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Distribution and Risk Factors of Carbapenem-Resistant Enterobacterales in General Hospitals in South Korea

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Abstract: The emergence of Carbapenem-Resistant Enterobacterales (CRE) presents a significant global health challenge due to its high resistance to broad-spectrum β-lactam antibiotics. CRE infections are increasingly common in hospital settings and are associated with high mortality rates. In South Korea, the increase in CRE infections necessitates a detailed investigation into their distribution and risk factors to inform effective management and prevention strategies. Therefore, the aim of this study was to analyze the distribution of CRE and its major risk factors through surveillance culture tests among high-risk patients at a small general hospital in Asan, South Chungcheong Province, South Korea from February 2023 to mid-May 2024, and compile basic data for managing and preventing CRE infections. Herein, 173 out of the 2,078 high-risk patients were CRE positive, with a positive rate of 8%. Carbapenemase-Producing Enterobacterales (CPE) accounted for 65% of the CRE-positive patients. Among the CRE- or CPE-positive strains, Klebsiella pneumoniae with the KPC gene was the most prevalent. Old age (>70 years, $p = 0.015$) and history of hospitalization in nursing homes ($p = 0.045$) or intensive care units ($p = 0.002$) were significant risk factors for CRE and CPE positivity. Significant age-related differences were observed, with CRE and CPE infections more frequent in patients aged >70 years. The study highlights a high prevalence of CRE and CPE, particularly in older adults, those transferred to nursing homes, and those with a history of admission to intensive care units. They should be closely monitored for underlying diseases, previous bacterial culture results, and use of invasive devices. To reduce CRE and CPE infections, rapid CPE gene detection and expanded surveillance culture targets are recommended, especially in high-risk settings, such as intensive care units and long-term care facilities.

Keywords: Carbapenemase-Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, Intensive Care Units

Introduction

The increased use of antibacterial agents worldwide is leading to the emergence of multidrug-resistant bacteria, with Carbapenem-Resistant Enterobacterales (CRE) being the most challenging bacteria. CRE is a family of Enterobacterales resistant to one or more carbapenem antibiotics, such as imipenem, meropenem, doripenem, and ertapenem, which belong to the β-lactam family (Lee and Kim, 2023).

CRE was first documented in North Carolina, USA, in 2001 (Gao *et al*., 2022; Seo *et al*., 2021) and was first reported in Korea in 2011 (Lee *et al*., 2016). They are the main cause of hospital-acquired infections, which have been continuously increasing since then according to a study by Yun *et al.* (2022). Looking at the status of multidrug-resistant bacterial infections in the medical institutions that participated in this study, CRE caused the highest proportion of multidrug-resistant infections at 40%, whereas methicillin-resistant Staphylococcus aureus, multiresistant Acinetobacter baumannii, multiresistant Pseudomonas aeruginosa, and vancomycin-resistant Enterococcus caused 32, 20, 4.5 and 3.5%, respectively, of all multidrug-resistant infections. In 2017,

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the World Health Organization (WHO) reported that the mortality rate due to CRE infection was 26% (Gao *et al*., 2022), highlighting the need for global action. Addressing this issue has become a major public health priority. CRE is problematic because carbapenem antibiotics, which are broad-spectrum beta-lactam antibiotics, are used as a last resort to treat infections caused by bacteria that produce extended-spectrum beta-lactamases (Nordmann *et al*., 2011; Chang *et al*., 2015). Therefore, the presence of CRE hinders successful treatment (Lee and Kim, 2023).

In addition, resistance to several classes of antibiotics other than carbapenems is common, making treatment of infections difficult and resulting in high mortality and morbidity rates (Gao *et al*., 2022; Jung and Park, 2022; Lee *et al*., 2021).

