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Research Article

Epidemiological Characteristics of Carbapenemase Producing Carbapenem-Resistant *Enterobacteriaceae* Colonization☆

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SUMMARY

Purpose: This study identified the epidemiological characteristics, including the size and major strains, of carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) and CP-CRE-related factors by comparing the characteristics of patients in the CP-CRE and non-CP-CRE groups and the CP-CRE and non-CRE groups.
Methods: This secondary data analysis study included 24 patients in the CP-CRE group, 113 patients in the non-CP-CRE group, and 113 in the non-CRE group. The size and type of CP-CRE were analyzed in terms of frequency and percentage, and CP-CRE risk factors were identified using multiple logistic regression analysis.
Results: The rate of CP-CRE positivity among patients with CRE was 17.5%, and the most common causative organism in the CP-CRE group was *Klebsiella pneumoniae* (81.8%). There were no significant differences between patients in the CP-CRE and non-CP-CRE groups. When compared with the non-CRE group, the isolation of multidrug-resistant organisms except for CRE, particularly vancomycin-resistant *Enterococcus*, was confirmed as a major risk factor.
Conclusion: To prevent CP-CRE acquisition, patients with multidrug-resistant organisms require treatment with more thorough adherence to CRE prevention and management guidelines.

Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) are antibiotic-resistant strains and refer to *Enterobacteriaceae* that have acquired resistance to carbapenem antibiotics [1]. CRE emerged after carbapenem antibiotics were used as a treatment for extended-spectrum beta-lactamase-producing gram-negative strains [2] and have become a global public health threat due to widespread antibiotic resistance and high mortality rates [3–7]. In the United States, there were 13,100 cases of CRE infection in 2019, with 1100 infections resulting in death [8]. In Korea, the number of reported CRE infections rose from 5717 in 2017 to 18,113 in 2020, with the number of deaths increasing sharply from 37 to 226 over the same period [9]. According to recent studies, including systematic literature review studies, exposure to antibiotics, especially carbapenems, is the most important risk factor for CRE acquisition [10,11]. In addition, underlying diseases, invasive procedures including mechanical ventilation, use of medical devices such as central venous tubes, admission to intensive care units (ICUs) [11–13], multidrug-resistant organism (MDRO) colonization or infection [13], Acute Physiology and Chronic Health Evaluation (APACHE) II score [12,13], and transfer between hospitals [12] are related to CRE acquisition.

Carbapenemase-producing CRE (CP-CRE) is a CRE that exhibits resistance to β-lactam antibiotics through the production of carbapenemase-producing enzymes [10,14] and is distinguished from non-CP-CRE, which exhibits antibiotic resistance through mechanisms such as the production of extended-spectrum β-

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lactamases (ESBL) or AmpC cephalosporinases with decreased outer membrane permeability [15,16]. Since the carbapenemase gene of CP-CRE is located in a mobile genetic element, such as a plasmid or transposon, it can demonstrate faster patient-to-patient transmission than non-CP-CRE [5,15]. Therefore, it is necessary to develop an effective CP-CRE management strategy based on an understanding of the characteristics that distinguish CP-CRE from non-CP-CRE or non-CRE.

According to previous studies, the positivity rate for CP-CRE differs depending on the CRE-infected or colonized patients varies widely from 20% [17] to 67.9% [18]. CP-CRE-related characteristics also showed different results depending on which of the CRE-infected or colonized patients were targeted. In a case-control study in which patients with CRE bacteremia were classified into CP-CRE and non-CP-CRE groups in China, old age, cancer, and use of carbapenem antibiotics were identified as risk factors for CP-CRE [19]. In a cohort study of US veterans, heart disease and gastroesophageal reflux disease [18] were identified as risk factors for CP-CRE. In contrast, in a study that divided patients with CRE into CP-CRE and non-CP-CRE groups at an Israeli tertiary hospital, prehospital antibiotic use, experience in nursing homes, and the presence or absence of pressure sores were identified as risk factors for CP-CRE; age was not a risk factor [20]. The use of mechanical ventilation was a protective factor for CP-CRE when the CP-CRE and non-CP-CRE groups were compared, whereas the use of mechanical ventilation appeared as a risk factor when compared with the non-CRE group [20]. In another study with CRE colonized group, the mechanical ventilation was identified as a risk factor for CP-CRE because the use of mechanical ventilation [21] in the CP-CRE group was higher than that of the non-CP-CRE group.

