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Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape

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Objectives: To assess the impact of carbapenem resistance on mortality in *Klebsiella pneumoniae* bloodstream infection (BSI) in the era of novel β-lactam/β-lactamase inhibitor combinations.

Material and methods: Retrospective study of patients with *K. pneumoniae* BSI between January and August 2020 in 16 centres (CARBANEW study within the MULTI-SITA project).

Results: Overall, 426 patients were included: 107/426 (25%) had carbapenem-resistant *K. pneumoniae* (CR-Kp) BSI and 319/426 (75%) had carbapenem-susceptible *K. pneumoniae* (CS-Kp) BSI. Crude cumulative 30 day mortality was 33.8% and 20.7% in patients with, respectively, CR-Kp BSI and CS-Kp BSI ($P=0.027$). Carbapenemase production or carbapenemase-encoding genes were detected in 84/98 tested CR-Kp isolates (85.7%), mainly

KPC (78/84; 92.9%). Ceftazidime/avibactam was the most frequently used appropriate therapy for CR-Kp BSI (80/107; 74.7%). In multivariable analyses, variables showing an unfavourable association with mortality after correction for multiple testing were age-adjusted Charlson comorbidity index (HR 1.20; 95% CI 1.10–1.31, $P<0.001$) and Pitt score (HR 1.33; 95% CI 1.15–1.55, $P<0.001$), but not carbapenem resistance (HR 1.28, 95% CI 0.74–2.22, $P=0.410$). In a propensity score-matched analysis, there was no difference in mortality between patients appropriately treated with ceftazidime/avibactam for CR-Kp BSI and patients appropriately treated with other agents (mainly meropenem monotherapy or piperacillin/tazobactam monotherapy) for CS-Kp BSI (HR 1.07; 95% CI 0.50–2.29, $P=0.866$).

Conclusions: Our results suggest that the increased mortality in CR-Kp BSI compared with CS-Kp BSI is not (or no longer) dependent on the type of therapy in areas where ceftazidime/avibactam-susceptible KPC-producing isolates are the most prevalent type of CR-Kp.

Introduction

In the last 15 years, bloodstream infections (BSIs) caused by carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) have been associated with high mortality in hospitalized patients worldwide.[1–7]

Several studies have also described an increased mortality of CR-Kp BSI compared with carbapenem-susceptible *K. pneumoniae* (CS-Kp) BSI.[3,8–10] In previous studies and meta-analyses, the unfavourable impact of carbapenem resistance on the outcome of *K. pneumoniae* BSI was not completely cancelled when models were adjusted for baseline comorbidities and other relevant prognostic factors (e.g. appropriateness of antimicrobial therapy and time to appropriate therapy from the onset of the infection). One of the most frequently suspected culprits for this residual difference in mortality was the unfavourable safety profile and the possible suboptimal efficacy of the few therapies showing activity against CR-Kp, such as polymyxin-based regimens.[3,11,12] From this standpoint, the availability of novel β-lactam/β-lactamases inhibitor (BL/BLI) combinations with a better safety profile than polymyxin-based regimens, and showing good activity against CR-Kp, may be expected to cancel the abovementioned unfavourable prognostic impact of carbapenem resistance after proper adjustment for other prognostic factors.

We therefore conducted a retrospective, multicentre study within the MULTI-SITA project, with the aim of assessing the impact of carbapenem resistance on mortality of *K. pneumoniae* BSI in the era of novel BL/BLI combinations.

Methods

Setting and objectives

The MULTI-SITA project is a novel platform developed by the Italian Society of Anti-Infective Therapy and dedicated to the conduct of observational studies on invasive bacterial and fungal diseases. The present study (CARBANEW study) is the first study conducted within the MULTI-SITA project. CARBANEW was a retrospective, multicentre study conducted in 16 Italian centres. The retrospective study period was from 1 January 2020 to 31 August 2020. Among novel BL/BLI combinations with activity against CR-Kp, ceftazidime/avibactam, which is active against many KPC- or OXA-producing CR-Kp, was the only one routinely available in participating hospitals at the time of the study. All patients who developed *K. pneumoniae* BSI in the participating centres during the study period were considered for inclusion in the study. Patients were excluded from the analyses if: (i) their age was less than 18 years; (ii) they had been already included in the study for a previous *K. pneumoniae* BSI episode; or/and (iii) they did not receive an appropriate antimicrobial therapy, or they received an appropriate antimicrobial therapy for less than 48 h. Minor deviations from the original study protocol are reported with reasons in the Supplementary material (available as Supplementary data at *JAC* Online). The primary study outcome measure was 30- day mortality, defined as a time-to-event endpoint. All primary, secondary and sensitivity analyses were conducted with respect to this primary outcome measure.

Microbiological procedures

Identification of *K. pneumoniae* isolates was performed by means of MALDI-TOF MS (MALDI Biotyper, Bruker Daltonics, Billerica, MA, USA; or VITEK MS MALDI-TOF MS, bioMérieux, Craponne, France) or automated systems according to local standard procedures. Antimicrobial susceptibility testing was also performed by means of automated systems (VITEK 2, bioMérieux, Craponne, France; MicroScan, Beckman Coulter, Brea, CA, USA; or Phoenix, Becton Dickinson Diagnostics, Sparks, MD, USA) according to local standard procedures. Results of susceptibility testing were interpreted in accordance with the EUCAST clinical breakpoints, version 13.0 (http://www.eucast.org/). Presence of carbapenemase-encoding genes was detected using Verigene BC-GN (Nanosphere, Northbrook, IL, USA), BioFire BCID2 panel (bioMérieux, Craponne, France), or Xpert Carba-R (Cepheid, Sunnyvale, CA, USA), while production of carbapenemases was assessed by NG-test CARBA 5 (NG Biotech, Guipry, France), based on local standard procedures at the time of the study.

