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Carbapenemase- and ESBL-producing Carbapenem-resistant *Klebsiella pneumoniae* in Thailand: A Systematic Review and Meta-analysis

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Abbreviations: AST: Antimicrobial susceptibility testing, MIC: Minimum inhibitory concentration, CLSI: Clinical and Laboratory Standards Institute, CRKP: carbapenem-resistant *Klebsiella pneumoniae,* EUCAST: European Committee on Antimicrobial Susceptibility Testing, ESBL: Extended-spectrum β-lactamase, WGS: Whole-genome sequencing, PCR: Polymerase chain reaction.

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Abstract

***Klebsiella pneumoniae* is one of the major pathogens associated with multidrug resistance. This study aims to estimate the prevalence and characterize the molecular epidemiology of carbapenem-resistant *K. pneumoniae* in Thailand. We conducted a comprehensive search of PubMed, Embase, Scopus, ScienceDirect, and a Thai Journals Online (ThaiJO) from inception to November 19, 2024. Subgroup, meta-regression, and heterogeneity analyses were conducted. Publication bias was assessed using funnel plots and Egger's test. The pooled prevalence estimates reflect proportions reported in published hospital-based studies. A total of 32 studies were included in the systematic review, with 27 studies included in the meta-analysis. The pooled proportion of carbapenem-resistant *K. pneumoniae* isolates was 87% (95% CI: 81%, 91%), with increasing trends observed for imipenem and meropenem resistance between 2014 and 2024. Ertapenem resistance remained high across regions, peaking in 2020 (100%) and 2024 (86%), particularly in the North and Northeast. The most prevalent carbapenemase gene was bla_{NDM} (50%). Among the ESBL-associated genes, the pooled prevalence estimate was highest for bla_{CTX-M} (86%). Co-harboring of bla_{NDM} and $bla_{OXA-48-like}$ was observed in 36% of the isolates. Co-harboring of ESBL genes was detected in 25% of isolates. Subgroup and meta-regression analyses confirmed significant heterogeneity across regions and years. This meta-analysis highlights a high and growing burden of carbapenem-resistant *K. pneumoniae* in Thailand, marked by notable geographic variation and a predominance of bla_{NDM} and ESBL genes. While the findings are indicative of important trends, the observed heterogeneity suggests that the results should be interpreted with caution.**

Keywords: *Klebsiella pneumoniae*, Carbapenem Resistance, Molecular Epidemiology, Carbapenemase, ESBL, Thailand

INTRODUCTION

Klebsiella pneumoniae, a Gram-negative, encapsulated bacterium within the order *Enterobacterales*, is frequently implicated in healthcare-associated infections such as pneumonia, urinary tract infections, bloodstream infections, and intra-abdominal infections.[1] Its clinical significance has escalated in recent years due to the increasing emergence of multidrug-resistant (MDR) strains, particularly those resistant to carbapenems—antibiotics often reserved as a last-resort treatment against extended-spectrum β-lactamase (ESBL)-producing organisms.[2,3] In response to this rising threat, the World Health Organization has designated carbapenem-resistant *K. pneumoniae* (CRKP) as a critical priority pathogen, and the U.S. Centers for Disease Control and Prevention lists it as an urgent threat due to its limited therapeutic options and high morbidity and mortality.[4,5] These associations between CRKP and elevated mortality rates, prolonged hospitalization, and constrained treatment options have made this pathogen a global public health concern.[6] The health burden created by CRKP is increasing globally, with reported prevalence rates ranging from 20%-40% in many hospital settings, including those in the Americas, Europe, and Southeast Asia.[7,8] In low- and middle-income countries, including those in Southeast Asia, the situation is further exacerbated by weaker infection control systems, unregulated antibiotic use, and limited surveillance infrastructure.[9] The mortality rates associated with CRKP infections vary by infection type and setting, with estimates ranging from 23%-75% overall.[10,11] Notably, pneumonia-related CRKP infections have been associated with mortality rates approaching 50%.[6]

Carbapenem resistance in *K. pneumoniae* is primarily mediated through the production of carbapenemases—enzymes capable of hydrolyzing carbapenems and other β-lactams. These enzymes are typically encoded on mobile genetic elements, such as plasmids, integrons, and transposons, which facilitate horizontal transmission between strains and species.[6,12] According to the Ambler classification, the major class A carbapenemase in *K. pneumoniae* is *K. pneumoniae* carbapenemase (KPC, encoded by bla_{KPC}). Class B carbapenemases identified in *K. pneumoniae* include New Delhi metallo-β-lactamase (NDM; encoded by bla_{NDM}), imipenemase (IMP; encoded by bla_{IMP}), and

Verona integron-encoded metallo-β-lactamase (VIM; encoded by bla_{VIM}). In contrast, class D carbapenemases are predominantly mediated by OXA-48-like enzymes, encoded by bla_{OXA-48}, $bla_{OXA-181}$, and $bla_{OXA-232}$ genes.[2,12] Increased resistance has been associated with the co-occurrence of multiple carbapenemase genes, such as bla_{NDM} with bla_{OXA-48}.[13] Non-carbapenemase-producing carbapenem-resistant *K. pneumoniae* strains have also been reported, with resistance mediated by a combination of ESBL (encoded by bla_{CTX-M}, bla_{TEM}, and bla_{SHV}) or AmpC (encoded by bla_{DHA}) production, porin loss/decreased expression, and efflux pump upregulation.[14]

The emergence of carbapenem-resistant *K. pneumoniae* in Thailand and other Southeast Asian countries is of particular concern.[15-17] The contributing factors include high antibiotic consumption, gaps in infection prevention practices, and inconsistent surveillance data.[18] Although multiple hospital-based studies have reported CRKP emergence,[4,10] comprehensive national data regarding the prevalence and molecular resistance patterns remain fragmented and inconsistent. Therefore, the aim of this systematic review and meta-analysis is to address this knowledge gap by exploring the prevalence of carbapenem resistance and characterizing the associated resistance genes among *K. pneumoniae* clinical isolates found in Thai hospital settings. Moreover, the distribution of resistant gene among different regions will be addressed. The findings of this study are expected to inform national antimicrobial stewardship programs, guide infection control policies, and provide a clear epidemiological understanding of CRKP within the Thai healthcare system.

MATERIALS AND METHODS

The protocol of this systematic review is registered with PROSPERO (CRD42024602884). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] A comprehensive search was conducted across the PubMed, Embase, Scopus, and ScienceDirect databases using various keyword combinations related to *K. pneumoniae* and antimicrobial resistance. In addition, the Thai database, Thai Journals Online (ThaiJO), was searched to identify studies reporting the prevalence of *K. pneumoniae* in Thai hospitals. The search strategy included the following terms: (carbapenem resistan* OR meropenem resistan* OR imipenem resistan* OR ertapenem resistan* OR doripenem resistan* OR carbapenem non-susceptible OR carbapenemase producer) AND (Klebsiella pneumoniae OR *K. pneumoniae* OR multidrug-resistant Klebsiella pneumoniae OR CRE OR Enterobacteriaceae OR Gram-negative bacteria) AND (Carriage OR gene OR resistan* gene) AND (Thailand) (Table S1). Articles published up to November 19, 2024, were included, with no restriction on the earliest publication date. EndNote X9.0 software was used to manage citations and remove duplicates. Title and abstract screenings were carried out independently by two reviewers according to predefined inclusion and exclusion criteria. Subsequently, two other investigators conducted a full-text assessment. Any disagreements in the study selection process were resolved by a third reviewer.

