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Changing Genotypic Distribution, Antimicrobial Susceptibilities, and Risk Factors of Urinary Tract Infection Caused by Carbapenemase-Producing *Pseudomonas aeruginosa*

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Background: Carbapenem-resistant *Pseudomonas aeruginosa* (CrPA) is a leading cause of healthcare-associated urinary tract infections (UTIs). Carbapenemase production is an important mechanism that significantly alters the efficacy of frequently used anti-pseudomonal agents. Reporting the current genotypic distribution of carbapenemase-producing *P. aeruginosa* (CPPA) isolates in relation to antimicrobial susceptibility, UTI risk factors, and mortality is necessary to increase the awareness and control of these strains.

Methods: In total, 1,652 non-duplicated *P. aeruginosa* strains were isolated from hospitalized patients between 2015 and 2020. Antimicrobial susceptibility, carbapenemase genotypes, risk factors for UTI, and associated mortality were analyzed.

Results: The prevalence of carbapenem-non-susceptible *P. aeruginosa* isolates showed a decreasing trend from 2015 to 2018 and then increased in the background of the emergence of New Delhi metallo-β-lactamase (NDM)-type isolates since 2019. The CPPA strains showed 100.0% non-susceptibility to all tested antibiotics, except aztreonam (94.5%) and colistin (5.9%). Carbapenems were identified as a risk and common predisposing factor for UTI (odds ratio [OR] = 1.943) and mortality (OR = 2.766). Intensive care unit (ICU) stay (OR = 2.677) and white blood cell (WBC) count (OR = 1.070) were independently associated with mortality.

Conclusions: The changing trend and genetic distribution of CPPA isolates emphasize the need for relentless monitoring to control further dissemination. The use of carbapenems, ICU stay, and WBC count should be considered risk factors, and aggressive antibiotic stewardship programs and monitoring may serve to prevent worse outcomes.

Key Words: Carbapenemase, Imipenemase, Metallo-β-lactamase, New Delhi metallo-β-lactamase, *Pseudomonas aeruginosa*, Urinary tract infection

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INTRODUCTION

Pseudomonas aeruginosa is an important nosocomial pathogen, particularly responsible for catheter-related urinary tract infections (UTIs) [1]. Owing to the natural resistance of *P. aeruginosa* to a large number of antimicrobial agents, treatment of

UTIs caused by this pathogen is challenging [2]. Carbapenems have been the mainstay treatment for severe infections because of their high potency against *P. aeruginosa* strains [3]. Carbapenem-resistant *P. aeruginosa* (CrPA) has emerged as a major healthcare-associated pathogen globally [4], constituting approximately 10–30% of all *P. aeruginosa* isolates in the United States [5, 6]. Resistance rates vary worldwide. In Korea, the resistance rate of *P. aeruginosa* to imipenem was determined to be 22% among 15,032 assessed clinical isolates, based on a survey performed in 2011 [7]. A recent report analyzing multicenter data from 1997 to 2016 showed that the rate of *P. aeruginosa* resistance to imipenem increased from 13.9% to 30.8% during the study period [8].

The production of carbapenemases [9], overproduction of the MexAB-OprM efflux pump and AmpC β-lactamase, and inactivation of the OprD outer membrane protein [10] have been highlighted as important mechanisms underlying carbapenem resistance. Carbapenemases significantly alter the efficacy of frequently used anti-pseudomonal agents. Carbapenemase-producing genes such as Guiana extended-spectrum β-lactamase (*GES*), imipenase (*IMP*), and New Delhi metallo-β-lactamase (*NDM*) are encoded on highly mobile elements, thereby enhancing the dissemination of resistance among multiple species [11]. Outbreaks caused by metallo-β-lactamase (MBL)-producing *P. aeruginosa* are frequently reported globally, and the IMP-producing type is the most common MBL in Korea [11, 12].

