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Systematic review and meta-analysis on the carbapenem-resistant hypervirulent *Klebsiella pneumoniae* isolates

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Abstract

Background The global dissemination of carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (CR-hvKp) poses a critical threat to public health. However, comprehensive data on the prevalence and resistance rates of CR-hvKp are limited. This systematic review and meta-analysis aim to estimate the pooled prevalence of carbapenem resistance among hvKp strains and assess the distribution of carbapenemase genes.

Materials and methods A systematic search of ISI Web of Science, PubMed, and Google Scholar was conducted to identify studies reporting carbapenem resistance rates in hvKp strains. The pooled prevalence of carbapenem resistance and carbapenemase genes was calculated using event rates with 95% confidence intervals.

Results A total of 36 studies encompassing 1,098 hvKp strains were included. The pooled resistance rates were 49% for imipenem, 53.2% for meropenem, and 38.2% for ertapenem. Carbapenemase gene prevalence was 19.1% for bla_{VIM}, 22.0% for bla_{NDM}, 43.4% for bla_{OXA-48}, and 58.8% for bla_{KPC}.

Conclusion The high prevalence of carbapenem resistance and the widespread distribution of carbapenemase genes among hvKp strains underscore their significant threat to global health. These findings highlight the urgent need for enhanced surveillance, rapid diagnostic tools, and stringent infection control measures to mitigate the spread of CR-hvKp. Future research should focus on understanding resistance mechanisms and developing targeted therapeutic strategies to address this critical challenge.

Keywords *K. pneumoniae*, Carbapenem, Hypervirulent *K. pneumoniae*, Antibiotic resistance

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Introduction

Klebsiella pneumoniae is one the most important omnipresent opportunistic bacteria that belongs to *Enterobacterales* [1]. This bacterium commonly colonized in the human colon can cause multiple infections including blood-stream infections (BSI), surgical-site infections, urinary tract infections (UTIs), ventilator-associated pneumonia, abscesses, and wound infections [2, 3]. The literature identifies two phenotypes of *Klebsiella pneumoniae*: classical *K. pneumoniae* (cKp) and *hypervirulent K. pneumoniae* (hvKp) [4]. cKp strains primarily cause infections in immunocompromised individuals, while hvKp strains can cause severe, invasive infections, including multiple-site infections, even in healthy individuals [5, 6]. HvKp strains possess additional virulence factors such as the hypermucoviscosity phenotype (e.g., *rmpA* and *rmpA2*) and siderophores, contributing to their ability to cause severe infections in healthy hosts, whereas cKp strains typically harbor antimicrobial resistance (AMR) genes and affect those with weakened immunity [7, 8]. HvKp strains can acquire virulence plasmids, leading to complicated infections in both immune-deficient and healthy individuals [9]. As a result, hvKp is associated with higher mortality rates compared to cKp [10, 11]. HvKp is linked to life-threatening community-acquired infections, such as liver abscesses, endophthalmitis, meningitis, and necrotizing fasciitis, while cKp generally causes hospital-acquired infections, including pneumonia, bloodstream infections, and urinary tract infections [12]. HvKp is more common in Asian countries but has been increasingly reported worldwide, whereas cKp is a leading cause of nosocomial infections globally [13]. The emergence of hybrid strains (CR-hvKp), which combine hvKp virulence traits and cKp resistance traits, poses significant concerns, as these strains exhibit enhanced fitness, multidrug resistance, and increased ability to cause severe disease, complicating treatment and infection control efforts [14]. Furthermore, multidrug-resistant hvKp strains are associated with poor clinical outcomes, including higher mortality rates [15].

Carbapenems are one of the important classes of antibiotics that first choice therapy for infections caused by multiple drug-resistant pathogens [16]. Yigit et al. (1996) reported the first case of carbapenem-resistant *K. pneumoniae* infection from Carolina [17]. Nowadays, there is a continuous increase in the trends of carbapenem-resistant gram-negative bacilli in the world [18]. The World Health Organization (WHO) declared *K. pneumoniae* as the pathogen of critical threat in the global priority list in 2017 [19]. Currently, carbapenem-resistant pathogens have gained international attention due to their challenges in human health situations [20]. Some limited antimicrobial agents remain effective against carbapenem-resistant infections, antibiotic options for carbapenem-resistant infections are less effective and more toxic for humans [21]. Furthermore, there are several evidence regarding the increase in poor clinical outcomes e.g., the mortality rate in carbapenem-resistant pathogens than susceptible pathogens [22].

There are two main mechanisms for resistance to carbapenem including (1) acquisition of carbapenemase e.g., KPC-type enzymes, metallo-β-lactamases (VIM, IMP, NDM), as well as OXA-48 type enzymes, (2) alternations of porin expression [23]. Unfortunately, carbapenemase-related genes are identified in bacterial strains that already have resistance to other multiple drugs [24, 25]. The emergence and global dissemination of carbapenem-resistant hvKp strains can cause a major challenge to the world. There are several reports regarding the presence of carbapenem-resistant hypervirulent *K. pneumoniae* infections [26–28]. The presence of carbapenem-resistant hvKp strains leads to fatal clinical outcomes, particularly in intensive care units. There is a need for global surveillance efforts to track antimicrobial resistance; However, a significant gap exists in the accurate reporting and monitoring of carbapenem resistance in hypervirulent *Klebsiella pneumoniae* (hvKp) strains, which are underrepresented in various regions, thereby hindering effective containment and treatment strategies. In this relation, there are no comprehensive documents to underscore the prevalence of carbapenem-resistant hvKp infections. Herein, this systematic review and meta-analysis examined the pooled prevalence of carbapenem-resistant hvKp burden throughout the world.

Materials and methods

Search strategy

A computer-assisted search was performed in electronic databases e.g., ISI Web of Science, PubMed, and Google Scholar. All potential relevant studies that examine the prevalence of carbapenem-resistant hvKp strains in patients hospitalized in intensive care units were collected. The medical terms including "*Klebsiella pneumoniae*", "carbapenem-resistant *Klebsiella pneumoniae*", "Carbapenem", "hypervirulent *K. pneumoniae*", "antibiotic resistance", "intensive care unit", as well as "ICU" were chosen as relevant keywords to identify potential articles from inception to November 2024. Furthermore, the bibliography of relevant studies was manually checked by the authors to avoid losing any possible articles. This process was performed by two independent authors.

