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ORIGINAL ARTICLE

Carbapenem-resistant *Pseudomonas aeruginosa* in Taiwan: Prevalence, risk factors, and impact on outcome of infections

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Background: The prevalence and clinical impact on mortality of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is unclear in Taiwan. We aim to clarify these clinical issues by using data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program.
Methods: Patients from five hospitals with their *P. aeruginosa* isolates collected by TSAR II-VII (2000–2010) program were considered as the potential study population. All patients with CRPA were enrolled as case patients. Patients with carbapenem-susceptible *P. aeruginosa* were randomly selected in a 1:1 ratio to case patients as control patients. CRPA isolates were tested for the presence of carbapenemase-producing genes. The clinical data were collected to identify risk factors for CRPA carriage and mortality of *P. aeruginosa* infection.
Results: The overall prevalence of CRPA was 10.2% (349/3408), which increased significantly by the TSAR period ($p = 0.007$). Among the 164 enrolled patients, the risk factor for carrying CRPA was previous fluoroquinolone exposure ($p = 0.004$). The risk factors for mortality among 80 patients with infection by *P. aeruginosa* included: intensive care unit (ICU) setting, receipt of antifungal therapy, and presence of invasive devices ($p = 0.001$, 0.010, and 0.017; respectively). Carbapenem resistance did not play a role. Among the 82 CRPA isolates enrolled in this study, 15 isolates were found to carry carbapenemase-producing genes.

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Conclusion: In Taiwan, the prevalence of CRPA and carriage of carbapenemase-producing genes was high. However, carbapenem resistance did not play a role in the mortality of patients with *P. aeruginosa* infections.

Introduction

Pseudomonas aeruginosa is one of the most common pathogens causing nosocomial infections. The ability to develop multidrug resistance makes these infections difficult to treat, and they are associated with high mortality rates, ranging from 18% to 61%.[1] As the use of antimicrobial agents becomes more extensive, the emergence of multidrug-resistant *P. aeruginosa* (MDRPA) has also increased. Carbapenems have been the main antibiotics used against MDRPA. However, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) has also emerged and caused many nosocomial outbreaks.[2,3] In recent years, several surveillance studies from the USA and Europe have reported increasing prevalence of CRPA isolates (an increase from 4% in the 1990s to 14—30% in the 2000s), and there are regional differences in rates.[4—6]

Carbapenem resistance is due to multiple mechanisms, including production of carbapenemases, over-expression of the efflux pump, or loss of outer membrane porins plus production of extended spectrum β-lactamase or AmpC β-lactamase.[7] Among these resistance mechanisms, production of carbapenemase is the most important because it was associated with higher mortality rates compared with noncarbapenemase-producing CRPA.[8] The reported carbapenemases in *P. aeruginosa* included nonmetallo-enzyme carbapenemase (NMC), *Serratia marcescens* enzyme (SME), *Klebsiella pneumoniae* carbapenemase (KPC), imipenem-hydrolyzing β-lactamase (IMI), Guiana extended-spectrum β-lactamase (GES), imipenemase (IMP), Verona integron-encoded metallo-β-lactamase (VIM), German imipenemase (GIM), Sao Paulo metallo-β-lactamase (SPM), New Delhi metallo-β-lactamase (NDM), and oxacillinase-48 (OXA-48), among which VIM has been the most predominant.[9]

Although there have been many updated epidemiological and microbiological studies on CRPA in several countries,[4—6] there are only a few reports from Taiwan on the prevalence of CRPA.[9—11] In addition, the effect of carbapenem resistance on the outcome of *P. aeruginosa* infections and risk factors for acquiring CRPA in Taiwan remain obscure. Therefore, the current burden, clinical epidemiology, and specific interventions designed according to the identified risk factors to prevent the spread of CRPA in Taiwan are also unclear. The present study was designed to clarify the above clinical issues.