Depending on the mechanism of antibiotic resistance, CRE can be classified into Carbapenemase-Producing Enterobacterales (CPE) and non-carbapenemase-producing Enterobacterales (non-CPE) (Yun *et al*., 2022). Carbapenemases are classified into three types according to the Ambler classification system (Korea Centers for Disease Control and Prevention, 2024): Class A (Serine Carbapenemases), class B (Metallo-B-Lactamases) and class D (oxacillinase carbapenemases). Carbapenemases commonly identified in Enterobacterales include Klebsiella Pneumoniae Carbapenemase (KPC) and Guiana extended-spectrum β-lactamase, which belong to class A and New Delhi Metallo-β-lactamase (NDM) and Imipenemase (IMP), which belong to class B. Class D includes Oxacillinase (OXA-48) (Woo, 2019). Carbapenemase-producing genes are usually located on plasmids and transposons that facilitate horizontal gene transfer; therefore, these genes can easily transfer to different gram-negative enteric bacteria (Lee and Kim, 2023; Yun *et al*., 2022; Kotsanas *et al*., 2013; Pan *et al*., 2019), leading to a drastic increase in the number of CPE cases within medical institutions (Yun *et al*., 2022; Korea Centers for Disease Control and Prevention, 2024; Logan and Weinstein, 2017). In addition, CPEs have a considerably higher incidence rate in medical institutions compared with non-CPEs (Korea Centers for Disease Control and Prevention, 2024; CDC, 2015). Therefore, prompt identification of patients with CPE infections and pathogen carriers is key to preventing the spread of infection (Nordmann *et al*., 2011; Yun *et al*., 2022; Park *et al*., 2020).

Due to the genetic factors mentioned before, CRE spread through contact transmission, including direct or indirect contact with patients with CRE infections or pathogen carriers, as well as through contaminated instruments, items, or environmental surfaces (Lee *et al*., 2021; Yeonju *et al*., 2020). Therefore, strict adherence to standard and contact precautions is important. In South Korea, CRE is legally classified as a class 2 infectious disease along with tuberculosis, measles, and cholera. The spread of CRE should be prevented through quarantine or reporting within 24 h, in accordance with the regulations for class 2 infectious diseases. The Korea Disease Control and Prevention Agency defines a cluster outbreak of CPE infection as the occurrence of CPE infection in two or more patients or pathogen carriers with confirmed epidemiological links in the same medical institution. Since June 2017, the Korea Centers for Disease Control and Prevention Agency has established a comprehensive surveillance system to report CRE infections, determine the scale of outbreaks, and conduct local epidemiological investigations to prevent the spread of CRE infections. In the USA, CRE causes 13,000 infections and 1,100 related deaths, accounting for the expenditure of $130 million towards medical care annually (Lee and Kim, 2023). The Centers for Disease Control and Prevention (CDC) in the USA recommends early identification of patients infected with CRE and implementation of infection control precautions to prevent transmission. For example, Illinois has implemented a statewide registry for broadly antimicrobial-resistant organisms. This is an interactive public health informatics tool that provides a standardized reporting mechanism for patients carrying CRE across all healthcare facilities across the state. This aids in reducing the spread of CRE and facilitates early detection and intervention in receiving facilities (Logan and Weinstein, 2017).

Purpose of the Study

The aim of this study was to analyze the distribution and major risk factors of CRE occurring in small general hospitals and thus compile basic data for the management and prevention of CRE infections. The following are the specific goals of this study:

1. CRE incidence survey: Between February 2023 and mid-May 2024, CRE surveillance culture tests were conducted on high-risk patients to detect CRE and investigate the incidence of CRE infection
2. Analysis of the distribution of major CRE pathogens: The distribution of major pathogens isolated from CRE-positive patients was analyzed to evaluate the proportion and importance of specific pathogens in CRE infections
3. CPE genotype distribution analysis: The distribution of CPE genotypes among CRE-positive patients was assessed. The prevalence of transmission rate may vary depending on the specific CPE genotype and treatment medications may vary. Therefore, identifying the genotype distribution can assist in

infection control and treatment

4. Analysis of CRE and CPE distribution by sex and age: Through the analysis of the distribution of CRE and CPE by sex and age, we evaluated the risk of infection within specific demographic groups. This will facilitate the development of customized infection control strategies
5. Risk factor analysis: The relationship between CRE and CPE infection with various risk factors, including Intensive Care Unit (ICU) hospitalization history, nursing facility hospitalization history, main diagnosis, and presence or absence of invasive device insertion was examined. Identifying key risk factors facilitates the development of prevention and management strategies and aids in creating indicators for proactive testing that focus on the identified risk factors
6. Analysis of correlation between the blood test and infection: The correlation between infection-related blood test values, including glucose levels, C-reactive protein (CRP) levels, and White Blood Cell (WBC) and CRE and CPE infections were evaluated to identify potential diagnostic indicators for the early detection and management of these infections

Thus, the aim of this study was to establish a scientific basis for the management and prevention of CRE infections in small general hospitals and to contribute to the establishment of future infection control policies and clinical responses in hospitals.

