ORIGINAL ARTICLE

Clinical Predispositions, Features, and Outcomes of Infections with Carbapenem-resistant *Enterobacterales* among Critical Care Patients

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Abstract

Background: Carbapenem-resistant *Enterobacterales* (CRE) infections pose a significant global public health threat. We aimed to assess the risk variables, clinical characteristics, and outcomes of CRE-caused infections in criticalcare patients.

Patients and methods: This prospective study enrolled 181 adult patients infected with *Enterobacterales* in the intensive care unit (ICU). Patients underwent clinical assessment and monitoring throughout their ICU stay. Carbapenem resistance was identified through antibiotic susceptibility testing and multiplex molecular detection of carbapenemase-encoding genes.

Results: The mean age of patients was 67.99 ± 12.89 years, with 71.3% being males. Of 181 patients, 111 (61.3%) were found to have CRE infections, including 39 *Klebsiella pneumoniae* and 31 *Escherichia coli* isolates. The CRE isolates showed the predominance of the *OXA-48* (74.8%), followed by the *NewDelhi Metallobetalactamase (NDM) carbapenemase* genes (20.7%). The risk factors associated with CRE infection included high sequential organ failure assessment (SOFA) score, prolonged length of stay (LOS) in ICU, prior use of broad-spectrum antimicrobials, hemodialysis, plasma exchange, and prolonged mechanical ventilation. Carbapenem-resistant *Enterobacterales* infections significantly required longer LOS, more need for mechanical ventilation, and exhibited lower rates of bacterial elimination than carbapenem-susceptible *Enterobacterales* (CSE) infections. The type of resistance gene did not significantly influence the mortality rate among CRE patients. The successful treatment of *OXA-48*-positive CRE showed a strong correlation with tigecycline and colistin antibiotics.

Conclusion: Carbapenem-resistant *Enterobacterales* infection in ICU patients was associated with adverse outcomes. Identification of high-risk patients is essential for early diagnosis and appropriate management. Therefore, it is crucial to improve infection control methods and implement antimicrobial stewardship to avoid spreading infections.

Keywords: Carbapenemase, Carbapenem-resistant *Enterobacterales*, *NDM* gene, Outcome, *OXA-48* gene, Risk factors.

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Highlights

- More than half of intensivecare unit (ICU) patients had infections with carbapenem-resistant *Enterobacterales* (CRE). *OXA-48* and *NDM* were the main underlying resistance genes
- Carbapenem-resistant *Enterobacterales* infections were associated with extended length of stay (LOS), prolonged mechanical ventilation, and previous antibiotic use
- Patients with CRE infections exhibited significant adverse outcomes

Introduction

Carbapenem-resistant *Enterobacterales* (CRE) is a prevalent group of bacteriological agents that commonly cause severe infections in hospitals and communities. The primary treatment for these infections is beta-lactam antimicrobial drugs.[1,2] Carbapenems are regarded as the most potent drugs of all Beta-lactams, exhibiting the broadest spectrum.[2] The production of enzymes, such as carbapenemases, can mediate the resistance of CRE to beta-lactam and carbapenem drugs. The encoding genes for these enzymes can be horizontally transferred across bacteria, resulting in the propagation of resistance to multiple antimicrobials.[3] Globally; there is a persistent increase in CRE infections that produce carbapenemases, which can pose severe threats to public health.[4]

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Carbapenem-resistant *Enterobacterales* often have few treatment options since they are resistant to all B-lactam drugs.[5,6] Tetracycline and polymyxins remain effective in combating the

majority of CRE strains. Antibiotic combinations such as ceftazidime-avibactam, along with other antibiotics such as aminoglycosides and quinolones, are considered effective treatment options for the klebsiella pneumoniae carabapenemase (KPC) and *OXA-48* carbapenemase-producing *Enterobacterales*. Nevertheless, those antibiotics are still not effective against CRE, which are *NDM*-producers.[7] Due to the poor response to the available antibiotics; prior studies on patients infected with CRE have shown mortality rates up to 65%.[8] Thus, the presence and spread of CRE infections pose considerable threats, particularly for highly vulnerable patients in the intensive care units (ICU).

Several studies conducted in Egypt have shown a continuous rise in the frequencies of extended-spectrum beta-lactamase (ESBL) and CRE infections in Egyptian hospitals and ICUs.[9] Determining the risk variables can steer early diagnosis, treatment, and prevention of CRE infections. Multiple studies conducted in various countries have found that factors such as prolonged hospital stays, indwelling medical devices, ICU hospitalizations, and previous antibiotic exposure have been implicated in aggravating the risk of contracting CRE infection.[10–12] However, there is a paucity of data regarding the predisposing factors and consequences of CRE infections in Egypt. Therefore, this study aimed to determine the clinical predispositions, features, and outcomes of CRE infections in an ICU of a tertiary-care hospital in Egypt.

