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*Proceeding Paper*

# Clinical-Epidemiological and Microbiological Characterization of Infections by Carbapenemase-Producing *Enterobacterales* in a Tertiary Hospital in Havana, Cuba †

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**Abstract: Introduction:** The spread of carbapenem-resistant *Enterobacterales* in hospitals constitutes an important epidemiological and therapeutic problem that especially affects vulnerable patients such as perioperative patients. **Materials and Methods:** We conducted a descriptive, observational, retrospective case-control study of patients infected with carbapenemase-producing carbapenem-resistant *Enterobacterales* (CP-CRE) and carbapenem-sensitive *Enterobacterales* during the perioperative period in a single-institution. **Results:** Metallo-beta-lactamase was detected in all the 124 CRE isolates, with NDM-type carbapenemase being dominant, while three isolates coproduced KPC-type enzyme. Steroid use (OR: 3.22, $p < 0.01$), prior use of two or more antibiotics (OR: 4.04, $p = 0.01$), prior use of broad-spectrum cephalosporins (OR: 2.40, $p = 0.04$) and prior use of carbapenem (OR: 4.77, $p = 0.03$) were the independent risk factors for progressing to CP-CRE infection. Bloodstream infections and pneumonia associated with CP-CRE had higher mortality risk. However, colistin-based combination therapy was not found to reduce the mortality risk for CP-CRE infection during hospitalization compared to patients treated by tigecycline- or fosfomycin-based regimens. **Conclusions:** High mortality is associated with nosocomial infections in the perioperative period caused by NDM carbapenemase-producing *Enterobacterales*, of which the dissemination in health care settings in Cuba is a public health challenge.

**Keywords:** carbapenemase; *Enterobacterales*; Cuba; NDM; risk factor; mortality

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## 1. Introduction

In recent years, carbapenem-resistant *Enterobacterales* (CRE) have become increasingly prevalent as etiologic agents of healthcare-associated infections (HAIs) and present a major clinical impact due to their very limited therapeutic options [1].

The emergence of CRE may be caused by a combination of mechanisms: production of carbapenemase enzymes, alteration of membrane permeability and active expulsion systems; however, enzymatic production is their main mechanism of resistance [2]. According to Ambler's criteria, carbapenemases are classified into three classes (A, B and D), class A carbapenemases (KPC like) are most prevalent in enteric bacteria in the USA, and are also widespread in the Latin American region, [3] followed by class B metallo-β-lactamases (MBLs) (VIM, IMP, NDM) and class D β-lactamases (OXA), especially the OXA-48 variant, have been already detected in some South American countries [4]. These

enzymes have become a major threat because they are located in mobile genetic elements, easily transferable among bacteria.

According to a worldwide surveillance of *Enterobacterales* by SENTRY, CRE infections showed a significant increase globally with greater impact in Latin America, with rates increasing from 0.8% in 1997 to 6.4% in 2016. The most predominant infections with CRE among hospitalized patients were pneumonia and bloodstream infection (BSI) (3.3% and 2.5%, respectively), while the prevalence in skin and soft tissue infection and urinary tract infection (UTI) was 1.8% and 1.2%, respectively [5].

Therefore, the prevention and control of CRE-associated infection becomes an important research topic. Currently, although general risk factors associated with the development of carbapenemase-producing carbapenem-resistant *Enterobacterales* (CP-CRE) infection have been described, the most associated factors are personal history of disease, invasive interventions and antibiotic use [6,7]. However, there are few studies relevant to perioperative patients.

The present study targeted nosocomial infections with CRE in perioperative patients in a single hospital in Cuba. We analyzed the microbiological characteristics of CP-CRE and explored the clinical-epidemiological factors of CP-CRE infection episodes.

## 2. Materials and Methods

### *2.1. Study Design and Description of the Institution*

We conducted a single-center retrospective study by a descriptive and observational analytical case-control method (patients with CP-CRE infection were included as cases, and compared with controls who were identified as patients infected by carbapenem-sensitive *Enterobacterales* to explore the risk factors for healthcare-associated infection due to CP-CRE. We further assessed mortality related to the same episode of infections in perioperative patients, as well as their microbiological characteristics of CRE, during the period 2017–2021.

