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Risk factors associated with carbapenem-resistant Enterobacterales infections in hospitalized patients: A case-control study

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SUMMARY

Background: Carbapenem-Resistant Enterobacterales (CRE) represent a critical public health threat.
Aim: To analyze risk factors for CRE infections in adults at a secondary hospital in Manta, Ecuador, during 2022.
Methodology: A case-control study (27 cases; 193 controls) compared CRE versus Carbapenem-Susceptible Enterobacterales (CSE). Univariable and Multivariable Firth logistic regression was performed to adjust for small-sample bias.
Results: In multivariable analysis, time to infection onset was the most consistent predictor of CRE (aOR: 1.08; 95% CI: 1.03–1.12; p=0.001). Other significant risk factors included chronic corticosteroid therapy (aOR: 43.10; 95% CI: 3.04–611.96; p=0.005), prior hospitalization (aOR: 14.52; 95% CI: 2.22–94.86; p=0.005), urinary catheter (aOR: 10.39; 95% CI: 2.20–49.00; p=0.003) and central venous catheterization (aOR: 13.46; 95% CI: 1.29–139.45; p=0.029). Nosocomial origin (aOR: 0.05; 95% CI: 0.003–0.86; p=0.039), and Internal Medicine management (aOR: 0.23; 95% CI: 0.06–0.94; p=0.041) showed protective associations.
Conclusions: In this setting, the cumulative duration of healthcare exposure (time to infection onset) was the primary driver of CRE risk. However, these risk factors are highly context-dependent and vary across different populations and facilities. Therefore, these results cannot be generalized, highlighting the need for localized surveillance and further multicenter studies to understand regional resistance dynamics.

Keywords: Enterobacterales, carbapenem-resistant enterobacterales, enterobacterales infections, risk factors.

BACKGROUND

The global pandemic of Carbapenem-Resistant Enterobacterales (CRE) began with certain carbapenemases dominating specific regions; however, many have spread globally [1]. A large-scale study conducted in 2022 determined CRE rates of 4.5% in the European Union (EUR), 10.4% in the Middle East (MEA), 11.3% in the Asia-Pacific, and 12.9% in Latin America [2]. Among these, *Klebsiella pneumoniae* (*K. pneumoniae*) and *Escherichia coli* (*E. coli*) account for approximately 90% of CRE strains [3, 4]. *Klebsiella* spp. strains are more common (>30% of cases) in countries such as Russia, Egypt, Brazil, Myanmar, Iran, and some Mediterranean nations, while *E. coli* (>20% of cases) is more frequent in regions such as Egypt and Sudan [3].
Notably, these figures are expected to rise due to recent outbreaks of *New Delhi metallo-beta-lactamase* (NDM)-producing CRE reported in countries including Spain, Greece, Portugal, and Italy [5-

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7]. Furthermore, this growing resistance can be directly related to the misuse and overuse of antibiotics in humans, livestock, and agriculture in recent years, highlighting that microbial evolution consistently outpaces the development of novel antimicrobials [8].

Currently, research on risk factors for CRE infections is highly heterogeneous, and results tend to vary depending on the population. A recent meta-analysis identified the following risk factors for subsequent CRE infection, including Intensive Care Unit (ICU) admission, renal disease, indwelling devices (urinary catheters, central venous catheters, and arterial catheters), mechanical ventilation, tracheostomy, nasogastric tubes, and prior exposure to carbapenems, fluoroquinolones, vancomycin, metronidazole, aminoglycosides, and tigecycline [9].

Additionally, a strong association has been demonstrated between high colonization pressure and prior duration of carbapenem use, and the subsequent acquisition of carbapenemase-producing CRE [1]. Likewise, a wide observational study (EURECA) identified a risk relationship between previous colonization/infection by CRE, urinary catheter, exposure to broad-spectrum antibiotics, time-dependent, chronic renal failure, and admission from home, and the acquisition of CRE, compared with Carbapenem-Susceptible Enterobacterales (CSE) and non-infected patients [10]. However, significant gaps in epidemiological data persist in low-income countries, suggesting these figures may be underestimated, particularly in developing regions with a high prevalence of antimicrobial resistance, such as Latin America [2, 3].

