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SYSTEMATIC REVIEW

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Systematic review and meta-analysis of colistin heteroresistance in *Klebsiella pneumoniae* isolates

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Abstract

Background Antibiotic heteroresistance is a common phenotype observed in a variety of pathogenic bacteria such as *K. pneumonia*: A subpopulation of cells with a higher MIC than the dominant population is defined as heteroresistance. Several studies have demonstrated colistin heteroresistance in *K. pneumonia* leading to treatment failures. Therefore, we performed a systematic meta-analysis to summarize the current evidence on the prevalence of colistin heteroresistance in *K. pneumonia* isolates.

Methods Multiple databases were searched to find relevant literature from 2008 to 2024, including PubMed, Scopus, Embase, and Web of Science.

Results The meta-analysis included eighteen articles. According to the random effects model, the pooled proportion of heteroresistant *K. pneumoniae* was 0.315 (95% CI: 0.179–0.492). The heterogeneity was substantial, with Q [17] = 335.020, $I^2 = 94.93\%$, and $p < 0.001$, suggesting that heteroresistance rates varied widely across the 18 included studies.

Conclusion In conclusion, our findings revealed that a prevalence of colistin heteroresistant detected in approximately 31.5%, of *K. pneumonia*. These findings are obtained and highlighted in this *meta-analysis* as a new guidance document for diagnosing and treating *K. pneumonia* infections is needed to raise the awareness of infectious disease specialists, gastroenterologists, and microbiologists to the heteroresistance to colistin in patients with a *K. pneumonia* infection.

Keywords *K. pneumoniae*, Resistance, Heteroresistance, Meta-analysis, Colistin

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Introduction

Klebsiella pneumonia is a Gram-negative bacterium that, in humans as an opportunistic pathogen, could cause different infections, such as wound and urinary tract infections [1–3]. It is also an important cause of healthcare-associated infections in hospitals, including pneumonia, bacteremia and post-operative meningitis and is a known risk factor for community-acquired infections [2, 3].

One of the most alarming threats to human health is the global increase in antibiotic-resistant bacteria. Eradication of *K. pneumoniae* is difficult as there are strains that produce ESBL and CRKP [4–6]. In addition, *polymyxin E*, also known as colistin, has been used to treat Gram-negative bacterial infections, particularly *K. pneumoniae* [7]. Due to the emergence of MDR microorganisms and the lack of effective antimicrobials, colistin has been reintroduced as a salvage therapy and therefore, remains one of the last options that was used to treat MDR strains [8].

On the other hand, On the other hand, heteroresistance phenomena leading to treatment failure have been reported. In heteroresistance, only a subset of cells within a bacterial population is resistant to an antibiotic. There are several reports of *K. pneumoniae* strains that are heteroresistant to colistin; therefore, heteroresistance to colistin plays an important role in the failure of last-line treatment [6].

The mechanisms behind colistin heteroresistance are not well understood, but a number of publications have shown that this phenomenon can be caused by mutations in the *mgrB* gene or in two-component enzymes, such as PhoPQ, PmrAB or PmrC. Mutations in *phoPQ* and *pmrAB* can lead to high expression of *pmrC* or *pmrE* operons, and the positive charge of LPS can reduce polymyxin affinity [9]. Also, changes in the *mgrB* gene due to deletion or mutation caused by IS1-like, IS3-like, and IS5-like elements are the most critical mechanisms of colistin heteroresistance in *Klebsiella* as the *mgrB* gene negatively regulate the PhoPQ and PmrAB systems. Hence, degrade and inactivate *mgrB* promote colistin resistance [10, 11]. In addition, there are mutations in CrrAB associated with colistin resistance mechanisms in *K. pneumoniae* ST11, ST29, and ST258, and ST280 [12, 13]. Other non-chromosomal mechanisms that may contribute to colistin heteroresistance include capsule overproduction, decreased interactions with bacterial levels, and increased expression of RFD-type efflux pumps [14]. So, colistin heteroresistance in *Klebsiella* specimens in highly resistant clinical strains has been previously described [15–17] as being associated with mortality [15] and mainly with loss of colistin activity.

Therefore, due to a challenging problem with colistin heteroresistance and insufficient information in this regard, this study aims to summarize the data on colistin heteroresistance of *K. pneumonia*.

Materials and methods

This review follows the guidelines of the PRISMA. This study was approved by the Research Ethics Committee of Ilam University of Medical Sciences with the code IR.MEDILAM.REC.1400.185.