Definitions and data collected for the study

CR-Kp was defined as *K. pneumoniae* resistant to any of the carbapenems (MIC > 8 mg/L for meropenem, MIC > 4 mg/L for imipenem and MIC > 0.5 mg/L for ertapenem). A sensitivity analysis considering only *K. pneumoniae* isolates with meropenem MICs within the resistant range as CR-Kp was also conducted (see statistical analysis below). *K. pneumoniae* BSI was defined as isolation of *K. pneumoniae* from at least one blood culture from patients with clinical signs consistent with infection. The time of origin of *K. pneumoniae* BSI (onset of *K. pneumoniae* BSI) was defined as the day when the first blood culture positive for *K. pneumoniae* was drawn. Appropriate therapy was defined as therapy with at least one antimicrobial drug showing *in vitro* activity against the causative *K. pneumoniae* isolate. Appropriate monotherapy was defined as therapy with only one antimicrobial drug showing *in vitro* activity against the causative *K. pneumoniae* isolate. Appropriate combination therapy was defined as therapy with at least two antimicrobial drugs showing *in vitro* activity against the causative *K. pneumoniae* isolate. Data collected for the study are detailed in the Supplementary material.

Sample size calculation

The primary study analysis was aimed to assess the independent impact of carbapenem resistance on 30 day mortality of *K. pneumoniae* BSI. The

prognostic predictor of greatest clinical interest, on which the calculation was based, was carbapenem resistance in *K. pneumoniae* isolates from BSI. Based on the available literature and previous local data, the expected proportion of carbapenem resistance in *K. pneumoniae* BSI was estimated to be approximately 30%, and the probability of death within 30 days from the onset of *K. pneumoniae* BSI (considering both CR-Kp BSI and CS-Kp BSI) was estimated to be approximately 20%. An HR of 2.0 was considered as a reasonable cut-off for defining a clinically meaningful unfavourable effect of carbapenem resistance on the prognosis of *K. pneumoniae* BSI. Therefore, a minimum sample size of 387 patients was calculated as necessary for guaranteeing a power (1−β) of 80% and a two-sided significance level (α) of 0.05 in the presence of an event probability of 20% and an expected frequency of carbapenem resistance of 30% (thus with a calculated SD of 0.46).[13]

Statistical analysis

Demographic and clinical characteristics of the study population were compared between patients with CR-Kp BSI and CS-Kp BSI for descriptive purposes, using the chi-squared test or the Fisher exact test for categorical variables, and the Wilcoxon test for continuous variables, as appropriate. The crude 30 day mortality from the onset of *K. pneumoniae* BSI was summarized graphically using the Kaplan–Meier method, and compared between patients with CR-Kp BSI and patients with CS-Kp BSI by means of the log-rank test.

With regard to the primary study analysis of assessing the independent impact of carbapenem resistance on 30 day mortality, we first performed Rubin's multiple imputation.[14] Proportion of missing data for each variable in our cohort is shown in Table S1. The association of carbapenem resistance and other collected variables with 30 day mortality was first assessed in univariable Cox regression models, with discharge within 30 days from the onset of BSI considered as a right-censoring event. Subsequently, all variables potentially associated with mortality in univariable comparisons ($P < 0.10$) were included in an initial multivariable Cox regression model, and further selected for inclusion the final multivariable Cox regression model (model A) by means of a backward stepwise procedure. Given the purpose of the study, the variables 'carbapenem resistance' and 'days without appropriate therapy' were included in model A independent of their selection by the stepwise procedure. Variables included in model A were also included in an additional multivariable Cox regression model (model B) that also included centre as shared frailty.[15] In all the Cox regression models described above, days without appropriate therapy (from the onset of *K. pneumoniae* BSI) was considered as a time-dependent variable (i.e. increase of one unit each passing day without appropriate therapy). To assess the impact on mortality of appropriate combination therapy versus appropriate monotherapy, we performed a landmark analysis, considering the eighth day after the onset of *K. pneumoniae* BSI (i.e. when all patients still on follow-up had initiated an appropriate antimicrobial therapy) as the time of origin for an additional multivariable Cox regression model (model C), still considering Day 30 after the onset of *K. pneumoniae* BSI as the time-to-event endpoint, and including all variables of model A plus the following: (i) type of appropriate therapy (combination therapy versus monotherapy as reference); and (ii) a term of interaction between type of appropriate therapy and carbapenem resistance. In the landmark analysis, days without appropriate therapy (from the onset of *K. pneumoniae* BSI) was considered as a fixed and not time-dependent variable. Variables included in model C were also included in an additional multivariable Cox regression model (model D) that also included centre as shared frailty.

Since all multivariable Cox regression models described above (A, B, C and D) were not purely exploratory (i.e. general, independent predictors of mortality of *K. pneumoniae* BSI had already been widely characterized in the literature), *P* values from all models were provided both before and after adjustment for multiple testing using the false discovery rate (FDR) approach, in order to reduce the risk of type 1 error.[16] Of note, appropriate ceftazidime/avibactam therapy was not included in these models due to collinearity with carbapenem resistance. The impact of appropriate ceftazidime/avibactam therapy was thus assessed by means of a dedicated propensity score-matched analysis (see below).

Predefined sensitivity analyses were conducted for both the primary multivariable Cox regression analysis (model A and model B) and the landmark analysis (model C and model D) in the following populations: (i) entire study population but with CR-Kp defined only as those *K. pneumoniae* isolates with meropenem MIC within the resistant category according to EUCAST; and (ii) patients with monomicrobial *K. pneumoniae* BSI only. Further sensitivity landmark analyses (model C and D) were also conducted considering the second, fourth and sixth day after the onset of *K. pneumoniae* as the time of origin, including patients still on follow-up and with initiated appropriate therapy at the selected time of origin. Finally, a sensitivity analysis of model A employing logistic regression instead of Cox regression, and considering discharged patients as alive at Day 30, was also performed.