CRE as emerged as one of the most critical threats to healthcare over the last decade, due to resistance to last-resort antibiotics, high morbidity and mortality rates, rapid spread within healthcare systems, prolonged hospitalizations, and substantial healthcare costs [9-11]. These strains are associated with mortality rates above 50%; however, this may depend on the resistance mechanism and the therapeutic regimen administered [9]. Notably, one study reported a mortality rate of 30.8% when patients received an antibiotic with in vitro activity, whereas those without appropriate treatment reached a mortality rate of approximately 64.3% [13].

Consequently, understanding the local epidemiology and risk factors for CRE is essential for developing effective prevention strategies, mitigating bacterial spread, and facilitating rapid diagnosis and treatment optimization [14]. This retrospective case-control study was conducted to analyze the risk factors associated with CRE infections in patients admitted to the Manta General Hospital (HGM) of the Ecuadorian Social Security Institute (IESS) in Manta, Ecuador, throughout 2022.

METHODS

Study design

Following the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative, the study was conducted using a retrospective observational case-control design to analyze risk factors associated with CRE versus CSE infections.

Participants

The study population included adult patients admitted with Enterobacterales infections at the Manta General Hospital of the IESS during 2022. The eligibility criteria were as follows:

Inclusion criteria

Patients admitted to medical wards, surgery unit, or ICU.

Patients diagnosed with urinary tract infection, pneumonia, bacteremia, or intra-abdominal infections, verified by ICD-10 coding in the medical record.

Patients with confirmed Enterobacterales isolates.

Hospital stay longer than 48 hours.

Patients aged > 18 years.

Exclusion criteria

Patients with Enterobacterales colonization (without clinical evidence of infection).

Pregnant and postpartum women, as physiological changes and pregnancy-inherent outcomes could act as confounding factors.

Study population

The study population comprised adult patients diagnosed with Enterobacterales infection admitted to the HGM during 2022. The HGM is a second-level facility providing health services to IESS beneficiaries. It has a capacity of 241 beds (including critical care, medical, and surgical wards). Although it was designed to provide health cov-

erage to the population of Manta (217,553 inhabitants), in 2022 it served 590,542 users from across the province (51% female, 49% male) [15].

Group assignment
Patients were identified through the microbiology department's epidemiological surveillance database. The data were filtered by microorganism type and antimicrobial resistance profile. Initially, stratified matching was considered; however, to avoid selection bias and because these variables were potential risk factors, a total population analysis was performed. A total of 220 patients met the eligibility criteria. Patients with CRE isolates were assigned to the case group, while those with CSE isolates were assigned to the control group. For recurrent episodes, only the index isolate was included. In cases of multiple infectious foci or polymicrobial cultures, isolates from sterile sites or those with the highest clinical significance were prioritized.

Characterization of positive cultures
The samples were processed in the microbiology department of the HGM. Clinical specimens were inoculated onto 5% sheep blood agar and chocolate agar. The isolates were identified *via* "Vitek 2 Compact" equipment for automated recognition of the microorganisms. Antimicrobial susceptibility testing (AST) was performed and interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [16]. Given the unavailability of molecular assays, Carbapenem Resistance (CR) was determined via Minimum Inhibitory Concentration (MIC) and disk diffusion methods (Oxoid and Bioanalyse). Phenotypic identification of Carbapenemase-Producing (CP) strains was conducted using boronic acid synergy tests for Class A carbapenemases and EDTA-based inhibition tests for Class B metallo-beta-lactamases [17]. Since microbiology reports occasionally indicated a 'phenotypic carbapenemase-producing' or 'carbapenem-producing' profile without simultaneous molecular subtyping or dual phenotypic confirmation, both CP and CR Enterobacterales were categorized under the collective term CRE for clarity and statistical consistency.

Data collection and measurement
Data collection was carried out via the AS400 electronic medical record system and hospitalization logs into a standardized database. The following variables were selected based on current literature:

Dependent variable
Carbapenem resistance: isolates of Enterobacterales that were resistant to at least one of the carbapenems according to EUCAST criteria or demonstrating phenotypic carbapenemase production through boronic acid or EDTA-based synergy assays.

