



Epidemiology of carbapenem-resistant *Klebsiella pneumoniae* in healthcare-associated infections – a retrospective study from Taiwan

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Abstract

Introduction and Objective. In recent years, carbapenem-resistant Enterobacteriaceae, particularly carbapenem-resistant *Klebsiella pneumoniae* (CRKP), have emerged as a global public health concern, posing substantial challenges to clinical treatment. The aim of the study is to investigate the prevalence of CRKP in healthcare-associated infections (HAIs), and to support the development of effective surveillance mechanisms and antimicrobial resistance containment strategies.

Materials and Method. A retrospective observational study was conducted using HAI data from a medical centre in central Taiwan, covering the period from January 2015 to December 2020. Cases of *Klebsiella pneumoniae* infection were categorized into two groups: CRKP (case group) and non-CRKP (control group). Risk factors were assessed using Pearson's χ^2 test or continuity correction (Fisher's exact); a t-test was applied alongside univariable and multivariable logistic regression analyses.

Results. Results indicated a high prevalence of CRKP in patients with cardiovascular disease (odds ratio [OR] = 3.33; 95% confidence interval [CI]: 1.24–8.97; $p = .017$), prior exposure to carbapenems (OR = 3.70; 95% CI: 1.69–8.10; $p = .001$), presence of urinary catheters (OR = 3.51; 95% CI: 1.30–9.50; $p = .013$), and haemodialysis catheters (OR = 6.57; 95% CI: 2.17–19.91; $p = .001$).

Conclusions. The incidence of CRKP-related HAIs demonstrated an upward trend over the study period. These findings suggest that patients with cardiovascular disease, or those requiring urinary or haemodialysis catheters, should avoid unnecessary invasive procedures. Enhanced monitoring and control of CRKP strains are imperative for preventing the emergence and spread of multi-drug-resistant and hypervirulent variants.

Key words

carbapenem; carbapenem-resistant *Klebsiella pneumoniae*; healthcare-associated infection (HAI)

INTRODUCTION

Cases of Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are increasing worldwide, raising considerable concern because of the spread of highly drug-resistant strains, including those responsible for hospital outbreaks and extensively drug-resistant phenotypes [1]. CRKP is frequently implicated in healthcare-associated infections (HAIs), such as urinary tract infections, pneumonia, sepsis, and infections of soft tissue [2] – infections associated with considerable morbidity and mortality [3]. Notably, CRKP infections have been linked to an increased incidence of *Klebsiella pneumoniae* infections among critically ill patients in Intensive Care Units (ICUs) [4].

In Taiwan, CRKP has emerged as a major cause of difficult-to-treat HAIs, and its incidence shows a rapidly increasing trend [5]. HAIs represent a critical patient safety concern in hospitals, particularly in ICUs, where they contribute to prolonged hospitalizations, increased morbidity and

mortality, and a substantial economic burden on the healthcare system [6]. As one of the principal complications of modern medical care, HAIs are most commonly associated with the use of invasive medical devices. The HAIs include central line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia, and surgical site infections. Moreover, HAIs are associated with mortality, prolonged hospital stays, and elevated healthcare costs. To mitigate these impacts, healthcare institutions should implement targeted strategies, such as minimizing pre-infection hospital stays and rationally managing medications [7].

CRKP has emerged as a relevant pathogen in many medical centres, with limited remaining therapeutic options, thereby underscoring the importance of stringent infection control measures [8]. In Taiwan, recent data on the risk factors and clinical outcomes associated with CRKP infections remain scarce. Therefore, the aim of the study is to investigate the association between HAIs and CRKP in the Central Taiwan Medical Centre. The findings are intended to inform HAI prevention efforts, support the establishment of a CRKP surveillance system, and contribute to the development of antimicrobial resistance containment strategies.

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MATERIALS AND METHOD

Study design. The study protocol was approved by the Institutional Review Board of JEN-AI Hospital (IRB No. 107–44). The research was conducted at a 2,480-bed medical centre located in central Taiwan. The study period spanned from 1 January 2015 – 31 December 2020. All hospitalized patients diagnosed with HAIs and with positive cultures for *Klebsiella pneumoniae* were included in the study. Based on antimicrobial susceptibility testing results, patients were categorized into two groups: CRKP and non-CRKP cases.

