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Prevalence of risk factors for carbapenem-resistant *Klebsiella pneumoniae* in hospitalized patients. Systematic review

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Abstract

Introduction. The cases of infection for Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) have increased. The patients with infection for Carbapenem-Resistant Klebsiella pneumonia have a terrible forecast and a high mortality rate. **Objective**. We determine the prevalence of risk factors in patients hospitalized for CRKP. **Methods**. We perform a search bibliographic of the literature in Pub Med, MEDLINE, and SCOPUS, to December 13, 2021. This systematic review included observational studies on risk factors in patients hospitalized for CRKP. We evaluated the quality methodologic of articles on the base of the Newcastle Ottawa Scale (NOS) of nine stars. **Results**. we observed that the majority were male (62.90%), the average age was 61 years, and 883 patients with CRKP were counted from the different studies. The main risk factors for CRKP were previous hospitalizations (67.9%), previous use of carbapenems and ß-lactam/ß-lactamase inhibitor (49.59% and 45.49%, respectively), previous venous catheterization (44.99%) and previous stay in the intensive care unit (ICU) (42.9%). **Conclusions**. In this systematic review, we was the conclusion that the prevalence of risk factors of CRKP in patients hospitalized are previous hospitalizations, use last of antibiotics as carbapenems, ß-lactams/inhibitors, ß-lactamase, previous procedures as central venous catheterization and earlier stays in intensive care units (ICU). These findings can promote the prevention of CRKP infections and rational control over the use of antibiotics from the Ministry of Health towards the general population.

Key word: *risk factors, Carbapenem-Resistant Klebsiella pneumoniae (Source: MeSH-NBCI).*

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Introduction

Carbapenem-resistant Enterobacteriaceae (CRE), primarily *Klebsiella pneumoniae*, is a major healthcare-associated problem posing a significant public health threat (1). Therefore, the percentage of Carbapenem-Resistant *Klebsiella pneumoniae* (CRKPs) continues to increase in all parts of the globe (1,2). Carbapenemase from *Klebsiella pneumoniae* originated in the northern United States. In the United States, before 2000, the infection spread throughout the world (3). In recent years, the emergence of carbapenem-resistant Enterobacteriaceae (CRE) strains has not been increasingly reported (4). CRE strains present a particular challenge because they are resistant to ß-lactam agents, and there are minimal treatment options for CRE-induced diseases.

Furthermore, these bacterial strains show an influential association with a spread in healthcare facilities. Infections with these CREs were associated with high rates of morbidity and mortality. Some studies showed that deaths attributable to CRE infections ranged from 26% to 44% (4, 5); another study reported that the 14-day mortality of 19 patients with CRKP bacteremia was 47% (6). Patients infected with CRKP often suffer from chronic and acute illnesses associated with increased mortality. Therefore, it is vital to prevent CRKP infection, not only to avoid poor prognosis and even death but also to avoid widespread transmission of carbapenem resistance through modifiable genetic elements. (7,8).

Patients with CRKP infection are difficult to treat, as carbapenems are often considered antibiotics of last resort for severe *Klebsiella pneumoniae* infections. Carbapenema-ses present in *Klebsiella pneumoniae* may result in resistance to carbapenems, making almost all available treatment options ineffective (9). In addition, *Klebsiella pneumoniae* infection is more common in causing nosocomial infections, such as sepsis, pneumonia and urinary tract infection, surgical site infection, and catheter-related infection (10).

Some studies evaluated the risk factors for CRKP infection. However, their results were controversial (11,12), such as a study that reported that treatment with the fluoroquinolone family is a risk factor for CRKP infection (13). In contrast, another study found no association between fluoroquinolone and CRKP infection (12). Therefore, knowledge of the risk factors associated with the

development of CRKP infection is essential to identify high-risk patients in the prevention of acquiring CRKP (14).

Therefore, we performed a systematic review to determine the risk factors in patients hospitalized for CRKP.

Methods

This systemic review report was conducted according to the reference items for publishing protocols for systemic review and meta-analysis (PRISMA) (15).

Eligibility

This systematic review included (a) observational studies, (b) studies on risk factors in patients hospitalized by CRKP, (c) studies with available text, and (d) studies in English and Spanish were included. Excluded were: (a) letters to the editor, abstracts, and documents; (b) studies on risk factors in patients not hospitalized by CRKP; (c) duplicate sources; (d) studies without reliable data; and (e) study noises other than English and Spanish.