Patients and methods

Bacterial isolates and patients

P. aeruginosa isolates were collected as part of the TSAR program from medical centers and regional hospitals in Taiwan. The participating hospitals and bacterial collection procedures of TSAR have been described in detail in previous reports.[12—14] The complete lists of *P. aeruginosa* isolates from TSAR II (2000) to VII (2010), and their source were retrieved first from the TSAR database. The site investigators of the TSAR participating hospitals were contacted to obtain their agreement to participate in the present study. After obtaining the approval of the Research Ethics Committee, patients with infection or colonization by CRPA from these hospitals were considered as case patients. Patients with infection or colonization by CSPA from the same hospital as the case patients were considered as the pool of control patients. A computer-generated random digital number table was used to randomly select the final control patients with a 1:1 ratio to case patients.

Antimicrobial susceptibility test

Antimicrobial susceptibilities to various antimicrobial agents, including amikacin, gentamicin, piperacillin, ticarcillin/clavulanic acid, piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, imipenem, meropenem, ciprofloxacin, levofloxacin, minocycline, colistin, and chloramphenicol were determined by minimum inhibitory concentration (MIC) using the microbroth dilution method and interpreted according to the criteria suggested by the Clinical and Laboratory Standards Institute (CLSI).[15,16] In this study, CRPA was defined as an isolate with imipenem and/or meropenem MICs $\geq$8 μg/mL.[17] The other *P. aeruginosa* isolates were considered as CSPA.[13]

Detection of carbapenemase-producing genes

All the CRPA isolates were subjected to detection of carbapenemase-encoding genes, including *NMC*, *SME*, *KPC*, *IMI*, *GES*, *IMP*, *VIM*, *GIM*, *SPM*, *NDM-1*, *NDM-2* and *OXA-48*, using polymerase chain reaction (PCR) methods as previously described.[9]

Data collection

A standardized case report form was used to collect the relevant demographic, clinical, and microbiological data. The following data were recorded: age and sex; comorbidities and underlying diseases; presence of neutropenia (absolute granulocyte count of $<$500 granulocytes/mL) and use of immunosuppressive therapy (chemotherapy, radiotherapy, or immunosuppressive drugs); past hospitalization and invasive therapy (hemodialysis or chemotherapy) within the past year; previous antibiotic use within the last 15 days; patients' setting and source of isolates; colonization or infection of CRPA and sites of primary infection;

clinical signs and laboratory data; antimicrobial treatment received and outcome. Empirical antimicrobial therapy was considered appropriate when the antimicrobial regimen included any active antimicrobial by *in vitro* susceptibility testing results administered during the infection episode.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) and compared using the Student *t* test, or described as the median as well as range, and compared with the Wilcoxon rank-sum test if their distributions were not normal. Categorical variables were compared with a Chi-square test or Fisher exact test if the expected values were less than 10. Risk factors for colonization and all-cause in-hospital mortality were identified using logistic regression models. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). All tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Descriptive epidemiology from the TSAR database

A total of 3408 *P. aeruginosa* isolates were collected from 26 hospitals in TSAR II—VII (2000—2010). Among these isolates, 349 (10.2%) were CRPA. There was a significant trend of increasing CRPA prevalence over this period ($p = 0.007$) (Fig. 1). Only 2.0% (7/349) of CRPA isolates were susceptible to imipenem, whereas 38.1% (133/349) were susceptible to meropenem. Colistin was the most effective antibiotic against CRPA isolates with a susceptibility of 93.90%. CSPA isolates were significantly more susceptible to piperacillin/tazobactam (93.40% vs. 68.19%), levofloxacin (88.75% vs. 38.68%), and amikacin (98.78% vs. 42.95%) compared to CRPA isolates.

