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Original article

Attributable mortality of infections caused by carbapenem-resistant Enterobacterales: results from a prospective, multinational case-control-control matched cohorts study (EURECA)

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ABSTRACT

Objectives: To assess the mortality attributable to infections caused by carbapenem-resistant Enterobacterales (CRE) and to investigate the effect of clinical management on differences in observed outcomes in a multinational matched cohort study.
Methods: A prospective matched-cohorts study (NCT02709408) was performed in 50 European hospitals from March 2016 to November 2018. The main outcome was 30-day mortality with an active post-discharge follow-up when applied. The CRE cohort included patients with complicated urinary tract infections, complicated intra-abdominal infections, pneumonia, or bacteraemia from other sources because of CRE. Two control cohorts were selected: patients with infection caused by carbapenem-susceptible Enterobacterales (CSE) and patients without infection. Matching criteria included type of infection for the CSE group, hospital ward of CRE detection, and duration of hospital admission up to CRE detection. Multivariable and stratified Cox regression was applied.
Results: The cohorts included 235 patients with CRE infection, 235 patients with CSE infection, and 705 non-infected patients. The 30-day mortality (95% CI) was 23.8% (18.8–29.6), 10.6% (7.2–15.2), and 8.4% (6.5–10.6), respectively. The difference in 30-day mortality rates between patients with CRE infection when compared with patients with CSE infection was 13.2% (95% CI, 6.3–20.0), (HR, 2.57; 95% CI, 1.55–4.26; p < 0.001), and 15.4% (95% CI, 10.5–20.2) when compared with non-infected patients (HR, 3.85; 95% CI, 2.57–5.77; p < 0.001). The population attributable fraction for 30-day mortality for CRE vs. CSE was 19.28%, and for CRE vs. non-infected patients was 9.61%. After adjustment for baseline variables, the HRs for mortality were 1.87 (95% CI, 0.99–3.50; p 0.06) and 3.65 (95% CI, 2.29–5.82; p < 0.001), respectively. However, when treatment-related time-dependent variables were added, the HR of CRE vs. CSE reduced to 1.44 (95% CI, 0.78–2.67; p 0.24).
Discussion: CRE infections are associated with significant attributable mortality and increased adjusted hazard of mortality when compared with CSE infections or patients without infection. Underlying patient characteristics and a delay in appropriate treatment play an important role in the CRE mortality.
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Introduction

Invasive infections caused by carbapenem-resistant Enterobacterales (CRE) have been associated with high mortality rates [1]. In Europe, the estimated burden of infections and deaths associated with carbapenem-resistant *Klebsiella pneumoniae* has increased by 6.16 times from 2007 to 2015 [2]. Therefore, CRE infections are considered an urgent public health problem and a priority for the discovery and development of new antibiotics [3]. In addition, resistance to novel agents are emerging rapidly [4].

Despite the perceived clinical importance of CRE, high-quality available data about their effect on the patient's outcomes are scarce because of the limitations of studies published [5–9]. In addition, if CRE infections are associated with a significant outcome effect, the relative importance of patients' characteristics, increased virulence of CRE [9] or problems related to antibiotic treatment [6] have not been well characterized.

The objectives of this study were to assess the attributable mortality of CRE infections and to investigate the effect of clinical management on the differences in observed outcome in a multinational matched cohort's study.

Methods

Study design, sites, and participants

EURECA is a multinational study (NCT02709408) investigating different aspects of CRE infections across 50 hospitals from 10 Southern European countries (Albania, Croatia, Greece, Italy, Kosovo, Montenegro, Romania, Serbia, Spain, and Turkey). The study protocol, along with a risk factor analysis, has been previously published [10,11], and is available as supplementary online material. The study period was from March 2016 to November 2018.

A prospective, nested matched-cohorts design was used for outcome analysis. The CRE cohort comprised consecutive admitted adult patients with complicated intra-abdominal infection (cIAI), pneumonia, complicated urinary tract infection (cUTI), and bloodstream infection from other sources (BSI-OS) microbiologically confirmed to be caused by CRE. The exclusion criteria included polymicrobial infection (except for cIAI), clinical trial participants, previous study participation, or life expectancy under 30 days.