CRKP identified. Microbiological laboratory criteria: inclusion required a confirmed diagnosis of pneumonia, urinary tract infection, or bloodstream infection caused by CRKP, along with the identification of a carbapenem resistance mechanism following the isolation of CRKP from patients. Cases were excluded when the patient's medical records were incomplete. Carbapenem resistance was defined as a minimum inhibitory concentration of ≥ 4 mg/L for meropenem or imipenem, or ≥ 2 mg/L for ertapenem. Bacterial identification and antimicrobial susceptibility testing were performed using a BD Phoenix M50 automated microbial identification and susceptibility testing system (BD Diagnostic Systems, Sparks, MD), or confirmed using the modified Hodge test. Blood cultures were processed and incubated using the BD BACTEC FX40 automated microbial fluorescence detection system.

Research procedure. The microbiology laboratory acceptance criteria were defined as follows: a confirmed diagnosis of pneumonia, urinary tract infection, or bloodstream infection caused by CRKP, along with the identification of carbapenem resistance mechanisms following the isolation of CRKP strains from individual patients. These criteria were applied for the monitoring of acute infections associated with medical care in healthcare institutions. According to the US CDC, such infections qualify as HAIs when they meet specific diagnostic and microbiological criteria. Based on these standards, a total of 242 cases were reviewed. Among them, 58 patients (24%) were classified into the CRKP group, while the remaining 184 patients (76%) comprised the non-CRKP group (Fig. 1).

The study employed a retrospective review of medical records. The paper-based and electronic medical records

of patients with CRKP and non-CRKP infections, who met the diagnostic criteria for HAIs, were collected and analyzed. Cases were categorized according to the type of inpatient ward at the time of infection, either general wards or ICUs. Demographic and clinical variables were examined, including gender, age, and underlying co-morbidities, such as cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, malignancies, liver cirrhosis, end-stage renal disease, cerebrovascular accidents, and long-term bed rest status. The use of invasive devices within 48 h prior to infection was assessed, including peripheral venous catheters, central venous catheters, arterial catheters, endotracheal tubes, tracheostomy, mechanical ventilation, in-dwelling urinary catheters, total parenteral nutrition, naso-gastric tubes, and haemodialysis catheters. Additionally, data on carbapenem use and other hospitalization-related variables were collected for analysis.

Data analysis. Data were entered into a computerized database and verified for accuracy prior to analysis using SPSS Version 22.0 (IBM Corp., Armonk, NY, USA). A significance level of $p < 0.05$ was applied throughout the study. Descriptive statistics, including pooled means, medians, and standard deviations, were calculated. Categorical variables were analyzed using Pearson's chi-square test, whereas continuous variables were compared between the CRKP and non-CRKP groups with Student's *t*-test. The association between CRKP and HAIs was examined using univariate analysis. Variables with $p < 0.1$ in univariate analysis were subsequently included in a multivariate logistic regression model for the identification of independent risk factors. The overall significance of the regression model was assessed using the Omnibus test, and model calibration was evaluated with the Hosmer-Lemeshow goodness-of-fit test. For categorical variables, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and used in estimating the strength of association between risk factors and CRKP-related infections. A p -value < 0.05 was considered statistically significant.

RESULTS

Several statistically significant differences between the CRKP and non-CRKP groups were identified in the study. Categorical variables showing significant associations included age ≥ 65 years, ICU admission, presence of cardiovascular disease, end-stage renal disease, prior exposure to carbapenems, and the use of central venous or arterial catheters. A total of 13 potential risk factors for CRKP infection were observed, encompassing the use of invasive devices, such as catheters, endotracheal tubes, mechanical ventilation, catheter placement, total parenteral nutrition, naso-gastric tubes, and haemodialysis catheters. Furthermore, the CRKP group exhibited a significantly higher mortality rate of 36.2%, compared to 16.3% in the non-CRKP group ($p < 0.05$) (Tab. 1).