Inclusion and exclusion criteria

Studies were eligible if they reported the prevalence of *K. pneumoniae* in clinical isolates or presented antibiotic resistance data specific to this organism and were published in English or Thai. Only studies involving clinical samples from patients were considered; those analyzing environmental isolates were excluded. Conference abstracts and proceedings were not included due to insufficient detail for quality evaluation. Dissertations and theses were also excluded. Duplicate publications were removed. Non-original articles, such as reviews, systematic reviews, meta-analyses, case reports, brief communications, editorials, letters, and commentaries, were not eligible. Studies lacking full-text access were excluded. Articles that included bacterial species other than *K. pneumoniae* or reported data from fewer than 10 isolates were also omitted.[20] Research presenting antibiotic resistance solely as MIC_{90} values or evaluating antibiotic synergism without reporting resistance prevalence were excluded. Studies that grouped *K. pneumoniae* within general categories of Gram-negative bacteria without providing species-specific resistance data were not considered. Lastly, studies testing only pre-identified resistant isolates or

reporting only infection rates without resistance profiles were excluded.

Study selection and data extraction

Full-text articles were independently assessed by two reviewers who extracted all relevant data using a standardized data collection form. The following information was recorded: first author's name, study period, year of publication, sample size, number of resistant *K. pneumoniae* isolates, and geographic location at both provincial and regional (6 regions including Northern, Northeastern, Central, Western, Eastern, and Southern regions) levels in Thailand. Key methodological details were captured, including the type of clinical specimens (e.g., blood, sputum, urine, pus), the antibiotic susceptibility testing (AST) methods used (i.e., agar dilution, broth microdilution, disk diffusion, E-test, MIC test strips, or automated systems like VITEK, Phoenix, or MicroScan), and the reported resistance rates to carbapenems (e.g., ertapenem, imipenem, meropenem, doripenem). Genotypic data were also extracted, including the carbapenemase genes (e.g., bla_{NDM}, bla_{OXA}, bla_{KPC}, bla_{VIM}, bla_{IMP}) and ESBL genes (e.g., bla_{CTX-M}, bla_{TEM}, bla_{SHV}). Information on co-harboring genes and the molecular detection techniques used (e.g., PCR, multiplex PCR, whole genome sequencing) was also included. Disagreements between reviewers during data extraction were resolved through discussion and consensus to ensure data accuracy and consistency.

Quality assessment

The methodological quality of the included studies was independently assessed by two reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for prevalence studies.[21] Each of the nine checklist items was assessed and scored as "Yes" = 1 point, and "No" or "Unclear" = 0 points, resulting in a maximum possible score of 9 per study. Studies achieving a total score of ≥5 were considered to be of high methodological quality. Any discrepancies between reviewers were resolved through discussion to ensure consistency in the quality assessment process.

Meta-analysis

Our meta-analysis was conducted using STATA version 18 (StataCorp, College Station, TX, USA), and a forest plot was generated to visualize the pooled prevalence of carbapenem-resistant *K. pneumoniae* along with the corresponding 95% confidence intervals (CI). To stabilize the variance and reduce the risk of negative proportions in cases of extremely high or low prevalence, the Freeman–Tukey double arcsine transformation was applied prior to pooling estimates. The transformed values were subsequently reverse-transformed to obtain the final pooled prevalence estimates. This transformation method was chosen because it has been recommended for meta-analyses of proportions in the context of antimicrobial resistance data, especially when dealing with extreme prevalence values.[22,23] Heterogeneity across studies was quantified using the I^2 statistic, where values of 0%-25% indicate low, 25%-50% moderate, 50%-75% substantial, and >75% considerable heterogeneity. When I^2 exceeded 50% and was statistically significant ($P < 0.10$) according to the Cochran's Q test, a random-effects model was employed to account for between-study variation. Potential publication bias was evaluated using Egger's regression test, with funnel plots constructed for visual inspection. A P-value of <0.05 in Egger's test was considered indicative of significant publication bias. The map shows the prevalence of major carbapenemase genes in Klebsiella pneumoniae isolates from Thailand, generated using QGIS 3.28.

Meta-regression analysis

A meta-regression analysis was conducted using a significance level of $P < 0.05$ to assess whether covariates (including publication year and sample size) could account for the observed between-study heterogeneity.

Subgroup meta-analysis

Potential sources of heterogeneity and regional or temporal variability were evaluated using a series of subgroup analyses. First, the pooled prevalence of carbapenem-resistant *K. pneumoniae* was stratified by the specific antibiotics ertapenem, imipenem, and meropenem. The studies were also grouped based

on the geographic regions of Thailand (Northern, Northeastern, Central, Western, Eastern, and Southern), in order to identify regional differences in resistance prevalence. A temporal subgroup analysis based on the publication year of each study was also conducted, as it was likely to identify trends in resistance over time. Beyond phenotypic resistance, the subgroup analyses were extended to molecular findings. Specifically, the prevalence of key resistance genes including carbapenemase genes such as bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$ carbapenemase variants including $bla_{OXA\text{-}48}$, $bla_{OXA\text{-}181}$, $bla_{OXA\text{-}232}$, and bla_{IMP}, as well as ESBL genes including $bla_{CTX\text{-}M}$, bla_{TEM} and bla_{SHV} was stratified according to region, as this would likely provide a better understanding of the distribution of genetic determinants of resistance across Thailand. The presence of publication bias within these subgroups was evaluated using Egger's test, followed by visual inspection of the funnel plots. A P-value < 0.05 was considered statistically significant and suggested the presence of publication bias.[24]

RESULTS

Characteristics of the included studies

The prevalence estimates presented below reflect reported proportions of carbapenem resistance among *K. pneumoniae* clinical isolates within published hospital-based studies. A total of 900 studies were initially identified by systematically searching five electronic databases. After 94 duplicates were removed, the remaining 806 articles were screened based on their titles and abstracts. This led to the exclusion of 686 articles. Among the remaining 120 articles, 3 could not be retrieved, leaving 117 for full-text assessment. The references for each included study were also screened, and 3 studies were identified that met our eligibility criteria. Ultimately, 32 studies were included in the systematic review, and 27 studies[25-56] were used for the meta-analysis, as depicted in Figure 1. These studies encompassed data collected between 2004 and 2024 across various provinces of Thailand, with sampling conducted in tertiary care centers, regional hospitals, and university-affiliated institutions. The geographic distribution covered the Northern, Northeastern, Central, Western, Eastern, and Southern regions of Thailand. The analyzed clinical specimens were diverse and included blood, urine, pus, sputum, wound swabs, tracheal aspirates, ascitic fluid, stool, bile, and rectal or throat swabs. Most studies included multiple specimen types, reflecting the wide range of clinical presentations associated with *K. pneumoniae* infections.