Study selection

To identify eligible studies, we included original research articles such as cross-sectional, case-control, and cohort studies that reported on the prevalence of carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (hvKp) strains. Studies on clinical samples and those that

assessed antimicrobial drug susceptibility testing using Clinical Laboratory Standard Institute (CLSI) guidelines were also included. Additionally, only articles published in the English language were considered. Whereas, exclusion criteria consisted of case reports, letters, editorials, congress abstracts, studies based on non-clinical specimens, articles with repetitive samples, studies published in languages other than English, duplicate studies, and studies with unclear or incomplete methodologies. The selection process was carried out by two independent authors, and any discrepancies were resolved through consultation with a third author to ensure consistency and accuracy in the study inclusion.

Data extraction

After applying inclusion and exclusion criteria, the required information such as first author, publication year, country, the number of hvKp strains, number of carbapenem-resistance genes i.e., bla_{VIM}, bla_{KPC}, bla_{NDM}, bla_{OXA-48}, mortality rates, resistance rate to Carbapenems such as imipenem, meropenem, ertapenem, resistance rate to colistin, ESBL-positive rate was extracted and summarized in Table 1. This section was also performed by two independent authors and inconsistency was decided through discussion.

Statistical analysis

We pooled the data using Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ). The pooled prevalence of carbapenem-resistance rates among hvKp strains was expressed using event rate with corresponding 95% confidence intervals. We used the Cochrane *Q*-test (p-value < 0.05) and *I*-squared (I^2) index to estimate the heterogeneity among eligible studies. The random-effects model was used in the presence of considerable heterogeneity. Publication bias was also assessed using Egger's p-value and asymmetry of the funnel plot.

Results

Characteristics of included studies

A total of 1101 records were identified through searching databases, duplicates were omitted. Subsequently, the title and abstracts of the remaining articles were evaluated. 153 articles were selected for detailed full-text evaluation. After applying the selection criteria, 36 eligible studies were included in a systematic review and quantitative synthesis (Fig. 1).

The main reason for rejection was (1) studies that were not conducted on *K. pneumoniae*, (2) studies that did not evaluate hypervirulent *K. pneumoniae*, (3) studies that did not evaluate carbapenem resistance in clinical isolates of hvKP strain, (4) studies that did not report carbapenem-resistance genes, (5) studies on non-human subjects, 5) review articles, (6) studies that did not have full-text available, and (7) studies with unclear methods and results. There are 36 eligible studies to underscore the carbapenem-resistance rate among hvKp strains [29–64]. The included studies were from China ($n = 21$), Iran ($n = 6$), Egypt ($n = 2$), India ($n = 5$), Russia ($n = 1$), and Sudan ($n = 1$) between 2014 and 2023. In the current study, the data of 5,667 *K. pneumoniae* strains were included. Of these, there are 1,098 hypervirulent *K. pneumoniae* strains which were assessed to pooled carbapenem-resistance rates.

The prevalence of hvKp infections among total *K. pneumoniae* strains was approximately 17.7% (95%CI: 12.8–24.0; I2: 95.4; p-value: 0.01; Egger's p-value: 0.1) (Fig. 2). In addition, the pooled prevalence of ESBL rate as well as resistance burden to colistin in hvKp strains was 38.3% (95%CI: 26.0-52.3; I^2: 83.5; p-value: 0.01; Egger's p-value: 0.09) and 13.1% (95%CI: 3.0-42.3; I^2: 73.7; p-value: 0.01; Egger's p-value: 0.9), respectively (appendix). The pooled mortality rate was also assessed as 28.0% (95%CI: 20.2–37.4; I^2: 69.5; p-value: 0.01; Egger's p-value: 0.4).

The pooled prevalence of imipenem was 49.0% (95%CI: 32.7–65.5; I^2: 87.7; p-value: 0.01; Egger's p-value: 0.3), 53.2% (95%CI: 35.6–70.1; I^2: 88.8; p-value: 0.01; Egger's p-value: 0.2) for meropenem, as well as 38.2% (95%CI: 5.4–87.0; I^2: 90.9; p-value: 0.01; Egger's p-value: 0.4) for mertapenem. Our findings reveal the presence of considerable resistance to carbapenem antibiotics among clinical hvKp strains (Fig. 3).

In the next stage, the prevalence of carbapenem-resistance genes was measured among hvKp clinical strains. The pooled prevalence of bla_{VIM} was 19.1% (95%CI: 5.0–91.0; I^2: 80.9; p-value: 0.01; Egger's p-value: 0.2), 22.0% (95%CI: 13.4–33.8; I^2: 73.4; p-value: 0.01; Egger's p-value: 0.4) for bla_{NDM}, 43.4% (95%CI: 24.9–63.9; I^2: 78.9; p-value: 0.01; Egger's p-value: 0.3) for bla_{OXA-48}, as well as 58.8% (95%CI: 25.3–85.8; I^2: 90.6; p-value: 0.01; Egger's p-value: 0.6) for bla_{KPC}.