Two control cohorts, matched to patients in the CRE cohorts, were included: (a) the CSE cohort (matched 1:1 to CRE cases), formed by admitted patients with infections caused by CSE, using equivalent eligibility criteria as for CRE cases and (b) the non-infected cohort (3 patients per patient infected with CRE), formed by admitted patients without infection. Matching was based on hospital and ward admission and previous length of hospital stay, calculated from admission to onset of infection for patients infected with CRE and CSE(day 0), and from admission to the matching time for the non-infected cohort; a difference of up to 3 days in the control groups was allowed, or 7 days if previous stay of the CRE case was >14 days); for the CSE cohort only, patients were also matched with CRE by the same type of infection and type of acquisition (community or nosocomial).

Patients with do-not-resuscitate order were not included in the study.

Study variables and definitions

The primary endpoint was all-cause 30-day mortality from day 0. Secondary outcomes were clinical and microbiological cure and infection-related mortality until day 21, length of hospital stay after

day 0, 30-day infection recurrence and superinfection, and therapy-related adverse events. Clinical cure was defined as the resolution of all infection-related signs and symptoms, making further antibiotic treatment unnecessary. Microbiological cure (eradication) implied no detectable causative pathogens in follow-up cultures; however, if cultures were not conducted because of clinical judgement but clinical cure was achieved, the case was regarded as presumptively microbiologically eradicated. Infection-related mortality was defined as death occurring in direct relation to the infection or its complications, with no other plausible cause. Exposure variables are listed in Table 1.

Standard criteria for the diagnosis of cUTI, pneumonia cIAI, and BSI-OS were used and are specified in the study protocol [10]. Source control included device removal for device-related infections, drainage of abscesses or closed-space infections, release of conduit obstruction, and correction of hollow visceral rupture. Source control was performed if needed within ≤3 days (or ≤24 hours for severe sepsis or shock) after diagnosis. Source control was considered not required if infection did not involve the above situations. Support therapy included fluid therapy, vasopressors, blood transfusions, oxygen therapy, and ventilator support, as needed. Empirical antibiotic therapy was initiated before susceptibility report and definitive thereafter. Antibiotic therapy was considered active if it included at least one *in vitro* active drug against the causative bacteria. Early active therapy was defined as administration of an *in vitro* active drug during the first 5 days after day 0 for ≥48 hours.

Microbiology studies

Bacterial identification and susceptibility testing were performed in the local laboratories. Enterobacterales with minimum inhibitory concentration (MIC) ≥1 mg/L (dilution methods) or ≤22 mm (disc-diffusion, 10 μg discs) for meropenem or imipenem were considered as putative CRE. The CRE isolates were preserved at −20°C and sent to central laboratories for identification, susceptibility confirmation (University of Antwerp, Belgium and Ramón y Cajal University Hospital, Madrid, Spain), and whole genome sequencing (University of Freiburg—Medical Center, Freiburg, Germany). For this study, Enterobacterales were considered CRE if resistant to meropenem or imipenem according to EUCAST breakpoints [12] or if carbapenemase-producing (regardless the MIC to carbapenems) [12], based on central laboratories results.

Ethical aspects and quality of data

The study was approved by the Andalusian review board (code FIS-ATB-2015-01) and by local ethic committees according

Table 1
Baseline characteristics of patients with infections caused by carbapenem-resistant Enterobacterales, carbapenem-susceptible Enterobacterales, and non-infected patients. Data are no. of patients (percentage) except where specified