Search or search strategy

A literature search was conducted at Pub Med, MEDLINE, and SCOPUS until November 13, 2021. The author developed the search strategies according to the recommendations of the Cochrane Manual of Systematic Reviews. Controlled vocabulary search terms for MEDLINE (MeSH) were used, linked in terms of text for each of the concepts selected using Boolean operators: "RISK FACTORS", "CARBAPENEM-RESISTANT ENTEROBACTERIACEAE", "KLEBSIELLA PNEUMONIAE RESISTANT TO CARBAPENEMS", "RISK FACTORS AND CARBAPENEM-RESISTANT ENTEROBACTERIACEAE", "RISK FACTORS AND KLEBSIELLA PNEUMONIAE RESISTANT TO CARBAPENEMS". No date filters or restrictions of the format of the search document were used. Search strategies were carried out using the advanced search tool in the database before a final consensus of search strategies was approved. The Mendeley Desktop program was used to manage bibliographic references and to eliminate duplicate articles.

Selection of studies and extraction of data

The full texts of the articles were retrieved to verify eligibility and the inclusion and exclusion list. Microsoft Excel software was used for data extraction, storage, and analysis. The reviewer (HMZ) independently extracted the relevant data according to the following data: author, reference, country, year, study quality, study type, CRKP/CSKP sample size, prior hospitalization time, and results of risk factor variables.

Synthesis of results

A formal narrative synthesis of the collected data was performed, but a formal statistical synthesis was not performed. The syntheses focused on the qualitative analysis of the published studies' clinical manifestations mentioned in each country.

Assessment of Study Quality

The methodological quality of the articles was evaluated based on the nine-star of Newcastle-Ottawa Scale (NOS) (16), which included three aspects of the evaluation of the methodology: selection of cases (4 items, 4 points), comparability of a case, sand controls (1 item, 2 points), and determination of exposure to risk factors (3 items, 3 points). Scores of 0 to 4 points indicate the quality of the research, while scores of 5 to 9 points Suggs high-quality research.

Ethics committee approval was waived due to the open availability of data. All the studies included in this systematic review were approved by the ethics and research committee.

Methods

Selection and characteristics of studies

Five hundred eighty results were identified in the initial search. Three hundred ninety-eight duplicate results were eliminated. After filtering by titles and abstracts, were evaluated 57 articles in full text. Initially, 13 articles providing specific information related to the objectives of this study were recorded. In addition, a secondary search was made of these 13 studies included initially, from which one additional study was added, resulting in 14 studies. Finally, 14 observational studies were attached for further analysis, and 17 studies on comments for this review study.

Most of the items come from Colombia (1/14), Taiwan (1/14) and China (11/14), and Turkey (1/14). The total population of this study was 33 854 patients. The majority were male (62. 90%), the average age was 61 years, and 883 patients with CRKP were from different studies. (Table 1).

Results of risk factors for CRKP in hospitalized patients (Table 2-4)

Hu Y et al. (17) conducted a retrospective observational study, which included 30,862 isolated samples of *Klebsiella pneumoniae* in several hospitals in China for 11 years. In addition, they found that the hospital risk factor, level IIIA (OR [odd rate]: 1. 83; 95% CI: 1. 08-3. 11; p=0. 027), had a higher proportion of CRKP compared to all other hospital levels (OR: 1. 14; 95% CI: 0. 67-1. 94; p=0. 785). Also, CRKP was more prevalent among *Klebsiella pneumoniae* isolated from Intensive Care Units (ICU) (OR: 4. 40; 95% CI: 4. 24-4. 56; p<0. 001) and from inpatients compared to those from non-ICU wards and outpatients, respectively. No significant differences were observed between the age groups of patients aged 0-2 years and 3-9 years (OR: 1. 12; 95% CI: 0. 85-1. 49; p=0. 422), whereas, for other age groups, the OR increased along with age, with the highest proportion of resistant isolates observed among those ≥ 60 years (OR: 7. 02; 95% CI: 6. 04-8. 16; p<0. 001).