Intensive care unit (ICU) stay and inadequate empirical therapy have been identified as risk factors for the emergence of carbapenemase-producing *P. aeruginosa* (CPPA) strains and are associated with worse clinical outcomes [2, 13]. Studies have reported an increasing prevalence of CPPA [9, 14, 15]; however, few studies have elucidated the risk factors for UTI from the acquisition of these isolates and analysis of outcomes after infection. Recent studies on changes in the genotypic distribution of CPPA isolates are lacking despite the increased prevalence of such isolates. Determining the latest status of the genotypic distribution of CPPA isolates in relation to antimicrobial susceptibilities, the risk factors of UTI, and outcomes such as mortality is necessary to increase the awareness and control of these strains. Accordingly, we aimed to investigate these predisposing factors as well as the recent genotypic distribution and antimicrobial susceptibilities of CPPA isolated from samples in a university hospital over a 6-yr period. We also evaluated combinations of routinely prescribed markers and clinical features for predicting mortality, which have rarely been reported in earlier studies, to identify useful tools for clinical practice.

MATERIALS AND METHODS

Bacterial strains

A total of 1,652 non-duplicated *P. aeruginosa* isolates were obtained from patients hospitalized between January 2015 and December 2020 at Kangnam Sacred Heart Hospital in Seoul, Korea. Among these, 258 isolates, most of which (84.9%, 219/258) were isolated from urine samples, harbored carbapenemase-producing genes. Subsequently, 503 *P. aeruginosa* strains were collected from urine samples for this study. Bacterial species were identified using a VITEK MS system (BioMérieux, Marcy-l'Etoile, France). The included strains were classified into three groups: carbapenem-susceptible *P. aeruginosa* (CsPA), carbapenem-non-susceptible and non-carbapenemase-producing *P. aeruginosa* (Cns-nCPPA), and carbapenem-non-susceptible and carbapenemase-producing *P. aeruginosa* (Cns-CPPA). Carbapenem non-susceptibility was determined based on a minimal inhibitory concentration (MIC) >2 g/mL for imipenem and/or meropenem.

Antimicrobial susceptibility testing

The MICs of piperacillin, piperacillin–tazobactam, ceftazidime, cefepime, aztreonam, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, and colistin for the included *P. aeruginosa* isolates were determined using a VITEK 2 system (BioMérieux). The results were interpreted according to CLSI guidelines (M100-S31) [16]. *P. aeruginosa* ATCC 27853 was used as the control strain for susceptibility testing.

Identification of carbapenemase–encoding genes

The genes encoding IMP-, Verona integron-encoded MBL (VIM)-, and NDM-type MBL in addition to *Klebsiella pneumoniae* carbapenemase and GES-type serine β-lactamases were detected using the PANA Real Typer CRE kit (PANAGENE Inc., Daejeon, Korea) for CrPA. Peptide nucleic acid-mediated multiplex real-time PCR was performed using primers and probes designed to identify the five carbapenemase genes and an internal control provided by PANAGENE, Inc.; the sequences have been reported previously [17]. Multiplex real-time PCR was performed in a 96-well plate using the CFX-96 Real-Time PCR detection system (Bio-Rad Laboratories Inc., Hercules, CA, USA), according to the manufacturer's instructions. Reaction mixtures comprised 19 μL of primer/probe and multiplex real-time PCR master mixture, 5 μL of genomic DNA, and 1 μL of Taq DNA polymerase. After each run, the threshold cycle (Ct) was measured based on the signal strength at which the fluorescence exceeded the threshold.

Samples with Ct values <35 were considered positive. RNase-free water was included as a negative control in each run.

Data for risk factor assessment

Clinical information was collected to assess the characteristics of UTIs. UTI was defined according to the criteria of the Centers for Disease Control and Prevention (CDC) [18]. The disease was confirmed by a single isolate at a density >100,000 colony-forming units (CFU)/mL in the urine. Patients with a density <100,000 CFU/mL of *P. aeruginosa* or more than two microorganisms in urine cultures were excluded owing to contamination concerns. Data were collected from the medical charts and hospital databases. This study was approved by the Institutional Review Board of Kangnam Sacred Heart Hospital (HKS 2020-03-020), Seoul, Korea, which waived the requirement for informed consent.

