOR) and their 95% confidence intervals (CIs).

Attributable mortality was defined as the excess mortality among patients with BSI caused by different types of MDR-GNB compared to the cohort of patients with BSI caused by susceptible GNB. Attributable mortality was calculated, as described by the DRIVE-AB Consortium with the following formula: [P0 (mortality in controls) × [aOR (adjusted odds ratio) − 1] × (1 − P0)]/[aOR × P0 + (1 − P0)], where P0 is the mortality proportions for the control group and aOR is the adjusted odds ratios for 30-day mortality.[12] aOR from the multivariable regression model was used to calculate the attributable mortality.

As sensitivity analysis, the impact of new antibiotics, including ceftazidime/avibactam for KPC or ceftazidime/avibactam in combination with aztreonam for metallo-β-lactamases (MBL), on 30-day mortality was evaluated in the subgroup of patients with CRE. No similar analysis was conducted in the subgroup of patients with CR non-fermenting GNB due to the limited number of patients treated with new antibiotics in this category.

Moreover, we calculated the mortality attributable to MDR aetiology in patients with solid cancer.

Statistical significance was established at $P \leq 0.05$. All reported P values are two-tailed. The results obtained were analysed using commercially available statistical software packages (IBM SPSS version 27, Armonk, New York; R version 4.1.2).

Results

A total of 347 patients with cancer were included. Table 1 shows the clinical characteristics of the study population. Most patients were affected by solid cancer (79%, $n = 274$), whereas the remaining 73 (21%) had haematological malignancies. The most common neoplasm types were colo-rectal and hepato-pancreato-biliary cancers (25.2% and 21.9%, respectively). Figure 1 reports the description of causative GNB. The 115 susceptible GNB included: 40 (34.8%) *Pseudomonas aeruginosa*, 39 (33.9%) *Escherichia coli*, 15 (13%) *Klebsiella pneumoniae*, five (4.3%) *Proteus mirabilis*, four (3.5%) *Enterobacter* spp., four (3.5%) *Acinetobacter* spp., two (1.7%) *Aeromonas* spp., two (1.7%) *Citrobacter freundii*, two (1.7%) *Serratia marcescens*, one (0.9%) *Achromobacter* spp. and one (0.9%) *Morganella morganii*. The 66.9% (232/347) of BSI were caused by MDR-GNB.

Overall, the 30-day mortality rate was 20.5% (71/347). Thirty-day mortality was higher in patients with BSI by MDR-GNB compared to those with BSI by susceptible GNB [27.2% (63/232) versus 7% (8/115), $P < 0.001$]. Figure 2 shows 30-day mortality rates according to causative pathogens. The highest mortality rate occurred among patients with BSI due to CRAB (9/16, 56.3%), followed by MBL-producing *Klebsiella pneumoniae* (10/18, 55.6%), CRPA (4/12, 33.3%), KPC-producing *Klebsiella pneumoniae* (19/66, 28.8%) and ESBL-producing Enterobacterales (21/120, 17.5%).

Compared to patients who survived, those who died were more commonly hospitalized in the intensive care unit (ICU),

Table 1. Demographic data and clinical characteristics of onco-haematological patients with BSI caused by CR-GNB