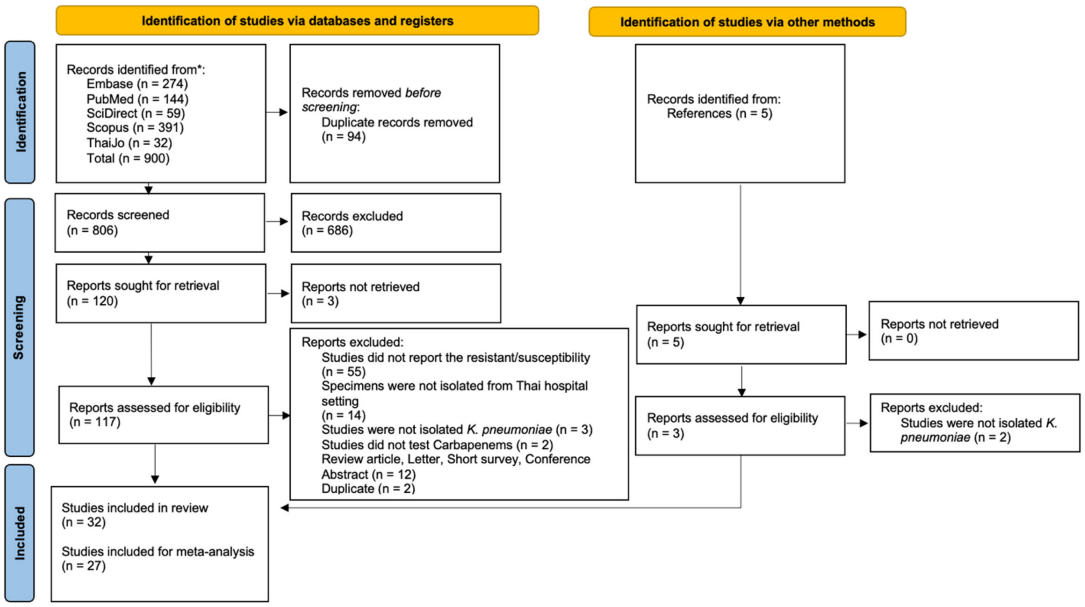

Figure 1. PRISMA 2020 flow diagram of the study selection

Table 1. Prevalence of carbapenem-resistant *K. pneumoniae* stratified by publication year and geographic region in Thailand

Subgroup	No. of studies	Prevalence (%)[95% CI]	P	Heterogeneity test		
				I^2	H^2	P
Year						
2014	1	12 [4, 22]	<0.01	-	-	-
2017	1	60 [52, 67]	<0.01	57.73	2.37	0.09
2018	1	95 [82, 100]	<0.01	77.56	4.46	0.01
2019	1	97 [79, 100]	<0.01	97.82	36.76	<0.01
2020	3	91 [82, 97]	<0.01	91.68	12.02	<0.01
2021	5	88 [80, 95]	<0.01	93.93	16.46	<0.01
2022	3	88 [70, 99]	<0.01	97.55	40.85	<0.01
2023	2	62 [9, 100]	<0.01	97.29	36.96	<0.01
2024	3	97 [91, 100]	<0.01	93.67	15.79	<0.01
Region						
Central	7	85 [74, 94]	<0.01	96.36	27.46	<0.01
Eastern	3	81 [66, 93]	<0.01	96.12	25.75	<0.01
Northeastern	1	95 [81, 100]	<0.01	88.82	8.95	<0.01
Northern	2	96 [92, 99]	<0.01	72.06	3.58	<0.01
Southern	3	74 [42, 97]	<0.01	98.27	57.70	<0.01
Western	-	-	-	-	-	-
Thailand*	4	91 [78, 99]	<0.01	97.62	42.06	<0.01

*Indicates studies did not specify the geographic region or collected the sample from across the country

Antimicrobial susceptibility testing (AST) methods included disk diffusion, broth microdilution (MIC), E-tests, and the use of automated systems such as VITEK 2. The majority of studies evaluated imipenem, meropenem, and ertapenem, while a few also included doripenem. The production of carbapenemase or ESBL was tested using the combination disk method according to the Clinical and Laboratory Standards Institute (CLSI).[25-38] Most studies reported adherence to interpretive criteria from either the CLSI or the European Committee on Antimicrobial Susceptibility Testing (EUCAST); however, two studies did not specify the guideline used. The data are shown in Table S2.

Regarding molecular resistance profiling, the most frequently identified genes were bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, and bla_{IMP}. Notably, bla_{KPC} and bla_{VIM} were reported in fewer instances. Some studies reported only ESBL genes, such as bla_{SHV}, $bla_{CTX\text{-}M}$, and bla_{TEM}, while six studies detected both carbapenemase and ESBL genes. Several isolates harbored multiple resistance genes concurrently, indicating a high degree of multidrug resistance. Quality assessment using the JBI Critical Appraisal Tool[21] showed that all included studies met the minimum threshold of five out of nine, indicating fair to good methodological quality. The detailed characteristics and quality scores of the individual studies are presented in Tables S2 and S3.

Prevalence of carbapenem-resistant *K. pneumoniae* in Thai hospitals

A total of 1,986 clinical isolates of *K. pneumoniae* were tested for carbapenem resistance, revealing a pooled prevalence of 87% (95% CI: 81%, 91%; P < 0.01) (Figure S1). Subgroup analysis showed that in the most recent year, the resistance rate peaked at 97% (95% CI: 91%, 100%; P < 0.01), with heterogeneity (I^2 = 93.67%), comparable to the levels reported in 2019 in Table 1. Regionally, the highest pooled prevalence was observed in the Northern region (96% [95% CI: 92%, 99%; P < 0.01]), followed by the Northeastern region, as detailed in Table 1. Publication bias risk evaluation using Begg's funnel plot analysis revealed a qualitatively symmetrical

plot distribution, indicating a low potential for bias (Figure S2). A leave-one-out sensitivity analysis demonstrated that the pooled prevalence of carbapenem resistance among the included isolates remained stable, with a variation of no more than 3% observed upon the exclusion of any individual study (Figure S3). To obtain a more in-depth understanding of carbapenem resistance, we also analyzed resistance rates based on specific antibiotics. Among the included studies, meropenem was the most frequently tested agent (reported in 19 articles), followed by imipenem (17 articles) and ertapenem (13 articles), allowing for a comprehensive comparison of resistance patterns across agents and time periods.

Among the carbapenem antibiotics, a high prevalence of resistance was observed in the clinical isolates of *K. pneumoniae* in Thailand. Resistance to ertapenem was reported in 1,216 isolates, with a pooled resistance rate of 92% [95% CI: 80%, 99%; P < 0.01], accompanied by considerable heterogeneity (I^2 = 97.23%). Similarly, imipenem resistance, tested in 1,861 isolates, yielded a pooled resistance rate of 82% [95% CI: 71%, 91%; P < 0.01] with high heterogeneity (I^2 = 96.77%). For meropenem, resistance was observed in 1,520 isolates, with a pooled estimate of 87% [95% CI: 78%, 94%; P < 0.01], and heterogeneity was present (I^2 = 95.93%). Overall, these findings highlight the widespread resistance to all three