To compare the prognostic impact of appropriate therapy with ceftazidime/avibactam in CR-Kp BSI versus appropriate therapy with other agents in CS-Kp BSI, we conducted a secondary landmark analysis (starting from the eighth day after the onset of *K. pneumoniae* BSI, as above) after propensity score matching (1:1) of cases (patients with CR-Kp BSI receiving appropriate therapy with ceftazidime/avibactam) and controls (patients with CS-Kp BSI receiving appropriate therapy with agents other than ceftazidime/avibactam). Cases and controls were matched 1:1 for all variables included in model A, except carbapenem resistance, by means of a greedy nearest neighbour-matching with propensity score as the distance measure. The propensity score is the conditional probability of assignment to a particular treatment given a vector of observed covariates.[17] More in detail, one case was matched to one control such that the difference in terms of propensity score was minimized. Caliper width was not specified in order to match all cases.[18] Sensitivity analyses were also conducted considering the second, fourth and sixth day after the onset of *K. pneumoniae* as the time of origin, and considering (for both the matching procedure and the analysis) only patients still on follow-up and with initiated appropriate therapy at the selected time of origin.

For descriptive purposes, cumulative mortality in cases and controls was summarized graphically using the Kaplan–Meier method and compared with the log-rank test. Finally, to specifically compare the prognostic impact of appropriate ceftazidime/avibactam-based combinations versus appropriate ceftazidime/avibactam monotherapy, we conducted a subgroup landmark analysis (starting from the eighth day after the onset of *K. pneumoniae* BSI, as above) only in cases (patients with CR-Kp BSI receiving appropriate therapy with ceftazidime/avibactam), by means of a multivariable Cox regression model including the same variables included in model C (with the exception of carbapenem resistance and the interaction term carbapenem resistance*combination therapy).

The proportionality of hazard assumption in all fixed Cox regression models was verified by weighted Schoenfeld residuals. The analyses were conducted using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R Statistical Software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

Ethics

Institutional review board statement

The MULTI-SITA project was approved by the ethics committee of the coordinating centre (Liguria Region Ethics Committee, registry number 390/2020). The amendment authorizing the conduct of the CARBANEW study within the MULTI-SITA project was approved by the Liguria Region Ethics Committee on 12 April 2022. The other participating centres followed the local ethical committees requirements.

Informed consent statement

Collection of an informed consent specific for the present study was waived due to the retrospective nature of the study.

Results

Overall, 426 patients were included in the analyses, of whom 107/426 (25%) and 319/426 (75%) had CR-Kp BSI and CS-Kp BSI, respectively (Figure S1). The median age in the entire study

Table 1. Baseline demographic and clinical characteristics of patients in the entire study population and in patients with CR-Kp BSI and CS-Kp BSI

	Study population	Patients with CR-Kp BSI	Patients with CS-Kp BSI	
Variables[a]	No. of patients (%) 426 (100)	No. of patients (%) 107 (25)	No. of patients (%) 319 (75)	*P* value
Demographics				
Age, years, median (IQR)	67 (55–78)	67 (57–76)	66 (53–78)	0.838
Male sex	137 (32)	37 (35)	100 (31)	0.536
Comorbidities and medical history				
Previous hospitalization	267 (63)	64 (60)	203 (64)	0.434
Previous ICU stay	61 (14)	21 (20)	40 (13)	0.072
Admission from LTCF	34 (8)	7 (7)	27 (9)	0.546
Diabetes mellitus	123 (29)	31 (29)	92 (29)	0.992
COPD	58 (14)	18 (17)	40 (13)	0.274
Previous myocardial injury	75 (18)	22 (21)	53 (17)	0.353
NYHA score, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.031
Chronic liver disease	37 (9)	9 (8)	28 (9)	0.887
Chronic kidney disease	96 (23)	28 (26)	68 (21)	0.313
Chronic intermittent haemodialysis	26 (6)	14 (13)	12 (4)	<0.001
Solid neoplasm	127 (30)	35 (33)	92 (29)	0.437
Metastatic solid neoplasm	49 (12)	9 (8)	40 (13)	0.250
Haematological malignancy	50 (12)	10 (9)	40 (13)	0.364
Previous HSCT	17 (4)	1 (1)	16 (5)	0.084
Previous SOT	25 (6)	6 (6)	19 (6)	0.883
HIV infection	8 (2)	1 (1)	7 (2)	0.685
Age-adjusted Charlson comorbidity index, median (IQR)	5 (3–8)	6 (3–7)	5 (3–8)	0.385
Previous chemotherapy	71 (17)	9 (8)	62 (20)	0.008
Previous steroid therapy	99 (24)	27 (26)	72 (23)	0.583
Previous therapy with immunosuppressants	63 (15)	12 (11)	51 (16)	0.241
Previous major surgery	89 (21)	28 (26)	61 (19)	0.125
Variables at *K. pneumoniae* BSI onset				
ICU stay	92 (22)	42 (39)	50 (16)	<0.001
Days from admission to *K. pneumoniae* BSI, median (IQR)	9 (0–22)	14 (5–29)	7 (0–19)	<0.001
SOFA score, median (IQR)	4 (2–6)	4 (2–7)	4 (2–6)	0.049
Pitt bacteraemia score, median (IQR)	1 (0–3)	2 (0–5)	1 (0–3)	0.001
Presence of CVC	231 (55)	73 (68)	158 (51)	0.002
Presence of urinary catheter	282 (67)	82 (78)	200 (64)	0.007
Presence of septic shock	75 (18)	26 (24)	49 (16)	0.040
Concomitant COVID-19	34 (8)	14 (13)	20 (6)	0.025
Polymicrobial bacteraemia	64 (15)	21 (20)	43 (13)	0.124
Concomitant candidaemia	15 (4)	9 (8)	6 (2)	0.004
Neutropenia	40 (10)	6 (6)	34 (11)	0.119
Mechanical ventilation	87 (21)	39 (37)	49 (15)	<0.001
CRRT	26 (6)	10 (10)	16 (5)	0.098
ECMO	12 (3)	4 (4)	8 (3)	0.508
Urinary source of *K. pneumoniae* BSI	130 (31)	21 (20)	109 (34)	0.005
Pulmonary source of *K. pneumoniae* BSI	44 (10)	12 (11)	32 (10)	0.728

