

Association Between Carbapenem-Resistant Enterobacterales (CRE) Colonization Status at Time of Hospital Admission and the Subsequent Development of CRE Infection and Mortality in High-Risk Patients

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Purpose: The study aimed to determine the impact of Carbapenem-resistant Enterobacterales (CRE) colonization status on development of CRE infection and 30-day mortality outcomes in high-risk patients.

Patients and Methods: This retrospective cohort study was conducted at King Faisal Specialist Hospital and Research Center in Jeddah, Saudi Arabia from October 2022 to July 2023. It included all patients aged 14 years and older admitted to the intensive care unit (ICU), the renal transplant unit and the oncology units who were screened for CRE colonization upon hospital admission.

Results: Overall, 246 patients comprised the study population and 37 patients (56.8% ICU, 13.5% renal transplant unit, and 29.7% oncology units) had a positive CRE screening test. The majority of the isolates (59.5%) were OXA-48. Almost one-third (32.1%) of the patients had diabetes mellitus and 55.3% had any underlying immunosuppression. Eight (3.3%) patients had a confirmed CRE infection and 35 (14.2%) patients died within 30 days of screening. A positive CRE screening test significantly increased the likelihood of 30-day mortality for this high-risk patient population (adjusted odds ratio [AOR] = 3.06, 95% CI = 1.10–8.51, $p = 0.03$).

Conclusion: A substantial percentage of the high-risk patients had a positive CRE screening test at the time of hospital admission and CRE-colonization status predicted 30-day mortality. Further studies are needed to determine the best practices for CRE screening as a strategy to prevent infection and mortality.

Keywords: carbapenem-resistant enterobacterales, CRE, epidemiology, OXA-48, Saudi Arabia

Introduction

Bacterial infection is a primary concern for over 50% of patients admitted to intensive care units (ICUs), with increasing prevalence globally and with an alarming impact on mortality, hospital resources, and cost burden.^{1–3} Infection caused by multi-drug-resistant organisms (MDROs) in particular, including Carbapenem-resistant Enterobacterales (CRE), is particularly challenging in terms of increased risk of ICU admission and a 50% chance of mortality.^{1,4}

The development of CRE infections has become more commonly and independently associated with solid organ transplant (SOT) recipients.^{5,6} Possible reasons for this include a frequent need for antimicrobial therapy, admission to the ICU, poor functional status, and the need for mechanical ventilation and prolonged hospitalization.^{5,6} There is great

variation in post-SOT CRE infection incidence by institution and by the type of transplant. A median time of <60 days from time of transplant to CRE infection has been reported in several studies, indicating that infection usually occurs early after transplant.⁷ Mortality rates between 30–50% have been reported for SOT patients that contract CRE infections and the one-year survival rate of 164 SOT recipients with invasive CRE infections that developed in the first year of transplant was 72%.^{8,9}

A systematic review of ten studies with a total 1806 patients looking at the risk of infection in CRE-colonized patients revealed a cumulative infection rate of 16.5%.¹⁰ A retrospective matched cohort study also showed that CRE-colonized ICU patients were at least twice as likely to develop CRE infection with the colonizing strain compared to matched non-colonized ICU patients.¹¹ Studies have shown increased risk of infection and mortality in CRE-colonized patients admitted to the ICU.^{11,12} In addition, a recently conducted retrospective study of hospitalized adult patients with COVID-19 reported that 30% of the patients were diagnosed with rectal carriage and 20% of the patients had blood-stream infections and/or pneumonia from *Klebsiella pneumonia* and/or carbapenem-resistant *Acinetobacter baumannii*.¹³ Although there was no significant impact on in-hospital mortality, further studies are needed to provide insight into the relationship between CRE colonization, infection, and mortality in this patient population.¹³

In Saudi Arabia where OXA-48 is the predominant carbapenemase, there is limited information concerning the relationship between CRE colonization, infection, and mortality.^{14,15} The current study aimed to determine if there is an association between CRE colonization status at the time of hospital admission and subsequent CRE infection and mortality within 30 days of the screening date for high-risk patients including critically ill ICU, renal transplant, and oncology patients at a tertiary care hospital.

Material and Methods

Study Design and Patient Population

Data for this retrospective cohort study came from the medical records of critically ill, renal transplant recipient, and oncology patients at King Faisal Specialist Hospital & Research Center, a tertiary care hospital in Jeddah, Saudi Arabia. Patients aged 14 years and older admitted to the intensive care unit (ICU) or for renal transplantation who consented to CRE screening and testing for CRE infection were included. The final study population consisted of 246 critically ill, renal transplant, and oncology patients admitted to the hospital between October 2022 and July 2023 inclusive.