	N = 347
Age, median, IQRs	69 (56–77)
Male sex	195 (56.2%)
Ward of hospitalization at BSI onset	
medical ward	222 (64%)
surgery	77 (22.2%)
ICU	48 (13.8%)
Haematological malignancy	73 (21%)
patients with solid cancer	274 (79%)
colo-rectal	69/274 (25.2%)
hepato-biliary	60/274 (21.9%)
urothelial	50/274 (18.2%)
breast	37/274 (13.5%)
lung	28/274 (10.2%)
gynaecologic	9/274 (3.3%)
upper gastrointestinal tract	9/274 (3.3%)
others	12/274 (4.4%)
Other comorbidities	
diabetes mellitus	94 (27.1%)
cardiovascular disease	112 (32.3%)
COPD	38 (11%)
chronic renal failure	55 (15.9%)
chronic liver disease	40 (11.5%)
Charlson Comorbidity Index, median (IQR)	6 (3–7)
Radio or chemotherapy, last 30 days	129 (37.2%)
Previous hospitalization, last 3 months	195 (56.2%)
Previous antibiotic therapy, last 30 days	208 (59.9%)
Recent or ongoing steroids	158 (45.5%)
Septic shock at BSI onset	52 (15%)
Fever at BSI onset	256 (73.8%)
SOFA score at BSI onset	3 (2–5)
Causative organism	
Susceptible GNB[a]	115 (33.1%)
MDR-GNB	232 (66.9%)
ESBL-producing Enterobacterales	120 (34.6%)
KPC-producing *K. pneumoniae*	66 (19%)
MBL-producing *K. pneumoniae*	18 (5.2%)
CR *P. aeruginosa*	12 (3.5%)
CR *A. baumannii*	16 (4.6%)
Source of infection	
urinary tract	77 (22.2%)
respiratory tract	37 (10.7%)
abdomen	86 (24.8%)
surgical site	7 (2%)
CVC-related	69 (19.9%)
unknown	67 (19.3%)
Source control[b]	188/243 (77.4%)
30-day mortality	71 (20.5%)

[a]Susceptible GNB included: 40 *Pseudomonas aeruginosa*, 39 *Escherichia coli*, 15 *Klebsiella pneumoniae*, 5 *Proteus mirabilis*, 4 *Enterobacter* spp, 4 *Acinetobacter* spp, 2 *Aeromonas* spp, 2 *Citrobacter freundii*, 2 *Serratia marcescens*, 1 *Achromobacter* spp and 1 *Morganella morganii*. [b]243 patients had removable sources of infection.

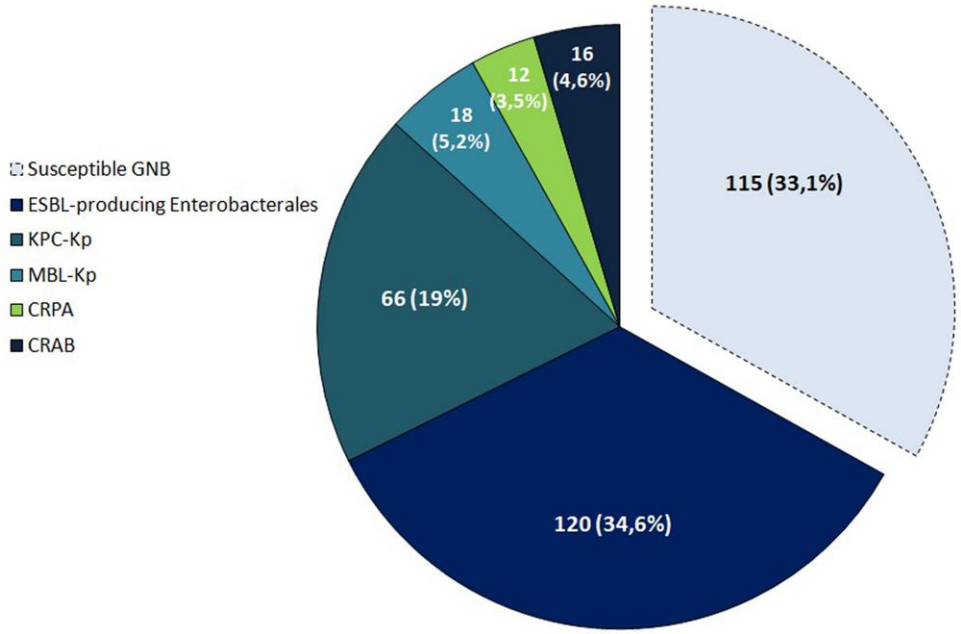

Figure 1. The description of causative GNB among cancer patients with BSI.