Table 1

Demographic characteristics and study selection

Author, #ref	Country	Age	Population (N)	Study of Quality	Type of study	Sample size	Previous Hospitalization of hospitalization
Hu Y y et al -17	China	2020	30 862 patients	Good	Retrospective	-	Hosp= 3 months ICU= 3 months
Hsu JY y et al -18	China	2021	108 patients H= 69 M=39 Average age= 57 years	Good	Prospective	36/72	Hosp= 14 days ICU= 30 days
Tian L y et al -19	China	2016	114 patients H= 74 M= 40 Average age= 56.37 years	Fair	Retrospective	33/81	Hosp= 30 days
Büyüktuna SA y et al. (20)	Turkey	2020	88 patients H= 35 M=53 Mean age= 74±15 years	Fair	Retrospective	32/56	Hosp= 28 days
Wang Z y et al -21	China	2018	96 patients H= 69 M= 27 Mean age= 65 years	Good	Retrospective	48/48	Hosp= 30 days ICU= 30 days
Chang H y et al -22	China	2020	285 patients H= 184 M= 101 Mean age= 62 years	Fair	Retrospective	46/239	Hosp= 30 days
Xiao T y et al. (23)	China	2020	371 patients H= 262 M= 109 Mean age= 61 years	Fair	Retrospective	104/267	ICU= 30 days
Liu KS y et al -24	Taiwan	2021	89 patients H= 53 M= 36 Mean age= 75.6 years	Fair	Retrospective	14/75	Hosp= 30 days ICU= 30 days
Li Y y et al -25	China	2020	492 patients H= 305 M= 187 Mean age= 59 years	Fair	Retrospective	164/328	Hosp= 30 days
Zhang Y y et al -26	China	2018	138 patients H= 80 M= 58 Mean age= 24.8 years	Fair	Retrospective	54/84	Hosp= 30 days
Zhang G y et al -27	China	2020	496 patients H= 281 M= 215 Mean age= 57 years	Fair	Retrospective	108/288	ICU= 30 days
Zhang H y et al -28	China	2021	138 patients H= 108 M= 30 Mean age= 80.5 years	Fair	Retrospective	97/41	Hosp ≥30 days
Yuan Y y et al -29	China	2020	239 patients H= 164 M= 75 Mean age= 55.5 years	Fair	Cases y controls	98/141	Hosp= 30 days ICU= 30 days
Cienfuegos-Gallet A y et al (30)	Colombia	2019	338 patients H= 198 M= 140 Mean age= 67 years	Fair	cohort and case-controls	49/289	Hosp ≤ 6 months ICU ≤ 6 months
Total			H=62,90% Age: 61 years old			883/2012	

N= population, ref= reference, M= male, F= female, CRKP= carbapenem-resistant Klebsiella pneumoniae, CSKP= carbapenem-sensitive Klebsiella pneumoniae, Hosp=

Table 2
Comorbidity outcomes in patients hospitalized for CRKP

Author, (# ref)	Existing comorbidity						
	HT	DM	Disease lung disease	cardiovascular disease	Neoplasia	liver disease	Disease of the biliary tract
Hu Y y et al -17	-	-	30	-	-	-	-
Hsu JY y et al -18	-	-	-	-	-	19,4%	-
Tian L y et al -19	-	9,1%	3,00%	12,1%	36,4%	15,2%	27,3%
Büyüktuna SA y et al. (20)	37,5%	28,1%	25%	37,5%	28,1%	-	-
Wang Z y et al -21	-	37,5%	12,5%	70,8%	27,1%	-	22,9%
Chang H y et al -22	-	-	6,5%	-	6,5%	-	43,5%
Xiao T y et al. (23)	38,9%	23,2%	38,9%	-	13,7%	-	22,1%
Liu KS y et al -24		59,6%	23,6%	64%	20,2%	16,9%	-
Li Y y et al -25	43,9%	20,7%	8,5%	22,6%	11,6%	-	-
Zhang Y y et al -26	-	-	-	-	43,3%	-	-
Zhang G y et al -27	37%	19,4%	28,7%	-	13,9%	-	-
Zhang H y et al -28	43,3%	29,9%	36,1%	59,8%	-	45,4%	-
Yuan Y y et al -29	30,6%	30,6%	50,2%	26,5%	11,2%	22,5%	36,7%
Cienfuegos-Gallet A y et al (30)	-	24,49%	14,29%	46,94%	20,41%	-	-
Total (%)	19,3%	23.55%	20,6%	28,35%	19,37%	9,18%	12,70%

Ref= reference, HT: hypertension, DM= diabetes mellitus, CRKP: carbapenem-resistant Klebsiella pneumoniae.