Eligibility criteria and search strategy

Studies were considered eligible if they focused on heteroresistant *K. pneumoniae*, clearly reported the proportion of resistant isolates, described the sample size in detail and were published as full-text articles in English. Among other things, non-English publications, case reports, single-arm or cohort studies and pharmacokinetic studies were excluded. A systematic search was conducted in four databases —Scopus, PubMed, Web of Science and EMBASE — up to a specified cut-off date. The search syntax for PubMed was adapted accordingly for the other databases. Duplicates were identified and removed using EndNote (version 20).

Selection criteria and data extraction

Two reviewers performed the data extraction independently. Discrepancies were discussed and decided by consensus. The primary outcome of interest was the prevalence of colistin heteroresistant *K. pneumoniae* isolates. Studies deemed eligible for inclusion based on our study criteria were analyzed as full-text articles. Information extracted from each study included: [1] first author; [2] year of publication; [3] sex and age of patients (mean, range, pediatric vs. adult); [4]; number of isolates; [5] the number of colistin heteroresistance; and [6] heteroresistance rates.

Heteroresistance data were excluded if: [1] no heteroresistance was detected; [2] no heteroresistance results were reported; and [3] data were from meta-analyzes and/or systematic reviews, non-original research, or conference abstracts.

Study risk of bias assessment

The JBI tool was employed to assess the methodological quality of each study. This quality evaluation was performed independently by two authors, and any discrepancies in scoring were resolved by a third reviewer. Studies were categorized as low quality, some concern, or high quality based on the agreed-upon JBI criteria.

Statistical analysis and synthesis

A random-effects meta-analysis was performed using the DerSimonian–Laird estimator to calculate the pooled proportion of heteroresistance [18]. Heterogeneity was assessed using the Q-test and the I^2 statistic. Whenever

