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# Prevalence and molecular epidemiology of carbapenem resistance in Asia: a systematic review and meta-analysis

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## Abstract

**Background** Carbapenems are a group of last-resort antibiotics used to treat serious life-threatening infections. The emergence of resistance to carbapenems is a major public health threat. However, comprehensive information on the prevalence and molecular epidemiology of carbapenem resistance (CR) among Asian countries is lacking. Therefore, we aimed to determine the prevalence of CR and associated molecular determinants quantitatively among Asian countries.

**Methods** In this systematic review and meta-analysis, we searched published reports in electronic databases such as PubMed, ScienceDirect, the Cochrane Library, and Web of Science from 1<sup>st</sup> of January 2014 to 31<sup>st</sup> of January 2024 that fulfilled these criteria; original studies conducted in Asian countries including clinical isolates, and published in English. Data extraction and risk-of-bias assessment were performed by two independent reviewers. The pooled prevalence of CR with 95% confidence interval (CI) was computed with a random effects model. Heterogeneity across studies was determined by  $I^2$ . The geographical location, income level, publication year, and sample size were analyzed as subgroups.

**Results** We identified 2518 eligible studies, of which 37 assessed the CR prevalence data of 10,433 patients. The pooled prevalence (PPr) of CR was 31.3% (95% CI: 0.22 to 0.40;  $I^2 = 99.9\%$ ;  $P = 0.00$ ). A trend of CR incidence was observed from 2004 to 2023, with PPr values ranging from 7.4% to 50.6%. A variation in the distribution of CR genes was observed, with  $bla_{NDM}$  being the most common gene, followed by  $bla_{OXA}$  and  $bla_{KPC}$ . Univariate meta-regression analysis indicated that geographical location, income level, publication year, and sample size did not significantly affect heterogeneity ( $P < 0.05$ ).

**Conclusion** The results suggest that surveillance of CR among Asian countries is essential to reduce the burden of antibiotic resistance. Mitigating the impact of CR infections will safeguard the efficacy of carbapenems for future generations and reduce further dissemination of CR genes.

**Systematic review registration** PROSPERO CRD42024515806.

**Keywords** Asia, Carbapenemase, Carbapenem resistance, Molecular determination, Prevalence, Systematic review and meta-analysis

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## Background

Carbapenems belong to the group of beta-lactam antibiotics and are considered as the last-line treatment option for infections caused by multidrug-resistant (MDR) bacteria [1, 2]. The emergence of resistance to carbapenem antibiotics is known to be a severe public health threat worldwide, causing increased mortality and morbidity rates [3]. The overuse and misuse of antibiotics, lack of proper infection control practices, and inadequacy of advanced diagnostic techniques lead to increased transmission and outbreaks caused by carbapenem-resistant organisms (CROs) [4].

Carbapenem resistance is mainly caused by the production of carbapenemases, which are encoded by carbapenemase-producing genes. CRO encompasses a wide variety of organisms, including *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* [5]. The epidemiology and molecular characteristics of these CROs have been studied extensively in different countries. Most reported CR genes worldwide are *bla*<sub>KPC</sub>, *bla*<sub>NDM</sub>, *bla*<sub>IMP</sub>, *bla*<sub>OXA-48</sub>, *bla*<sub>OXA-181</sub>, and *bla*<sub>VIM</sub>, of which *bla*<sub>NDM</sub> is more common among Asian countries [6–8]. The dissemination of these CR genes among different organisms causes an increase in infections, leading to a major threat in clinical settings.

Asia is the largest continent in the world. Recently, it became a hot spot for the dissemination of CR due to the high population density, less infrastructure facilities, and poor antibiotic stewardship programs [9, 10]. Studies conducted in Asian countries reported alarming CR rates among Gram-negative bacteria (GNB). Particularly, carbapenem-resistant *A. baumannii* (CRAB) rates were ranged from 2.8% in Japan to 88% in South Korea as per the Antimicrobial Testing Leadership and Surveillance (ATLAS) program conducted in between 2012 and 2019 challenging the management of infections caused by CROs [9, 11]. However, comprehensive data summarizing the prevalence and molecular determinants of CR pathogens are lacking. The diversity of health care systems, economic disparities, and differences in surveillance and reporting further complicate the assessment of CR prevalence in different Asian countries. Although, increased trends in CR rates have been reported in several studies. There is a need for a systematic synthesis of data, for the better understanding of the prevalence of CR in Asia. To the best of our knowledge, a comprehensive systematic review and meta-analysis has not yet been conducted including Asian countries. Therefore, this study has the potential to address this considerable evidence gap in CR among Asian countries and thereby support the formulation of country-specific public health priorities. In addition, it provides a clear understanding of the epidemiological trends, regional variations, and

molecular determinants driving CR infections in Asian countries. These findings may provide valuable insights for healthcare policy-makers and practitioners for the development and implementation of targeted strategies to combat the further spread of infections caused by CROs.

## Methods

This systematic review was carried out following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [12] and the Cochrane Guidelines [13]. The protocol of this study was registered in PROSPERO (CRD42024515806) [14].

## Search strategy

A systematic literature search was conducted in databases including PubMed, ScienceDirect, Cochrane Library, and Web of Science for related studies matching with the inclusion and exclusion criteria, published in Asian countries between 1<sup>st</sup> of January 2014 and 31<sup>st</sup> of January 2024 to identify eligible studies. The Asian countries considered were Sri Lanka, India, Bangladesh, Pakistan, Afghanistan, Nepal, Bhutan, Maldives, Iran, China, Japan, Korea, Mongolia, Indonesia, Philippines, Vietnam, Thailand, Myanmar, Malaysia, Cambodia, Laos, Singapore, Timor-Leste, Brunei, Turkey, Iraq, Saudi Arabia, Yemen, Syria, Jordan, Azerbaijan, United Arab Emirates, Israel, Qatar, Oman, Georgia, Kuwait, Armenia, Bahrain, Cyprus, Palestine, Uzbekistan, Kazakhstan, Turkmenistan, Tajikistan, Kyrgyzstan, and Russia. Since CR has increasingly reported in recent years, a duration of 10 years was selected. The search strategy was developed by combining Medical Subject Headings (MeSH) terms and phrases related to prevalence and CR with Boolean operators (AND, OR), by referring to published literature and discussing with subject experts. Assistance of the librarian was received when deciding the databases to be used and in designing the search strategy. The same search terms with different syntax requirements were used in different bibliographic databases as the search strategy. Search terms related to prevalence were “surveillance,” “prevalence,” “prevalence rate,” “incidence,” and “occurrence.” The search terms for carbapenem resistance were “carbapenem resist\*,” “carbapenem resistance\*” and “carbapenem non-susceptible.” These search terms were combined and searched with “Asia,” “Asian countries,” “South Asia,” “Sri Lanka,” “India,” “Bangladesh,” “Pakistan,” “Afghanistan,” “Nepal,” “Bhutan,” “Maldives,” “Iran,” “China,” “Japan,” “Korea,” “Mongolia,” “Indonesia,” “Philippines,” “Vietnam,” “Thailand,” “Myanmar,” “Malaysia,” “Cambodia,” “Laos,” “Singapore,” “Timor-Leste,” “Brunei,” “Turkey,” “Iraq,” “Saudi Arabia,” “Yemen,” “Syria,” “Jordan,” “Azerbaijan,” “United Arab Emirates,” “Israel,”

“Qatar,” “Oman,” “Georgia,” “Kuwait,” “Armenia,” “Bahrain,” “Cyprus,” “Palestine,” “Uzbekistan,” “Kazakhstan,” “Turkmenistan,” “Tajikistan,” “Kyrgyzstan,” and “Russia,” from 2014–2024 (supplementary file 1).

