SYSTEMATIC REVIEW/META-ANALYSIS

Prevalence, Risk Factors, and Clinical Outcomes of Hypervirulent *Klebsiella pneumoniae* Strains among *Klebsiella pneumoniae* Infections: A Systematic Review and Meta-analysis

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Abstract

Aim and background: Hypervirulent *Klebsiella pneumoniae* (HvKp) is a virulent strain associated with invasive infections. While initially community-acquired, hospital-acquired HvKp (HA-HvKp) and carbapenem-resistant HvKp (CR-HvKp) are increasingly reported. This meta-analysis evaluates the prevalence, risk factors, and clinical outcomes associated with HvKp, including CR-HvKp and HA-HvKp, among Kp infections.

Methodology: A systematic search of PubMed, Scopus, Embase, and Cochrane Library was conducted until December 2024. Observational studies comparing HvKp vs classical Kp (cKp), CR-HvKp vs carbapenem-sensitive HvKp (CS-HvKp), and HA-HvKp vs community-acquired HvKp (CA-HvKp) were included. Quality was assessed using the Joanna Briggs Critical Appraisal Tool, and pooled prevalence and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results: Fifty studies with 6,663 participants were included. The HvKp prevalence was 33.0%, with most studies from Asia, predominantly China. Temporal analysis revealed an increase in HvKp prevalence (27.7% in 2006–2018 to 38.5% in 2019–2024). The CR-HvKp prevalence rose from 9.5% to 16.5% (2016–2024). The HA-HvKp prevalence increased from 25.9 to 47.1%. Key risk factors included diabetes mellitus (OR = 1.56), CA-Kp (OR = 2.59), and hypermucoviscous (HM)-phenotype (OR = 29.79). Complications included liver abscess (OR = 6.35), metastatic spread (OR = 4.74), meningitis (OR = 11.14), and septic shock (OR = 1.30). Mortality was higher in HvKp infections but not statistically significant (p = 0.219). HA-HvKp and immunosuppression were significant CR-HvKp risk factors, with CR-HvKp showing higher mortality.

Conclusions: Diabetes mellitus, CA-Kp infections, and HM-phenotype are significant risk factors for HvKp. The rising prevalence of CR-HvKp and HA-HvKp highlights the need for early detection, infection control, and targeted treatment strategies.

Keywords: Carbapenem-resistant, Clinical outcomes, Hospital-acquired infections, Hypervirulent *Klebsiella pneumoniae*, Prevalence, Risk factors.

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Highlights

This systematic review/meta-analysis identifies community-acquired hypervirulent *Klebsiella pneumoniae* (HvKp), diabetes mellitus, and hypermucoviscous-phenotype as risk factors for HvKp-infections. The HvKp increases the risk of liver abscess, meningitis, and septic shock. The prevalence of HvKp is rising, with an increasing trend of hospital-acquired-HvKp and carbapenem-resistant-HvKp (CR-HvKp) strains. The CR-HvKp infections were associated with higher odds of mortality.

Introduction

Klebsiella pneumoniae (Kp) is a gram-negative, lactose-fermenting bacterium belonging to the *Enterobacteriaceae* family, responsible for pneumonia, sepsis, and of late has been associated with multidrug-resistant (MDR) infections.[1–4] Hypervirulent Kp (HvKp) has a hypermucoviscous (HM) phenotype, which is identified by a positive string test (mucoviscous string > 5 mm). Still, it is shown to be nonspecific and requires confirmation with hypervirulent genes, such as *rmpA* and *rmpA2*, and iron chelators like aerobactin, yersiniabactin, and salmochelin.[5–7] Classical Kp (cKp) is primarily associated with MDR infections in hospital settings. However, now, there is a rising prevalence of HvKp in nosocomial infections, with

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one study from India reporting an 87.5% mortality rate.[8–10] Though the HM-phenotype was initially linked to HvKp, studies have also identified it in cKp.[11–14]

The prevalence, specific risk factors, and clinical outcomes of HvKp infections require further study. Though studies report a rising prevalence of HvKp infections in the recent past, the specific trends of rising prevalence remain unclear.[8–10] Additionally, there are conflicting reports on the role of diabetes mellitus (DM) in both HvKp and cKp infections.[6,7] Likewise, concerning clinical outcomes, studies report varied mortality outcomes between HvKp- and cKp-infected patients.[8–18] Studies depict pyogenic abscesses, bacteremia, and pneumonia as clinical conditions associated with HvKp.[19–23] However, there is no comparison between HvKp and cKp regarding the odds of specific clinical outcomes, such as septic shock, which could serve as an early warning for clinicians.

Another growing concern is the emerging resistance of HvKp to antimicrobial agents, including carbapenems.[24–26]

The primary objective was to determine the risk factors and clinical outcomes of HvKp compared with cKp infections. The secondary objectives were to assess the prevalence of HvKp among Kp infections, carbapenem-resistant HvKp (CR-HvKp) among CR-Kp infections, and hospital-acquired HvKp (HA-HvKp) among HvKp infections.

Methodology

The study protocol was registered in PROSPERO with registration number CRD42023469827. The findings were reported following the PRISMA guidelines.

Inclusion Criteria (PICO)

Participants/Patients

Studies involving adult patients with culture-proven Kp infections.

Interventions and Comparators

No specific interventions. Studies that compared risk factors (age, source of infection, DM, biliary tract disease, immunosuppression, intensive care unit (ICU) infections, HM-phenotype, mechanical ventilation, abdominal surgery, recent hospitalization, and antibiotic use) and clinical outcomes (metastatic spread, liver abscess, renal abscess, endophthalmitis, meningitis, ICU admission, ICU stay, length of hospitalization, relapse, and mortality) associated with HvKp infections were included. Only studies defining HvKp based on hypervirulence genes were considered for analysis to compare the HM-phenotype as a risk factor between HvKp and cKp.

Outcomes

The primary outcome is mortality due to HvKp infections compared with cKp infection. The other clinical outcomes studied were liver abscess, metastatic spread of infection, septic shock, meningitis, renal abscess, endophthalmitis, and infection relapses in HvKp infections compared with cKp infections.

The secondary outcomes were the prevalence of HvKp among Kp isolates, CR-HvKp among CR-Kp isolates, and HA-HvKp among HvKp isolates.

Study Design

All the published randomized clinical trials and observational studies like case-control, cohort, and cross-sectional studies were included. Case reports, case series, narrative/systematic reviews, *in-vitro*, and studies on pediatric patients were excluded.

Source of support: Nil
Conflict of interest: None

Literature Search

A comprehensive search for studies in all languages was conducted in PubMed/Medline, Scopus, Embase, and the Cochrane Library from inception to December 2024. Relevant keywords and MeSH terms were used to develop a search strategy. The search string used was: (antimicrobials OR anti-infectives OR antibiotics OR anti-microbial) AND (hypermucoviscous OR hypervirulence OR hypervirulent) AND (*Klebsiella pneumoniae* OR hyalococcus pneumoniae). Citation searching of the included studies was done to identify additional studies. Detailed search strategy is available in Supplementary 1A.

Study Selection and Data Retrieval

All retrieved titles and abstracts were screened for eligibility. Suitable studies were assessed in full text for inclusion. Data collected included details on the first author, publication year, country, study design, sample size, patient characteristics, diagnosis, HvKp characteristics, antibiotic resistance patterns, and virulence factors. The CR-HvKp prevalence data was extracted from antimicrobial susceptibility testing (AST) data. For the risk factor analysis of CR-HvKp, studies reporting possible risk factors were included. Two independent reviewers (DN and SC) performed the study selection and data extraction.

Quality Assessment

The Joanna Briggs Institute (JBI) Critical Appraisal tool was used to assess the risk of bias, tailored to each study design.[27] Two independent reviewers (DN and SC) assessed the study quality, with any discrepancies resolved through discussion with a third reviewer (VS). The quality assessment of the included studies is available in Supplementary 1B.