The primary outcomes of interest in this study were a diagnosis of CRE infection and mortality within 30 days of screening for CRE colonization.

Microbiological Procedures

The main exposure of interest, CRE gastrointestinal carriers, was assessed during active surveillance testing by means of rectal swab specimen collection. Patients were screened for CRE carriage using molecular testing upon admission to the hospital for oncology and transplant patients, and upon ICU admission for critical care patients. The rectal swabs were collected within the first 24 hours after a patient's admission to the unit. A nylon flocked swab system was utilized for sample collection, which was promptly transported to the laboratory for subsequent processing. Early detection enabled the rapid identification of colonized patients, allowing for timely implementation of targeted infection control measures, including patient isolation and contact precautions. This proactive approach is essential for mitigating the risk of CRE transmission and preventing hospital-wide outbreaks.¹⁶

The gene associated with CRE was tested to confirm colonization during baseline surveillance. The baseline surveillance test was completed within one hour and 20 minutes. CRE was detected using the rectal swab and reported as detected or not detected. Patients who developed CRE infection were further evaluated by confirming the infection through culture methods, molecular testing, and assessment of antimicrobial susceptibility. Laboratory tests were performed to determine molecular typing of positive CRE screening and infection results.

Once the isolated colony of bacteria grew on blood agar, the Vitek 2 system (bioMérieux, Marcy L'Étoile, France) was used for bacterial identification and the N-291 card was used for susceptibility testing as phenotypic methods for confirming CRE following the methodology from the Clinical Laboratory Standards Institute (M-100, 33rd Edition).

Molecular methods have only recently become available for detecting carbapenemase genes directly from clinical specimens. When carbapenem susceptibility results were inconclusive of carbapenemase production in bacterial isolates of Enterobacterales, the E-test including imipenem and meropenem was used as a confirmation for carbapenemase production.

The Cepheid Xpert Carba-R assay (Cepheid, Sunnyvale, CA, USA), an automated in vitro diagnostic test for the qualitative detection of the *bla*_{KPC}, *bla*_{NDM}, *bla*_{VIM}, *bla*_{OXA-48}, and *bla*_{IMP} gene sequences differentiates these sequences that have been linked to carbapenem resistance in gram-negative bacteria and provides a non-detected result for other sequences.¹⁷ Gene resistance is associated with carbapenem nonsusceptibility in Enterobacterales. The Xpert Carba-R assay was used to test confirmed isolates from the culture following recommended procedures to detect and differentiate *bla*_{KPC}, *bla*_{NDM}, *bla*_{VIM}, *bla*_{OXA-48}, and *bla*_{IMP} gene sequences. This assay is performed using the GeneXpert instrument system and can be used with rectal swab specimens.

Data Collection and Statistical Analysis

Information abstracted from the medical records concerning possible predictors of CRE infection and mortality included: demographic data, intensive care unit (ICU) admission status, comorbid conditions, Charlson Comorbidity Index (CCI), underlying immunosuppression, laboratory tests performed within 24 hours of admission, need for interventions such as mechanical ventilation in the 30 days prior to CRE screening, and antibiotics taken by patients.

Descriptive statistics were generated for exposure, outcome, and predictor variables according to distribution of the data. Normality was assessed for continuous variables using Shapiro–Wilk and Kolmogorov–Smirnov tests and by observing the mean, median, skewness, kurtosis, and histogram results for each variable. The associations between the CRE screening test result and exposure variables and the outcome of mortality and predictor variables were determined using the Wilcoxon rank-sum test, the Chi-Square test, and Fisher’s exact tests. The associations between CRE screening test result and CRE infection and between CRE infection and mortality within 30 days were also described using Fisher’s exact test. All predictor variables significantly associated with the CRE screening test result and with mortality in univariate analysis, in addition to gender, were included in a multivariable logistic model to predict mortality within 30 days. SAS software version 9.4 was used to perform analyses and significance was determined at an $\alpha = 0.05$ level. This study was approved by the King Faisal Specialist Hospital & Research Center institutional review board in Jeddah.