All patients originated from a clinical-surgical hospital in Havana that provides third-level health care for the country's National Health System. The institution has 513 beds, including clinical area (253), surgical area (235), and critical care (25).

### *2.2. Microbiological Study*

A total of 124 CRE isolates were received at the National Reference Laboratory for Healthcare-Associated Infections (NRL-HAIs) of the Pedro Kouri Institute of Tropical Medicine during period from 2017 to 2021. Species identification was performed by conventional microbiological methods according to the Diagnostic Procedures Operations Manual (MOPD) of the NRL-HAIs, and the susceptibility was measured by the Epsilometer test (E-test) method and disk diffusion (Kirby-Bauer) on Müeller Hinton agar (Oxoid Ltd.).

Detection and characterization of carbapenemase type were conducted by phenotypic method, immunochromatographic method and molecular method by polymerase chain reaction (PCR). The phenotypic method used was the combined tablet method KPC-MBL Confirm ID Pack (Rosco Diagnostica, Denmark) for which the manufacturer's instructions were followed. For the immunochromatographic method, the commercial kit RESIST-4.O.K.N.V (Coris BioConcept®) was used according to the manufacturer's instructions. PCR was performed to determine the presence of *bla*KPC, *bla*NDM, *bla*IMP, *bla*VIM, *bla*SPM, *bla*GIM, *bla*SIM and *bla*OXA-48 genes. PCR primers and conditions described by Nordmann et al. (2011) were used [8].

### *2.3. Description of Populations*

After verification of 124 strains, through elimination of duplicate isolates and review of medical records, 88 patients with nosocomial CP-CRE infections were identified, forming the case group. These cases were matched with 88 controls of patients infected with carbapenem-sensitive *Enterobacterales* (CSE) with balanced age, hospitalization period,

distribution of services and sites of infection compared to the cases (Figure 1). The diagnosis of infections was based on the diagnostic criteria for nosocomial infection published by the United States Center for Disease Control (CDC) [9].