As a result of the literature review, studies on the CP-CRE positivity rate and related factors have been limited to a few countries, such as the United States, Israel, and China; therefore, information on epidemiologic characteristics is limited, and consistent results are not reported, with varying findings depending on the study population or design. In particular, the Korean government is strengthening efforts to identify the epidemiological characteristics of CP-CRE through the revision of regulations by requiring that CP-CRE clusters are identified, and an epidemiological investigation conducted to identify the source of infection [22]; nevertheless, there is very little research in this regard. Therefore, the purpose of this study was to identify the epidemiological characteristics of CP-CRE colonization in patients admitted to the ICU, a department where patients are at high risk of acquiring CRE. The specific objectives of this study were to investigate the size and major strains of CP-CRE and identify the CP-CRE-related factors by comparing the characteristics of patients in the CP-CRE and non-CP-CRE groups and the CP-CRE and non-CRE groups.

Methods

Study design

This case-control study used secondary data analysis to understand the epidemiological characteristics of CP-CRE in patients in the ICU.

Study participants

The primary data for this study came from previous studies that developed a CRE acquisition risk prediction model [13] and evaluated the external validity of the developed predictive model [23]. Each study was conducted using data between October 1, 2016 and October 31, 2017 and between November 1, 2017 and May 31, 2018, respectively. Eight hundred fifty-eight patients admitted to the ICU of a tertiary general hospital located in Y-city, and acquired CRE from the CRE active surveillance culture test at least once within 1 week of admission and from 1 week after admission until discharge, were included in the primary data (137 in the CRE acquisition group and 721 in the nonacquired group). In the study hospital, CRE active surveillance culture test was performed for every patient admitted to the ICUs using a perirectal swab within 7 days of hospitalization (baseline screening), and weekly thereafter until 7 days after discharge [13,23]. And all patients with CRE isolated from clinical specimens were also subjected to the test. CRE acquisition was confirmed not using clinical specimens but using a rectal swab for the purpose of active surveillance testing for CRE colonization. CRE colonization was confirmed by carbapenem antimicrobial susceptibility testing (imipenem $\leq$22 mm, $\geq$2 μg/mL minimum inhibitory concentration (MIC); ertapenem $\leq$21 mm, $\geq$1 μg/mL MIC) using the disk diffusion method, which was performed in accordance with the legal communicable disease diagnostic criteria of the KCDC [24]. For CRE cases, carbapenemase production was tested using the modified Hodge test (MHT) method based on the Clinical & Laboratory Standards Institute's recommendations. MHT is known to have a high level of sensitivity (>90%) and specificity (>90%) in detecting *Klebsiella pneumoniae* carbapenemase-type carbapenemases [25]. As a result of the test, 24 and 113 patients were allocated to the CP-CRE and non-CP-CRE groups, respectively.

The study participants were classified into three groups: CP-CRE, non-CP-CRE, and non-CRE groups. The non-CRE group was randomly selected to have the same number of participants as the non-CP-CRE group. For achieving this, 721 people in the non-CRE group were assigned a serial number; random numbers were generated using Excel, and 113 subjects with a serial number matching the generated numbers were selected as the non-CRE group. Therefore, the final numbers of the study participants were 24, 113, and 113 in the CP-CRE, non-CP-CRE, and non-CRE groups, respectively. The sample size for the case-control study design was calculated using an online program called the Open Source Epidemiologic Statistics for Public Health [26] at 0.05 as the significance level (α), 0.80 as the power, and 1:5 as the ratio of cases to controls [27]. For an exposure ratio of 20.8% and odds ratio of 4.1 for the control group, assuming that mechanical ventilation was a risk factor for CP-CRE based on a previous study [21], the minimum sample required was 19–24 in the case group and 94–119 in the control group.