Materials and Methods

Participants

From February 1, 2023, to May 15, 2024, CRE surveillance culture tests were conducted among high-risk patients who visited a small general hospital. Although there is no domestic law that defines small and medium-sized hospitals, the Korean Small and Medium-sized Hospital Association is based on hospitals with 300-500 beds or less, not university hospitals. At the medical institution investigated in this retrospective study, the high-risk group included patients with a history of CRE or CPE isolation within 3 months or those with a history of hospitalization in long-term care facilities, such as nursing hospitals or nursing homes, ICUs, or acute care hospitals within 3 months. When patients in the high-risk group were hospitalized, both a CRE surveillance culture test and a carbapenemase genetic test employing the Xpert Carba-R assay using the Gene × pert system (Cepheid, Sunnyvale, CA, USA) were conducted simultaneously in Fig. (1).

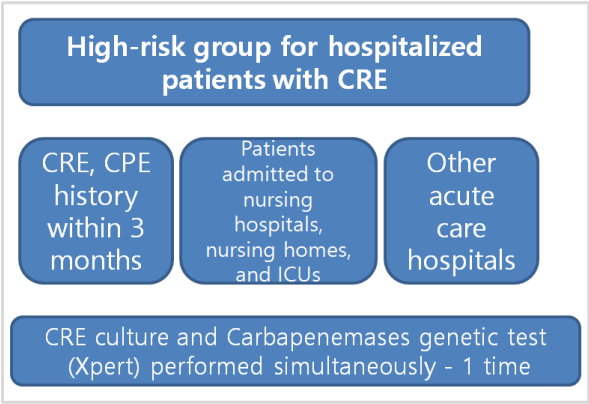

Fig. 1: CRE screening test criteria for hospitalized patients at high risk for CRE

For patients with a history of CRE and CPE isolation within the past 3 months, the tests were performed twice at 24-h intervals. In addition, all ICU patients were screened and CRE surveillance cultures were performed every Wednesday. In cases where CRE colonies were reported more than once, only the number of colonies reported first was used for data analysis. During the study period, 2,078 inpatients who visited our institution and were classified as high-risk patients for CRE underwent CRE culture tests. We retrospectively analyzed the results of 173 patients suspected of having CRE among 2,078 high-risk patients.

Research Methods

CRE screening culture tests were performed using rectal swab samples from high-risk patients. The commissioned samples were analyzed after aerobic incubation at 35-37°C for 18-24 h in ChromeAgar KPC (Product HANG, Gunpo City, South Korea). CHROMagar™ KPC is a selective and differential color development culture medium for use in qualitative direct detection of gastrointestinal colonies using CRE to aid in the prevention and control of CRE in medical settings. In this medium, carbapenem-resistant *E. coli* becomes dark pink to reddish, and carbapenem-resistant Klebsiella spp., Enterobacter spp., and Citrobacter spp. Become metallic blue. When colonies suspected to be CRE colonies grew, bacterial identification and antimicrobial susceptibility tests were performed. Microscans WalkAway from Beckman Coulter (Brea, CA, USA) were used from February 2023 to March 2024 and bioMérieux's (French Marcyl'Etoyle) VITEK-2 was used from April 2024. According to the CLSI Guidelines (M100-Ed33), Enterobacterales that showed resistance to one or more of the carbapenem antibacterial agents doripenem, imipenem, meropenem, and ertapenem were classified as CRE. However, Proteus spp., Morganella morganii, and Providencia spp. were

excluded from imipenem testing. Strains identified as CRE were subcultured and sent to the Chungnam Health and Environment Research Institute for confirmatory testing and genotyping for the presence or absence of CPE. The Chungnam Institute of Health and Environment took more than a week to complete the results of the confirmation test, which required rapid CPE genotype confirmation due to complicated infection control efforts. Although various assay methods were available, carbapenemase genetic testing was performed via Xpert Carba-R assay of rectal swab samples. Through this method, results could be obtained within 1 h. In addition, the GeneXpert system is an instrument based on multiple real-time polymerase chain reaction technologies and can detect blaVIM, bla IMP, bla NDM, bla KPC, and bla OXA-48-like alleles (Jin *et al*., 2020).

