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Extended-spectrum beta-lactamase and carbapenemase-producing Gram-negative bacteria in urinary tract infections in Ethiopia: a systematic review and meta-analysis

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Abstract

Background Urinary tract infection (UTI) is one of the most common infections worldwide, particularly in developing countries. It also is among the most prevalent nosocomial infections, largely due to the widespread use of urinary catheters in hospitalized patients. These catheters often act as reservoirs for multidrug-resistant bacteria, including extended-spectrum beta-lactamase- and carbapenemase-producing pathogens, which significantly limit treatment options and delay appropriate care. This systematic review and meta-analysis, therefore, aimed to assess the pooled prevalence of ESBL- and carbapenemase-producing Gram-negative bacteria associated with UTIs in Ethiopia.

Methods A systematic literature search of all available electronic databases such as PubMed, Hinari, Google Scholar and EMBASE, Scopus, and African journal online was performed. The quality of the included studies was assessed via the Joanna Briggs Institute critical appraisal tool. The data were extracted from the eligible studies via Microsoft Excel 2019 and analysed via STATA version 17. The presence of between-study heterogeneity was checked via the Cochrane Q statistic, and the magnitude was quantitatively measured via I^2 statistics. To determine the possible sources of heterogeneity, a subgroup analysis was performed. Additionally, a sensitivity analysis was conducted to determine the influence of single studies on the pooled estimates. Publication bias was checked via funnel plots and Egger's regression tests. A p value of less than 0.05 was evidence of heterogeneity and small study effects according to the Cochrane Q statistic and Egger's test, respectively. The protocol was registered (PROSPERO ID: CRD42024564656).

Results A total of 20 studies with 1010 and 557 Gram-negative bacterial isolates from 6263 and 2199 study participants for extended-spectrum beta-lactamase and carbapenemase, respectively, were included. The overall pooled prevalence rates of extended-spectrum beta-lactamase-producing and carbapenemase-producing Gram-negative bacteria in Ethiopia were 30.92% (95% CI: 21.23–40.61, $P < 0.001$) and 15.12% (95% CI: -0.28–30.52, $P < 0.001$), respectively. The most common extended-spectrum beta-lactamase producers were *Klebsiella* spp., 43.91% (95% CI: 30.63–57.18, $P < 0.001$), followed by *E. coli*, 31.14% (95% CI: 21.27–41.01, $P < 0.001$). Similarly, the predominant carbapenemase producer was *Klebsiella* spp., 17.78% and *E. coli*, 11.42%.

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Conclusion and recommendations.

In this meta-analysis, the pooled prevalence of extended-spectrum beta-lactamase- and carbapenemase-producing Gram-negative bacteria was significantly high. During the development of empiric treatment protocols for urinary tract infections, extended-spectrum beta-lactamase- and carbapenemase-producing uro-pathogens should not be underestimated.

Keywords Urinary tract infection, Extended-spectrum beta-lactamase, Carbapenemase, Gram-negative bacteria

Introduction

Urinary tract infection (UTI) is one of the most common infections worldwide, particularly in developing countries. This infection is observed in all age groups of people of both sexes and affects more than 150 million people, resulting in over $6 billion in cost per year globally [1]. The majority of UTIs are caused by bacteria, especially Gram-negative bacteria. Among Gram-negative bacteria, *Escherichia coli* (*E. coli*) is the most common, followed by *Proteus* species, *Klebsiella* species, *Pseudomonas aeruginosa*, *Enterobacter* species, and *Citrobacter* species, which are the common isolates that affect the urinary system [2–4]. These bacteria are transferred from the gastrointestinal tract to the urethral opening and begin to multiply. They cause subsequent infection of any part of the urinary system, including the urethra, bladder, ureters, and kidneys [5].

Clinically, UTIs are classified as uncomplicated or complicated infections. The former can affect healthy individuals who have no renal system structural or functional abnormalities. However, the latter occurs in patients who have structural or functional abnormalities in the renal system [5, 6]. Bacterial UTIs occur in both community and, most commonly, hospital settings and account for 40% of all nosocomial infections [7]. As 15–25% of hospitalized patients use urinary catheters [8], the most common nosocomial UTI is catheter-associated UTI, which accounts for 75–80% of all nosocomial urinary infections [8–10] and 30–40% of all hospital-acquired infections [11].