In the subgroup analyses, an increasing trend in colistin resistance rates among hvKp strains over time was observed, whereas unstable trends were noted for carbapenem-resistant and ESBL-producing hvKp strains (Fig. 4). However, the uneven distribution of studies across regions poses significant challenges to the reliability of conclusions regarding global trends in carbapenem resistance. This underrepresentation may result in an incomplete understanding of the global burden and regional variability in resistance mechanisms. Therefore, the results should be interpreted with more caution. Furthermore, we pooled the prevalence of carbapenem-resistance rates in hvKp strains based on WHO region classification (Fig. 5). The details of carbapenem-resistance rates in WHO regions are listed in Table 2. There is a considerably high pooled prevalence

Table 1 Characteristics of included studies

First author	Year	Country	hvKP	bla_{VIM}	bla_{KPC}	bla_{NDM}	bla_{OXA}	Mortality	IMP: imipenem	MEM: meropenem	ETP: ertapenem	COL	ESBL	Ref
Liu	2014	China	22/70	NA	NA	NA	NA	1/22	22/22	22/22	NA	NA	2/22	[29]
Shah	2017	China	39/96	NA	NA	NA	NA	NA	1/39	0/39	NA	NA	11/39	[30]
Tabrizi	2018	Iran	5/53	5/5	NA	NA	NA	4/5	5/5	5/5	5/5	NA	NA	[31]
Lu	2018	China	5/112	NA	NA	NA	NA	1/5	1/5	NA	NA	1/5	1/5	[32]
EL-Mahdy	2018	Egypt	4/65	NA	NA	NA	NA	2/4	0/4	0/4	NA	NA	1/4	[33]
Remya	2018	India	9/370	NA	NA	2/9	2/9	2/9	2/9	NA	NA	NA	9/9	[34]
Li	2018	China	35/143	NA	20/35	NA	NA	13/35	19/35	20/35	NA	NA	NA	[35]
Liu	2018	China	34/73	NA	NA	NA	NA	14/34	8/34	9/34	NA	NA	13/34	[36]
Liu	2019	China	13/106	NA	6/13	7/13	NA	6/13	13/13	13/13	13/13	0/13	NA	[37]
Hao	2019	China	33/48	NA	NA	1/33	NA	NA	1/33	NA	NA	NA	2/33	[38]
Rastegar	2019	Iran	22/146	NA	NA	NA	NA	NA	2/22	NA	NA	NA	NA	[39]
Li	2019	China	23/562	0/23	13/23	1/23	0/23	3/23	23/23	NA	NA	NA	NA	[40]
Liu	2019	China	80/175	NA	NA	NA	NA	14/80	1/80	2/80	NA	NA	13/80	[41]
Lin	2020	China	124/428	NA	3/124	8/124	NA	NA	10/124	10/124	NA	0/124	40/124	[42]
Taraghian	2020	Iran	11/105	NA	NA	NA	NA	NA	2/11	1/11	NA	NA	7/11	[43]
Tang	2020	China	135/613	NA	NA	NA	NA	16/135	5/135	4/135	5/135	NA	13/135	[44]
Vasilyev	2020	Russia	10	NA	NA	NA	NA	NA	5/10	1/10	NA	NA	6/10	[45]
Albasha	2020	Sudan	10	NA	NA	2/10	8/10	NA	10/10	NA	NA	NA	NA	[46]
Kong	2021	China	14/47	NA	NA	NA	NA	6/14	14/14	14/14	NA	NA	NA	[47]
Shankar	2021	India	27	NA	NA	4/27	23/27	NA	27/27	27/27	NA	NA	NA	[48]
Shao	2021	China	32	NA	32/32	NA	NA	NA	32/32	32/32	NA	0/32	32/32	[49]
Sanikhani	2021	Iran	102/477	NA	NA	33/102	55/102	NA	61/102	59/102	NA	NA	NA	[50]
Shankar	2022	India	9	NA	NA	NA	9/9	4/9	9/9	9/9	NA	NA	NA	[51]
Ouyang	2022	China	41/62	NA	39/41	NA	NA	7/41	41/41	41/41	NA	0/0	NA	[52]
Liu	2022	China	7	NA	NA	NA	NA	2/7	7/7	7/7	NA	1/7	NA	[53]
Saki	2022	Iran	17/153	0/8	NA	2/8	0/8	NA	8/17	9/17	8/17	0/17	8/8	[54]
Wei	2022	China	80	NA	NA	NA	NA	36/80	51/51	50/51	NA	NA	NA	[55]
Shoja	2022	Iran	16/400	NA	NA	NA	NA	NA	1/16	5/16	NA	NA	15/16	[56]
Liu	2022	China	10/720	NA	1/10	NA	1/10	1/10	7/10	9/10	NA	NA	1/10	[57]
Raj	2022	India	14/120	NA	NA	5/14	10/14	4/14	NA	NA	NA	2/14	10/14	[58]
Li	2022	China	4/61	NA	NA	NA	NA	NA	4/4	4/4	NA	4/4	NA	[59]
Osama	2023	Egypt	21/50	NA	NA	NA	NA	NA	12/21	12/21	NA	0/21	15/21	[60]
Mukherjee	2023	India	28/107	NA	NA	9/28	15/28	NA	NA	9/28	NA	NA	NA	[61]
Dan	2023	China	32/96	NA	NA	NA	NA	NA	4/32	5/32	NA	NA	5/32	[62]
Tang	2023	China	8	NA	8/8	4/8	NA	NA	1/8	NA	NA	8/8	NA	[63]
Pei	2023	China	26	NA	NA	NA	1/26	NA	0/26	0/26	0/26	NA	6/26	[64]