Methodology

Study Population

This prospective cohort study was carried out on adult intensive-care unit (ICU) patients in Cairo University Hospital, Egypt, in the period between January 1, 2021, and December 31, 2022. The study included ICU adult patients who had *Enterobacterales* infections represented by positive microbial culture with Enterobacterales microorganisms. The study excluded patients with infections caused by other types of microorganisms. Enrolled patients were clinically managed by the standard clinical protocols. The isolated *Enterobacterales* in culture were subjected to phenotypic susceptibility to antimicrobials including carbapenem antibiotics to identify CRE, as well as concomitant molecular detection of underlying genetic determinants of carbapenem resistance using multiplex PCR.

Ethical Approval

The Research Ethics Committee of the Faculty of Medicine, Cairo University (N13-2020) approved the study. The study adhered to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Patients or their first-degree family members provided informed written consent. Each patient was assigned a distinct identification number to ensure his or her confidentiality.

Microbiological Investigations

Microbiological cultures were performed on all patients admitted to ICU, according to the standard microbiological procedures. *Enterobacterales* bacterial identification and antimicrobial susceptibility testing were carried out using the VITEK-2 system (Biomerieux, France). The study only included patients having infections with *Enterobacterales*, where only the first isolate obtained from each patient was considered for further microbiological investigations. The antimicrobial susceptibility results were determined according to the interpretative guidelines of the Clinical Laboratory Standards Institute.[13] Carbapenem-resistant *Enterobacterale* infections were defined as infections caused by *Enterobacterales* bacteria resistant to imipenem, meropenem, or ertapenem.[13] All isolated carbapenem-resistant and carbapenem-susceptible *Enterobacterales* (CRE and CSE) were tested for the presence of carbapenemase encoding genes using multiplex polymerase chain reaction (PCR), following the procedure previously described by Poirel et al.[14]

Clinical Assessment

Upon admission, patients were clinically evaluated and continuously monitored during their ICU stay. In addition, upon admission to the ICU, data was collected regarding the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA), patient's demographics, medical diagnosis, underlying morbidities, immune condition, history of antibiotic intake within the previous 90 days and history of previous surgeries or admissions to healthcare facilities within the last 30 days. These factors may contribute as predisposing factors for the acquisition of antimicrobial resistance.[10–12] For assessing the clinical course, data was collected on vital signs, laboratory test results, the use of vasopressors, the length of stay (LOS) in the ICU, and the time gap between successive admissions. Several metrics reflecting the clinical outcome were utilized, including the number of days spent in the ICU, duration of mechanical ventilation, estimations of bacterial elimination by negative cultures, and rates of 7-day and 14-day survival.[10–12]

Statistical Analysis

The SPSS software, version 26.0, was used for data analysis. Univariate and multivariate analyses were performed to evaluate the variations between the carbapenem-sensitive (CSE) and CRE groups. The Kaplan–Meier statistical method was utilized to analyze survival. Additionally, the differences in survival curves between the CRE and CSE groups were assessed using the log-rank test.[15]

Results

The study enrolled a total of 181 patients infected with *Enterobacterales*. The mean age of patients was 67.99 ± 12.89 years, 71.3% of whom were males. *Klebsiella pneumoniae* ($n = 150$) and *E. coli* ($n = 31$) constituted 82.9 and 17.1% of the causative *Enterobacterales*, respectively. We identified CRE at an overall rate of 61.3% ($n = 111$). All were *K. pneumoniae* isolates, while CSE was identified at a rate of 38.6% ($n = 70$) in the form of *K. pneumoniae* ($n = 39$) and *E. coli* ($n = 31$). Carbapenem-resistant *Enterobacterales* genes were identified in all CRE isolates, while no genes were identified in CSE isolates. The detected CRE genes included *OXA-48* (74.8%), *NDM* (20.7%), and both *NDM* and *OXA-48* (4.5%) (Fig. 1).

When comparing the demographic data and comorbidities of patients with CRE and CSE, there was no significant difference in age. However, there was a significantly higher percentage of males among CSE patients. The CRE cohort had significantly higher rates of smoking, diabetes, COPD, and ESRD, while CSE patients had higher rates of heart disease and glucocorticoid use. Patient demographics and history are depicted in Table 1.

By comparing risk factors, the APACHE score was significantly higher in the CSE group, especially among patients infected with *E. coli*. Conversely, the SOFA score was significantly higher for CRE patients. Patients admitted with trauma, septic shock, stroke, and respiratory failure were at higher risk for infection with CRE. In contrast, COVID-19 pneumonia was significantly more prevalent among the CSE group. The CRE group significantly required