Continued

Table 1. *Continued*

Variables[a]	Study population No. of patients (%) 426 (100)	Patients with CR-Kp BSI No. of patients (%) 107 (25)	Patients with CS-Kp BSI No. of patients (%) 319 (75)	*P* value
Therapeutic variables				
Days without appropriate therapy, median (IQR)	0 (0–1)	1 (0–2)	0 (0–1)	<0.001
Appropriate combination therapy	83 (20)	51 (48)	32 (10)	<0.001
Adequate source control (performed or not necessary)	235 (65)	62 (62)	173 (66)	0.501

COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; NYHA, New York Heart Association; LTCF, long-term care facility; SOT, solid organ transplantation.
[a]Results are presented as no. of patients/total of patients unless otherwise indicated. Number of missing values per variable were as follows: SOT (*n* = 2/426); haematological malignancy (*n* = 2/426); HSCT (*n* = 2/426); solid neoplasm (*n* = 3/426); metastatic solid neoplasm (*n* = 3/426); previous chemotherapy (*n* = 1/426); COPD (*n* = 2/426); diabetes mellitus (*n* = 2/426); chronic kidney disease (*n* = 2/426); chronic liver disease (*n* = 3/426); previous myocardial injury (*n* = 4/426); age-adjusted Charlson comorbidity index (*n* = 1/426); previous hospitalization (*n* = 2/426); previous ICU stay (*n* = 5/426); previous steroid therapy (*n* = 9/426); previous therapy with immunosuppressants (*n* = 5/426); days from admission to *K. pneumoniae* BSI (*n* = 3/426); previous major surgery (*n* = 1/426); admission from LTCF (*n* = 24/426); presence of CVC (*n* = 7/426); presence of urinary catheter (*n* = 7/426); neutropenia (*n* = 13/426); mechanical ventilation (*n* = 3/426); SOFA score (*n* = 15/426); Pitt bacteraemia score (*n* = 3/426); ECMO (*n* = 2/426); chronic intermittent haemodialysis (*n* = 4/426); CRRT (*n* = 4/426); septic shock (*n* = 3/426); concomitant COVID-19 (*n* = 5/426); HIV infection (*n* = 45/426); concomitant candidaemia (*n* = 10/426); adequate source control (*n* = 63/426). No missing values were registered for all other remaining variables.

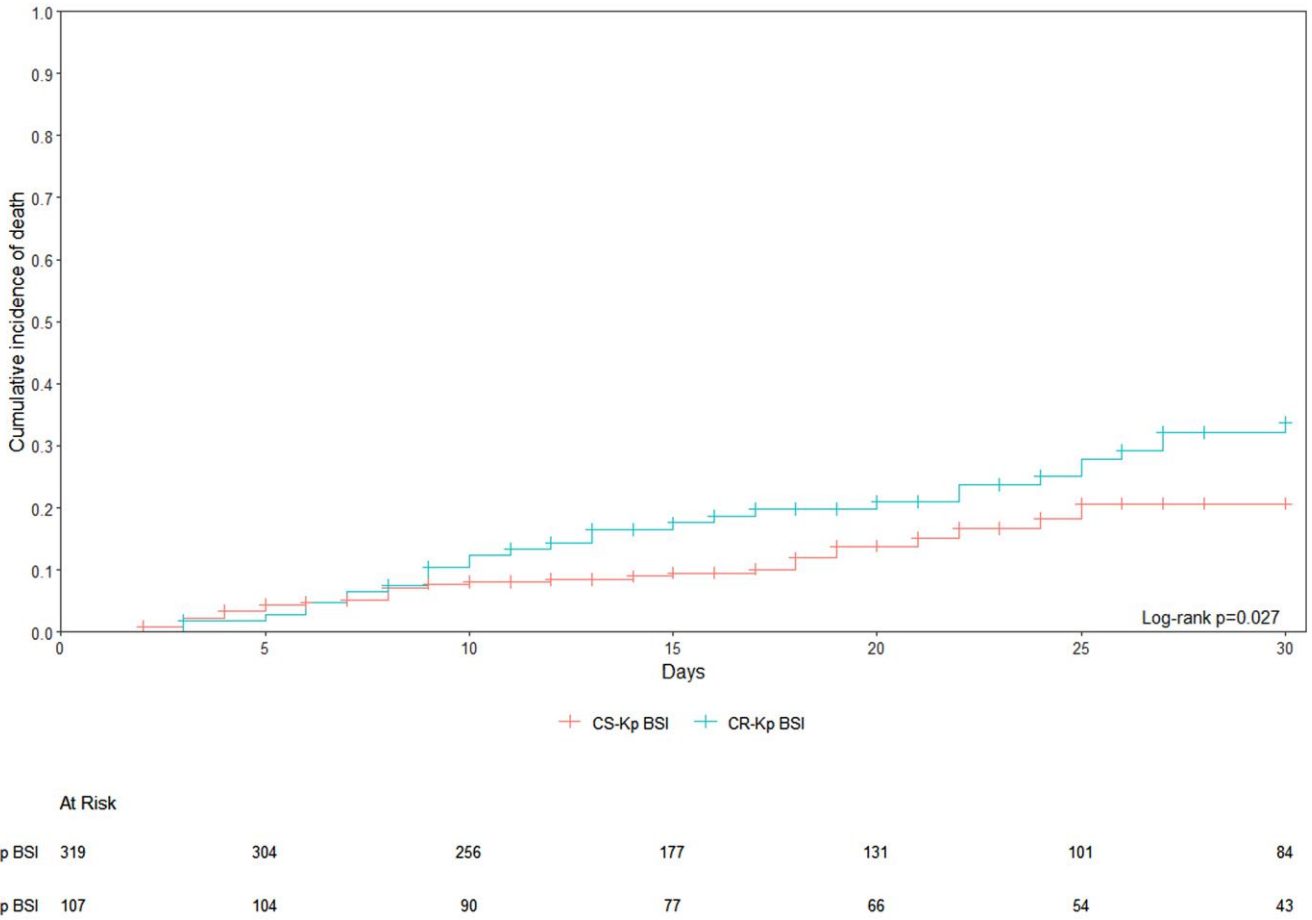

Figure 1. Unadjusted cumulative mortality up to Day 30 in patients with CR-Kp BSI and CS-Kp BSI. The time of origin was set as the day when the first positive blood culture for CR-Kp or CS-Kp was collected. Death was the event of interest and right-censoring was applied at the end of follow-up (hospital discharge or Day 30, whichever came first). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 2. Univariable analysis of factors associated with 30 day mortality in the study population