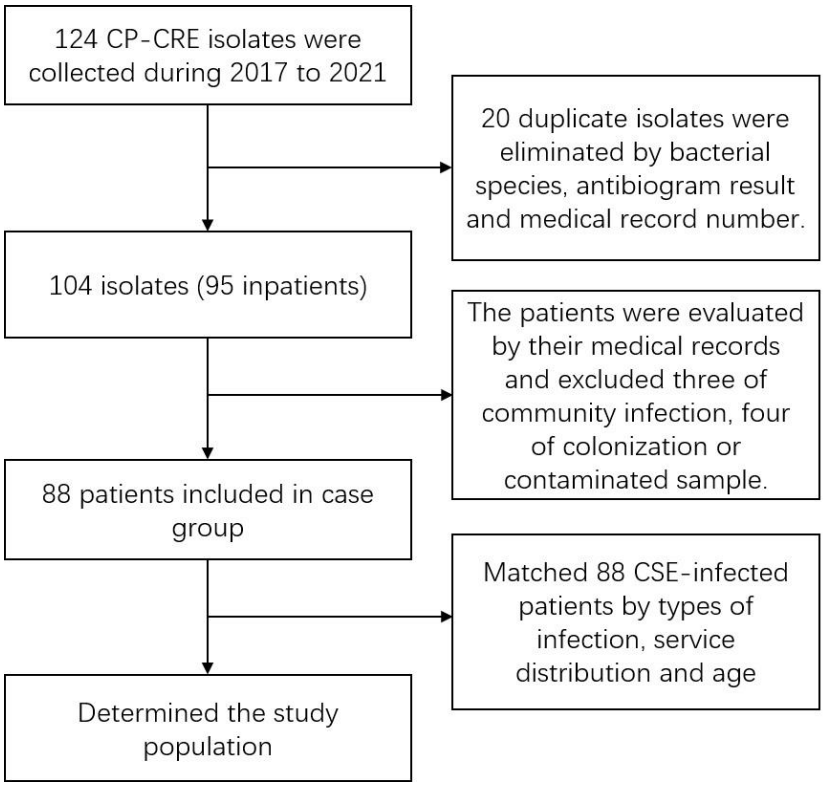


**Figure 1.** Flow chart of population identification.

### *2.4. Data Collection*

The study focused on the first episode of *Enterobacterales*-acquired infection during hospitalization, even if recurrent infections occurred. Demographic data, comorbidities (according to the Chalson index), date of admission and discharge, date of infection, risk factors present before diagnosis of infection (prolonged derivation, deep venous catheterization, urinary catheters or nephrostomy, nasogastric tube, mechanical ventilation, surgical operation, dialysis, previous admission within six months, transfer from other health centers, steroid use, previous antibiotic therapy), subsequent antibiotic treatment of this infection and clinical outcome were recorded.

### *2.5. Statistical Analysis*

Data were described using mean ± SD (quantitative variables) and percentages (qualitative variable). Comparison between groups for metric variables was performed using Student's *t*-test, while for non-parametric variables, the chi-square test and odds ratio were used. For the identification of risk factors for evolution to carbapenem resistance, binary logistic regression analysis was applied for multivariate comparison. Survival curve (Kaplan-Meier) and Cox regression were used for mortality analysis. The analyses were performed with SPSS 22.0 and Excel.

## 3. Results

**Microbiological study.** The confirmation of CP-CRE and characterization of carbapenemases are shown in Table 1. A wide dissemination of carbapenemases was observed in the *Enterobacterales* family, the highest prevalence of isolates corresponded to *K. pneumoniae*, followed by other species such as *E. cloacae*, *E. coli*, *K. aerogenes*, *S. marcescens*.

Identification of the type of carbapenemase was performed by two methods. A total of 124 metallo-betalactamase-producing isolates were identified. Of these, 55 isolates were processed by PCR, detecting 52 with a single NDM carbapenemase and three isolates with co-production of NDM and KPC. The remaining isolates (69 isolates) were confirmed as NDM enzyme producers by imunochromatographic test.

**Table 1.** Distribution of carbapenemase types according to methodology and bacterial species (*n* = 124 isolates).

| Methods | Carbapenemase Types | Species | | | | | |
|---|---|---|---|---|---|---|---|
| | | ***K. peumoniae*** **(Strains = 88)** | ***E. cloacae*** **(Strains = 16)** | ***E. coli*** **(Strains = 7)** | ***K. aerogenes*** **(Strains = 4)** | ***S. marcescens*** **(Strains = 4)** | **Others * (Strains = 5)** |
| **PCR (55 strains)** | **NDM** | 38 | 5 | 4 | 1 | 1 | 3 |
| | **NDM + KPC** | 2 | 0 | 0 | 1 | 0 | 0 |
| | **KPC** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Inmunocromatographic CORIS (69 strains)** | **NDM** | 48 | 11 | 3 | 2 | 3 | 2 |
| | **VIM** | 0 | 0 | 0 | 0 | 0 | 0 |
| | **OXA-48** | 0 | 0 | 0 | 0 | 0 | 0 |

*** Others:** *C. koseri*, *C. freundii*, *K. oxytoca*, *M. morganii*.

**Population study.** A total of 88 cases of CP-CRE healthcare-associated infections were diagnosed in the study period. The age distribution of cases ranged from 20–87 years, mean 55.5 ± 14.8; The distribution of cases according to hospital services, more than half of of patients were from intensive care unit (28.4%) and urology department (25%); About the infection site, the majority CP-CRE isolates were derived from blood (34.1%), urine (34.1%), surgical wound (20.5%). Patients infected with CSE were consecutively selected in a 1:1 ratio for controls (88 controls), matched for age, services and types of infection. The *p*-values of all these variables were greater than 0.05, and there were no statistically significant differences between cases and controls with respect to age, services and infection sites. (Table 2).