Hsu JY et al. (18) performed a prospective study where they included 108 patients (69 men and 39 women, mean age was 57 years) with bloodstream infection (BSI); in addition, they included the two groups: CRKP group (n=36 patients) and carbapenem-sensitive *Klebsiella pneumoniae* (CSKP) (n=72 patients). The patients had as predisposing factors to CRKP were: liver cirrhosis (19.4%; OR: 5.61; 95% CI: 1.26-24.98; p=0.024), patients who are ≥ 65 years old (OR: 1.01; 95% CI: 0.98-1.03; p=0.730), males were more predisposed to in-hospital CRKP (63.9%; OR: 1.00; 95% CI: 0.44-2.30; p=1.0), hospital stay before 14 days (OR: 1.23; 95% CI: 1.09-1.38; p<0.001), use of antibiotics such as carbapenem before 14 days (55.6%; OR: 6.07; 95% CI: 1.77-20.90; p<0.004) and previous infection or colonization 14 days (41.7%).

Tian L et al. (19) performed a retrospective study where they included 114 patients (74 males and 40 females, mean age was 56. 37 ± 16. 36 years) with BSI infected by CRKP and grouped into two groups (CRKP [n= 33 cases] and CSKP [n= 81 cases]). In addition, they found that the risk factors for CRKP were: infected patients in ICU (42.4%; OR: 5.82; 95% CI: 2.0-17.2; p=0.002); patients ≥ 50 years (p<0.051); patients with biliary tract disease (27.3%); patients with chronic liver disease (15.2%); patients with immunosuppression (30.3%); patients with skin and soft tissue infection (30.3%; OR: 26.63; 95% CI: 4.8-146.8; p<0.001); patients with intra-abdominal infection (36.4%), patients with pulmonary infection (15.2%); patients with catheter infection (15.2%) and exposure to antibiotic therapy in the last 30 days before BSI onset (90.9%; OR: 4.04; 95% CI: 1.0-16.5; p=0.052).

Büyüktuna SA et al. (20) carried out a retrospective study involving 88 patients (53 women and 35 men, mean age 74 ± 15 years) with the growth of *Klebsiella pneumoniae* in blood, urine, and tracheal aspirate collected 48 hours after treatment. ICU admission. They were considered agent related and treated with antibacterial therapy. They were divided into CRKP (n=32 patients) and CSKP (n=56 patients).

Table 3

Hospitalization and invasive procedure outcomes

Author, (# ref)	Previous hospitalization (≥14 days)		Prior invasive procedures				
	Hospitalization	ICU	Urinary catheter	CVC	MV	Gastric tube	surgery
Hu Y y et al -17	90%	90%	-	-	-	-	-
Hsu JY y et al -18	75%	-	-	41,7%	-	-	-
Tian L y et al -19	100%	42,4%	-	-	-	-	63,3%
Büyüktuna SA y et al. (20)	90%	-	100%	96,9%	93,8%	-	-
Wang Z y et al -21	68,8%	52,1%	68,8%	27,1%	54,2%	70,8%	20,8%
Chang H y et al -22	47,8%	56,5%	-	-	26,1%	-	21,7%
Xiao T y et al. (23)	67,3%	67,3%	81,7%	76,9%	76.00%	81,7%	39,9%
Liu KS y et al -24	73.00%	33,7%	-	-	-	-	-
Li Y y et al -25	73,8%	70,7%	-	86,6%	57,3%	71,3%	53.00%
Zhang Y y et al -26	79,6%	9,3%	-	68,5%	18,5%	-	14,8%
Zhang G y et al -27	-	78,7%	-	79,6%	78,7%	-	29,6%
Zhang H y et al -28	39,2%	-	74,2%	50,5%	70,1%	54,6%	-
Yuan Y y et al -29	79,6%	83,7%	-	59,2%	74,5%	71,4%	81,6%
Cienfuegos-Gallet A y et al (30)	67,35%	16,33%	42,86%	42,86%	22,45%	-	46,94%
Total (%)	67,9%	42,90%	26,25%	44,99%	40,83%	24,98%	26,54%

Ref= referral, ICU= intensive care unit, CVC= central venous catheter, MV= mechanical ventilation.

In addition, they observed that the risk factors in patients with CRKP were: hypertension (37.5%), cerebrovascular disease (37.5%), diabetes mellitus (28.1%), neoplasia (28.1%), disease chronic obstructive pulmonary disease (25%), urinary tract infection (10%), a central venous catheter (96.9%), mechanical ventilation (93.8%). They also observed that antibiotics were used in the last 03 months, ß-lactam/ß-lactamase inhibitors (68.8%), carbapenems (53.1%), glycopeptides (37.5%), cephalosporins (28.1%), macrolides (25%), quinolones (15.6%) and aminoglycosides (15.6%).