Independent variables:
Clinical data: Sex, age (in years), body mass index (BMI), Charlson Comorbidity Index (CCI) >3, prior hospitalization within the last year, recent ICU admission (90 days), recurrent outpatient healthcare contact (90 days), and chronic corticosteroid therapy.
*Current hospitalization***:** mechanical ventilation (tracheostomy or endotracheal tube), hemodialysis, central venous catheter (CVC), urinary catheter, nasogastric tube, surgical procedures, COVID-19 diagnosis, sepsis (assessed by qSOFA), and time to infection (days from admission to isolate recovery).
*Microbiological and Facility Data***:** Nosocomial infection, clinical ward (ICU, internal medicine, or surgery), and site of infection (respiratory, urinary, bloodstream, intra-abdominal, or skin and soft tissue).
Prior Antimicrobial Therapy (within 90 days): Exposure to carbapenems, quinolones, 3rd/4th generation cephalosporins, polymyxins, and aminoglycosides.
Other microorganisms isolated (previous 90 days): ESBL-producing Enterobacterales, carbapenem-resistant Gram-negative bacilli (*Acinetobacter* spp. or *Pseudomonas* spp.), and methicillin-resistant *Staphylococcus aureus* (MRSA).

Data analysis
A comparative analysis of groups was conducted using contingency tables and the Chi-square test for qualitative variables, while quantitative variables were summarized using medians and interquartile ranges, followed by the Mann-Whitney U test. Subsequently, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated through univariable Firth logistic regression to address the low frequency of events and prevent overestimation of effects.
A multivariable penalized (Firth) logistic regres-

sion model was developed due to the low number of events (n = 27). Variables were selected based on biological plausibility and the minimization of the Akaike Information Criterion (AIC). The potential confounding effects of age and sex were assessed a priori using the change-in-estimate method. The variable sex was excluded from the final model as its removal did not alter the coefficients of the main predictors by more than 10% and improved model parsimony (lower AIC). The variable age was retained as an adjustment factor, as its inclusion optimized the overall model fit (AIC = 65.80). The model's performance was assessed using the penalized log-likelihood, the Wald chi-square test ($p < 0.001$), and Nagelkerke's pseudo R^2 (0.748). Multicollinearity was ruled out via the Variance Inflation Factor (VIF), yielding a mean of 1.42 and a maximum of 2.30. Diagnostic accuracy was determined through the area under the ROC curve (AUC=0.95), sensitivity, and specificity. Data analysis was performed using STATA version 18 (StataCorp, TX) and the firthlogit package, with a 95% confidence level and an alpha error of 0.05.

Ethical aspects

In compliance with the 2021 Ecuadorian Data Protection Law in its article 32 [18], anonymized data collection was conducted by assigning sequential identification codes based on the database record order. This study was authorized by the HGM and the Human Research Ethics Committee of the Universidad Técnica de Manabí (CEISH-UTM) under code CEISH-UTM-EXT_24-11-11_VLZC. Following the Declaration of Helsinki, the data and results were managed with confidentiality, integrity, and responsibility.

RESULTS

A total of 235 patients initially met the eligibility criteria; however, 15 were excluded due to incomplete clinical records or inaccessible data. Thus, 220 patients remained for analysis and were categorized into CRE cases (n=27) and CSE controls (n=193). The selection process is detailed in the flowchart presented in *Figure 1*.

Epidemiological and Microbiological Characteristics

During the study period (2022), 3,680 admissions were recorded across medical, surgical, and intensive care units. Based on the 27 identified CRE infections, the overall rate at the HGM was 7.3 cases per 1,000 admissions. Notably, 88.9% (n=24) of the cases were phenotypically identified as CPE through boronic acid or EDTA-based synergy