Variable	HR (95% CI)	*P* value
Carbapenem resistance (CR-Kp BSI)	1.68 (1.06–2.68)	0.029
Age, years	1.04 (1.02–1.06)	<0.001
Male sex	1.36 (0.85–2.18)	0.200
Previous hospitalization	1.13 (0.70–1.82)	0.619
Previous ICU stay	0.65 (0.32–1.30)	0.223
Admission from LTCF	1.46 (0.73–2.92)	0.280
Diabetes mellitus	2.01 (1.26–3.20)	0.004
COPD	1.26 (0.68–2.35)	0.460
Previous myocardial injury	1.04 (0.58–1.85)	0.906
NYHA score	1.33 (1.05–1.69)	0.021
Chronic liver disease	2.46 (1.33–4.55)	0.004
Chronic kidney disease	2.26 (1.41–3.64)	0.001
Chronic intermittent haemodialysis	0.33 (0.08–1.36)	0.125
Solid neoplasm	1.66 (1.04–2.66)	0.035
Metastatic solid neoplasm	1.52 (0.78–2.97)	0.222
Haematological malignancy	0.62 (0.26–1.50)	0.289
Previous HSCT	0.33 (0.05–2.39)	0.273
Previous SOT	0.19 (0.03–1.39)	0.102
HIV infection	1.00 (0.14–7.30)	0.999
Age-adjusted Charlson comorbidity index	1.20 (1.12–1.29)	<0.001
Previous chemotherapy	0.37 (0.14–0.99)	0.048
Previous steroid therapy	0.50 (0.26–0.94)	0.033
Previous therapy with immunosuppressants	0.41 (0.17–1.03)	0.057
Previous major surgery	0.88 (0.50–1.56)	0.665
ICU stay	1.84 (1.15–2.96)	0.012
Days from admission to *K. pneumoniae* BSI	1.00 (1.00–1.01)	0.271
SOFA score	1.23 (1.16–1.32)	<0.001
Pitt bacteraemia score	1.28 (1.19–1.38)	<0.001
Presence of CVC	1.43 (0.88–2.33)	0.146
Presence of urinary catheter	1.80 (1.01–3.19)	0.045
Presence of septic shock	3.03 (1.90–4.83)	<0.001
Concomitant COVID-19	1.41 (0.70–2.83)	0.334
Polymicrobial bacteraemia	1.97 (1.16–3.35)	0.013
Concomitant candidaemia	2.81 (1.27–6.21)	0.011
Neutropenia	0.56 (0.20–1.53)	0.259
Mechanical ventilation	1.82 (1.13–2.94)	0.014
CRRT	1.74 (0.86–3.51)	0.125
ECMO	0.99 (0.31–3.16)	0.988
Urinary source of *K. pneumoniae* BSI	0.87 (0.52–1.46)	0.596
Pulmonary source of *K. pneumoniae* BSI	2.11 (1.21–3.70)	0.009
Days without appropriate therapy	0.97 (0.82–1.16)	0.747
Adequate source control (performed or not necessary)	0.70 (0.43–1.14)	0.150

Analyses conducted after multiple imputation (see study methods). COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; NYHA, New York Heart Association; LTCF, long-term care facility; SOT, solid organ transplantation.

Table 3. Multivariable analysis of factors associated with 30 day mortality in patients with *K. pneumoniae* BSI

Model A[a]	HR (95% CI)	*P* value	*P* value (FDR-adjusted)
Carbapenem resistance (CR-Kp BSI)	1.28 (0.74–2.22)	0.373	0.410
Solid neoplasm	1.84 (0.98–3.45)	0.058	0.107
Previous chemotherapy	0.46 (0.17–1.28)	0.139	0.169
Chronic liver disease	1.69 (0.89–3.22)	0.110	0.151
Charlson comorbidity index	1.20 (1.10–1.31)	<0.001	<0.001
Previous steroid therapy	0.53 (0.26–1.06)	0.073	0.114
Pulmonary source of *K. pneumoniae* BSI	2.01 (1.04–3.87)	0.038	0.084
Mechanical ventilation	0.44 (0.21–0.95)	0.037	0.084
SOFA score	1.12 (1.01–1.24)	0.025	0.084
Pitt bacteraemia score	1.33 (1.15–1.55)	<0.001	<0.001
Days without appropriate therapy	0.94 (0.78–1.15)	0.571	0.571

Analyses conducted after multiple imputation (see study methods).
[a]Model B, also including centre as shared frailty[15] in addition to variables included in model A, provided the same results of model A in terms of HR (95% CI) and *P* values (data not shown).

population was 67 years (IQR 55–78) and 32% were male (137/426). The complete baseline demographic and clinical characteristics in the entire study population and in the subgroups of patients with CR-Kp BSI and CS-Kp BSI are reported in Table 1. Overall, CR-Kp BSI developed more frequently than CS-Kp BSI in ICU patients (39% versus 16%, respectively), whereas a urinary source of *K. pneumoniae* BSI was more frequent in CS-Kp BSI than in CR-Kp BSI (34% versus 20%). As shown in Figure 1, the unadjusted cumulative 30 day mortality was 33.8% and 20.7% in patients with CR-Kp BSI and in patients with CS-Kp BSI, respectively (log-rank test, $P=0.027$). Carbapenemase production or presence of carbapenemase-encoding genes was reported for 84/98 tested CR-KP isolates (85.7%). The most frequently detected enzyme among CR-Kp isolates was KPC (78/84; 92.9%), followed by KPC plus VIM (4/84; 4.8%), OXA-48-like (1/84; 1.2%) and OXA plus NDM (1/84; 1.2%) enzymes. Overall, 92/107 CR-Kp isolates were susceptible to ceftazidime/avibactam (86.0%). Ceftazidime/avibactam was the most frequently appropriate agent employed for treating CR-Kp BSI (80/107; 74.7%). Ceftazidime/avibactam was administered as monotherapy or in combination with other agents in 38/80 (47.5%) and 42/80 (52.5%) episodes of CR-Kp BSI, respectively. Companion agents of ceftazidime/avibactam were mostly tigecycline (17/42; 40.5%) and fosfomycin (13/42; 31.0%). Patients with CS-Kp BSI were mostly treated with appropriate monotherapy (287/319; 90.0%), mainly meropenem monotherapy (99/319; 31.0%) and piperacillin/tazobactam monotherapy (98/319; 30.7%).