Wang Z et al. (21) conducted a retrospective study, which included 96 patients (69 men and 27 women, mean age 65 years) with positive culture for *Klebsiella pneumoniae*, divided into two groups: patients infected with CRKP (n =48 cases) and patients infected with CSKP (n=48 cases). The study observed that the risk factors for patients with CRKP were: patients with cardiovascular disease (70.8%), kidney disease (43.8%), and neurological disease (45.8%). They also found that the results of risk factors for CRKP were present in hospitalized patients in the last 30 days (68.8%), ICU patients (52.1%; OR: 15.486; 95% CI: 3.175-75.541; p=0.001), previous surgery (20.8%) and patients with previous use of antibiotics in the last semester (93.8%). In addition, some risk factors were the combination of ß-lactams and ß-lactamase inhibitors (60.4%; OR: 4.765; 95% CI: 1.508-15.055; p=0.008), exposure to carbapenems (33.3%), exposure to cephalosporins (31.3%; OR: 8.033; 95% CI: 1.623-39.763; p=0.011) and exposure to fluoroquinolones (29.2%; OR: 6,090; 95% CI: 1,343 -27.613, p=0.019). Invasive procedures were important risk factors for CRKP: gastric tube indwelling (70.8%), urethral tube indwelling (68.8%; OR: 6.164; 95% CI: 1.847-20.578; p=0.003)

Table 4
Results on previous antibiotic use and site of infection

Author, (# ref)	Prior use of antibiotics						Site of infection		
	CARBP	ß-lactamic /Inh ß-lactam	CEF	ANTF	AMIN	FLUOR	PTB	Inf Abd	Inf Pm
Hu Y y et al -17	-	-	-	-	-	-	-	-	-
Hsu JY y et al -18	55,6%	100%	97,2%	-	-	86,1%	-	-	-
Tian L y et al -19	97,2%	90,9%	-	-	-	-	30,3%	36,4%	15,2%
Büyüktuna SA y et al. (20)	53,1%	68,8%	28,1%	-	-	15,6%	-	-	-
Wang Z y et al -21	33,3%	60,4%	31,3%	29,2%	-	29,2%	-	-	-
Chang H y et al -22	80,4%	43,5%	21,7%	52,2%	-	36,9%	-	-	-
Xiao T y et al. (23)	52,9%	55,8%	15,4%	-	28,2%	18,3%	-	19,2%	52,6%
Liu KS y et al -24	41,6%	-	-	-		-	-	-	-
Li Y y et al -25	58,5%	62,8%	18,3%	-	23,2%	48,8%	-	-	-
Zhang Y y et al -26	40,7%	38,9%	75,9%	51,9%	9,3%	3,7%	-	-	-
Zhang G y et al -27	20,4%	-	-	-	19,4%	-	-	-	-
Zhang H y et al -28	39,2%	28,9%	-	30,9%	5,2%	25,8%	-	-	96,9%
Yuan Y y et al -29	80,6%	52.00%	30,6%	21,4%	12,2%	15,3%	-	-	64,3%
Cienfuegos-Gallet A y et al (30)	40,81%	34,69%	-	-	12,24%	28,57%	4,08%	12,24%	6,12%
Total (%)	49,59%	45,49%	22,75%	13,26%	7,83%	22,02%	2,45%	4,85%	16,79%

CARBP= carbapenems, CEF= cephalosporins, ANTF= antifungals, FLUOR= fluoroquinolones, PTB= skin and soft tissues, Inf Abd= abdominal infection, Inf Pm= pulmonary infection.

and mechanical ventilation (54.2%).

Chang H et al. (22) conducted a retrospective cohort study where they examined 285 patients (184 males and 101 females, mean age was 62 years) hospitalized with BSI. They were divided into CSKP (n=239) and CRKP (n=46). In this study, they observed that the risk factors in CRKP-infected patients were as follows: patients aged 55 years (OR: 0.972; 95% CI: 0.947-0. 998; p=0.04), pancreatic and hepatobiliary disease (43.5%), malignant tumors (23.9%), chronic lung disease (6.5%; OR: 5.020; 95% CI: 1.275-19.768; p=0.02), hematological malignancy (6.5%; OR: 8.539; 95% CI: 2.162-33.721; p=0.002), history of hospitalization one month prior to BSI onset (47.8%), carbapenems treatment (80.4%), glycopeptide treatment (63%), ß-lactam/lactamase treatment (43.5%), quinolone treatment (36.9%), ICU (56.5%; OR: 5.506; 95% CI: 2.258-13.424; p<0.001) and tracheostomy (26.1%).