Statistical Analysis

Statistical analysis was conducted using Comprehensive Meta-Analysis (CMA) software.[28] Pooled prevalence was calculated with a 95% confidence interval (CI). Categorical outcomes were expressed as odds ratios (OR) with 95% CI, and continuous outcomes as standard differences in means (SDM) with 95% CI. For mean differences in age, ICU stay, and length of hospital stay (LOHS) between HvKp and cKp groups, data was converted from the median and interquartile range to mean and standard deviation. A fixed effect model (FE) was used for nonsignificant heterogeneity ($I^2 < 50\%, p > 0.05$), while a random effects model (RE) was used for substantial heterogeneity ($I^2 > 50\%, p < 0.05$). Sensitivity analysis was performed by eliminating a single study to determine which had the most impact on the outcomes.[29]

Publication Bias

The funnel plot was visually examined to evaluate any potential publication bias. The CMA was used to construct a funnel plot. Moreover, publication bias was statistically analyzed using Begg and Egger's test. A p-value ≤ 0.05 was deemed statistically significant.[30]

Results

Study Selection

A total of 6,813 articles were screened based on their titles and abstracts, with the exclusion of 5,861 articles. After removing

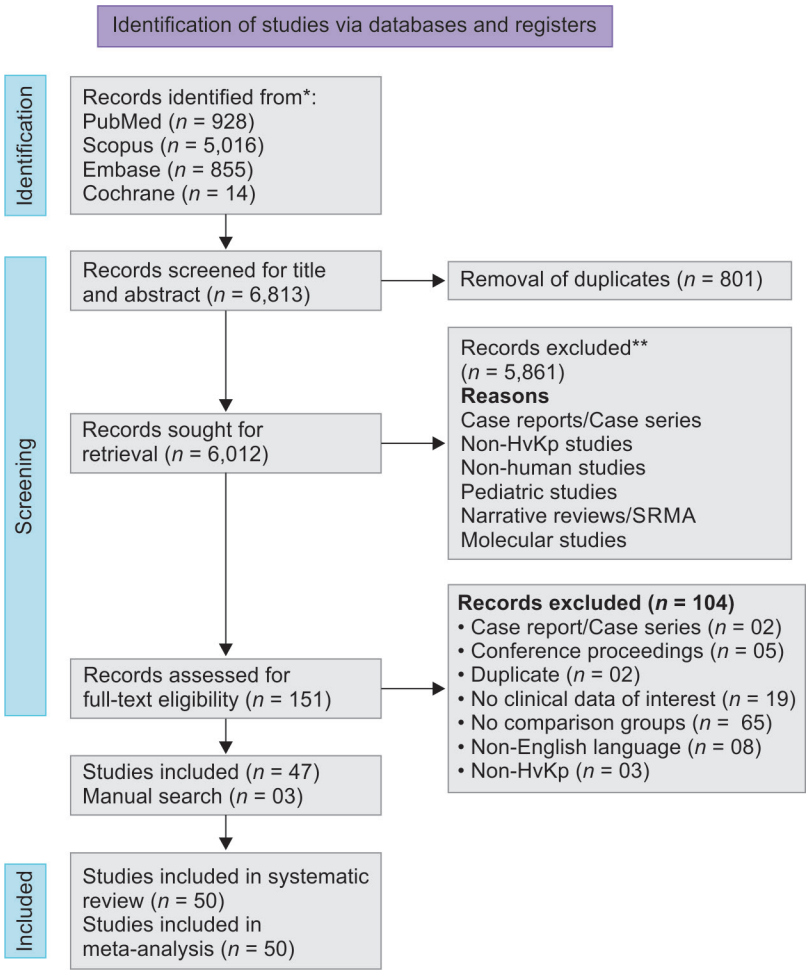

Fig. 1: PRISMA flowchart showing screening and inclusion of studies with hypervirulent *K. pneumoniae*
Source: Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/bmj.n.71

duplicates, 151 articles underwent full-text screening, of which 47 were included. Additionally, a snowball search of the references yielded three more articles, bringing the total number of studies included to 50. Data on the prevalence, risk factors, and clinical outcomes of HvKp were extracted from 46 studies, while four studies provided data specifically on the risk factors and outcomes of CR-HvKp. One study from the 46 contributed data for both the prevalence and risk factors of HvKp and CR-HvKp. Figure 1 presents the PRISMA flow diagram summarizing the study selection process. The excluded studies with reason are given in Supplementary 1C.

Characteristics of the Included Studies

A total of 50 studies with 6,663 participants were included.[9,11,12,15,16,19–26,31–65,78,79] These studies were published between 2006 and 2024, with the majority conducted in China, spanning five continents Asia, Europe, Africa, North America, and Oceania. All studies were observational, consisting of 9 prospective studies are[9,23,25,39,50,51,55,57,58] and 41 retrospective designs.[11,12,15,16,19–22,24,26,31–38,40–49,52–54,56,59–65,78–80] Sample sizes ranged from 26 to 878 participants. The HvKp was defined in five studies by a combination of the HM-phenotype and hypervirulence genes, while 19 studies defined HvKp by the presence of hypervirulent genes, particularly *iucA* and *rmpA* (Refer Supplementary 1D). One study defined HvKp solely by capsular serotypes K1/K2 (Refer Supplementary 1D).

Diagnosis, Site of Isolation, and Source of Infection

The reported diagnoses included bacteremia ($n = 15$), ventilator-associated pneumonia ($n = 3$), urinary tract infections ($n = 2$), pyogenic-infections($n = 2$), meningitis ($n = 1$), surgical-site infections (SSIs) ($n = 1$), and hepatobiliary infections ($n = 1$). Most HvKp infections were community-acquired, though five studies reported an increase in hospital-acquired infections.

The detailed study characteristics are provided in Table 1.

Antimicrobial Susceptibility/Resistance Patterns and Phenotypic and Genotypic Characteristics

A total of 32 studies reported the antimicrobial susceptibility/resistance pattern (Refer Supplementary 1D). In the majority of studies, cKp exhibited higher resistance across all antibiotic groups compared with HvKp (Refer Supplementary 1D). In 10 studies, both HvKp and cKp showed complete resistance to ampicillin (Refer Supplementary 1D). In a study by Li et al., both strains exhibited higher rates of *Klebsiella pneumoniae* carbapenemases production.[38] Increasing trends of resistance to carbapenems

Table 1: Clinical characteristics of the included studies

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Jung SW et al., 2013[11]	Korea	Multicenter retrospective study	Total-33 HvKp-14 (42.42%) cKp-19 (57.57%)	Bacteremia	NA	HvKp Blood-100% cKp Blood-100%
Li et al., 2013[12]	China	Single-center retrospective study	Total-88 HvKp-29 (33.0%) cKp-59 (67.0%)	NA	51.4 ± 12.1 Males-68.2% Females-31.8%	HvKp Blood-28% Urine-0% Sputum-14% Ascites-28% Bile-14% Abscess fluid-7% cKp Blood-34% Urine-10% Sputum-34% Ascites-14% Bile-7% Abscess fluid-5%
Liu YM et al., 2014[31]	China	Single-center retrospective cohort study	Total-70 HvKp-22 (31.42%) cKp-48 (68.57%)	Bacteremia	>60 years-38 HvKp-40.9% cKp-60.4% HvKp Male-90.9% Female-9.01% cKp Male-62.5% Female-37.5%	HvKp Liver abscess-45.45% Bacteremia-18.18% Biliary tract-13.6% Urological-13.6% Peritonitis-4.5% cKp Liver abscess-0% Bacteremia-18.75% Biliary tract-18.75% Urological-10.41% Peritonitis-0%
Yan Q et al., 2016[32]	China	Single-center retrospective study	Total-49 HvKp-14 (28.57%) cKp-35 (71.42%)	Ventilator-associated pneumonia	56.0 ± 19.0 Male-79.6% Female-20.4%	HvKp Et aspirate-100% cKp Et aspirate-100%
Yu WL et al., 2016[33]	Taiwan	Single-center retrospective study	Total-48 HvKp-19 (39.5%) cKp-29 (60.4%)	Bacteremia	HvKp-68 (57–76) cKp-72 (61–77)	HvKp Bacteremia-100% cKp Bacteremia-100%
Zhang Y et al., 2016[34]	China	Multicenter retrospective study	Total-230 HvKp-87 (37.8%) cKp-143 (62.1%)	NA	HvKp-55.9 ± 1.5 Male-62 (77.5%) Female-18 (22.5%) cKp-51.8 ± 1.7 Male-79 (67.5%) Female-38 (32.47%)	HvKp Bacteremia-27.5% Abdominal infection-18.39% cKp Bacteremia-24.47% Abdominal infection-18.8%
Kim YJ et al., 2017[35]	Korea	Multicenter retrospective study	Total-81 HvKp-10 (12.34%) cKp-71 (87.65%)	UTI	Age (median, Q1–Q3) HvKp-58.5 (54.7–77.2) Male-40% cKp-62 (16–78) Male-26%	HvKp Bacteremia-60% UTI-70% Renal abscess-10% cKp Bacteremia-7% UTI-56.3% Renal abscess-1.4%

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Guo Y et al., 2017[37]	China	Single-center retrospective study	Total-369 HvKp-84 (22.76%) cKp-285 (77.23%)	NA	HvKp Male-67.5% Female-35.7% cKp Male-61.4% Female-38.5%	HvKp Blood-17.1% Pus-32.3% Drainage-23.5% Pleural effusion-100% Bile-5% Ascites-25% Tissue-11.1% Catheter tip-7.7% cKp Blood-82.9% Pus-67.7% Drainage-76.5% Pleural effusion-0% Bile-95% Ascites-75% Tissue-88.9% Catheter tip-92.3%
Li J et al., 2017[38]	China	Single-center retrospective study	Total-143 HvKp-35 (24.47%) cKp-108 (75.5%)	Bacteremia	HvKp 54.9 ± 17.1 Male-74.2% Female-25.7% cKp 53.9 ± 17.2 Male-65.7% Female-34.2%	HvKp Unknown-11.4% Respiratory tract-17.1% Intra-abdominal-51.4% Liver abscess-14.3% Vascular catheter-5.7% Others-0% cKp Unknown-25.9% Respiratory tract-11.1% Intra-abdominal-38.9% Liver abscess-1.9% Vascular catheter-14.8% Others-7.4%
Xu M et al., 2018[16]	China	Single-center retrospective cohort study	Total-285 HvKp-69/285 (24.2%) cKp-216/285 (75.78%)	Bacteremia	HvKp Male-46/69 (66.6%) Female-23/69 (33.4%) cKp Male-153/216 (70.8%) Female-63/216 (29.16%)	HvKp Respiratory tract-9 (13.04%) Intraabdominal-10 (14.49%) Soft tissue-4 (5.79%) IV catheter-0% Urinary tract-1 (1.44%) Biliary tract-16 (23.1%) Liver abscess-15 (21.73%) Unknown-0% CNS infection-2 (2.89%)