**Table 2.** Baseline demographic and clinical data of the population.

| Variables | Cases (*n* = 88) | Controls (*n* = 88) | *p*-Value |
|---|---|---|---|
| **Mean Age ± SD (range)** | 55.5 ± 14.8 (20–87) | 53.2 ± 15.5 (22–86) | 0.31 |
| **Services** | | | |
| Critical Care Unit (ICU y CCU) | 25 (28.4%) | 23 (26.1%) | 0.74 |
| Urology/Lithotripsy | 22 (25.0%) | 22 (25.0%) | 1 |
| General Surgery | 7 (8.0%) | 6 (6.8%) | 0.77 |
| Hematology | 4 (4.5%) | 4 (4.5%) | 1 |
| Nephrology | 4 (4.5%) | 4 (4.5%) | 1 |
| Internal Medicine | 6 (6.8%) | 5 (5.7%) | 0.76 |
| Transplantation | 4 (4.5%) | 6 (6.8%) | 0.51 |
| Neurology/Neurosurgery | 4 (4.5%) | 4 (4.5%) | 1 |
| Miscellaneous | 12 (13.6%) | 14 (15.9%) | 0.67 |
| **Infection Sites** | | | |
| Bloodstream infection | 30 (34.1%) | 30 (34.1%) | 1 |
| Urinary tract infection | 30 (34.1%) | 31 (35.2%) | 0.87 |
| Surgical site infection | 18 (20.5%) | 18 (20.5%) | 1 |
| Pneumonia | 7 (8.0%) | 6 (6.8%) | 0.77 |
| Intra-abdominal infection | 2 (2.3%) | 2 (2.3%) | 1 |
| Intracranial infection | 1 (1.1%) | 1 (1.1%) | 1 |

**Risk factors.** Risk factors associated with CP-CRE and CSE infections are shown in Table 3. By univariate analysis, CP-CRE infection was associated with length of hospitalization ($p < 0.01$), prolonged derivation ($p = 0.03$), nasogastric tube ($p = 0.01$), mechanical ventilation ($p = 0.03$), transfer from another healthcare facility ($p = 0.02$), steroid use ($p < 0.01$), prior use of two or more antibiotics ($p < 0.01$), prior use of 3rd or 4th generation cephalosporins ($p < 0.01$), prior use of aminoglycosides ($p < 0.01$) and prior use of carbapenem ($p < 0.01$). In multivariate analysis, prior steroid use (OR: 3.22, 95%CI: 1.36–7.66, $p < 0.01$), prior use of two or more antibiotics (OR: 4.04, 95%CI: 1.40–11.71, $p = 0.01$), prior use of extended-spectrum cephalosporins (OR: 2. 40, 95%CI: 1.06–5.44, $p = 0.04$) and prior use of carbapenem(OR: 4.77, 95%CI: 1.17–19.35, $p = 0.03$) were the independent risk factors for the progression of CP-CRE infection.