Characteristic	CRE group (n = 235)	CSE group (n = 235)	p[a]	Non-infected group (n = 705)	p[b]
Demographics[c]					
Median age (y) (IQR)	73 (62–82)	70 (59–79)	0.081	67 (53–77)	<0.001
Male sex	134 (57.4)	126 (53.6)	0.42	412 (58.4)	0.69
Chronic underlying conditions[c]					
Median Charlson index (IQR)	3 (2–4)	2 (1–4)	0.008	2 (0–3.5)	<0.001
Diabetes mellitus	70 (29.8)	66 (28.1)	0.66	170 (24.1)	0.083
Chronic pulmonary disease	44 (18.7)	36 (15.3)	0.31	109 (15.5)	0.22
Chronic heart failure (NYHA ≥2)	44 (18.7)	28 (11.9)	0.038	84 (11.9)	0.005
Dementia	37 (15.7)	22 (9.4)	0.025	34 (4.8)	<0.001
Chronic liver disease	15 (6.4)	14 (6.0)	0.83	64 (9.1)	0.63
Chronic renal failure (grades 3 or 4)	65 (27.7)	33 (14)	<0.001	88 (12.5)	<0.001
Solid organ cancer	64 (27.2)	57 (24.3)	0.41	143 (20.3)	0.014
Haematologic cancer	12 (5.1)	12 (5.1)	1.00	35 (5.0)	0.90
Bone marrow/stem cell transplantation	1 (0.4)	1 (0.4)	1.00	10 (1.4)	0.17
Neutropenia (<500 cells/μL)	13 (5.8)	8 (3.4)	0.23	27 (3.8)	0.13
Solid organ transplantation	16 (6.8)	13 (5.5)	0.53	28 (4)	0.028
HIV infection	1 (0.4)	2 (0.9)	0.57	14 (2)	0.14
Immunosuppressive drugs (last 3 months)	59 (25.1)	52 (22.1)	0.40	121 (17.2)	0.002
Invasive procedures[c]					
Central venous catheter (last week)	78 (33.2)	60 (25.5)	0.020	152 (21.6)	<0.001
Urinary catheter (last week)	153 (65.1)	120 (51.1)	0.001	216 (30.6)	<0.001
Mechanical ventilation (last week)	42 (17.9)	45 (19.1)	0.58	96 (13.6)	0.013
Surgery (last month)	71 (30.2)	65 (27.7)	0.41	133 (18.9)	<0.001
Acute severity of disease/infection					
Median Pitt score at day 0 (IQR)	1 (0–3)	0 (0–2)	0.096	0 (0–1)	<0.001
Median SOFA score at day 0, median (IQR)	3 (1–5)	2 (1–4)	0.013	1 (0–3)	<0.001
SOFA ≥2 at day 0	162 (68.9)	143 (60.9)	0.066	313 (44.4)	<0.001
Severe sepsis or septic shock at day 0	40 (17.0)	27 (11.4)	0.086	NA	NA
Bacteraemia, any source	90 (38.3)	85 (36.2)	0.70	NA	NA
Etiology					
Klebsiella spp.	208 (88.5)	74 (31.4)	<0.001	NA	NA
Enterobacter spp.	11 (4.7)	17 (7.2)	0.23	NA	NA
Escherichia coli	7 (3.0)	113 (48.5)	<0.001	NA	NA
Proteus mirabilis	6 (2.6)	13 (5.5)	0.10	NA	NA
Serratia spp.	1 (0.4)	6 (2.6)	0.06	NA	NA
Citrobacter spp.	2 (0.9)	4 (1.7)	0.41	NA	NA
Morganella morganii	0	2 (0.9)	0.16	NA	NA
Other Enterobacterales	0	6 (2.6)	0.008	NA	NA

p values calculated by conditional logistic regression.
NA, not applicable.
[a] p value for CRE vs. CSE groups.
[b] p value for CRE vs. non-infected groups.
[c] Already published data (ref. 11), shown here for understanding of the analyses.

to local requirements. The need to obtain written informed consent was waived because of the observational nature of the study.

All data were monitored remotely for missing information and consistency. For this report, the STROBE recommendations were followed (Table S1).

Statistical analysis

For an expected mortality rate in patients infected with CRE of 35%, and 20% in control groups, and the possibility to include 12–17 variables in multivariable outcome analysis, the inclusion of 240 patients infected with CRE and their corresponding matched control patients was planned. According to previous studies [13,14], around 50% of patients with cUTI were expected.

Missing data were analysed by the Little's MCAR test for randomness, and multiple imputation was performed using the Markov-Chain-Monte-Carlo method. We calculated the population attributable fraction (PAF) of mortality for CRE vs. CSE and for CRE vs. non-infected patients [15], the incidence rate ratio, and the absolute risk difference. The estimation of the PAF for CRE-associated mortality was based on two prevalence scenarios from participating hospitals (please see supplementary Methods and Table S6).