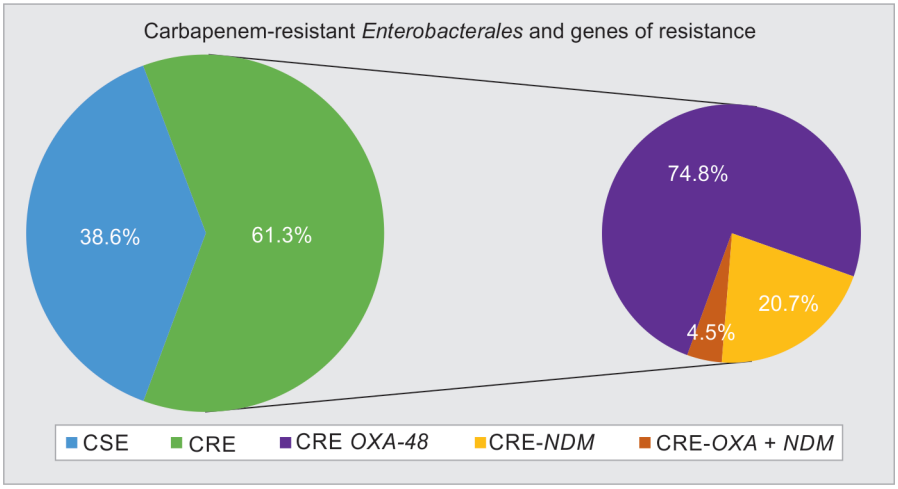

Fig. 1: Proportions of CRE and genes of resistance

Table 1: Demographic and past history data of patients in the CRE and CSE groups

	CRE (n = 111) and encoding genes			*CSE (n = 70)*				
Patient data	*OXA-48 (n = 83)*	*NDM (n = 23)*	*OXA-48 + NDM (n = 5)*	*Klebsiella pneumoniae (n = 39)*	*E. coli (n = 31)*	*Total CRE (n = 111)*	*Total CSE (n = 70)*	*p-value*
Age	67 ± 13.4	67.5 ± 20.8	67 ± 0	67.4 ± 13.8	71.2 ± 6.4	67.1 ± 14.9	69.4 ± 8.8	0.236
Sex								
Male *n* (%)	48 (57.8)	19 (82.6)	1 (20)	36 (92.3)	21 (67.7)	68 (61)	57 (81.4)	0.004
Female *n* (%)	35 (42.2)	4 (17.4)	4 (80)	3 (7.7)	10 (32.3)	43 (39)	13 (18.6)	
Past history								
Smoking *n* (%)	8 (9.6)	5 (21.7)	0	0	0	13 (11.7)	0	0.003
Diabetes mellitus *n* (%)	70 (84.3)	17 (73.9)	5 (100)	38 (97.4)	11 (35.5)	92 (82.8)	49 (70)	0.042
Hypertension *n* (%)	58 (69.9)	10 (43.5)	5 (100)	33 (84.6)	21 (67.7)	73 (65.7)	54 (77.1)	0.103
Lung disease								
BA *n* (%)	5 (6)	0	0	0	2 (6.5)	5 (4.5)	2 (2.8)	0.576
COPD *n* (%)	4 (4.8)	4 (17.4)	0	0	0	8 (7.2)	0	0.022
IPF *n* (%)	1 (1.2)	0	0	0	0	1 (0.9)	0	0.426
Heart disease								
Heart failure *n* (%)	11 (13.3)	4 (17.4)	0	10 (25.6)	18 (58.1)	15 (13.5)	28 (40)	<0.001
IHD *n* (%)	18 (21.7)	1 (4.3)	1 (20)	22 (56.4)	20 (64.5)	20 (18)	42 (60)	<0.001
Renal disease								
CKD *n* (%)	4 (4.8)	0	1 (20)	0	0	5 (4.5)	0	0.072
ESRD *n* (%)	36 (43.4)	13 (56.6)	4 (80)	10 (25.6)	2 (6.5)	53 (47.7)	12 (17.1)	<0.001
Immune status								
Immuno-compromised *n* (%)	0	0	0	0	1 (3.2)	0	1 (1.4)	0.207
Glucocorticoids *n* (%)	9 (10.8)	0	1 (20)	17 (43.6)	8 (25.8)	10 (9)	25 (35.7)	<0.001
Immunosuppressives *n* (%)	2 (2.40)	0	0	0	2 (6.5)	2 (1.8)	2 (2.8)	0.638
Surgical history *n* (%)	8 (9.6)	1 (4.3)	0	9 (23.1)	1 (3.2)	9 (8.1)	10 (14.3)	0.187
Liver cell failure *n* (%)	3 (3.6)	1 (4.3)	0	0	0	4 (3.6)	0	0.108
Solid organ tumor (RCC) *n* (%)	1 (1.2)	0	0	0	0	1 (0.9)	0	0.425
Previous hospitalization *n* (%)	6 (7.2)	0	0	4 (10.3)	0	6 (5.4)	4 (5.7)	0.929

BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRE, carbapenem-resistant *Enterobacterales*; CSE, carbapenem-susceptible *Enterobacterales;* ESRD, end-stage renal disease; IHD, ischemic heart disease; IPF, interstitial pulmonary fibrosis; RCC, renal cell carcinoma; previous hospitalization and surgical history (in the past 30 days)

hemodialysis, plasma exchange, cavity drainage, and repeated blood transfusions. No significant difference was detected regarding the LOS in the ICU before infection. Table 2 shows that the CRE group had a significantly higher percentage of prior use of quinolones, meropenem, and extended-spectrum cephalosporins, along with a lower percentage of macrolides, vancomycin, and metronidazole. Univariate regression analysis revealed that male sex and having comorbidities were identified as independent risk factors for contracting CRE in ICU patients. Based on both univariate and multivariate regression analysis, the risk factors identified were a high SOFA score, prolonged LOS in the ICU, prior use of antimicrobials with a broad gram-negative spectrum, hemodialysis and plasma exchange, and prolonged duration of mechanical ventilation (Table 3).