**Table 3.** Risk factors associated with CRE and CSE infections.

| Factors | Cases (N = 88) | Controls (N = 88) | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| | | | OR (IC 95%) | p-Valor | OR (IC 95%) | p-Valor |
| **Clinical characteristics** | | | | | | |
| Mean Charlson Index score ± SD | 3.1 ± 1.9 | 3.1 ± 2.2 | 1.01 (0.88–1.17) | 0.86 | — — | — — |
| Average length of hospitalization before infection | 27.1 ± 20.0 | 18.1 ± 14.5 | 1.03 (1.01–1.05) | **<0.01** | **1.00 (0.97–1.03)** | 0.95 |
| Previously admitted within 6 months | 36 (40.9%) | 28(31.8%) | 1.48 (0.80–2.75) | 0.21 | — — | — — |
| ** Prolonged Derivation (Brain, Thoracic, Abdominal) | 20 (22.7%) | 9 (10.2%) | 2.58 (1.10–6.05) | **0.03** | 0.93 (0.30–2.95) | 0.91 |
| Deep venous catheterization | 43 (48.9%) | 31 (35.2%) | 1.76 (0.96–3.22) | 0.07 | 0.52 (0.19–1.43) | 0.21 |
| Urinary catheters (>48 h) | 66 (75.0%) | 57 (64.8%) | 1.63 (0.85–3.13) | 0.14 | 1.52 (0.63–3.68) | 0.36 |
| Nasogastric tube | 36 (40.9%) | 20 (22.7%) | 2.35 (1.22–4.53) | **0.01** | 1.45 (0.37–5.76) | 0.60 |
| Mechanical ventilation | 26 (29.5%) | 14 (15.9%) | 2.22 (1.07–4.61) | **0.03** | 0.52 (0.12–2.23) | 0.34 |
| Surgery | 71 (80.7%) | 74 (84.1%) | 0.79 (0.36–1.72) | 0.55 | — — | — — |
| Dialysis | 9 (10.2%) | 10 (11.4%) | 0.89 (0.34–2.31) | 0.81 | — — | — — |
| Transfer from other health centers | 15 (17.0%) | 5 (5.7%) | 3.41 (1.18–9.84) | **0.02** | 2.98 (0.91–9.69) | 0.07 |
| Steroid use | 39 (44.3%) | 16 (18.2%) | 3.58 (1.80–7.11) | **<0.01** | 3.22 (1.36–7.66) | **<0.01** |
| Prior use of two or more antibiotics | 63 (71.6%) | 23 (26.1%) | 7.12 (3.67–13.83) | **<0.01** | 4.04 (1.40–11.71) | **0.01** |
| **Previous antibiotic use (with course ≥ 7 d)** | | | | | | |
| β-lactamase inhibitors | 20 (22.7%) | 14 (15.9%) | 1.56 (0.73–3.32) | 0.25 | — — | — — |
| Cephalosporin 1st or 2nd generation | 8 (9.1%) | 4 (4.5%) | 2.10 (0.61–7.25) | 0.24 | — — | — — |
| Cephalosporin 3rd or 4th generation | 53 (60.2%) | 26 (29.5%) | 3.61 (1.93–6.75) | **<0.01** | 2.40 (1.06–5.44) | **0.04** |
| Aminoglycoside | 38 (43.2%) | 13 (14.8%) | 4.39 (2.13–9.05) | **<0.01** | 2.06 (0.74–5.72) | 0.16 |
| Quinolone | 31 (35.2%) | 21 (23.9%) | 1.74 (0.90–3.35) | 0.1 | 0.78 (0.28–2.17) | 0.63 |
| Carbapenem | 27 (30.7%) | 4 (4.5%) | 9.30 (3.09–27.94) | **<0.01** | 4.77 (1.17–19.35) | **0.03** |
| Sulfonamide | 11 (12.5%) | 6 (6.8%) | 1.95 (0.69–5.54) | 0.21 | — — | — — |

** Prolonged Derivation: Brain derivation > 5 days; thoracic derivation > 3 days; abdominal derivation > 3 days.

**All cause 60-days mortality after CP-CRE acquisition.** The 60-days all-cause mortality in case group patients was 21.6% (19/88), compared to CSE-infected patients who had a mortality of 10.2% (9/88) ; the risk of mortality between the two groups was not significantly different, but *p*-value was close to the limit (HR = 2.094, $p = 0.068$) (Figure 2). Among those infected with CP-CRE, when comparing the risk of mortality in the different sites of infection, a higher risk was found in bloodstream-associated infections and pneumonia (Figure 3).

About the treatment for CRE-PC infection, 60.2% (53/88) patients were treated with combination therapy, 75.5% (40/53) of them were treated by colistin-based combination, 24.5% (13/53) by other combination (tigecycline or fosfomycin-based regimens). There are nine (22.5%) deceased patients who received colistin-based regimen, and three (23.1%) deaths from other regimens. The different combination therapy options on the probability of survival in CP-CRE infected patients was not significantly different ($p = 0.938$) (Figure 4).