Study variables

The variables examined in this study were demographic characteristics, clinical characteristics at the time of admission to the ICU, and clinical characteristics during ICU stay, which were mainly considered for CRE-related factor studies [11–13,17] or CP-CRE-related factor studies [18–21]. Sex and age variables were included as demographic characteristics, and clinical characteristics at the time of admission to the ICU included APACHE II score, Charlson comorbidity index score (CCIS), and underlying diseases (diabetes, heart disease, respiratory disease, renal disease, liver disease, and solid cancer). APACHE II score was used instead of APACHE III because the study hospital uses a computerized system that automatically calculates the APACHE II score. A recent study showed a very similar diagnostic accuracy of in-hospital mortality between APACHE II and III [28]. Clinical characteristics during the ICU stay included three items: invasive procedures and instruments, use of antibiotics, and isolation of multidrug-resistant organisms (MDROs). Invasive procedures and instruments included surgery, transplantation, endoscopy, bronchoscopy, continuous renal replacement therapy, indwelling catheters, central venous

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catheters, ventilators, and drainage tubes. Antibiotics comprised penicillin, carbapenem, cephalosporin, fluoroquinolone, and vancomycin. The isolation of multidrug-resistant bacteria included vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL), and MDR *Acinetobacter baumannii*. Data were collected from the date of hospitalization until the date of CRE colonization for the CRE-colonized group (CP-CRE group and non-CP-CRE group) and until the date of discharge from ICUs for the non-CRE group.

Data analysis

The collected data were analyzed using the SPSS/WIN software (version 25.0; IBM Corp., Armonk, NY, USA). A two-tailed test was performed with a significance level (α) of 0.05. The size and type of CP-CRE and participants' baseline characteristics were analyzed as frequency and percentage for categorical data and median and interquartile range for continuous data because they were not normally distributed.

Bivariate analysis was conducted using simple logistic analysis to compare the baseline characteristics between the two groups (CP-CRE group vs. non-CP-CRE or non-CRE group), and the unadjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated. With all variables as significant factors at a significance level (α) of 0.05, the adjusted ORs and the associated 95% CIs were calculated through forward stepwise multiple logistic regression analysis after confirming no deviation from the assumption of multicollinearity with a coefficient of determination of less than .80 [29], and variance inflation factor of ranging from 1.03 to 1.19.

Ethical considerations

This study was conducted after receiving approval of exemption from review (No. 05-2021-127) from the Institutional Review Board (IRB) of Pusan National University Yangsan Hospital. All data were anonymized.

Results

Among the 137 patients in the CRE group in this study, 24 patients were included in the CP-CRE group, giving a CP-CRE positivity rate of 17.5%. The most common infectious agent in the CP-CRE group was *K. pneumoniae* (79.1%), followed by *Escherichia coli* (12.5%); in the non-CP-CRE group, *K. pneumoniae* (82.3%) was the most common, followed by *Enterobacter* spp. (8.8%) and *E. coli* (7.1%) (Table 1).

Table 2 presents the baseline characteristics of the participants. For the CP-CRE group, 62.5% were male, 20.8% were transferred from another medical institution, the median CCIS score was 1.5, 79.2% had an underlying disease, 50.0% underwent bronchoscopy, 41.7% received carbapenem antibiotics, and 79.2% had MDROs other than CRE. There was no significant difference in variables between the CP-CRE and non-CP-CRE groups; however, the CP-CRE group had a higher median CCIS score (1.50 vs. 1.00, $p = .044$), bronchoscopy rate (50.0% vs. 26.5%, $p = .027$), and overall MDROs (except MRSA) isolation rate (79.2% vs. 34.5%, $p < .001$) than those in the non-CRE group (Table 2).

Table 3 shows the results of multiple logistic regression analyses to identify the CRE risk factors using variables that were significant in the simple logistic regression analysis for the CP-CRE and non-CRE groups as explanatory variables. In Model 1, regardless of the type of multidrug-resistant bacteria, isolation was used as an explanatory variable, and as a result, the risk factor for acquiring CP-CRE was confirmed as an isolate of multidrug-resistant bacteria, which was related to a 5.88 times increase the risk of acquiring CP-CRE ($p = .001$) relative to when multidrug-resistant bacteria were not isolated. In Model 2, when individual multidrug-resistant bacteria were included in the model, only VRE was identified as a risk factor for acquiring CP-CRE.