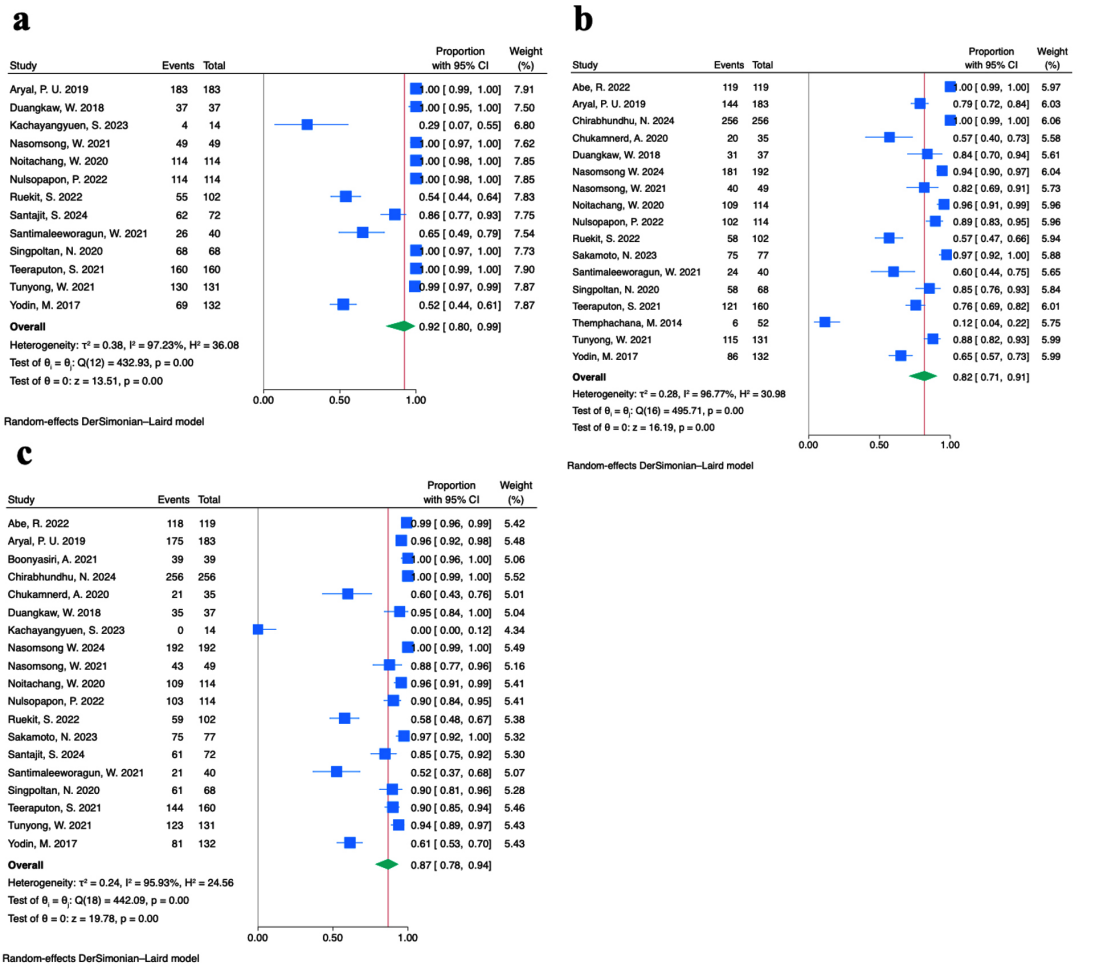

Figure 2. Pooled prevalence of carbapenem resistance in *Klebsiella pneumoniae* clinical isolates from Thailand. The forest plots show the pooled prevalence of resistance among clinical isolates to three specific carbapenems: (a) Ertapenem, (b) Imipenem, and (c) Meropenem

tested carbapenems, indicating that carbapenem resistance poses a major clinical challenge when using this last-line antimicrobial to treat *K. pneumoniae* infections in Thailand (Figure 2).

Prevalence of carbapenem resistance among *K. pneumoniae* stratified by year and region

The pooled prevalence of ertapenem-resistant *K. pneumoniae* isolates in Thailand showed temporal fluctuations. High resistance rates were reported in 2018-2022, with proportions exceeding 95% in most years (2020: 100% [95% CI: 99%, 100%]; 2021: 98% [95% CI: 85%, 100%]; 2022: 96% [95% CI: 12%, 100%]), whereas a substantial drop was observed in 2023 (29% [95% CI: 7%, 55%]). Regionally, the resistance was highest in the Northeastern, Northern, and Southern regions (all 100%), whereas lower estimates were observed in the Central region (88% [95% CI: 49%, 100%]). However, the pooled prevalence was almost the same as in the Eastern region. Studies that did not report specific regions or that collected samples from more than two different regions had resistance rates of 96% [95% CI: 9%, 100%] (Table S4).

In the case of imipenem resistance, the prevalence gradually increased from 2014 (12% [95% CI: 4%, 22%]), reaching nearly complete resistance in 2024 (100% [95% CI: 90%, 100%]). Studies from 2020 to 2022 demonstrated considerable heterogeneity (I^2 > 80%), with high pooled prevalence estimates (2022: 92% [95% CI: 55%, 100%]). Regionally, resistance was highest in the Northern (92% [95% CI: 77%, 100%]) and Central (89% [95% CI: 76%, 100%]) regions, while the Southern region reported a lower rate (48% [95% CI: 3%, 95%]) with significant heterogeneity (I^2 = 97.73%). The studies with unspecified regions showed estimated pools at 92% [95% CI: 74%, 100%] (Table S5).

Meropenem resistance was consistently high across all years, with the pooled prevalence rising from 61% [95% CI: 53%, 70%] in 2017 to 99% [95% CI: 90%, 100%] in 2024. However, in 2023, a

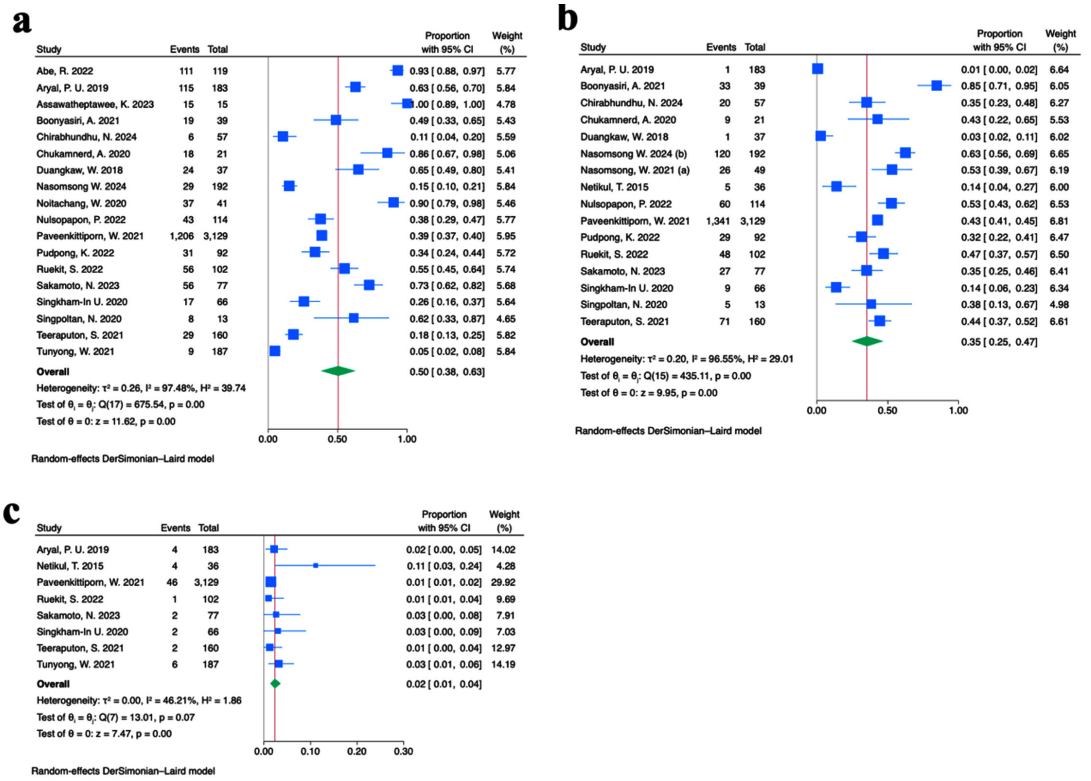

Figure 3. Pooled prevalence of carbapenemase genes in *Klebsiella pneumoniae* clinical isolates from Thailand. The forest plots show the pooled prevalence of three carbapenemase genes: (a) bla_{NDM}, (b) $bla_{OXA\text{-}48\text{-}like}$, and (c) bla_{IMP}