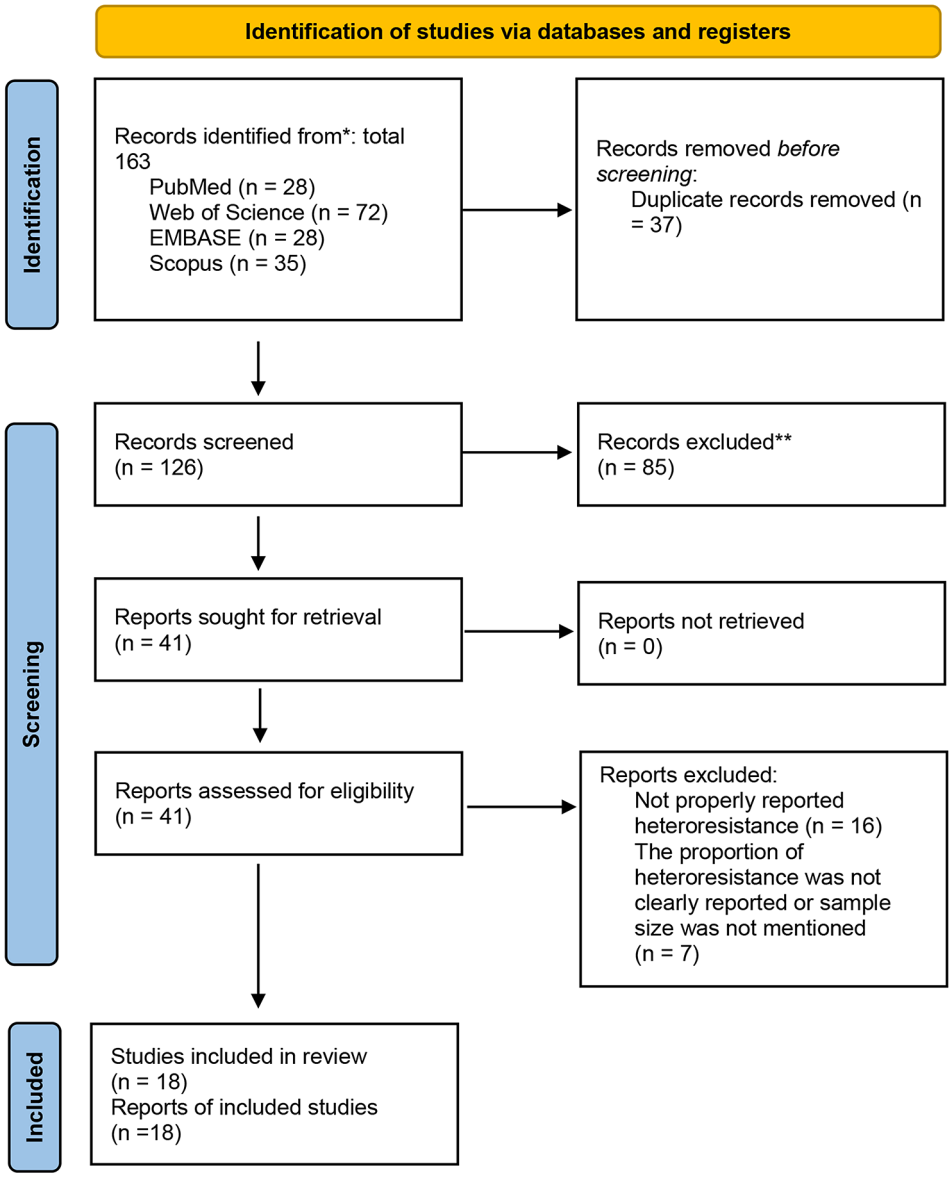

Fig. 1 The study Prisma flow diagram

the variance component (τ^2) was greater than zero, meta-regression was performed to investigate whether publication year, among other potential moderators, influenced heteroresistance rates. Outlier and influence diagnostics were performed using studentized residuals and Cook's distances, respectively. Publication bias was examined by visualizing funnel plots and tested using Begg–Mazumdar and Egger's procedures [19, 20].

All analyzes were performed in R (version 4.2.1) using the metafor package (version 3.8.1).

Results

Descriptive statistics

One hundred sixty-three records as results of the systematic search were collected in reference manager software (EndNote version 20) and 37 duplicated articles were removed. One hundred twenty-six articles were assessed in the title abstract for the section; 18 full-text articles were evaluated. Sixteen articles were excluded for the following reasons; non-relevant data, not mentioning colistin heteroresistance *K. pneumoniae* prevalence [1, 2, 7, 15, 17, 21–24]. Eventually, 18 studies satisfied all inclusion criteria and were retained for meta-analysis. Figure 1 (PRISMA flow chart) outlines the screening and selection process.

These studies originated from 12 countries, spanning five continents, and covered the publication years from 2008 to 2024. Table 1 presents a summary of the included studies, detailing the total sample size, number

Table 1 Characteristics of included studies

Author	Year	Year group	Countries	Continents	Resistance profile	Quality group	Total	*hKP
Aurelie Jayol et al.	2015	2008_2022	South Africa	Africa	MDR	Low quality	1	1
Toyotaka Sato et al.	2020	2008_2022	Japan	Asia	CRKp	Low quality	3	1
Weng, Yue. et al.	2023	2023_2024	China	Asia	CRKp	Low quality	455	28
Wang, Ta. et al.	2023	2023_2024	China	Asia	CRKp	Low quality	9	2
Meheissen, M. A. et al.	2022	2023_2024	Egypt	Africa	CSKp	Low quality	30	7
Teysir Halaby et al.	2016	2008_2022	Netherlands	Europe	ESBL	Some concern	13	5
Wang, Yi et al.	2022	2023_2024	China	Asia	CRKp	Some concern	96	69
Lucie Bardet et al.	2017	2008_2022	France	Europe	CRKp	Some concern	6	2
Wang Xiaoli et al.	2024	2023_2024	China	Asia	CRKp	Some concern	109	76
Sanchez-Leon, I. et al.	2023	2023_2024	Spain	Europe	CRKp	Some concern	9	9
Rajakani, S. G. et al.	2023	2023_2024	Belgium	Europe	MDR	Some concern	16	3
Foldes, An. et al.	2022	2023_2024	Romania	Europe	CRKp	Some concern	14	4
Anima Poudyal et al.	2008	2008_2022	Australia	Oceania	MDR	High quality	21	15
Felipe Morales-Leon et al.	2020	2008_2022	Chile	Americas	ESBL	High quality	60	8
Jessie E. Wozniak et al.	2019	2008_2022	United States	Americas	CRKp	High quality	265	1
Victor I. Band et al.	2018	2008_2022	United States	Americas	CRKp	High quality	2	2
Braspenning, Ajmm et al.	2024	2023_2024	Belgium	Europe	MDR	High quality	288	108
Victor I. Band et al.	2021	2008_2022	United States	Americas	CRKp	High quality	286	24