In developing countries, the empirical management of UTI may contribute to the emergence and spread of resistant strains, such as extended-spectrum beta-lactamase (ESBL)- and carbapenemase-producing bacteria [12]. Prolonged use of urinary catheters can further serve as a reservoir for these multidrug-resistant bacteria [13].

Extended-spectrum beta-lactamases are enzymes that are able to break down penicillins, cephalosporins, and monobactams [14]. Carbapenemases are also enzymes that have the ability to hydrolyse penicillins, cephalosporins, monobactams, and carbapenems [15]. The ESBL and carbapenemase genes are plasmids, and transposon-mediated genes can be spread easily to other species of bacteria. Furthermore, the plasmids and transposons that carry ESBL and carbapenemase genes also commonly encode resistance genes for many non-beta-lactam antibiotics [16]. Therefore, ESBL- and carbapenemase-producing strains are often co-resistant to other classes of antibiotics, including trimethoprim/sulfamethoxazole, fluoroquinolones, and aminoglycosides [17].

The ESBL and carbapenemase-producing pathogens limit therapeutic options and lead to delays in appropriate treatment. Compared with infections caused by other pathogens, infections caused by ESBL- and carbapenemase-producing pathogens are associated with prolonged hospitalization, increased health costs, morbidity, and mortality [14]. In developing countries such as Ethiopia, overuse and misuse of antibiotic agents occur in clinical and nonclinical settings. Furthermore, weak health systems, environmental contamination, poor water, sanitation, hygiene infrastructure and practices propel emergencies and spread ESBL- and carbapenemase-producing pathogens [18].

The existing review related to UTIs in Ethiopia focused on the prevalence of UTIs among different populations, such as pregnant women and diabetes mellitus patients, who account for 14.5–16% [4, 19, 20], and 12.8% of people living with human immunodeficiency virus (HIV) [21]. However, the magnitude of ESBL- and carbapenemase-producing pathogens among UTIs is still lacking. Therefore, this systematic review and meta-analysis aimed to identify ESBL- and carbapenemase-producing Gram-negative bacteria related to UTIs in Ethiopia.

Methods

Study design and protocol registration

The protocol of this review was registered (PROSPERO ID: CRD42024564656), and this systematic reviews and meta-analyses was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (S1 Table).

Search strategy

Two authors (MT, MA) searched the PubMed, Hinari, Google Scholar and EMBASE, Scopus, and African journal online electronic databases until July 16, 2024, to identify eligible studies. The search methods were established via "AND" and "OR" Boolean operators. Articles

were identified via MeSH terms and keywords of the title, for example, ((((((extended-spectrum beta-lactamases) OR (ESBL)) OR (carbapenemase)) OR (multidrug resistance)) AND ((((gram-negative bacteria) OR (enterobacteriaceae)) OR (enterobacterales)) OR (*E. coli*))) AND ((urinary tract infection*) OR (UTI))) AND (Ethiopia).

Outcome of interest

The main outcomes were the rates of ESBL- and carbapenemase-producing Gram-negative bacteria related to UTIs in Ethiopia. We estimated the prevalence of ESBL- and carbapenemase-producing uropathogens by dividing the number of ESBL- and carbapenemase-producing pathogens by the total number of tested isolates.

Eligibility criteria

We used the CoCoPop (Condition, Context, and Population) approach, where the prevalence of ESBL- and carbapenemase-producing Gram-negative bacilli was considered the condition (CO), individuals suspected of having UTIs constituted the population (POP), and Ethiopia served as the context (CO) for determining the inclusion and exclusion criteria.

Therefore, studies were considered pertinent to our analysis when they reported the total number of Gram-negative bacterial isolates from laboratory-confirmed UTI cases and ESBL-producing and/or carbapenemase-producing isolates without restrictions on publication year and studies conducted in Ethiopia. In addition, all participants from all age groups and all full-text articles written in English were included in this systematic review and meta-analysis. However, case reports, case series studies, and samples other than urine were excluded.