Results

Overall, 246 critically ill, renal transplant recipient, and oncology patients comprised the study population aged 14 years and older with 56.5% of the population being male (Table 1). The median (interquartile range [IQR]) for patient age was 52.5 (36.0–65.0) years. Just under half (45.7%) of the patients were admitted to the ICU during their hospital stay while 23.7% were included from the renal transplant unit and 30.6% were included from the oncology units. Almost one-third (32.1%) of the patients had diabetes mellitus and over half (55.3%) had an underlying immunosuppression. There were

Table 1 Demographic and Clinical Characteristics of Study Population at Baseline (n=246)

Variable	n (%)	Median (IQR) ^a
Age (years)		52.5 (36.0–65.0)
Gender		
Male	139 (56.5)	
Female	107 (43.5)	
Patient type		
ICU	112 (45.7)	
Renal transplant	58 (23.7)	
Oncology	75 (30.6)	

(Continued)

Table 1 (Continued).

Variable	n (%)	Median (IQR) ^a
Comorbidities		
IHD	28 (11.4)	
HF	24 (9.8)	
PVD	16 (6.5)	
CVA	24 (9.8)	
CKD	45 (18.3)	
ESRD	50 (20.3)	
HIV	1 (0.4)	
Dementia	5 (2.0)	
COPD	5 (2.0)	
Connective tissue disease	2 (0.8)	
Peptic ulcer disease	0 (0.0)	
Chronic liver disease	13 (5.3)	
DM	79 (32.1)	
Hemiplegia/paraplegia	1 (0.4)	
Solid malignancy	65 (26.4)	
Hematological malignancy	43 (17.5)	
Solid organ transplant	15 (6.1)	
Bone marrow transplant	8 (3.3)	
Other ^b	35 (14.2)	
Any underlying immunosuppression	136 (55.3)	
Charlson comorbidity Index		4 (2–6)
Previous hospitalization within 3 months	107 (43.5)	
In the 30 days prior to CRE screening:		
Carbapenem exposure	43 (17.5)	
Mechanical ventilator	28 (11.4)	
Central line	35 (14.3)	
Peg tube feeding	4 (1.6)	
Need for vasopressors	46 (18.7)	
SOFA score at admission		4 (1–6)
WBC (10 ⁹ /L) at admission		7.9 (5.5–12.7)
CRE screening test		
Positive	37 (15.0)	
Negative	209 (85.0)	
Molecular typing of screening test (n=37) ^c		
KPC	3 (8.1)	
NDM	16 (43.2)	
VIM	5 (13.5)	
OXA-48	22 (59.5)	

Notes: ^areported according to distribution of the data; ^bincludes more than 20 different conditions; ^cmore than one CRE molecular type possible per patient.

Abbreviations: SD, standard deviation; IQR, Interquartile Range; ICU, intensive care unit; IHD, ischemic heart disease; HF, heart failure; PVD, peripheral vascular disease; CVA, cerebral vascular accident; CKD, chronic kidney disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CRE, Carbapenem-resistant Enterobacterales; SOFA, sequential organ failure assessment; WBC, white blood cell.

107 (43.5%) patients that had been hospitalized within the previous three months. Thirty days prior to CRE screening, 17.5% of the patients had exposure to carbapenem and 14.3% had a central line placed. The median Charlson comorbidity index was 4 and the median sequential organ failure assessment (SOFA) score was 4 for this patient

population. There were 37 (15.0%) patients with a positive CRE screening test upon admission to the hospital with the majority of the isolates (59.5%) being OXA-48 producers (Table 1).

During their hospital stay, 8 (3.3%) patients developed a confirmed CRE infection by positive culture (three *Escherichia coli* and five *Klebsiella pneumoniae* isolates) that was clinically established within 30 days of CRE screening with most of these isolates (37.5%) also being OXA-48 (Table 2). Our protocol for the treatment of CRE infections is as follows: patients with molecular typing revealing the OXA 48 gene are treated with Ceftazidime/Avibactam, while those with the NDM gene are treated with a combination of Ceftazidime/Avibactam in addition to Aztreonam. Just over three-quarters (78.0%) of the patients were discharged from the hospital during the study period while 35 (14.2%) patients died within 30 days of CRE screening (Table 2).

Univariate analyses showed that the association between the Charlson comorbidity index score and the screening test result was significant with a median score of 6.0 for patients with a positive CRE screening test compared to a median of 3.0 for patients with a negative screening test result ($p = 0.00$) (Table 3). While 8.1% of the patients with a positive screening test had dementia, 1.0% of the patients with a negative screening test had this comorbid condition ($p = 0.03$) whereas 19.6% of the patients with a negative screening test had a hematological malignancy compared to 5.4% of the patients with a positive screening test having this condition ($p=0.04$). Having been hospitalized in the previous 3 months ($p = 0.00$) and exposure to carbapenem in the 30 days prior to CRE screening ($p < 0.00$) were also significantly associated with the CRE screening test result. While 13.5% of the patients with a positive CRE screening test developed a CRE infection within 30 days, 1.4% of the patients with a negative CRE screening test developed a CRE infection ($p=0.00$) (Table 3).