*hK.P: Heteroresistant *K. pneumoniae*

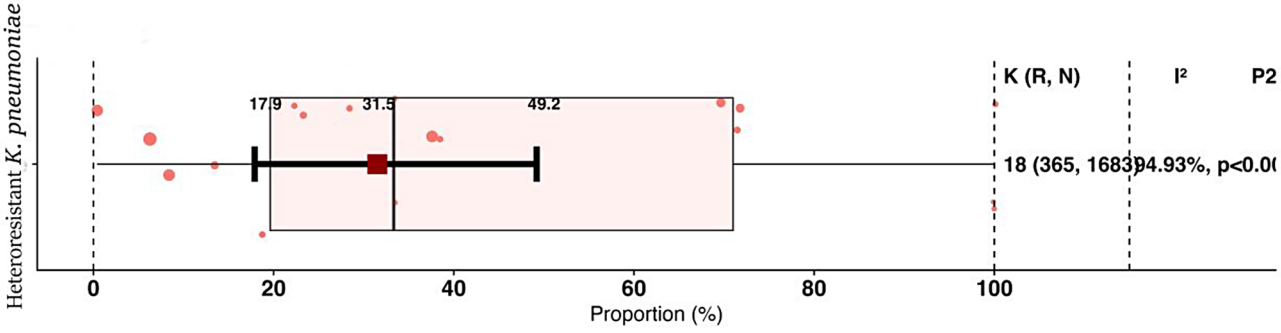

Fig. 2 Forest plot of pooled heteroresistance proportions. Displays individual study estimates, pooled proportion (red squares), and 95% confidence intervals

of heteroresistant isolates, country, continent, resistance profiles, and quality assessment [1, 7, 17, 21, 24–38].

Presents authors, publication year, geographic data, total isolates, number of heteroresistant isolates, and quality ratings.

Overall pooled proportion of heteroresistant *K. pneumoniae*

Data on 1683 total isolates and 365 heteroresistant isolates were included. Under the random-effects model, the pooled proportion of heteroresistant *K. pneumoniae* was 0.315 (95% CI: 0.179–0.492), a finding that was significantly different from zero (z = – 2.043, $p = 0.041$). Heterogeneity was considerable, with Q [17] = 335.020, I^2 = 94.93%, and $p < 0.001$, indicating that heteroresistance rates varied extensively across the 18 included studies. Figure 2 shows the forest plot of individual study proportions and the pooled estimate.

After applying the trim-and-fill method, the adjusted pooled estimate was 0.256 (95% CI: 0.143–0.413), suggesting the potential impact of publication bias was modest. However, neither the Begg–Mazumdar nor the Egger test indicated statistically significant funnel plot asymmetry, as shown in Fig. 3.

Subgroup analyses

To investigate sources of heterogeneity, subgroup analyses were carried out by year group, country, continent, resistance profile, and quality assessment, as summarized in Fig. 4 and detailed in table 2. When studies were stratified by year group (2008–2022 vs. 2023–2024), the estimated proportions showed a slight increase over time, although this difference was not statistically significant ($p = 0.459$). Analysis by country revealed substantial variability, with some nations (e.g., Spain and Australia) reporting higher prevalence estimates,