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
						cKp Respiratory tract-40 (14.03%) Intraabdominal-26 (9.1%) Soft tissue-6 (2.1%) IV catheter-10 (3.5%) Urinary tract-13 (4.56%) Biliary tract-36 (12.63%) Liver abscess-13 (4.56%) Unknown-60 (21.05%) CNS infections-11 (3.85%)
Liu C et al., 2018[15]	China	Single-center retrospective study	Total-202 Elderly population-≥65 years HvKp-96/202 (47.5%) cKp-106/202 (52.47%)	NA	84.43 ± 7.84 years HvKp-83.24 ± 7.35 cKp-85.5 ± 8.14	HvKp Pneumonia 79.2% Urinary infection-13.5% Invasive infection-30.2% Bacteremia-8.3% Liver abscess-10.4% Any other abscess-26% cKp Pneumonia-66% Urinary infection-27.4% Invasive infection-7.5% Bacteremia-3.8% Liver abscess-0% Any other abscess-2.8%
Liu C et al., 2018[19]	China	Single-center retrospective study	Total-73 Elderly population HvKp-34/73 (46.57%) cKp-39/73 (53.42%)	VAP	84.96 ± 8.33 HvKp 83.06 ± 8.55 cKp 86.62 ± 0.87	ET sectretions-100%
El-Mahdy R et al., 2018[39]	Egypt	Single-center cross-sectional study	Total-65 (HAI) HvKp-4/65 (6.1%) cKp-61/65 (93.84%)	NA	<60 years HvKp Male-2/4 (50%) Female-2/4 (50%) cKp Male-30/61 (49.1%) Female-31/61 (50.9%)	HvKp BSI-0% UTI-0% Pneumonia-50% Surgical site infection-50% cKp BSI-18% UTI-34.4% Pneumonia-39.3% Surgical site infection-8.1%

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Liu C et al., 2019[40]	China	Single-center retrospective study	Total-175 Elderly population-≥65years HvKp-80/175 (45.71%) cKp-95/175 (54.28%)	NA	84.84 ± 8.48 Males-170/175 (97.14%) Females-5/175 (2.85%) HvKp-83.2 ± 8.75 Male-77/80 (96.25%) Female-3/80 (3.75%) cKp-86.2 ± 8.04 Male-93/95 (97.8%) Female-2/95 (2.1%)	HvKp UTI-10% Bacteremia-6.3% Liver abscess-10% Other abscess-16.3% Abdominal infections-22.5% cKp UTI-21.1% Bacteremia-4.2% Liver abscess-1.1% Other abscess-3.2% Abdominal infections-6.3%
Xu Min et al., 2019[41]	China	Single-center retrospective cohort study	Total-48 HvKp-22/48 (45.83%) cKp-26/48 (54.16%)	Meningitis	50.3 ± 16.0 HvKp 55.2 ± 13.4 Male-13/22 (59.09%) Female-9/22 (40.9%) cKp 48.3 ± 17.6 Male-16/22 (72.7%) Female-8/22 (36.3%) (44 analyzed)	HvKp- Bacteremia-40.9% Pneumonia-50% Liver Abscess-4.5% Brain Abscess-4.5% cKp- Bacteremia-31.8% Pneumonia-31.8% Liver abscess-0% Brain abscess-0%
Namikawa H et al., 2019[21]	Japan	Single-center retrospective study	Total-114 HvKp-24/114 (21.05%) cKp-90/114 (78.94%)	Bacteremia	HvKp Mean age-67.8 Male-17 (70.8%) Female-7 (29.16%) ≥ 65 years-66.7% cKp Mean age-65.6 Male-53 (58.8%) Female-37 (41.1%) ≥ 65 years-58.9%	HvKp UTI-25% Biliary tract-20.8% Pneumonia-16.7% Intravascular device-4.2% Others-4.2% Unknown-29.2% cKp UTI-15.6% Biliary tract-32.2% Pneumonia-6.7% Intravascular device-5.6% Others-3.3% Unknown-36.7%
Harada S et al., 2019[23]	Japan	Multicenter prospective cross-sectional study	Total-140 HvKp-26 (18.57%) cKp-76 (54.28%) Others-38 (27.1%)	Bacteremia	Median (IQR)-74 (67–81) Male-87/140 (62.14%) Female-53/140 (37.8%)	HvKp Biliary tract-23.1% Urinary Tract-30.8% Intra-abdominal-3.8% Pneumonia-15.4% Intravenous catheter related-0% Liver abscess-15.4% Disseminated infection-11.5% cKp Biliary tract-42.1% Urinary Tract-28.9%

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
						Intra-abdominal-3.9% Pneumonia-3.9% Intravenous catheter related-3.9% Liver abscess-2.6% Disseminated infection-2.6%
Zhao Qiang et al., 2020[42]	China	Single-center retrospective study	Total-51 HvKp-26/51 (50.98%) cKp-25/51 (49.01%)	Surgical site infections	49.5 ± 15.6 Male-36/51 (70.5%) Female-15/51 (29.4%) HvKp 46.0 ± 16.7 Male-18/26 (69.2%) Female-8/26 (30.8%) cKp 53.2 ± 13.8 Male-18/25 (72%) Female-7/25 (28%)	NA
Hwang JH et al., 2020[43]	Korea	Single-center retrospective study	Total-91 HvKp-39/91 (42.8%) cKp-52/91 (57.14%)	Pneumonia	HvKp 68 ± 14 Male-27/39 (69.2%) Female-12/39 (30.7%) cKp 67 ±15 Male-38/52 (73.52%) Female-14/52 (26.9%)	Bacteremia HvKp-2.6% cKp-9.6%
Wei DD et al., 2020[44]	China	Single-center retrospective study	Total-156 HvKp-39 (25%) cKp-78 (50%) K57-Kp-39 (25%)	NA	HvKp 55.59 ± 14.14 cKp 54.78 ± 18.56 K57-Kp 57.82 ± 11.17	NA
Liu Chao et al., 2020[26]	China	Multicenter retrospective study	Total-158 HvKp-79 (50%) cKp-79 (50%)	-	HvKp- Male-68 Female-11 cKp Male-65 Female-14	HvKp Wound-3/79 (3.7%) Pneumonia-60/79 (75.9%) UTI-26/79 32.9%) Bacteremia-6/79 (7.5%) Liver abscess-2/79 (2.5%) Other abscess-8/79 (10.1%) Abdominal infection-8/79 (10.1%) cKp Wound-6/79 (7.5%) Pneumonia-61/79 (77.2%) UTI-19/79 (24.05%)

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
						Bacteremia-8/79 (10.1%) Liver abscess-2/79 (2.5%) Other abscess-1/79 (1.26%) Abdominal infection-7/79 (8.86%)
Ding Z et al., 2022[45]	China	Single-center retrospective study	Total-123 HvKp-53 (43.08%) cKp-70 (56.91%)	NA	51.04 ± 22.75 Males-81 (65.8%) Females-42 (34.14%) HvKp 53.6 ± 16.5 cKp 49.2 ± 26.0	Bacteremia HvKp-12 (22.6%) cKp-3 (4.3%)
Su C et al., 2021[46]	China	Single-center retrospective study	Total-115 HvKp-68/115 (59.1%) cKp-47/115 (40.86%)	NA	HvKp 57.01 ± 19.00 cKp 57.26 ± 16.20	NA
Yang F et al., 2022[47]	China	Single-center retrospective study	Total-88 HvKp-69 cKp-19	Kp infections in the hepatobiliary systems	HvKp 60.84 ± 12.36 cKp 65.00 ± 12.45	Hepatobiliary system HvKp-69 (78.4%) cKp-19 (21.5%)
Sheng Z et al., 2022[48]	China	Single-center retrospective study	Total-66 HvKp-29 cKp-37	Bacteremia	HvKp 63 (50–74) cKp 58 (50–73) HvKp Male-15 (51.7%) Female-14 (48.3%) cKp Male-24 (64.9%) Female-13 (35.1%)	HvKp Pneumonia-10 (34.5%) UTI-5 (17.2%) Abdominal infections-1 (3.4%) Skin and soft tissue infections-2 (6.9%) cKp Pneumonia-16 (43.2%) UTI-10 (27%) Abdominal Infections-9 (24.3%) Skin and soft tissue infections-1 (2.7%)
Vandhana V et al., 2022[9]	India	Single-center prospective study	Total-129 HvKp-18/129 cKp-111/129	NA	NA	NA
Raj S et al., 2022[25]	India	Single-center prospective, cross-sectional study	Total-108 HvKp-14/108 cKp-94/108	NA	HvKp Male-10/14 Female-4/14 cKp Male-51/94 Female-43/94	HvKp UTI-4/14 (28.5%) Blood-7/14 (50%) Respiratory-3/14 (21.4%) Pus and tissue-0/14 (0%) cKp UTI-35/94 (37.2%) Blood-26/94 (27.65%) Respiratory-17/94 (18.08%) Pus and tissue-16/94 (17.02%)