The following variables were included: age; sex; source from which the isolate was recovered; year of isolation; hospitalization ward; comorbid conditions such as pulmonary disease and diabetes mellitus (DM); and prior use of carbapenems such as imipenem, meropenem, doripenem, and ertapenem at least three months before *P. aeruginosa* isolation. Laboratory findings related to infection, such as white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and procalcitonin, C-reactive protein (CRP), glucose, and lactate dehydrogenase (LD) levels, were also investigated. Clinical outcomes such as in-hospital mortality were evaluated based on the evolution to hospital discharge or death. A total of 499 patients with *P. aeruginosa* detected in urine samples were included after excluding four patients without complete clinical information. The data for this study were deposited in Harvard Dataverse and are accessible at https://doi.org/10.7910/DVN/8LDTYM.

Statistical analyses

The non-susceptibility rates of bacterial pathogens were calculated by dividing the number of non-susceptible isolates by the total number of strains. Univariate and multivariate binary logistic regression analyses were used to assess variables that correlated independently with the presence of UTI and mortality in patients with *P. aeruginosa* detected in urine samples. Variables independently related to mortality after multivariate analysis were included in ROC analysis. ROC curves were plotted to assess the ability of these variables to differentiate between survivors and non-survivors. The area under the ROC curve (AUC) of the combined markers was classified as follows: no discrimination (AUC<0.5), acceptable (0.7<AUC<0.8), excellent (0.8<AUC<0.9), or outstanding (AUC<0.9). All statistical tests were two-tailed, and $P<0.05$ was considered to indicate statistical significance. Statistical analyses were performed using Analyse-it Method Evaluation Edition software version 2.26 (Analyse-it Software Ltd., Leeds, UK) and MedCalc software version 19.8 (MedCalc Software Ltd., Ostend, Belgium).

RESULTS

Distribution of *P. aeruginosa* isolates

A total of 1,652 non-duplicated *P. aeruginosa* strains (345 in 2015, 258 in 2016, 279 in 2017, 274 in 2018, 254 in 2019, and 242 in 2020) from hospitalized patients were included for analysis. The isolates, stratified by year, sample type, and susceptibility to carbapenems, are summarized in Supplemental Data Table S1. The respiratory tract (47.3%, 781/1,652) followed by urine (30.4%, 503/1,652) and wounds (7.7%, 127/1,652) were the most common sites of the *P. aeruginosa* isolates. The non-susceptibility rate to carbapenems decreased from 2015 to 2018 (42.0% in 2015, 38.4% in 2016, 31.9% in 2017, and 25.2% in 2018). However, it increased in 2019 (33.9%) and 2020 (35.1%) (Supplemental Data Fig. S1).

Among the 1,652 strains, 258 strains were Cns-CPPA (88 in 2015, 45 in 2016, 33 in 2017, 23 in 2018, 31 in 2019, and 38 in 2020), 84.9% of which were isolated from urine samples (Fig. 1). Other samples included respiratory tract (7.0%) and wound (2.3%) samples. From 2015 to 2018, all Cns-CPPA isolates were

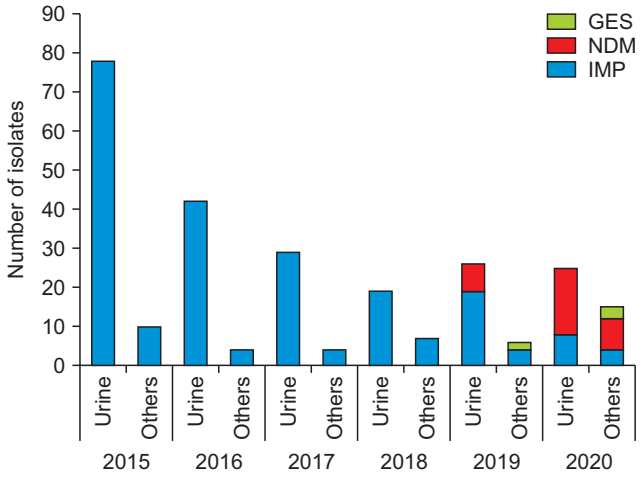

Fig. 1. Distribution of carbapenem-non-susceptible and carbapenemase-producing *Pseudomonas aeruginosa* isolates detected between 2015 and 2020. Urine samples were predominant (84.9%); other samples included respiratory tract (7.0%) and wound (2.3%) samples.
Abbreviations: GES, Guiana extended-spectrum β-lactamase; IMP, imipenase; NDM, New Delhi metallo-β-lactamase.