Within the matched cohorts of CRE-CSE and CRE-non-infected, bivariate and multivariate analyses were performed using stratified Cox proportional hazard regression for matched-pair analysis to evaluate the association of various variables with 30-day mortality. Variables with a univariate $p < 0.20$ were considered for the multivariable models and selected using a manual stepwise backward process; those with a $p < 0.1$ were kept. The variable CRE was forced in all the models. The final multivariable models, optimized by the Akaike information criterion, included: (a) demographics, patient characteristics, and invasive procedures; (b) also including treatment-related variables (active antimicrobial treatment, source control, and support therapy) as time-dependent co-variates; and (c) including variables related to the severity of the infection. Finally, we also performed a model in the sub-cohort of matched patients infected with CRE and CSE who both had received early active treatment.

All analyses were performed using the software packages IBM SPSS version 26.0 and R version 4.3.1 (survival, epiR, and tidyverse libraries).

Results

During the study period, the first 235 patients infected with CRE detected in the participating sites who could be matched to controls were included in this analysis. Therefore, 235 matched patients infected with CRE and CSE, and 705 matched patients without infection were included (Fig S1).

Baseline features of patients

The patients' demographics, underlying conditions, and exposure to invasive procedures were previously reported [11] and are summarised (Table 1). The types of CRE and CSE infection were: cUTI, 133 patients (56.7%); pneumonia, 44 (18.7%); and cIAI and BSI-OR, 29 each (12.3%). Those with CRE were typically older and had a greater Charlson comorbidity index, with more instances of chronic heart failure, renal insufficiency, and dementia. Several invasive procedures were more frequent in CRE than in CSE or non-infected patients. The median (IQR) SOFA score at day 0 was higher for patients infected with CRE (3 (1–5)) than in patients infected with CSE (2 (1–4)), or non-infected patients (1(0–3)) (Table 1). Each group had 138 (58.7%) patients with hospital-acquired infections.

The proportion of patients with infection because of *Klebsiella* spp. was higher in patients infected with CRE, whereas those because of *Escherichia coli* were more frequent in patients infected with CSE (Table 1). Overall, 191 isolates (81.2%) from 235 patients were carbapenem-resistant according to EUCAST breakpoints. The carbapenemase genes found in CRE isolates encoded for OXA-48 enzymes in 112 isolates (47.6%), *Klebsiella pneumoniae* carbapenemase (KPC) in 84 (35.7%) and metallo-β-lactamases in 44 (18.7%); in 13 there were more than one carbapenemase gene found. No carbapenemase genes were found in seven isolates.

Therapeutic management data for CRE and CSE cohorts

Fewer patients in the CRE group received active empirical treatment than in the CSE group (80 [34.0%] vs. 179 [76.2%]). The median (IQR) delay in administration of active therapy was 3 (1–5) days in patients infected with CRE and 1 (0–3) day in patients infected with CSE. Early active therapy was administered in 167 of the 226 (73.8%) and 215 of the 234 (91.8%) patients infected with CRE and CSE, respectively (Table 2). The most frequent target drugs administered in patients infected with CREs were aminoglycosides (53 patients) and colistin (41 patients), and carbapenems in

Table 2
Treatment of patients with infections caused by carbapenem-resistant and carbapenem-susceptible Enterobacterales. Data are no. of patients (percentage) except where specified

Treatment	CRE group (n = 235)	CSE group (n = 235)	p
Antimicrobial treatment			
Active empirical treatment	80 (34.0)	179 (76.2)	<0.001
Active therapy in ≤5 days (patients who died before are excluded)	167/226 (73.8)	215/234 (91.8)	<0.001
Median days to adequate treatment (IQR)	3 (1–5)	1 (0–3)	<0.001
Source control[a]			
Not needed[b] or not possible	92 (39.1)	117 (48.9)	0.02
Needed and performed	78 (33.2)	61 (26)	0.09
Needed but not performed	65 (27.7)	57 (24.3)	0.40
Supportive therapy: fluids and vasoactive agents			
Not needed[b]	195 (83.0)	208 (88.5)	0.39
Needed and performed[c]	25 (10.6)	19 (8.1)	0.34
Needed and not performed	15 (6.4)	8 (3.4)	0.13

p values calculated by conditional logistic regression.

[a] Source control included device removal for device-related infections, drainage of abscesses or closed-space infections (i.e. empyema, peritonitis, arthritis, or bone sequestrum), release of conduit obstruction (i.e. urinary or biliary tracts), and correction of hollow visceral rupture.

[b] Source control was considered not needed if infection did not involve the above situations, and in case of lung infections or surgically-implanted devices in patients without severe sepsis or shock.