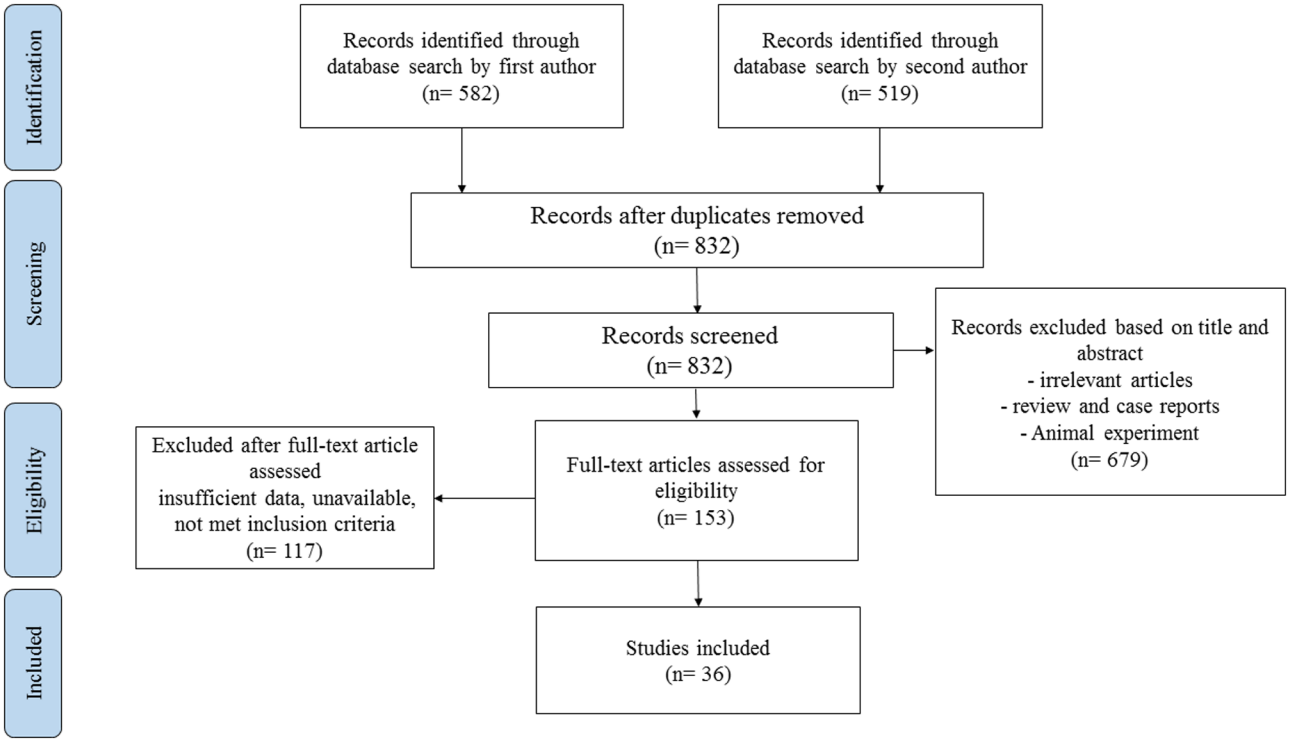

Fig. 1 Flowchart of the studies included in the analysis

of carbapenem-resistance rate of hvKp strains among all of the WHO-West Pacific region, Eastern Mediterranean region, South-East Asian Region, European Region, as well as the African region. Our results showed that bla_{KPC} is common in the West Pacific region. Bla_{OXA-48} is more common in both South-East Asian as well as African regions, while bla_{NDM}, and bla_{VIM} is popular in the Eastern Mediterranean region as well as the South-East Asian Region (Table 2).

Publication bias

There are several items to underscore the presence of publication bias in the eligible studies. Both Egger's plot and symmetry in the funnel plot confirmed the lack of publication bias in the included studies (Fig. 6).

Discussion

According to the literature, carbapenem-resistant *K. pneumoniae* is one of the top seven leading death pathogens. More than 50,000 human deaths are attributed to this pathogen annually [26]. Carbapenem-resistant pathogens are considered one of the most serious human threats, mostly leading to clinical outcomes i.e., high mortality rates, prolonged hospitalization, as well as high medical costs [65].

Carbapenem-resistant *K. pneumoniae* is considered a global challenge so limited therapeutic options remain against these pathogens [66]. Unfortunately, the rate of carbapenem resistance in recent years has significantly increased in recent years as studies have shown that the rate of carbapenem-resistant *K. pneumoniae* has increased from 3 to 23.1% from 2005 to 2021. In addition, carbapenem-resistant *A. baumannii* has been reported from 31.0 to 71.5% [67]. This analysis included 36 eligible studies regarding the carbapenem-resistant *K. pneumoniae* rate. To the best of our knowledge, this is the first document, that investigated the pooled prevalence of carbapenem-resistant *K. pneumoniae* throughout the world. In this analysis, we evaluated data of 5,667 *K. pneumoniae* strains from 36 included studies that were performed between 2014 and 2023.

The pooled prevalence of ESBL-producing hvKp strains and colistin resistance rate was 38.3% (95%CI: 26.0-52.3) and 13.1% (95%CI: 3.0-42.3) measured. Furthermore, mortality rates in hvKp infections was also measured at 28.0% (95%CI: 20.2–37.4). In this relation, Xu et al. (2017) showed that infection with carbapenem-resistant *K. pneumoniae* strains significantly increased the risk of mortality compared with carbapenem-susceptible strains [65]. However, some studies have also shown no association between infection with carbapenem-resistant pathogens and death [68, 69]. According to the literature, drug-resistant pathogen infections in individuals with underlying diseases and comorbidities tend to increase mortality rates [70, 71]. Our results showed that the carbapenem-resistance rate including imipenem was 49.0%,