Data Analysis

Statistical analyses were conducted using Microsoft Excel (2007) and Jamovi (version 2.3.21; Jamovi, Sydney, Australia). To evaluate the distribution of CRE, frequencies, and percentages were calculated using descriptive statistics. A cross-tabulation chi-square test was used to compare sex, age, risk factors, and CPE between the two groups, and blood tests and CPE were subjected to correlation analysis. All risk factors and mortality were also analyzed using correlation analysis. Statistical significance was set at $p < 0.05$.

Results

CRE Incidence Rate and CPE Genotype Distribution Pattern

Among 2,078 study participants, 1,110 men and 968 women aged ≥18 years were classified as high-risk patients for CRE incidence and underwent CRE screening from February 1, 2023, to May 15, 2024. Of these participants, 173 tested positive for CRE, yielding a positivity rate of 8%. Moreover, 1,338 (64%) were over 70 years old, indicating that there were many older adults. Among the 173 CRE-positive patients, Klebsiella pneumoniae was identified in 130 patients (75%); Escherichia coli in 16 patients (9%); Enterobacter aerogenes in 7 patients (4%) and Enterobacter cloacae in 7 patients (4%). Additionally, 14 cases (8%) with Enterobacter spp. and 1 with Raoultella ornithinolytica were identified. Klebsiella oxytoca appeared in 1 case and *K*. pneumoniae was identified in most cases. Additionally, the number of cases in which two or more types of intestinal bacteria were isolated was 12 (7%). The distribution of CRE and CPE according to bacterial species was not statistically significant ($p = 0.773$). CPE was identified in 113 patients (65%). Regarding the CPE genotype distribution, KPC-2 was the most prevalent, accounting for 104 cases (92%). Additionally, NDM-1 or -5 was identified in 6 cases (5.3%), OXA-81 in 1 case (0.9%), and a combination of KPC-2 and NDM-1 in 2 cases (1.8%). The distribution of CRE and CPE according to CPE genotype was also not statistically significant ($p = 1.000$). Regarding the mortality rate by genotype of CRE-positive patients, those with the KPC-2 genotype exhibited the highest mortality rate at 36%, with 39 out of 104 patients dying. CRE-positive patients with NDM-1/-5 showed a mortality rate of 33% and 1 patient with the OXA-81 genotype died. Non-CPE genotypes also resulted in a high mortality rate of 28%, with 17 out of 60 patients dying Table (1).

CRE and CPE Distribution Patterns According to Sex and Age

The distribution patterns of CRE and CPE according to sex and age showed that the number of CRE cases was almost evenly distributed between men (87 cases) and women (86 cases). Regarding age distribution, most CRE-positive patients were aged >70 years (128 cases, 74%), Cross-analysis of CPE data indicated a significant difference between age groups ($p = 0.015$). This suggests that CPE is more prevalent among patients aged >70 years Table (2).

Table 1: CRE colonization rate and characteristics

CRE colonization rate (N = 2,078)					n	%
CRE	Negative				1,905	92%
	Positive				173	8%
species	CPE genotype				Non -CPE	Total
	KPC-2	NDM 1/5	OXA-81	KPC-2 + NDM-1		
K. pneu moniae	89	1	1	1	38	130 (75%)
E. coli	2	3	0	0	11	16 (9%)
Enterobacter spp.	2	2	0	0	10	14 (8%)
Other	1	0	0	0	1	2 (1%)
Two or more types	10	0	0	1	1	12 (7%)
Total	104 (92%)	6 (5.3%)	1 (0.9%)	2 (1.8%)	60	173
Death	39 (36%)	2 (33%)	1 (100%)	0 (0%)	17 (28%)	

Table 2: CRE distribution by sex and age

	Sex		Total	
Age (years)	Male	Female		
<50	5	5	10 (6%)	
50–70	22	13	35 (20%)	
>70	60	68	128 (74%)	
Total	87	86	173	
	CPE			
	Yes	No	Total	χ^2 (P-value)
Sex				
Male	54	33	87	0815 (0.367)
Female	59	27	86	
Total	113	60	173	
Age (years)				
<50	10	0	10	
50–70	18	17	35	8.36 (0.015*)
>70	85	43	128	
Total	113	60	173	