Bacterial isolates tested for the presence of carbapenemase-producing genes

Eighty-two CRPA isolates from five hospitals and another 82 CSPA isolates from the same hospitals were enrolled in the present study. Among the 82 CRPA isolates, 15 (15/82, 18.3%) were found to carry carbapenemase-producing genes, which all belonged to the VIM family. Comparison of antimicrobial susceptibilities between the carbapenemase-positive and non-carbapenemase-producing CRPA isolates is listed in Table 1. Isolates with carbapenemase genes were more resistant to various antibiotics than carbapenemase non-producers except piperacillin/tazobactam, imipenem, aztreonam, and colistin. Among carbapenemase producers, the most susceptible antibiotic was colistin (100%). Among non-carbapenemase-producers, the most effective antibiotics were amikacin and colistin with a susceptible rate of 94.03% and 92.54%, respectively. For these tested CRPA isolates, all carbapenemase-producers were resistant to amikacin. The susceptibility to amikacin had a very high positive predictive value (PPV) for the non-carbapenemase-producing isolates (PPV = 100%).

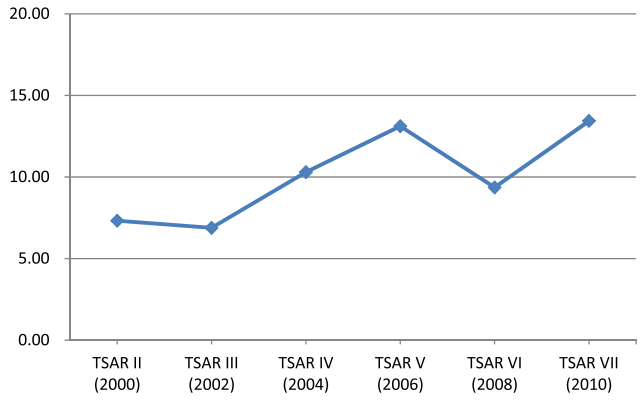

Figure 1. Trend of carbapenem resistance in *Pseudomonas aeruginosa* from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program.

Risk factors for carriage of CRPA

The medical records of the 164 index patients were reviewed. The mean age was 65 years, with a male to female ratio of 2.3:1. The most common underlying diseases were coronary artery disease and neurologic disease. More than half of the patients had prior hospitalization history, and most patients were hospitalized in general wards when their *P. aeruginosa* isolates were identified. Sputum was the most common specimen source, followed by urine.

Comparing patients with CSPA or CRPA isolates by univariate logistic analysis (Table 2), patients with CRPA tended to have renal disease ($p = 0.044$), be a colonizer only ($p = 0.044$), and have prior carbapenem and fluoroquinolone exposure ($p = 0.018$ and 0.004, data not shown). Using multivariate logistic analysis, previous fluoroquinolone exposure was the only independent risk factor for acquiring CRPA isolates [adjusted odds ratio (AOR), 4.64; 95% confidence interval (CI), 1.64—13.14, $p = 0.004$].

P. aeruginosa infection and outcome

Among the 164 source patients colonized or infected with CRPA and CSPA, there were 93 *P. aeruginosa* infected patients, of whom 45.2% (42/93) were infected with CRPA and 54.8% (51/93) with CSPA. We randomly selected a total of 42 CSPA-infected patients with a 1:1 ratio (from the same hospital) to 42 CRPA-infected patients to analyze the risk factors for mortality of infection. The clinical data regarding the outcome of two patients with CRPA infection were missed and therefore were excluded from the final analysis (also, two corresponding patients with CSPA infection were excluded). For the 80 *P. aeruginosa* infected patients, the all-cause in-hospital mortality rate was 23.8%. The most common infection focus was urinary tract infection (39/80, 48.8%), followed by lower respiratory tract infection (25/80, 31.3%).