### Selection criteria

Prior to the study, a basic literature search on the intended research question was conducted by the authors and found a scarcity of pooled data in the Asian region. Therefore, a systematic review and meta-analysis was conducted to fill this research gap. The inclusion criteria were as follows: published studies conducted in Asian countries encompassing both adults and children groups without specifically considering the age of the study participants, studies conducted with only clinical isolates, studies published in English, and studies published between January 1<sup>st</sup>, 2014, and January 31<sup>st</sup>, 2024. Studies fulfilled the following criteria were excluded: studies that did report data on the prevalence of CR in Asian countries; studies that reported resistance rates to antibiotics other than carbapenems; publications other than original studies including reviews, editorials, commentaries, notes, and conference proceedings; and animal studies. The gray literature search resulted none of the studies matching with the inclusion and exclusion criteria. Duplicates were removed via the EndNote reference management software. Identified studies from different databases were uploaded to Rayyan web-based application. Initially, the two reviewers (NJ and SS) independently screened the titles and abstracts of all the articles that met the inclusion and exclusion criteria, and then the full texts of the selected studies were reviewed. Reasons for exclusion were recorded for each of the reference screened. Discrepancies between two reviewers were resolved by consensus or by discussion with a third senior reviewer (TS and/or DN).

The following are the case definitions to interpret prevalence and incidence of CR.

- Incidence of CR is the number of new CR cases that develop in the study population, within the study duration.
- Prevalence of CR is the proportion of patients who were tested as positive for CROs within the study duration.

### Data extraction

Relevant data were extracted from each of the included published report and entered into a Microsoft Excel sheet. The variables extracted included the following: first author, year of publication, study period, study design, sample size, country of publication, sample type, name

of the pathogen, carbapenem antibiotics used, prevalence rate, and genes detected. The data extraction was also conducted by two independent reviewers (NJ and SS), and conflicts were resolved through consensus or by discussion with a third senior reviewer (TS and/or DN).

### Data synthesis and analysis

The extracted data were entered in the Microsoft Excel sheet and imported into SPSS version 29 software, and meta-analysis was performed. The pooled prevalence (PPr) of CR (95% CI) in different Asian countries was analyzed. The United Nations (UN) Asian country classification was followed to classify the studies conducted in South Asia, East Asia, Southeast Asia, West Asia, Central Asia, and North Asia [15]. We categorized studies according to the World Bank country classification by gross domestic product by total population (GDP per capita), as low-income (LI), lower-middle-income (LMI), upper-middle-income (UMI), and high-income (HI) countries, to observe the variation in PPr across countries with different income levels [16]. In addition, studies were categorized by their publication year as 2014–2016, 2017–2019, and 2020–2023, and by sample size, i.e., < 100, 100–200, and > 200 for analysis purposes.

DerSimonian and Laird's random-effects meta-analysis model at a 95% CI was used. Statistical heterogeneity was assessed by the  $I^2$  (inverse variance index) measure. For  $I^2$ , above 75.0% was considered as having high heterogeneity [13]. Clinical heterogeneity was assessed by subgroup analysis and sensitivity analysis.

In the initial analysis, we estimated the pooled prevalence (PPr) rates from the raw data, to obtain the PPr of CR. To assess the potential sources of heterogeneity between studies, stratified analysis and random-effects meta-regression analysis were conducted considering geographical location, income level, publication year, and sample size. Sensitivity analysis was conducted to assess the influence of individual studies on the results by removing one study at a time and recalculating the PPr among the remaining studies. Finally, Egger's test was conducted to assess publication bias, and the results were visually presented with funnel plots. A  $P$ -value of less than 0.05 was considered as the cutoff for statistical significance.

### Risk of bias and quality assessment

The selected studies were categorized as prevalence studies, case-control studies, cohort studies, or cross-sectional studies. The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess and grade the risk of bias (ROB). Studies with an overall score higher than 70% were classified as having a high quality, those with a score in between 50 and 70% as having medium

quality, and those with a score less than 50% as having low quality. The certainty of the evidence provided in included studies was assessed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [13]. The evidence was rated as high, moderate, low, and very low. Initially, all the studies were assigned a high grade by default and subsequently downgraded considering pre-determined standards, risk of bias (studies biased in study population selection, etc.), inconsistency (poor overlapping of CIs in different studies,  $I^2$  values > 50%), indirectness (the presence of factors generalizing the results), imprecision (sample sizes of included studies were small and wide CI), and other considerations. Two independent reviewers (NJ and SS) assessed the quality and certainty of included studies. Disagreements between reviewers were resolved by discussions between reviewers or after discussion with a third senior member (TS and/or DN) of the review team. The credibility levels of the included studies are presented in a table.

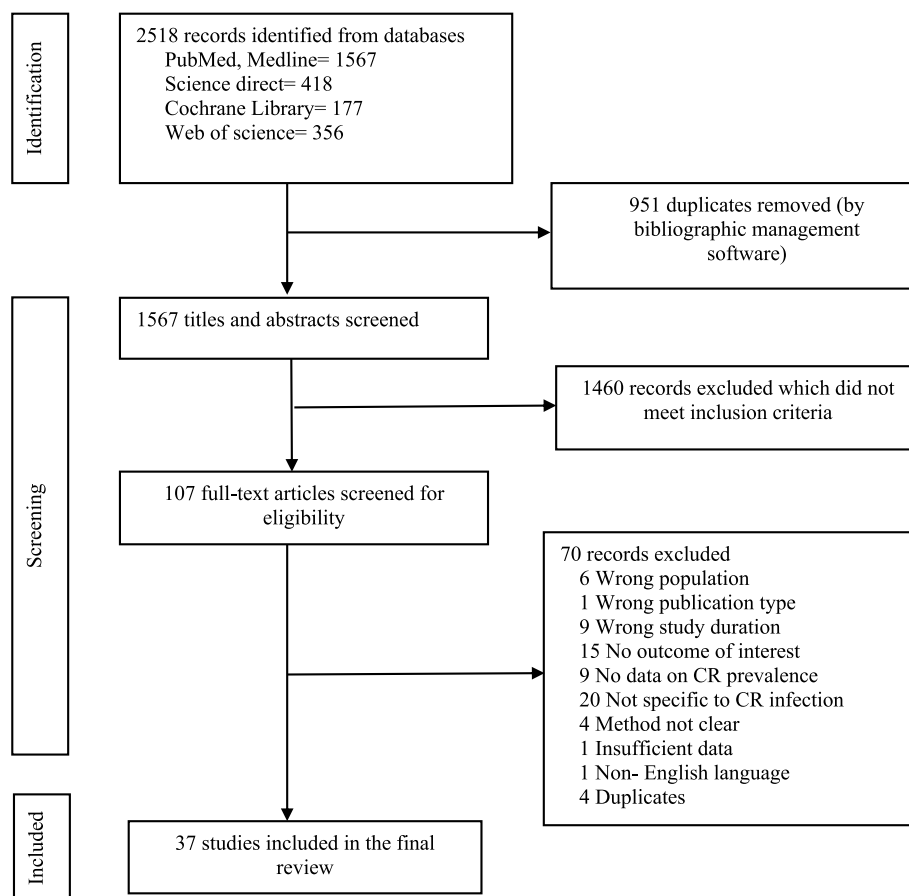
## Results

### Characteristics of the included studies

A total of 2518 studies were identified after the initial search of electronic databases and available resources, of which 37 (10,433 patients) were included in this systematic review and meta-analysis on the basis of the inclusion and exclusion criteria. The study selection process is described in Fig. 1.

The basic characteristics of 37 included studies are displayed in Table 1.