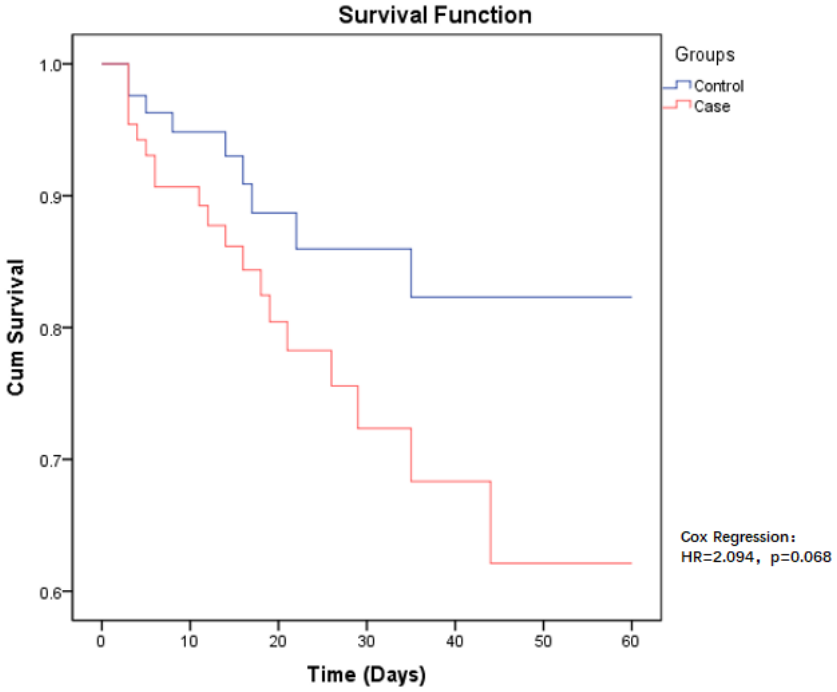


**Figure 2.** Kaplan-Meier estimates (and 95% confidence limits) of the survival probability for all-cause mortality in CP-CRE (Case) and CSE (Control) infections, 60 day follow up.

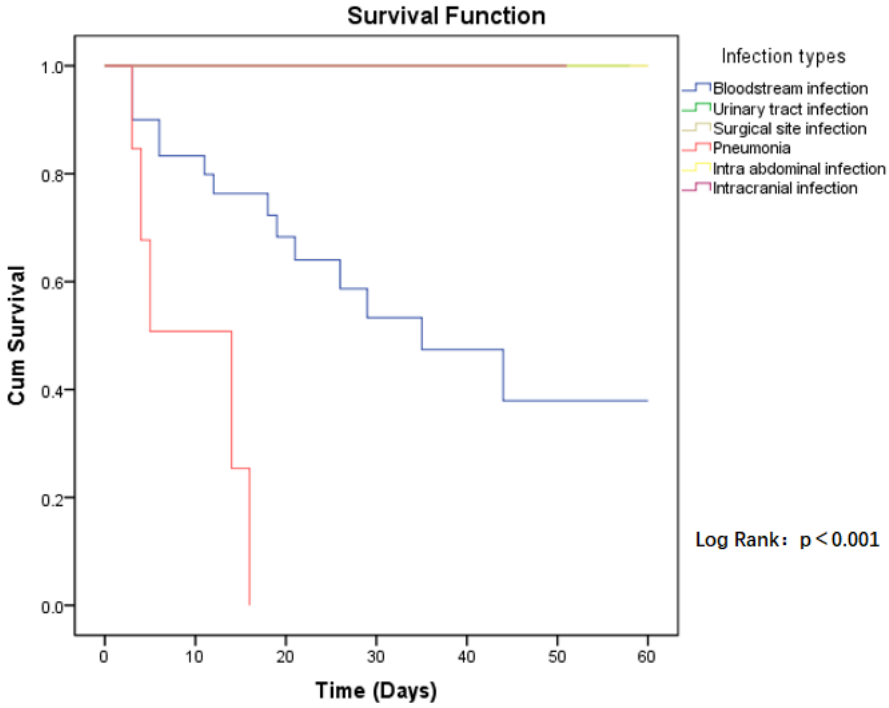


**Figure 3.** Kaplan-Meier estimates (and 95% confidence limits) of the survival probability for infection types in CP-CRE infections, 60 day follow up.