Regarding the clinical course of patients after diagnosis of infection, the CRE group broadly had a worse clinical course, more use of vasopressors, lower hemoglobin concentration, platelet count and white blood cells (WBCs) count, and higher levels of D-dimer, serum creatinine, C-reactive protein (CRP) and procalcitonin (Table 4). Regarding the outcome of infection, patients infected with CRE required significantly longer LOS in the ICU and more mechanical ventilation, along with a lower percentage of bacterial clearance. The mean and median survival days for the patients with CRE were 8.93 and 7, respectively, compared to 6.88 and 7, for the CSE patients. Tigecycline, colistin, and ceftazidime/avibactam, whether monotherapy or in combination with carbapenems, were associated with significantly fewer ICU days ($p < 0.001$), fewer mechanical ventilation days ($p = 0.002$) and a higher percentage of bacterial clearance ($p < 0.001$) in CRE patients with the *OXA-48* gene. Furthermore, CRE patients with the *NDM* gene and multiple resistance genes exhibited less favorable outcomes compared to those with the *OXA-48* gene. Mortality rates were 62.2 and 55.7% for CRE and CSE, respectively. No statistically significant differences in the mortality rate were detected between the two groups or according to the type of carbapenemase genes. However, infection with *E. coli* was associated with a significant survival rate compared to *K. pneumoniae* (Table 5 and Fig. 2).

Discussion

With the aggravated incursion of antimicrobial resistance on a global scale, the CRE is listed among the urgent, threatening superbugs to public health.[16] In the present study; we identified carbapenem resistance (CR) at a rate of 61.3% among total collected *Enterobacterales* causing infections in critical care unit patients. Our data validate earlier studies that have reported a significant prevalence of CRE in Egypt, reaching 47.9%.[9] Consistent with our findings, previous studies in Egypt reported carbapenem resistance among *Enterobacterales* at high rates of 62.7 and 40%.[17,18] However, lower rates (6.5–34.1%) were recorded in other studies.[19–21] The differences in CR rates can be attributed to geographical variations, disparities in the type of specimens, bacterial species, and other influencing factors such as duration of hospital stay, adherence to infection control measures, and implemented antibiotic policies in different healthcare centers.[19] Carbapenem resistance was recorded at rates of 15 and 11.4% in neighboring countries of the Arab Gulf region and North Africa, respectively.[22,23] Those rates are comparable to the officially declared percentages in other Arab, African, and Asian countries.[24–26] In our study, we observed that critical care units are often the main sources of antimicrobial-resistant superbugs, particularly CRE. This is primarily due to the aggressive antibiotics utilization, high exposure to invasive devices, and the vulnerability of patients' health conditions.[19] These factors can explain the high-observed CRE rates in our study, which aligns with former reports on the highest rates of CRE recovery in ICUs.[9,19]

Klebsiella pneumoniae and E. coli are the primary members of multidrug-resistant *Enterobacterales,* responsible for causing infections.[27] In our study, *K. pneumoniae* represented the majority of identified *Enterobacterales* (82.9%), which is consistent with other studies reporting the high prevalence of *Klebsiella* in ICU infections.[28] All detected CRE were of *K. pneumoniae* (100%), where no CR was detected among *E. coli* isolates. These findings align with recent studies that also found a higher incidence of CR among *Klebsiella* (68 and 51%) than among *E. coli* isolates (22 and 28%).[19,20]

The molecular study of underlying genetic determinants of carbapenem resistance in our isolates by multiplex PCR showed OXA and *NDM* resistance genes at rates of 74.8 and 20.7%, respectively. The predominance of *OXA-48* genes was previously reported in Europe, Middle Eastern, and African countries,[29] with preceding rates of *OXA-48* (96 and 40.6%) over the *NDM* (54 and 23.7%) genes reported by previous studies.[27,30] Conversely, other studies have shown that *NDM* genes are more common than *OXA-48* genes in CRE.[19,31] A literature review conducted in Egypt has confirmed that *NDM* and OXA resistance genes are commonly found among CRE.[32] Earlier, the *OXA-48* CR gene exhibited a high prevalence in Egypt. Nevertheless, in recent times, the *NDM* genes have become more prevalent.[19]