Table 3: Distribution of CRE and CPE according to CRE risk factors

	CPE			
	Yes	No	Total	χ^2 (P-value)
ICU				
Yes	75	25	100	
No	38	35	73	9.81 (0.002**)
Total	113	60	173	
Nursing institution				
Yes	46	34	80	
No	67	26	93	4.02 (0.045*)
Total	113	60	173	

CRE and CPE Distribution Patterns According to CRE Risk Factors

We investigated the distribution patterns of CRE and CPE according to known CRE risk factors, including history of hospitalization in ICUs or nursing facilities, main diagnosis, and presence of invasive devices. Among the 173 CRE-positive patients, 100 had a history of ICU hospitalization and 75 (75%) of them were found to possess the CPE genotype. Cross-analysis between CPE and history of ICU hospitalization showed a statistically significant result ($p = 0.002$). In addition, among the CRE-positive patients, 80 were transferred from nursing facilities and cross-analysis between CPE and transfers from nursing facilities showed a significant result ($p = 0.045$). In addition, the odds ratio (OR) was 2.76, suggesting that CPE infection occurs more often in patients hospitalized in ICUs Table (3).

Regarding the distribution of CRE and CPE by main diagnosis, respiratory diseases were the most common diagnosis, accounting for 56 cases (32%), with 36 of these cases being CPE-positive. Among respiratory diseases, pneumonia was the most prevalent disease. Neurological diseases followed, accounting for 42 cases (24%), including 32 CPE-positive cases. Among the neurological diseases, cerebral infarction was the most common disease. However, neither respiratory nor neurological diseases showed statistical significance ($p = 0.844$ and $p = 0.089$, respectively). Analysis of other disease categories, such as digestive, urinary, musculoskeletal, and cardiovascular diseases, as well as cancer and diabetes, did not show any statistically significant results.

In addition, we investigated the insertion of invasive devices at the time of hospitalization. Among the 173 CRE-positive patients, 42 did not have invasive devices inserted and the remaining 131 had invasive devices inserted. Foley catheters were inserted in the majority of patients (89 patients, 68%). Analysis of invasive devices showed that only the insertion of the endotracheal tube ($p = 0.05$) was statistically significant, whereas that of other invasive devices did not achieve significant results in Table (4).

We also examined blood tests showing significance for infection and the distribution patterns of CRE and CPE.

Table 4: Distribution of CRE and CPE according to CRE risk factors

	CPE			
	Yes	No	Total	χ^2 (P-value)
Underlying disease				
Respiratory disease	36	20	56	0.0389 (0.844)
Digestive disease	11	11	22	2.6100 (0.106)
Renal disease	5	2	7	0.1200 (0.729)
Neurological disease	32	10	42	2.8900 (0.089)
Musculoskeletal disease	5	3	8	0.0294 (0.864)
Heart disease	5	4	9	0.3990 (0.527)
Cancer	4	3	7	0.2150 (0.643)
Diabetes	4	0	4	2.1700 (0.140)
Other	11	7	18	0.1570 (0.692)
Total	113	60	173	
Invasive device				
Central line	2	2	4	0.4240 (0.515)
Foley catheter	42	36	68	0.6240 (0.429)
Foley catheter+Levin tube	10	5	15	0.0132 (0.909)
Foley catheter+endotracheal tube	5	1	6	0.890 (0.345)
Levin tube	7	5	12	0.278 (0.598)
Endotracheal tube	14	2	16	3.830 (0.050*)
Other	8	2	10	1.010 (0.315)
No	25	17	42	0.822 (0.365)
Total	113	60	173	

To determine the correlation between diabetes patients and CPE infection, we analyzed the glucose levels of 167 CRE-positive patients and found that 116 (69%) had glucose levels higher than the normal glucose level (>106 mg/dL). Although glucose levels alone are not sufficient to diagnose diabetes, we analyzed the results of postprandial blood glucose tests that were above the reference level. Statistically, no significant correlation was observed in the correlation analysis between glucose levels and CPE positivity ($p = 0.489$). Regarding inflammation markers related to infection, we examined the WBC count and CRP levels. Among 149 CRE-positive patients who underwent CRP testing, 121 (81%) had levels >0.9 mg/dL, suggesting a correlation with inflammation during infection. However, no significant correlation was found ($p = 0.535$). Similarly, WBC analysis showed no significant correlation ($p = 0.568$), with 91 patients (53%) having counts below the normal value (10,000/μL) Table (5). Thus, the blood marker analysis did not provide statistically significant results, possibly due to the insufficient sample size of the study or the low sensitivity of certain biomarkers. Future studies should conduct blood marker analysis with various biomarkers and have a larger sample size.