The studies were conducted in South Asian countries, including India [28, 43], Pakistan [25, 33, 35, 48], Bangladesh [49], Sri Lanka [36, 51], and Iran [19, 20, 22, 27, 32, 50, 52]; East Asian countries: China [26, 30, 31, 38, 44, 53] and Japan [23]; Southeast Asian countries, including Thailand [39, 45–47], Vietnam [29, 37], Indonesia [42] and Myanmar [24]; and West Asian countries, including Kuwait [18, 34], Turkey [40], Saudi Arabia [17], Iraq [41] and Lebanon [21]. None of the studies conducted in Central and North Asian countries was matched with the inclusion and exclusion criteria of the present study. According to the World Bank country classification by



**Fig. 1** Study selection

**Table 1** Characteristics of studies describing the prevalence of CR in Asian countries

| Sr. no. | Study ID                        | Sample size | Country      | Sample type                                                               | Name of pathogen   | Carbapenems used   | Overall CR prevalence | Genes detected                                               | Percentage of genes                            |
|---------|---------------------------------|-------------|--------------|---------------------------------------------------------------------------|--------------------|--------------------|-----------------------|--------------------------------------------------------------|------------------------------------------------|
| 1       | Aljindan et al. (2015) [16]     | 565         | Saudi Arabia | Rectal swab                                                               | AB                 | NA                 | 6.20%                 | AB-OXA                                                       | 86.2%                                          |
| 2       | Jamal et al. (2016) [17]        | 764         | Kuwait       | Urine, wound swabs, tissue, blood, respiratory secretion, other specimens | KP, ECI, other GNB | IMI, MEM, ERT      | 8.00%                 | KP-NDM<br>EC-NDM<br>ECI-NDM<br>MM NDM<br>PS-NDM              | 66.6%<br>19.0%<br>4.7%<br>4.7%                 |
| 3       | Sadeghi et al. (2016) [18]      | 307         | Iran         | Different clinical specimens                                              | KP, EC, ECI        | IMI, MEM, ERT      | 8.79%                 | CRE-NDM<br>CRE-KPC<br>CRE-OXA                                | 25.9%<br>7.4%<br>40.7%                         |
| 4       | Hosseinzadeh et al. (2017) [19] | 211         | Iran         | Different clinical samples                                                | KP                 | IMI, MEM           | 13.74%                | KP-NDM<br>KP-OXA                                             | 10.9%<br>0.9%                                  |
| 5       | Christophy et al. (2017) [20]   | 41          | Lebanon      | Stool                                                                     | EC, other GNB      | IMI, MEM, ERT      | 24.39%                | EC-OXA<br>PS-OXA<br>EA-OXA                                   | 10.0%<br>10.0%<br>10.0%                        |
| 6       | Solgi et al. (2017) [21]        | 95          | Iran         | Rectal swabs                                                              | KP, EC, ECI        | IMI, MEM           | 37.90%                | KP-NDM<br>KP-OXA<br>KP-Other<br>EC-NDM<br>EC-OXA<br>EC-other | 4.6%<br>14.8%<br>14.8%<br>1.8%<br>5.6%<br>4.7% |
| 7       | Yamamoto et al. (2017) [22]     | 1507        | Japan        | Fecal samples                                                             | CRE                | IMI, MEM           | 12.21%                | CRE-IMP                                                      | 95.7%                                          |
| 8       | Aung et al. (2018) [23]         | 426         | Myanmar      | Urine, wound swab, sputum, HVS, pus, blood, throat swabs, pleural fluid   | EC                 | IMI, MEM           | 8.20%                 | EC-NDM<br>EC-OXA                                             | 13.2%<br>5.7%                                  |
| 9       | Braun et al. (2018) [24]        | 425         | Pakistan     | Blood, urine, wound swab pus, throat swab, other specimens                | KP, EC, AB         | IMI, MEM           | 19.29%                | CRE-NDM<br>CRE-IMP<br>CRE-OXA<br>CRE-VIM<br>CRE-other        | 50.8%<br>1.6%<br>15.2%<br>13.1%<br>3.9%        |
| 10      | Li et al. (2018) [25]           | 7249        | China        | Different clinical samples                                                | KP, EC, other GNB  | IMI, MEM, ERT      | 18.10%                | EC-NDM<br>EC-KPC<br>KP-NDM<br>KP-KPC<br>KP-IMP               | 52.9%<br>11.8%<br>4.5%<br>88.4%<br>1.5%        |
| 11      | Shoja et al. (2018) [26]        | 170         | Iran         | Urine, blood, wound, sputum, other body fluids                            | KP                 | IMI, MEM, ERT, DOR | 7.05%                 | KP-NDM                                                       | 2.4%                                           |
| 12      | Jaggi et al. (2019) [27]        | 528         | India        | Pus, urine, sputum, stool, blood, body fluids                             | KP, EC             | NA                 | 29.54%                | KP-other<br>EC-other                                         | 35.9%<br>77.0%                                 |
| 13      | Tran et al. (2019) [28]         | 2233        | Vietnam      | Rectal swabs                                                              | KP, EC, E          | NM                 | 52.0%                 | NR                                                           | NR                                             |
| 14      | Li et al. (2019) [29]           | 507         | China        | Blood, sputum, other body fluids                                          | KP                 | IMI, MEM, ERT      | 48.10%                | NR                                                           | NR                                             |
| 15      | Pan et al. (2019) [30]          | 880         | China        | Fecal samples                                                             | KP, other GNB      | IMI, MEM, ERT      | 3.60%                 | CRE-NDM                                                      | 31.3%                                          |
| 16      | Ranjibar et al. (2019) [31]     | 163         | Iran         | Burn wound infections                                                     | AB                 | IMI, MEM           | 94.50%                | AB-OXA<br>AB-VIM                                             | 85.1%<br>60.5%                                 |
| 17      | Ahmed et al. (2020) [32]        | 227         | Pakistan     | Blood, sputum, urine and pus                                              | PA                 | IMI, MEM           | 92.50%                | PA-KPC<br>PA-OXA<br>PA-other                                 | 17.0%<br>15.0%<br>32.3%                        |

**Table 1** (continued)

| Sr. no. | Study ID                            | Sample size | Country   | Sample type                                                                | Name of pathogen                                        | Carbapenems used   | Overall CR prevalence | Genes detected                                                                                            | Percentage of genes                                                                       |
|---------|-------------------------------------|-------------|-----------|----------------------------------------------------------------------------|---------------------------------------------------------|--------------------|-----------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 18      | Fadhil et al. (2020) [33]           | 590         | Kuwait    | Rectal swabs                                                               | KP, EC, E, other GNB                                    | IMI, MEM, ERT      | 9.80%                 | CRE-OXA<br>CRE-other                                                                                      | 37.1%<br>10.9%                                                                            |
| 19      | Khurshid et al. (2020) [34]         | 156         | Pakistan  | Urine, sputum, blood wound swabs, body fluids, catheter tips               | AB                                                      | MEM                | 89.10%                | AB-OXA                                                                                                    | 87.2%                                                                                     |
| 20      | Kumudunie et al. (2020) [35]        | 593         | Sri Lanka | Urine, blood, other sterile fluids, respiratory specimens, wound/pus swabs | KP, EC, ECI, other GNB                                  | IMI, MEM, ERT, DOR | 9.60%                 | KP-KPC<br>KP-OXA<br>KP-other<br>EC-OXA<br>CF-NDM<br>PR-NDM<br>ECI-NDM<br>KA-VIM                           | 4.5%<br>88.6%<br>6.8%<br>100%<br>50.0%<br>100%<br>100%<br>100%                            |
| 21      | Garpvall et al. (2021) [36]         | 941         | Vietnam   | Fecal samples                                                              | KP, AB, PA                                              | NA                 | 35.80%                | NR                                                                                                        | NR                                                                                        |
| 22      | Huang et al. (2021) [37]            | 26820       | Taiwan    | Clinical isolates of KP and EC                                             | KP, EC                                                  | IMI, MEM           | 1.43%                 | NR                                                                                                        | NR                                                                                        |
| 23      | Paveenkittiporn et al. (2021) [38]  | 4296        | Thailand  | Urine, sputum, pus, blood, sterile fluids                                  | KP, EC, ECI, other GNB                                  | IMI, MEM, ERT      | 93.00%                | KP-NDM                                                                                                    | 55.0%                                                                                     |
| 24      | Unlu et al. (2021) [39]             | 83          | Turkey    | Blood, urine, sputum, CSF, tissue, tracheal aspirate                       | KP                                                      | IMI, MEM           | 67.00%                | NR                                                                                                        | NR                                                                                        |
| 25      | Albadery et al. (2022) [40]         | 120         | Iraq      | Urine                                                                      | EC                                                      | IMI                | 54.54%                | EC-KPC<br>EC-IMP<br>EC-VIM                                                                                | 22.7%<br>22.7%<br>59.1%                                                                   |
| 26      | Anggraini et al. (2022) [41]        | 1263        | Indonesia | Urine, sputum, pus, blood, other                                           | AB                                                      | IMI                | 49.96%                | AB-OXA                                                                                                    | 96.5%                                                                                     |
| 27      | Kumari et al. (2022) [42]           | 101         | India     | Blood, vascular catheter tip, urine, pus, sputum, other fluids             | KP, EC, PA, AB                                          | IMI, MEM           | 16.80%                | KP-NDM<br>KP-OXA<br>EC-NDM<br>EC-OXA<br>AB-NDM<br>PA-NDM<br>PA-OXA                                        | 4.0%<br>4.0%<br>3.0%<br>4.0%<br>1.0%<br>1.0%<br>2.0%                                      |
| 28      | Liu et al. (2022) [43]              | 510         | China     | Blood                                                                      | KP                                                      | IMI, MEM           | 15.10%                | KP-NDM<br>KP-KPC<br>KP-IMP                                                                                | 10.4%<br>87.0%<br>2.6%                                                                    |
| 29      | Ruekit et al. (2022) [44]           | 431         | Thailand  | Pus, urine, rectal swabs, sputum, and blood                                | KP, EC, AB, PA, other GNB, <i>Staphylococcus aureus</i> | IMI, MEM, ERT      | 51.00%                | KP-NDM<br>KP-IMP<br>KP-OXA<br>EC-NDM<br>EC-KPC<br>EC-OXA<br>AB-NDM<br>AB-OXA<br>PA-NDM<br>PA-VIM<br>E-NDM | 55.0%<br>1.0%<br>47.0%<br>4.0%<br>0.5%<br>1.0%<br>4.0%<br>97.0%<br>5.0%<br>10.0%<br>25.0% |
| 30      | Saengsuwan et al. (2022) [45]       | 289         | Thailand  | Sputum, urine, secretions                                                  | PA                                                      | IMI, MEM           | 55.70%                | PA-IMP<br>PA-OXA<br>PA-VIM                                                                                | 23.0%<br>4.8%<br>27.7%                                                                    |
| 31      | Assawathep-tawee et al. (2023) [46] | 1175        | Thailand  | Stool, urine                                                               | KP                                                      | MEM                | 1.27%                 | KP-NDM                                                                                                    | 1.3%                                                                                      |