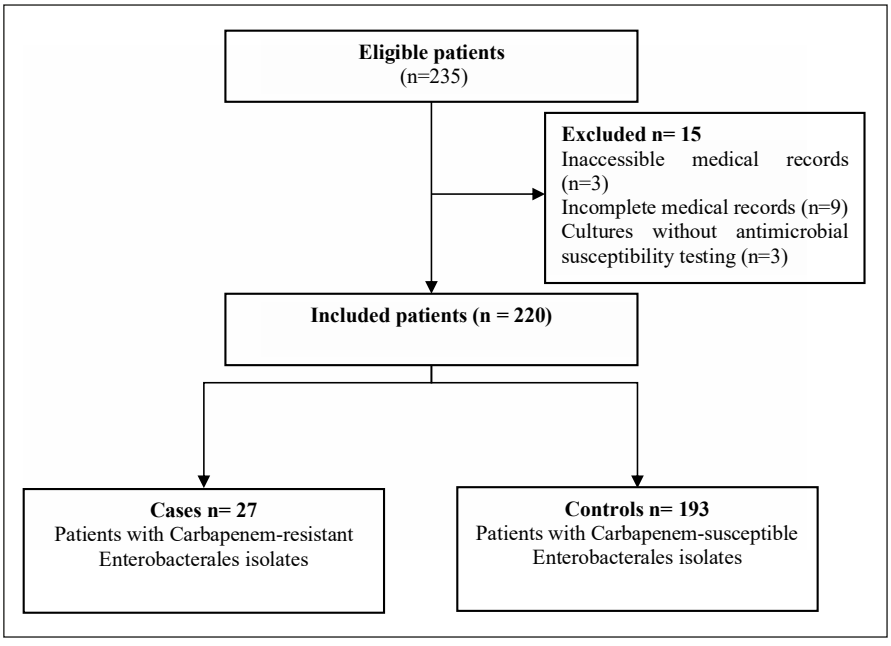

Figure 1
Flowchart for the selection of cases and controls.

tests, while the remaining 11.1% (n=3) were categorized as CRE based on minimum inhibitory concentration (MIC) values.

The distribution of Enterobacterales significantly differed between groups (p<.001). Among CRE cases, *K. pneumoniae* was the predominant pathogen, accounting for 74.1% (n=20) of isolates, compared to its prevalence in the CSE control group (18.7%; n=36). In contrast, *E. coli* was the most frequent isolate in the CSE group (66.8%; n=129), while being rare among CRE cases (3.7%; n=1). Other species, including *Proteus mirabilis* and *Enterobacter* spp., showed marginal and comparable distributions across both groups regardless of the resistance (*Table 1*).

Table 2 summarizes the clinical and microbiological characteristics of the study population. The groups were comparable in terms of age (p= 0.929), sex (p=0.678), BMI (p=0.796), and baseline comorbidities (p=0.936). In contrast, CRE cases exhibited a higher burden of healthcare-related factors and chronic immunosuppression due to corticosteroid therapy (p<0.001).

During the index hospitalization, CRE acquisition was strongly associated with greater clinical severity and medical intensity. This was evidenced by significantly higher rates of sepsis (92.5%), COVID-19 co-infection, and the requirement for invasive procedures, including mechanical ventilation and hemodialysis (p<0.001). Furthermore, the median time to infection was significantly protracted in the CRE group (14 vs. 1 day, p<0.001), highlighting a predominantly late-onset nosocomial pattern compared to the early-onset susceptible controls. Ward distribution also varied, with nearly half of CRE cases managed in the ICU (48.1%), whereas CSE controls predominated in Internal Medicine (69.4%). Urinary tract

Table 1 - Comparative analysis of Enterobacterales strains between the case-control groups.

Enterobacterales	*Total N= 220*	*CRE Cases n=27*	*CSE Controls n=193*	*p-value*
Klebsiella Pneumoniae	56 (25.5%)	20 (74.1%)	36 (18.7%)	<0.001
Proteus mirabilis	9 (4.1%)	2 (7.4%)	7 (3.6%)	
Enterobacter spp.	14 (6.4%)	2 (7.4%)	12 (6.2%)	
Escherichia coli	130 (59.1%)	1 (3.7%)	129 (66.8%)	
Serratia marcescens	4 (1.8%)	1 (3.7%)	3 (1.6%)	
Citrobacter spp.	2 (0.9%)	1 (3.7%)	1 (0.5%)	
Morganella morganii	5 (2.3%)	0 (0%)	5 (2.6%)	

Table 2 - Comparative analysis of demographic, clinical, and microbiological variables between the case-control groups.

