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ORIGINAL RESEARCH

Evaluating the Clinical Benefit of Carbapenem-Resistant *Enterobacteriaceae* Screening in a Tertiary Care Center in Saudi Arabia

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Background: Limited data exist regarding the risk of infection in patients who test positive during Carbapenem-resistant *Enterobacteriaceae* (CRE) screening. This study evaluates the clinical impact of CRE screening on infection risk and outcomes in patients with positive screening results.

Objective: Compare CRE infection rates between patients with positive and negative CRE screening results.

Design: Retrospective, non-experimental descriptive cohort study.

Study Setting: Conducted at King Faisal Specialist Hospital and Research Center (KFSHRC), a tertiary care center in Madinah, Saudi Arabia.

Subjects and Methods: Over one year, 1070 admitted patients were screened for CRE. Propensity score matching was used to create comparable cohorts of positive and negative screening patients. The study compared the subsequent CRE infection risk, 90-day mortality, total days of hospitalization, ICU admissions, and duration of antibiotic treatment in patients who tested positive for CRE.

Main Outcome Measures: CRE infection rates among patients with positive and negative screening results.

Results: Propensity score matching resulted in 66 patients with positive CRE screens matched to 133 negative-screen patients. Of those who screened positive, 35% developed a confirmed CRE infection during their hospital stay, compared to 4.6% in the negative group. CRE-positive patients experienced longer hospital stays (mean 21.2 vs 14.7 days, $p < 0.001$), higher readmission rates (38% vs 19%, $p = 0.004$), and increased mortality (24% vs 11%, $p = 0.019$). No significant differences were noted in ICU admission rates.

Conclusion: Nearly one-third of patients with positive CRE screening results were at risk of developing subsequent CRE infections. Additionally, positive CRE screening was associated with higher mortality.

Limitations: Small sample size and potential selection bias due to screening being performed only in ICU-required patients, potentially skewing results toward poorer outcomes. Findings apply only to hospitalized patients.

Plain Language Summary: This study investigated the impact of screening for Carbapenem-resistant *Enterobacteriaceae* (CRE), which is a type of antibiotic-resistant bacteria, at King Faisal Specialist Hospital and Research Center in Saudi Arabia. The researchers found that patients who tested positive for CRE were more likely to develop serious infections, have longer hospital stays, and face a higher risk of death compared to those who tested negative. These findings highlight the importance of screening in identifying patients who require special care to prevent complications. While the study offers valuable insights, more research is needed to improve how we manage these patients and reduce the spread of CRE in healthcare settings.

Keywords: CRE, infection, outcome, risk, screening, Saudi Arabia

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Introduction

Antimicrobial resistance remains a significant medical and public health challenge worldwide, including in the Middle East.[1] The Centers for Disease Control and Prevention (CDC) has updated the definition of Carbapenem-resistant *Enterobacteriaceae* (CRE) to include organisms that are non-susceptible to imipenem, meropenem, doripenem, and ertapenem, as well as documented isolates that produce a carbapenemase. A variety of species within the *Enterobacteriaceae* family, such as *Klebsiella pneumoniae, Citrobacter freundii, Escherichia coli, Acinetobacter baumannii*, and *Enterobacter aerogenes*, have been identified as carrying carbapenemases.[2]

Infections caused by CRE pose a significant healthcare challenge as these isolates are often extensively drug resistant and linked to high rates of morbidity and mortality.[3,4] In addition, studies have found colonization to be a prerequisite for infection.[5]

The World Health Organization (WHO) and the CDC reported the current and future threat of infections by antimicrobial-resistant microorganisms with a high level of concern.[6,7] Annually, CRE results in 1100 deaths and 13,100 infections in the USA,[7] with a high proportion of these infections likely resulting in death due to limited antibiotic therapies.[7,8]

Screening is a crucial component of infection control measures to prevent the spread of carbapenem-resistant organisms in both acute and long-term care facilities.[9] Data from Saudi Arabia mainly focused on the prevalence of CRE and identifying risk factors for colonization or infection with CRE.[1,10,11] A study conducted across 11 hospitals in the Gulf Cooperation Council countries assessed rectally screened CRE patients admitted to the intensive care units (ICU) for risk factors, but it did not evaluate infection rates or mortality.[12]

There are limited data in the region detailing the CRE infection rate in CRE-screened patients. The authors thus conducted this study to evaluate the clinical impact of CRE screening on infection risk and outcomes for those with positive CRE results.

Methods

Study Design

This research was a retrospective cohort study conducted at the King Faisal Specialist Hospital and Research Center (KFSHRC), a tertiary care center located in Madinah, Saudi Arabia.