In a univariate model predicting mortality, a positive CRE screening test result was significantly associated with death where 40.0% of patients who died had a positive CRE test result compared to 10.9% of patients who did not die having a positive test result ($p < 0.00$) (Table 4). Almost three-fourths (74.3%) of the patients who died were male ($p=0.02$) and were ICU patients ($p=0.00$). Higher median Charlson comorbidity index and SOFA scores were also significantly associated with mortality in univariate analyses ($p < 0.00$). Almost half of the patients who died needed vasopressors compared to 13.7% of the patients who did not die ($p < 0.00$). There was no significant association between CRE infection status and mortality ($p = 0.09$) in this patient population (Table 4).

The multivariable model predicting mortality for this high-risk patient population revealed that a positive CRE screening test significantly increased the likelihood of 30-day mortality (adjusted odds ratio [AOR] = 3.06, 95% CI = 1.10–8.51, $p = 0.03$) (Table 5). Patients who had exposure to carbapenem in the 30 days prior to CRE screening were

Table 2 Outcomes of Study Population (n=246)

Variable	n (%)
CRE infection within 30 days from CRE screening date	8 (3.3)
<i>Escherichia coli</i> (n=3)	
<i>Klebsiella pneumoniae</i> (n=5)	
Type of CRE infection (n=8)	
Urinary tract infection	6 (75.0)
Hospital acquired pneumonia	1 (12.5)
Central line-associated bloodstream infection	1 (12.5)
Molecular typing of CRE infection (n=8) ^a	
VIM	1 (12.5)
OXA-48	3 (37.5)
Other	2 (25.0)
Discharged from hospital ^b	188 (78.0)
Death within 30 days	35 (14.2)

Notes: ^anot available for all patients with one patient having more than one CRE infection type including VIM and OXA-48; ^binformation available for n=241 patients.

Abbreviation: CRE, Carbapenem-resistant Enterobacterales.

Table 3 Univariate Analyses of the Associations Between Demographic/Clinical Variables and Positive CRE Screening Test Result

Demographic/Clinical Variable	CRE Screening Test ^a		p-Value
	Positive (n=37)	Negative (n=209)	
Age (years)	56.3 (45.6–70.0)	50.6 (35.0–64.1)	0.03
Charlson comorbidity Index	6.0 (3.0–9.0)	3.0 (2.0–6.0)	<0.01
SOFA Score	4.0 (3.0–8.0)	4.0 (1.0–6.0)	0.05
WBC (10 ⁹ /L)	9.3 (5.5–17.4)	7.8 (5.5–12.1)	0.21
Gender			
Male	20 (54.1)	119 (56.9)	0.74
Female	17 (45.9)	90 (43.1)	
Patient type			
ICU	21 (56.8)	91 (43.8)	0.22
Renal transplant	5 (13.5)	53 (25.5)	
Oncology	11 (29.7)	64 (30.8)	
DM ^b	15 (40.5)	64 (30.6)	0.23
Dementia ^b	3 (8.1)	2 (1.0)	0.03
Hematological malignancy ^b	2 (5.4)	41 (19.6)	0.04
Any underlying immunosuppression	22 (59.5)	114 (54.6)	0.58
Previous hospitalization within 3 months	25 (67.6)	82 (39.2)	<0.01
Need for vasopressors	13 (35.1)	33 (15.8)	0.01
Carbapenem exposure	15 (40.5)	28 (13.4)	<0.01
Mechanical ventilator	6 (16.2)	22 (10.5)	0.40
Central Line	9 (25.0)	26 (12.4)	0.05
Peg tube feeding	2 (5.4)	2 (1.0)	0.11
CRE infection within 30 days of screening date	5 (13.5)	3 (1.4)	<0.01

Notes: ^avalues provided according to statistical test performed with median (IQR) for non-normally distributed variables and n(%) for Chi-sq/Fisher's exact tests; ^bincludes just comorbidities with significant associations; percentages may total > 100 due to rounding.

Abbreviations: SOFA, sequential organ failure assessment; WBC, white blood cell; ICU, intensive care unit; DM, diabetes mellitus; CRE, Carbapenem-resistant Enterobacterales.