	Total N= 220	*CRE Cases n=27*	*CSE Controls n=193*	*p-value*
Clinical data				
Age[a]	66 (53.3 - 73)	68 (60 - 71)	66 (53 - 73)	.929
Male	114 (51.8%)	15 (55.6%)	99 (51.3%)	.678
BMI[a]	26.3 (23.2 - 29.9)	25.1 (23.2 – 30.5)	26.5 (23.1 – 29.9)	.796
Charlson Comorbidity Index>3	42 (19.1%)	5 (18.5%)	37 (19.2%)	.936
Prior hospitalization within the last year	73 (33.2%)	16 (59.3%)	57 (29.5%)	.002
Recent UCI admission	9 (4.1%)	2 (7.4%)	7 (3.6%)	.353
Recurrent outpatient healthcare contact	53 (24.1%)	11 (40.7%)	42 (21.8%)	.031
Chronic corticosteroid therapy	6 (2.7%)	4 (14.8%)	2 (1%)	<.001

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	Total N= 220	*CRE Cases n=27*	*CSE Controls n=193*	*p-value*
Current hospitalization				
Mechanical ventilation	25 (11.4%)	14 (51.9%)	11 (5.7%)	<.001
Hemodialysis	15 (6.8%)	7 (25.9%)	8 (4.1%)	<.001
Central venous catheter	21 (9.5%)	13 (48.1%)	8 (4.1%)	<.001
Urinary catheter	43 (19.5%)	17 (63%)	26 (13.5%)	<.001
Nasogastric tube	29 (13.2%)	15 (55.6%)	14 (7.3%)	<.001
Surgical procedures	21 (9.5%)	10 (37%)	11 (5.7%)	<.001
COVID-19 diagnosis	22 (10%)	6 (22%)	16 (8.3%)	.024
Sepsis (Qsofa)	135 (61.4%)	25 (92.5%)	110 (57%)	<.001
Time to infection[a]	1 (1 - 3.75)	14 (7 – 29)	1 (1 - 2)	<.001
Microbiological and Facility Data				
Nosocomial infection	57 (25.9%)	17 (63%)	40 (20.7%)	<.001
Internal Medicine ward	141 (64.1%)	7 (25.9%)	134 (69.4%)	<.001
Surgery ward	49 (22.3%)	7 (25.9%)	42 (21.8%)	.626
ICU	30 (13.6%)	13 (48.1%)	17 (8.8%)	<.001
Site of infection				
Urinary tract	119 (54.1%)	9 (33.3%)	110 (57%)	.021
Bloodstream	35 (15.9%)	5 (18.5%)	30 (15.5%)	.692
Respiratory tract	15 (6.8%)	7 (25.9%)	8 (4.1%)	<.001
Skin and soft tissue	44 (20%)	6 (22.2%)	38 (19.7%)	.758
Intraabdominal	7 (3.2%)	0 (0%)	7 (3.6%)	.315
Prior Antimicrobial Therapy				
Carbapenems	17 (7.7%)	10 (37%)	7 (3.6%)	<.001
Quinolones	30 (13.6%)	9 (33.3%)	21 (10.9%)	.001
3rd/4th generation cephalosporins	21 (9.5%)	11 (40.7%)	10 (5.2%)	<.001
Polymyxins	4 (1.8%)	3 (11.1%)	1 (0.5%)	<.001
Aminoglycosides	15 (6.8%)	5 (18.5%)	10 (5.2%)	.010
Other microorganisms isolated				
ESBL-producing Enterobacterales	5 (2.3%)	5 (18.5%)	0 (0%)	<.001
Carbapenem-resistant Gram-negative bacilli	7 (3.2%)	4 (14.8%)	3 (1.6%)	<.001
Methicillin-resistant *Staphylococcus aureus*	1 (0.5%)	1 (3.7%)	0 (0%)	.007

[a] Nonparametric variable; the median and quartiles were obtained.

infections were the most common site across both groups, and most CRE infections were of nosocomial origin. In contrast, respiratory tract infections were significantly more frequent in the CRE group (p<0.001). Finally, CRE status was strongly linked to antimicrobial exposure in the previous 90 days, specifically carbapenems, polymyxins, and third- and fourth-generation cephalosporins (p<0.001) and prior isolation of multidrug-resistant organisms (p<0.001).