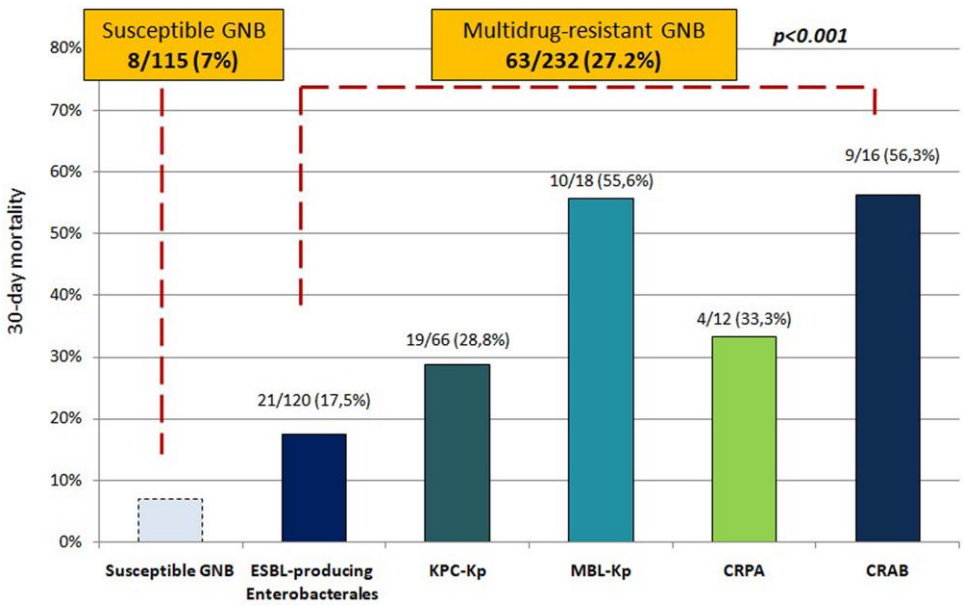

Figure 2. Thirty-day mortality rates of cancer patients with BSI due to GNB according to causative pathogens.

more likely to be affected by haematological malignancies, had more frequently septic shock at BSI onset and received less frequent appropriate antibiotic therapy within 24 hours from BSI onset (Table 2). MDR aetiology was more common in patients who died. On multivariable analysis, ESBL-producing Enterobacterales (aOR 8.734, 95% CI 1.411–54.077, $P=0.02$), KPC-producing Enterobacterales (aOR 8.548, 95% CI 1.296–56.411, $P=0.026$), MBL-producing Enterobacterales (aOR 15.802, 95% CI 1.408–68.667, $P=0.022$), CR-NFGNB (aOR 53.373, 95% CI 5.104–89.146, $P<0.001$), haematological malignancy (aOR 6.0.28, 95% CI 1.581–22.987, $P=0.009$), ICU stay (aOR 3.859, 95% CI 1.159–12.848, $P=0.028$) were factors independently associated with 30-day mortality, whereas source control was a protective factor (aOR 0.054, 95% CI 0.017–0.175, $P<0.001$) (Table 3). Attributable mortality to all MDR pathogens was 43%. According to type of causative pathogen, attributable mortality was 33% in ESBL, 32% in KPC, 47% in MBL and 73% in CR-NFGNB.

Table 2. Comparison of onco-haematological patients who died and those who survived within 30 days from bloodstream infection onset