The results of univariable and multivariable analyses of factors associated with 30 day mortality in patients with *K. pneumoniae* BSI are reported in Tables 2 and 3, respectively. As shown in Table 3, variables retained in the final multivariable model (model A) and showing an unfavourable association with mortality after correction for multiple testing were age-adjusted Charlson

Table 4. Landmark analysis of factors associated with 30 day mortality in patients with *K. pneumoniae* BSI

Factor	HR (95% CI)	*P* value	*P* value (FDR-adjusted)
Model C			
Carbapenem resistance (CR-Kp BSI)	1.73 (0.21–14.22)	0.608	0.718
Solid neoplasm	1.86 (0.84–4.14)	0.128	0.262
Previous chemotherapy	0.35 (0.09–1.42)	0.141	0.262
Chronic liver disease	1.63 (0.72–3.70)	0.242	0.392
Charlson comorbidity index	1.21 (1.09–1.35)	<0.001	0.005
Previous steroid therapy	0.52 (0.22–1.23)	0.138	0.262
Pulmonary source of *K. pneumoniae* BSI	3.05 (1.42–6.55)	0.004	0.019
Mechanical ventilation	0.38 (0.14–1.05)	0.061	0.199
SOFA score	1.07 (0.94–1.21)	0.317	0.459
Pitt bacteraemia score	1.35 (1.11–1.64)	0.002	0.016
Days without appropriate therapy	0.99 (0.80–1.22)	0.901	0.958
Combination therapy	0.53 (0.12–2.37)	0.409	0.531
Combination therapy*CR-Kp BSI	1.05 (0.18–6.04)	0.958	0.958
Model D[a]			
Carbapenem resistance (CR-Kp BSI)	1.82 (0.22–15.05)	0.578	0.684
Solid neoplasm	1.85 (0.83–4.13)	0.132	0.260
Previous chemotherapy	0.35 (0.08–1.42)	0.140	0.260
Chronic liver disease	1.57 (0.68–3.62)	0.287	0.466
Charlson comorbidity index	1.22 (1.09–1.36)	<0.001	0.005
Previous steroid therapy	0.51 (0.21–1.22)	0.129	0.260
Pulmonary source of *K. pneumoniae* BSI	3.04 (1.41–6.58)	0.005	0.020
Mechanical ventilation	0.40 (0.15–1.09)	0.073	0.238
SOFA score	1.06 (0.94–1.20)	0.343	0.495
Pitt bacteraemia score	1.35 (1.11–1.64)	0.003	0.017
Days without appropriate therapy	0.98 (0.79–1.22)	0.865	0.937
Combination therapy	0.54 (0.12–2.41)	0.426	0.549
Combination therapy*CR-Kp BSI	1.02 (0.18–5.91)	0.980	0.980

Analyses conducted in patients with *K. pneumoniae* BSI and still on follow up on Day 8 after the onset of BSI ($n=384$), see study methods.
[a]Model D also included centre as shared frailty.[15]

comorbidity index (HR 1.20 for every point increase; 95% CI 1.10–1.31, $P<0.001$) and Pitt bacteraemia score (HR 1.33 for every point increase; 95% CI 1.15–1.55, $P<0.001$), but not carbapenem resistance (HR 1.28, 95% CI 0.74–2.22, $P=0.410$). The inclusion of centre as shared frailty did not change results of model A (see Table 3 legend). Overall, 384/426 patients (90.1%) were still on follow-up on Day 8 after the onset of *K. pneumoniae* BSI and were included in the landmark analysis. As shown in Table 4, the use of combination therapy was not associated with statistically significant changes in mortality in comparison with monotherapy (HR 0.53; 95% CI 0.12–2.37, $P=0.531$), whereas pneumonia as source of BSI (HR 3.05; 95% CI 1.42–6.55; $P=0.019$), Charlson comorbidity index (HR 1.21 for every point increase; 95% CI 1.09–1.35, $P=0.005$) and Pitt bacteraemia score (HR 1.35 for every point increase; 95% CI 1.11–1.64, $P=0.016$) were independent predictors of mortality. Similar results were observed for model D, also including centre as shared frailty (Table 4). The results of sensitivity analyses are available in Tables S2 to S9 and are in line with the results of primary analyses.

Overall, 72/80 (90.0%) patients with CR-Kp BSI appropriately treated with ceftazidime/avibactam were still on follow-up on Day 8 after the onset of *K. pneumoniae* BSI and were included as cases for propensity score matching. The characteristics of cases and controls after 1:1 matching are available in Table S10, showing the absence of substantial residual confounding with respect to matching variables. The mostly commonly employed appropriate therapy for the treatment of CS-Kp BSI in controls was meropenem monotherapy (23/72; 31.9%), followed by piperacillin/tazobactam monotherapy (20/72; 27.8%). There were no differences in mortality between patients appropriately treated with ceftazidime/avibactam for CR-Kp BSI and patients appropriately treated with other active agents for CS-Kp BSI (HR 1.07; 95% CI 0.50–2.29, $P=0.866$). The same was observed when the result was adjusted by adding centre as shared frailty (HR 1.07; 95% CI 0.50–2.32, $P=0.863$) and in sensitivity analyses considering the second, fourth or sixth day after the onset of *K. pneumoniae* BSI as the time of origin (Table S11). Cumulative 30 day mortality from the onset of *K. pneumoniae* BSI in cases and controls is also compared graphically in Figure 2 (log-rank test, $P=0.865$). As shown in Table S12, appropriate ceftazidime/avibactam-based combination therapy was not associated with reduced mortality in comparison