As of the end of 2022, KFSHRC's policy mandated automatic screening for multidrug-resistant organisms (MDROs), with the aim to specifically target CRE, vancomycin-resistant *Enterococcus*, and methicillin-resistant *Staphylococcus aureus*. This policy applies to all new admissions or transfers of inpatient encounters to both adult and pediatric ICUs as well as to oncology. If a patient does not have any MDRO results documented in the seven days prior to admission, a screening order will be automatically triggered upon their admission to either the ICU or oncology. All eligible patients for inclusion were adult patients who were screened for CRE between January 1, 2023 and December 31, 2023. Researchers then compared the positively screened patients with a propensity score matched with the negatively screened patients.

Researchers performed CRE screenings using the Xpert® Carba-R, the KFSHRC's preferred screening test. This test, utilizing an automated real-time polymerase chain reaction and performed on the GeneXpert® Instrument Systems, is a qualitative in vitro diagnostic test designed for the detection and differentiation of the blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP gene sequences that are associated with carbapenem-nonsusceptibility.

The Institutional Review Board (IRB) at KFSHRC (RAC No: 2231317) approved this study. The IRB waived written informed consent because the study was a retrospective chart review that involves minimal risk to the subjects. The study data were anonymized and therefore compliant with the Declaration of Helsinki's mandate to maintain the confidentiality of patient data.

Propensity Score Matching

We employed propensity score methods to create a matched cohort of positively and negatively screened patients. To estimate the propensity score of each patient, a logistic regression model used to predict the probability of a positive screening result. The variables included in the logistic regression model were age, gender, and primary disease. The estimated propensity scores for each patient from the logistic regression model were then used to perform 1:2 matching

based on the nearest neighbor method without replacement, using calipers of width equal to 0.2 standard deviations of the estimated propensity score.[13]

Outcomes Measurement

The primary research question of this study was to compare the CRE infection rate between CRE screening-positive and CRE screening-negative patients. The secondary line of inquiry was to compare the population with positive CRE screening to the population with negative screening for 90-day mortality, cumulative days of admission, ICU admissions, and days of antibiotics in CRE culture-positive patients. Researchers also included demographic information for both groups and evaluated the risk factors for CRE infection among those who tested positive in their rectal screenings.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics including medians, means, standard deviations, counts, and proportions. The sensitivity of the CRE screening was calculated as the proportion of positive screens among those with confirmed CRE-CRPA cultures, and the specificity was determined as the proportion of negative screens among those without confirmed CRE-CRPA cultures. Researchers used nonparametric Mann–Whitney tests to compare the average antibiotic days and length of hospital stay between positive and negatively screened patients and employed Pearson's Chi-squared tests of independence to compare differences in hospital readmission, ICU admission, and mortality between the two groups. The level of significance was set at $P < 0.05$ for all statistical analyses, and all reported P values reflected two-tailed tests. All analyses were conducted using R 4.3.0 statistical programming.[14]

Results

During the study period, a total of 1070 patients were screened for CRE. There were 66 (6.2%) positive CRE screens. Propensity score matching yielded 66 patients with positive CRE screens corresponding to 133 negative screen patients based on age, gender, and primary disease, forming the analytic cohort.

Overall, the mean age of the cohort was 61 ± 18 years, with slightly more males than females (47% female, 53% male). Nearly half of patients were nonimmunocompromised (49%), 33% had a primary disease of oncology/malignancy, and 18% had hematologic conditions. Half of the patients had cardiovascular disease, and just over one-third had diabetes. The positive CRE screening group was similar to the negative screening group in terms of age, sex, and primary disease, suggesting that the propensity score model was adequate in creating comparable groups (Table 1).

Table 1 Demographic and Other Characteristics of the Analytic Cohort

Characteristic	Negative Screen, N = 133	Positive Screen, N = 66 [⊥]	*P*-value [‖]
Age, years	62 (51, 74)	59 (50, 71)	0.6
Sex			0.2
Female	58 (44%)	35 (53%)	
Male	75 (56%)	31 (47%)	
Primary disease			0.4
Nonimmunocompromised	68 (51%)	29 (44%)	
Oncology/Malignancy	44 (33%)	22 (33%)	
Hematology	21 (16%)	15 (23%)	
Comorbidities			
Cardiovascular disease	64 (48%)	35 (53%)	0.5
Diabetes	49 (37%)	23 (35%)	0.8
Renal disease	11 (8.3%)	11 (17%)	0.075
Liver disease	3 (2.3%)	8 (12%)	**0.007**
Lung disease	21 (16%)	11 (17%)	0.9
Rheumatic disease	4 (3.0%)	2 (3.0%)	>0.9

Notes: [⊥] Number of positive CRE screened patients. [‖] Indicates *P*-value. P-values (bold indicate significant, * \ 0.05, ** \ 0.0001).

