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Factors Associated with Carbapenem-resistant *Klebsiella pneumoniae* Infections among Inpatients in a Tertiary Health Care Hospital

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Abstract Carbapenem-resistant *Klebsiella pneumaoniae* infections (CRKPIs) are major health problems of drug resistance worldwide. The present study aimed to determine factors associated with CRKPIs among inpatients in a tertiary healthcare hospital. A hospital-based case-control study was based on the medical records of the patients who were infected with *K. pneumoniae* after being admitted for more than 48 hours in the Nopparat Rajathanee Hospital (NRH) from January 1, 2020 to December 31, 2020. 145 patients with CRKPIs were assigned as cases while 290 patients with carbapenem-susceptible *K. pneumoniae* infections (CSKPIs) as controls. Descriptive statistics and multivariable logistic regression were used in data analysis. The average age of the study subjects was 69.3 years (SD = 15.6) among cases. The mean length of hospital stay among cases was 22.2 days (SD = 14.9). Multivariable logistic regression showed significant associations with CRKPIs, renal diseases (Adjusted OR = 2.1; 95%CI = 1.1-3.8), previous hospitalizations (Adjusted OR = 2.1; 95%CI = 1.2-3.8), central venous catheterization (CVC) > 7 days (Adjusted OR = 2.7; 95%CI = 1.1-6.8), and urinary catheter > 7 days (Adjusted OR = 2.7; 95%CI = 1.1-6.4). Therefore, it should be a guideline for surveillance of risk factors of CRKPIs among inpatients. Additionally, the results of the study can be used to monitor and assess the risk of CRKPIs to prevent the complications of patients.

Keywords Carbapenem-Resistant *Klebsiella pneumoniae* Infections, Inpatients, Tertiary Health Care Hospital

1. Introduction

The rise of antimicrobial resistance (AMR) is a major threat to public health worldwide, with serious health and financial consequences [1-4]. AMR increases the cost of healthcare, length of hospitalization, severe medical illness, and mortality in many countries. Presently, at least 700,000 people die due to drug-resistant diseases each year. A recent report predicts that by 2050, 10 million people die each year from causes of AMR infections. Asia will have the most deaths with 4.7 million people, followed by Africa, with 4.1 million people annually. As a result, the global gross domestic product (GDP) decreased by 2-3.5% and had a loss of up to 100 trillion USD from the global economy. If these problems are not resolved by 2050, people around the world will die from drug-resistant diseases due to a lack of effective antimicrobials [5]. One AMR is carbapenem-resistant Enterobacteriaceae infections (CREIs) that are very difficult to treat because commonly used antibiotics do not respond to treatment and become resistant to all available antibiotics, thus posing a public health threat [5-7]. Of CREIs, the most top three are CRKPIs, and mechanisms of CRKPIs have gotten increasingly complex and difficult to treatment [8]. These CRKPIs are global problems, with recent reports indicating that infections are widespread in the United States [9], China [10,11], and Mediterranean countries [12]. In 2014-2019, published data from a tertiary hospital in North China showed a significant increase in the proportion and mortality rate of CRKPIs, with resistance to meropenem increased from 16.7 to 41.8% [10]. In 2005-2018, data from the China Antimicrobial Surveillance Network (CHINET), CRKPIs were increased from 3.0 to 25% and 2.9 to 26.3 %, respectively [11]. In 2015-2017, in a retrospective epidemiological surveillance study within a medical center in southern China, the results indicated that CRKPIs incidence was 2.7 per 100,000 patient day [12]. In Mediterranean countries, such as Spain, there has been a slight increase in CRKPIs from 0.3% in 2011 to 2.3% in 2014 [13]. In Thailand, the trend of CRKPIs has rapidly increased from 6.3-13.5% in 2016-2020 [14]. NRH is a tertiary health care hospital with 569 beds under the Department of Medical Services, Ministry of Public Health. Based on a review of clinical microbiology laboratory data over the past 6 years (from 2015 to 2020), AMR among CREIs continued to increase with 8.9, 9.4, 11.4, 16.0, 17.4, and 18.8%, respectively. Of these CREIs, CRKPIs were the most common infections and increased slightly percentages of isolates as follows: 77, 76, 74.2, 75.8, 77.1, and 84, respectively [15,16]. Therefore, the management of CRKPIs is a challenging task for both physicians and infection control staff. Despite these obstacles, there are scant evidence-based data on the risk variables associated with higher CRKPIs. The goal of this study was to determine possible risk factors for CRKPIs among inpatients in the NRH. The results of the study are used to monitor and assess the risk of CRKPIs in order to improve the efficiency of treatment and prevention of outbreaks of CRKPIs in the future.