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identified as IMP-type strains. NDM-type MBL-encoding strains were observed among the Cns-CPPA isolates obtained from urine samples in 2019 (26.9%, 7/26) and 2020 (68.0%, 17/25).

Antimicrobial susceptibility profile

The antimicrobial susceptibility profiles of 503 *P. aeruginosa* strains (130 in 2015, 96 in 2016, 87 in 2017, 69 in 2018, 58 in 2019, and 63 in 2020) from urine samples are shown in Fig. 2. The isolates comprised 227 CsPA, 57 Cns-nCPPA, and 219 Cns-CPPA (195 IMP-type and 24 NDM-type).

The non-susceptibility rates of the 503 *P. aeruginosa* strains were as follows: 59.6% for piperacillin, 52.3% for ceftazidime, 51.5% for cefepime, 62.0% for aztreonam, 47.7% for amikacin, 49.5% for gentamicin, 56.5% for ciprofloxacin, and 3.6% for colistin. The non-susceptibility rates to CsPAs were 29.1% for aztreonam, 17.2% for piperacillin, and 11.0% for ciprofloxacin (Fig. 2A). More than 50% of the Cns-CPPA strains demonstrated non-susceptibility to piperacillin (73.7%), ciprofloxacin (70.2%), and aztreonam (68.4%) (Fig. 2B). The Cns-CPPA strains showed 100.0% non-susceptibility to all the antibiotics examined, except for aztreonam (94.5%) and colistin (5.9%) (Fig. 2C). MBL-producing *P. aeruginosa* isolates exhibited higher rates of non-susceptibility to ceftazidime, cefepime, aztreonam, amikacin, gentamicin, ciprofloxacin, and carbapenems than the CsPA and Cns-nCPPA isolates. According to the MBL type, strains harboring bla_{IMP} showed non-susceptibility rates of 97.4% to aztreonam and 6.2% to colistin, whereas isolates with bla_{NDM} exhibited 70.8% and 4.2% non-susceptibility rates against aztreonam and colistin, respectively.

Risk factors for UTI

Among the 499 patients positive for infection with *P. aeruginosa* strains identified from urine samples and having complete clinical information, 321 (64.3%) met the CDC criteria for UTI (Supplemental Data Table S2). The risk factors for UTI based on univariate and multivariate analyses are presented in Table 1. According to logistic univariate analyses, carbapenem use (odds ratio [OR] = 2.072; P = 0.001), CRP level (OR = 1.004; P = 0.042), WBC count (OR = 1.045; P = 0.036), and NLR (OR = 1.029; P = 0.036) were associated with UTI. Among the subgroups, the same analysis revealed that the use of carbapenems and ertapenem (OR = 2.740; P = 0.001) was significantly associated with UTI. Multivariate analysis with UTI as the binary dependent variable and carbapenem use, CRP level, WBC count, and NLR as predictors revealed an independent association between carbapenem administration (OR = 1.943; P = 0.011) and UTI.

Risk factors for mortality

The distribution and risk factors for mortality in patients positive for *P. aeruginosa* isolates obtained from urine samples are shown in Supplemental Data Table S3 and Table 2, respectively.