**Table 1** (continued)

| Sr. no. | Study ID                     | Sample size | Country    | Sample type                                           | Name of pathogen | Carbapenems used | Overall CR prevalence | Genes detected                                         | Percentage of genes                              |
|---------|------------------------------|-------------|------------|-------------------------------------------------------|------------------|------------------|-----------------------|--------------------------------------------------------|--------------------------------------------------|
| 32      | Ehsan et al. (2023) [47]     | 540         | Pakistan   | Urine                                                 | EC               | MEM              | 34.00%                | EC-KPC<br>EC-OXA<br>EC-VIM                             | 14.0%<br>16.2%<br>3.4%                           |
| 33      | Farzana et al. (2023) [48]   | 1893        | Bangladesh | Wound swabs, urine, blood                             | EC, KP, PM, ECI  | IMI, MEM         | 10.60%                | CRE-NDM<br>CRE-KPC<br>CRE-OXA                          | 21.6%<br>0.8%<br>3.9%                            |
| 34      | Hashemian et al. (2023) [49] | 103         | Iran       | Urine, respiratory secretions, blood, other specimens | KP, EC, AB       | IMI, MEM         | 14.28%                | KP-NDM<br>KP-OXA<br>EC-OXA                             | 66.6%<br>50.0%<br>16.6%                          |
| 35      | Perera et al. (2022) [50]    | 422         | Sri Lanka  | Urine                                                 | KP, EC, E        | IMI, MEM, ERT    | 11.00%                | KP-NDM<br>KP-OXA<br>EC-NDM<br>EC-OXA<br>E-NDM<br>E-OXA | 13.0%<br>15.3%<br>4.5%<br>19.0%<br>7.5%<br>17.0% |
| 36      | Sales et al. (2023) [51]     | 100         | Iran       | Blood, wounds, sputum, urine                          | KP               | IMI, MEM         | 25.00%                | KP-KPC<br>KP-IMP<br>KP-OXA<br>KP-VIM                   | 18.0%<br>1.0%<br>1.0%<br>3.0%                    |
| 37      | Xiao et al. (2023) [52]      | 285         | China      | Blood                                                 | PA               | IMI, MEM         | 34.04%                | NR                                                     | NR                                               |

NA Not applicable, CR Carbapenem resistance, KP *Klebsiella pneumoniae*, EC *Escherichia coli*, AB *Acinetobacter baumannii*, PA *Pseudomonas aeruginosa*, E *Enterobacter* spp., ECI *Enterobacter cloacae*, MM *Morganella morganii*, PM *Proteus mirabilis*, CF *Citrobacter freundii*, EA *Enterobacter aerogenes*, PS *Pseudomonas stuartii*, KA *Klebsiella aerogenes*, CRE Carbapenem-resistant enterobacteriaceae, GNB Gram-negative bacteria, NDM New Delhi metallo-beta-lactamase, KPC *Klebsiella pneumoniae* carbapenemase, IMP Imipenemase, OXA Oxacillinase, VIM Verona integron-encoded metallo-beta-lactamase, IMI Imipenem, MEM Meropenem, ERT Ertapenem, DOR Doripenem

income level, more than half of the studies were conducted in lower-middle-income countries ( $n=21$ ), followed by upper-middle-income countries ( $n=12$ ). Only four studies were conducted in high-income countries, and none of the studies conducted in low-income countries was eligible for the study. Overall JBI score of the included studies was higher than 70%, indicating high quality (supplementary file 2). Summary of the grade evaluation of evidences according to GRADE method is shown in supplementary file 3. Findings confirm that the evidence was classified as low to very low grading. Possibility of bias, heterogeneity, width of CI, and publication bias were the main contributory factors to downgrade the evidence.

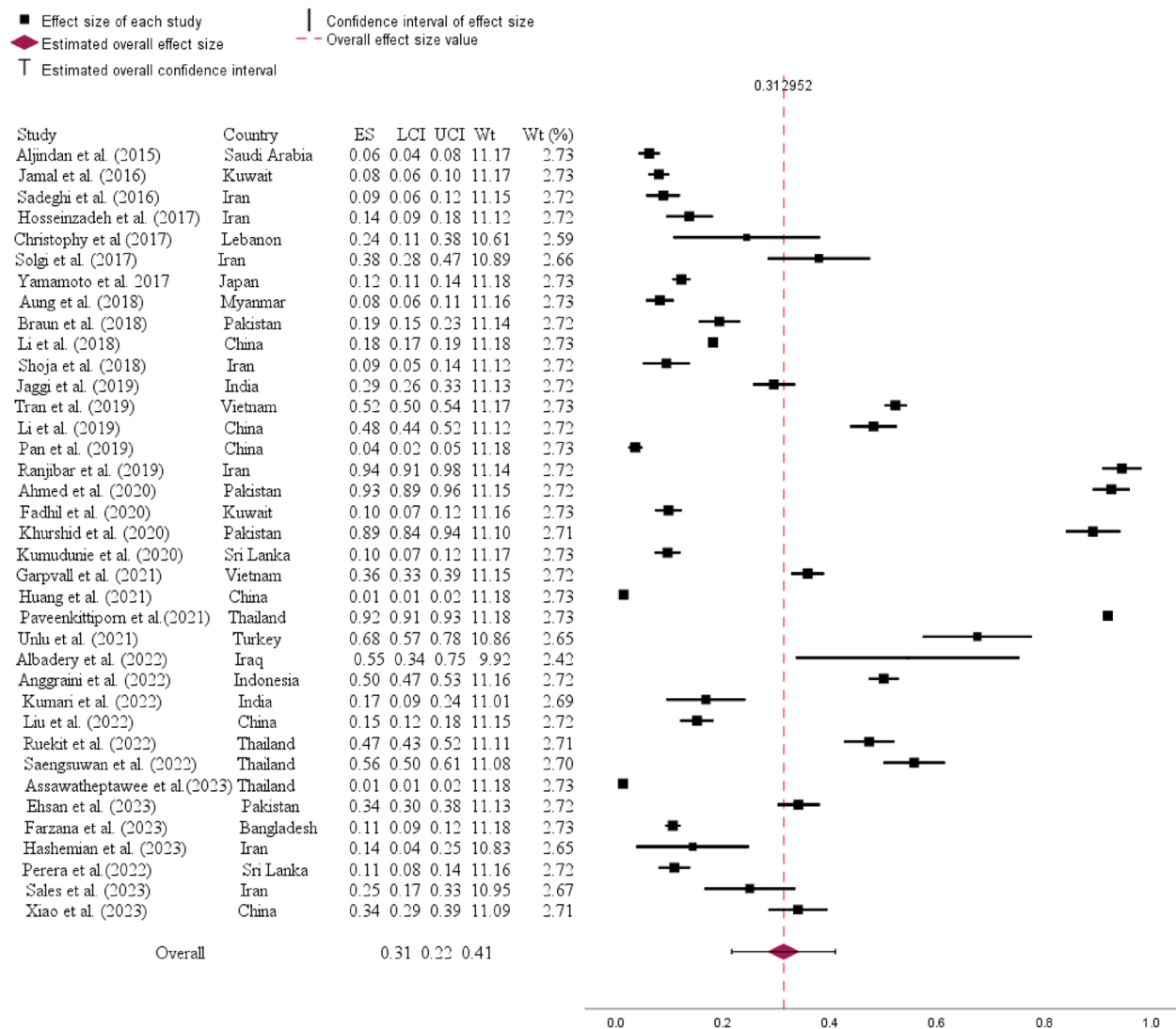
In summary, a total of 56,788 people were studied among 37 research articles, out of which 10,433 patients were diagnosed with infections caused by any CRO. The reported CR incidence rate varied from 1.00 to 94.50% across the studies. According to the meta-analysis results, the pooled prevalence (PPr) of CR was 31.3% (95% CI: 21.6%–41.0%), with a considerable heterogeneity ( $I^2=99.9\%$ ,  $P=0.00$ ) (Fig. 2). The authors deemed a meta-analysis is appropriate since it provided a robust PPr (31.3%) from reliable studies, despite the high heterogeneity ( $I^2=99.9\%$ ). These results highlighted the importance of understanding the available data on prevalence