Definition

Carbapenem-resistant Klebsiella pneumoniae infections (CRKPIs) refer to infections of one or more carbapenem-resistant K. pneumoniae [17].

Carbapenem-susceptible Klebsiella pneumoniae infections (CSKPIs) refer to infections of K. pneumoniae that is susceptible to all carbapenem agents [18].

CRKPIs and CSKPIs were tested with the antimicrobial susceptibility of carbapenems from the microbiology laboratory of the NRH and they were diagnosed with the medical doctors.

2. Methods

2.1. Ethics Approval

This study offered to request an ethical review of human research from the human research ethics committee of the Faculty of Public Health Mahidol University (Committee's reference number: 43/2564 on 3rd March 2021) and the human research ethics committee of the NRH (Committee's reference number: 7/2564_EXP on 15th April 2022) and agreed with the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP). It requested permission to use the patient's information from the director of the NRH. The authors used the secondary data from the medical records of the NRH from January 1 to December 31, 2020. Participants' names were unidentified in questionnaires; confidentiality was conducted throughout the study by the anonymous technique and the results were analyzed as a whole group.

2.2. Study Design

A hospital-based matched case-control (1:2) was conducted at the NRH, Bangkok. The study subjects were patients aged ≥18 years who were admitted as inpatients from January 1, 2020 to December 31, 2020.

2.3. Sample Size Estimation

The sample size was calculated using a case-control formula of Schlesselman [19], with $Z_{\alpha/2}$=1.96 at α=0.05, Z_β =1.28 at β=0.10, OR=3 and p_0 =0.06 [20], c=2. The calculated sample size was at least 435. A sample size of 145 was used in the cases and 290 in the controls. Therefore, the total number of samples used in this study was 435.

2.4. Data Collection

Samples were selected from the medical records of inpatients of the NRH in 2020. Cases and controls were patients who were admitted as inpatients, aged ≥18 years, both female and male. Cases were diagnosed with CRKPIs while controls were diagnosed with CSKPIs according to the doctor's diagnosis criteria. The structured questionnaire comprised personal characteristics, environmental factors, therapeutic factors and CSKPI results of study subjects.

2.5. Data Analysis

The verified data were entered into the code and analyzed by using the statistical software package. Descriptive statistics were expressed using: frequency, percentage, mean, and standard deviation. Univariable analysis was used to determine between the independent variables and CRKPIs by the unconditional logistic regression for the crude odds ratio (Crude OR). A p-value < 0.05 was considered statistically significant. Adjusted odds ratio (adjusted OR) and 95% CI of OR of the multivariable logistic regression analysis were used to assess the magnitude of the relationship among factors related to CRKPIs, for adjusting the confounders. All statistical analyses were performed using two-sided tests and a p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the Participants

Of all study subjects, there were 145 cases of patients with CRKPIs and 290 controls of patients with CSKPIs. The majority were male (53.8%), 60-79 years old (46.2% in cases and 45.5% in controls), and unemployed (72.4%). The top three underlying diseases among cases included renal diseases (55.2%), diabetes mellitus (DM) (53.8%), and heart diseases (40%) while controls were neurological diseases (40.0%), DM (39.0%), and renal diseases (30.0%), respectively (Table 1).

A univariable analysis was shown in Table 2. It was found that patients who had the underlying diseases with diabetes mellitus, renal diseases and heart diseases were significantly associated with CRKPIs. An interesting finding was the association between previous hospitalization and CRKPIs, and patients who were previously hospitalized had a 2.1 times higher risk of developing CRKPIs. Patients with LOS > 14 days had a higher risk of developing CRKPIs. Patients of admission wards and received immunosuppressive therapy such as dexamethasone and hydrocortisone were significantly associated with CRKPIs. Additionally, there was a statistically significant relation between patients who utilized the medical invasive devices and CRKPIs, namely mechanical ventilator > 7 days, central venous catheter (CVC) > 7 days, urinary catheter > 7 days, nasogastric tube > 7 days, surgical drain > 7 days, and hemodialysis ($p<0.05$).