Univariable and multivariable analysis

Univariate analysis identified several critical determinants for CRE infection (*Table 3*). Regarding medical history, chronic corticosteroid therapy emerged as a major clinical predictor, increasing

Table 3 - Univariable and Multivariable logistic regression analysis of risk factors for CRE infections (CRE vs CSE).

	OR (CI 95%)	*p-value*	*OR adjusted* (CI 95%)*	*p-value*
Clinical data				
Age [a]	0.99 (0.97 – 1.01)	.419	0.96 (0.92 – 0.99)	.046
Male	1.2 (0.53-2.62)	.687	–	
BMI [a]	0.99 (0.92-1.09)	.992	–	
Charlson Comorbidity Index>3	0.9 (0.38 – 2.77)	.969	–	
Prior hospitalization within the last year	3.4 (1.51 – 7.68)	.003	14.52 (2.22 – 94.86)	.005
Recent UCI admission	2.4 (0.55 – 10.82)	.241	–	
Recurrent outpatient healthcare contact	2.5 (1.09 – 5.68)	.031	–	
Chronic corticosteroid therapy	14.7 (2.9 – 72.9)	.001	43.10 (3.04 - 611.96)	.005
Current hospitalization				
Mechanical ventilation	17.0 (6.58 – 46.12)	<.001	–	
Hemodialysis	7.9 (2.70 – 23.57)	<.001	3.66 (0.81 – 16.55)	.092
Central venous catheter	20.3 (7.39 – 55.84)	<.001	13.46 (1.29 - 139.45)	.029
Urinary catheter	10.5 (4.66 – 25.09)	<.001	10.39 (2.20 – 49.00)	.003
Nasogastric tube	15.3 (6.13 – 38.42)	<.001	–	
Surgical procedures	9.5 (3.61 – 25.11)	<.001	–	
COVID-19 diagnosis	3.2 (1.12 – 8.95)	.022	–	
Sepsis (qSOFA)	7.7 (2.04 – 29.13)	.003	–	
Time to infection [a]	1.1 (1.05 – 1.13)	<.001	1.08 (1.03 – 1.12)	.001
Microbiological and Facility				
Nosocomial infection	6.3 (2.73 – 14.29)	<.001	0.05 (0.003 – 0.86)	.039
Internal Medicine ward	0.2 (0.06 – 0.39)	<.001	0.23 (0.06 – 0.94)	.041
Surgery ward	1.2 (0.49 – 3.18)	.627	–	
ICU	9.4 (3.86 – 22.85)	<.001	–	
Site of infection				
Urinary tract	0.4 (0.17 – 0.89)	.026	–	
Bloodstream	1.3 (0.48 – 3.59)	.600	–	
Respiratory tract	7.9 (2.7 – 23.57)	<.001	–	
Skin and soft tissue	1.2 (0.44 – 3.09)	.758	–	
Prior Antimicrobial Therapy				
Carbapenems	14.9 (5.18 – 42.95)	<.001	–	
Quinolones	4.1 (1.67 – 10.15)	.002	–	
3rd/4th generation cephalosporins	12.2 (4.59 – 32.34)	<.001	4.46 (0.93 – 21.48)	.062
Polymyxins	18.3 (2.58 – 129.9)	.004	–	
Aminoglycosides	4.3 (1.39 – 13.10)	.011	–	
Other microorganisms isolated				
Carbapenem-resistant Gram-negative bacilli	10.4 (2.42 – 44.93)	.002	–	

* The multivariable Firth logistic regression analysis was adjusted for age.