Table 4 Univariate Analyses of the Association Between Predictor Variables and Mortality

Predictor	Died ^a		P-Value
	Yes (n=35)	No (n = 211)	
Age (years)	62.1 (45.2–70.0)	50.4 (33.8–64.2)	0.01
Charlson comorbidity Index	7.0 (4.0–9.0)	3.0 (2.0–6.0)	<0.01
SOFA Score	8.0 (4.0–12.0)	4.0 (1.0–5.0)	<0.01
WBC (10 ⁹ /L)	10.0 (4.6–19.0)	7.9 (5.7–11.9)	0.54
Gender			
Male	26 (74.3)	113 (53.6)	0.02
Female	9 (25.7)	98 (46.6)	
Patient type			
ICU	26 (74.3)	86 (41.0)	<0.01
Renal transplant	1 (2.9)	57 (27.1)	
Oncology	8 (22.9)	67 (31.9)	
PVD ^b	6 (17.1)	10 (4.7)	0.02
DM ^b	17 (48.6)	62 (29.4)	0.02
Chronic liver disease ^b	6 (17.1)	7 (3.3)	0.00
Any underlying immunosuppression	22 (62.9)	114 (54.0)	0.33
Previous hospitalization within 3 months	20 (57.1)	87 (41.2)	0.08

(Continued)

Table 4 (Continued).

Predictor	Died ^a		P-Value
	Yes (n=35)	No (n = 211)	
Need for vasopressors	17 (48.6)	29 (13.7)	<0.01
Carbapenem exposure	21 (60.0)	22 (10.4)	<0.01
Mechanical ventilator	7 (20.0)	21 (10.0)	0.09
Central Line	9 (25.7)	26 (12.4)	0.04
Peg tube feeding	1 (2.9)	3 (1.4)	0.46
CRE screening test (positive)	14 (40.0)	23 (10.9)	<0.01
CRE infection within 30 days of screening date	3 (8.6)	5 (2.4)	0.09

Notes: ^avalues provided according to statistical test performed with median (IQR) for non-normally distributed variables and n(%) for Chi-square (Chi-sq)/Fisher's exact tests; ^bincludes just comorbidities with significant associations; percentages may total > 100 due to rounding.

Abbreviations: SOFA, sequential organ failure assessment; WBC, white blood cell; ICU, intensive care unit; PVD, peripheral vascular disease; DM, diabetes mellitus; CRE, Carbapenem-resistant Enterobacterales.

Table 5 Multivariable Analysis Predicting Mortality by CRE Screening Test and Predictor Variables

Predictor	OR	95% CI	p-Value
Age (years)	0.99	(0.96–1.02)	0.41
Gender (female)	0.25	(0.09–0.69)	0.01
Charlson comorbidity Index	1.32	(1.08–1.61)	0.01
CRE screening test (positive)	3.06	(1.10–8.51)	0.03
Carbapenem exposure	6.49	(2.35–17.9)	<0.01
Need for vasopressors	2.76	(0.94–8.04)	0.06
Central line	0.44	(0.13–1.54)	0.20

Abbreviations: CRE, Carbapenem-resistant Enterobacterales; OR, odds ratio; CI, confidence interval.

6.49 times more likely than patients who did not have exposure to carbapenem to die (AOR = 6.49, 95% CI = 2.35–17.9, $p = 0.00$). A one unit increase in Charlson comorbidity score was associated with the odds of death being increased by 32% (AOR = 1.32, 95% CI = 1.08–1.61, $p = 0.01$). Female patients had a 75% decrease in the odds of mortality compared to male patients (AOR = 0.25, 95% CI = 0.09–0.69, $p = 0.01$). (Table 5) The association between CRE screening test result and mortality remained significant when type of patient was included in the multivariable model.

Discussion

The principal findings in this study revealed that a considerable percentage of the high-risk patients included (15.0%) had a positive CRE screening test at the time of hospital and ICU admission. The patients colonized with CRE were significantly more likely to: have dementia; have higher Charlson comorbidity index scores; have been hospitalized within the previous 3 months; have a need for vasopressors; have had previous exposure to Carbapenems; and have developed CRE infection within 30 days of CRE screening. After adjusting for other factors, the relationship between CRE-colonization at the time of hospital admission and 30-day mortality in this patient population remained significant while, in a previous study, the relationship between 90-day mortality and CRE colonization was only significant in univariable analysis.¹² A systematic review, however, showed that colonization or infection by CRE was associated with an overall mortality of 10%.¹⁰

The multivariable model in this study indicated there are several predictors of 30-day mortality in this patient population. As seen in this study, previous studies have shown that Charlson comorbidity index score and previous exposure to carbapenems are predictors of mortality in similar populations of patients either colonized with or infected with CRE.^{10–12,18,19} In this patient population, being female was protective against 30-day mortality. Similar to previous

findings, a significantly higher percentage of patients in the current study colonized with CRE were more likely to develop CRE infection compared to non-colonized patients with the majority of the isolates being OXA-48.¹¹