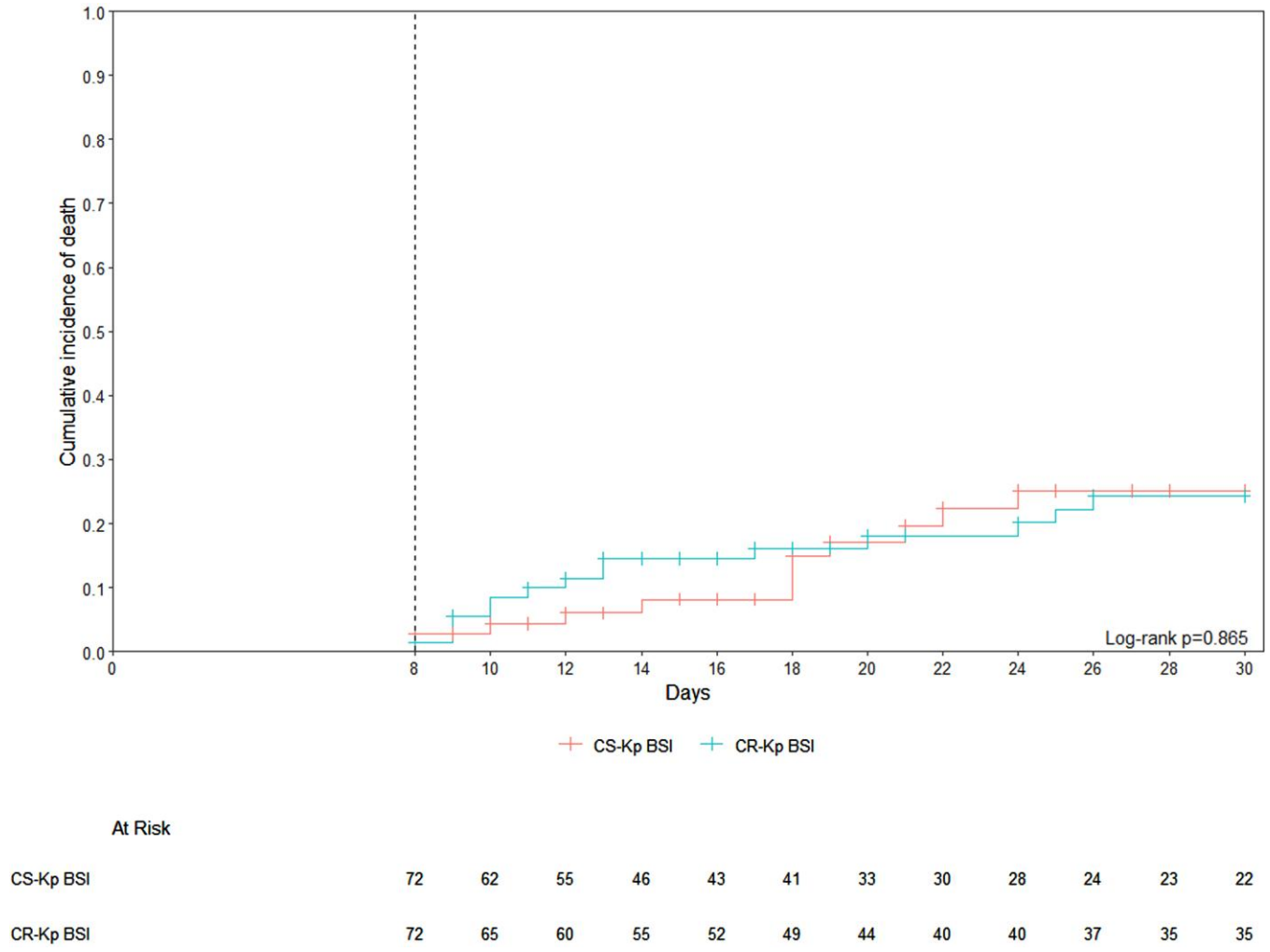

Figure 2. Landmark analysis of cumulative mortality up to Day 30 in patients with CR-Kp BSI receiving appropriate therapy with ceftazidime/avibactam (cases) versus patients with CS-Kp BSI receiving appropriate therapy with agents other than ceftazidime/avibactam (controls). The time of origin of this landmark analysis was set at the eighth day after the onset of *K. pneumoniae* BSI (i.e. when all patients still in follow-up had started appropriate therapy). The onset of *K. pneumoniae* BSI was defined as the day when the first positive blood culture for CR-Kp or CS-Kp was collected. Death was the event of interest and right-censoring was applied at the end of follow-up (hospital discharge or Day 30, whichever came first). Using propensity score matching, each case was matched to one control for the following variables: solid neoplasm; previous chemotherapy; chronic liver disease; Charlson comorbidity index; previous steroid therapy; pulmonary source of *K. pneumoniae* BSI; mechanical ventilation; SOFA score; Pitt bacteraemia score; days without appropriate therapy (from the onset of *K. pneumoniae* BSI). Appropriate therapy was defined as therapy with at least one antimicrobial drug showing *in vitro* activity against the causative *K. pneumoniae* isolate. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

with appropriate ceftazidime/avibactam monotherapy in cases (HR 0.71; 95% CI 0.21–2.39, $P = 0.672$).

Discussion

In the present study, despite our observation of a large difference in crude cumulative 30 day mortality between CR-Kp BSI and CS-Kp BSI (33.8% versus 20.7%, respectively), carbapenem resistance was not found independently associated with an increased mortality in *K. pneumoniae* BSI after adjustment for other prognostic factors. Furthermore, there was no difference in mortality between patients with CR-Kp BSI receiving appropriate treatment with ceftazidime/avibactam and patients with CS-Kp BSI treated with other appropriate agents (mostly carbapenems or piperacillin/tazobactam).