Finally, the correlation between the risk factors investigated in this study and mortality was evaluated. History of ICU admission ($p = 0.006$) had the most significant correlation with mortality, followed by blood parameters related to infection and inflammation, such as CRP level ($p = 0.027$) and WBC count ($p = 0.012$). In addition, sex ($p = 0.050$) showed a significant correlation, with 59% of the deceased patients being male. Other risk factors, such as CPE prevalence ($p = 0.818$) and genotype ($p = 0.819$), were not significant Table (6).

Table 5: Correlation between CRE and CPE distribution patterns and CPE according to blood tests

	CPE			Correlation with CPE P-value
	Yes	No	Total	
Glucose				
>106 mg/dL	77	39	116	
<106 mg/dL	31	20	51	0.489
Total	108	59	167	
CRP				
>0.9 mg/dL	81	40	121	
<0.9 mg/dL	17	11	28	0.535
Total	98	51	149	
WBC				
>10,000 μL	55	26	81	
<10,000 μL	58	33	91	0.568
Total	113	59	172	

Table 6: Correlation between mortality and various risk factors

	Correlation with mortality P-value
CPE prevalence	0.818
CPE genotype	0.819
Bacterial species	0.610
Sex	0.050*
Age	0.646
ICU	0.006**
Nursing institution	0.708
Underlying disease	0.654
Invasive devices	0.256
Glucose level	0.724
CRP level	0.027*
WBC count	0.012*

*p<0.05; **p<0.01

Discussion

In this study, CRE surveillance culture tests were performed on patients classified as having high risk at a small general hospital. As described in. Figure (1), high-risk patients included those with a history of fewer than 3 months of hospitalization in an ICU (McConville *et al*., 2017; Falagas *et al*., 2007; Ling *et al*., 2015), nursing homes, or other acute care hospitals. These patients underwent CRE culture and CPE carbapenemase genetic testing using the Gene × pert system. In the CRE screening test for 2,078 high-risk patients, the CRE positivity rate was 8%. Overall, 113 of 173 CRE-positive patients (65%) were CPE-positive with a carbapenemase production gene. The CPE positivity rate has shown a gradual increase over the years, as reported by the Korea Disease Control and Prevention Agency: 49.8% in 2018, 57.8% in 2019, 61.9% in 2020, 63.4% in 2021 and 70.2% in 2022 (Korea Centers for Disease Control and Prevention, 2024). The CPE positivity rate at the medical institution in this study was 65%, slightly lower than the recent national rate. As previously mentioned, CPE has a higher incidence rate than non-CPE (Korea Centers for Disease Control and Prevention, 2024; CDC, 2015) and the mortality rate is 1.7-5.9 times higher (Patel *et al*., 2008; Goren *et al*., 2010). Therefore, quick and accurate CPE gene testing is crucial. Accordingly, the medical institution in this study conducted tests for five genotypes (KPC, NDM, VIM, OXA-48, IMP-1) using the GeneXpert system. This facilitates same-day testing, which is crucial for promptly confirming the CPE genotype, selecting treatment drugs, and preventing rapid spread. Among the CRE- and CPE-positive strains, *K. pneumoniae* showed the highest prevalence at 75%, followed by E. coli at 9%. Klebsiella pneumoniae and *E. coli* are the most frequently isolated bacterial species in various clinical specimens (Lee and Kim, 2023). Despite not being CRE-positive, patients may become CRE carriers due to continuous antibiotic use and cross-infection. Therefore, careful attention must be paid to infection control. Among CPE genotypes, KPC was the most prevalent at 92%, followed by NDM at 6%. Previous domestic studies have reported KPC rates of 75-78% and NDM rates of 20-22% (Lee and Kim, 2023). Another domestic study reported that the KPC ratio was 90.1% and the NDM ratio was 3.9% (Kim *et al*., 2012). In particular, in the second study and our study, it was found that the KPC ratio was >90% and the NDM ratio was <6%, which was almost similar. Although the ratios are different, these findings indicate that KPC and NDM are the predominant CPE genotypes in Korea (Lee and Kim, 2023; Kim *et al*., 2012). Consistent with other studies, this study also found that K. pneumoniae is mainly associated with KPC production (Park *et al*., 2020; Lee and Kim, 2023; Lee *et al*., 2023; Yun *et al*., 2022). In the analysis of CRE and CPE distribution by sex and age, no significant differences were observed between men and women or between CRE and CPE rates. However, 59% of the deceased patients were male, indicating a correlation between sex and mortality rate. Additionally, 74% of the CPE-positive patients were aged 70 years or older, and more than 80% of the deaths occurred among these patients, indicating that the prevalence and mortality of CPE are higher among the elderly. As the population ages, older patients often have many underlying health conditions, such as diabetes, heart diseases, and cerebrovascular diseases, which restrict treatment options and complicate the management of CRE infections. Consequently, the incidence of CRE and CPE infections is expected to continue increasing. Therefore, establishing strict infection control standards for older patients is imperative. According to the present study, hospitalization in a nursing facility or ICU was a significant risk factor for CRE infection. We found that ICU admission was also correlated with mortality. The Korea Disease Control and Prevention Agency also designates patients hospitalized in nursing facilities and ICUs as high-risk and recommends CRE surveillance culture testing (Yeonju *et al*., 2020). Common characteristics of nursing facilities and ICUs, including the hospitalization of older or critically ill patients, long-term use of antibiotics, long-term hospitalization, use of multiple invasive devices, close proximity of beds, and continuous medical care by staff, contribute to increased risk of CRE infection (Jung and Park, 2022).