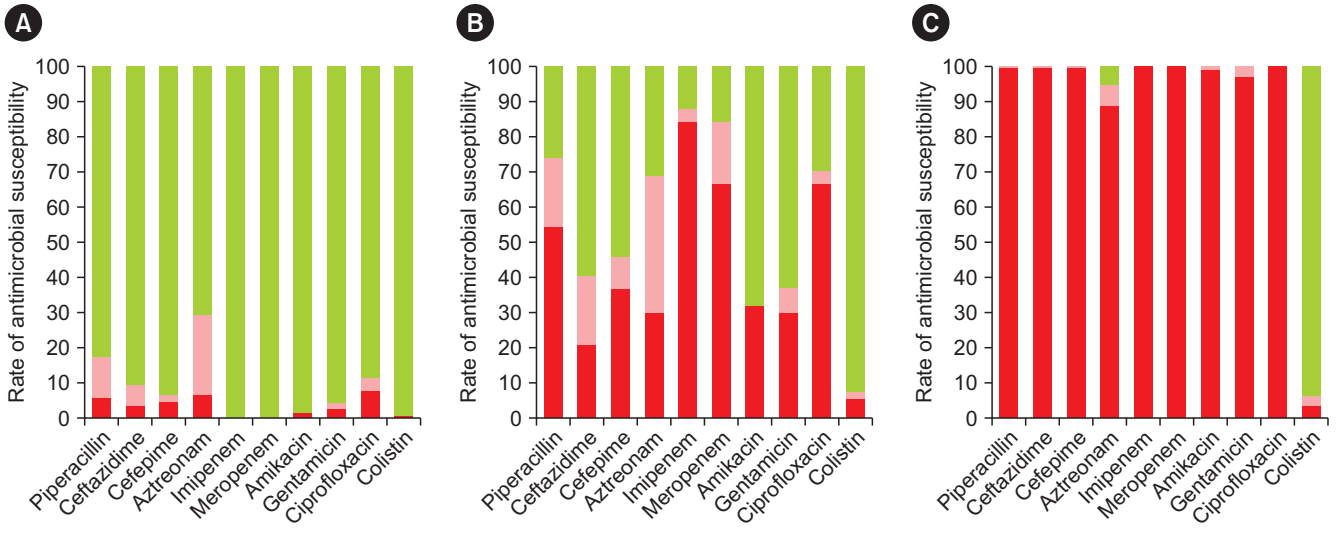

Fig. 2. Antimicrobial susceptibilities of 503 urinary *Pseudomonas aeruginosa* isolates from inpatients detected between 2015 and 2020. (A) Carbapenem-susceptible isolates (N = 227); (B) carbapenem-non-susceptible and non-carbapenemase producers (N = 57); and (C) carbapenem-non-susceptible and carbapenemase producers (N = 219). The red, pink, and green bars represent the antimicrobial-resistant, -intermediate, and -susceptible isolates, respectively.

Table 1. Univariate and multivariate analyses of patients with UTI caused by *Pseudomonas aeruginosa* detected in urine samples*

Variable	Univariate		Multivariate†	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.000 (0.990–1.009)	0.944	1.089 (1.017–1.166)	0.015
Sex				
Male	Reference			
Female	0.867 (0.596–1.262)	0.458		
Comorbidity				
Pulmonary disease	1.365 (0.890–2.093)	0.154		
DM	0.753 (0.514–1.105)	0.148		
Susceptibility to carbapenem				
CsPA	Reference			
Cns-nCPPA	0.717 (0.395–1.300)	0.273		
Cns-CPPA	1.018 (0.688–1.505)	0.931		
Carbapenem use	2.072 (1.339–3.204)	0.001	1.943 (1.163–3.248)	0.011
Imipenem	0.275 (0.025–3.054)	0.293		
Meropenem	-			
Doripenem	1.737 (0.954–3.164)	0.071		
Ertapenem	2.740 (1.455–5.161)	0.001		
Laboratory finding				
Procalcitonin (ng/mL)	0.981 (0.927–1.037)	0.492		
CRP (mg/L)	1.004 (1.000–1.009)	0.042	1.003 (0.998–1.008)	0.230
WBC (10^9/L)	1.045 (1.001–1.091)	0.036	0.996 (0.938–1.059)	0.908
NLR	1.029 (1.000–1.059)	0.036	1.013 (0.970–1.058)	0.557
Glucose (mg/dL)	0.998 (0.994–1.003)	0.466		
LD (IU/L)	1.000 (1.000–1.001)	0.819		