the odds of infection nearly 15-fold (p=0.001). Among hospital-based exposures, invasive procedures demonstrated the highest impact (p<0.001), specifically central venous catheterization (OR: 20.3) and mechanical ventilation (OR: 17.0). The healthcare setting also significantly influenced the risk profile; ICU admission was associated with a 9.4-fold increase in the odds of CRE, whereas management in the Internal Medicine ward and urinary tract infections functioned as protective factors (OR: 0.2 and 0.4, respectively (p<0.05). Furthermore, the respiratory tract was the site most strongly linked to CRE infections (OR: 7.9). Prior antimicrobial exposure to polymyxins and carbapenems increased the odds of CRE by 18.3 and 14.9 times, respectively. In addition, CRE infection risk was further compounded by a history of prior isolation of other carbapenem-resistant Gram-negative bacilli (OR: 10.4).

The multivariable model demonstrated goodness-of-fit (Wald p=0.001, Nagelkerke R-squared: 0.748, AIC: 65.8) and high discriminatory capacity (Area Under the Curve 0.95; sensitivity 66.7% and specificity 100%). In this adjusted model (*Table 3*), time from admission to infection was confirmed as a strong predictor; for each additional day, the odds of developing a CRE infection increased by 8% (p=0.001). Chronic corticosteroid therapy (aOR: 43.10, p=0.005), prior hospitalization (aOR 14.52, p=0.005), urinary catheter (aOR: 10.39, p=0.003) and central venous catheterization (aOR 13.46, p=0.029) were independently associated with a significantly higher odd of CRE infections. In contrast, infections of nosocomial origin (aOR: 0.05, p=0.039) and managed in the Internal Medicine ward (aOR: 0.23, p=0.041) presented a significant protective association. Age, which was included in the model as a confounder, demonstrated a discrete protective association for CRE infections (aOR: 0.96, p=0.046).

Clinical outcomes

Regarding clinical outcomes, 30-day mortality was significantly higher in patients with CRE infections (40.7% vs. 9.3% in controls, p<0.001), representing a substantial clinical impact. Hospital stay from the onset of infection was also significantly prolonged in the CRE group (Median 17 days) compared to the CSE group (Median 9 days, p=0.049). This difference highlights a significant burden on hospital resources.

DISCUSSION

The emergence of CRE represents a critical public health crisis in Latin America, driven by the rapid dissemination of antimicrobial resistance mechanisms [2]. This acceleration is likely associated with irrational antibiotic use, suboptimal infection control measures, and the healthcare system strain observed in the post-COVID-19 era [19]. This study identified an incidence rate of 7.3 CRE cases per 1,000 hospital admissions.

Since 88.9% of isolates were susceptible to boronic acid or EDTA inhibition, our phenotypic findings may suggest a Class A carbapenemase dominance, likely bla_{KPC}, which is the most prevalent genotype in Ecuador [19, 20]. Furthermore, we found a predominance of *K. pneumoniae* within the CRE group (74.4%), whereas *E. coli* was more frequent among CSE isolates. This distribution aligns with global trends in China, the United States, and Europe (particularly Greece, Italy, and Romania), where *K. pneumoniae* is the primary CP organism; unlike Mexico or Japan, where *E. coli* and *Enterobacter cloacae* are more prevalent [2, 3, 21].

A critical methodological distinction in our study is the comparison between CRE infection and CSE infection, rather than CRE colonization. Due to the lack of resources for universal rectal screening, we adopted a pragmatic approach to identify clinical

Table 4 - Comparative analysis of clinical Outcomes between the case-control groups.

Outcomes	*CRE Cases n=27*	*CSE Controls n=193*	*p-value*
Hospital stay from admission [a]	25 (15 – 61)	11 (8 – 19)	<.001
Hospital stay from infection onset [a*]	17 (5 – 34)	9 (7 – 15)	.049
Mortality at 30 days [**]	11 (40.7%)	18 (9.3%)	<.001

[a]Nonparametric variable; the median and quartiles were obtained. *Patients transferred to another facility or discharged against medical advice were excluded from the analysis due to incomplete follow-up (CRE n=23, CSE n=175). **Thirty-day mortality data were obtained from national online registries to prevent loss to follow-up.

risk factors for active infection. In the multivariable analysis, the most significant finding was the time to infection onset, which showed an 8% risk increase for each additional day of hospitalization. This is consistent with evidence suggesting that prolonged stay enhances the colonization pressure, facilitating the acquisition of opportunistic pathogens through environmental exposure [22-24]. Furthermore, CRE colonization serves as a critical predictor of increased mortality risk [23, 25, 26].