Considering these risk factors, measures to prevent the spread of CRE and CPE infection among patients admitted to long-term care facilities and ICUs should prioritize activities such as appropriate management of antibiotic use, limited use of invasive devices, active surveillance culture testing, hand hygiene, and environmental disinfection (Jung and Park, 2022; Yun *et al*., 2022; Logan and Weinstein, 2017). In fact, the following activities were implemented in the ICU of our medical institution to prevent the infection and spread of CRE and CPE. First, to quickly confirm the presence or absence of CRE infection, isolate patients, and prevent the spread of infection, a CRE culture test was conducted on ICU patients every Wednesday. In addition, an environmental cleaning checklist was created and environmental cleaning and disinfection of the ICU were performed periodically using 1,000 ppm sodium hypochlorite under the thorough supervision of the infection control office. The infection control office of our medical institution periodically visited the ICU and conducted environmental cultures of places frequently touched by medical staff, such as sink faucets, taps, and bed rails, to check whether environmental disinfection was successful. In addition, we monitored whether the ICU medical staff were

educated about hand hygiene and implemented it at work. Active support was provided to encourage contact precautions. Automatic sensor faucets were installed to prevent contact with sink faucet handles and trash cans that could be opened by stepping on a pedal were used as medical waste boxes, to minimize hand contact, which is the main cause of the spread of CRE and CPE infections. Through such efforts, medical institutions can manage and prevent CRE and CPE infections.

Another risk factor investigated was the presence of underlying diseases in CRE-positive patients, but no significant results were found. Nonetheless, pneumonia, a respiratory disease, and cerebral infarction, a neurological disease, were the most common diseases among CRE- and CPE-positive patients. Patients with these diseases were classified as being at higher risk, warranting active CRE surveillance culture tests and stricter infection control measures. Moreover, the results were not statistically significant; however, 51% of CRE and CPE-positive patients had indwelling Foley catheters. This should be noted, as many studies have identified indwelling urinary catheters as a risk factor for CRE infection due to urinary tract infections (Guh *et al.*, 2015).

Among CRE or CPE-positive patients, no significant correlations were observed between the results of the infection-related blood tests (glucose levels, CRP levels, and WBC count), but the CRP level and WBC count were notably correlated with mortality. The normal range for CRP levels is 0-0.9 mg/dL. Among 149 CRE-positive patients, 121 (81%) had CRP levels exceeding this normal range of 0.9 mg/dL. CRP is used as an indicator of systemic inflammation. If an infected patient with a significantly weakened immune system stays in a hospital environment for an extended period, inflammation may occur in various parts of the body (Gao *et al*., 2022). The high CRP levels observed in most patients with CRE infection are significant, as they indicate a systemic inflammatory response that is crucial for understanding the impact of CRE infections on patients with compromised immune systems.