Baseline surveillance in the form of screening has been recommended to shed light on the epidemiology of CRE in different settings.²⁰ While some institutions have responded to outbreaks with stringent screening programs, other institutions may not have active programs due to limited resources and a lack of clarity for how to implement a screening policy.²⁰ In order to reduce morbidity and mortality associated with this global infectious threat, prevention and control of CRE needs to be improved.^{18,19} Surveillance at the molecular level can provide insight regarding antibiotic resistance and can provide knowledge to inform prevention and control measures.²¹ Based on the CRE screening test findings in this study and previous studies from this region, institutions could benefit from implementing policies to increase CRE screening.^{22–25}

The United States Center of Diseases Control and Prevention (CDC) advises that patients in high-risk hospital settings undergo screening for CRE colonization.²⁶ This strategy has been widely utilized though the outcome on infection control and antimicrobial stewardship remains uncertain and the expenses involved in the screening process are considerable.^{27,28} Some investigators have reported success in controlling infection spread using MDRO screening and using fewer antimicrobials in the United States, Europe, and China.^{29–31}

Similar to findings in this study where a substantial number of patients included had a positive CRE screening test upon hospital admission, a previous study of 338 ICU patients revealed that 28% were colonized with cephalosporin-resistant Enterobacteriaceae or with CRE upon ICU entry.¹² CRE screening is performed using a highly sensitive and specific test to determine whether a patient is colonized with resistant gram-negative organisms.³² Molecular based screening tools provide a means to obtain test results more rapidly and whole genome sequencing allows for identification of organisms through molecular typing.^{33,34} CRE screening may also be helpful in predicting the likelihood of other infections developing including pneumonia, bacteremia, and sepsis in critically ill and transplant patients similar to the patient population in this study.^{35–38}

Rapid identification of molecular typing has major infection control implications to prevent CRE spread within hospitals. In addition, it can help guide antimicrobial therapy. A recent study evaluated a rapid diagnostic algorithm to identify Gram-negative species and detect resistance markers from blood cultures.³⁹ To prevent morbidity and mortality, it is essential to reduce time to results in identifying bacterial type and antimicrobial susceptibility in CRE infections.

The current study has several strengths and limitations. A robust sample size and access to molecular testing for CRE screening and subsequent infection provided further insight into the molecular epidemiology of CRE prevalence in the region. Being able to follow the patients over time upon admission to a tertiary care hospital allowed for observation and collection of possible predictor conditions and the subsequent outcomes of CRE infection and mortality. One limitation was the small number of patients (n=8, 3.3%) that developed CRE infection during the study period with regards to being able to further elucidate the relationship between CRE colonization, infection, and subsequent mortality. Due to the retrospective nature of this cohort study, there may be other covariates that were not measured or not recorded in the medical records that could be associated with CRE colonization, infection, and subsequent 30-day mortality.