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Huang Y et al., 2022[49]	China	Single-center retrospective study	Total-109 HvKp-45/109 cKp-64/109	NA	HvKp 60 (51.0–68.0) Male-33/45 (73.3%) Female-12/45 (26.6%) cKp 59.5 (50.8–70.0) Male-42/64 (65.6%) Female-22/64 (34.3%)	HvKp Pneumonia-29 (64.4%) BSI-19 (42.2%) UTI-4 (8.9%) Liver abscess-4 (8.9%) Other abscess-4 (8.9%) Abdominal infection-4 (8.9%) Wound-2 (4.4%) cKp Pneumonia-28 (43.8%) BSI-17 (26.6%) UTI-27 (42.2%) Liver abscess-0% Other abscess-0% Abdominal infection-4 (6.3%) Wound-5 (7.8%)
Kim SH et al., 2022[50]	China	Single-center retrospective cohort study	Total-179 HvKp-67 cKp-112	Bacteremia from extra hepatobiliary tract infection	70.54 ± 11.94 HvKp 70.56 ± 12.11 cKp 70.53 ± 11.89	HvKp Primary bacteremia-16.4% UTI-34.4% Central catheter-related infection-3.0% Pulmonary infection-38.9% Purulent respiratory infections-14.9% Intra-abdominal Infections-1.5% Soft tissue infections-4.5% Bone and joint infections-1.5% Others-3.0% cKp Primary bacteremia-16.1% UTI-34.8% Central catheter-related infection-11.6% Pulmonary infection-21.6% Purulent respiratory infections-5.4% Intra-abdominal infections-9.8% Soft tissue infections-3.0% Bone and joint infections-0% Others-1.8%

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Yang Z et al., 2023[20]	China	Single-center retrospective study	Total-54 HvKp-33/54 cKp-21/54	Kp causing pyogenic infections	54.00 (24.00–87.00) HvKp 60.50 (24.00–87.00) cKp 64.00 (26.00–86.00) Male HvKp-16 (48.4%) cKp-12 (57.14%) Female HvKp-17 (52.03%) cKp-9 (42.8%)	HvKp Liver Abscess-15 (45.45%) Gallbladder abscess-4 (12.12%) Skin or soft tissue abscess-6.0 (18.18%) Abdominal or pelvic abscess-3.0 (9.09%) Renal abscess-4.0 (12.21%) Lung abscess-1.0 (3.03%) cKp Liver abscess-6.00 (28.57%) Gallbladder abscess-7.00 (33.33%) Skin or soft tissue abscess-2.00 (9.52%) Abdominal or pelvic abscess-2.00 (9.52%) Renal abscess-3.00 (18.29%) Lung abscess-1.00 (4.76%)
Rafat C et al., 2018[51]	France	Single-center prospective observational study	Total-26 HvKp-12/26 cKp-14/26	Community-acquired Kp infections which are contributing to ICU admissions	HvKp 55.2 (44.5–59.3) cKp 67.5 (56.1–74.4)	HvKp Community-acquired pneumonia-6 Aspiration pneumonia-4 Liver abscess-2
Guo S et al., 2016[53]	China	Single-center retrospective study	Total-43 HvKp-14/43 cKp-29/43	ventilator-associated pneumonia	57.0 ± 15.0 Male-32 Female-11	NA
Hao Z et al., 2019[54]	China	Single-center prospective observational study	Total-48 HvKp-33 cKp-15	NA	HvKp 55.48 ± 13.5 Male-27 (81.8%) Female-6 (18.18%) cKp 66.27 ± 14.07 Male-8 (53.3%) Female-7 (46.6%)	NA
Chen D et al., 2022[55]	China	Single-center retrospective study	Total-225 HvKp-114/225 cKp-111/225	NA	HvKp 63 ± 10 Male-74 (64.9%) Female-40 (35.08%) cKp 66 ± 15 Male-66 (59.4%) Female-45 (40.5%)	HvKp Liver-69.3% Lung-42.1% Bone and soft tissue-3.5% UTI-4.4% Blood-0% cKp Liver-81.1% Lung-27.9% Bone and soft tissue-1.8% UTI-4.5% Blood-2.7%

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Yang Y et al., 2020[56]	China	Single-center retrospective study	Total-113 HvKp-59 cKp-54	NA	HvKp 65.64 ± 1.805 Male-43 (72.8%) Female-16 (27.11%) cKp 56.59 ± 3.359 Male-36 (61.01%) Female-18 (30.50%)	HvKp Pulmonary disease-62.71% Liver abscess-3.39% Urinary infection-3.39% cKp Pulmonary disease-22.22% Liver abscess-0% Urinary infection-3.64%
Qu T et al., 2015[22]	China	Single-center retrospective study	Total-45 HvKp-13 cKp-32	*K. pneumoniae* liver abscess	HvKp 52.3 ± 8.7 Male-8 (61.5%) Female-5 (38.4%) cKp 54.3 ± 12.2 Male-18 (56.2%) Female-14 (43.7%)	NA
Wu H et al., 2017[36]	China	Multicenter retrospective study	Total-165 HvKp-64 cKp-101	Bacteremia	NA	NA
Cubero M et al., 2015[52]	Spain	Single-center retrospective study	Total-878 HvKp-53 cKp-825	Bacteremia	HvKp 56.7 ± 8.3 Male-33 (62.2%) Female-20 (37.8%) cKp 64.7 ± 14.6 Male-550 (66.7%) Female-275 (30.9%)	HvKp Liver abscess-18.6% Pneumonia-11.6% Urinary-51.1% Catheter related bacteremia-6.9% Abdominal-6.9% Biliary-16.27% Primary bacteremia-9.3% SBP-2.3% Others-0% cKp Liver abscess-0.7% Pneumonia-3.6% Urinary-28.24% Catheter related bacteremia-23.27% Abdominal-4.9% Biliary-18.54% Primary bacteremia-16.84% SBP-1.2% Others-2.5%
Lee H et al., 2006[60]	Taiwan	Single-center retrospective study	Total-200 HvKp-83 cKp-117	Bacteremia	HvKp 59.3 ± 12.8 Male-48 (57.8%) Female-35 (42.16%) cKp 63.6 ± 4.7 Male-77 (65.8%) Female-40 (34.18%)	HvKp Pneumonia-20.5% UTIs-10.8% Biliary tract-8.4% Soft tissue infections-6.0% Spontaneous bacterial peritonitis-2.4% cKp

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
						Pneumonia-14.5% UTIs-25.6% Biliary tract-17.9% Soft tissue infections-6.8% Spontaneous bacterial peritonitis-4.3%
Yu WL et al., 2006[61]	Taiwan	Multicenter retrospective study	Total-151 HvKp-58 cKp-93	NA	NA	NA
Peirano G et al., 2013[62]	Alberta Canada	Multicenter retrospective, population-based surveillance cohort design	Total-134 HvKp-10 cKp-124	Bacteremia	HvKp 63 (mean age) Males-60% Female-40% cKp 66 (mean age) Male-52.4% Female-47.6%	HvKp Primary bacteremia-0% Pneumonia-0% UTI-10% Biliary-20% Intra-abdominal abscess-10% Pancreatitis-0% Liver abscess-40% CNS infections-20% cKp Primary bacteremia-12.1% Pneumonia-5.6% UTI-33.9% Biliary-33.9% Intra-abdominal abscess-8.9% Pancreatitis-3.2% Liver abscess-2.4% CNS infections-0%
Fauvet T et al., 2020[59]	New Caledonia	Single-center retrospective study	Total-55 HvKp-15 cKp-40	Bacteremia	HvKp 55.7 (±11.7) Male-8 (53.3%) Female-7 (46.7%) cKp 57.3 (±18.7) Male-17 (42.5%) Female-23 (57.5%)	HvKp UTI-26.7% Lungs-60% CNS-13.3% Eyes-0% Muscles and skin-26.7% Gallbladder and digestive tract-53.3% Liver abscess-13.3% Bones-6.7% cKp UTI-27.5% Lungs-27.5% CNS-0% Eyes-0% Muscles and skin-25% Gallbladder and digestive tract-40% Liver abscess-2.5% Bones-0%