Xiao T et al. (23) conducted a retrospective study, which included 371 patients (262 males and 109 females, mean age 61 years) not transplanted with BSI for *Klebsiella pneumonia*. They were divided into 267 patients with CSKP and 104 patients with CRKP. They reported that the risk factors in patients infected with BSI by CRKP were: pulmonary infection (52. 6%), arterial hypertension (HTA) (38. 9%), pulmonary disease (38. 9%), diabetes mellitus (23. 2%), hepatobiliary disease (22. 1%), malignant neoplasia (13. 7%), catheter-related infection (3. 2%). Prior ICU stays before 30 days of onset of BSI (67. 3%) and prior hospitalization before the onset of BSI (67. 3%), urinary catheterization before 30 days of onset of BSI (66. 3%), gastric catheterization before 30 days of onset of BSI (85. 6%), central venous catheterization

before 30 days of onset of BSI (76. 9%), mechanical ventilation within 30 days of onset of BSI (76%), corticosteroid use within 30 days of onset of BSI (29. 8%), ß-lactam/ß-lactamase inhibitor combination for 30 before BSI (55. 8%), carbapenem use within 30 before to BSI (52. 9%), tigecycline within 30 days before BSI (28. 2%) and quinolone use within 30 days before BSI (18. 3%).

Liu KS et al. (24) conducted a retrospective study, which included 89 patients (53 males and 36 females, mean age was 75. 6 years) with BSI due to CRKP. They were divided into CRKP (n=14 patients) and CSKP (n=75 patients). The primary outcome was to evaluate risk factors for mortality at 30 days. In the study, they observed that the risk factors in patients infected with CRKP were: cardiovascular disease (64. 0%), diabetes mellitus (59. 6%), chronic lung disease (23. 6%), malignant neoplasia (20. 2%), chronic liver disease (16. 9%), prior hospitalization within 30 days of onset of BSI (73. 0%) and admission to ICU within 30 days of onset of BSI (33. 7%).

Li Y et al. (25) conducted a retrospective case-control study, which included 492 patients (305 males and 187 females, mean age were 59 years) with BSI due to *Klebsiella pneumonia*. They were grouped into CRKP (n=164) and CSKP (n=328). They observed that the risk factors in patients with CRKP were: prior hospitalization before three months (73. 8%), ICU admission (70. 7%), ETS (43. 9%), diabetes mellitus (20. 7%), a central venous catheter (86. 6%a), a urinary catheter (76. A 8%)a nasogastric catheter (71. 3%), tracheal cannula (57. 3%), previous surgery (53. 0%), ß-lactam/ß-lactamase inhibitor (62. 8%), carbapenems (58. 5%), quinolones (48. 8%), tigecycline (23. 2%) and systemic steroid use (28%).

Zhang Y et al. (26) conducted a retrospective case-control study where 138 patients (80 males and 58 females, mean age were 24.8 years) with BSI due to *Klebsiella pneumoniae* were included. In addition, they were grouped into two groups: CRKP (n= 54 patients) and CSKP (n= 84 patients). They observed that the risk factors in CRKP patients in this study were as follows: hematologic malignancy (43.3%), previous hospitalization (79.6%), previous ICU admission (9.3%), previous intravascular catheter (68.5%), previous immunosuppressive therapy (61.1%), previous neutropenia (55.6%), previous surgery (14.8%) and previous antibiotic therapy (90.7%) such as cephalosporins (75.9%) and glycopeptides (55.6%).

Zhang G et al. (27) performed a retrospective cohort study that included 496 patients (281 males and 215 females, mean age were 57 years) with BSI due to *Klebsiella pneumoniae*. They grouped the population into CRKP (n= 108 patients) and CSKP (N= 288 patients). Risk factors for patients with CRKP were: respiratory failure (50.9%), AHT (37.0%), renal failure (28.7%), diabetes mellitus (19.4%), previous ICU admission (78.7%), previous central venous catheter (79.6%), previous surgery (29.6%), previous carbapenem therapy (20.4%), tigecycline (19.4%) and carbapenem with tigecycline (48.2%).

Zhang H et al. (28) conducted a retrospective study including 138 patients (108 males and 30 females, mean age 80.5 years) with BSI due to *Klebsiella pneumoniae*. They grouped the population into CRKP (n= 97 patients) and CSKP (n= 41 patients). In addition, they observed that the risk factors in patients with CRKP were: cardiovascular disease (59.8%), hypoalbuminemia (55.7%), liver disease (45.4%), AHT (43.3%), renal disease (41.2%), diabetes mellitus (29.9%), previous hospitalization 30 days (18.6%), previous hospitalization within 90 days (39.2%), previous antibiotic use within 30 days: carbapenem (39.2%), antifungal agents (30.9%), ß-lactam/ß-lactamase inhibitor (28.9%), quinolones (25.8%), glucocorticoids (17.5) and macrolides (16.5%). The previous invasive procedures in 7 days were: mechanical ventilation (70.1%), an indwelling gastric catheter (54. 6%), and a central venous catheter (50.5%).