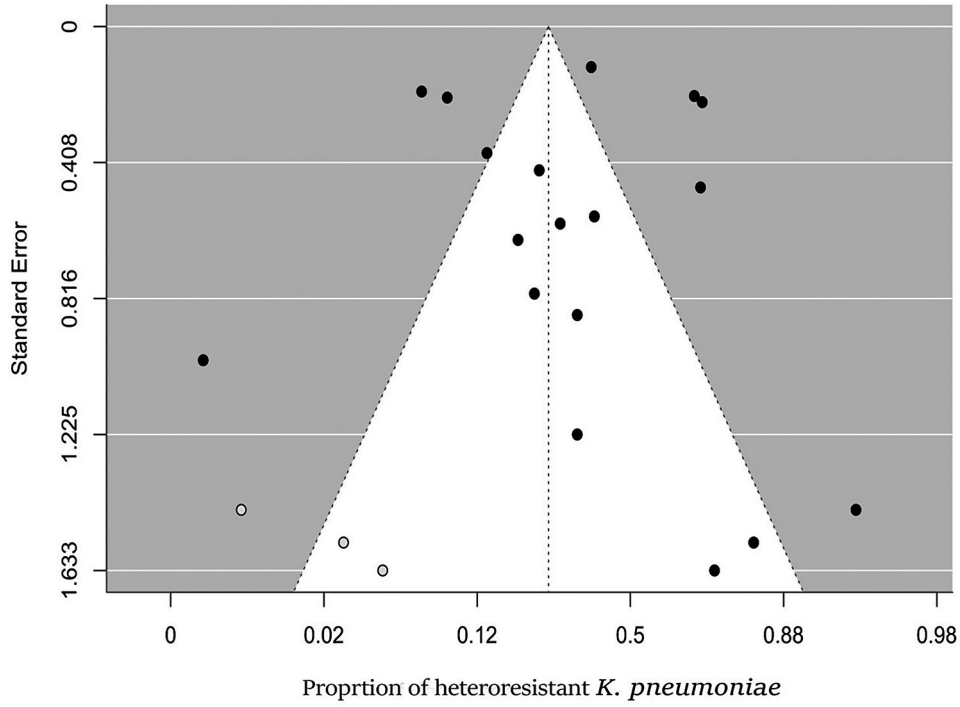

Fig. 3 Funnel plot for publication bias. Shows no significant asymmetry, based on Begg–Mazumdar and Egger tests

whereas others (e.g., Chile and the United States) exhibited lower estimates.

The variability extended to continental groupings, where Oceania showed the highest pooled rate and the Americas showed the lowest. Examination by resistance profile (MDR, CRKp, CSKp, and ESBL) confirmed that heteroresistance was not confined to carbapenem-resistant isolates alone, but it was also observed in other resistance phenotypes, albeit with varying degrees of prevalence and heterogeneity. Additionally, classification by study quality (low, some concern, high) indicated that higher methodological quality did not necessarily correspond to lower or higher heteroresistance rates, underscoring the complexity and multifactorial nature of the condition.

Meta-regression analysis

A meta-regression was performed to detect potential trends over the examined years, illustrated in Fig. 5. Although the point estimate for heteroresistance appeared somewhat higher in studies published more recently, this trend was not statistically significant, implying that other factors—such as the clinical setting, patient population, and testing methodologies—may be equally or more influential in determining heteroresistance rates. And also, the global prevalence of heteroresistance *K. pneumoniae* summarized in Fig. 6.

Discussion

Klebsiella pneumoniae causes a variety of infections, but due to the production of ESBL and CRKP, treatments for *K. pneumonia* infections are complex. Therefore, colistin has proven to be a satisfactory agent for the treatment of most infections [1, 2]. Recently, many researchers have pointed out that clinically undetected heteroresistance could significantly compromise treatment efficacy. Therefore, polymyxin heteroresistance threatens the clinical use of polymyxins. Colistin heteroresistance (defined as "the emergence of colistin resistance in a subpopulation from an otherwise sensitive (MIC of 2 mg/liter) population", possibly related to a suboptimal polymyxin concentration) is an emerging problem as it can lead to treatment failure [3]. Therefore, we investigated this review and meta-analysis in *K. pneumonia*.

This meta-analysis, which includes 18 studies and a total of 1683 isolates, provides a comprehensive estimate of heteroresistant *K. pneumoniae* worldwide.

The pooled prevalence of approximately 31.5% is remarkably high and indicates that heteroresistance is both widespread and clinically relevant. The considerable heterogeneity observed between studies highlights how geographical differences, differences in study design and different protocols for susceptibility testing may influence the reported estimates. Subgroup and meta-regression analyzes indicate that neither time period nor