In the analysis of factors associated with mortality, variables considered include age and sex, comorbidities and underlying diseases, past hospitalization and invasive therapy, patients' setting and sites of primary infection, clinical signs and laboratory data, presence of invasive devices, and antimicrobial treatment received were tested

Table 1 Comparison of antimicrobial susceptibilities between VIM gene-positive and negative carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

Antimicrobial agents	VIM gene-positive CRPA ($N = 15$)				VIM gene-negative CRPA ($N = 67$)			
	MIC (μg/mL)			Susceptibility (%)	MIC (μg/mL)			Susceptibility (%)
	Range	MIC_{50}	MIC_{90}		Range	MIC_{50}	MIC_{90}	
AMK	32–64	>32	>32	0	≤1–>32	4	16	94.03
TZP	32–>256	64	256	53.33	≤2–>256	32	>64	59.70
TIM	>128	>128	>128	33.33	8–>128	>64	>128	64.18
CAZ	>32–>128	>32	>128	0	≤1–128	16	32	47.76
FEP	32–64	32	>32	0	≤0.5–32	8	32	53.73
IMP	16–>128	>16	>128	0	1–64	16	>16	4.48
MEM	8–64	16	64	0	≤0.25–>16	8	16	46.27
ATM	≤4–128	16	64	26.67	≤2–128	32	>32	35.82
CIP	>4–>32	>4	32	0	≤0.06–>32	2	>4	43.28

AMK = amikacin; ATM = aztreonam; CAZ = ceftazidime; CIP = ciprofloxacin; COL = colistin; CRPA = carbapenem-resistant *P. aeruginosa*; FEP = cefepime; IMP = imipenem; MEM = meropenem; MIC = minimum inhibitory concentration; TIM = ticarcillin/clavulanate; TZP = piperacillin/tazobactam; VIM = Verona integron–encoded metallo-β-lactamase.
The colistin (COL) MIC and susceptibility.

Table 2 Comparison of demographics, clinical characteristics, infection status, and outcome of patients with carbapenem-susceptible and carbapenem-resistant *Pseudomonas aeruginosa* (CSPA and CRPA)

Parameters	CSPA ($N = 82$)	CRPA ($N = 82$)	*p*
Age, mean ± SD (y)	63.5 ± 23.2	66.6 ± 18.1	0.364
Male, *n* (%)	55 (67.1)	59 (72.0)	0.498
Underlying disease, *n* (%)			
Diabetes mellitus	23 (28.1)	31 (37.8)	0.184
Respiratory disease	22 (26.8)	29 (35.4)	0.238
Coronary artery disease	43 (52.4)	41 (50.0)	0.755
Gastrointestinal disease	21 (25.6)	30 (36.6)	0.129
Hepatobiliary disease	6 (7.3)	7 (8.5)	0.773
Renal disease	14 (17.1)	25 (30.5)	0.044
Neurologic disease	36 (43.9)	46 (56.1)	0.118
Cancer	10 (12.2)	10 (12.2)	1.000
Immunosuppression	5 (6.1)	7 (8.5)	0.549
Autoimmune disease	1 (1.2)	1 (1.2)	1.000
Other	30 (36.6)	34 (41.5)	0.522
Hospitalization within the past year, *n* (%)	59 (72.0)	62 (75.6)	0.594
Invasive therapy (hemodialysis, chemotherapy) within the past year, *n* (%)	21 (25.6)	22 (26.8)	0.859
Locations, *n* (%)			0.651
Community	12 (14.8)	8 (10.0)	
Ward	52 (64.2)	54 (67.5)	
ICU	17 (21.0)	18 (22.5)	
Previous antibiotic use within the past 15 d, *n* (%)	50 (61.0)	54 (65.9)	0.517
Isolated specimen site, *n* (%)			0.556
Blood	4 (4.9)	5 (6.1)	
Sputum	41 (50.0)	41 (50.0)	
Urine	15 (18.5)	20 (24.4)	
Pus/wound	8 (9.9)	6 (7.3)	
Throat swab	1 (1.2)	0	
Nasal swab	0	2 (2.4)	
Others	12 (14.8)	8 (9.8)	
Infection or colonization, *n* (%)			0.239
Colonization	20 (28.2)	30 (41.7)	
Infection	51 (71.8)	42 (58.3)	
Mortality, *n* (%)	16 (19.5)	18 (22.0)	0.925

CSPA = carbapenem-susceptible *P. aeruginosa*; CRPA = carbapenem resistant *P. aeruginosa*; ICU = *intensive care unit;* TSAR = Taiwan Surveillance of Antimicrobial Resistance.