[c] Source control was considered performed if it was needed and done in ≤3 days (≤24 hours in patients with severe sepsis or shock).

Table 3
Outcomes of patients with infections caused by carbapenem-resistant and carbapenem-susceptible Enterobacterales, and non-infected matched patients. Data are number of patients (percentage) except where specified

Outcomes	CRE group (n = 235)	CSE group (n = 235)	p[a]	Non-infected cohort (n = 705)	p[b]
All-cause mortality up to day 30	56 (23.8)	25 (10.6)	<0.001	59 (8.4)	<0.001
Complicated urinary tract infection	24/133 (18.0)	11/133 (8.3)	0.032	22/399 (5.5)[c]	<0.001
Pneumonia	16/44 (36.4)	9/44 (20.5)	0.068	26/132 (19.7)[c]	0.054
Complicated intraabdominal infection	4/29 (13.8)	3/29 (10.3)	0.69	3/87 (3.4)[c]	0.070
Bloodstream infection, other sources	12/29 (41.4)	2/29 (6.9)	0.032	8/87 (9.2)[c]	<0.001
Bloodstream infection, any source	22/90 (24.4)	5/85 (5.9)[d]	<0.012	18/271 (6.6)[c]	<0.001
Infection-related mortality, day 30	44 (18.7)	12 (5.1)	0.006	NA	NA
Clinical cure, day 21	106 (45.1)	142 (60.4)	0.001	NA	NA
Microbiological cure, day 21	144 (61.3)	198 (84.3)	<0.001	NA	NA
Infection recurrence	32 (13.6)	16 (6.8)	0.021	NA	NA
Superinfection	47 (20.0)	27 (11.5)	0.020	NA	NA
Therapy-related events	51 (21.7)	33 (14.0)	0.042	NA	NA
Median days of hospital stay after day 0 (IQR)	18 (12–30)	12 (8–23)	<0.001	8 (4–20)	<0.001

NA, not applicable.
[a] p value for CRE vs. CSE groups.
[b] p value for CRE vs. non-infected groups.
[c] Data refers to matched patients.
[d] Data refers to patients without BSI, regardless matching.

patients infected with CSE (65 patients). Only 27 patients were treated with ceftazidime-avibactam (Table S2).

The proportion of patients in whom source control was needed but not timely performed was similar in CRE (65 [27.7%]) and CSE groups (57 [24.3%]). Supportive therapy was administered with a similar frequency in patients infected with CRE and CSE (Table 2). Specific aspects of source control and support therapy are shown in Table S3.

Outcomes analysis for CRE, CSE, and non-infected cohorts

By day 30, mortality rates (95% CI) were 23.8% (18.8–29.6) for CRE, 10.6% (7.2–15.2) for CSE, and 8.4% (6.5–10.6) for non-infected cohorts (Table 3 and Fig. 1). Therefore, the absolute difference in mortality rate for CRE was 13.2% (95% CI, 6.3–20.0) when compared with CSE and 15.4% (95% CI, 10.5–20.2) when compared with non-infected, with a crude HR of 2.57 (95% CI, 1.55–4.26; p < 0.001) and 3.85 (95% CI, 2.57–5.77; p < 0.001), respectively (Table S4).

Mortality rates were higher for all types of CRE infections (Table 3); the crude difference in mortality in comparison with matched patients infected with CSE ranged from 9.7% (95% CI, 1.5–17.8) in cUTI to 35.5% (95% CI, 13.6–57.3) in BSI-OS, and was similarly superior when compared with matched non-infected patients (Table S4).

The incidence rate ratio for CRE infections compared with CSE infections and to non-infected patients were 2.25 and 2.83, respectively. The estimated PAF of mortality was 66.72% and 19.28% when compared with CSE in high and low exposure prevalence scenarios, respectively, and 47.36% and 9.61% when compared with non-infected patients in the same scenarios (Table S5).