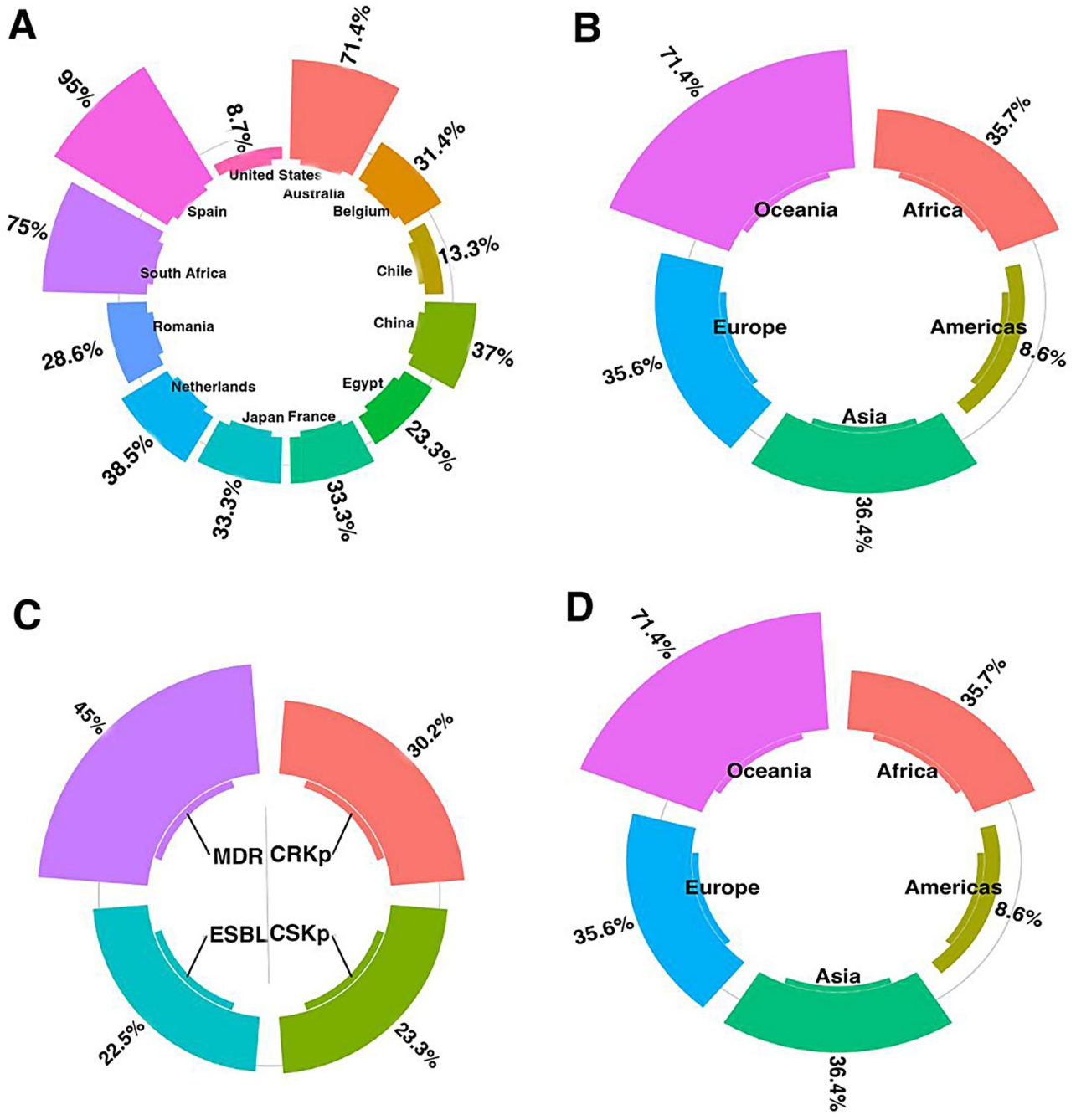

Fig. 4 Subgroup analysis results. This figure presents comparisons between subgroups based on geographic location (**A** and **B**), resistance profile (**C**), and quality group (**D**)

study quality alone fully explain the observed differences, suggesting a multifaceted interplay of factors. These findings underscore the need for standardized definitions of heteroresistance, consistent laboratory protocols, and transparent reporting of study methods to enable more accurate cross-comparisons. Improved surveillance measures, combined with molecular and epidemiologic investigations, will further elucidate the mechanisms and clinical outcomes associated with heteroresistant *K. pneumoniae*. Such efforts could enable targeted therapeutic strategies and antibiotic stewardship programs to curb the increasing burden of resistant infections.