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Alharbi MT et al., 2023[57]	Saudi Arabia	Single-center cross-sectional study	Total-120 HvKp-19 cKp-101	NA	HvKp 31.26 ± 0.47 Male-10 (52.6%) Female-9 (47.4%) cKp 55.63 ± 1.43 Male-56 (56.4%) Female-45 (43.6%)	Kp Respiratory secretions-40% Urine-31.66% Blood-15% Wound-13.3% HvKp Respiratory secretions-7.5% Urine-6.66% Blood-0% Wound-1.66% cKp Respiratory secretions-32.5% Urine-25% Blood-15% Wound-11.66%
Li J et al., 2022[58]	China	Single-center prospective observational study	Total-120 HvKp-30 cKp-91	UTI	HvKp Median age-59.5 Male-17 (56.7%) Female-13 (43.3%) cKp Median age-56.9 Male-45 (49.5%) Female-46 (50.5%)	HvKp (30) Bacteremia-22 (73.3%) Catheter-10 (33.3%) Complicated UTI-23 (76.7%) cKp (91) Bacteremia-75 (82.4%) Catheter-25 (27.5%) Complicated UTI-54 (59.3%)
Hassan NAM et al., 2024[64]	Egypt	Single-center cross-sectional study	Total-100 HvKp-64 cKp-36	NA	HvKp 62.7 ± 20.5 Male-42 (65.6%) Female-24 (37.5%) cKp 63.9 ± 24.9 Male-26 (72.2%) Female-10 (27.8%)	HvKp VAP-14 (14%) Pneumonia-38 (38%) SSI-10 (10%) UTI-2 (2%) cKp VAP-4 (4%) Pneumonia-24 (24%) SSI-2 (2%) UTI-4 (4%)
Moutel M et al., 2024[65]	France	Single-center retrospective observational study	Total-70 HvKp-9 cKp-61	Bacteremia	HvKp 50 (41–68) Male-9 (100%) Female-0 (0%) cKp 66 (56–70) Male-46 (75%) Female-15 (25%)	HvKp Pulmonary-5 (56%) Digestive-1 (11%) Catheter-related-1 (11%) Urinary-2 (22%) Others-0% Unknown-0% cKp Pulmonary-17 (28%) Digestive-13 (21%) Catheter-related-10 (16%) Urinary-9 (15%) Others-2 (4%) Unknown-10 (16%)

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Table 1: *(Contd...)*

Study ID	*Country*	*Study design*	*Sample size*	*Study diagnosis*	*Age (mean/median), gender*	*Sites of isolation*
Yao B et al., 2015[24]	China	Single-center retrospective observational study	Total-32 CR-HvKp-3 CR-cKp-29	NA	CR-HvKp Age > 60–63 Male-2 (66.6%) Female-1 (33.3%) CR-cKp Age > 60–25 Male-11 (37.9%) Female-18 (62.06%)	NA
Wei T et al., 2022[63]	China	Single-center retrospective observational study	Total-80 CR-HvKp-51 CR-cKp-29	NA	CR-HvKp 85.0 (75.0–88.0) Male-40 (78.4%) Female-11 (21.6%) CR-cKp 78.0 (69.5-86.0) Male-20 (68.9%) Female-9 (31.03%)	NA
Ouyang P et al., 2022[78]	China	Single-center retrospective observational study	Total-62 CR-HvKp-41 CR-cKp-21	NA	CR-HvKp 57.07 ± 18.14 Male-30 (73.2%) Female-11 (26.8%) CR-cKp 56.86 ± 23.50 Male-11 (52.3%) Female-10 (47.6%)	CR-HvKp Respiratory tract-14 (34.2%) Biliary tract-5 (12.2%) Abdomen-8 (19.5%) Blood-7 (17.1%) Wound-3 (7.3%) Pus-2 (4.9%) Urinary tract-1 (2.4%) Reproductive tract-1 (2.4%) CR-cKp Respiratory tract-11 (52.4%) Biliary tract-6 (28.6%) Abdomen-1 (4.8%) Blood-1 (4.8%) Wound-1 (4.8%) Pus-1 (4.8%) Urinary tract-0% Reproductive tract-0%
Wang Q et al., 2022[79]	China	Single-center retrospective observational study	Total-417 CR-HvKp-43 CR-cKp-374	NA	CR-HvKp Age > 70–33 CR-cKp Age > 70–315	NA

BSI, blood stream infection; cKp, classical *Klebsiella pneumoniae*; CNS, central nervous system; CR-cKp, carbapenem-resistant classical *Klebsiella pneumoniae;* CR-HvKp, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*; ET, endotracheal tube; HvKp, hypervirulent *Klebsiella pneumoniae*; Kp, *Klebsiella pneumoniae*; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection

in HvKp strains have also been noted (Refer Supplementary 1D). Mohamed et al. and Raj et al. reported higher resistance among HA-HvKp strains as compared with cKp across various antimicrobial classes, including the polymyxin group.[25,64] In 19 studies, HvKp was defined by the HM-phenotypic character (Refer Supplementary 1D).

The detailed antimicrobial susceptibility patterns and microbiological characteristics are provided in Supplementary 1D.

Prevalence of Various HvKp Strains

Prevalence of HvKp among Kp Infections

A total of 46 studies involving 6,134 patients with Kp infections were included to assess the prevalence of HvKp. The overall prevalence of HvKp among Kp-infections was 33% (Fig. 2). Subgroup analysis by continent showed prevalence rates of 41.5% in Africa ($n = 2$), 34% in Asia ($n = 39$), 33.1% in Europe ($n = 3$), 24.8% in North America ($n = 1$), and 15.8% in Oceania ($n = 1$) (Supplementary Table 1E). A temporal analysis showed increased HvKp prevalence from 27.7% in 2006–2018 to 38.5% in 2019–2024.

Prevalence of CR-HvKp among HvKp Infections

A total of 21 studies with 1,068 HvKp patients were included to assess the prevalence of CR-HvKp. The overall prevalence of CR-HvKp was 13.8%, with an increase from 9.5% in 2016–2018 to 16.5% in 2019–2024 (Supplementary 1F.1).

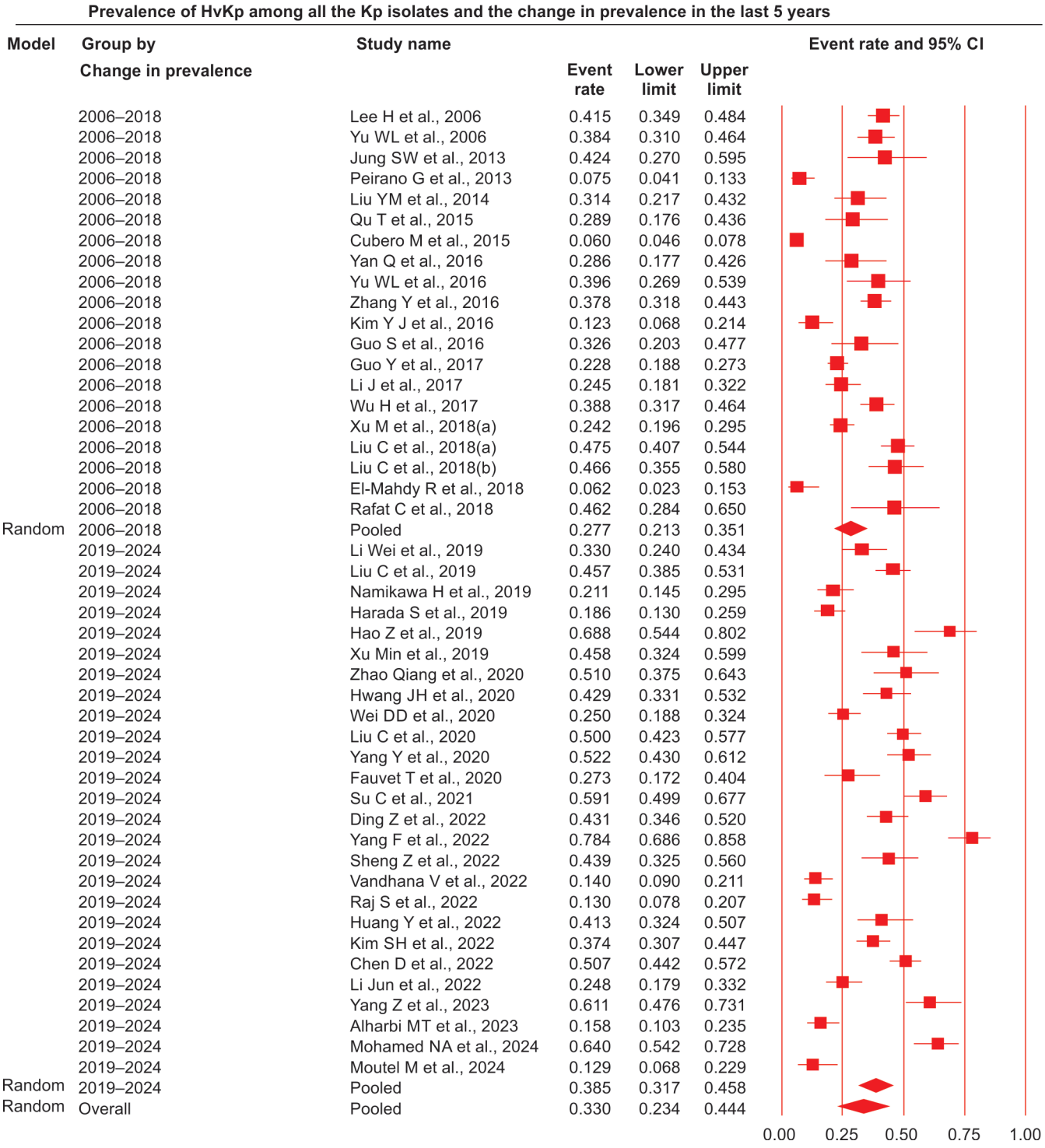

Fig. 2: Prevalence of HvKp and changing of prevalence over two time periods (2006–2018 and 2019–2024)

Prevalence of CA-HvKp and HA-HvKp among HvKp Infections

The prevalence of CA-HvKp was 63.4% and HA-HvKp was 36.0%. The prevalence of HA-HvKp increased from 25.9% in 2006–2018 to 47.1% in 2019–2024 (Supplementary 1F.2).