In conclusion, our study revealed that a considerable proportion of high-risk patients are colonized with CRE. Additionally, we identified risk factors associated with CRE colonization and their impact on patient outcomes. Although data is still limited in our region, the molecular epidemiology of CRE infection in this region is quite distinct where OXA-48 and NDM are the main genes associated with infection. Further studies are needed in this region and globally to determine the best practices moving forward with regards to CRE screening as a strategy to prevent infection and mortality in high-risk patients.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study proposal was approved by the institutional review board (IRB) of King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia (RAC # 2023-156). Since this was a retrospective study, a waiver for informed consent was granted by the IRB. The data for this study were anonymized and confidentiality was maintained throughout the study in compliance with the Declaration of Helsinki. We can confirm that all organs were donated voluntarily with written informed consent and that all procedures were conducted in accordance with the Declaration of Istanbul.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Vincent J-L. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323. doi:10.1001/jama.2009.1754
2. Kernéis S, Lucet J-C. Controlling the diffusion of multidrug-resistant organisms in intensive care units. *Semin Respir Crit Care Med*. 2019;40(04):558–568. doi:10.1055/s-0039-1696980
3. Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med*. 2009;37(4):1463–1469. doi:10.1097/CCM.0b013e31819ced02
4. Guidelines for control and prevention of CRE infections in healthcare facilities. 2021 Accessed Sep 4, 2021. Available from: <https://www.cdc.gov/hai/organisms/cre/cre-facilities.html>.
5. Patel G, Huprikar S, Sh F, Sg J, Dp C. Outcomes of Carbapenem-Resistant Klebsiella pneumoniae Infection and the Impact of Antimicrobial and Adjunctive Therapies. *Infect Control Hosp Epidemiol*. 2008;29(12):1099–1106. doi:10.1086/592412
6. Nguyen M, Eschenauer GA, Bryan M, et al. Carbapenem-resistant Klebsiella pneumoniae bacteremia: factors correlated with clinical and microbiologic outcomes. *Diagn Microbiol Infect Dis*. 2010;67(2):180–184. doi:10.1016/j.diagmicrobio.2010.02.001
7. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, et al. Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation. *Transpl Infect Dis*. 2012;14(2):198–205. doi:10.1111/j.1399-3062.2011.00688.x
8. Pereira MR, Scully BF, Pouch SM, et al. Risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. *Liver Transpl*. 2015;21(12):1511–1519. doi:10.1002/lt.24207
9. Huprikar S, Casner L, Pierrotti LC, et al. Outcomes associated with carbapenem-resistant Enterobacteriaceae infection after solid organ transplantation in a multicenter study. In: *Program and Abstracts of the 16th American Transplant Congress*. Boston, MA: American Society of Transplant Surgeons and the American Society of Transplantation. 2016
10. Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobacteriaceae: a systematic review. *Am J Infect Control*. 2016;44(5):539–543. doi:10.1016/j.ajic.2015.12.005
11. Dickstein Y, Edelman R, Dror T, Hussein K, Bar-Lavie Y, Paul M. Carbapenem-resistant Enterobacteriaceae colonization and infection in critically ill patients: a retrospective matched cohort comparison with non-carriers. *J Hosp Infect*. 2016;94(1):54–59. doi:10.1016/j.jhin.2016.05.018
12. McConville TH, Sullivan SB, Gomez-Simmonds A, Whittier S, Uhlemann A-C. Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study. *PLoS One*. 2017;12(10):e0186195. doi:10.1371/journal.pone.0186195
13. Casle R, Bianco G, Bastos P, et al. Prevalence and Impact on Mortality of Colonization and Super-Infection by Carbapenem-Resistant Gram-Negative Organisms in COVID-19 hospitalized Patients. *Viruses*. 2023;15(9):1934. doi:10.3390/v15091934
14. Alotaibi F. Carbapenem-Resistant Enterobacteriaceae: an update narrative review from Saudi Arabia. *J Infect Public Health*. 2019;12(4):465–471. doi:10.1016/j.jiph.2019.03.024
15. Alraddadi B, Saedi M, Qutub M, Alshukairi A, Hassanien A, Wali G. Efficacy of ceftazidime-avibactam in the treatment of infections due to Carbapenem-resistant Enterobacteriaceae. *BMC Infect Dis*. 2019;19(1):772. doi:10.1186/s12879-019-4409-1
16. Chitnis AS, Caruthers PS, Rao AK, et al. Outbreak of carbapenem-resistant Enterobacteriaceae at a long-term acute care hospital: sustained reductions in transmission through active surveillance and targeted interventions. *Infect Control Hosp Epidemiol*. 2012;33(10):984–992. doi:10.1086/667738
17. Bianco G, Boattini M, Comini S, et al. Implementation of Chromatic Super CAZ/AVI® medium for active surveillance of ceftazidime-avibactam resistance: preventing the loop from becoming a spiral. *Eur J Clin Microbiol Infect Dis*. 2022;41(9):1165–1171.
18. Gualtero S, Valderrama S, Valencia M, et al. Factors associated with mortality in Infections caused by Carbapenem-resistant Enterobacteriaceae. *J Infect Develop Count*. 2020;14(6):654–659. doi:10.3855/jidc.12267
19. Kassem A, Raed A, Michael T, et al. Risk factors and outcomes of patients colonized with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae. *Infect Control Hosp Epidemiol*. 2020;41(10):1154–1161. doi:10.1017/ice.2020.266
20. Taimur S, Pouch SM, Zubizarreta N, et al. Impact of pre-transplant carbapenem-resistant Enterobacteriales colonization and/or infection on solid organ transplant outcomes. *Clinical Transplant*. 2021;35(4):e14239.
21. Richter S, Marchaim D. Screening for carbapenem-resistant Enterobacteriaceae: who, When, and How? *Virulence*. 2017;8(4):417–426. doi:10.1080/21505594.2016.1255381
22. Ma J, Song X, Li M, et al. Global spread of carbapenem-resistant Enterobacteriaceae: epidemiological features, resistance mechanisms, detection and therapy. *Microbiol Res*. 2023;266:127249. doi:10.1016/j.micres.2022.127249
23. Abdalhamid B, Elhadi N, Alabdulqader N, Alsamman K, Aljindan R. Rates of gastrointestinal tract colonization of carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa in hospitals in Saudi Arabia. *New Microbe and New Infect*. 2016;10:77–83. doi:10.1016/j.nmni.2016.01.014