Table 3. A multivariable analysis was shown to assess the relationship among factors and CRKPIs. Some factors with a p-value < 0.05 were selected into the model with the enter method. Results of the final analysis showed when adjusted for possible confounders, patients who had renal diseases, previous hospitalization, CVC >7 days, and urinary catheter >7 days were at higher risk of CRKPIs ($p < 0.05$).

Table 1. Personal characteristics of patients among cases and controls

Characteristics	Total	Cases (n = 145)		Controls (n = 290)	
		Number	%	Number	%
Age group (years)					
< 40	18	6	4.1	12	4.1
40 - 59	91	31	21.4	60	20.7
60 - 79	199	67	46.2	132	45.5
≥ 80	127	41	28.3	86	29.7
Mean (SD)		69.3 (15.6)		69.3 (15.8)	
Min - Max		21 - 98		18 - 98	
Gender					
Female	201	67	46.2	134	46.2
Male	234	78	53.8	156	53.8
Race					
Thai	430	143	98.6	287	99.0
Foreigners	5	2	1.4	3	1.0
Occupation					
Unemployed	315	105	72.4	210	72.4
Employee	103	36	24.8	67	23.1
Trade	13	3	2.1	10	3.4
Others	4	1	0.7	3	1.1
Underlying diseases					
DM					
No	244	67	46.2	177	61.0
Yes	191	78	53.8	113	39.0
Renal diseases					
No	268	65	44.8	203	70.0
Yes	167	80	55.2	87	30.0
Neurological diseases					
No	274	100	69.0	174	60.0
Yes	161	45	31.0	116	40.0
Heart diseases					
No	297	87	60.0	210	72.4
Yes	138	58	40.0	80	27.6
Digestive diseases					
No	341	107	73.8	234	80.7
Yes	94	38	26.2	56	19.3
Pulmonary diseases					
No	371	117	80.7	254	87.6
Yes	64	28	19.3	36	12.4
Cancers					
No	387	132	91.0	255	87.9
Yes	48	13	9.0	35	12.1
Liver diseases					
No	398	135	93.1	263	90.7
Yes	37	10	6.9	27	9.3

Abbreviations: DM = Diabetes mellitus

Table 2. Univariable analysis among factors associated with CRKPIs

Variables	Cases (n = 145) Number (%)	Controls (n = 290) Number (%)	Crude OR	95% CI	p-value
Age group (years)					
< 40	6 (4.1)	12 (4.1)	1		
40 - 59	31 (21.4)	60 (20.7)	1.0	0.4-3.0	0.952
60 - 79	67 (46.2)	132 (45.5)	1.0	0.4-2.8	0.977
≥ 80	41 (28.3)	86 (29.7)	0.9	0.3-2.7	0.929
Gender					
Female	67 (46.2)	134 (46.2)	1		
Male	78 (53.8)	156 (53.8)	1.0	0.7-1.5	1.000
Underlying diseases					
DM					
No	67 (46.2)	177 (61.0)	1		
Yes	78 (53.8)	113 (39.0)	1.8	1.2-2.7	0.003*
Renal diseases					
No	65 (44.8)	203 (70.0)	1		
Yes	80 (55.2)	87 (30.0)	2.9	1.9-4.3	< 0.001*
Neurological diseases					
No	100 (69.0)	174 (60.0)	1		
Yes	45 (31.0)	116 (40.0)	0.7	0.4-1.0	0.069
Heart diseases					
No	87 (60.0)	210 (72.4)	1		
Yes	58 (40.0)	80 (27.6)	1.8	1.2-2.7	0.009*
Digestive diseases					
No	107 (73.8)	234 (80.7)	1		
Yes	38 (26.2)	56 (19.3)	1.5	0.9-2.4	0.101
Pulmonary diseases					
No	117 (80.7)	254 (87.6)	1		
Yes	28 (19.3)	36 (12.4)	1.7	0.9-2.9	0.057
Cancers					
No	132 (91.0)	255 (87.9)	1		
Yes	13 (9.0)	35 (12.1)	0.7	0.4-1.4	0.332
Liver diseases					
No	135 (93.1)	263 (90.7)	1		
Yes	10 (6.9)	27 (9.3)	0.7	0.3-1.5	0.397
Residence of nursing home					
No	143 (98.6)	282 (97.2)	1		
Yes	2 (1.4)	8 (2.8)	0.5	0.1-2.4	0.375
Previous hospitalization					
No	89 (61.4)	223 (76.9)	1		
Yes	56 (38.6)	67 (23.1)	2.1	1.4-3.2	0.001*