Refer to Supplementary Table 1E for detailed data on the continent-specific prevalence of HvKp strains.

Risk Factors of Various HvKp Strains

Risk Factor Analysis of HvKp Strains as Compared with cKp Strains

The analysis revealed DM as a significant risk factor for HvKp infections (OR = 1.561). Community-acquired Kp infections (OR = 2.59) and a positive string test (OR = 29.79) are strongly associated

with HvKp as compared with cKp. Conversely, biliary tract diseases (OR = 1.53), immunosuppression (OR = 2.26), and hospital-acquired infections (OR = 2.87) are linked to cKp infections as compared with HvKp infections.

Risk Factor Analysis of CR-HvKp Strains as Compared with CR-cKp Strains

Males are at a significantly higher risk of CR-HvKp infections compared with females (OR = 8.47). Although hospital-acquired Kp infections increase the risk of CR-HvKp, this association is not statistically significant. Patients with underlying malignancies, DM, cardiovascular diseases, or neurological conditions also have higher odds of developing CR-HvKp; however, these findings lack statistical significance.

Risk Factor Analysis of HA-HvKp Strains as Compared with HA-cKp Strains

The results showed that DM (OR = 1.98) and the HM-phenotype (OR = 43.94) are significantly associated with an increased risk of HA-HvKp infections. Patients with HA-HvKp infections are younger than those with HA-cKp, with a statistically significant difference in mean age.

Risk Factor Analysis of CA-HvKp Strains as Compared with CA-cKp Strains

Underlying conditions such as pulmonary disease, DM, and male gender are associated with increased odds of CA-HvKp infections, although these findings are not statistically significant. In contrast, malignancy significantly increases the risk of CA-cKp infections ($p < 0.05$). Patients in the CA-HvKp group are younger than those with CA-cKp, with a statistically significant difference in mean age.

When comparing risk factors between CR-HvKp and CS-HvKp, HA-HvKp and an immunosuppressed state are significant risk factors for CR-HvKp. In contrast, community-acquired HvKp is a predictor for CS-HvKp.

Risk factors analysis forest plots are given in Supplementary 1G. Detailed data on the risk factors of HvKp, CR-HvKp, CA-HvKp, and HA-HvKp strains is presented in Supplementary Table 1H.

Clinical Outcomes Analysis of Various HvKp Strains (Table 2)

Clinical Outcomes Analysis of HvKp Strains as Compared with cKp Strains

The results showed that HvKp infections significantly increase the risk of liver abscess (OR = 6.35), metastatic spread (OR = 4.74), meningitis (OR = 11.14), and septic shock (OR = 1.30) compared with cKp infections. While the risk of endophthalmitis is higher in HvKp infections, the difference is not statistically significant. Mortality odds were higher in HvKp infections but not statistically significant (OR = 1.20).

No significant differences were observed between HvKp and cKp infections in terms of length of hospital stay, length of ICU stay, relapse rates, or frequency of renal abscesses.

Clinical Outcomes Analysis of CR-HvKp Strains as Compared with CR-cKp Strains

The analysis reported higher odds of abscess formation in CR-HvKp infected patients as compared with CR-cKp infected patients but was not statistically significant.

Clinical Outcomes Analysis of HA-HvKp Strains as Compared with HA-cKp Strains

HA-HvKp infections were associated with increased odds of sepsis and mortality compared with HA-cKp, though not statistically significant.

Clinical Outcomes Analysis of CA-HvKp Strains as Compared with CA-cKp Strains

CA-HvKp infections demonstrated significantly higher odds of liver abscess (OR = 4.17) compared with CA-cKp infections ($p < 0.001$).

Clinical Outcomes Analysis of CR-HvKp Strains as Compared with CS-HvKp Strains

CR-HvKp infections showed higher mortality odds than CS-HvKp (OR = 40.21, p-value = 0.001).

Detailed data on the clinical outcomes of HvKp strains is presented in Table 2. Clinical outcomes analysis forest plots are given in Supplementary 1I.

The publication bias was statistically analyzed using Egger's test and visually represented by the funnel plot. It showed no significant publication bias (p-value = 0.39) (Fig. 3).

Figure 4 depicts the types of HvKp, the various risk factors, and clinical outcomes of the various comparisons within HvKp.

The summary of the results of the systematic review/meta-analysis (SRMA) regarding the prevalence and clinical outcomes of HvKp as compared with cKp is provided as a pictorial representation in Figure 5.

Discussion

Hypervirulent *K. pneumoniae*, a hypervirulent variant of Kp, is emerging as a global public health concern due to its significant clinical implications and increasing prevalence. This meta-analysis comprehensively evaluates HvKp's risk factors and clinical outcomes, including CR-HvKp and HA-HvKp strains. The findings highlight the pathogen's adaptability to healthcare environments and its rising resistance to antibiotics.

Hypervirulent *K. pneumoniae* accounted for 33% of Kp infections, with its prevalence increasing from 27.7% (2006–2018) to 38.5% (2019–2024), alongside rising proportions of CR-HvKp (13.8%) and HA-HvKp (36.0%), reflecting its adaptation to healthcare settings and growing resistance. Prevalence was highest in Africa (41.5%), followed by Asia (34%), Europe (33.1%), North America (24.8%), and Oceania (15.8%). Although data from Africa were limited to two studies, these findings underscore the increasing global dissemination of HvKp, which was historically considered predominantly an Asia-Pacific pathogen. The increasing prevalence of hypervirulent strains, raises concerns, especially in Asia, where genetic and geographic factors may enhance pathogen acquisition and colonization.[23] The emergence of HA-HvKp and CR-HvKp reflects a troubling shift toward nosocomial adaptation, with HA-HvKp accounting for 36% of HvKp infections. This trend has intensified in recent years, rising from 25.9% to 47.1%. Similarly, CR-HvKp has increased from 9.5 in 2016–2018 to 16.5% in 2019–2024, underscoring the pathogen's growing resistance to carbapenems and other last-resort antibiotics.

This meta-analysis identifies DM, CA-Kp infections, and the HM-phenotype as significant risk factors for HvKp infections, aligning with findings from Su et al.,[46] and Liu et al.[15,24,25] The *rmpA/A2* and *magA* genes, particularly the latter's role in capsular

Table 2: Clinical outcomes analysis

Clinical outcomes associated with HvKp in comparison with cKp infection				
Clinical outcomes	*No. of studies*	*Population size*	*95% CI; combined OR*	*p-value*
Liver abscess	26	4,143	6.35 (4.851–8.335)	<0.001*
Metastatic spread	22	2,277	4.74 (3.632–6.197)	<0.001*
Meningitis	2	212	11.14 (1.26–97.93)	0.030*
Septic shock	15	2,753	1.30 (1.020–1.647)	0.035*
Relapse	4	537	1.07 (0.567–2.024)	0.832
Renal abscess	4	356	2.73 (0.841–8.888)	0.094
Endophthalmitis	3	461	1.66 (0.595–4.659)	0.331
Mortality	31	4,252	1.20 (0.932–1.554)	0.213
Clinical outcomes				
LOICUS	4	466	0.18 (–0.307 to 0.675)	0.463
LOHS	10	920	–0.08 (–0.217 to 0.053)	0.233
Clinical outcomes of CR-HvKp in comparison with CR-cKp infections				
Mechanical ventilation	5	636	0.83 (0.52–1.32)	0.450
Central-venous catheterization	4	219	0.62 (0.30–1.28)	0.199
Abscess formation	3	202	2.49 (0.87–7.10)	0.08
Mortality	5	221	1.001 (0.54–1.85)	0.99
Clinical outcomes of HA-HvKp in comparison with HA-cKp infections				
Sepsis	2	190	1.37 (0.28–6.56)	0.691
Mortality	5	376	1.82 (0.66–4.98)	0.240
Clinical outcomes of CA-HvKp in comparison with CA-cKp infections				
Liver abscess	4	427	4.17 (2.31–7.52)	<0.001*
Mortality	4	374	1.55 (0.89–2.71)	0.120
Clinical outcomes for HA-HvKp in comparison with CA-HvKp infections				
Mortality	2	74	1.43 (0.22–9.08)	0.703
Clinical outcomes for CR-HvKp in comparison with CS-HvKp infections				
Mortality	2	122	40.21 (4.81–336.16)	0.001*