	Survivors N = 276 (%)	Non-survivors N = 71 (%)	P value
Age, median, IQRs	68.5 (56.25–76)	69 (56–80)	0.118
Male sex	152 (55.1%)	43 (60.6%)	0.406
Ward of hospitalization at BSI onset			
medical ward	177 (64.1%)	45 (63.4%)	0.907
surgery	68 (24.6%)	9 (12.7%)	0.031
ICU	31 (11.2%)	17 (23.9%)	0.006
Haematological malignancy	45 (16.3%)	28 (39.4%)	<0.001
solid cancer			0.491
hepato-biliary	49 (21.2%)	11 (25.6%)	
colo-rectal	58 (25.1%)	11 (25.6%)	
urothelial	38 (16.5%)	12 (27.9%)	
breast	33 (14.3%)	4 (9.3%)	
lung	25 (10.8%)	3 (7%)	
gynaecologic	8 (3.5%)	1 (2.3%)	
upper gastrointestinal tract	9 (3.9%)	0	
others	11 (4.8%)	1 (2.3%)	
Main comorbidities			
diabetes mellitus	78 (28.3%)	16 (22.5%)	0.333
cardiovascular disease	86 (31.2%)	26 (36.6%)	0.380
COPD	32 (11.6%)	6 (8.5%)	0.449
chronic renal failure	43 (15.6%)	12 (16.9%)	0.786
chronic liver disease	27(9.8%)	13 (18.3%)	0.045
Charlson Comorbidity Index, median (IQR)	6 (3–6)	5 (2–7)	0.866
Radio or chemotherapy, last 30 days	115 (41.7%)	14 (19.7%)	0.001
Previous hospitalization, last 3 months	159 (57.6%)	36 (50.7%)	0.296
Previous antibiotic therapy, last 30 days	162 (58.7%)	46 (64.8%)	0.35
Recent or ongoing steroids	125 (45.3%)	33 (46.5%)	0.858
Septic shock at BSI onset	29 (10.5%)	23 (32.4%)	<0.001
Fever at BSI onset	205 (74.3%)	51 (71.8%)	0.676
SOFA score at BSI onset	3 (1–4)	5 (3–8))	<0.001
MDR Gram-negative bacilli	169 (61.2%)	63 (88.7%)	<0.001
Source of infection			
urinary tract	70 (25.4%)	7 (9.9%)	0.005
respiratory tract	15 (5.4%)	22 (31%)	<0.001
abdomen	75 (27.2%)	11 (15.5%)	0.042
surgical site	3 (1.1%)	4 (5.6%)	0.015
CVC-related	62 (22.5%)	7 (9.9%)	0.018
unknown	49 (17.8%)	18 (25.4%)	0.148
Source control[a]	178/212 (84%)	10/31 (32.3%)	<0.001
Active antibiotic therapy within 24hours	155 (56.2%)	26 (36.6%)	0.003
Active antibiotic therapy within 48 hours	199 (72.1%)	33 (46.5%)	<0.001

[a]243 patients had removable sources of infection.

Sensitivity analysis

In the CRE-BSI group, 30-day mortality was 8/38 (21.1%) in patients treated with new antibiotics compared to 19/43 (44.2%) in patients treated with old antibiotics ($P = 0.035$) (Table S1, available as Supplementary data at *JAC-AMR* Online). However, antibiotic regimens did not result independently associated with 30-day mortality at multivariable analysis (Table S2).

Among patients with solid cancer, 30-day mortality was confirmed to be higher in patients with BSI due to MDR-GNB (38/174, 21.8%) compared to those with BSI by susceptible GNB (5/100, 5%, $P < 0.001$). Multivariable analyses of factors independently associated with 30-day mortality is reported in Table S3. Mortality attributable to MDR aetiology in patients with solid cancer was 32%.

Discussion

Our study shows that in patients with cancer who developed a BSI due to GNB, MDR aetiology is associated with a high

Table 3. Multivariable analysis of factors associated with 30-day mortality (stepwise)

	aOR (95% CI)	*P* value
Causative pathogen		
Susceptible GNB	*Reference variable*	—
ESBL-producing Enterobacterales	8.734 (1.411–54.077)	0.02
KPC-producing Enterobacterales	8.548 (1.296–56.411)	0.026
MBL-producing Enterobacterales	15.802 (1.408–68.667)	0.022
CR-NFGNB	53.373 (5.104–89.146)	<0.001
Haematological malignancy	6.0.28 (1.581–22.987)	0.009
ICU stay	3.859 (1.159–12.848)	0.028
Source control	0.054 (0.017–0.175)	<0.001

Included and not retained: surgery, chronic liver disease, radio or chemotherapy, septic shock, source of infection (compared to urinary tract), active therapy within 24 hours. Despite statistically significant at univariate analysis, SOFA score was not included due to collinearity with septic shock.

attributable mortality (43%), ranging from 32% in BSI caused by KPC-producing CRE until to 73% in those by CR-NFGNB. This finding is confirmed in the subgroup of patients with solid cancer (attributable mortality 32%), which represents the most prevalent group of cancer patients (79%).