notable decline was observed (46% [95% CI: 0%, 100%]). Subgroup analysis by region demonstrated high resistance in the Northern region (95% [95% CI: 91%, 98%]) followed by the Northeastern and Southern regions. The studies that did not report a specific region or collected samples from more than one region showed high resistance, with pooled estimates of 95% [95% CI: 72%, 100%, I^2 = 97.87%] (Table S6).

The meta-regression results demonstrated a statistically significant association between publication year and resistance rate for imipenem (P = 0.03), suggesting a temporal influence on resistance trends. However, no significant association was observed for carbapenem overall (P = 0.09) or for ertapenem (P = 0.77) or meropenem (P = 0.89) (Figure S4).

Prevalence of carbapenemase among *K. pneumoniae* isolated from Thai hospitals

Among the included studies, the bla_{NDM} gene was the most frequently reported carbapenemase, detected in 18 studies with a combined total of 4,644 clinical *K. pneumoniae* isolates. The pooled prevalence of bla_{NDM} was 50% [95% CI: 38%, 63%], and heterogeneity was observed (I^2 = 97.48%). The $bla_{OXA\text{-}48\text{-}like}$ gene including $bla_{OXA\text{-}48}$, $bla_{OXA\text{-}181}$, $bla_{OXA\text{-}232}$ gene was identified in 16 studies comprising 4,367 isolates, yielding a pooled prevalence of 35% [95% CI: 25%, 47%] with heterogeneity (I^2 = 96.55%). In contrast, the bla_{IMP} gene was reported in 8 studies involving 3,940 isolates, with a significantly lower pooled prevalence of 2% [95% CI: 1%, 4%] and with moderate heterogeneity (I^2 = 46.21%) (Figure 3). The prevalence of carbapenemase genes across different regions is shown in Figure 4. These results indicate that bla_{NDM} is the dominant carbapenemase gene among the resistant *K. pneumoniae* clinical isolates in Thailand.

Geographic distribution of carbapenemase genes in clinical *K. pneumoniae* isolates in Thailand

A regional subgroup analysis of carbapenemase genes among *K. pneumoniae* clinical isolates in Thailand demonstrated significant variability across different geographic regions. For the bla_{NDM} gene, the prevalence was highest in the Northern region (81% [95% CI: 50%, 100%]) followed by the Northeastern (62% [95%

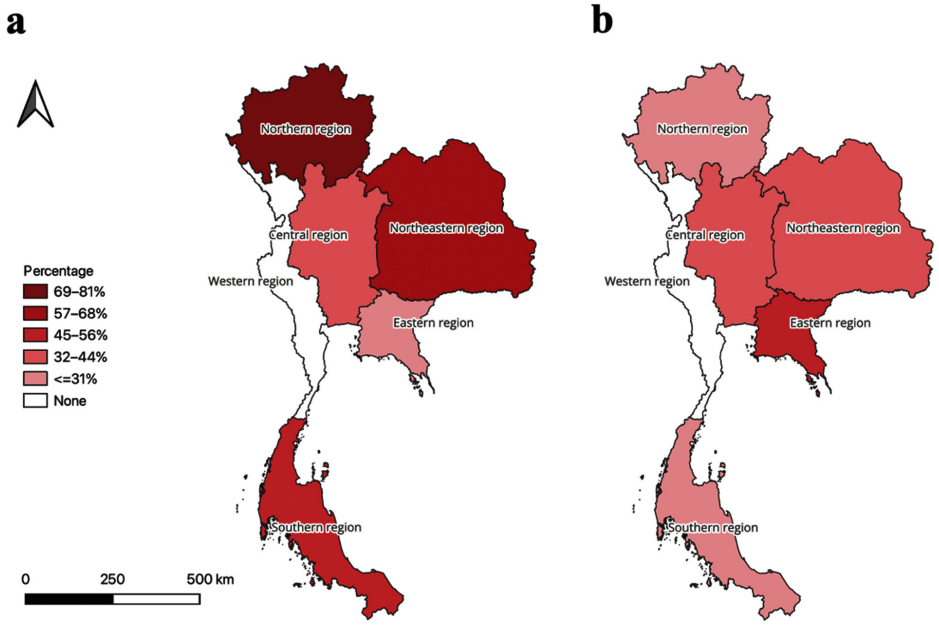

Figure 4. Prevalence of the major carbapenemase genes in *Klebsiella pneumoniae* isolates from Thailand. The map illustrates the overall prevalence of (a) bla_{NDM} and (b) $bla_{OXA\text{-}48\text{-}like}$ as reported in the included studies (Source: Software QGIS 3.28)

Table 2. Regional prevalence of carbapenemase genes among *K. pneumoniae* clinical isolates across different regions of Thailand

Subgroup		No. of studies	Prevalence (%) [95% CI]	P	Heterogeneity test		
					I^2	H^2	P
bla_{NDM}	Region						
	Central	5	33 [12, 58]	<0.01	95.61	22.77	<0.01
	Eastern	2	18 [0, 90]	0.40	98.98	97.79	<0.01
	Northeastern	1	62 [33, 86]	<0.01	-	-	-
	Northern	2	81 [50, 100]	<0.01	86.40	7.35	0.01
	Southern	3	61 [34, 85]	<0.01	93.48	15.34	<0.01
	Western	-	-	-	-	-	-
	Thailand*	5	60 [32, 85]	<0.01	98.58	70.49	<0.01
$bla_{OXA-48-like}$	Region						
	Central	7	39 [23, 56]	<0.01	92.19	12.80	<0.01
	Eastern	1	47 [37, 57]	<0.01	-	-	-
	Northeastern	1	38 [14, 67]	<0.01	-	-	-
	Northern	1	3 [0, 11]	0.15	-	-	-
	Southern	3	15 [0, 60]	0.21	97.51	40.22	<0.01
	Western	-	-	-	-	-	-
	Thailand*	3	52 [39, 66]	<0.01	93.66	15.77	<0.01
bla_{IMP}	Region						
	Central	4	3 [1, 7]	<0.01	53.95	2.17	0.09
	Eastern	2	2 [1, 5]	<0.01	17.57	1.21	0.27
	Northeastern	-	-	-	-	-	-
	Northern	-	-	-	-	-	-
	Southern	1	2 [0, 5]	-	-	-	-
	Western	-	-	-	-	-	-
	Thailand*	1	1 [1, 2]	-	-	-	-