Table 1 *Microbiological Characteristics of CP-CRE and Non-CP-CRE.*

Microorganisms	CP-CRE (n = 24) n (%)	Non-CP-CRE (n = 113) n (%)	Total (137) n (%)
Klebsiella pneumoniae	19 (79.1)	93 (82.3)	112 (81.8)
Escherichia coli	3 (12.5)	8 (7.1)	11 (8.0)
Enterobacter aerogens	0 (0.0)	6 (5.3)	6 (4.4)
Enterobacter cloacae	0 (0.0)	4 (3.5)	4 (2.9)
Citrobacter freundii	1 (4.2)	1 (0.9)	2 (1.5)
Serratia marcescens	1 (4.2)	0 (0.0)	1 (0.7)
Providencia rettgeri	0 (0.0)	1 (0.9)	1 (0.7)

CP-CRE = Carbapenemase producing carbapenem-resistant *Enterobacteriaceae*.

Discussion

In this study, CP-CRE was confirmed in 17.5% of patients in the CRE group. This result is similar to the 20.0% CP-CRE-positive rate [17] obtained in a study in patients with CRE admitted to ICUs and transplant wards of a single hospital in the United States. However, it is much lower than the 27.7% [18] reported in a study using a cohort of patients admitted to 127 veterans hospitals in the United States and the 31.5% reported by the US Centers for Disease Control and Prevention' Antibiotic Resistance Laboratory Network [30], and 44.7% of national surveillance report using both active surveillance cultures and clinical samples from 189 institutions in Korea [31]. This result may be related to the difference in the sample mix; colonized by or infected with CRE. The former two studies, including this study, targeted those colonized by CRE, while the latter three studies with higher positivity rates for CP-CRE examined the CRE-infected group or both. In particular, it showed a higher CP-CRE positivity rate in patients with bloodstream infections. Zou et al [19] study of patients with CRE bacteremia showed a CP-CRE-positive rate of 67.9%. In a cohort study of patients with CRE bacteremia at a tertiary hospital in Korea, the CP-CRE positivity rate was as high as 47.4% [32]. Therefore, even in the same CRE group, it seems that the CP-CRE positivity rate is higher in patients who are infected, especially in the bloodstream infection stage, compared with those at the colonized stage. Nevertheless, it is necessary to confirm this through repeated studies in various settings.

The major strain in the CP-CRE group in this study was *K. pneumoniae*, which supports the results of previous studies which reported that *K. pneumoniae* was the most common CP-CRE strain, regardless of whether it was a CP-CRE-colonized [21] or CP-CRE-infected group [18,19]. In addition, *K. pneumoniae* is the most common CP-CRE strain over the past 10 years from the analysis of national surveillance data in the Republic of Korea [31,33]. *K. pneumoniae* accounted for 62.8% [31] to 88.7% [21] of CP-CRE strains, and the result in this study was within this range. The next most frequently isolated strains were *E. coli* and *Enterobacter* spp., which is consistent with the previous reports using national surveillance data [31,33]. However, the rankings differed depending on the study. *E. coli* was found in 4.4% [18] to 20% [19,21] of the CP-CRE group, and *Enterobacter* spp. in 9.1% [19] to 13.1% [18]. In this study, only *E. coli* was detected in the CP-CRE group, whereas both strains were detected in the non-CP-CRE group.

For CP-CRE-related factors, some variables, such as invasive procedures and instruments, and antibiotics, were analyzed for

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Table 2 *Comparison of Characteristics of Study Participants Among Three Groups.*