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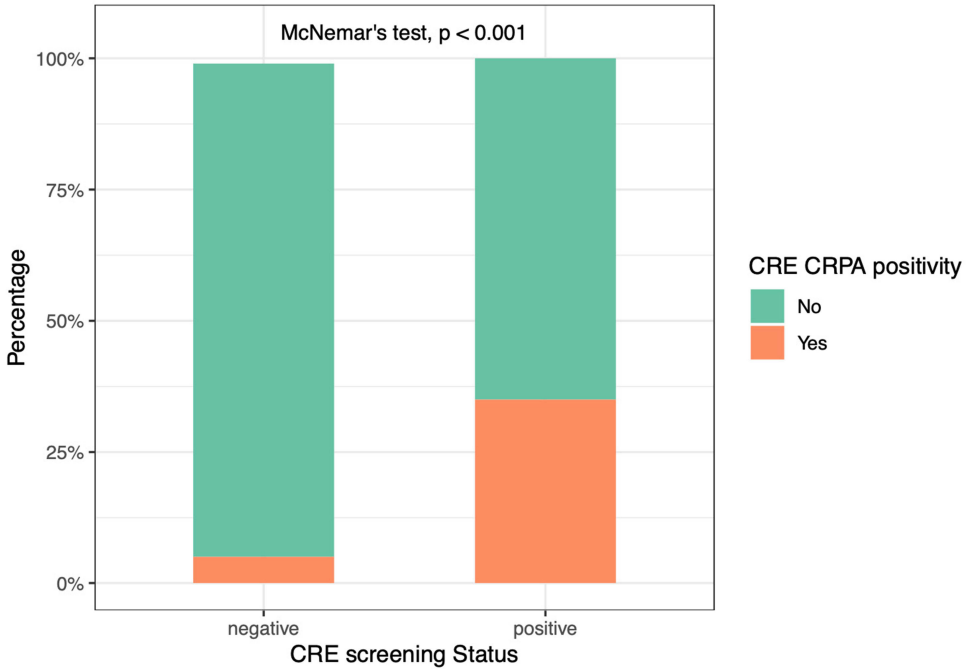

Figure 1 CRE Infection Rates in Screen-Positive vs Screen-Negative Patients. Proportion of patients with confirmed carbapenem-resistant Enterobacteriaceae (CRE) infection among those with positive rectal screening (n = 66) versus those with negative screening (n = 133). CRE-positive patients had significantly higher infection rates (35%) compared to screen-negative patients (4.6%) (p < 0.001). Percentages reflect infections confirmed during hospitalization.
Abbreviation: CRE, carbapenem-resistant Enterobacteriaceae.

Among patients who screened positive, 35% (23 patients) had a confirmed positive CRE culture during their admission compared to 4.6% (6 patients) in the group that screened negative (p-value <0.001) (Figure 1).

Most positive cultures (87%) were classified as infections rather than colonizations. *Klebsiella pneumoniae* was the most common (69%) isolated bacteria followed by *Pseudomonas aeruginosa* (17%). The infectious syndrome suspected on admission was bacteremia in nearly half of the patients, while urinary tract infection was suspected in 41% of patients (Table 2). Two genes were associated with CRE infection: NDM and OXA-48. Researchers noted no other genes in the CRE-infected patients. One patient had both genes.

Researchers performed a further analysis of the established risk factors for those with positive CRE results and found that nearly 78% of the patients who screened positive for CRE had a history of previous hospitalization. Further, 45% of these patients had a urinary catheter.

Table 2 Additional Details for CRE-Infected Patients

	N = 29 ‡
Micro-organism isolated	
Klebsiella pneumoniae	20 (69%)
Pseudomonas aeruginosa	5 (17%)
Proteus mirabilis	3 (10%)
Escherichia coli	2 (6.9%)
Enterobacter cloacae	1 (3.4%)
Site of the culture	
Respiratory	7 (24%)
Skin	6 (21%)
Urine	6 (21%)

(*Continued*)

Table 2 (Continued).

	N = 29 ‡
Blood	4 (14%)
Other	4 (14%)
Gastrointestinal	2 (6.9%)
Suspected diagnosis on admission	
Bacteremia	14 (48%)
Urinary tract	12 (41%)
Respiratory tract	10 (34%)
Gastrointestinal	5 (17%)
Skin and soft tissue	1 (3.4%)
Bone joint	1 (3.4%)
Febrile neutropenia	1 (3.4%)
Empirical treatment	1 (3.4%)
Carbapenemase Genes	
OXA-48 gene	16 (55%)
NDM gene	14 (48%)

Note: ‡ n (%).