*Indicates studies did not specify the geographic region or collected the sample from across the country

CI: 33%, 86%]) and Southern (61% [95% CI: 34%, 85%]) regions, with heterogeneity (I^2 ranging from 93.48% to 97.94%). The Central region exhibited a moderate prevalence of 33% [95% CI: 12%, 58%], while the Eastern region had the lowest prevalence, at 18% [95% CI: 0%, 90%] (Table 2). For the $bla_{OXA-48-like}$ gene, the Eastern region showed the highest prevalence (47% [95% CI: 37%, 57%]), followed by the Central region (39% [95% CI: 23%, 56%]). The Northeastern region reported a moderate prevalence of 38% [95% CI: 14%, 67%], while the Northern and Southern regions showed much lower rates. The non-specified regions had a prevalence of 52% [95% CI: 39%, 66%]. The prevalence of the bla_{IMP} gene was consistently low across all reporting regions. The Central region had the highest observed prevalence, at 3% [95% CI: 1%, 7%], followed by the Eastern (2%) and Southern (2%) regions. Heterogeneity in these subgroups was generally low (I^2 = 17.57%-41.11%) (Table 2).

Prevalence of ESBL genes among *K. pneumoniae* isolated from Thai hospitals

The pooled prevalence of ESBL genes among *K. pneumoniae* clinical isolates in Thailand was assessed across seven studies, encompassing a total of 493 isolates tested for bla_{CTX-M}, and 456 isolates tested for both bla_{TEM} and bla_{SHV}. The pooled prevalence of bla_{CTX-M} was estimated at 86% [95% CI: 49%, 100%], with heterogeneity observed (I^2 = 98.48%, P < 0.01), while bla_{TEM} was estimated at 73% [95% CI: 65%, 81%], with moderate heterogeneity observed (I^2 = 69.91%, P < 0.01). In comparison, bla_{SHV} demonstrated a higher pooled prevalence of 82% [95% CI: 59,

98%], accompanied by substantial heterogeneity (I^2 = 96.19%, P < 0.01) (Figure 5). The considerable heterogeneity across studies may reflect variations in regional distribution, co-expression with other resistance genes, and methodological differences in the detection assays.

Subgroup analyses based on geographical region revealed that the *bla*$_{TEM}$ gene was most prevalent in the Northern region (89% [95% CI: 77%, 98%]), followed by the Eastern region (82% [95% CI: 74%, 89%]). Similarly, the highest prevalence of *bla*$_{SHV}$ was also reported in the Northern region (92% [95% CI: 80%, 99%]) and Southern region (92% 95% CI: 12%, 100%), followed by the Central region (90% [95% CI: 85%, 94%]) (Table 3). These findings highlight the widespread dissemination of ESBL-producing *K. pneumoniae* strains across multiple regions of Thailand and the potential implications for empirical therapy and infection control practices.

Co-existence of carbapenemase and ESBL genes in *K. pneumoniae* clinical isolates

The pooled prevalence of co-harbored *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$ genes among the Thai *K. pneumoniae* clinical isolates was 36% [95% CI: 23%, 49%], based on 13 included studies (4,266 isolates) (Figure 6a). Heterogeneity was observed among the studies (I^2 = 97.35%, P < 0.01). In contrast, the prevalence of co-harbored *bla*$_{IMP}$ and *bla*$_{OXA-48-like}$ was much lower, with a pooled estimate of 4% [95% CI: 0%, 11%] derived from two studies (347 isolates), and heterogeneity was observed (I^2 = 83.84%, P = 0.01) (Figure 6b). For co-harbored *bla*$_{TEM}$ and *bla*$_{SHV}$, three studies (260 isolates) were analyzed, yielding a pooled prevalence of 25% [95% CI: 0%, 78%], with significant heterogeneity (I^2 = 98.11%, P < 0.01) (Figure 6c).

The subgroup analysis conducted to observe co-harboring of *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$ across different regions in Thailand revealed the highest prevalence in the Southern (49% [95% CI: 18%, 81%]) and Central (44% [95% CI: 28%, 61%]) regions, while a lower prevalence was reported in the Northern (5%) and Eastern (14%) regions (Table 4). Studies without region specificity showed a pooled prevalence of 30%, with heterogeneity (I^2 = 98.98%). These findings highlight the considerable regional differences occurring in the molecular epidemiology of carbapenem resistance among *K. pneumoniae* isolates in Thailand while also emphasizing the

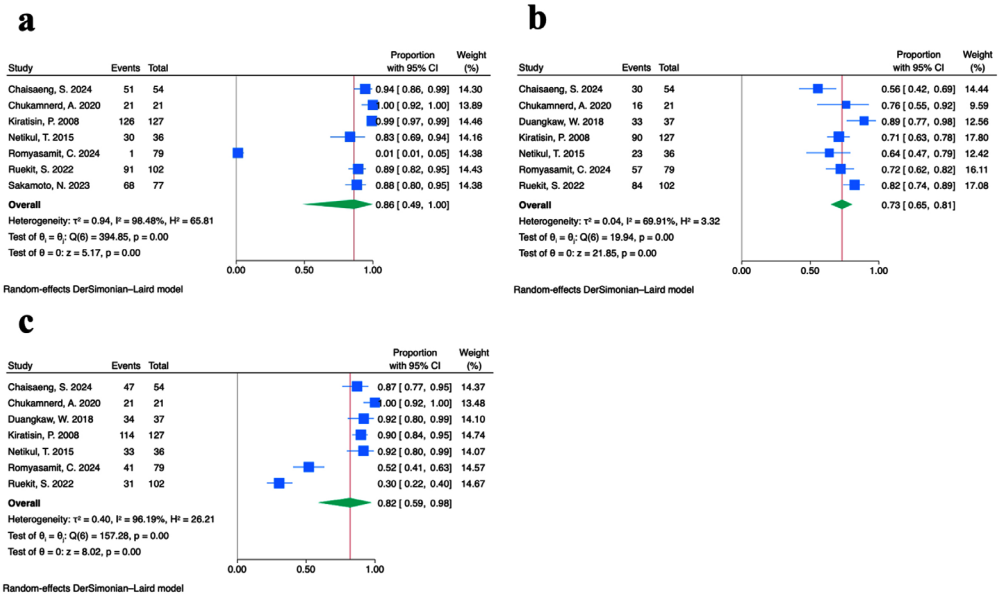

Figure 5. Pooled prevalence of extended-spectrum β-lactamase (ESBL) genes in *Klebsiella pneumoniae* clinical isolates from Thailand. The forest plots illustrate the pooled prevalence of the most common ESBL gene families: (a) *bla*$_{CTX-M}$ (b) *bla*$_{TEM}$ (c) *bla*$_{SHV}$

Table 3. Regional prevalence of extended-spectrum β-lactamase (ESBL) genes in *K. pneumoniae* clinical isolates across different regions of Thailand