*UTI was defined according to the CDC criteria [18]. Among 499 patients, 321 (64.3%) met the CDC criteria for UTI, whereas the remaining 178 (35.7%) patients were designated as a non-UTI group.
†Variables with $P<0.05$ in univariate analysis were included in the multivariate analysis.
Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; Cns-CPPA, carbapenem-non-susceptible and carbapenemase-producing *P. aeruginosa*; Cns-nCPPA, carbapenem-non-susceptible and non-carbapenemase-producing *P. aeruginosa*; CRP, C-reactive protein; CsPA, carbapenem-susceptible *P. aeruginosa*; DM, diabetes mellitus; OR, odds ratio; UTI, urinary tract infection; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; LD, lactate dehydrogenase.

Older age, female sex, pulmonary disease, DM, ICU stay, Cns-nCPPA, Cns-CPPA, carbapenem use, CRP level, WBC count, NLR, and glucose level were significantly associated with mortality based on univariate analyses. For the subgroups of carbapenem use, all carbapenems tested, including meropenem, doripenem, and ertapenem, were consistently associated with mortality. Predictive factors with $P<0.001$ in univariate analyses, such as ICU stay, carbapenem use, WBC count, and NLR, were included in the multivariate analysis to address the issue of multicollinearity. ICU stay (OR=2.677; $P=0.029$), use of carbapenems (OR=2.766; $P=0.005$), and WBC count (OR=1.070; $P=0.039$) were independently associated with mortality. These factors were used to construct the ROC curve for mortality, and the AUC value was 0.760, indicating acceptable performance (Fig. 3).

DISCUSSION

This study revealed that the prevalence of non-susceptible *P. aeruginosa* isolates initially had a decreasing trend but then increased in the later period of the study, with NDM-type CPPA isolates emerging prominently as of 2019. CPPA strains were predominately isolated from urine samples and were more resistant to various antimicrobial agents than the CsPA and Cns-nCPPA strains. Carbapenem administration was identified as a predom-

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Table 2. Univariate and multivariate analyses of mortality in patients with *Pseudomonas aeruginosa* infection detected from urine samples*

Variable	Univariate		Multivariate†	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.025 (1.003–1.047)	0.027		
Sex				
Male	Reference			
Female	2.186 (1.163–4.110)	0.015		
Comorbidity				
Pulmonary disease	2.186 (1.15–4.153)	0.017		
DM	2.417 (1.287–4.542)	0.006		
ICU stay	4.966 (2.165–11.390)	<0.001	2.677 (1.105–6.485)	0.029
Susceptibility to carbapenem				
CsPA	Reference			
Cns-nCPPA	2.972 (1.152–7.668)	0.024		
Cns-CPPA	2.114 (1.025–4.363)	0.043		
Carbapenem use	3.978 (2.095–7.553)	<0.001	2.766 (1.363–5.614)	0.005
Imipenem	-			
Meropenem	4.206 (1.832–9.658)	<0.001		
Doripenem	2.304 (1.074–4.943)	0.043		
Ertapenem	2.313 (1.106–4.836)	0.026		
Laboratory finding				
Procalcitonin	1.029 (0.967–1.094)	0.374		
CRP	1.008 (1.003–1.012)	0.001		
WBC	1.115 (1.062–1.170)	<0.001	1.070 (1.004–1.141)	0.039
Neutrophil	1.057 (1.026–1.089)	<0.001		
Lymphocyte	0.929 (0.891–0.969)	<0.001		
NLR	1.057 (1.027–1.088)	<0.001	1.032 (1.000–1.070)	0.093
Glucose	1.009 (1.004–1.015)	0.001		
LD	1.001 (1.000–1.002)	0.401		

*Among 499 patients, 43 (8.6%) belonged to the mortality group and the remaining 456 (91.4%) patients were designated to the survivor group.
†Variables with $P < 0.001$ in univariate analysis were included in the multivariate analysis.
Abbreviations: CI, confidence interval; Cns-CPPA, carbapenem-non-susceptible and carbapenemase-producing *P. aeruginosa*; Cns-nCPPA, carbapenem-non-susceptible and non-carbapenemase-producing *P. aeruginosa*; CRP, C-reactive protein; CsPA, carbapenem-susceptible *P. aeruginosa*; DM, diabetes mellitus; ICU, intensive care unit; OR, odds ratio; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; LD, lactate dehydrogenase.

inant risk and common predisposing factor for UTI and mortality, respectively. ICU stay and WBC count were independently associated with mortality.