Yuan Y et al. (29) conducted a case-control study involving 239 patients (164 males and 75 females, mean age 55.5 years) with BSI due to *Klebsiella pneumoniae*. The population was grouped into CRKP (n= 98 patients) and CSKP (n= 141 patients). In addition, in a univariate analysis, the risk factors for CRKP were the following: previous hospitalization (79.6%), hospitalization for an ICU (83.7%), infectious disease (64.3%), respiratory disease (52.0%), digestive disease (36.7%), diabetes and HT (30.6%), neurological disease (28.6%), cardiovascular disease (26.5%). Invasive processes were: surgery within the last 3 months (81.6%), catheter (74.5%), tracheal intubation (74.5%), history of repeated transfusions (74.5%), central venous catheterization (59.2%). Finally, previous antibiotic exposures were observed, such as: carbapenem (80.6%), ß-lactam/ß-lactamase inhibitor (52.0%), cephalosporins (30.6%), antifungals (21.4%) and quinolones (15.3%).

Cienfuegos-Gallet A et al. (30) conducted a cohort and case-control study where they included 338 patients (198 males and 140 females, mean age were 67 years) with BSI due to *Klebsiella pneumoniae*. They were grouped into CRKP (n= 49 patients) and CSKP (n= 289 patients). In addition, the risk factors in patients infected by CRKP were: cardiovascular disease (46.94%), diabetes mellitus (24.49%), neoplasia (20.41%), chronic obstructive pulmonary disease (14.29%), hospitalization prior to 6 months of BSI onset (67.35%) and prior ICU admission before six months of BSI onset (16.33%). Invasive procedures before BSI by CRKP were: a urinary catheter (42.86%), a central venous catheter (42.86%), and mechanical ventilation (22.45%). Finally, they observed previous antibiotic uses in patients with CRKP: carbapenem (40.81%), ß-lactam/ß-lactamase inhibitor (34.69%), quinolones (28.57%,) and aminoglycosides (12.24%).

Discussion

CRKP is one of the most severe potential fatal nosocomial pathogens worldwide. CRKP infections are prevalent in most countries where the studies included in our review were conducted (China, Turkey, Taiwan, and Colombia). In the study by Chang H et al. (22), they observed that resistance to carbapenems increased significantly in

recent years, and the absolute number of *Klebsiella pneumoniae* late from hospitals almost doubled between the periods of 2008 (n= 24 734) and 2018 (n= 42 522). The European countries most severely affected by carbapenem resistance are Greece and Italy in 2019, where 68.7% and 32.7% of *Klebsiella pneumoniae* infections showed carbapenem resistance (31). Identifying CRKP risk factors is the start of finding-risk patients and settings autoroute limited resources efficiently toward preventing and treating CRKP infections.

Many studies have investigated the risk factors for CRKP infection and have reached divergent or contradictory conclusions. Wei-min Z et al. (1) and Tzouvelekis L et al. (3) have reported that exposition to carbapenems increases the risk of CRKP infection, but other studies did not find the same results (4,5). These discrepancies could reflect differences in population sizes and lack of statistical performance, which led us to perform a systematic review to assess risk factors in the most reliable and thorough study. We found the prevalence of the male gender over females (62.9% vs. 37.1%, respectively) in CRKP infections in ICUs and hospitalizations. In comparison, studies by Hsu JY et al. (18) and Tian L et al. (19) showed that the frequency of hospitalized males was higher than females (63.9% and 64.9%) from both indies. On the contrary, some studies observance of women in hospital wards and ICU (20).

Age is essential data in patients admitted to hospitalization and ICU. In our review, the mean age of all patients in the various studies was 61 years. Collaborating with the studies conducted by Xiao T et al. (23) and Chang H et al. (22), they found that patients admitted to hospitalization had a mean age of 61 years and 62 years, respectively. In addition, in other studies of this review, the age of the patients comprised a mean age of 50 to 70 years (18-20). On the contrary, in the study by Zhan et al. (26), the mean age of patients was 24.8 years, comprising adolescents and adults
.