Subgroup		No. of studies	Prevalence (%) [95% CI]	P	Heterogeneity test		
					I^2	H^2	P
bla_{CTX-M}	Region						
	Central	3	93 [79, 100]	<0.01	89.25	9.31	<0.01
	Eastern	1	89 [82, 95]	<0.01	-	-	-
	Northeastern	1	94 [86, 99]	<0.01	-	-	-
	Northern	-	-	-	-	-	-
	Southern	2	52 [0, 100]	<0.01	99.16	119.38	<0.01
	Western	-	-	-	-	-	-
bla_{TEM}	Region						
	Central	2	69 [62, 76]	<0.01	0.00	1.00	0.41
	Eastern	1	82 [74, 89]	-	-	-	-
	Northeastern	1	56 [42, 69]	-	-	-	-
	Northern	1	89 [77, 98]	-	-	-	-
	Southern	2	73 [64, 81]	<0.01	0.00	1.00	0.77
	Western	-	-	-	-	-	-
bla_{SHV}	Region						
	Central	2	90 [85, 94]	<0.01	0.00	1.00	0.84
	Eastern	1	30 [22, 40]	<0.01	-	-	-
	Northeastern	1	87 [77, 95]	<0.01	-	-	-
	Northern	1	92 [80, 99]	<0.01	-	-	-
	Southern	2	92 [12, 100]	<0.01	96.60	29.42	0.01
	Western	-	-	-	-	-	-

importance of using geographically targeted antimicrobial resistance surveillance strategies, as in the present meta-analysis.

DISCUSSION

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is an escalating global health threat. Previous studies have shown that the emergence of carbapenemases, particularly metallo-β-lactamases such as New Delhi metallo-β-lactamase (NDM), represents the most common resistance mechanism, accounting for approximately 64.3% of resistance cases worldwide.[57] In Bahrain, for example, antibiotic susceptibility testing revealed resistance to multiple drug classes among *K. pneumoniae* isolates, with 92% showing resistance to meropenem and 88% showing resistance to imipenem. Molecular analysis demonstrated that most CRKP strains carried bla_{NDM-1} (95.8%), followed by bla_{OXA-48} (91.6%), bla_{OXA-51} (45.8%), and bla_{OXA-23} (41.6%).[58] Similarly, a systematic review in Africa reported a pooled prevalence of 34.0% for carbapenemase-encoding genes,[59] while in Asia the prevalence of bla_{NDM}-producing *K. pneumoniae* was estimated at 32.5% in 2017.[60] Despite these global and regional insights, the prevalence and molecular epidemiology of CRKP in Thailand have not been well characterized, underscoring the need for systematic evaluation.

Our study highlights the alarmingly high and increasing prevalence of CRKP in Thailand over the past two decades. The pooled prevalence of resistance to carbapenems among clinical isolates was 87% [95% CI: 81%, 91%], with substantial resistance noted against individual agents, such as imipenem, meropenem, and particularly ertapenem, which consistently showed high resistance proportions across multiple years. Notably, the resistance rate to ertapenem peaked at 100% in 2018 and remained high at 86% in 2024. These findings underscore a growing public health threat, as carbapenems are regarded as last-line agents for multidrug-resistant Gram-negative infections, particularly *K. pneumoniae* infection.[2,3] Our subgroup analyses revealed considerable regional variation, with the Northern,

Northeastern, and Southern regions exhibiting the highest pooled resistance rates across all carbapenems. Notably, we were unable to locate any study that had analyzed the Western region, pointing to a further need for studies that focus on regional resistance variations. The regional variations observed in carbapenem resistance are the products of complex and interdependent factors that encompass the healthcare infrastructure disparities, healthcare practices, population mobility and cross-border dynamics, microbial dynamics, regional disparities in antimicrobial usage, socioeconomic factors, and healthcare access in a given region.[18]

In terms of methods for determining resistance, the combined disk test (CDT) remains a useful phenotypic method for confirming ESBL production in Enterobacterales. The test is based on the inhibition of β-lactamase activity by clavulanic acid, and resistance is confirmed by a clear increase in the inhibition zone when cephalosporin disks are combined with the inhibitor. In this study, the CDT results correlated well with the detection of bla_{SHV}, bla_{TEM}, and

Table 4. Regional prevalence of co-harbored bla_{NDM} and bla_{OXA} genes in *K. pneumoniae* clinical isolates across different regions of Thailand

Subgroup	No. of	Prevalence	P	Heterogeneity test		
	studies	(%) [95% CI]		I^2	H^2	P
Co-harboring bla_{NDM} and $bla_{OXA-48-like}$	Region					
	Central	5	44 [28, 61]	<0.01	90.21	10.21	<0.01
	Eastern	1	14 [10, 20]	<0.01	-	-	-
	Northeastern	-	-	-	-	-	-
	Northern	1	5 [0, 14]	-	-	-	-
	Southern	2	49 [18, 81]	<0.01	85.56	0.01	<0.01
	Western	-	-	-	-	-	-
	Thailand*	4	30 [5, 63]	<0.01	98.98	97.59	<0.01

*Indicates studies did not specify the geographic region or collected the sample from across the country

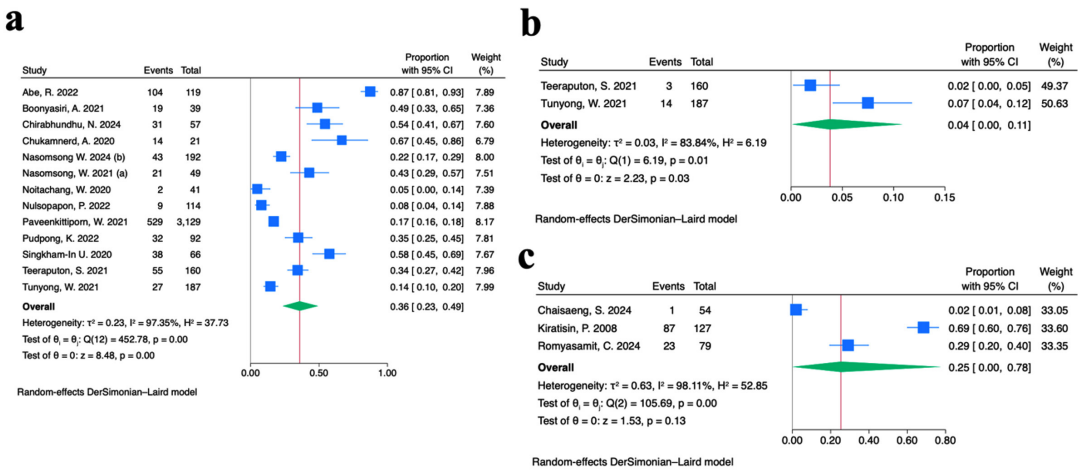

Figure 6. Pooled prevalence of carbapenemase and ESBL gene coexistence in *Klebsiella pneumoniae* clinical isolates from Thailand. The forest plot shows the pooled prevalence for the coexistence of specific gene pairs. Panels illustrate the coexistence of carbapenemase genes (a) bla_{NDM} and $bla_{OXA-48-like}$ (b) bla_{IMP} and bla_{OXA} as well as the coexistence of ESBL genes (c) bla_{TEM} and bla_{SHV}

bla$_{CTX-M}$ genes, confirming the reliability of this test. The molecular data revealed a widespread dissemination of key carbapenemase genes. The most prevalent gene, *bla*$_{NDM}$, was detected in 50% of isolates, with regional prevalence ranging from 18%-81%, depending on the province. This predominance aligns with current global trends, particularly in South and Southeast Asia, where NDM-type metallo-β-lactamases have become endemic.[61,62] The *bla*$_{NDM}$ gene is a plasmid-borne gene that is transferred via conjugation and is often found embedded in mobile genetic elements, which enables rapid intra- and interspecies dissemination in hospital and community settings.[63]