CRKP-related HAIs were recorded during the period 2015 – 2020. Among CRKP cases, urinary tract infections were the most common, accounting for 30 patients (51.72%), followed by bloodstream infections in 26 patients (44.83%). Pneumonia and surgical site infections were each observed in one patient (1.72%). By contrast, among non-CRKP cases, bloodstream infections were the most frequent – 85 patients (46.20%), followed by urinary tract infections – 82 patients

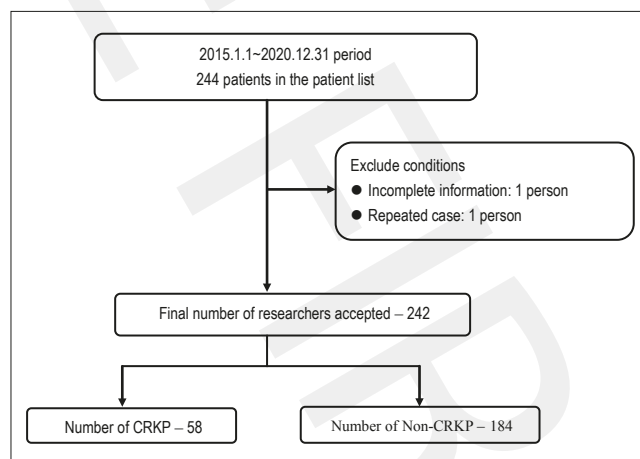


Figure 1. Research process and number of people

Table 1. Comparison of clinical characteristics of CRKP and Non-CRKP

Variable	CRKP (n=58) n (%)	Non-CRKP (n=184) n (%)	t / χ^2	P-value
Age (years) mean $\pm$ SD ^a	70.0 $\pm$ 21.0	61.4 $\pm$ 22.0	2.56	.011†*
Age (years) median	78(58-85)	65(52-78)	--	.007‡*
Age $\geq$ 65 years ^b	39 (67.2)	94 (51.1)	4.65	.031†*
Gender (male)	36 (62.1)	98 (53.3)	1.385	.239†
Intensive Care Unit	28 (48.3)	45 (24.5)	11.88	.001†*
Conservation agency transferred in	7 (12.1)	22 (12.0)	0.001	.982
Cardiovascular diseases	51 (87.9)	89 (48.4)	28.31	<.001†*
Chronic obstructive pulmonary disease	19 (32.8)	38 (20.7)	3.59	.058†
diabetes	37 (63.8)	115 (62.5)	0.03	.859†
hypertension	51 (87.9)	143 (77.7)	2.89	.089†
Malignant tumor	41 (70.7)	117 (63.6)	0.98	.322†
Liver cirrhosis	8 (13.8)	21 (11.4)	0.24	.626†
End-stage renal disease	42 (72.4)	81 (44.0)	14.22	<.001†*
Cerebrovascular disease	20 (34.5)	55 (29.9)	0.44	.510†
Long-term bed rest	40 (69.0)	117 (63.6)	0.56	.454†
Antibiotic use (within one year)	58 (100)	183(99.5)	0.00	1.00†c
Carbapenem exposed	28 (48.3)	27 (14.7)	28.352	<.001†*
Peripheral venous catheter	58 (100)	183 (99.5)	0.00	1.00†c
Central venous catheter	28 (48.3)	62 (33.7)	4.01	.045†*
Arterial catheter	11 (19.0)	14 (7.6)	6.14	.013†*
Endotracheal tube	25 (43.1)	25 (13.6)	23.44	<.001†*
Tracheotomy	51 (87.9)	161 (87.5)	0.01	.931†
Respirator use	30 (51.7)	33 (17.9)	26.15	<.001†*
Catheter indwelling	47 (81.0)	96 (52.2)	18.572	<.001†*
Total intravenous nutrition infusion	4 (6.9)	0 (0)	12.90	<.001†*
Nasogastric tube placement	43 (74.1)	90 (48.9)	11.34	.001†*
Hemodialysis catheter placement	18 (31.0)	14 (7.6)	21.09	<.001†*
Mortality rate	21 (36.2)	30 (16.3)	10.50	.001†*

Note: a. Age is a continuous variable, and the ages of the two groups are expressed as mean $\pm$ standard deviation and median (interquartile range).

b. Age is classified as $\geq$ 65 years old or <65 years old, which is a binary category variable. Chi-square test or †c continuous correction; ‡student's t test; † median test; *p value <.05. Wards are classified as general wards or intensive care centers; ages are classified as $\geq$ 65 years old or <65 years old. CRKP: Carbapenem-resistant CRKP; Carbapenem-resistant KP; Non-CRKP; Non-Carbapenem-resistant KP; SD: Standard deviation

(44.57%), pneumonia – 9 patients (4.89%), and surgical site infections – 8 cases (4.35%) (Tab. 2).