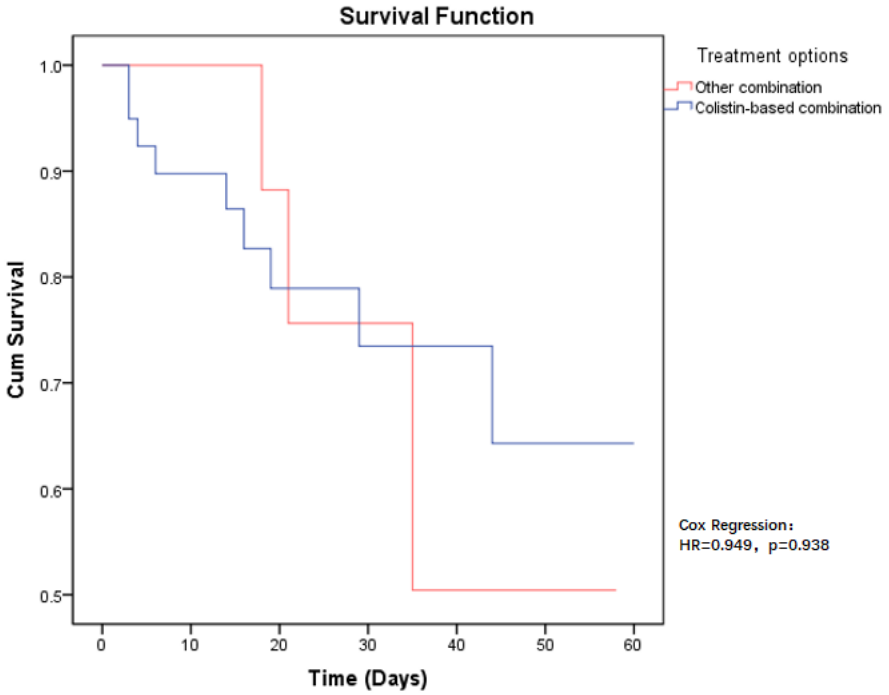


**Figure 4.** Kaplan-Meier estimates (95% CI) of the probability of survival for colistin-based combination therapy versus other combination (tigecycline or fosfomycin-based regimens) with 60-day follow-up.

## 4. Discussion

Carbapenem resistance among *Enterobacterales* is an emergent phenomenon of great importance in clinical and public health terms. According to the report of La Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA), from 2010 to 2019, a constant increase in resistance was reported in Latin America and the Caribbean, reaching prevalence above 60% in some countries [10].

Faced with this progressive public health problem, exploring the risk factors for its prevention and control, and seeking the best treatment option have become essential research.

Previous studies reported similar risk factors associated with CRE infection that are associated with length of hospitalization, ICU admission, central venous catheters use, solid-organ or stem cell transplantation, mechanical ventilation, and exposure to extended-spectrum antibiotics [11–13]. In this study, the independent factors were found to be associated with CP-CRE infection including steroid use and prior use (with course more than seven days) of two or more antibiotics. Among antibiotics, prior exposure (with course more than seven days) to cephalosporins (third or fourth generation) or carbapenem was associated with CRE-PC infection. It is important to note that in this study, because the control group selected was an CSE-infected patients, therefore, these risk factors are involved in the conversion of carbapenem-sensitive to carbapenem-resistant *Enterobacterales*. Another similar study, except that carbapenem use was consistent with this study, length of hospitalization and invasive procedures were also independent risk factors for progressing to CRE [14].

The NDM-type carbapenemase was detected form all isolates in this study. However, this contrasts with a review (2021), which describes widespread dissemination in mainly carbapenemase-producing *Enterobacterales* of the KPC type in the Latin American and Caribbean region [15]. In addition, since 2019, more and more reports from national reference laboratories members of ReLAVRA, have issued alerts about the increase in the number of isolates expressing double carbapenemases, especially the co-production of NDM and KPC are more frequent [16–18]. Cuba is not an exception from this problem; three *Klebsiella* spp. with co-production of NDM and KPC were detected in the present study.

The NDM-type carbapenemase is encoded by the plasmid gene *bla*NDM, easily transferable between bacteria, its rapid spread presents major epidemiological repercussions worldwide. In addition, the resistance patterns of Enterobacterales with the NDM enzyme present extensive resistance to β-lactam antibiotics and is not inhibited by beta-lactamase inhibitors, except aztreonam. However, when co-expression is present, especially, there are remarkable associations between $bla_{NDM}$ genes and multiple other resistance genes, such as genes encoding extended-spectrum β-lactamases (BLEE), AmpC or other class of carbapenemases (KPC) that lead to resistance to aztreonam, [19] also, combined with ribosomal rRNA methylases (16S-RMTases) additionally confer a high level of resistance to all aminoglycosides [20]. Most clinical bacteria carrying NDM gene are only sensitive in vitro to colistin, tigecycline and fosfomycin, or both [21]. For this reason, they are associated with high mortality rates. The present study documents an overall mortality rate at sixty days after CP-CRE infection of 21.6%, especially, it presented a higher risk of mortality in bloodstream-associated infections and pneumonia. However, other studies report even higher mortality rates, such as a review study (2016) reporting mortality rates between 30% and 75% for CP-CRE infections [22]. In addition, this study analyzed the probability of survival between patients infected by CP-CRE and ESC, under the same underlying conditions of patients (age, Charson index and hospitalization services), the mortality risk of patients infected by CP-CRE was twice as high as patients infected by CSE in the hospital setting, although the *p*-value is in borderline margin (IC95%, $p = 0.068$).