The cumulative duration of stay often correlates with increased clinical intensity. We observed a significant association between CRE and central venous catheterization. Pathophysiologically, this is attributed to the ability of CP strains to form robust polymicrobial biofilms on medical devices, which protect bacteria from antibiotics and host immune responses [27]. This mechanical factor, combined with high colonization pressure, significantly transitions a colonized patient toward a symptomatic infection [1, 9, 26].

Healthcare-related factors, such as prior hospitalizations and chronic corticosteroid therapy, were major independent predictors. Glucocorticoids trigger systemic immunosuppression and severe gut dysbiosis, which inhibits host autoregulation and facilitates the colonization of resistant pathogens [28]. Our findings align with recent literature identifying steroids as primary drivers of CRE-related bacteremia [22, 29]. Similarly, previous hospitalization highlights the persistence of CRE in the patient's microbiome and the hospital's environmental memory, where biofilms can survive even terminal disinfection [10, 27].

Management in the Internal Medicine ward and nosocomial origin appeared as "protective" factors. This may be explained by the lower density of invasive procedures in medical wards compared to intensive care or surgical units [30]. Regarding nosocomial origin, although seemingly contradictory, these patients may be subject to earlier microbiological surveillance and stricter preemptive isolation than those with community-onset, healthcare-associated infections, who are often not isolated upon admission [22, 30].

While exposure to third – and fourth-generation cephalosporins showed a non-significant trend, their role cannot be dismissed. Cephalosporins are the most prescribed antibiotics in Latin America; their contribution to microbiome imbalance necessitates a stringent antimicrobial stewardship approach [31]. Interestingly, older age showed a marginal protective effect, differing from authors who report it as a risk factor [9, 10].

In our setting, this may indicate that younger patients in critical areas receive more aggressive interventions than the elderly. Finally, we determined a 30-day mortality rate of 40.7%, which is consistent with the 42.2% reported in a recent meta-analysis [9]. This figure is notably higher than those reported in high-income countries, such as Italy (33.3%), China (20.8%), and the UK (10%) [32–34]. This mortality gap compared to European cohorts may be attributed to limited access to novel β-lactam/β-lactamase inhibitors and the diagnostic delay inherent in non-universal screening settings.

This study has several limitations, primarily a smaller-than-anticipated case group. Althoug h the 1:7 (CRE:CSE) ratio was unexpected, it reflects the inherent challenge of studying rare conditions like CRE infections. Given the heterogeneity in risk-factor literature, we included all isolates without selective sampling or matching. To address group imbalance and small-sample bias, we employed Firth's penalized likelihood logistic regression. The multivariate analysis used backward stepwise elimination, incorporating variables based on statistical significance and clinical relevance. A ten-variable model was selected for its superior performance over a parsimonious three-variable alternative, as Firth's regression is the gold standard for controlling overestimation.

Furthermore, the lack of molecular biology infrastructure may lead to diagnostic misclassification. Consequently, we focused on providing pragmatic clinical data for identifying high-risk patients. To minimize retrospective observational bias, we standardized diagnostic criteria and implemented a peer-review protocol for medical record abstraction.

In conclusion, while cumulative healthcare exposure (time to infection onset) was the primary driver of CRE risk, these factors remain highly context-dependent. Thus, these findings may not be broadly generalizable, underscoring the need for localized surveillance and multicenter studies to further elucidate regional resistance dynamics.

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Conflict of interest
The authors declare that they have no conflicts of interest.

Author contributions
Z.V. contributed to the study design, literature search, data collection, data analysis, interpretation, writing, and validation. V.F. contributed to the study design, data collection, data analysis, revisions, and validations. B.M. contributed to the revision and validation of the study. All the authors read and approved the final manuscript.

Ethical approval and consent to participate
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