Table 2 continued

LOS prior to infection (days)					
1 – 14	53 (36.6)	238 (82.1)	1		
> 14	92 (63.4)	52 (17.9)	7.9	5.1-12.5	< 0.001*
Admission wards					
Non-ICU stay	72 (49.7)	179 (61.7)	1		
ICU stay	73 (50.3)	111 (38.3)	1.6	1.1-2.5	0.017*
Ventilation of wards					
Open air	101 (69.7)	193 (66.6)	1		
Closed air	44 (30.3)	97 (33.4)	0.9	0.6-1.3	0.515
Patient isolation rooms					
Isolation rooms	44 (30.3)	97 (33.4)	1		
Non-isolation rooms	101 (69.7)	193 (66.6)	1.2	0.8-1.8	0.515
Dexamethasone					
No	110 (75.9)	243 (83.8)	1		
Yes	35 (24.1)	47 (16.2)	1.7	1.0-2.7	0.047*
Hydrocortisone					
No	136 (93.8)	288 (99.3)	1		
Yes	9 (6.2)	2 (0.7)	9.5	2.0-44.7	0.004*
Mechanical ventilator (days)					
No	54 (37.2)	175 (60.3)	1		
1-7	22 (15.2)	81 (27.9)	0.9	0.5-1.5	0.656
> 7	69 (47.6)	34 (11.7)	6.6	3.9-10.9	< 0.001*
CVC (days)					
No	96 (66.2)	269 (92.8)	1		
1-7	6 (4.1)	9 (3.1)	1.9	0.7-5.4	0.247
> 7	43 (29.7)	12 (4.1)	10.0	5.1-19.8	< 0.001*
Urinary catheter (days)					
No	14 (9.7)	85 (29.3)	1		
1-7	29 (20.0)	133 (45.9)	1.3	0.7-2.7	0.428
> 7	102 (70.3)	72 (24.8)	8.6	4.5-16.3	< 0.001*
Nasogastric tube (days)					
No	23 (15.9)	92 (31.7)	1		
1-7	18 (12.4)	120 (41.4)	0.6	0.3-1.2	0.137
> 7	104 (71.7)	78 (26.9)	5.3	3.1-9.2	< 0.001*
Surgical drain (days)					
No	123 (84.8)	250 (86.2)	1		
1-7	6 (4.1)	27 (9.3)	0.5	0.2-1.1	0.087
> 7	16 (11.0)	13 (4.5)	2.5	1.2-5.4	< 0.001*
Hemodialysis					
No	121 (83.4)	272 (93.8)	1		
Yes	24 (16.6)	18 (6.2)	3.0	1.6-5.7	< 0.001*

* Statistical significance at p-value < 0.05

Abbreviations: CRKPIs = carbapenem-resistant *Klebsiella pneumoniae* infections, Crude OR = Crude odds ratio, 95% CI = 95% Confidence interval, DM = Diabetes mellitus, LOS = Length of stay, CVC = Central venous catheter