Our finding is remarkable since cancer causes a heavy burden of disease in developed countries and is one of the world's top killers, with nearly 10 million deaths per year due to the disease. However, in the last decades great efforts in research led to the implementation of new pharmacological and non-pharmacological treatments that are changing the natural history of patients with cancer, leading to prolonged survival and new hopes of treatment and care.[13] These include target therapies, immunotherapies, molecular medicine and new surgical strategies.[14] As a result, cancer patients experience prolonged life expectancy while on continuous treatment; subsequently non-cancer-related deaths are now a significant cause of mortality in cancer patients, with infections being a main contributor.[15,16] In this study we found that AMR has a great impact on the outcome of cancer patients. Our results are in line with recent data from a multicentre study by Gupta *et al.*, which demonstrated that outpatient cancer patients are at significantly higher risk of infections caused by resistant pathogens, including MDR Enterobacteriaceae and carbapenem-non-susceptible *Pseudomonas aeruginosa*.[17] Our findings should raise several considerations.

First, continuous surveillance programmes are essential to monitor the burden and trends of MDR infections in cancer patients, enabling early detection of outbreaks and timely interventions. Creating robust surveillance networks may facilitate identification of risk factors and implementation of targeted infection control strategies. Second, early diagnosis through rapid microbiological techniques and routine screening for colonization with MDR organisms (such as rectal screening for CRE) should be integrated into routine care in oncology settings. This would allow timely initiation of active empirical therapy and minimize delays in treatment in patients with septic shock.[18–20] Third, antimicrobial stewardship programmes should be considered as a part of clinical practice guidelines for the treatment of cancer patients. Involvement of infectious disease (ID) specialists in the management of cancer patients should become standard practice to optimize antimicrobial therapy and guide management decisions increasing the appropriateness of antibiotic prescriptions in cancer patients. It is important to avoid over-reliance on broad-spectrum antibiotics such as fluoroquinolones and cephalosporins, which are known drivers of resistance.[21] Fourth, strict infection control measures should be enforced to prevent colonization and cross-transmission of resistant pathogens, especially in high-risk hospital wards. Fifth, while the development of novel antibiotics provides new therapeutic options, their rational use is essential to avoid emergence of antibiotic resistance.[6,22–25] However, several national antimicrobial stewardship programmes are based on restrictions of these new antibiotics to reduce their inappropriate use and to reduce costs. This last goal is largely questionable in the field of oncology. In fact, these patients usually need for new innovative and very expensive oncological therapies and the occurrence of infections caused by MDR organisms may undermine the value and the positive effects of new anticancer therapies, since a significant proportion of patients die within 30 days from the onset of infection.

It is also noteworthy to consider that an MDR aetiology is associated with an excess mortality of 43%, compared to the mortality recorded in patients with infections caused by susceptible strains. This increase in mortality is likely and partially related to the higher frailty and severity of the patients with MDR-GNB infection, but it could be also attributable to the delay in appropriate empirical antibiotic therapy in these cases. Prospective interventional studies are needed to assess whether implementing early diagnostic tools and ensuring timely initiation of effective antimicrobial therapy can improve outcomes in cancer patients with MDR-GNB BSI.

Our study has several limitations. First, it is an observational study, therefore a comparison of the effects on outcome due to different antimicrobial regimens is not possible and subgroup analysis should be read with caution. Second, this is a secondary analysis of a study that has not been specifically designed to evaluate patients with cancer;[5] consequently, data about cancer status at the time of BSI (e.g. remission, progression, or stable disease) are lacking. This information may play a relevant role in determining the outcomes of cancer patients with BSI but was not available because the study cohort was derived from a previously established dataset not specifically designed to investigate cancer-related variables. Thus, future prospective studies designed for this special population are warranted. Finally, the wide CIs observed in the multivariable analysis highlights the need for confirmation of these findings in larger cohorts to ensure greater precision and generalizability of the results.

Finally, our data come from a country with high prevalence of MDR-GNB. Thus, the generalizability of our findings to regions with different prevalence of MDR-GNB may be unclear.

In conclusion, AMR represents a great challenge in cancer patients being responsible for an excess of mortality in these subjects. Multifaceted interventions including enhanced surveillance, early diagnosis, ID consultation, infection prevention and timely diagnostic stewardship to improve antibiotic prescribing are urgently needed in this population. Further studies are warranted

to increase our knowledge about risk of infections and their outcome in cancer patients who undergo new innovative targeted therapy and immunotherapy.

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Transparency declarations

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Supplementary data

Tables S1–S3 are available as Supplementary data at *JAC-AMR* Online.

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