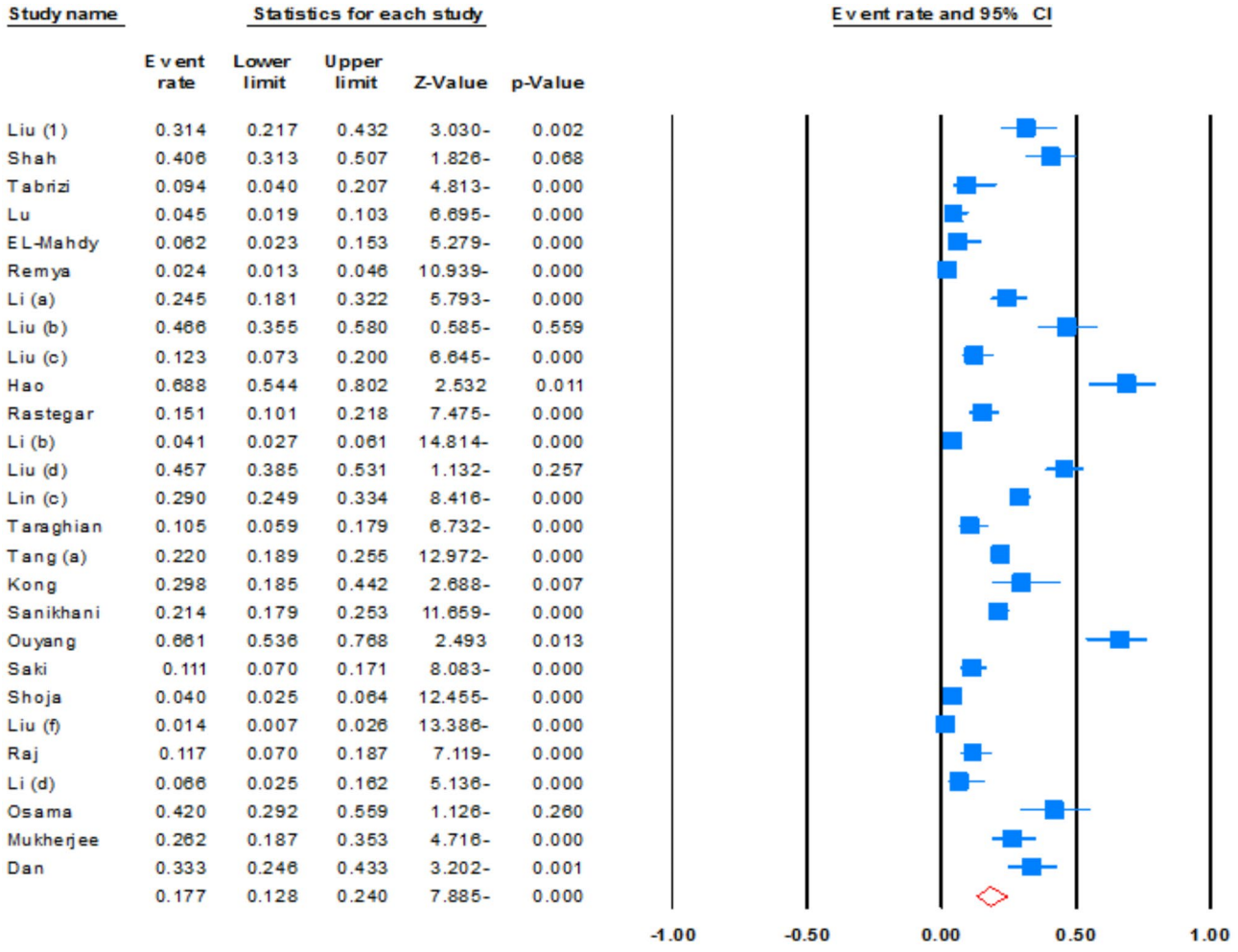

Fig. 2 Forest plot of the meta-analysis on the prevalence of hypervirulent *Klebsiella pneumoniae* (hvKp) infections

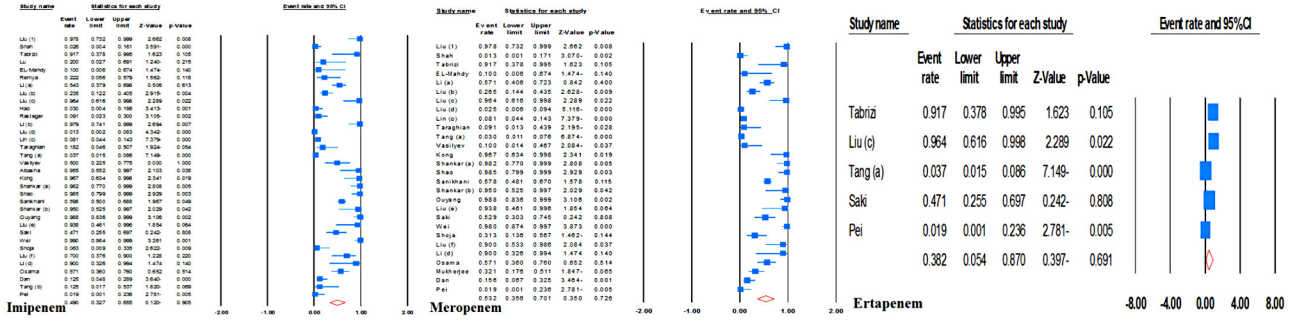

Fig. 3 Forest plot of the meta-analysis on the resistance rates of hypervirulent *Klebsiella pneumoniae* (hvKp) strains to Imipenem, Meropenem, and Ertapenem

meropenem was 53.2%, and ertapenem was about 38.2%. Tesfa et al. (2022) reported the pooled prevalence of colonization with carbapenem-resistant *K. pneumoniae* at about 5.43% [20]. Vaez et al. (2018) reported the prevalence of CR *K. pneumoniae* in Iranian populations was about 11.3% [16]. The carbapenem-resistance rate is more common in hvKp strains. In line with these results, Beig et al. (2024) estimated the carbapenem-resistant rate among hvKp strains such as imipenem (45.7%), meropenem (51.0%), and ertapenem (40.6%) [72].

Various mechanisms contribute to carbapenem resistance, including Ambler class A beta-lactamases (e.g., KPC, GES, IBC, SFC enzymes), metallo-beta-lactamases (VIM, IMP, NDM, SPM, GIM, and AIM), and Ambler