The optimal treatment for CP-CRE infections has not yet been defined and usually involves the use of tigecycline, colistin, amikacin and fosfomycin, alone or in combination with each other and with carbapenems [23]. However, the vast majority of studies and

different expert consensuses currently recommend combination therapy for patients with CP-CRE infection [24,25]. A meta-analysis study (2018) that evaluated the effect of treatments on mortality outcomes in patients with severe CP-CRE infections, monotherapy led to an increased risk of mortality, patients receiving only one antimicrobial had twice the probability of mortality compared to those treated with multiple active antibiotics; This risk increased markedly in patients with bacteraemia or generalized sepsis, where those treated with monotherapy were 3.8 times more probably to have mortality compared to patients receiving combination therapy [26]. On the other hand, combination therapy, in addition to their synergistic antibacterial effect to improve efficacy, from the perspective of prevention and control, this strategy can also be effective in preventing the evolution of resistance [27]. In this study, the majority of CP-CRE patients received combination therapy, mainly with a colistin-based regimen. However, this combination regimen was not found to reduce the risk of mortality for CP-CRE infection during hospitalization compared to patients treated with tigecycline or fosfomycin-based regimens. Currently, studies related to treatment options for CP-CRE usually focus on KPC or OXA-48 carbapenemase-producing Enterobacterales, in vitro studies or clinical trials found that in addition to combinations based on tigecycline, polymyxin or carbapenems presented a synergistic effect, newer drugs such as ceftazidime-avibactam, meropenem-vaborbactam and plazomycin, these possess greater advantages for carbapenemase KPC- or OXA-48-producing enterobacteria [23,25]. For MBLs-producing *Enterobacterales* in particular those that co-produce β-serine-type lactamases, treatment options are still limited. Preclinical and anecdotal clinical data support the use of aztreonam in combination with avibactam (aztreonam plus ceftazidime-avibactam or a new drug combination aztreonam-avibactam) against these pathogens, because aztreonam is a monobactam stable to hydrolysis by MBLs and avibactam is a β-lactam inhibitor that effectively inhibits serine carbapenemases, but other aztreonam-based combinations have not been explored [28,29].

**Limitations.** A limitation of the study is the relatively small number of patients; since it is a single-center study, these results may not be generalized to other centers where different factors could be contributing to similar infections. However, this study was necessary due to the observation of a rising trend of infections due to CP-CRE in Cuba, while it was the first case-control study addressing this issue for perioperative patients in the region.

The emergence and dissemination of NDM-type carbapenemase-producing *Enterobacterales* associated with HAIs is a great challenge for Cuban public health. From this single-center, observational study of cases and controls, it is reported that use of steroids and previous use (more than seven days) of two or more antibiotics, previous exposure (more than seven days) to cephalosporins (third or fourth generation) or carbapenem are the independent factors for the development of carbapenem-sensitive to carbapenem-resistant *Enterobacterales*. The infection by CP-CRE presented a higher mortality compared to CSE, especially in bacteraemia and pneumonia. Although treatment for infection by NDM-producing *Enterobacterales* is still limited, a combination therapy remains the currently preferred treatment option, but there is no evident difference in survival advantage for a colistin or tigecycline or fosfomycin-based regimen. Improved hand hygiene, barrier precautions, continuous education and surveillance, and antimicrobial stewardship are important measures to limit transmission of CRE in healthcare settings.

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**Conflicts of Interest:** The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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