Variables	CP-CRE (n = 24)	Non-CP-CRE (n = 113)	Non-CRE (n = 113)	CP-CRE vs. Non-CP-CRE		CP-CRE vs. non-CRE	
	n (%) or median (IQR)	n (%) or median (IQR)	n (%) or median (IQR)	OR (95% CI)	*p*	OR (95% CI)	*p*
Demographic characteristics							
Male sex	15 (62.5)	76 (67.3)	67 (59.3)	0.81 (0.33–2.03)	.654	1.14 (0.46–2.84)	.771
Age (years)	56.5 (24–69)	59.0 (26–67)	60.0 (28–74)	1.00 (0.98–1.02)	.951	1.00 (0.98–1.01)	.646
Clinical characteristics at ICU admission							
Transfer from LTCF	4 (16.7)	7 (6.2)	7 (6.2)	0.73 (0.25–2.12)	.561	0.88 (0.30–2.59)	.817
APACHE II	19 (12–27)	21 (16–25)	16 (12–22)	0.97 (0.91–1.03)	.289	1.06 (1.00–1.14)	.069
CCIS	1.50 (0–3)	2.00 (0–3)	1.00 (0–2)	1.03 (0.79–1.33)	.846	1.35 (1.01–1.82)	.044
Underlying disease							
DM	4 (16.7)	26 (23.0)	23 (20.4)	0.67 (0.21–2.13)	.497	0.78 (0.24–2.51)	.681
CHD	11 (45.8)	44 (38.9)	56 (49.6)	1.33 (0.55–3.22)	.532	0.86 (0.36–2.08)	.740
CRD	4 (16.7)	13 (11.5)	7 (6.2)	1.54 (0.46–5.21)	.489	3.03 (0.81–11.31)	.099
CLD	5 (20.8)	22 (19.5)	18 (15.9)	1.09 (0.37–3.24)	.879	1.39 (0.46–4.20)	.561
CKD	1 (4.2)	11 (9.7)	7 (6.2)	0.40 (0.05–3.28)	.396	0.66 (0.08–5.61)	.702
Cancer	4 (16.7)	19 (16.8)	9 (8.0)	0.99 (0.30–3.22)	.986	2.31 (0.65–8.24)	.197
Any disease	19 (79.2)	82 (72.6)	80 (70.8)	1.44 (0.49–4.18)	.506	1.57 (0.54–4.55)	.408
Clinical characteristics during ICU stay							
Invasive procedures/device							
Surgery	11 (45.8)	52 (46.0)	36 (31.9)	0.99 (0.41–2.40)	.987	1.81 (0.74–4.43)	.194
Transplantation	4 (16.7)	18 (15.9)	13 (11.5)	1.06 (0.32–3.46)	.929	1.54 (0.46–5.21)	.489
Bronchoscopy	12 (50.0)	51 (45.1)	30 (26.5)	1.22 (0.50–2.94)	.664	2.77 (1.12–6.82)	.027
Endoscopy	7 (29.2)	28 (24.8)	15 (13.3)	1.25 (0.47–3.33)	.655	2.69 (0.96–7.57)	.061
CRRT	6 (25.0)	41 (36.3)	25 (22.1)	0.59 (0.22–1.59)	.294	1.17 (0.42–3.27)	.760
Urinary catheter	23 (95.8)	108 (95.6)	105 (92.9)	1.07 (0.12–9.55)	.955	1.75 (0.21–14.71)	.605
CVC	21 (87.5)	106 (93.8)	93 (82.3)	0.46 (0.11–1.93)	.291	1.51 (0.41–5.54)	.538
MV	19 (79.2)	98 (86.7)	71 (62.8)	0.58 (0.19–1.79)	.345	2.25 (0.78–6.47)	.133
Drainage tube	14 (58.3)	71 (62.8)	48 (42.5)	0.83 (0.34–2.03)	.680	1.90 (0.78–4.63)	.160
Antibiotic treatment							
Penicillin	18 (75.0)	91 (80.5)	67 (59.3)	0.73 (0.26–2.04)	.543	2.06 (0.76–5.58)	.156
Carbapenem	10 (41.7)	61 (54.0)	28 (24.8)	0.61 (0.25–1.49)	.276	2.17 (0.87–5.43)	.098
Cephalosporin	20 (83.3)	84 (74.3)	80 (70.8)	1.73 (0.55–5.47)	.354	2.06 (0.66–6.50)	.216
Fluoroquinolone	17 (70.8)	78 (69.0)	62 (54.9)	1.09 (0.42–2.86)	.862	2.00 (0.77–5.19)	.156
Vancomycin	9 (37.5)	52 (46.0)	37 (32.7)	0.70 (0.29–1.74)	.447	1.23 (0.49–3.08)	.654
MDROs carrier							
VRE	14 (58.3)	46 (40.7)	23 (20.4)	2.04 (0.83–4.99)	.118	5.48 (2.16–13.91)	<.001
MRSA	2 (8.3)	20 (17.7)	6 (5.3)	0.42 (0.09–1.94)	.269	1.62 (0.31–8.57)	.569
ESBL	7 (29.2)	46 (40.7)	13 (11.5)	0.60 (0.23–1.56)	.295	3.17 (1.11–9.08)	.032
MDR *A. baumannii*	6 (25.0)	31 (27.4)	10 (8.8)	0.88 (0.32–2.43)	.807	3.43 (1.11–10.62)	.032
Any MDROs	19 (79.2)	93 (82.3)	39 (34.5)	0.82 (0.27–2.45)	.718	7.21 (2.50–20.79)	<.001