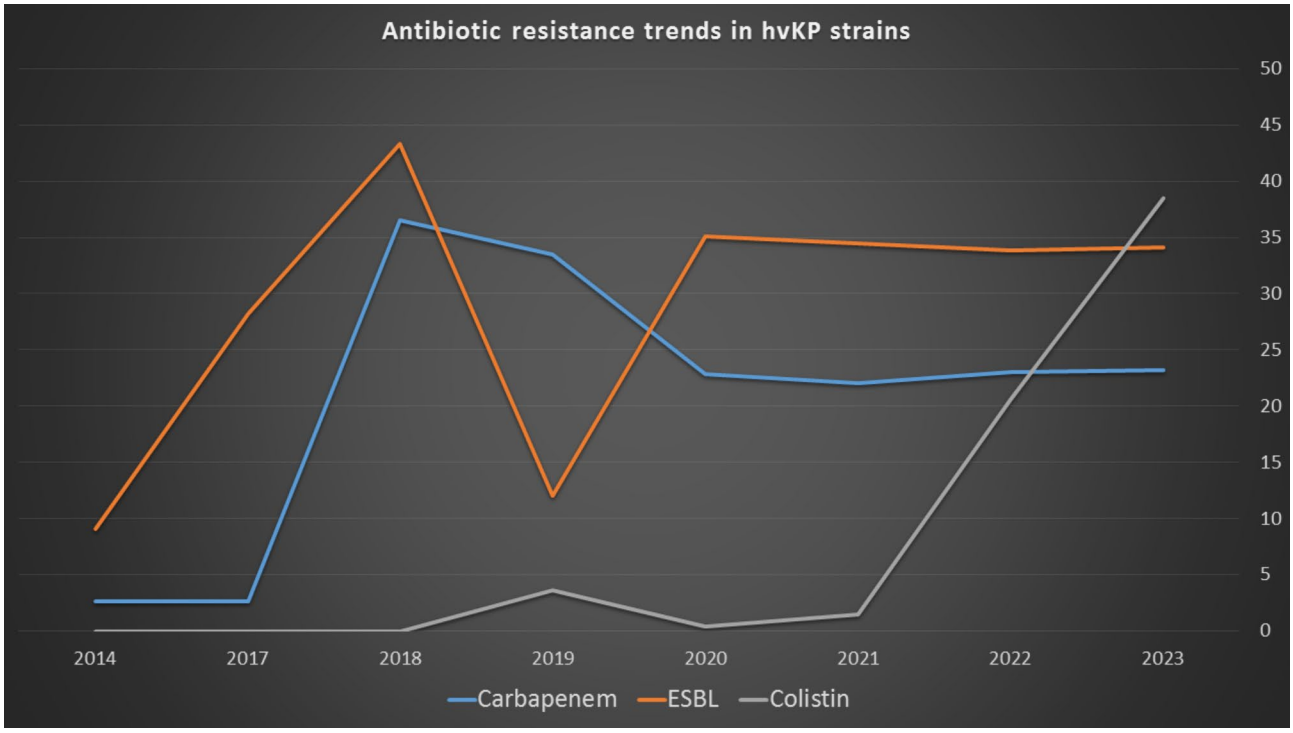

Fig. 4 Global trends in antibiotic resistance patterns of hypervirulent *Klebsiella pneumoniae* (hvKp) Strains

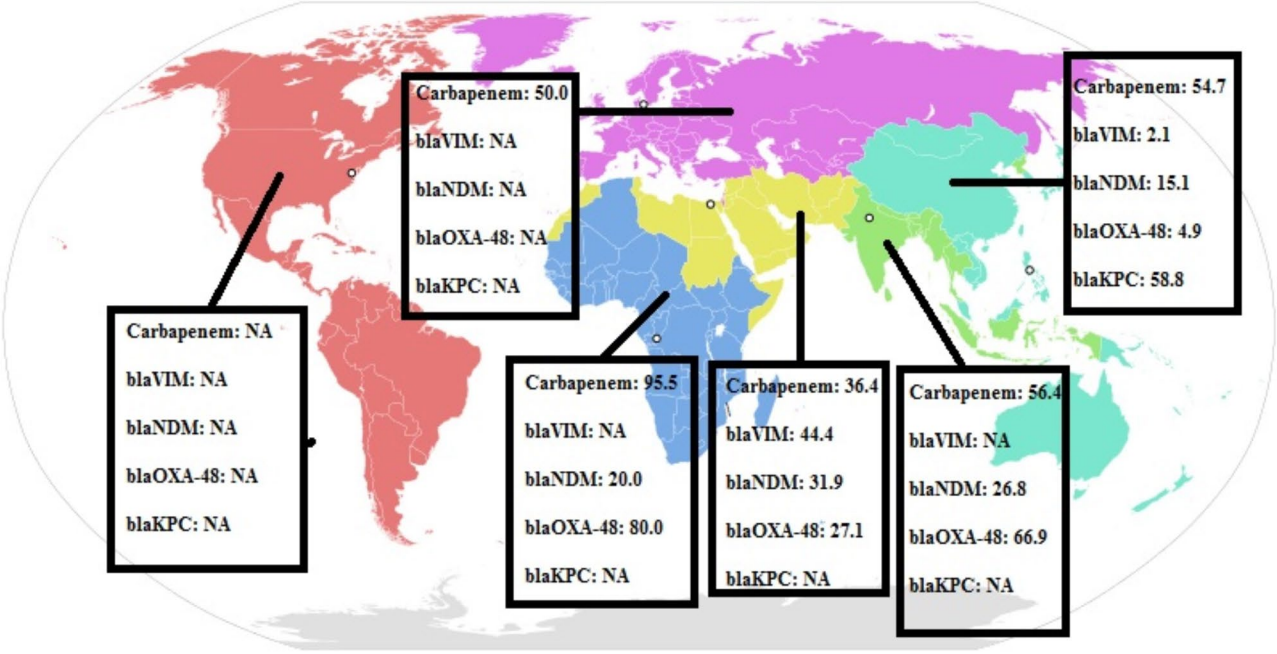

Fig. 5 Global distribution of carbapenemase variants in hypervirulent *Klebsiella pneumoniae* (hvKp) strains

class D enzymes (OXA-type enzymes). Among these, KPC, VIM, IMP, and NDM are the most prevalent carbapenemases with widespread distribution [73, 74]. The mechanisms underlying carbapenem resistance involve enzymatic properties, genetic organization, and modes of dissemination. In this context, the bla_{KPC} gene encodes *Klebsiella pneumoniae* carbapenemase (KPC), a class A beta-lactamase capable of hydrolyzing carbapenems. It is typically carried on *Tn4401* transposons, embedded within conjugative plasmids, and is endemic in North and South America [75]. Conversely, the $bla_{\mathrm{OXA\text{-}48}}$ gene encodes *OXA_48* carbapenemase, a class D

Table 2 Summary of event rates with confidence intervals (CIs) for carbapenem-resistant hvKp strains