Table 2 Summary of meta-analysis and subgroup results

Category	Subgroup	K (*n*, *N*)	Proportion 95%CI(LCI, HCI)	I^2	P1	P2	P3
Overall	NA	18 (365, 1683)	0.315 (0.179, 0.492)	94.93%	$p=0.041$	$p<0.001$	NA
Year group	2008_2022	9 (59, 657)	0.255 (0.097, 0.521)	88.43%	$p=0.069$	$p<0.001$	$p=0.459$
	2023_2024	9 (306, 1026)	0.373 (0.180, 0.616)	96.41%	$p=0.305$	$p<0.001$	
Countries	South Africa	1 (1, 1)	0.750 (0.109, 0.987)	0.00%	$p=0.501$	$p>0.999$	$p=0.910$
	Japan	1 (1, 3)	0.333 (0.043, 0.846)	0.00%	$p=0.571$	$p>0.999$	
	China	4 (175, 669)	0.370 (0.067, 0.827)	98.58%	$p=0.620$	$p<0.001$	
	Egypt	1 (7, 30)	0.233 (0.116, 0.415)	0.00%	$p=0.006$	$p>0.999$	
	Netherlands	1 (5, 13)	0.385 (0.170, 0.656)	0.00%	$p=0.410$	$p>0.999$	
	France	1 (2, 6)	0.333 (0.084, 0.732)	0.00%	$p=0.423$	$p>0.999$	
	Spain	1 (9, 9)	0.950 (0.525, 0.997)	0.00%	$p=0.042$	$p>0.999$	
	Belgium	2 (111, 304)	0.314 (0.164, 0.516)	53.44%	$p=0.069$	$p=0.143$	
	Romania	1 (4, 14)	0.286 (0.111, 0.561)	0.00%	$p=0.121$	$p>0.999$	
	Australia	1 (15, 21)	0.714 (0.492, 0.866)	0.00%	$p=0.058$	$p>0.999$	
	Chile	1 (8, 60)	0.133 (0.068, 0.245)	0.00%	$p<0.001$	$p>0.999$	
	United States	3 (27, 553)	0.087 (0.005, 0.628)	88.01%	$p=0.109$	$p<0.001$	
Continents	Africa	2 (8, 31)	0.357 (0.072, 0.800)	45.51%	$p=0.560$	$p=0.176$	$p=0.405$
	Asia	5 (176, 672)	0.364 (0.079, 0.793)	98.11%	$p=0.565$	$p<0.001$	
	Europe	6 (131, 346)	0.356 (0.240, 0.492)	40.23%	$p=0.039$	$p=0.137$	
	Oceania	1 (15, 21)	0.714 (0.492, 0.866)	0.00%	$p=0.058$	$p>0.999$	
	Americas	4 (35, 613)	0.086 (0.025, 0.257)	83.78%	$p<0.001$	$p<0.001$	
Resistance profile	MDR	4 (127, 326)	0.450 (0.231, 0.689)	74.29%	$p=0.693$	$p=0.009$	$p=0.888$
	CRKp	11 (218, 1254)	0.302 (0.111, 0.600)	96.69%	$p=0.186$	$p<0.001$	
	CSKp	1 (7, 30)	0.233 (0.116, 0.415)	0.00%	$p=0.006$	$p>0.999$	
	ESBL	2 (13, 73)	0.225 (0.069, 0.533)	76.12%	$p=0.077$	$p=0.041$	
Quality group	Low quality	5 (39, 498)	0.200 (0.072, 0.447)	79.02%	$p=0.021$	$p<0.001$	$p=0.102$
	Some concern	7 (168, 263)	0.512 (0.332, 0.689)	79.16%	$p=0.900$	$p<0.001$	
	High quality	6 (158, 922)	0.202 (0.070, 0.462)	95.16%	$p=0.027$	$p<0.001$	

Provides overall and subgroup-specific proportions, 95% CIs, and heterogeneity metrics (I^2 and p-values)

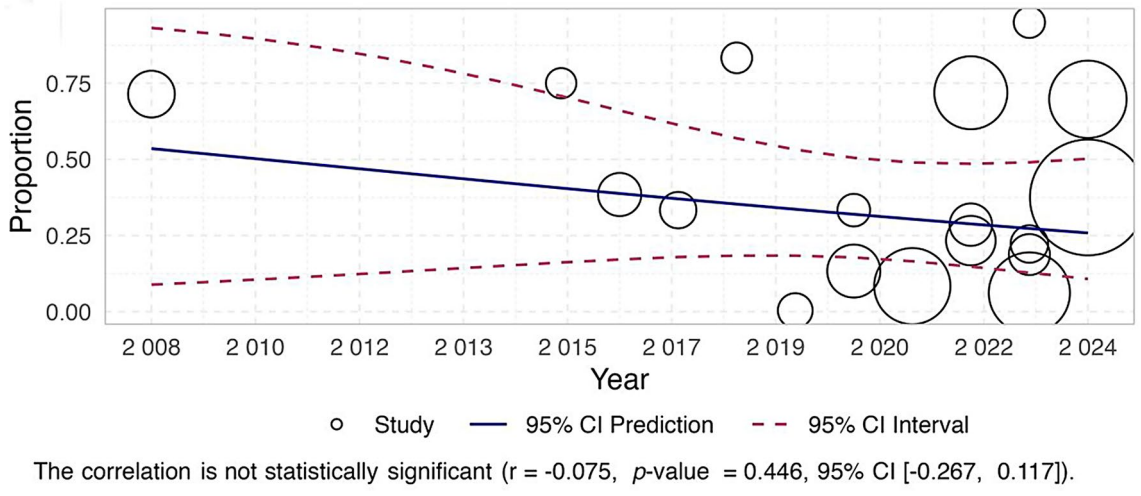

Fig. 5 Meta-regression scatter plot. This scatter plot illustrates the relationship between publication year and heteroresistance rates. No significant temporal trend was observed