APACHE = Acute physiology and chronic health evaluation; CCIS = Charlson comorbidity index score; CHD = Chronic heart disease; CI = Confidence interval; CKD = Chronic kidney disease; CLD = Chronic liver disease; CP-CRE = Carbapenemase producing carbapenem-resistant *Enterobacteriaceae;* CRD = Chronic respiratory disease; CRE = Carbapenem-resistant *Enterobacteriaceae*; CRRT = Continuous renal replacement therapy; CVC = Central venous catheter; d = days; DM = Diabetes mellitus; Dx = Disease; ESBL = Extended spectrum beta-lactamase; IQR = Interquartile range; MDROs = Multidrug resistant organisms; MRSA = Methicillin resistant *Staphylococcus aureus*; OR = Odds ratio; VRE = Vancomycin resistant *Enterococci*.

Table 3 *Multivariate Analysis of Risk Factors of CP-CRE: CP-CRE versus non-CRE.*

Variables	B	SE	OR (95% CI)	*p*	*VIF*
Model 1					
Charlson comorbidity index score	0.27	0.17	1.32 (0.95–1.82)	.097	1.03
Any MDROs isolated	1.77	0.55	5.88 (1.99–17.43)	.001	1.12
Bronchoscopy	0.66	0.50	1.93 (0.73–5.13)	.187	1.10
Model 2					
Charlson comorbidity index score	0.19	0.17	1.21 (0.86–1.70)	.280	1.11
Vancomycin resistant *enterococci*	1.37	0.51	3.92 (1.44–10.70)	.008	1.15
Extended spectrum beta-lactamase	0.76	0.61	2.14 (0.65–6.99)	.210	1.05
MDR *A. baumannii*	0.98	0.68	2.67 (0.70–10.13)	.150	1.14
Bronchoscopy	0.51	0.53	1.67 (0.59–4.75)	.339	1.19

APACHE = Acute physiology and chronic health evaluation; CI = Confidence interval; HR = Hazard ratio; CP-CRE = Carbapenemase producing carbapenem-resistant *Enterobacteriaceae*; CRE = Carbapenem-resistant *Enterobacteriaceae*; SE = Standard error; VIF = Variance inflation factor.

correlations with CP-CRE depending on whether they were used [19–21] or their period of use [18]. In this study, only the model including this category was used because there was a difference in the data collection period between the CRE group and non-CRE group, which may distort the results. After confirming the factors related to CP-CRE, there were no distinct characteristics between the CP-CRE and non-CP-CRE groups. However, when compared with the non-CRE group, the isolation of MDROs except for CRE, particularly VRE, was confirmed as a major risk factor. A previous study showed that the presence of MDRO colonization within one year in patients admitted to acute-care hospitals from long-term care facilities is a risk factor for new MDRO colonization [34]. However, it is difficult to find results suggesting that other types of MDRO are risk factors for CP-CRE. In a study conducted in Israel, other types of multidrug-resistant bacteria were associated with CP-CRE, but these were not identified as significant variables in the multiple logistic regression analysis [21]. Unlike other MDROs, VRE was derived as a risk factor for acquiring CRE. The reason may relate to the fact that the major reservoir of VRE and CRE is common in the lower gastrointestinal tract [35]. A healthy gastrointestinal microbiota can provide resistance to multi-drug resistant organisms such as VRE and CRE. However, antibiotic-mediated destruction of the intestinal microbiota and consequent loss of colonization resistance leads to antibiotic-resistant organisms' colonization and infection [11,36–38].