CAI, community-acquired infection; CA-HvKp, community-acquired hypervirulent *Klebsiella pneumoniae*; CA-cKp, community-acquired classical *Klebsiella pneumoniae*; cKp, classical *Klebsiella pneumoniae*; HvKp, hypervirulent *Klebsiella pneumoniae*; CR-HvKp, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*; CR-cKp, carbapenem-resistant classical *Klebsiella pneumoniae*; CS-HvKp, carbapenem-sensitive hypervirulent *Klebsiella pneumoniae*; HA-cKp, hospital-acquired classical *Klebsiella pneumoniae*; HA-HvKp, hospital-acquired hypervirulent *Klebsiella pneumoniae*; LOICUS, length of ICU stay; LOHS, length of hospital stay; OR, odds ratio; The *p*-value represents the pooled *p*-value of the studies to determine significance; *p-value <0.05; Std Diff, standard difference in mean length of hospital and ICU stay

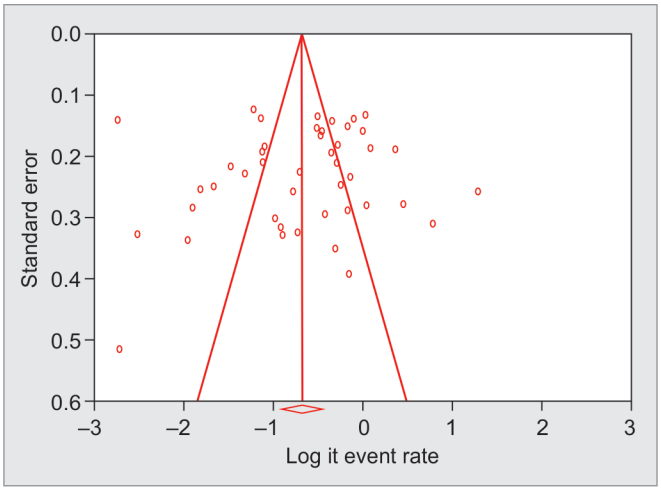

Fig. 3: Funnel plot

polysaccharide synthesis, are associated with the HM-phenotype of HvKp.[26] Although genes like *iucA* and *rmpA* are considered reliable biomarkers for HvKp, their presence in cKp limits their specificity.[7,12,27–30] In resource-limited settings, where genomic analysis may not be feasible, phenotypic methods such as the string test remain a practical and reliable alternative for HvKp identification and complication prediction.

This meta-analysis shows that the HvKp strain significantly increases the risk of liver abscess, metastatic spread, meningitis, and septic shock in Kp infections. Thus, clinicians should be aware of the variant of the Kp isolates in patients to prevent the possible onset of septic shock associated with HvKp infections. Poorly controlled DM is strongly associated with metastatic complications in HvKp infections.[31] Lin et al. found that inadequate glycemic control impairs neutrophil-mediated phagocytosis of HvKp, especially serotypes K1/K2.[80] Russo et al. suggest that diabetes-induced vascular patency loss facilitates HvKp's metastatic spread during bacteremia.[7] However, HvKp does not significantly

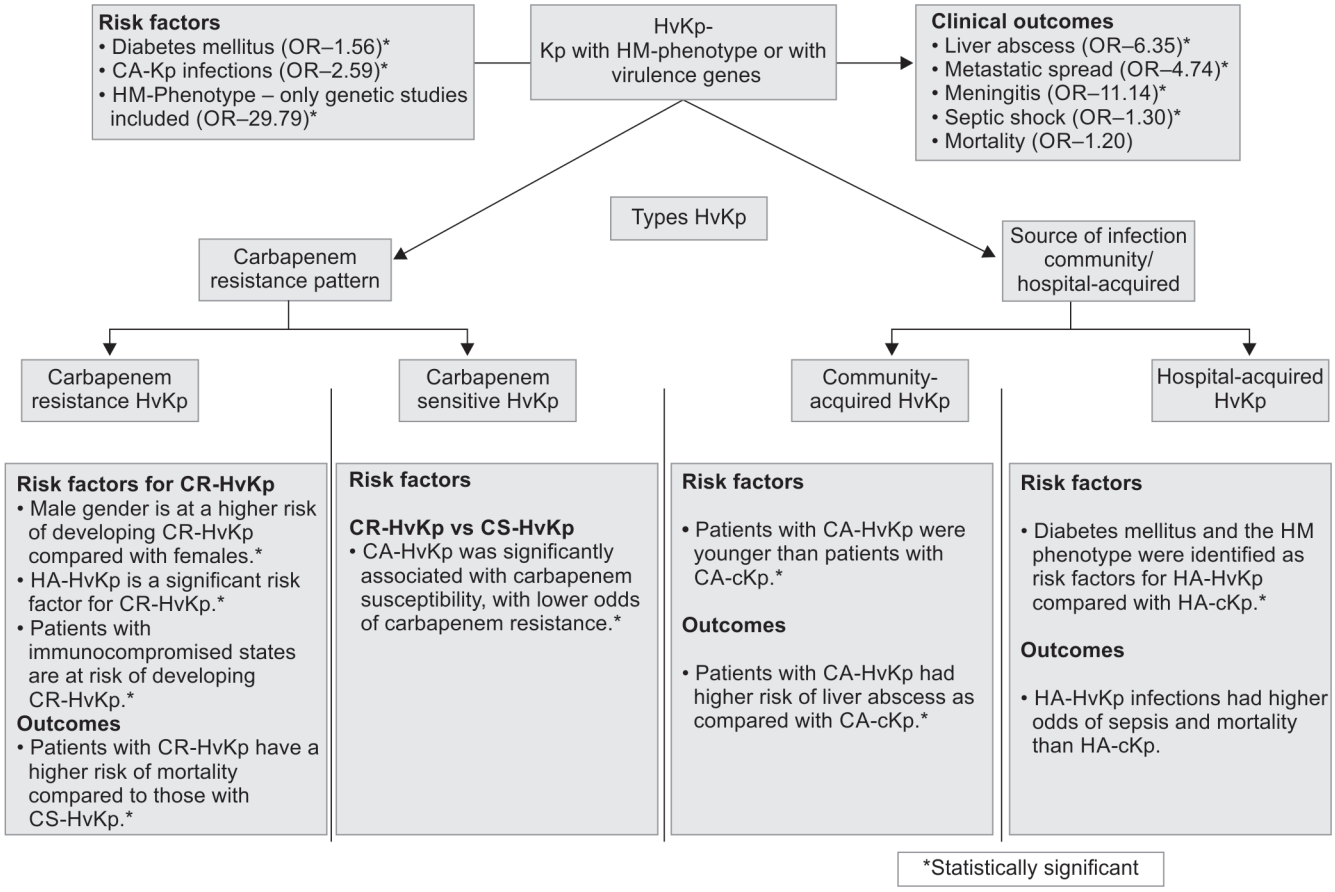

Fig. 4: Definition of HvKp in this SRMA, types of HvKp, risk factors, and outcomes

increase mortality compared with cKp when compared in a total study population of 4,252 patients. This shows that even though HvKp may lead to metastatic spread of infections and a higher incidence of septic shock, the mortality rates were not higher than cKp. It may be due to higher rates of antimicrobial resistance and MDR prevalence among cKp strains as compared with HvKp.[11,12,15,21,25,26,31,36,41–46] However, because of the rising MDR patterns found in HA-HvKp strains, the mortality outcomes may increase in the future.