and molecular epidemiology of carbapenem resistance in Asian countries.

According to the trend chart, the variation in the PPr of CR gradually increased from  $PPr=0.074$  to  $PPr=0.506$ , over the past 10 years (Fig. 3).

The highest pooled prevalence was reported in studies published in Turkey ( $PPr=0.675$ ), whereas the lowest PPr was reported in Saudi Arabia. Iran reported the highest number of studies ( $n=7$ ), with a PPr of 0.06 (Fig. 4).

Analyses were performed to determine CR gene distribution among the included studies. Thirty-one studies have reported data on drug resistance genes, including  $bla_{NDM-1}$ ,  $bla_{NDM-4}$ ,  $bla_{NDM-5}$ ,  $bla_{NDM-7}$ ,  $bla_{KPC-2}$ ,  $bla_{IMP}$ ,  $bla_{VIM}$ ,  $bla_{OXA-48}$ ,  $bla_{OXA-51}$ ,  $bla_{OXA-23}$ ,  $bla_{OXA-181}$ ,  $bla_{OXA-1}$ , and  $bla_{OXA-232}$ , as the single gene occurrences, while multiple co-occurrences, such as  $bla_{NDM-1}+bla_{OXA-48}$ ,  $bla_{NDM-5}+bla_{OXA-181}$ ,  $bla_{NDM-7}+bla_{OXA-48}$ ,  $bla_{NDM}+bla_{OXA-181}$ ,  $bla_{KPC-2}+bla_{OXA-181}$ , and  $bla_{VIM}+bla_{OXA-181}$ , have also been reported.  $bla_{NDM}$  was the commonly reported CR gene (19.6%), and the commonly observed gene co-occurrence was  $bla_{NDM-1}+bla_{OXA-48}$  (25.0%). In summary,  $bla_{NDM}$  represented the majority, accounting for 19.6%, followed by  $bla_{OXA}$  (14.8%) and  $bla_{KPC}$  (13.2%).  $bla_{IMP}$  and  $bla_{VIM}$  represented only 0.4% and 0.2%, respectively.



**Fig. 2** Forest plot of random-effects meta-analysis for the prevalence of carbapenem-resistant organisms (pooled prevalence measure = ES) (ES, effect size; LCI, lower confidence interval; UC, upper confidence interval; Wt, weight; Wt (%), percentage weight)

Different gene co-occurrences were observed in 3.9% of the tested isolates.

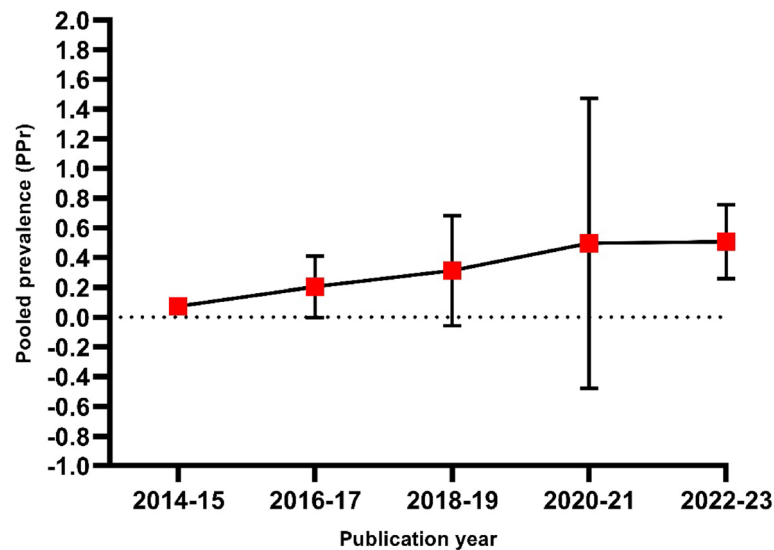
The five main CR genes and different gene co-occurrences were observed in *K. pneumoniae* and CRE, of which *bla<sub>NDM</sub>* was the highest recorded gene, whereas gene co-occurrences were not reported in *A. baumannii* and *Enterobacter* spp. *bla<sub>IMP</sub>* and *bla<sub>KPC</sub>* were not detected in *A. baumannii*. The Fig. 5 shows the distribution of CR genes among different CROs.

Studies conducted in Vietnam [37], Turkey [40], China [53], and Iran [29] did not assess molecular determinants of CR. The Table 2 shows the distribution of CR genes among different Asian countries.