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CCIS and bronchoscopy use were associated with CP-CRE in the univariate analysis but not with CP-CRE in multivariate analyses. The CCIS score of the CP-CRE group was higher than that of the non-CRE group in this study. In a study by Kassem et al [20] conducted in Israel, the CCIS score was significantly higher in the non-CP-CRE group than in the CP-CRE group, but multiple logistic regression analysis showed that CCIS was not related, which was consistent with the finding that it was not a risk factor for CP-CRE. CCIS is an index developed to predict the risk of death within one year of hospitalization based on the number of comorbidities and is often used to evaluate the prognosis or survival of patients [39]. Kassem et al [20] reported that as the CCIS score increased by 1 point, the in-hospital mortality rate increased by 1.09 times, indicating that CCIS reflects in-hospital mortality. The CCIS score has been reported to be related to increased mortality rates for the coronavirus disease in 2019 [40]. Regarding the relationship between bronchoscopy and CRE infection, Mehta & Muscarella [41] reported suspected cases of CRE infection due to inappropriate reprocessing of bronchoscopy following literature review and Internet searches. In these cases, the risk of CRE transmission due to bronchoscopy is underestimated, emphasizing the interest of healthcare workers and the importance of appropriate reprocessing of bronchoscopies [41]. In this study, the statistical power of the use of bronchoscopy was only 42%; therefore, it was not confirmed as a factor related to CP-CRE. Repeated studies using a larger sample are required in the future.

Clinical implications

As a result of this study, CP-CRE acquisition was found to occur frequently in patients admitted to the ICU. Factors that increase the risk of CP-CRE in patients with CRE were not identified, but the risk of CP-CRE increases when MDROs are isolated from patients without CRE. When a specific MDRO is identified in a patient, even though precautions such as contact isolation are applied, inappropriate or incomplete application of precaution or the patient's vulnerability to any kind of MDRO should be considered [21]. If MDROs are isolated from a patient for any reason, such patients require treatment with more thorough adherence to CRE prevention and management guidelines. Our findings added the importance of prevention and control of CRE acquisition and spread in the ICUs, as CP-CRE is more easily transmitted between patients by using a mobile genetic element than non-CP-CRE [5,15]. In addition, with the advancement of personalized care, CP-CRE/non-CP-CRE/non-CRE stratification can better guide the prevention and control of CP-CRE acquisition.

Strengths and limitations

Management of CP-CRE through an understanding of the epidemiologic characteristics of CP-CRE is important to prevent the rapid transmission of CRE. In particular, when the CP-CRE test is difficult to perform or the patient refuses the test, the population at high risk of CP-CRE can be managed more effectively by identifying the characteristics that distinguish CP-CRE from non-CP-CRE or non-CRE. Given that studies on the epidemiologic characteristics of CP-CRE at home and abroad are very limited, the results of this study can improve understanding of the progression of CP-CRE among CRE-colonized patients or non-CRE patients admitted to ICUs.

However, careful interpretation of the results is required because of the following limitations. First, since this study is a secondary data analysis study using existing data, variables identified as CP-CRE-related factors in previous studies [20] but were not included in the primary data sources (for example, pressure ulcers and use of antibiotics prior to admission) were excluded from the explanatory variables. Second, data were collected from the date of hospitalization until the date of CRE colonization for the CRE colonized group (CP-CRE group, non-CP-CRE group) and until the date of discharge from the ICU for the non-CRE group, where differences in data collection time can influence the length of stay in the ICU. Therefore, the duration of ICU stay was not considered in this study. Consequently, while the length of stay in the ICU has been identified as a factor related to CP-CRE in previous studies [19], it was excluded as an explanatory variable in this study. Third, this study could not identify the factors related to the acquisition of CP-CRE among those with CRE colonization. This is thought to be because poor statistical power was expected when the sample size was calculated, and repeated studies using a larger sample are suggested in the future. Last, the primary data included ICU patients hospitalized in a single hospital, and the generalizability of the findings to other hospitals or settings may be limited.

Conclusion

As a result of this study, approximately 2 out of 10 patients who were colonized by CRE after admission to the ICU had CP-CRE, and the most common causative strain was *K. pneumoniae*. The CP-CRE group did not have any characteristics distinguishing it from the non-CP-CRE group; however, the isolation rate of multidrug-resistant bacteria, especially VRE, was higher than that in the non-CRE group. When multidrug-resistant bacteria are primarily isolated from hospitalized patients, strict adherence to CRE prevention and management guidelines is required to prevent the rapid spread of CRE between patients. In the case of patients with isolated VRE, it is recommended to conduct a screening test to confirm the presence of CP-CRE colonization and isolate carriers promptly, according to the results. Q3,4

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