A trend analysis of multidrug-resistant hospital-acquired bacterial infections was performed to assess the impact of COVID-19, demonstrating that the OR (1.84) and incidence rate ratio (1.78) for CrPA both increased significantly following the outbreak of COVID-19 (March 2020 to September 2021) compared with rates recorded in the pre-pandemic period (March 2018 to September 2019) [19]. The prevalence of non-susceptible *P. aeruginosa* isolates also increased during the COVID-19 pandemic, especially in clinical samples from Korea [20]. Our data confirmed elevated rates of non-susceptible *P. aeruginosa* isolates, with decreasing trends during the COVID-19 pandemic. The increased consumption of carbapenems during the pandemic period compared with the pre-pandemic period (25.9% in the wards and 12.1% in the ICU) could be attributed to the development of these trends with respect to non-susceptible *P. aeruginosa* isolates [20]. The breakdown of antimicrobial stewardship and infection control programs may be attributed to an evident

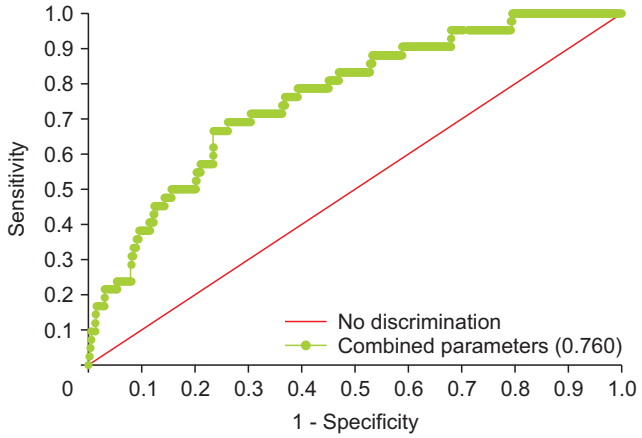

Fig. 3. Performance of combined variables (the use of carbapenems, intensive care unit stay, and white blood cell count) for predicting mortality in patients with urinary *Pseudomonas aeruginosa* isolates.

increase in CrPA infections [21]. Thus, antimicrobial stewardship programs to minimize the use of empirical antibiotics during the COVID-19 pandemic are indispensable for reducing the burden of healthcare-associated infections [22].

According to our data, the NDM-type has emerged and become more prominent in Korea in recent years. Similarly, the emergence of NDM-producing *P. aeruginosa* during the COVID-19 pandemic was reported in Brazil [23]. In Korea, VIM-2-producing *P. aeruginosa* was first reported in 2002 [24]. In 2009, IMP-6 was the predominant MBL type in *P. aeruginosa* clinical isolates in Korean hospitals [25]. IMP-6 has greater hydrolyzing activity against meropenem than against imipenem compared with other IMP enzyme subtypes [11], suggesting that the predominance of IMP-6 is associated with the use of meropenem, which is used approximately twice as often as imipenem in clinical settings. During the COVID-19 pandemic, strains harboring bla_{NDM-1}, which are considered high-risk clones with multiple virulence factors, emerged and spread widely after their first isolation in 2021 [26, 27]. *P. aeruginosa* isolates containing NDM-1 presented a synergism for the ceftazidime/avibactam plus aztreonam combination, which is an option to treat infections caused by MBL-producing organisms [28, 29]. This strategy is based on the ability of avibactam to inhibit serine-β lactamases and the lack of hydrolytic activity of MBLs against aztreonam [30]. Consequent changes in genetic distribution emphasize the urgent need for continuous monitoring to control further dissemination of these high-risk CPPA types.