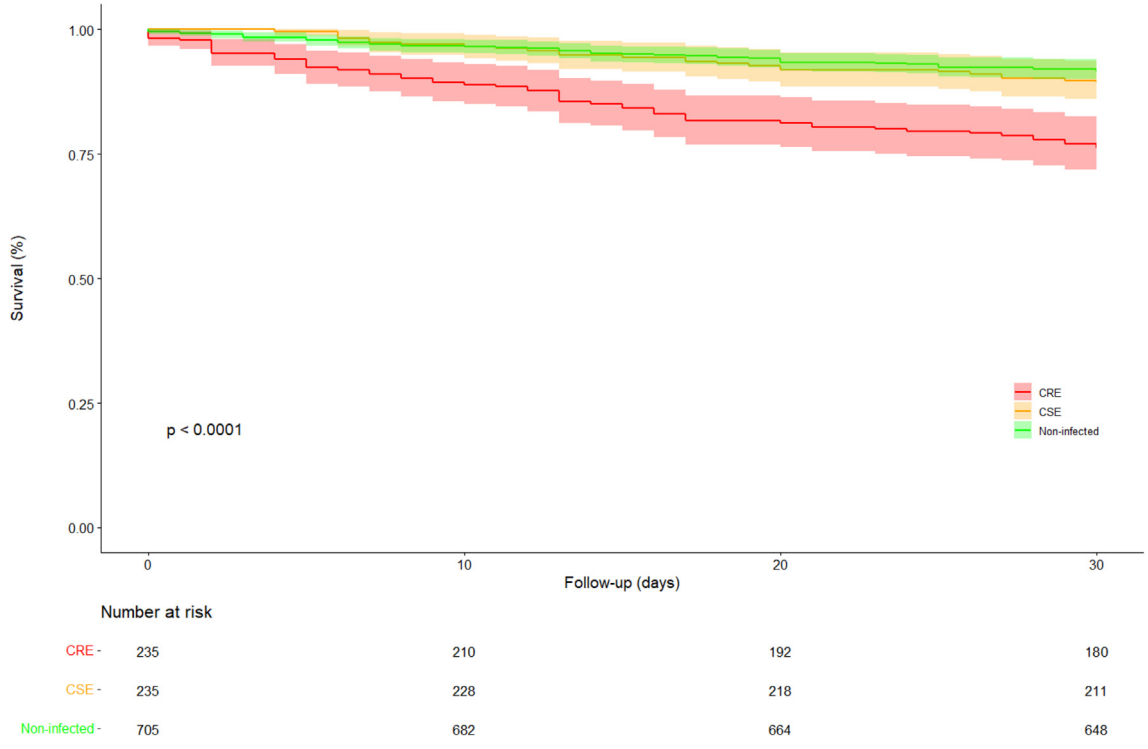

Fig. 1. Survival up to day 30 of patients with CRE infections, CSE infections, and non-infected patients.

Secondary outcomes revealed that patients infected with CRE (Table 3) had higher infection-related mortality, infection recurrences, superinfections, and lower clinical and microbiological cure than patients infected with CSE; length of stay after day 0 was longer in CRE than in CSE and non-infected patients.

Initial bivariate analysis showed factors individually associated with mortality in the matched CRE-CSE cohort, including the CRE infection variable (compared to CSE infection), as presented in Table S6. Multivariate models indicated the following hazard ratios (HR, 95% CI) for mortality in patients with CRE infections: (a) In the model that considered demographic characteristics, underlying conditions, and invasive procedures: 1.87 (0.99–3.50; p=0.06); (b) In the model that also incorporated active treatment, source control, and support therapy as time-dependent co-variates: 1.44 (0.78–2.67; p=0.24); and (c) In the model that further included the severity of the infection: 1.41 (0.74–2.68; p=0.29) (Table S7, S8 and S9). The different hazard estimations in these different models are shown in Fig. 2. Finally, in the sub-cohort of matched patients infected with CRE and CSE receiving early active antimicrobial treatment (n = 240), the HR for mortality was 1.40 (0.55–3.63; p=0.43; Table S10).

The bivariate analysis of factors associated with mortality within the matched cohort of patients infected with CRE and non-infected patients can be found in Table S6. The adjusted multivariate analysis only included demographic characteristics, underlying conditions, and invasive procedures, as treatment-related variables do not apply on the non-infected population. The adjusted HR for death of CRE regarding non-infected patients was 3.65 (2.29–5.82; p < 0.001; Table S11). Finally, we also estimated the mortality of patients infected with CSE vs. non-infected patients; the crude HR was 1.27 (95% CI, 0.80–2.04; p=0.30), and the adjusted HR was 1.09 (95% CI, 0.68–1.75; p=0.70).