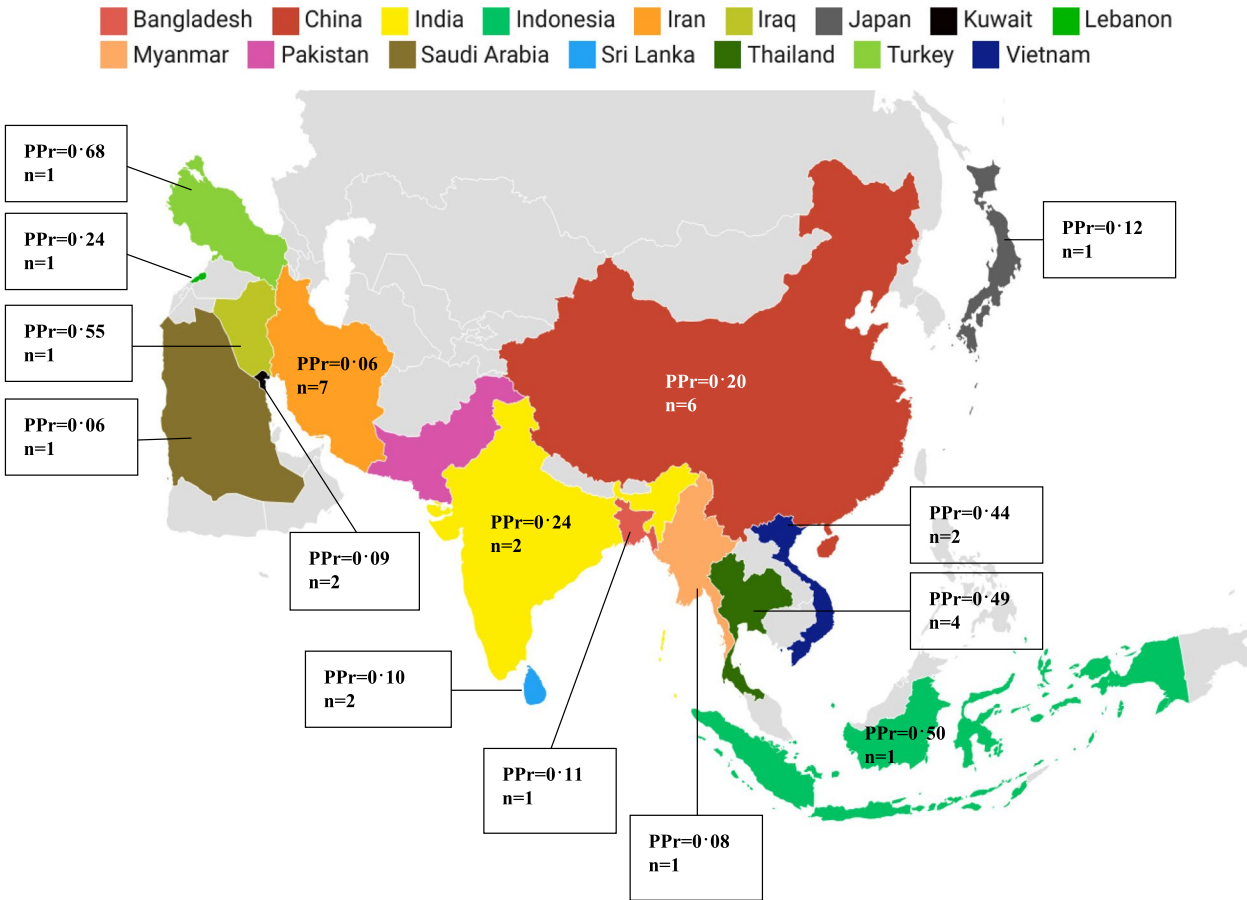
Since substantial heterogeneity was observed in CR prevalence among the reported studies, stratified analysis was conducted to explore potential sources of heterogeneity between studies. Substantial heterogeneity was observed among all the considered subgroups such as; geographical location ( $I^2=99.9$ ), income level ( $I^2=99.9$ ), publication year ( $I^2=99.9$ ), and sample size ( $I^2=99.9$ ). Only the studies published between 2014 and 2016 presented low heterogeneity, with an  $I^2$  of 21.3%.

The results of the statistical tests based on the PPr revealed that studies published between 2014 and 2016 reported a lower CR incidence (7.4%) than studies

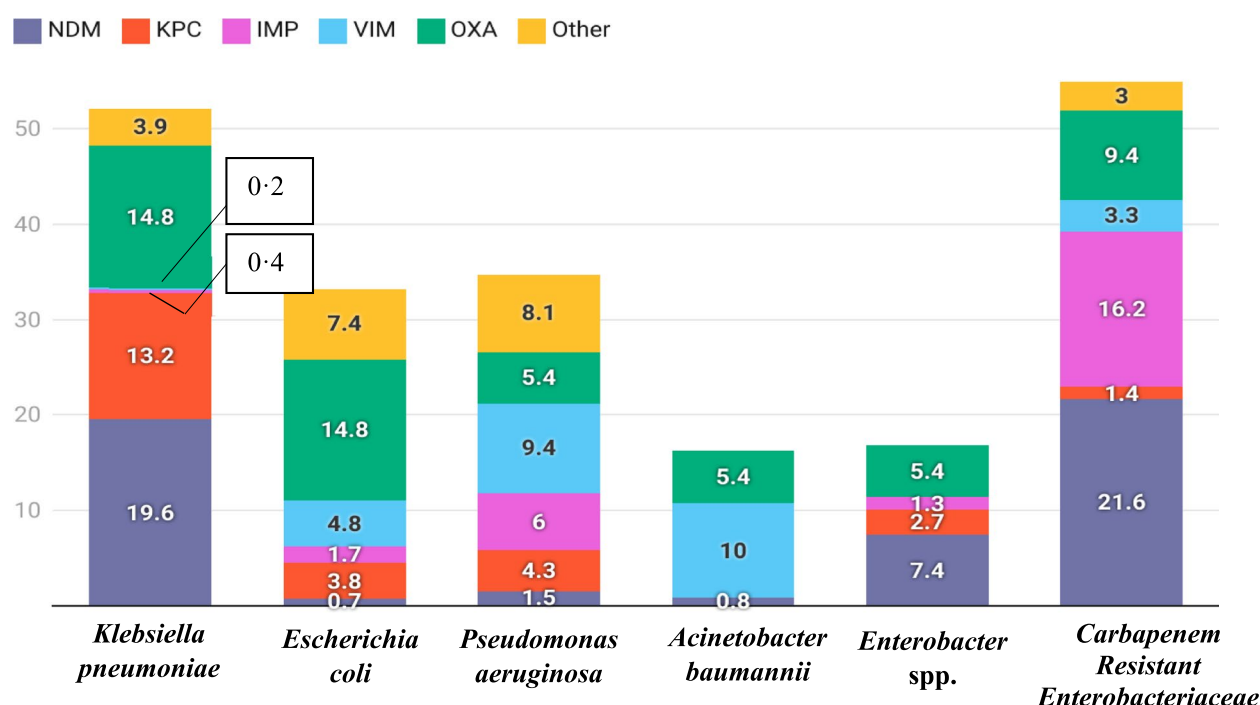




**Fig. 3** Trend chart for the pooled prevalence of carbapenem resistance



**Fig. 4** Pooled prevalence of carbapenem resistance and number of included studies (n) reported in different Asian countries



**Fig. 5** Percentage distribution of carbapenem resistant genes among different carbapenem-resistant organisms

**Table 2** Distribution of carbapenem resistant genes among different Asian countries during the study period

| Country      | <i>bla</i> <sub>NDM</sub> | <i>bla</i> <sub>OXA</sub> | <i>bla</i> <sub>KPC</sub> | <i>bla</i> <sub>IMP</sub> | <i>bla</i> <sub>VIM</sub> | Other gene combinations |
|--------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|-------------------------|
| Saudi Arabia | 0.0%                      | 86.2%                     | 0.0%                      | 0.0%                      | 0.0%                      | 0.0%                    |
| Kuwait       | 9.9%                      | 18.8%                     | 0.0%                      | 0.0%                      | 0.0%                      | 0.0%                    |
| Iran         | 15.6%                     | 18.6%                     | 3.6%                      | 1.0%                      | 9.1%                      | 0.0%                    |
| Lebanon      | 0.0%                      | 10.0%                     | 0.0%                      | 0.0%                      | 0.0%                      | 0.0%                    |
| Japan        | 0.0%                      | 0.0%                      | 0.0%                      | 95.7%                     | 0.0%                      | 0.0%                    |
| Myanmar      | 13.2%                     | 5.7%                      | 0.0%                      | 0.0%                      | 0.0%                      | 0.0%                    |
| Pakistan     | 50.8%                     | 29.7%                     | 14.0%                     | 1.6%                      | 4.1%                      | 3.9%                    |
| China        | 11.7%                     | 0.0%                      | 22.9%                     | 0.7%                      | 0.0%                      | 0.0%                    |
| India        | 1.1%                      | 1.3%                      | 0.0%                      | 0.0%                      | 0.0%                      | 28.2%                   |
| Sri Lanka    | 49.9%                     | 46.0%                     | 0.0%                      | 0.0%                      | 50.0%                     | 0.0%                    |
| Thailand     | 18.7%                     | 13.3%                     | 0.1%                      | 6.2%                      | 9.4%                      | 0.0%                    |
| Iraq         | 0.0%                      | 0.0%                      | 22.7%                     | 22.7%                     | 59.1%                     | 0.0%                    |
| Indonesia    | 0.0%                      | 0.0%                      | 96.5%                     | 0.0%                      | 0.0%                      | 0.0%                    |
| Bangladesh   | 3.9%                      | 0.8%                      | 0.0%                      | 0.0%                      | 0.0%                      | 0.0%                    |

published after 2016. Among different geographical locations, the highest and lowest CR rates were recorded in South Asia and East Asia, respectively. The studies published in upper-middle-income countries reported the highest PPr of CR ( $PPr=37.4\%$ ), as shown in the Table 3.