The HvKp strain shows significantly higher siderophore production than the cKp strain, with a 6-10-fold increase.[74] Siderophores help bacteria absorb iron, promoting their growth in the host and contributing to HvKp's increased virulence. Holden et al. found that siderophores impact tissue damage, bacterial spread, and survival during infection. They also suggested that siderophores may stimulate cytokine secretion, enhance bacterial dissemination, and stabilize hypoxia-inducible factor-1α, a key transcription factor that increases susceptibility to sepsis and septic shock.[73]

Namikawa et al.'s SRMA identified liver abscesses and diabetes as predictors for HvKp infections. However, the review included only studies that used multivariate analysis, which resulted in the inclusion of studies primarily from Asian countries.[74] In another SRMA, Namikawa et al. specifically focused on the HM-phenotype of Kp in bacteremia patients to assess clinical outcomes like abscess formation and all-cause mortality.[75] They found a significant association between the HvKp strain and abscess formation.[71] One study was limited to multivariate analysis studies from Asia, while another focused-on bacteremia patients with the HM-phenotype.[70,71]

The prevalence of HA-HvKp among HvKp isolates is 36.0%, with an increase from 25.9 to 47.1%, indicating a shift from community-acquired to hospital-acquired infections. This trend may be driven by ongoing clonal transmission among Kp strains.[37] Healthcare-associated HvKp strains exhibit increased virulence and mortality rates, with higher mortality likely linked to rising antimicrobial resistance.[6,12,27] Resistance to reserved antibiotics is increasing among HA-HvKp strains, with some strains developing resistance to last-resort antibiotics.[38,39] Strict infection prevention and antimicrobial stewardship are essential to prevent clonal transmission and resistance. Vandhana et al. reported that 65.2% of HvKp strains were MDR, despite a low HvKp prevalence.[9] Increased resistance to β-lactam/β-lactamase inhibitors has been observed by Yang et al. and Liu et al.[20,26] In few studies, HvKp strains also show higher production of ESBL and carbapenem resistance compared with cKp.[15,20,37–39,54]

Traditionally, HvKp strains were susceptible to antimicrobial agents, but our study found that 13.8% of HvKp infections were CR-HvKp. A subgroup analysis revealed an increasing trend, with CR-HvKp rising from 9.5 to 16.5% in the last 5 years. Carbapenem resistance development is driven by two main mechanisms in HvKp: hypervirulent strains acquiring carbapenem resistance plasmids or integrating resistant genes into virulent plasmids, and CR-Kp strains obtaining virulent plasmids from hypervirulent strains.[41] Our study also showed that HA-HvKp infections had nearly six times

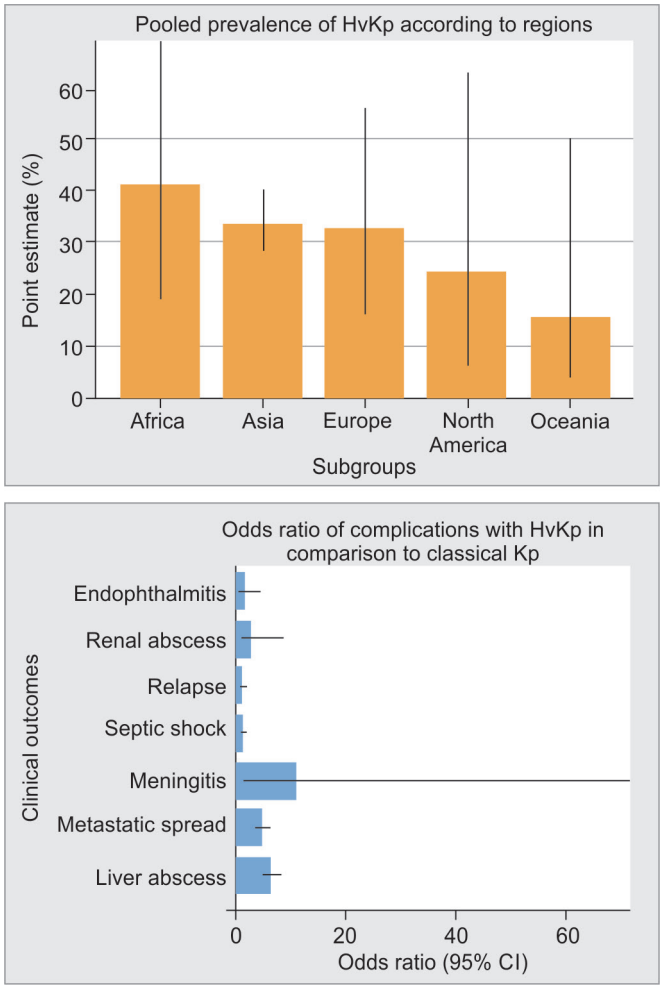

Fig. 5: The prevalence of HvKp according to regions and the various clinical outcomes are depicted
HvKp, hypervirulent *Klebsiella pneumoniae;* Kp, *Klebsiella pneumoniae*

higher odds of carbapenem resistance compared with CA-HvKp, with significantly higher mortality in CR-HvKp infections than in CS-HvKp.

Studies report significant correlations between the MDR and the HM-phenotype.[6,19] This association could be attributed to the presence of MDR genes or the acquisition of plasmid-mediated drug resistance, which may be the underlying reason for this observed correlation. The convergence of MDR/extensively drug-resistant genes with hypervirulent plasmids poses a formidable risk, and this merging of resistant genes with virulent plasmids has the potential to create a superbug. Given HvKp's emerging global dissemination, there is an augmented need for increased prioritization of continued surveillance to monitor the drug-resistant strain of HvKp.

This is the first meta-analysis which comprehensively evaluated the risk factors and clinical outcomes associated with HvKp, including CR-HvKp and HA-HvKp. Additionally, we reported an increasing prevalence of HvKp over the last 5 years. One novel study finding is that HvKp significantly increases the risk of septic shock among patients with Kp infections. Clinicians may assiduously monitor patients with HvKp infection for risk of development of septic shock, and such patients may be admitted in high-dependency monitored areas. The HM-phenotype of Kp significantly increases the risk of HvKp, including the HA-HvKp infection. Therefore, in settings with limited microbiological lab facilities, the string test can be employed to identify the HvKp strain, as knowing the strain is of utmost importance to tailor specific treatment interventions. Another new finding in the study is an increasing trend of CR-HvKp infections among HvKp isolates. There has also been a significantly rising trend of HA-HvKp infections in recent years. The HA-HvKp infection is a significant risk factor for carbapenem resistance and is associated with higher mortality.

This study has several limitations. First, the geographic concentration of prevalence data is a significant concern, as most studies are from Asian countries, particularly China. This limits the generalizability of the findings to other regions and only encompasses some countries necessary for a comprehensive assessment of HvKp prevalence among Kp infections. Additionally, the analysis was restricted to studies that compared HvKp and cKp patients and reported relevant risk factors or clinical outcomes. A further limitation is the need for more information on infection control measures implemented in the studied settings, which could impact the findings. The review was confined to articles published in English, and there were no restrictions regarding the cause of death (whether infection-attributed or not) or the time frame between diagnosis and death. Furthermore, the determination and

analysis of risk factors and clinical outcomes for CR-HvKp, CS-HvKp, HA-HvKp, and CA-HvKp, were limited to only two original studies.

The findings of our SRMA regarding types of HvKp itself have certain clinical significance. The HA-HvKp and HvKp in immunosuppressed individuals is more likely to be a carbapenem resistant strain as compared with CA-HvKp. The CR-HvKp exhibits a significantly higher mortality risk as compared with the CS-HvKp. Thus, clinicians should be aware of the possible poor outcomes in CR-HvKp and consider aggressive antimicrobial therapy. Second, as compared with HA-HvKp, the CA-HvKp has higher propensity to cause liver abscesses, and therefore such patients should be screened for possible occult hepatic abscesses.

Future studies should prioritize the development of a reliable clinical biomarker for accurately detecting HvKp strain, given the absence of a specific single gene for this purpose. Research should focus on exploring potential treatment regimens through interventional studies on patients with HvKp infections to reduce the risk of metastatic spread and septic shock. Additionally, post-hospital discharge follow-up studies need to analyze relapse patterns and associated genes, emphasizing the importance of research on familial transmission and effective preventive measures. Studies are crucial to uncover the association between specific genes of HvKp and the risk of clinical complications like septic shock, meningitis, liver abscess, and antimicrobial resistance in nosocomial HvKp strain, leading to the formulation of specific guidelines to mitigate the transmission and resistance of this virulent pathogen. Given the limited number of case-control studies, it is recommended that future research address this gap to enhance our understanding of HvKp infections. Future studies should focus on specific clinical outcomes based on HA-HvKp vs CA-HvKp, along with their antimicrobial resistance patterns.

Conclusion

This meta-analysis shows that a community-acquired Kp infection, presence of DM, and a positive string test are the risk factors for HvKp among Kp infections. Though HvKp infections are not associated with a higher mortality rate as compared with cKp, HvKp infections are associated with severe complications, including septic shock, liver abscesses, meningitis, and metastatic spread of infection. Rising HA-HvKp and CR-HvKp prevalence trends reflect the pathogen's adaptability and growing resistance, necessitating early detection and robust infection control measures. Future research should focus on developing reliable biomarkers, targeted therapeutic strategies, and understanding nosocomial transmission dynamics to mitigate HvKp-related morbidity and mortality.

Clinical Significance

This meta-analysis reveals critical information for clinicians managing Kp infections. The emergence of hypervirulent strains (HvKp), now prevalent in 33% of cases, poses unique challenges due to its association with severe complications such as liver abscesses, metastatic infections, meningitis, and septic shock. Rising carbapenem-resistant (CR-HvKp) and HA-HvKp infections highlight the need for heightened vigilance in healthcare settings. Key risk factors like DM and HM phenotype can aid in early identification. Clinicians are urged to implement prompt diagnostic strategies, optimize infection control measures, and tailor therapies to address this pathogen's growing virulence and resistance.

Author Contributions

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Supplementary Materials

All the supplementary materials are available on the website www.ijccm.com

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