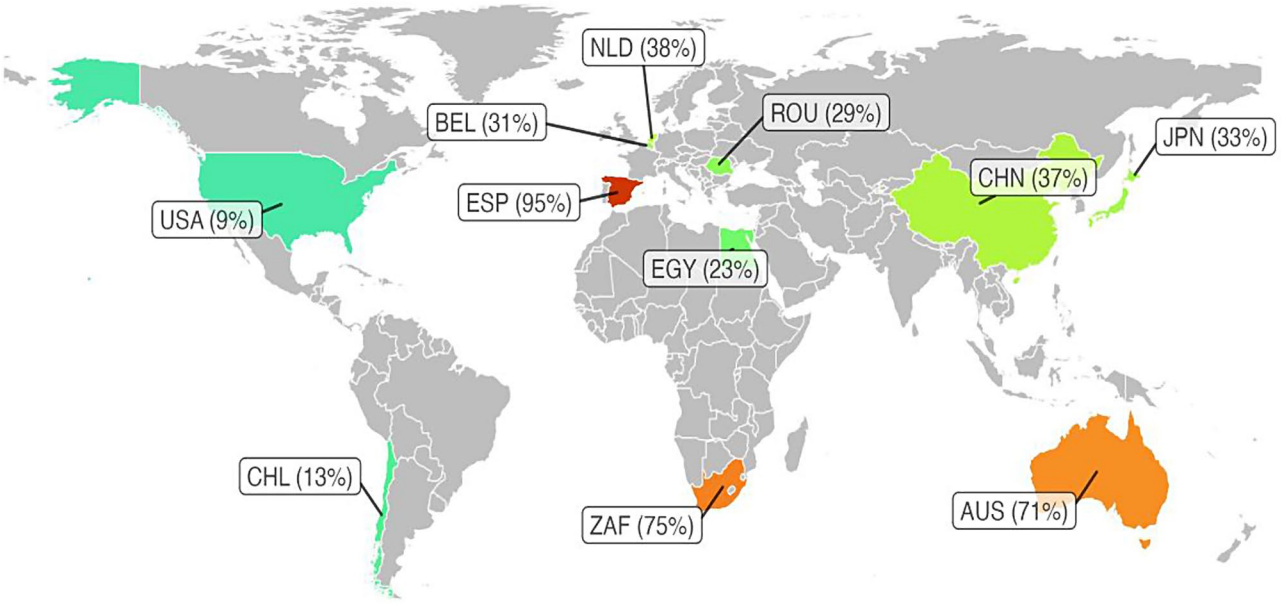

Fig. 6 Global map of prevalence in heteroresistance *K. pneumoniae*

Conclusion

In conclusion, the pooled prevalence of heteroresistant *K. pneumoniae* isolates stands at roughly 31.5%, with extensive heterogeneity across settings and study designs. Future research should emphasize standardized susceptibility testing, robust epidemiologic data collection, and harmonized reporting standards to better understand and address the emerging challenge of heteroresistant *K. pneumoniae*.

Abbreviations

K. pneumonia	Klebsiella pneumonia
MIC	Minimum Inhibitory Concentration
ESBL	Extended-Spectrum-β-Lactamases
CRKP	Carbapenem-Resistant K. pneumoniae
CSKP	Carbapenem-Susceptible K. pneumoniae
MDR	Multidrug-Resistant
RFD-type	Reverse Flow Diverter-type
ST	Sequence Type
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines
JBI	Joanna Briggs Institute

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Author contributions

(A) Hassan Valadbeigi, (B) Saeed Khoshnood, (C) Mohammad Hossein Haddadi, (D) Nourkhoda Sadeghifard, (E) Abbas Maleki, (F) Ebrahim Kouhsari. A, B: Search strategy and study selection, Data Extraction, data collection, and reading the abstract of articles. A, C, D: Read the full articles and wrote the main manuscript text and revise the grammatical language. B, E: Statistical analysis and prepared figures and tables. A to F: Wrote and reviewed the manuscript. All authors reviewed the manuscript.

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Data availability

All data generated or analyzed during this study are included here and are available from the corresponding author on editor request.

Declarations

Ethical approval

This project was approved by the Ilam University of Medical Sciences Ethics Committee(IR.MEDILAM.REC.1400.185).

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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