In this study, the distribution and major risk factors of CRE infection in a small general hospital in South Korea were analyzed. The results highlight the need for CRE management in the Korean healthcare environment by providing specific data reflecting the regional characteristics of South Korea, which were consistent with global trends. Thus, this analysis provides crucial insights for developing strategies for preventing and managing infections in the hospital, particularly emphasizing the need for strengthened infection control measures for patients in ICUs and nursing facilities.

However, this study had limitations. First, the study was conducted over a short period, from February 2023 to mid-May 2024, which may have limited the ability to identify long-term trends and changes in CRE distribution. Future research should incorporate long-term data to better understand these dynamics. Second, this study was conducted in a small general hospital and provided results limited to high-risk patients. Therefore, the results of this study cannot be generalized to other regions or diverse populations. Future studies should encompass a wider geographical range and diverse patient groups, as the distribution and risk factors of CRE may vary across regions or hospitals of different sizes. In addition, it is necessary to continuously refer to national or international trends and fluctuations in CRE prevalence, rather than focusing only on our results. Third, this study analyzed multiple risk factors, including the history of ICU and nursing home admissions, major diagnoses, and the presence of invasive devices, but did not fully consider other potential risk factors, such as the history of antibiotic use (Correa *et al*., 2013), past infections, immunity, and lifestyle habits, as specific information on the antibiotics used or past infections was missing from the medical records. This may have restricted the ability to identify the complex causes of CRE infection. In addition, the correlation analysis of some risk factors and blood tests did not yield statistically significant results. This may be due to limitations in sample size or failure to sufficiently reflect complex interactions between variables. Fourth, although the CPE genotype analysis identified predominant genotypes (e.g., KPC-2 and NDM), the study did not explore a wider range of genotypes. This could limit understanding of the diversity of genotypes and associated infection risks. Lastly, the retrospective design and reliance on past data may impact data accuracy and completeness. Potential data collection errors or incomplete records may affect the study results.

To address the limitations identified in this study, several measures can be incorporated in future studies. First, employing a prospective research design with real-time data collection across multiple institutions—small, medium-sized, and large-scale hospitals in various regions-can enhance the accuracy and completeness of the data. Second, extending the research period will facilitate the analysis of long-term CRE distribution and trend changes. This can facilitate the identification of CRE infection patterns and factors influencing change over time. Third, a more comprehensive risk factor analysis should be conducted, including factors such as antibiotic use history, surgical history, and other potential risk factors. This will enable a more accurate understanding of the complex causes of CRE infection. Fourth, international comparative research should be conducted to analyze and contrast domestic CRE distribution and risk factors with those in other countries. For example, new policy changes or recommendations could be implemented based on the results of various international studies. These proposed measures aim to

provide a more thorough and accurate understanding of CRE infection distribution and risk factors, ultimately contributing to the formulation of more effective infection control and prevention strategies.

Conclusion

This study emphasized the high prevalence of CRE and CPE in South Korea. In particular, the results of the investigation of risk factors related to CRE infection suggested that elderly patients, and patients with a history of hospitalization in long-term care facilities and ICUs are classified as being at high risk for CRE infection, suggesting that detailed criteria for CRE screening tests should be presented. In particular, elderly patients and patients with a history of ICU admission should be monitored more closely because most of them have underlying diseases and invasive devices and are exposed to many risk factors such as long-term antibiotic use. (Lee, 2023) In addition, admission to ICUs showed a significant correlation with mortality ($p = 0.006$). Detailed criteria were used in CRE screening tests including CRE surveillance culture tests and rapid CPE gene detection tests in high-risk environments such as long-term care facilities and ICUs, with the goal of preventing the spread of CRE infection. In addition, continuous attention to CRE prevention and infection control through the maintenance of thorough hand hygiene and environmental disinfection in the ICU is essential.

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Author's Contributions

Mijin Kang and Bokyeung Jung: Contributed equally to this study.

Jaekyung Kim: Kim critically reviewed and edited the manuscript, improving the language, structure, and overall quality of the paper. Kim takes full responsibility for this study.

All authors contributed to the writing, review, and editing of the final manuscript and approved the submission for publication.

Ethics

The study protocol was approved by the Institutional Review Board of Dankook University (IRB file No. 2024-06-022-002).

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

All data are available within the article or its supplementary materials.

Patient Consent

This study was a retrospective data-only study; therefore, the need for obtaining informed consent from the patients was waived by the Dankook University IRB.

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