In the past 15 years, several observational studies and meta-analyses of aggregated data pointed out an increased mortality in patients with CR-Kp BSI compared with patients with CS-Kp BSI.[8–10] We also previously conducted an individual patient data meta-analysis of 1952 patients from 14 studies comparing mortality of CR-Kp BSI and CS-Kp BSI, in the attempt of adjusting for appropriateness of therapy and Charlson comorbidity index.[3] We eventually found that carbapenem resistance remained associated with increased mortality even after

adjustment for appropriateness of therapy, timing of therapy (empirical versus targeted), and Charlson comorbidity index. In our opinion, such a residual difference in mortality was possibly reflecting the suboptimal efficacy and increased toxicity of appropriate therapies used for treating CR-Kp BSI in the studies included in the meta-analysis, mostly polymyxin-based regimens.[3] In the present more recent study, where CR-Kp BSIs were mostly caused by KPC-producing isolates and were mostly treated appropriately with ceftazidime/avibactam, carbapenem resistance was not independently associated with increased mortality. This is in line with a subgroup analysis of a recent prospective study by Falcone and colleagues.[19] Indeed, while they found that among 1276 patients with monomicrobial BSI due to Gram-negative bacilli, carbapenem resistance was associated with an excess in mortality after adjustment for other prognostic factors, this was not true for BSI caused by KPC-producing Enterobacterales, with an estimated, non-significant excess in mortality conferred by carbapenem resistance of only 5% (adjusted OR for death 1.43, with 95% CI 0.92–2.22). Notably, like in our study, the majority of KPC-producing Enterobacterales in the study by Falcone and colleagues were treated with ceftazidime/avibactam (155/304; 50.7%).[19]

An important strength of our study is that its design was specifically aimed to assess the impact of appropriate therapy on the prognostic effect conferred by carbapenem resistance in *K. pneumoniae* BSI. This was owing to specific inclusion criteria (i.e. at least 48 h of appropriate therapy) and dedicated secondary analyses such as the propensity score-matched cohort to specifically assess the impact of ceftazidime/avibactam treatment. Another strength is the real-time review of consistency and quality of data included in the MULTI-SITA electronic case report form. Nonetheless, our approach is not exempt from limitations. For example, although associated with increased mortality in some previous studies,[2,5] delaying appropriate therapy (modelled as days without appropriate therapy in our analysis) was not associated with increased mortality in our study. While this could truly reflect the rapid initiation of appropriate therapy in our cohort (median 1 and 0 days for CR-Kp BSI and CS-Kp BSI, respectively), it may also depend on our inclusion criteria (patients should have survived at least 48 days after initiation of appropriate therapy), which may have artificially mitigated the prognostic impact of delaying appropriate therapy (by including in the analysis only those patients most likely to survive). Notably, the presence of an immortal time bias artificially reducing the mortality difference between CR-Kp BSI and CS-Kp BSI is very unlikely, both in landmark analyses, since divergence of the two curves in the entire cohort occurred after the eighth day from the onset of BSI (see Figure 1) and in the propensity score-matched analysis, since cases were matched to controls with respect to days without appropriate therapy. In addition, no significant deviations from the main results were observed in sensitivity analyses conducted by selecting the second, fourth or sixth day after the onset of *K. pneumoniae* BSI as the time of origin, both for landmark analyses (Tables S6 to S8) and for the propensity score-matched analysis (Table S11). Another limitation worth noting is the fact that some carbapenemases (e.g. GES variants with carbapenemase activity) could not be detected by methods employed in this real-life retrospective study. However, this is very unlikely to have affected study results, since major carbapenemases (primarily KPC, over VIM, NDM and OXA-48-like enzymes) were detected in most cases. Finally, two limitations worth reporting that affected our secondary analyses are: (i) we were unable to increase the number of controls in the propensity score-matched analysis beyond 1:1, owing to significant residual confounding when increasing the number of controls; and (ii) the secondary analysis of the prognostic impact of ceftazidime/avibactam-based combination versus ceftazidime/avibactam monotherapy in cases was hampered by the small sample of this specific subgroup analysis, and its results should thus be interpreted cautiously pending further dedicated investigation.

In conclusion, our study suggests that the increased mortality of CR-Kp BSI compared with CS-Kp BSI is not (or no longer) dependent on the type of therapy in areas where ceftazidime/avibactam-susceptible KPC-producing isolates are the prevalent type of CR-Kp and ceftazidime/avibactam is employed for treating most cases of CR-Kp BSI. The potential extrapolation of these findings to other novel BL/BLI combinations could merit dedicated investigation.

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Author contributions

Conceptualization: D.R.G., M.B.; methodology D.R.G., C.M., A.S.; formal analysis: C.M., A.S.; data curation: D.R.G., C.M., G.C., C.F., G.D.M., M.Ma., C.P., A.Ca., A.L., C.A., A.R.L., F.R., A.Co., M.Mil., F.D.P., S.C., A.M., G.R., F.B.C., C.O., F.S.S., E.M., M.S., L.G., E.M.T., M.Me., F.D.A.; writing—original draft preparation: D.R.G., C.M., V.D.P.; writing—review and editing: D.R.G., C.M., G.C., C.F., G.D.M., M.Ma., C.P., A.Ca., A.L., C.A., A.R.L., F.R., A.Co., M.Mil., F.D.P., S.C., A.M., G.R., F.B.C., C.O., F.S.S., E.M., M.S., L.G., E.M.T., M.Me., F.D.A., D.F., A.G., V.D.B., M.Mik., V.D.P., A.M.C., E.P., F.G.D.R., M.G., C.T., A.M., A.V., M.B.; supervision: D.F., A.G., V.D.B., M.Mik., A.M.C., E.P., F.G.D.R.,

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Data availability

The data presented in this study will be available from the corresponding author on reasonable request and provided all regulatory and privacy requirements are fulfilled.

Supplementary data

Figure S1 and Tables S1 to S12 are available as Supplementary data at *JAC* Online.

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