Discussion

In this multinational study, CRE infections had a higher 30-day mortality than matched patients with infections caused by CSE or non-infected patients; we provided estimations for the PAF and HR for mortality for CRE infections, and found that the estimated mortality hazard was reduced when treatment-related variables were considered.

We used two control groups to analyse two populations: patients with infections because of Enterobacterales and admitted patients. The CRE infections were associated with increased mortality hazards and substantial attributable mortality as estimated by PAF relative to CSE infections and non-infected conditions. The PAF of mortality, particularly pronounced in high prevalence environments, suggest that an important amount of mortality would theoretically be avoidable by preventing CRE infections considering the drugs used for treatment. Because only a minority of patients in our cohort received some of the newer drugs against CRE, it would be appropriate to investigate to what extent these new drugs are able to reduce the attributable mortality of CRE. The mortality HR for CRE vs. CSE in our cohorts aligns with previous meta-analyses, showing a CRE mortality risk ranging from 2.0 to 3.39 [1,5–9]. It should be noted that in the individual studies included in these meta-analyses, there was a predominance of KPC-producing *K. pneumoniae* and BSI, while our study included different carbapenemase-types and infection sites. Hauck et al. [16] compared mortality of patients with CRE infection with those colonised, and found higher mortality in patients with BSI or pneumonia in infected patients but no excess of mortality in patients with UTI.

The variables related to acute severity of the infection were initially considered to be in the causal pathway from the microorganism to the outcome, and therefore were not considered as potential confounders [17]; in fact, SOFA and Pitt scores were higher in patients infected with CRE than in those infected with CSE, which might be related to a higher virulence of CRE. However, including the severity of the infection in multivariate analyses barely altered the results. Because infections due to *Klebsiella* spp. have been associated to worse outcomes compared to *E. coli* [1,3,16]; we included this variable in the multivariate models.

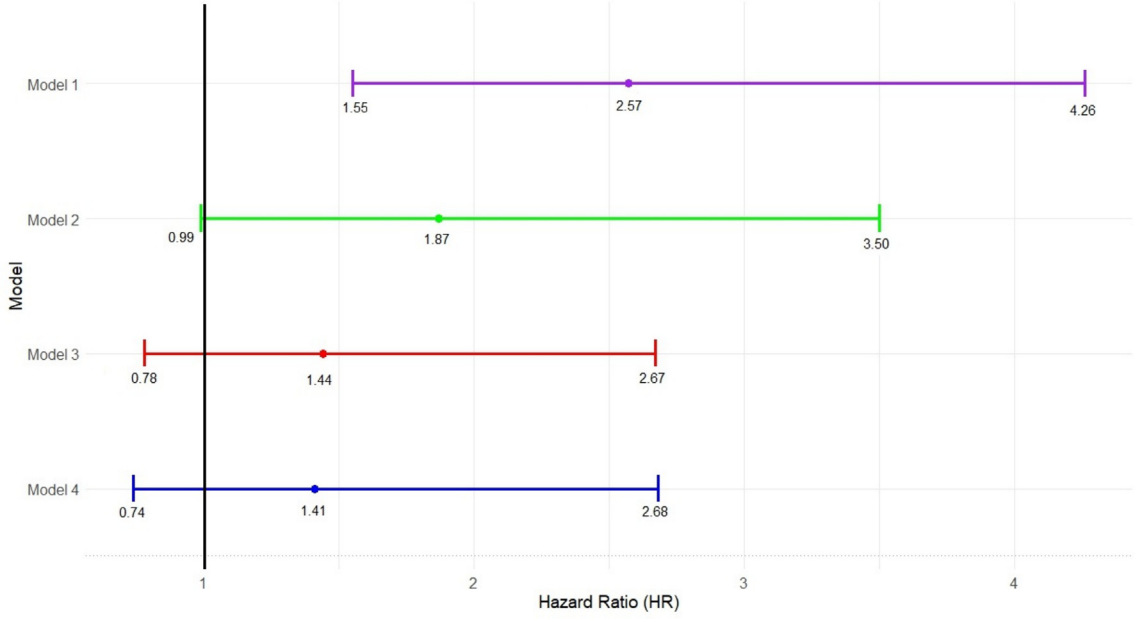

Fig. 2. Hazard ratios with 95% CI for mortality with infection caused by CRE regarding infection caused by CSE in different models. 1) Bivariate analyses of CRE vs. CSE. 2) Multivariable analyses of all patients including only baseline variables (demographics, underlying conditions, invasive procedures, and aetiology of infection). 3) Variables considered as in model 2 plus time-dependent co-variates of active treatment and support therapy. 4) Variables considered as in model 3 plus variables related to severity of infection (Pitt score).