In terms of demographic data, we found that the CRE and CSE groups did not differ significantly in terms of age. Nevertheless, we identified male predominance in the CRE group.[33–35] Other studies found no noticeable differences in age or sex between the CRE and CSE patients.[33–35] We identified smoking, diabetes, COPD, and ESRD as risk factors having significant association with CRE patients. Similarly, Zawawi et al.[36] reported a significant association with chronic kidney illnesses. In contrast, Lee et al. found no discernible variation in comorbidities,[33] whereas Pérez-Galera et al.[35] identified other comorbidities, e.g., chronic heart failure and dementia These variations reflect differences in the population in different ICUs. Patients diagnosed with sepsis shock, stroke, trauma, or respiratory failure were significantly more likely to be admitted if they had CRE infections. A previous study identified infection upon admission as a risk factor.[37] The CRE group's SOFA score was significantly higher than that of the CSE group. However, other studies revealed no differences.[12]

Throughout the hospitalization, our CRE group had a significantly higher need for hemodialysis, abdominal cavity drainage, plasma exchange, and repeated transfusions. According to Kotb et al.,[9] there was no statistically significant difference in mechanical ventilation, endotracheal intubation, or central lines between the CRE and CSE groups. Before infection, LOS showed no significant difference between CRE and CSE patients. Conversely, Kotb et al.[9] and Guo et al.[38] reported that CRE patients had more extended ICU stays. Consistent with prior studies, the CRE group showed significantly higher percentages of prior use of vasopressors and broad-spectrum antibiotics with Gram-negative coverage, including quinolones, meropenem, and extended-spectrum cephalosporins.[33] The CRE had more abnormal laboratory findings and a significantly higher rate of ARDS, which agrees with other studies.[39] Conversely, Guo et al.[38] reported no discernible differences.

Table 2: Comparative description of risk factors among patients with CRE and CSE infections

	CRE (n = 111) and encoding genes				*CSE (n = 70)*					
Variables	*OXA-48 (n =83)*	*NDM (n = 23)*	*OXA-48 + NDM (n = 5)*	*p-value*	*Klebsiella pneumoniae (n = 39)*	*E. coli (n = 31)*	*p-value*	*Sum CRE (n = 111)*	*Sum CSE (n = 70)*	*p-value*
APACHE score	24 ± 9.8	16.6 ± 8.8	24.8 ± 0.4	0.005	22.5 ± 9.8	37 ± 0	<0.001	22.5 ± 9.8	32.7 ± 22.8	<0.001
SOFA score	14.3 ± 7.6	17 ± 8.6	18.8 ± 2.7	0.179	15 ± 7.8	13 ± 0	0.173	15 ± 7.8	10.7 ± 5.8	<0.001
ICU–LOS (days)	18.7 ± 19.9	7.4 ± 6.9	11 ± 2.2	0.023	9.2 ± 13.8	7 ± 0	0.395	16 ± 18	11.4 ± 12.3	0.060
Medical diagnosis *n* (%)										
Pneumonic illness	5 (6)	9 (39.1)	0		2 (5.1)	18 (58.1)		10 (9)	20 (28.6)	
Trauma	4 (4.8)	0	0		0	0		4 (3.6)	0	
Sepsis	29 (34.9)	14 (6)	0		13 (33.3)	1 (3.2)		43 (38.7)	14 (20)	
Respiratory failure	21 (25.3)	0	4 (80)		4 (10.3)	0		25 (22.5)	4 (5.7)	
COVID-19	11 (3.3)	0	1 (20)	<0.001	14 (35.9)	8 (25.8)	<0.001	12 (10.8)	22 (31.4)	<0.001
Cardiac tamponade	1 (1.2)	0	0		0	0		1 (0.9)	0	
Post-arrest	4 (4.8)	0	0		0	2 (6.5)		4 (3.6)	2 (2.8)	
Stroke	5 (6)	0	0		1 (2.6)	0		5 (4.5)	1 (1.4)	
Encephalopathy-renal	0	0	0		1 (2.6)	0		0	1 (1.4)	
Invasive procedures *n* (%)										
Tracheostomy	31 (37.3)	6 (26.1)	0	0.162	7 (17.9)	21 (67.7)	<0.001	37 (33.3)	28 (40)	0.363
Endotracheal intubation	46 (55.4)	6 (26.1)	5 (100)	0.004	26 (66.7)	27 (87.1)	0.009	57 (51.3)	53 (75.7)	0.001
Mechanical ventilation	54 (65.1)	10 (43.5)	5 (100)	0.716	28 (71.8)	7 (87.1)	0.321	69 (62.1)	55 (78.5)	0.021
Dialysis catheterization	33 (39.8)	13 (56.5)	4 (80)	0.099	7 (17.9)	1 (3.2)	0.066	50 (45)	8 (11.4)	<0.001
Nasogastric intubation	53 (63.9)	10 (43.5)	5 (100)	0.040	24 (61.5)	27 (87.1)	0.003	68 (61.2)	51 (72.8)	0.109
Repeated blood transfusion	30 (36.1)	5 (21.7)	5 (100)	0.004	10 (25.6)	1 (3.2)	0.014	40 (36)	11 (15.7)	0.003
Hemodialysis and plasma exchange	34 (41)	13 (56.5)	4 (80)	0.122	7 (17.9)	1 (3.2)	0.066	51 (45.9)	8 (11.4)	<0.001
Abdominal cavity drainage-tube	5 (6.2)	1 (4.3)	0	0.811	0	0	-	6 (5.4)	0	0.048
Prior antibiotic intake *n* (%)										
Combined-Penicillins										
Piperacillin-tazobactam	37 (44.6)	13 (56.5)	5 (100)	0.042	12 (30.8)	20 (64.5)	0.005	55 (49.5)	32 (45.7)	0.615
Amoxicillin-clavulanate	3 (3.6)	1 (4.3)	0	0.165	0	0	0.002	4 (3.6)	0	0.108
Cephalosporins										
Ceftazidime	0	0	0	–	0	6 (19.4)	0.004	0	6 (8.5)	0.002
Ceftriaxone	25 (30.1)	2 (8.7)	1 (20)	0.178	5 (12.8)	0	0.039	28 (25.2)	5 (7.1)	0.002
Cefepime	0	0	0	–	13 (33.3)	0	<0.001	0	13 (18.5)	<0.001
Meropenem	31 (37.3)	11 (47.8)	4 (80)	0.143	3 (7.7)	3 (9.7)	0.711	46 (41.4)	6 (8.5)	<0.001
Levofloxacin	21 (25.3)	5 (21.7)	0	0.421	4 (10.3)	2 (6.5)	0.572	26 (23.4)	6 (8.5)	0.011
Tigecycline	6 (7.2)	0	0	0.343	6 (5.4)	0	0.021	6 (5.4)	6 (8.5)	0.404
Vancomycin	4 (4.8)	0	4 (80)	<0.001	11 (28.2)	1 (3.2)	0.008	4 (3.6)	12 (17.1)	0.002
Azithromycin	7 (8.4)	0	1 (20)	0.202	17 (43.6)	0	<0.001	8 (7.2)	17 (24.3)	0.001
Linezolid	14 (16.9)	2 (8.7)	0	0.395	17 (43.6)	0	<0.001	16 (14.4)	17 (24.3)	0.093
Metronidazole	2 (2.4)	0	4 (80)	<0.001	8 (20.5)	0	0.009	2 (1.8)	8 (11.4)	0.006