Table 3 Comparison of Outcomes Between the Positive and Negative Screened Groups

Outcome	Negative Screen, N = 133	Positive Screen, N = 66 ⊥	*P*-Value ‖
Mean length of hospital stay (SD)	14.7 (19.5)	21.2 (21.6)	**<0.001**
Hospital readmission, n (%)	25 (19%)	25 (38%)	**0.004**
ICU admission, n (%)	54 (41%)	27 (41%)	>0.9
Mortality, n (%)	15 (11%)	16 (24%)	**0.019**

Notes: ⊥ Number of positive CRE screened patients. ‖ Indicates *P*-value. P-values (bold indicate significant, * \ 0.05, ** \ 0.0001).

Positive CRE-screened patients had on average a longer hospital stay (mean 14.7 vs 21.2, p <0.001), were more likely to be re-admitted to the hospital (19% vs 38%, p = 0.004), and had a higher mortality rate (11% vs 24%, p = 0.019) than the negative CRE-screened group (Table 3). The difference in ICU admission rates was not statistically significant between the two groups.

Researchers compared the therapy duration for CRE-infected patients who screened positive and negative and found no significant difference between the two groups (median 11 vs 14 days).

Discussion

In this retrospective matched control study, researchers found that 35% of patients who tested positive during CRE screening subsequently had a confirmed positive CRE culture during their hospital admission. Notably, the genetic pattern of resistance is consistent with the most commonly identified carbapenemase in the Gulf region and Saudi Arabia, NDM and OXA-48, with both representing approximately half of the cases each in this study.[1] Further, a positive CRE screening result was linked to an extended hospital stay, an increased likelihood of readmission, and elevated mortality rates.

There is limited evidence in extant literature regarding the risk of developing infections among patients with positive CRE results. In one study involving patients with positive CRE results,[15] the infection rate for Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) was 9% among 464 patients with CRKP rectal colonization. This study's data not only focused on CRE infection among those with positive screening results but also discovered a 4.6% infection rate among those with negative screening results; this may be attributable to hospital-acquired infections. A systematic review of 10

studies[16] involving heterogeneous populations (four in ICU patients and one in liver transplant patients) reported a variable risk of CRE infection, with rates ranging from 7.6% to 44.4%; the overall percentage from the review was 16.5%.

The observed infection rate in this study (20 of the 66, 30%) was much higher, possibly due to a selection bias associated with the KFSHRC requirement of CRE screening before ICU admissions. These findings suggest that clinicians carefully consider initiating empirical CRE-targeted treatment in patients with possible or confirmed sepsis who have screened positive, while awaiting microbiological culture results. However, further studies are essential before establishing definitive recommendations.

The difference in mortality rate in this study versus previous studies is noteworthy. In this study, the overall mortality among patients with positive CRE results was 24%. Three previous studies that reported mortality rates for patients with clinical infection or colonization found a range of 30% to 75%.[15,17,18] These poor outcomes can be attributed, in part, to the underlying comorbidities and severity of illness in these patients. It should be noted that CRE infections disproportionately affect vulnerable populations, such as immunocompromised individuals, critically ill patients, and those with chronic medical conditions, all of whom often have significant healthcare exposure. Given the high mortality rate associated with CRE infections and the challenges in treatment, further research is needed to develop strategies aimed at eliminating CRE colonization.[16] Two studies in this study's review of the literature have touched on potential decolonization strategies that showed some efficacy in eradicating the CRE colonization.[19,20]

The use of contact precautions is critical in preventing the transmission of multidrug-resistant organisms (MDROs) and remains a cornerstone of infection control programs. Unidentified colonized patients can act as potential reservoirs for MDRO transmission.[21] While combining active screening cultures with contact precautions has been shown to lead to sustained reductions in CRE incidence,[22,23] current guidelines from the WHO and the European Society of Clinical Microbiology and Infectious Diseases do not recommend active screening as a primary strategy for preventing the spread of CRE in healthcare settings.[24,25]

Rather than relying on the single intervention of CRE screening, effective prevention requires a multifaceted approach. Outcomes observed in randomized controlled trials may differ from real-world practice, where the efficacy of interventions may be lower due to strict and high compliance settings. It is important to note that some patients who screened negative still developed CRE infections.

There is a notable gap in the literature regarding the relationship between CRE colonization and mortality, particularly in more homogeneous populations such as immunocompromised patients. This study had the additional strength of including admitted patients who were mainly immunocompromised. A key limitation in this study is the small sample size and the ICU admission-required screening, which may have introduced selection bias. By enrolling sicker patients, the results may reflect poorer outcomes, potentially skewing the findings. Moreover, the study's conclusions apply only to hospitalized patients; general screening for CRE in individuals not requiring admission as an outpatient setting may be less meaningful or relevant to produced results.

Conclusion

This study found that nearly one-third of the patients who tested positive for CRE were at an increased risk of subsequent infections and had a higher mortality rate. These results highlight the importance of CRE screening in identifying at-risk patients and the need for proactive management to improve outcomes and reduce mortality.

Disclosure

The authors report no conflicts of interest in this work.

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