WHO region	Carbapenem	Random-effect model		Heterogeneity		Publication bias
		%	95%CI	I^2	*p*-value	Egger's *p*-value
West pacific region	Carbapenem	54.7	29.5–77.6	90.2	0.01	0.01
	bla_{VIM}	2.1	0.1–25.9	0.0	0.9	NA
	bla_{NDM}	15.1	3.7–45.6	86.1	0.01	0.8
	bla_{OXA-48}	4.9	1.4–15.7	0.0	0.6	0.5
	bla_{KPC}	58.8	25.3–85.8	90.6	0.01	0.6
Eastern Mediterranean region	Carbapenem	36.4	18.7–58.8	75.19	0.01	0.1
	bla_{VIM}	44.4	0.5–99.3	84.2	0.01	NA
	bla_{NDM}	31.9	23.8–41.1	0.0	0.6	NA
	bla_{OXA-48}	27.1	2.1–86.5	75.8	0.01	NA
	bla_{KPC}	NA	NA	NA	NA	NA
South-East Asian Region	Carbapenem	56.4	23.6–84.4	76.9	0.01	0.1
	bla_{VIM}	NA	NA	NA	NA	NA
	bla_{NDM}	26.8	17.9–38.1	0.0	0.4	0.6
	bla_{OXA-48}	66.9	41.2–85.4	71.8	0.01	0.6
	bla_{KPC}	NA	NA	NA	NA	NA
European Region	Carbapenem	50.0	22.5–77.5	0.0	0.9	NA
	bla_{VIM}	NA	NA	NA	NA	NA
	bla_{NDM}	NA	NA	NA	NA	NA
	bla_{OXA-48}	NA	NA	NA	NA	NA
	bla_{KPC}	NA	NA	NA	NA	NA
African Region	Carbapenem	95.5	55.2–99.7	0.0	0.9	NA
	bla_{VIM}	NA	NA	NA	NA	NA
	bla_{NDM}	20.0	5.0-54.1	0.0	0.9	NA
	bla_{OXA-48}	80.0	45.9–95.0	0.0	0.9	NA
	bla_{KPC}	NA	NA	NA	NA	NA

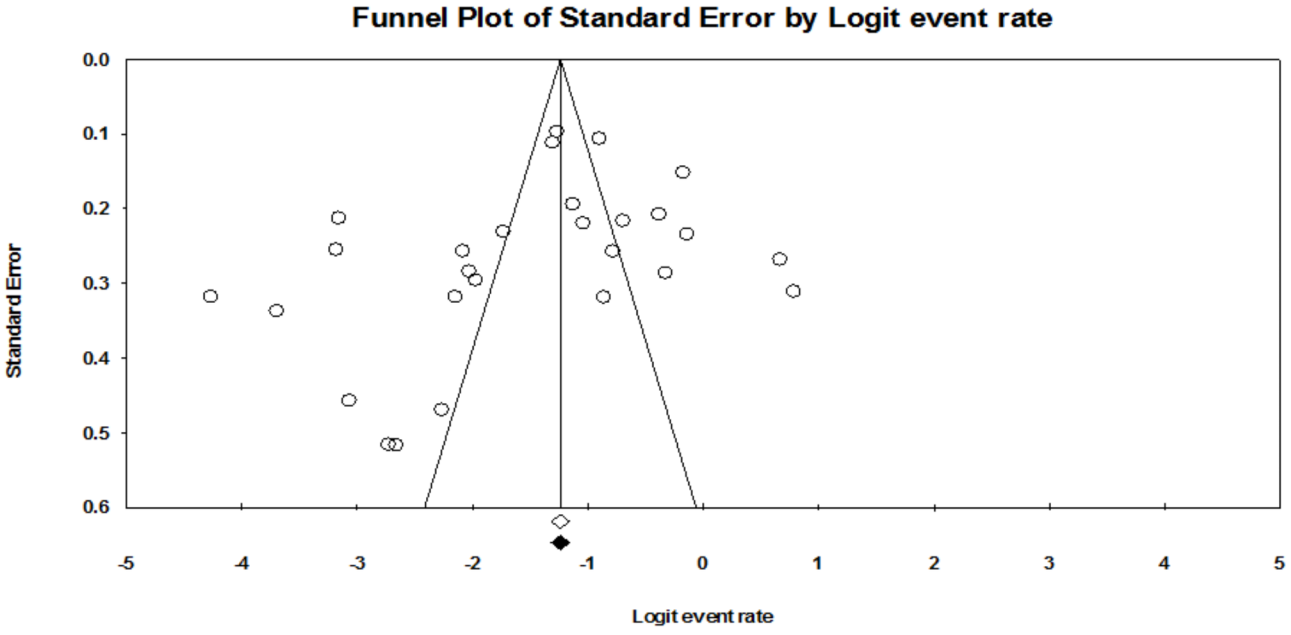

Fig. 6 Funnel plot of the meta-analysis on the prevalence of Carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (hvKp) strains

beta-lactamase with restricted hydrolytic activity against carbapenems. It is generally carried on *Tn1999* transposons, often harbored on cryptic plasmids, and is predominantly found in the Middle East, North Africa, and parts of Southern Europe [76]. The regional dominance of carbapenemases is influenced by various aspects, including antibiotic usage patterns, horizontal gene transfers dynamics, geographic variability in infection control measures, as well as international travel [77, 78].

Our findings suggested that bla_{KPC} and bla_{VIM} were the most common and least common genes associated with carbapenem resistance among hvKp strains, respectively. Consistent with our results, KPC enzymes are the most frequent carbapenemase hydrolyzing enzymes that are predominant throughout the world [79]. KPC-producing *K. pneumoniae* has been reported from various WHO regions in the United States, Latin America, European, and Asian countries [80]. Previous studies revealed that KPC-producing *K. pneumoniae* is not only resistant to all β-lactam antibiotics but also has convergence resistance to other antimicrobial agents such as aminoglycosides and fluoroquinolones [81]. These findings could be explained by higher mortality rates of KPC-encoding *K. pneumoniae* [82]. Thus, infection with KPC-positive *K. pneumoniae* infections can be considered an independent risk factor for mortality [67, 68].