(Table 3). By univariate analysis, patients with hepatobiliary disease, acquisition of *P. aeruginosa* while staying in ICUs, and prior exposure to antifungal treatment were associated with a higher mortality ($p = 0.016$, 0.001, and 0.040, respectively). The severity of disease, including hypotension and presence of invasive devices, also led to poorer outcome ($p = 0.002$ and 0.005, respectively).

By multivariate logistic analysis, patients staying in ICUs, prior exposure to antifungal therapy and presence of invasive devices, remained independent risk factors for

Table 3 Factors associated with mortality identified using logistic regression models

Parameters	Univariate analysis			Multivariate analysis	
	Survival ($N = 61$)	Mortality ($N = 19$)	p	p	AOR (95% CI)
Age, mean ± SD (y)	61.6 ± 21.2	73.0 ± 13.8	0.010	0.072	
Male, *n* (%)	42 (68.9)	15 (79.0)	0.396	—	
Underlying disease, *n* (%)					
Diabetes mellitus	21 (34.4)	7 (36.8)	0.847	—	
Respiratory disease	21 (34.4)	5 (26.3)	0.510	—	
Coronary artery disease	24 (39.3)	7 (36.8)	0.845	—	
Gastrointestinal disease	18 (29.5)	7 (36.8)	0.547	—	
Hepatobiliary disease	3 (4.9)	5 (26.3)	0.016	0.788	
Renal disease	12 (19.7)	5 (26.3)	0.537	—	
Neurologic disease	31 (50.8)	7 (36.8)	0.287	—	
Cancer	7 (11.5)	5 (26.3)	0.144	—	
Immunosuppression	1 (1.64)	2 (10.5)	0.139	—	
Autoimmune disease	1 (1.64)	0	1.000	—	
Other	27 (44.3)	6 (31.6)	0.327	—	
Charlson comorbidity index, mean ± SD	2.7 ± 2.1	3.7 ± 3.2	0.210	—	
Hospitalization within the past year, *n* (%)	45 (73.8)	13 (68.4)	0.648	—	
Invasive therapy in the past year, *n* (%)	16 (26.2)	9 (47.4)	0.083	—	
Locations, *n* (%)			<0.001	<0.001	15.61 (3.61–67.47)
Community	6 (10.0)	0			
Ward	49 (81.7)	8 (42.1)			
ICU	5 (8.3)	11 (57.9)			
Site of infection, *n* (%)			0.867	—	
Pneumonia	20 (32.8)	5 (26.3)			
Urinary tract infection	29 (47.5)	10 (52.6)			
Others	12 (19.7)	4 (21.1)			
Clinical signs & laboratory data, *n* (%)					
Fever/hypothermia	45 (73.8)	17 (89.5)	0.214	—	
Tachycardia	51 (83.6)	18 (94.7)	0.445	—	
Tachypnea	18 (29.5)	8 (42.1)	0.306	—	
Hypotension	18 (29.5)	13 (68.4)	0.002	0.319	
Leukocytosis	42 (68.9)	14 (73.7)	0.688	—	
Presence of invasive device, *n* (%)	10 (16.4)	10 (52.6)	0.005	0.017	5.85 (1.38–24.82)
Antimicrobial therapy, *n* (%)					
Anti-pseudomonal penicillins	11 (18.0)	3 (15.8)	1.000	—	
Penicillins/beta-lactamase inhibitors	13 (21.3)	4 (21.1)	1.000	—	
Anti-pseudomonal third-generation cephalosporins	17 (27.9)	7 (36.8)	0.456	—	
Fourth-generation cephalosporins	3 (4.9)	1 (5.3)	1.000	—	
Carbapenems	13 (21.3)	10 (52.6)	0.084	—	
Aztreonam	1 (1.64)	0	1.000	—	
Floroquinolones	25 (41.0)	6 (31.6)	0.463	—	
Macrolides/tetracyclines	6 (9.8)	5 (26.3)	0.120	—	
Aminoglycoside	23 (37.7)	6 (31.6)	0.628	—	
Anti-fungal agents	1 (1.6)	3 (15.8)	0.040	0.010	31.19 (2.27–429.11)
Appropriate antimicrobial therapy, *n* (%)	39 (63.9)	10 (52.6)	0.377	—	