24. Hala S, Anthony CP, Alshehri M, et al. First report of *Klebsiella quasipneumoniae* harboring *bla_{KPC-2}* in Saudi Arabia. *Antimicrob Resist Infect Control*. 2019;8(1):203. doi:10.1186/s13756-019-0653-9
25. Aldali HJ, Khan A, Alshehri AA, et al. Hospital-Acquired Infections Caused by Carbapenem-Resistant Enterobacteriaceae: an Observational Study. *Microorganisms*. 2023;11(6):1595. doi:10.3390/microorganisms11061595
26. CDC. Multidrug-resistant organisms (MDRO) Management. 2020. Accessed September 4, 2021. Available from: <https://www.cdc.gov/infection-control/guidelines/mdro/index.html>.
27. Diekema DJ, Pfaller MA. Rapid detection of antibiotic-resistant organism carriage for infection prevention. *Clin Infect Dis*. 2013;56(11):1614–1620. doi:10.1093/cid/cit038
28. Bhattacharya S. Early diagnosis of resistant pathogens. *Virulence*. 2013;4(2):172–184. doi:10.4161/viru.23326
29. Weiner LM, Fridkin SK, Aponte-Torres Z, et al. Vital Signs: preventing Antibiotic-Resistant Infections in Hospitals — United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(9):235–241. doi:10.15585/mmwr.mm6509e1
30. Tschudin-Sutter S, Lavigne T, Grundmann H, et al. Differences in infection control and diagnostic measures for multidrug-resistant organisms in the tristate area of France, Germany and Switzerland in 2019 - survey results from the RH(E)IN-CARE network. *Swiss Med Wkly*. 2021;1(151):w20454. doi:10.4414/smww.2021.20454
31. Ma X, Xie J, Yang Y, et al. Antimicrobial stewardship of Chinese ministry of health reduces multidrug-resistant organism isolates in critically ill patients: a pre-post study from a single center. *BMC Infect Dis*. 2016;16(1):704. doi:10.1186/s12879-016-2051-8
32. Eltahlawi RA, Jiman-Fatani A, Gad NM, et al. Detection of Carbapenem-resistant in CRE by Comparative Assessment of RAPIDEC CARBA® NP and Xpert™ Carba-R Assay. *Infect Drug Resist*. 2023;16:1123–1131. doi:10.2147/IDR.S393739
33. Tenover FC, Canton R, Kop J, et al. Detection of colonization by carbapenemase-producing gram-negative bacilli in patients by use of the xpert mdro assay. *J Clin Microbiol*. 2013;51(11):3780–3787. doi:10.1128/JCM.01092-13
34. Facility guidance for control of Carbapenem-resistant Enterobacteriaceae (Cre): November 2015 update - CRE toolkit. Accessed Sep 12, 2022. Available from: <https://stacks.cdc.gov/view/cdc/79104>.
35. Forde BM, Bergh H, Cuddihy T, et al. Clinical implementation of routine whole-genome sequencing for hospital infection control of multi-drug resistant pathogens. *Clin Infect Dis*. 2022;3:ciac726.
36. Yang G-T, Tzeng I-S, Shui H-A, et al. Early screening of risk for multidrug-resistant organisms in the emergency department in patients with pneumonia and early septic shock: single-center, retrospective cohort study. *Shock*. 2021;55(2):198–209. doi:10.1097/SHK.0000000000001599
37. Mascitti H, Duran C, Nemo E-M, et al. Factors associated with bacteraemia due to multidrug-resistant organisms among bacteraemic patients with multidrug-resistant organism carriage: a case control study. *Antimicrob Resist Infect Control*. 2018;7(1):116. doi:10.1186/s13756-018-0412-3
38. Zhou Y, Yu F, Yu Y, Zhang Y, Jiang Y. Clinical significance of MDRO screening and infection risk factor analysis in the ICU. *Am J Transl Res*. 2021;13(4):3717–3723.
39. Comini S, Bianco G, Boattini M, et al. Evaluation of a diagnostic algorithm for rapid identification of Gram-negative species and detection of extended-spectrum β -lactamase and carbapenemase directly from blood cultures. *J Antimicrob Chemother*. 2022;77(10):2632–2641. doi:10.1093/jac/dkac230

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