Univariate meta-regression was conducted to further explore whether the prevalence of CR in Asian countries differs by geographical location, income level, publication

year, and sample size (dependent variable—different subgroups, independent variable—PPr of CR). The meta-regression results for PPr revealed that the prevalence of CR was significantly greater in studies with sample sizes of less than 100 (coefficient =  $-0.400$ ,  $p=0.162$ ), than in studies with 100–200 isolates (coefficient =  $-0.202$ ,  $p=0.289$ ). However, none of the factors was significantly associated with the considered subgroups (Table 3).

**Table 3** Subgroup analysis and univariate meta-regression analysis of potential variables affecting the prevalence of carbapenem resistance among Asian countries

| Variable              | Subgroup            | No. of studies | Pooled prevalence | Sub-group analysis |                               |                    | Univariate meta-regression analysis |                |                         |                              |
|-----------------------|---------------------|----------------|-------------------|--------------------|-------------------------------|--------------------|-------------------------------------|----------------|-------------------------|------------------------------|
|                       |                     |                |                   | 95% CI             | p-value of sub-group analysis | I <sup>2</sup> (%) | Coefficient                         | Standard error | 95% confidence interval | p-value from meta-regression |
| Geographical location | East Asia           | 7              | 18.6%             | 10.7–26.6          | 0.000                         | 99.7               | –0.450                              | 0.329          | –1.145 to 0.245         | 0.190                        |
|                       | West Asia           | 6              | 13.8%             | 15.5–32.0          | 0.000                         | 96.9               | Reference                           | -              | -                       | -                            |
|                       | South Asia          | 16             | 32.3%             | 17.2–47.3          | 0.000                         | 99.7               | –0.124                              | –0.394         | –0.787 to 0.539         | 0.698                        |
|                       | Southeast Asia      | 8              | 42.8%             | 6.4–79.2           | 0.021                         | 100.0              | –0.315                              | –0.311         | –0.972 to 0.342         | 0.326                        |
| Income level          | High income         | 4              | 9.1%              | 6.3–11.8           | 0.000                         | 87.1               | Reference                           | -              | -                       | -                            |
|                       | Upper-middle income | 13             | 37.4%             | 1.92–5.55          | 0.000                         | 100.0              | 0.338                               | 0.382          | –0.468 to 1.145         | 0.388                        |
|                       | Lower-middle income | 20             | 31.9%             | 19.5–44.2          | 0.000                         | 99.6               | 0.151                               | 0.404          | –0.702 to 1.004         | 0.713                        |
| Publication year      | 2014–2016           | 3              | 7.4%              | 6.0–8.9            | 0.000                         | 21.3               | –0.044                              | 0.225          | –0.519 to 0.431         | 0.848                        |
|                       | 2017–2019           | 13             | 30.2%             | 18.5–41.9          | 0.000                         | 99.6               | 0.029                               | 0.119          | –0.224 to 0.281         | 0.814                        |
|                       | 2020–2023           | 21             | 35.4%             | 20.8–50.0          | 0.000                         | 99.9               | Reference                           | -              | -                       | -                            |
| Sample size           | < 100               | 21             | 16.3%             | 12.9–19.7          | 0.000                         | 97.1               | –0.400                              | 0.162          | –0.742 to –0.058        | 0.025*                       |
|                       | 100–200             | 7              | 46.5%             | 24.1–68.8          | 0.000                         | 99.8               | –0.202                              | 0.185          | –0.593 to 0.188         | 0.289                        |
|                       | > 200               | 9              | 48.6%             | 18.2–79.0          | 0.002                         | 100.0              | Reference                           | -              | -                       | -                            |

\* Statistically significant difference was noted

The sensitivity analysis detected that the PPr did not change significantly when any one of the studies was excluded, indicating the stability of the results of the meta-analysis. The funnel plot of standard error with the proportion supplemented by statistical tests provided insights on the publication bias of studies reporting CR prevalence data (Egger's test,  $P=0.00$ ) (Fig. 6).

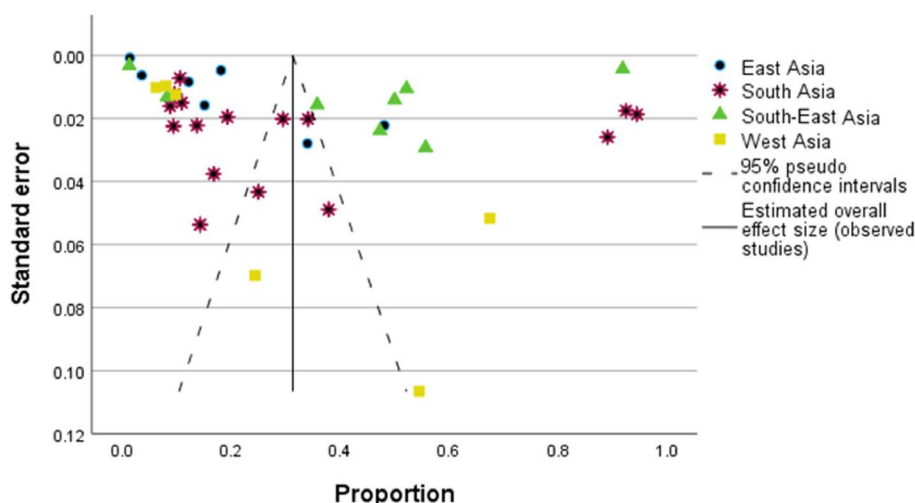
## Discussion

This systematic review and meta-analysis included 37 original studies addressing the prevalence and molecular determinants of CROs in Asian countries. We assessed data from 10,433 patients who were diagnosed with infections caused by CROs, from different Asian countries over a period of 10 years (from January 1<sup>st</sup> 2014 to January 31<sup>st</sup> 2024). To the best of our knowledge, this is the first attempt to study the prevalence of CR and molecular determinants in different geographical regions in Asia. In 2017, the WHO published its first list of “antibiotic-resistant priority pathogens,” which pose a significant threat to public health. This includes CRE (e.g., *E. coli*, *Klebsiella* spp., *Serratia* spp., and *Proteus* spp.), CR *Acinetobacter*, and CR *Pseudomonas* in the most critical group [54]. Therefore, by systematically reviewing and synthesizing reported data, we aimed to identify the prevalence rates, resistance patterns, and trends of CR to minimize further dissemination of CR across Asian countries and around the globe.

The pooled prevalence of CR in the present study was 31.3%, with considerable heterogeneity observed across subgroups (95% CI; 0.22–0.4;  $I^2=99.9\%$ ;  $P=0.00$ ). This indicates an extensive public health challenge that needs urgent attention and coordinated action in infection

control. A notable increase in the prevalence of CR was observed in the last decade from 2014 to 2024, i.e., from a PPr of 7.4% in studies published between 2014 and 2015 to a PPr of 50.6% from 2022 to 2023. The highest CR incidence was reported in Iran (94.5%), followed by Pakistan (92.5% and 89.1%). In both of these studies, one pathogen type was included as the study sample, particularly *P. aeruginosa* in the Iranian study [32] and *A. baumannii* in the Pakistan study [33]. In addition, majority of the included studies ( $n=7/37$ , 18.9%) were conducted in Iran, suggesting that there may be a trend towards CR in Iran. This increasing trend is in agreement with a study conducted in Pakistan, in which the PPr of CR from 2009 to 2010 was reported as 36.0% [55]. In addition, another study reported that the PPr of CR was 30% among Enterobacteriaceae [56]. If this trend of CR continues, carbapenems cannot be used as a drug of choice for the treatment of GNB in the near future [55]. Interestingly, a similar CR trend was reported approximately a decade ago, by the China antimicrobial resistance surveillance program in between 2005 and 2014, from 1.0 to 13.4% [57], and it has continued until 2024 in which the present study reported PPr of CR as 31.3%. In addition, the considerable heterogeneity observed may not be due to publication bias but, may be due to different prevalence rates reported in different geographical regions and the small number of eligible articles included in the present study from each region.