Of importance, when the effect of antimicrobial treatment and supportive therapy were controlled for, the risk estimate shifted towards nonsignificance, suggesting that an important reason for incremental mortality risk in CRE infections is related to delay in treatment.

Our study has several limitations. First, despite all efforts, residual confounding might still exist. Second, the new drugs active against CRE were only in a small number of patients. Third, although the phenotypic definition used for CRE probably captured most CPE, some might have been missed, especially some producing OXA-48-like enzymes [18]. Fourth, although our study design offers strong control for confounding variables, estimating the PAF necessitates understanding the exposure prevalence in the source population, which isn't directly measured in a case-control study. This approach enables us to calculate and interpret PAF, highlighting the potential public health implications of CRE infections in our population. Finally, the statistical power may have been limited to detect relevant differences in subgroups. Strengths of the study include its multinational nature, the inclusion of diverse carbapenemases, organisms and infections, and the design used.

In conclusion, CRE infections are associated with significant attributable mortality and increased mortality risk. Underlying patient characteristics and delay in appropriate treatment and support therapy seem to play an important role in CRE mortality. These results highlight the importance of providing rapid susceptibility results, of availability of active drugs against CRE and of the prevention of CRE infections.

Data sharing

Data collected for the study, including de-identified participant data and a data dictionary defining each field in the set, will be made available to other investigators upon request to the corresponding author, after approval of a proposal by the senior authors' institution and the COMBACTE-CARE consortium.

Author contribution

Conceptualisation: JR-B, BG-G, JMB-F, T K, MEAK, JF, RC, HaG, HeG, and MJB. Data curation: MP-G, JMB-F, SP-G, TK, and JS. Formal analysis: BG-G, MP-G, JMB-F, MK, JF, and JR-B. Funding acquisition: JR-B and LKT, HeG, and MJB. Investigation: MP-G, JMB-F, SP-G, TK, RC, GLD, BC, GD, LR, AH, PV, and MA. Methodology: JR-B, BG-G, JMB-F, TK, MEAK, JF, RC, HaG, HeG, and MJB. Project administration: JMB-F, LT, HeG, MJB, and JR-B. Resources: RC, GLD, BC, GD, LR, AH, PV, MA, JMR, JT-C, AB, SAF, SB, LB, AA, VK, HaG, HeG, MJB, and JR-B. Software: JMB-F and JS. Supervision: JR-B, HeG, and MJB. Validation: JMB-F, BG-G, JR-B. Visualisation: SP-G, JMB-F, MP-G, BG-G, and JR-B. Writing—original draft: MP-G, JMB-F, BG-G, JR-B. Writing—review and editing: SP-G, TK, MEAK, JF, JS-D, JS, RC, GLD, BC, GD, LKT, LR, AH, PV, MA, JMR, JT-C, AB, SAF, SB, LB, AA, VK, HaG, HeG, and MJB. MP-G, JMB-F, SP-G, MEAK, JF, JS, BG-G and JR-B had access to data. JMB-F, BG-G and JR-B verified all data. All authors read and approved the final version of the manuscript.

Transparency declaration

GLD reports personal fees from Pfizer, personal fees from MSD, outside the submitted work. LKT is an employee of and holds shares in GSK. PV reports grants from Shionogi and Gilead; personal fees from Shionogi, MSD, Allianz, Nordic, InfectoPharm, MundiPharm, and Angelini, outside the submitted work. JMR reports non-financial support from Pfizer. JT-C reports personal fees from MSD, Pfizer, Menarini, and Shionogi; and non-financial support from Pfizer, Shionogi, and Gilead, outside the submitted work. MJB reports grants paid to his institution from Janssen Vaccines, Novartis, CureVac, and Merck; participation in Advisory Boards with payment to his institution from Spherecydes, Pfizer, Merck, and Astra-Zeneca, and participation in Data Safety Monitoring Boards with payment to his institution from Sanofi. All other authors have no conflicts to declare.

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Appendix A. Supplementary data

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