Our study's previous hospitalization duration was approximately 30 days in the hospital wards and ICU. Similarly, in the studies of Liu KS et al. (24) and Yuan Y et al. (29), the last time of hospital stay and ICU were approximately 30 days. However, the previous hospitalization time of patients in some studies was 6 months (17,30). In addition, the last time patients in hospital wards and ICU were different from admission.

Regarding the pre-existing diseases of hospitalized patients and ICU, in our review study, cardiovascular diseases were the main ones, together with diabetes mellitus and pulmonary disease (28.61%, 23.55%, and 20.61%, respectively). Likewise, studies conducted by Liu KS et al. (24), Büyüktuna SA et al. (20), and Wang Z et al. (21) showed a high prevalence of patients with cardiovascular disease in hospitalization and ICU (64%; 37.5% and 70.80%, respectively), this was followed by studies that observed diabetes mellitus as a significant pre-existing disease (21,23,24,30), after cardiovascular diseases and pulmonary diseases were important comorbidity in hospitalized and ICU patients (24,27). In contrast, liver and biliary tract diseases were less prevalent in our study (12.70% and 9.18%, respectively). Similarly, some studies showed the prevalence of liver and biliary tract diseases (21,29).

In this review, it was observed that patients with the previous hospitalization $\geq$ 14 days were 67.9%, and patients with a previous stay in the ICU were (42.9%) of all the studies; similarly, the studies by Tian L et al. (19) and Hu Y et al. (17), where patients with ith previous hospitalization were 100% and 90%, respectively. Studies of patients with previous ICU stays show a statistically significant rate of previous hospitalization rates of CRKP-infected patients (23,29). Airborne and contact transmission of resistant bacteria in the inpatient and ICU environments probably led to nosocomial infection in most patients admitted to inpatient and ICU settings for at least 14 days, especially for patients in ICUs with prolonged stays, who may undergo invasive procedures and be treated with broad-spectrum antibiotics.

Undergoing invasive procedures increases the risk of carbapenem-resistant Enterobacteriaceae infection. The results of previous invasive procedures in our study were mainly the central venous catheter procedure (44.99%), followed by mechanical ventilation and tracheotomy (40.83%), followed by surgery (26.54%), a urinary catheter (26.25,%) and gastric catheter (24.98%). This also contrasts with the studies reviewed in this work (18-23). Central venous catheters have become essential in current medical practice. Their use is routine in different ICUs and emergency rooms. It is increasingly frequent in hospital wards, leading to increased incidence and severity of mechanical and infectious complications such as CRKP (11).

The use of any antibiotic in the last month and exposure to ß-lactam/ ß-lactamase inhibitor combinations, cephalosporins, aminoglycosides, and fluoroquinolones instead of carbapenems were associated with the increase of CRKP infections in recent years (13). In our review, patients who previously used any antibiotic or combination were mainly carbapenems (49.59%), followed by ß-lactam/ß-lactamase inhibitors (45.49%), cephalosporins (22.75%,) and fluoroquinolones (22.02%). Our findings are consistent with those of other studies, which have reported a strong association between exposure to carbapenems sic agents and CRKP infection (19,24,29). In addition, using carbapenems may cause selective pressure on resistant microorganisms, thereby increasing the risk of infection (29). Furthermore, fluoroquinolones may generate resistance not only to fluoroquinolones but also to carbapenems as quinolones generate positive regulation of the multidrug efflux pump MexEF-OprN and negative regulation of the OprD porin, which is involved in carbapenem resistance (1).

In CRKP infection sites, our study had a prevalence of poor pulmonary infections (16.79%), determined by pulmonary pneumonia, followed by intra-abdominal infection (4.85%) and skin and tissue infection (2.45%). This finding allows us to deduce that bacteria can move to various organs or tissues, not only the urinary tract when conditions favor them (19,29,30).

The limitations of our study are as follows. First, we

only included published studies from three databases. Therefore, relevant articles published in other databases and unpublished studies may have been missed. Second, we excluded some studies due to unclear infection diagnosis criteria, which led to small data collection at inclusion and limited the statistical power to detect independent outcomes. Third, significant heterogeneity of some risk factors was detected because we had strict reference inclusion criteria (only observational studies were included).

Conclusion

In this systematic review, we conclude that the prevalence of risk factors for CRKP in hospitalized patients are previous hospitalizations, previous antibiotic use such as carbapenems and ß-lactam/ß-lactamase inhibitors, and previous procedures such as central venous catheterization, and the previous ICU stays. These findings can drive the prevention of CRKP infections and rational control over the use of antibiotics from the Ministry of Health to the general population.

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Conflict of interest

The author declares no conflicts of interest with institutions or other authors.

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