AOR = adjusted odds ratio; CI = confidence interval; ICU = intensive care unit.

mortality (AOR: 15.61, 31.19, and 5.85, respectively; 95% CI, 3.61—67.47, 2.27—429.11, and 1.38—24.82, respectively; $p = 0.001$, 0.010, and 0.017, respectively). However, carbapenem resistance and appropriate antibiotic treatments were not associated with mortality.

Discussion

CRPA has emerged as a significant pathogen worldwide, but the prevalence varied by geographic region, specimen source, patient age, patient setting, and selective pressure from broad spectrum antibiotics.[18] In the Carbapenem Antimicrobials Pseudomonas Isolate Testing At regional Locations (CAPITAL) surveillance program in the USA during 2010, the resistant rate ranged from 7.4% to 35.4%.[18] According to the Taiwan Nosocomial Infections Surveillance System, the proportion of CRPA isolates among all *P. aeruginosa* isolates in the ICUs of medical centers was 18.1% in 2011, which was higher than that identified by the present study (10.2%).[19] These varied results implied the prevalence of CRPA was different among different geographic areas, patient population, and clinical setting. Every institution should regularly monitor the resistant rate of pathogens and the antibiotics consumption, and integrate the information into infection control programs.[20] In the present study, the overall prevalence of CRPA from 2000 to 2010 in Taiwan was 10.2%. This prevalence was similar to previous surveillance.[10] During our study period, the prevalence of carbapenem resistance among *P. aeruginosa* isolates in Taiwan increased significantly. Several studies from other countries also showed the same finding in recent years.[21]

In our study, CRPA were more resistant to multiple drugs than CSPA isolates, and the most effective antibiotic against CRPA isolates was colistin (100% susceptible). Carbapenem resistance may result from multiple mechanisms with or without the production of carbapenemase. In the carbapenemase-producing CRPA, metallo-β-lactamases (MBLs) have been reported from many countries,[22] suggesting that these enzymes are an important mechanism of carbapenem resistance among *P. aeruginosa*. MBLs belong to Ambler class B carbapenemases, and AIM (Adelaide imipenemase), GIM, IMP, NDM, SPM, and VIM type MBLs have been described globally. Among them, bla_{AIM} belongs to subclass B3 and is a potential transferable gene, but is less known than the other subclass B1 MBLs. In a previous study in Taiwan during 2000—2002, the prevalence of MBL-producing CRPA among all CRPA isolates was 17—36%, which was higher than a recent report on CRPA from French ICUs during 2010.[7,23] Similar to those studies, we detected MBL in 18.3% of the CRPA studied, and all were the VIM-type.[19,20]

Carbapenemase-producing CRPA exhibited higher rates of resistance to various antibiotics except colistin and piperacillin/tazobactam, which was similar to a previous study.[23] However, the MIC of carbapenemase-producing CRPA to piperacillin/tazobactam tended to be higher than noncarbapenemase-producing CRPA (MIC_{50}, >32 vs. 4; MIC_{90}, >32 vs. 16). Among carbapenemase-negative CRPA isolates, amikacin had a similar susceptibility rate to that of colistin, and the positive predictive value of amikacin susceptibility for MBL-negative CRPA was 100%. For CRPA isolates in Taiwan, amikacin-susceptibility may be a hint for the absence of MBL genes.