The present study reported notable differences in the prevalence of CR across different Asian regions. The highest prevalence was observed in Southeast Asia ( $PPr=42.8\%$ ), followed by South Asia ( $PPr=32.3\%$ ). In agreement with the findings of the present study, a high



**Fig. 6** The funnel plot depicting publication bias among studies evaluating the pooled prevalence of carbapenem-resistant organisms according to different regions in Asia

prevalence of CRAB in South Asia and Southeast Asia was reported in a previously published meta-analysis [9]. The absence of eligible studies from Central and Northern Asia suggests a gap in research and surveillance in these regions, which may be due to limited resources or differing healthcare priorities. The key cause for this increase in CR in South Asia and Southeast Asia may be due to excessive and improperly prescribed antibiotics, in which 10.0 to 50.0% of all antibiotics are improperly prescribed. The presence of few antibiotic prescription policies and/or no antibiotic stewardship or beginning to implement such programs may have caused this inappropriate antibiotic prescription [9]. In addition, high population density and lack of infection control strategies also cause high CR rates in Southeast Asia, and South Asia. The variations present in CR rates emphasize the need for region-specific interventions and the implementation of policies in the local epidemiological context.

The highest prevalence of CR was observed among upper-middle-income countries ( $PPr=37.4\%$ ), followed by lower-middle-income countries ( $PPr=31.9\%$ ). In high-income countries, the  $PPr$  of CR is as low as 9.1%. The reported pooled prevalence of the use of non-prescribed antibiotics was considerably high (78.0%) in low- and middle-income countries, which may ultimately lead to antibiotic resistance [58]. The unaffordability of the cost of healthcare and access to antibiotics, the high burden of infectious diseases due to a lack of infrastructure facilities and the use of antibiotics as a “quick fix” to fracture the infrastructure, weak regulatory mechanisms, self-medication with antibiotics against common infections, purchase of medicines from unregulated drug dispensaries, etc. are potential causes of the disproportionately high rate of carbapenem resistance among low- and middle-income countries [10, 58]. In addition, infections caused by CROs are associated with increased hospital stays and mortality, mainly in low-income and middle-income countries, creating a considerable burden [59].

Relatively high percentage of included studies ( $n=31/37$ , 83.78%) have investigated the molecular determinants of CR. The distribution of these resistant genes varied across different regions and CROs indicating the diverse nature of mechanisms driving CR. The highest prevalence of  $bla_{NDM}$  (19.6%) was observed with  $bla_{NDM-1}$  variant being the commonest, supporting previously published studies, where they have mentioned  $bla_{NDM-1}$  as the common variant in India and China, followed by  $bla_{OXA}$  (14.8%) and  $bla_{KPC}$  (13.2%) [9, 55, 60].  $bla_{NDM-1} + bla_{OXA-48}$  was the most repeatedly reported gene co-occurrence (25.0%).  $bla_{NDM-1}$  was the predominant genetic determinant in CR *K. pneumoniae* accounting for 19.6% of the total resistant genes, which is in accordance with the published data. Disparities were

observed where, Umair et al. [55] reported  $bla_{NDM-1}$  as the predominant CR gene in *E. coli*, but in the present study,  $bla_{NDM}$  was reported only in 0.7% of the *E. coli*. Identifying molecular epidemiology of CR is crucial in the development of targeted interventions. Co-occurrence of multiple CR genes in one organism complicates treatment options, and further highlights the need for ongoing research to monitor the evolution of CR genes.

The  $PPr$  reported in the present study during the period from 2014 to 2023 maximally describes the current status of CR among different regions in Asia. These comparatively high CR rates cause a significant burden in clinical practice. Infections caused by CROs cause a substantial burden on healthcare-associated costs due to prolonged hospital stays, and frequent and continuous antibiotic treatment. Effective strategies to combat this CR threat, including strengthening antibiotic stewardship programs, implementing and improving infection control strategies, and enhancing antibiotic surveillance programs at the regional and national levels to monitor resistance trends, should be considered.

A major strength of this study is that, it fills the gap in collective data on current rates of CR prevalence and reported molecular determinants in Asia, which is the largest continent with the highest population density in the world. Despite the comprehensive nature of this study, several limitations were also noted. Out of 2518 records initially screened, only one study was aligned with the inclusion criteria of the present study and excluded, due to publication in a non-English language. In addition, although English is considered as the second language in many of the Asian countries, we noticed that most of the studies were published in English language. Therefore, exclusion of non-English articles cannot be introduced as a limitation. The heterogeneity across selected studies represents a critical limitation, and we attempted to minimize heterogeneity by using narrow inclusion criteria and assessing the quality of selected studies via the JBI quality appraisal tool. Although the overall number of patients included was high, due to the inclusion of a limited number of studies, the power to assess publication bias was limited. Owing to the interpretation of non-significant data with significant data, non-uniformity of the geographical distribution of CROs, etc. may be causative for the publication bias observed in the present study and elsewhere [55, 61]. Heterogeneity among studies, varying methodologies, varying sample sizes, varying organism types, and differences in reporting methodologies may affect the pooled prevalence and comparability of results. Standardized reporting of antibiotic resistance data should be ensured to facilitate further accurate comparisons and analyses. In addition, this study did not report the status of CR in Central and

Northern Asia, as none of the studies met the inclusion criteria. Although India is known to be a hot spot for CR gene prevalence, especially for *bla*<sub>NDM</sub> [7], one study conducted in India was included in the present study since only one study met the inclusion criteria.

In conclusion, our systematic review and meta-analysis provide a detailed overview of the prevalence and associated molecular determinants of CR among Asian countries, addressing a critical gap in global antibiotic resistance surveillance. This growing prevalence over time emphasizes the need for continuous surveillance, robust antibiotic stewardship programs, and enhanced infection control strategies tailored to the national and regional context to reduce further spread of CR. Therefore, reducing the impact of CR infections will safeguard the efficacy of carbapenem antibiotics to improve patient care in the future. Surveillance studies should be conducted in different regions, including Europe, America, and Africa, to study the overall prevalence of CR to obtain a global picture on evolution of CR.

#### Abbreviations

|        |                                                                    |
|--------|--------------------------------------------------------------------|
| CR     | Carbapenem resistance                                              |
| CRE    | Carbapenem-resistant Enterobacteriaceae                            |
| CRO    | Carbapenem resistance organisms                                    |
| GRADE  | Grading of Recommendations, Assessment, Development and Evaluation |
| PRISMA | Preferred Reporting Items for Systematic reviews and Meta-Analyses |
| MeSH   | Medical Subject Headings                                           |
| PPr    | Pooled prevalence                                                  |
| WHO    | World Health Organization                                          |
| NJ     | Nishadi Jayathilaka                                                |
| SS     | Sashini Shehana                                                    |
| TS     | Thamarasi Senaratne                                                |
| DN     | Dilini Nakkawita                                                   |

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13643-025-02776-5>.

Supplementary Material 1. Search strategy (for PubMed).

Supplementary Material 2. Risk of bias assessment with Joanna Briggs Institute (JBI) critical appraisal tool. Case control studies. Cohort studies. Cross sectional studies. Prevalence studies.

Supplementary Material 3. Summary of the grade evaluation of evidences according to GRADE method.

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#### Patient and public involvement

Not applicable.

#### Authors' contributions

NJ and TS generated the idea for this work. NJ and SS conducted the literature search, data extraction, data analyses, and prepared the figures and tables. DN and TS accessed and resolved the discrepancies and verified the data. NJ drafted the original manuscript. NJ, DN, and TS edited the manuscript. All authors had full access to all the data in the study and agreed to submit for publication.

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#### Data availability

All the data generated or analyzed during this review are included in this manuscript and supplementary files.

#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare that they have no competing interests.

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