APACHE II score, acute physiology and chronic health evaluation II; CRE, carbapenem-resistant *Enterobacterales*; CSE, carbapenem-susceptible *Enterobacterales;* SOFA, sequential organ failure assessment

Table 3: Regression analyses of risk variables associated with CRE acquisition

	Multivariate analysis		*Univariate analysis*	
Variables	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*
Sex	2.458	0.075	2.458 (1.780, 4.458)	0.049
Medical diagnosis	–	–	11.139 (2.976, 12.262)	0.234
Comorbidities				
Kidney disease	2.704 (0.025, 2.532)	0.676	3.421 (1.003, 4.765)	<0.0001
Cardiac disease	1.740 (0.130, 2.139)	0.884	4.006 (1.333, 12.039)	0.013
Pulmonary disease	1.001 (0.00, 1.312)	0.999	9.229 (1.003, 11.003)	<0.0001
Smoking	1.110 (0.054, 1.231)	0.946	1.125 (1.029, 1.546)	0.006
Severity scores				
APACHE	–	–	0.984 (0.961, 1.009)	0.206
SOFA	4.098 (2.106, 7.992)	0.038	4.098 (0.999, 11.943)	0.045
LOS-ICU	2.050 (1.040, 3.769)	<0.0001	1.960 (0.940, 2.980)	<0.0001
Invasive procedures				
Hemodialysis	0.999 (0.321, 1.542)	0.049	0.865 (0.021, 0.395)	<0.0001
Dialysis catheter	1.345 (0.932, 2.706)	0.020	1.258 (0.094, 1.706)	0.008
Cavity drainage tube	–	–	0.091 (0.148, 1.683)	0.456
Duration of mechanical ventilation	2.765 (1.012,4.006)	<0.0001	1.974 (0.955, 2.993)	<0.0001
Chest X-ray infiltration	–	–	0.420 (0.024, 0.843)	0.123
Prior antibiotics intake				
Combined penicillins	1.621 (0.231, 2.002)	0.045	1.355 (0.162, 1.774)	0.009
Cephalosporins	6.999 (2.221, 21.003)	<0.0001	6.677 (2.221, 20.077)	0.001
Levofloxacin	2.937 (0.901, 3.877)	<0.0001	2.937 (0.901, 3.877)	<0.0001
Meropenem	1.391 (0.099, 2.105)	<0.0001	1.184 (0.083, 1.405)	<0.0001
Linezolid	–	–	1.312 (0.136, 1.714)	0.006
Azithromycin	1.101 (0.040, 1.509)	0.068	0.5003 (0.020, 1.004)	0.098