Based on our sub-group analysis, the carbapenem resistance rate in hvKp strains was relatively high across WHO regions, particularly the West Pacific region as well as the Southeast Asian region. The carbapenem resistance rate in Europe and Africa was reported to be over 50%. The studies that reported carbapenem-resistant hvKp strains are limited in African and European countries. Therefore, this picture does not represent the resistance rate in these regions. In this relation, the previous epidemiological studies reported high carbapenem-resistant *K. pneumoniae* rates in India (22%), China (21%), Egypt (19%), Spain (16%), and the USA (15%) [17]. The results of studies could be varied due to different backgrounds such as previous hospitalization, ICU admission, previous exposure to antibiotics, and distribution of resistance genes in various geographical regions [83, 84]. We found that the pooled prevalence of bla_{KPC} and $bla_{OXA\text{-}48}$ was higher than other carbapenemases. Bla_{KPC} and bla_{OXA} are carried by multiple plasmids such as IncFIIK1, FIIK2, FIA, I2, X, and A/C [85]. Early studies have shown a widespread global distribution of bla_{KPC} and $bla_{OXA\text{-}48}$ beta-lactamases [86, 87]. Consistent with our results, carbapenemases such as bla_{KPC}, bla_{NDM}, and $bla_{OXA\text{-}48}$ are present in most eastern countries [78, 88–90]. Furthermore, North Africa and the Middle East are reservoirs for the global dissemination of $bla_{OXA\text{-}48}$ and $bla_{NDM\text{-}1}$ [91–94]. Research literature suggests that carbapenem-resistant *K. pneumoniae* dissemination in European counters has polyclonal from bla_{KPC}-encoding pathogens [95]. However, there is no comprehensive data regarding these carbapenemases because bla_{IMP} and bla_{VIM} are challenging to trace [96].

Carbapenem-resistant hvKp strains present significant clinical challenges due to their dual threat of multidrug resistance and hypervirulence, which often leads to invasive infections particularly liver abscesses, endophthalmitis, and meningitis [97]. Current treatment options are severely limited, particularly as traditional last-line agents like carbapenems are rendered ineffective [98]. Combination therapies involving polymyxins, tigecycline, and ceftazidime-avibactam have shown some efficacy, but their success is inconsistent and constrained by factors such as suboptimal pharmacokinetics and emerging resistance [99]. In addition, reliance on polymyxins is associated with considerable nephrotoxicity, further complicating patient management [100]. The emergence of novel β-lactamase inhibitors, such as cefiderocol and combinations like meropenem-vaborbactam, offers some promise but remains limited in regions where bla_{OXA-48}-like carbapenemases predominate, as these agents are less effective against OXA-48-producing strains [101, 102]. This geographical variation in resistance mechanisms necessitates a tailored therapeutic approach, highlighting the importance of rapid diagnostic tools to guide targeted therapy [103]. Future strategies should focus on developing agents capable of addressing both resistance and hypervirulence. Furthermore, optimizing combination regimens and investigating the role of adjunctive therapies, such as bacteriophage therapy, immunomodulators, and novel antimicrobials, could provide new hope in managing these challenging infections [104, 105]. To address these gaps, policymakers and researchers should prioritize investments in diagnostic advancements to enhance the detection of resistant pathogens and enable timely, precise interventions. Additionally, strengthening antimicrobial stewardship programs is essential to curb the emergence and spread of resistance, with an emphasis on optimizing antibiotic use and promoting adherence to evidence-based treatment guidelines.

This meta-analysis has several limitations. First, the small number of included studies reduces the robustness of the conclusions and limits the generalizability of the findings. Second, the eligible studies only provided unadjusted data, making it impossible to account for potential confounding factors that could influence the results. Third, considerable heterogeneity persisted across the included studies despite sensitivity analyses, likely due to differences in study design, population characteristics, and methodologies that could not be fully addressed. This heterogeneity complicates the synthesis of results and diminishes the precision of the pooled estimates. Furthermore, restricting the analysis to English-language

articles introduces a language bias, potentially excluding valuable data from non-English publications and contributing to the observed heterogeneity. Lastly, we did not measure the prevalence of variants of carbapenem-resistance genes in hvKp strains. To overcome these limitations, future research should include a larger and more diverse set of high-quality studies with adjusted data to address confounding variables. Efforts to standardize study methodologies and population characteristics are essential to reduce heterogeneity. Additionally, expanding the analysis to include studies published in other languages would help mitigate language bias and enhance the comprehensiveness of the findings.

Conclusion

The current analysis highlights an alarming surge in carbapenem-resistant hvKp strains across most regions of the world, underscoring the urgent need for robust control and prevention strategies. These strategies should prioritize the implementation of advanced diagnostic methods and the establishment of comprehensive surveillance systems to monitor and curb the dissemination of these highly resistant pathogens. However, the uneven distribution of studies across regions presents a critical challenge, limiting the generalizability of findings and potentially overlooking resistance trends in underrepresented areas such as Africa and American regions. This gap emphasizes the importance of expanding research efforts and surveillance to ensure a more accurate global representation. Moreover, the considerable heterogeneity observed among the included studies complicates the synthesis of data and highlights the need for standardized methodologies and reporting practices in future research. Further investigations led by clinicians should focus on addressing these gaps, including exploring regional variations in resistance mechanisms, optimizing antimicrobial therapies, and identifying effective treatment regimens for carbapenem-resistant hvKp infections. By tackling these issues, the global research and medical communities can develop more targeted and equitable strategies to combat this growing public health threat.

Abbreviations

hvkp	Hypervirulent *Klebsiella pneumoniae*
hypervirulent *K. pneumoniae*	Hypervirulent *Klebsiella pneumoniae*
BSI	Blood-stream infections
UTI	Urinary tract infections
WHO	World Health Organization
CLSI	Clinical Laboratory Standard Institute guidelines

Supplementary Information

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Supplementary Material 1

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Author contributions

Study conception and design: MQN. Acquisition of data: MQN, ZA, and FD. Statistical analysis: MK. Drafting of the manuscript: FD and ZA. Critical revision of the manuscript: SD and AKV. Supervision: SD and RR. All authors contributed to the article and approved the submitted version. All authors read and approved the final manuscript.

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No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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Competing interests

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