Considering the antimicrobial susceptibility profiles of the examined isolates, the Cns-CPPA stains exhibited 100.0% non-susceptibility to all tested antibiotic agents, except for aztreonam (94.5%) and colistin (5.9%). Carbapenemase producers show a multidrug-resistant profile as these strains hydrolyze all β-lactams except aztreonam and harbor gene cassettes containing resistance genes [31]. The relatively low susceptibility of CPPA to aztreonam may account for the different mechanisms of non-susceptibility in *P. aeruginosa* [32]. β-Lactamase inhibitors such as avibactam can be administered as a partner drug in combination with aztreonam [33].

Consistent with previous studies [34, 35], our study demonstrated that the use of carbapenems was an independent risk factor for UTI. Patients exposed to carbapenems are vulnerable to many invasive procedures involving medical devices, facilitating the cross-transmission of drug-resistant isolates [36]. A previous study demonstrated that urine was the main source of CPPA isolates associated with the presence of urinary catheters [37]. Therefore, UTI caused by these isolates could be associated with exposure to carbapenems, highlighting the need to carefully select an appropriate antibiotic in such cases.

Based on our findings, exposure to carbapenems may be a risk factor for mortality and UTI. The severity of infection in patients receiving carbapenems for treatment should be considered. A previous study [38] showed that carbapenem use was associated with 30-day mortality in patients positive for infection caused by *P. aeruginosa*. The duration of antibiotic therapy and the total dose, including carbapenems, were determined to be significant factors for patients with MBL-producing *P. aeruginosa* isolates [37], which have also been reported to be closely related to mortality [38, 39]. *P. aeruginosa* strains are particularly affected by the emergence of resistance during treatment [36]. ICU stay was identified as a very well-established risk factor for mortality in several studies [2, 38]. A study of nosocomial infections with MBL-producing *P. aeruginosa* exhibited an OR of 4.01 for ICU stay [2], which is similar to the ORs (4.966 for univariate and 2.677 for multivariate analyses) in our study. Severe conditions in ICU patients can also influence outcomes. WBC count was also significantly associated with mortality in our data. The elevation in the WBC count itself might indicate infectious conditions, thus providing little information [40]; however, it can be used to predict mortality when combined with clinical features such as the use of carbapenems and ICU stay. The combination of significant factors in multivariate analyses has seldom been reported in earlier studies. The AUC (0.760) determined in the present study indicates that patients with exposure to carbapenems and an elevated WBC count in the ICU should receive aggressive management and monitoring to prevent in-hospital

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mortality.

This study had some limitations. First, this was a retrospective study. Therefore, several variables that could not be controlled at the beginning of the study are present. A multivariate logistic regression model was used to adjust for the clinical features of patients. Second, the limited study population might have influenced the matching of cases, such as UTI, mortality, and control groups, leading to some unforeseen confounding factors. Third, some Cns-CPPA isolates may have been included in the Cns-nCPPA group because Cns-CPPA was defined by the detection of carbapenemase-encoding genes via multiplex real-time PCR.

In conclusion, the prevalence of non-susceptible *P. aeruginosa* isolates from urine samples between 2015 and 2020 was examined, demonstrating an increasing trend in CPPA prevalence in recent years, with NDM-type CPPA isolates emerging as the predominant type during the COVID-19 pandemic period. The CPPA strains were non-susceptible to almost all tested antibiotics, greatly challenging the treatment strategy for infection. Our findings suggest that the risk factors associated with the development of UTI and mortality should be evaluated in patients with *P. aeruginosa* infections. Our results revealed that the use of carbapenems is an important risk factor for both UTI and mortality. The combination of the use of carbapenems, ICU stay, and WBC count should be considered when predicting mortality. Aggressive antibiotic stewardship programs and vigilant monitoring may help prevent poor outcomes in cases of such infections.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3343/alm.2024.44.1.38

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AUTHOR CONTRIBUTIONS

Conceptualization: Song W; data curation: Jeong S; methodology: Jeon K; validation: Lee N; writing—original draft: Jeong S; writing—review and editing: Park MJ and Song W. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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