APACHE II score, acute physiology and chronic health evaluation II; LOS,length of stay; SOFA, sequential organ failure assessment

According to patients' follow-up, treatment of the *OXA-48* gene-positive CRE by tigecycline and colistin was linked with a significantly shorter stay in ICU, fewer days on mechanical ventilation, and a higher rate of bacterial elimination. CRE patients with the *NDM* gene and multiple resistance genes exhibited less favorable outcomes. In other studies, the most frequently administered antibacterial agents were tigecycline (37%), colistin (28%), amikacin (21%), and gentamicin (11%).[28] One study reported that carbapenem-resistant *K. pneumoniae* isolates had low resistance to tigecycline (35.8%) and colistin (10.8%), respectively.[40] In our patients, mortality rates were 62.2 and 55.7% for CRE and CSE, respectively. In other studies, CRE infections had mortality rates reaching 46.7 and 57.8%.[41,42] In addition, the mortality rate increases with delayed initiation of appropriate therapy. These findings highlight the importance of prompt laboratory identification of resistance and promptly initiating treatment with active antimicrobials to improve clinical results.[43]

According to the univariate regression analysis, the primary risk variable for developing CRE infection in ICU patients comprised male sex and underlying comorbidities. Multivariate and univariate regression analysis demonstrated that CRE acquisition was linked to high SOFA score risk factors, extended LOS in ICU, prior intake of broad-spectrum antibiotics, hemodialysis, and prolonged mechanical ventilation. Additionally, Kotb et al. found a significant association between the occurrence of carbapenem resistance and previous hospitalization as well as a more extended ICU stay.[9]

The alarming concerns regarding CRE superbugs revolve around the potential loss of efficacy of salvage carbapenem antibiotics, as well as the development of resistance to extended-spectrum cephalosporins and other antibiotics. This could lead to the failure of treatment for multidrug-resistant Gram-negative infections.[44–46] Additionally, the challenging control of infections is due to the high likelihood of genetic transfer of resistance between bacteria, and the role of hospital environment in mediating microbial resistance transmission.[9] The primary strengths of our study include a comprehensive evaluation of predictors of CRE infection, clinical course, and consequences in an ICU. However, the study has some limitations, such as the small sample size and single-center data source. In addition, pediatric patients were not among our study population. In this context, we recommend conducting further meticulously designed prospective studies with bigger sample sizes.

To effectively address the risk posed by CRE to global health, it is imperative to adhere to infection control protocols, employ antimicrobial drugs judiciously, establish antimicrobial stewardship, and employ rapid diagnostic methods for prompt identification of infectious agents and their resistance markers.

Table 4: Patients' clinical course parameters after infection by CRE

Parameters	*CRE (n = 111)*	*CSE (n = 70)*	*p-value*
Heart rate (beat/minute)	97.6 ± 17.8	107.6 ± 22	<0.001
Temperature (°C)	38.1 ± 1.0	37.5 ± 0.8	0.005
Systolic blood pressure (mm Hg)	120 ± 20.2	106.1 ± 19	0.933
Diastolic blood pressure (mm Hg)	62.8 ± 13.8	65 ± 14.6	0.028
Vasopressors used before infection			
Not used	94 (84.7)	70 (100)	0.003
Norepinephrine	12 (10.8)	0	
Norepinephrine and dopamine/dobutamine	5 (4.5)	0	
Vasopressors used after infection			
Not used	46 (41.4)	38 (54.3)	<0.001
Norepinephrine	55 (49.5)	10 (14.3)	
Phenylephrine	0	18 (25.7)	
Norepinephrine and dopamine/dobutamine	10 (9)	4 (5.7)	
Renal function tests			
Mean (+SD) serum creatinine (µmol/L)	180.6 ± 103.8	130.5 ± 81.7	<0.001
Mean (+SD) BUN (mg/dL)	23.8 ± 21.1	21.9 ± 8.8	0.488
Liver function tests			
Mean (+SD) ALT (µ/L)	70.2 ± 91.3	139.6 ± 142.4	<0.001
AST (µ/L)	55.8 ± 42.4	95.7 ± 70.5	<0.001
Mean (+SD) direct bilirubin (µmol/L)	16.9 ± 18.9	16.5 ± 15.8	0.836
Total bilirubin (µmol/L)	36.8 ± 29	36.9 ± 22.3	0.597
Mean (+SD) Albumin(g/l)	23.8 ± 4.4	25.1 ± 4.3	0.054
Blood picture			
Mean (+SD) hemoglobin (g/dL)	9.2 ± 2	10 ± 1.3	0.042
Mean (+SD) white blood cells ($\times 10^3$/µL)	14.8 ± 9.1	18.8 ± 7.5	0.003
Mean (+SD) platelets ($\times 10^3$/µL)	169.9 ± 126.4	253.4 ± 169.1	<0.001
Coagulation tests			
Mean (+SD) APTT (sec)	35.5 ± 8.8	32.7 ± 11.9	0.073
Mean (+SD) INR	1.8 ± 1.8	1.5 ± 0.4	0.178
Mean (+SD) D-dimer (mg/L)	3.1 ± 1.8	2.2 ± 1.3	<0.001
Inflammatory markers			
Mean (+SD) CRP (mg/L)	150.8 ± 115.4	99.7 ± 101.2	0.003
Mean (+SD) Procalcitonin (ng/mL)	7.3 ± 10.9	2.6 ± 4.8	<0.001