Other detected carbapenemase genes included *bla*$_{OXA-48}$ (35%) and *bla*$_{IMP}$ (2%), with co-harboring of *bla*$_{NDM}$ and *bla*$_{OXA}$ observed in 36% of tested isolates. The *bla*$_{OXA-48}$ gene is also found in conjugative plasmids, while *bla*$_{IMP}$ is found in class 1 integrons, which can be located on conjugative plasmids.[63] Importantly, this study showed that the co-harboring of carbapenemases, such as *bla*$_{NDM}$ with *bla*$_{OXA}$ and *bla*$_{IMP}$ with *bla*$_{OXA}$, is widespread. The ESBL genes were widely disseminated among the *K. pneumoniae* isolates, with *bla*$_{CTX-M}$ being the most prevalent, followed by *bla*$_{SHV}$ and *bla*$_{TEM}$. Multiple ESBL genes, particularly *bla*$_{TEM}$ and *bla*$_{SHV}$, showed co-harboring in approximately 25% of isolates. Notably, *bla*$_{CTX-M}$, and especially *bla*$_{CTX-M-15}$, was also frequently encountered, consistent with its global emergence as the dominant ESBL genotype.[27-29,32] This gene is often located on transferable plasmids that carry additional resistance determinants, thereby contributing to multidrug-resistant phenotypes.

This study also identified non-carbapenemase-producing carbapenem-resistant *K. pneumoniae* (N-CRKP) harboring ESBL genes. The included studies showed frequent reports of the presence of ESBL genes in non-carbapenemase-producing *K. pneumoniae*, with prevalence rates ranging from 4.76%-88%. Importantly, these isolates exhibited resistance to all tested carbapenem agents.[28,32,43] Netikul et al. reported the presence of ESBL genes in non-carbapenemase-producing *K. pneumoniae*.[32] Of particular concern, the ESBL-positive isolates showed complete resistance to ertapenem despite their absence of carbapenemase genes.[32] Molecular investigations have revealed mutations or deletions in the outer membrane porins OmpK35 and OmpK36 that reduce membrane permeability.[32,52] Further decreases in carbapenem effectiveness have also been linked to overexpression of efflux pumps, such as AcrAB-TolC and OqxAB,[64] together with hyperproduction of ESBLs or AmpC β-lactamases.[14]

This multifactorial resistance underscores the adaptive plasticity of *K. pneumoniae* and highlights the importance of conducting molecular surveillance that extends beyond carbapenemase detection. Regionally, the northern part of Thailand exhibited the highest prevalence of both the carbapenemase gene *bla*$_{NDM}$ and ESBL genes (*bla*$_{SHV}$ and *bla*$_{TEM}$), corresponding to higher phenotypic resistance to all tested carbapenems. The co-carriage of carbapenemase and ESBL genes raises concerns about genetic platforms that can facilitate horizontal gene transfer.[65] Most of the resistance determinants are plasmid-encoded and can be readily disseminated among *Enterobacterales* via conjugative plasmids, transposons, and integrons.[65] The high frequency observed for co-harboring genes suggests a selective advantage that could support the possible clonal expansion of successful multidrug-resistant strains.[66] This may explain the persistently high prevalence of resistance observed in recent years, even in areas in which molecular diagnostics are not routinely employed.[67,68]

The presence of resistance genes is an important marker; however, it may not always correlate directly with phenotypic expression due to regulatory or fitness factors.[69,70] Thus, the relationship between gene prevalence and resistance phenotype should be interpreted cautiously and explored in greater depth using whole-genome sequencing. This study revealed considerable heterogeneity across studies, with I^2 values often exceeding 90% in pooled analyses. Several factors likely contributed to this heterogeneity. First, methodological differences were prominent, as the included studies employed a variety of AST methods (disk diffusion, broth microdilution, E-test, and automated systems) with inconsistent application of interpretive criteria (CLSI vs. EUCAST).[71] Second, differences in study period, sample size, and hospital setting (e.g., tertiary vs. provincial hospitals) may have affected resistance detection rates.[72] Third,

variable laboratory capacity and inconsistent reporting of gene prevalence data could have contributed to differences in molecular findings. Finally, temporal factors may also account for some variation, as newer studies tend to report a higher prevalence, reflecting the progressive spread of resistance over time.

High antibiotic pressure in both hospital and community settings is another likely driver of carbapenem resistance in Thailand. Numerous studies have documented inappropriate or excessive use of broad-spectrum antibiotics, including third-generation cephalosporins and carbapenems, resulting in the selection of resistant clones and the promotion of persistence in clinical and environmental reservoirs.[73] Inadequate antibiotic stewardship programs, a lack of prescription control in community pharmacies, and the use of antimicrobials in livestock further exacerbate this issue.[74-76] Thus, our analysis also underscores the urgent need for strong infection-prevention strategies.

While our results are robust, their interpretation is constrained by several factors, as outlined below. First, data from some regions (e.g., Northern and Northeastern Thailand) are underrepresented compared to those retrieved from Central and Southern areas, resulting in a potential skewing of national estimates. In addition, no data from the Western region were available. Second, most studies relied on phenotypic methods and limited gene panels, which may underestimate emerging or uncommon resistance mechanisms. Third, publication bias may have favored studies reporting high prevalence or molecular findings, although Egger's test did not confirm significant bias in most subgroup analyses. Lastly, inconsistent reporting of sample sizes, confidence intervals, and testing methods complicated any between-studies analysis. Because many included studies selectively analyzed isolates in published hospital-based studies, the pooled prevalence estimates likely overrepresent resistance, many of which selectively included carbapenem-resistant isolates, compared with population-based surveillance data and should not be interpreted as national prevalence. However, by focusing on data representative of hospital-based studies rather than site-specific infections, our objective was to offer a general overview of prevalence or molecular findings, which has not been previously accomplished.

CONCLUSION

In conclusion, Thailand has a substantial and rising burden of carbapenem-resistant *K. pneumoniae*, driven by a complex interplay of antimicrobial pressure, horizontal gene transfer, and regional disparities in healthcare infrastructure. The dominance of the bla_{NDM} gene and its co-expression with ESBL genes underscores the need for nationwide molecular surveillance and stronger stewardship programs. Standardized diagnostic protocols and integrated genomic epidemiology are critical to mitigating the spread and clinical impact of these multidrug-resistant pathogens in Thailand and in other regions worldwide.

SUPPLEMENTARY INFORMATION

Supplementary information accompanies this article at https://doi.org/10.22207/JPAM.20.3.65

Additional file: Table S1-S6 and Figure S1-S4.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

NL and WM conceptualized the study. NL and WM conducted the literature review and retrieved relevant studies. NP, SA, Nat-Ta, Nit-Ta, NL, and PY screened the studies. NP, SA, Nat-Ta, NL, and PY performed data collection. TK, PTY, and NL conducted the quality assessment. WM performed the data analysis and visualization. WM and NL interpreted the findings. NL, WM, TK, SS, and PTY wrote the manuscript. All authors reviewed, revised, and approved the final manuscript for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript and/or in the supplementary files.

ETHICS STATEMENT

Not applicable.

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