The distribution of strains of infectious, based on the source of clinical specimens, was as follows: among the 58 CRKP isolates, 30 strains (51.72%) were derived from urine

Table 2. Distribution of infection sites related to CRKP and Non-CRKP in HAIs

Site of infection	CRKP		Non-CRKP	
	n	%	n	%
Bloodstream infection	26	44.83	85	46.20
Urinary tract infection	30	51.72	82	44.57
pneumonia	1	1.72	9	4.89
Surgery site infection	1	1.72	8	4.35

samples, 26 strains (44.83%) from blood samples, and 2 strains (3.45%) from sputum. One isolate each (1.72%) was obtained from body fluid, pus, or wound specimens. In the non-CRKP group (n = 184), blood samples accounted for the highest number of isolates, with 85 cases (46.20%), followed by urine samples with 82 cases (44.57%). Sputum specimens yielded 9 isolates (4.89%), and 5 isolates (2.72%) were obtained from pus or wound specimens. Additionally, 3 isolates (1.63%) were recovered from cerebrospinal fluid specimens (Tab. 3).

Table 3. Proportion of specimen types of CRKP and Non-CRKP

Type of specimen	CRKP		Non-CRKP	
	n	%	n	%
Blood	26	44.83	85	46.20
Urine	30	51.72	82	44.57
Sputum	1	1.72	9	4.89
Pus/wound	1	1.72	5	2.72
CSF	0	0	3	1.63

Statistical analysis using univariate logistic regression identified several significant risk factors associated with CRKP infection, including underlying cardiovascular disease (odds ratio [OR] = 7.78; $p < 0.001$), prior exposure to carbapenems (OR = 5.43; $p < 0.001$), and the use of invasive devices, such as mechanical ventilation (OR = 4.90; $p < 0.001$), urinary catheter placement (OR = 4.89, $p < 0.001$), and haemodialysis catheter placement (OR = 5.46; $p < 0.001$).

In the subsequent multivariate logistic regression analysis, the following variables remained independently associated with CRKP infection: cardiovascular disease (OR = 3.33; 95% CI: 1.24–8.97; $p = 0.017$), carbapenem exposure (OR = 3.70; 95% CI: 1.69–8.10; $p = 0.001$), in-dwelling catheter use (OR = 3.51; 95% CI: 1.30–9.50; $p = 0.013$), and haemodialysis catheter placement (OR = 6.57; 95% CI: 2.17–19.91; $p = 0.001$).

These findings indicate that patients with cardiovascular disease had a 3.33-fold higher risk of CRKP infection compared to those without, those exposed to carbapenems had a 3.70-fold increased risk, patients with indwelling catheters had a 3.51-fold risk, and patients with haemodialysis catheters were 6.57 times as likely to acquire CRKP infection as those without such devices. A summary of these risk factors is presented in Table 4.

Table 4. Logistic regression analysis of related risk factors of CRKP

Variable	OR	P-value	OR (95%CI)	P-value
Age $\geq$ 65 years	1.97	0.03	1.57 (0.70-3.49)	.273
Intensive Care Unit	2.88	0.001	0.76(0.24-2.43)	.642
Cardiovascular diseases	7.78	<0.001	3.33 (1.24-8.97)	.017*
End-stage renal disease	3.34	<0.001	1.09 (0.47-2.54)	.836
carbapenem exposed	5.43	<0.001	3.70 (1.69-8.10)	.001*
Central venous catheter	1.82	0.05	0.86 (0.37-2.00)	.733
Arterial catheter	2.84	0.02	0.74 (0.21-2.57)	.634
Endotracheal tube	4.82	<0.001	1.56 (0.38-6.40)	.535
Respirator use	4.90	<0.001	2.02 (0.41-10.10)	.390
Catheter in-dwelling	4.89	<0.001	3.51 (1.30-9.50)	.013*
Nasogastric tube placement	2.99	0.001	0.86 (0.35-2.07)	.732
Haemodialysis catheter placement	5.46	<0.001	6.57 (2.17-19.91)	.001*

Wards are classified as general wards or intensive care centers; ages are classified as $\geq$ 65-years-old or <65-years-old; * p value <.001

DISCUSSION

The study found that hospitalized patients who underwent invasive treatments were at elevated risk for CRKP infection, particularly those over the age of 65, and those admitted to ICUs. Most CRKP cases were associated with infections of the bloodstream and urinary tract. These findings are consistent with a 2022 study by Blot et al., which reported that patients with in-dwelling central dialysis catheters had a significantly higher likelihood of acquiring CRKP infections, compared to those without such catheters [9]. Similarly, Vanegas et al. [10] highlighted that patients undergoing haemodialysis are at increased risk of colonization by multi-drug-resistant organisms. These individuals typically received haemodialysis 3 times per week in closed clinical environments, which may facilitate the cross-transmission of multi-drug-resistant pathogens. The rise in CRKP infections may also be attributed to the inappropriate use of broad-spectrum antibiotics, such as carbapenems, and the challenges of maintaining rigorous infection control protocols in high-pressure clinical settings. Inadequate implementation of essential measures, including hand hygiene and contact precautions, further contributes to the spread.