Table 3. Multivariable analysis among factors associated with CRKPIs

Variables	Crude OR	95% CI	Adjusted OR	95% CI	p-value
DM					
No	1		1		
Yes	1.8	1.2-2.7	1.6	0.9-2.8	0.110
Renal diseases					
No	1		1		
Yes	2.9	1.9-4.3	2.1	1.1-3.8	0.017*
Heart diseases					
No	1		1		
Yes	1.8	1.2-2.7	1.4	0.7-2.5	0.326
Previous hospitalization					
No	1		1		
Yes	2.1	1.4-3.2	2.1	1.2-3.8	0.012*
LOS prior to infection (days)					
1 - 14	1		1		
> 14	7.9	5.1-12.5	1.7	0.9-3.5	0.120
Admission wards					
Non-ICU stay	1		1		
ICU stay	1.6	1.1-2.5	1.1	0.6-2.1	0.832
Dexamethasone					
No	1		1		
Yes	1.7	1.0-2.7	1.1	0.6-2.3	0.727
Hydrocortisone					
No	1		1		
Yes	9.5	2.0-44.7	1.7	0.3-11.3	0.588
Mechanical ventilator (days)					
No	1		1		
1-7	0.9	0.5-1.5	0.8	0.3-1.8	0.588
> 7	6.6	3.9-10.9	1.3	0.5-3.5	0.550
CVC (days)					
No	1		1		
1-7	1.9	0.7-5.4	3.0	0.7-12.7	0.134
> 7	10.0	5.1-19.8	2.7	1.1-6.8	0.032*
Urinary catheter (days)					
No	1		1		
1-7	1.3	0.7-2.7	1.9	0.8-4.3	0.140
> 7	8.6	4.5-16.3	2.7	1.1-6.4	0.025*
Nasogastric tube (days)					
No	1		1		
1-7	0.6	0.3-1.2	0.4	0.2-1.0	0.061
> 7	5.3	3.1-9.2	1.1	0.5-2.8	0.773

Table 3 continued

Surgical drain (days)					
No	1		1		
1-7	0.5	0.2-1.1	1.1	0.3-3.7	0.944
> 7	2.5	1.2-5.4	1.5	0.6-4.3	0.411
Hemodialysis					
No	1		1		
Yes	3.0	1.6-5.7	1.4	0.5-3.7	0.493

* Statistical significance at p-value < 0.05

Abbreviations: CRKPIs = carbapenem-resistant *Klebsiella pneumoniae* infections, Crude OR = Crude odds ratio, Adjusted OR = Adjusted odds ratio, 95% CI = 95% Confidence interval, DM = Diabetes mellitus, ICU = Intensive care units, LOS = Length of stay, CVC = Central venous catheter

4. Discussion

Our findings demonstrated that most patients were the elderly (75%), and patients with the underlying diseases such as diabetes mellitus, renal diseases, and heart diseases were higher risk groups for CRKPIs, which is in agreement with similar studies [21, 22]. In a multivariable logistic regression analysis, there was also an association between renal diseases and CRKPIs that was similar to a previous study [23]. The underlying diseases, namely, neurological diseases, digestive diseases, pulmonary diseases, liver diseases, and cancers were not associated with CRKPIs, and most patients in our study might be elderly, so the elderly patients mostly had also chronic diseases among cases and controls. As a result, the elderly people were likely to be infected due to inefficient immune response of impaired functional immunity. This study also found that the previous hospitalization was an independent factor for CRKPIs, which corresponded with the previous studies [24,25]. The result might explain that patients with previous hospitalization had higher risk for infections because of prolonged exposure to invasive devices and antimicrobial use. LOS prior to infection, a univariable analysis indicated that patients with longer LOS were associated with CRKPIs, which has also been identified by other studies [26,27]. As mentioned, the susceptible older patients with the underlying diseases had higher chances to have complicated treatment which resulted in prolonged hospitalization. A recent study found a significantly longer hospitalization among patients with CRKPIs [28]. Among invasive procedures, > 7 days indicated that CVC and urinary catheter were associated with CRKPIs, which agreed with other studies [25,29,30]. This may be patients undergoing invasive procedures; > 7 days often were the patients with poorer condition and it should be needed for invasive procedures longer. Therefore, they were at higher risk for infections including CRKPIs.

Because the data collection was retrospective using secondary data and this study was conducted in a tertiary health care hospital. So, the research result could not be referred to other tertiary health care hospitals.

5. Conclusions

The results suggested that risk groups among inpatients with CRKPIs should consider the renal diseases, previous hospitalizations, CVC >7 days, and urinary catheter > 7 days. Therefore, continuous surveillance of risk groups should be monitored to reduce the complications of them.

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Declarations

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Authors' Contributions

W.T. and W.C. were responsible for the conceptualization, data curation, methodology, data validation, project administration, resource, software, supervision, writing review and editing. P.E. was responsible for conceptualization, data curation and methodology. S.M. was responsible for data analysis, software and methodology. Subsequent drafts of the manuscript were edited and finalized by all authors. The authors read and approved the final manuscript.

Conflicts of Interest

No conflict of interest was declared by the authors.

Data Availability

All data generated or analyzed during this study are included in this published article.

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