The normal values for serum creatinine were 0.7–1.3 mg/dL and 61.9–114/9 µmol/L, respectively. The normal serum BUN level was 6–24 mg/dl or 2.1–8.5 mmol/L. The serum ALT concentration was 7–56 U/l, and the AST concentration was 10–40 U/l. ALT, alanine transaminase; AST, aspartate transaminase; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CRP, C-reactive protein; CRE, carbapenem-resistant *Enterobacterales*; CSE, carbapenem-susceptible *Enterobacterales;* INR, international normalized ratio

Table 5: Analysis of clinical outcomes of CRE infections compared with CSE

	CRE (n = 111) and coding genes						
Outcome of infection	*OXA-48 (n = 83)*	*NDM (n = 23)*	*OXA-48 + NDM (n = 5)*	*p-value*	*Total CRE (n = 111)*	*Total CSE (n = 70)*	*p-value*
Mechanical ventilation duration (days)	22 ± 17.5	8 ± 11.4	19.4 ± 9.8	0.002	19 ± 17	12.8 ± 12	0.009
ICU- stay duration (days)	36.2 ± 20.1	17.7 ± 13.3	19.4 ± 9.8	<0.001	31.6 ± 20.1	24.1 ± 19.3	0.014
Survival days	4.8 ± 3.8	5.6 ± 4.5	12.4 ± 3.1	<0.001	6.2 ± 4.6	5.2 ± 2.2	0.089
Bacterial elimination (%)	63.4 ± 18.9	39.9 ± 10.4	51.6 ± 18.8	<0.001	58 ± 19.8	64.4 ± 18.3	0.030
Discharge	29 (35)	9 (39.1)	4 (80)	<0.001	42 (37.8)	31 (44.3)	0.389
Death	54 (65)	14 (60/9)	1 (20)	0.129	69 (62.2)	39 (55.7)	0.389

CRE, carbapenem-resistant *Enterobacterales*; CSE, carbapenem-susceptible *Enterobacterales*

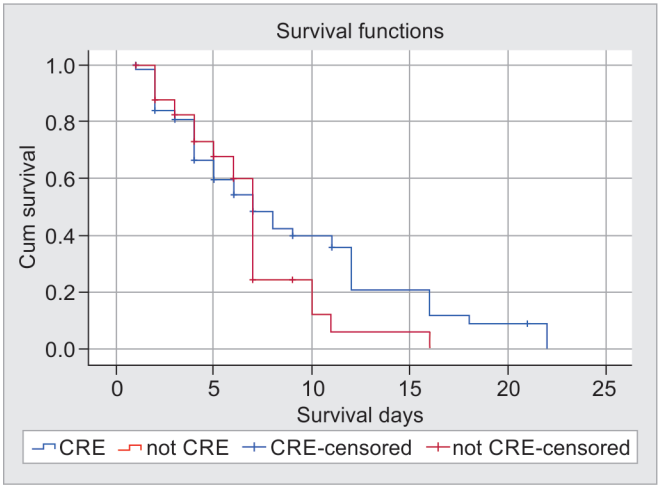

Fig. 2: Kaplan–Meier survival plot for CRE and CSE groups

Conclusion

The findings of this study provide crucial insight into the clinical and microbiological features of CRE infection among ICU patients in a tertiary-care hospital in Egypt. Our results suggest that specific risk variables such as prolonged length of stay (LOS) in the ICU, prolonged mechanical ventilation, and prior use of broad-spectrum antimicrobials are related to CRE infections. Carbapenem-resistant *Enterobacterales*-infected patients required a more extended hospital stay and mechanical ventilation. In addition, they had less bacterial clearance and higher mortality rates compared to CSE-infected patients.

Authors' Contribution

The conceptualization of the study was made by HE and AE. Ahmed R ElKaramany Shoala (ARES) conducted the practical work. Data collection was done by YN and Aliaa Abdel-Fattah (AA). ARES, Amani ElKoly (AE), and Noha Salah Soliman (NSS) performed analysis and interpretation of results. All authors approved the manuscript after a final review by HE and AE.

Availability of Data and Materials

Data generated or analyzed during this study are included in this published article.

Ethics Approval and Patient Consent to Participate

The Research Ethics Committee of the Faculty of Medicine, Cairo University (N13-2020) approved the study. The study adhered to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Patients or their first-degree family members provided informed written consent. Each patient was assigned a distinct identification number to ensure his or her confidentiality.

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