To curb CRKP transmission, healthcare institutions must enforce robust infection control strategies and promote the judicious use of antibiotics. A multi-disciplinary approach, integrating physicians, pharmacists, nurses, and infection control specialists, is essential for antimicrobial stewardship. Such collaborative efforts are critical for reducing antimicrobial resistance, enhancing patient safety, and improving overall healthcare quality.

The current study further confirmed that CRKP infection is significantly associated with the use of in-dwelling catheters, a form of invasive medical intervention that has been recognized as a risk factor. CRKP infection has been consistently identified in previous studies as independently associated with the presence of in-dwelling catheters [11–13]. Invasive procedures and medical devices often serve as entry points or reservoirs for pathogens, particularly among transplant recipients and other immunocompromised patient populations, thereby increasing the risk of HAIs [12]. In-dwelling urinary catheters, in particular, have been identified as an independent risk factor for CRKP infection because of the direct and prolonged contact between the catheter and the mucosal surface. Repeated invasive interventions and prolonged catheter placement can disrupt the mucosal barrier, compromise host defences, and ultimately facilitate colonization and infection by CRKP.

The current study also identified cardiovascular disease as an independent risk factor for CRKP infection. This finding is consistent with those of Chen et al. [14], who reported that age, male gender, and cardiovascular disease are significant independent risk factors for CRKP infection, especially in the context of cardiovascular disease. Patients with cardiovascular diseases are approximately 3 times more susceptible to CRKP infections than patients without cardiovascular diseases [14]. Furthermore, the current study and the findings of Wei et al. [15] suggest that the association between CRKP infection and cardiovascular disease risk is more pronounced in older patients, which is underscored by recent evidence that there is a clinical threat posed by CRKP in older patients with cardiovascular diseases. Given the emergence of CRKP as a multi-drug-resistant nosocomial

pathogen, which may affect hospitalized older patients, infection control measures should be strengthened to curb further dissemination in nosocomial settings in Taiwan.

In the current analysis, patients in the CRKP group exhibited significantly higher mortality than those in the non-CRKP control group. This result suggests that CRKP has greater invasiveness. Previous studies have demonstrated CRKP to be an independent risk factor for increased in-patient mortality [16]. Similarly, Xu et al. [17] reported that CRKP bloodstream infections are also associated with high mortality. Therefore, investigating and controlling the risk factors for CRKP infection is crucial for preventing the emergence and spread of CRKP.

Limitations of the study. First, due to the retrospective design of the study, it was not possible to determine the specific types of carbapenemases present in the CRKP isolates, as molecular analyses were not routinely performed at our institution. Second, the retrospective nature of the study also limited its ability to establish causal relationships between potential risk factors and CRKP infection. Additionally, there may have been unmeasured confounding variables that influenced the observed associations. Third, it was not possible to apply a standardized comorbidity index to quantify the severity of underlying conditions, which may have introduced selection bias. Fourth, data on adherence to infection control practices among healthcare workers were not available, despite this being a potentially significant factor in the transmission of CRKP.

Despite these limitations, the study provides valuable insights into the epidemiology and risk factors associated with healthcare-associated CRKP infections, and highlights areas for improved clinical management and infection prevention strategies. Future prospective studies are necessary to address these gaps and better elucidate the role of infection control compliance

CONCLUSIONS

The study investigated the risk factors associated with CRKP and HAIs. The findings identified haemodialysis catheter placement, prior carbapenem exposure, in-dwelling catheter use, and cardiovascular disease as significant risk factors for CRKP infection. These results underscore the importance of implementing enhanced infection control measures and robust antimicrobial stewardship programmes, particularly for patients with cardiovascular comorbidities and those undergoing invasive medical procedures. Future research should focus on prospective cohort studies incorporating molecular typing to validate these associations and elucidate the transmission dynamics.

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