The risk factors for acquiring CRPA may be related to the host condition, infection control practice, and antimicrobial consumptions.[20,24,25] Our data showed that prior exposure to fluoroquinolone was the only independent risk factor for acquiring CRPA. The association between prior fluoroquinolone use and CRPA isolates has been well established in previous studies.[26,27] Exposure to fluoroquinolone leads to upregulation of the multidrug efflux pump MexEF-OprN and reduced levels of OprD porin,[28] with subsequent resistance to both fluoroquinolones and carbapenems.[7,23,27] In Taiwan, we noted an increase in the use of piperacillin/tazobactam, broad-spectrum cephalosporins, carbapenems, and fluoroquinolones.[20,24] To reduce the prevalence of CRPA, it would be important to prescribe flluoroquinolones prudently.

Several studies have found higher mortality rates of *P. aeruginosa* infection to be related to patients' comorbidity, the site of primary infection, disease severity, multidrug resistance, and inappropriateness of empirical therapy.[29,30] In this study, the independent risk factors for all-cause in-hospital mortality in patients with *P. aeruginosa* infection were ICU stay, prior exposure to antifungal agents, and presence of invasive devices. All the independent risk factors in our study were indicators of severe comorbidities and illness. The critically ill patients who need ICU admission are associated with higher disease severity and in-hospital mortality rate.[31] Fungal infection and antifungal therapy is related to more severe comorbidities including neoplasm with immunosuppressive agents, prior severe infection requiring the use of broad-spectrum antibiotics, and receiving aggressive surgery.[32] Invasive catheters are important tools in critically ill patients, and their widespread use may lead to several complications, significant morbidity, and mortality.[33]

Our study did not find carbapenem resistance or inappropriate treatment as a significant factor associated with the mortality of patients infected with *P. aeruginosa*. Several retrospective studies suggested higher mortality rates among patients infected by nonsusceptible *P. aeruginosa* isolates.[25,34] However, a few prospective cohort studies also showed that carbapenem resistance did not have a significant impact on mortality.[17,35] In addition, some studies did not find an adverse impact of inappropriate therapy on mortality.[17,25] The insignificant effect of carbapenem resistance and inappropriate treatment on patient outcome might result from the fact that the outcome of an infection is mostly dependent on the severity of the underlying disease, the primary site of infection, and the virulence of the pathogens.[17,36] Some *in vitro* studies suggested that the resistance mutations can alter the fitness of microorganisms and make them less virulent, but the impact of resistance mutations on the virulence of clinical isolates has yet to be elucidated.[37,38]

Our study has several limitations. Firstly, this was a retrospective cohort study. The retrospective nature with a 1:1 matched ratio may preclude accurate comparisons because of many confounding factors such as underlying disease, severity of infection, occult bias, and other hidden confounding factors. To diminish these biases, we recorded

related factors in detail and used multivariate logistic analysis to find the independent risk factors. However, our study results need further investigation for verification. Secondly, although we detected the presence of carbapenemase producing genes, its association with outcome was not investigated due to the small sample size. Further studies should be performed to clarify if the presence of carbapenem-resistance genes affects the clinical outcome.[38] Thirdly, the overall prevalence of CRPA was calculated using the data from the TSAR program. Different TSAR periods enrolled different hospitals. This might lead to the comparison of TSAR II—VII from data of different hospitals. However, 18 hospitals continuously and consistently participated in the TSAR II—VII program, but there were 13 hospitals not consistently participating in the TSAR program. The effect of different hospitals was not considered to be major. Finally, our study was conducted in Taiwan, and the situation may differ in other countries.

In conclusion, the CRPA prevalence in Taiwan was higher than in previous studies. However, the proportion of carbapenemase producers among CRPA was similar. ICU admission, prior antifungal therapy, and the presence of invasive devices are three factors independently associated with the all-cause in-hospital mortality of *P. aeruginosa* infection in our study. Contrary to previous beliefs, the mortality was not related to carbapenem resistance and appropriate treatment.

Conflicts of interest

All authors have no conflicts of interest to declare.

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