Quality assessment

The quality of studies was assessed via standard critical appraisal tools prepared by the Joanna Briggs Institute (JBI) for prevalence, case–control and cohort studies [22]. The JBI appraisal checklist contains 9, 10 and 11 questions for cross-sectional, case–control and cohort studies, respectively. These critical appraisal tools have yes, 'no', 'unclear', and 'not applicable' options. For each question, a score of 0 was assigned for 'no', 'unclear', and 'not applicable' and 1 for 'yes'. The total score is calculated by counting the number of "yes" in each row. Two reviewers (MT. and MA.) were independently assessed to check the quality of the included studies. The discrepancies were solved by taking the average score. On the basis of the score of the quality assessment tool, the highest score had the minimum risk of bias. Overall scores range from 0–4, 5–6, and 7–9 for prevalence studies; from 0–4, 5–7, and 8–10 for case–control studies; and from 0–4, 5–8, and 9–11 for cohort studies, which are declared high, moderate, and low risk of bias, respectively [23]. Finally, studies with a score of five and above for "yes" (have moderate and low risk of bias) were included in the systematic review and meta-analysis (S1, Table).

Data extraction and management

All the records from different electronic databases were combined and properly exported to Endnote version 9.2 (Clarivate Analytics, Philadelphia, PA, USA). The articles were merged into one folder to identify and remove duplicate articles. All duplicate studies were removed, and the full-text articles were downloaded manually via Endnote software. Data screening was carried out by two reviewers (MT. MA.) who independently reviewed the titles and abstracts of all relevant studies from downloaded articles on the basis of the predefined inclusion criteria.

All important parameters were extracted from each study by two authors (MT. & MA.) independently via Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). Discrepancies between them were resolved through consensus or with an additional reviewer (G.A). The data extraction format was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines. For each study, the primary author, year of publication, sample size, study design, study year, study area, age group, and methods of detection for ESBL and carbapenemase were extracted. In addition, individual ESBL-producing and carbapenemase-producing isolates with the respective total number of carbapenemase-producing and ESBL-producing isolates were extracted.

Statistical analysis

The extracted data were exported to STATA software version 17 for analysis. We conducted a meta-analysis via the random effects model of DerSimonian and Laird to estimate the pooled prevalence and 95% confidence intervals (CIs) for carbapenemase- and ESBL-producing isolates [24]. The presence of between-study heterogeneity was checked by using the Cochrane Q statistic. The magnitude of heterogeneity between the included studies was quantitatively measured by the index of heterogeneity (I^2 statistic). $I^2 < 25\%$ indicates low heterogeneity, $I^2 = 50–75\%$ indicates moderate heterogeneity, and $I^2 > 75\%$ indicates high heterogeneity. The significance of heterogeneity was determined by the p value of the Cochrane Q statistic, and a p value of less than 0.05 was evidence of heterogeneity [25]. To minimize the variance of estimated points between primary studies, a subgroup analysis was performed in reference to the study regions, study year, age categories, and methods of confirmation for the outcome. Additionally, a sensitivity

analysis was conducted to determine the influence of single studies on the pooled estimates. Publication bias (small study effect) was checked by using a funnel plot test graphically and more objectively through Egger's regression tests. A statistically significant Egger's test (*P* value < 0.05) indicates the presence of a small study effect [26].

Results

Study selection and identification

We identified a total of 433 studies: 432 from available scientific databases and 1 from reference tracing. Of these, 276 were removed due to duplication. One hundred fifty-seven studies were screened by reviewing their titles, abstracts, and full texts, and 104 studies were excluded for the following reasons: 37 studies were conducted outside Ethiopia, 53 involved specimens other than urine, and 14 were review articles. Subsequently, 53 studies were assessed for eligibility. Among these, 24 studies were excluded because outcomes such as ESBL- and CP-producing isolates were not reported. Six studies were excluded because ESBL-producing isolates were reported from mixed specimens, making it difficult to extract data specifically for urine specimens. Three articles were removed: two did not meet the quality criteria, and one did not report the sample size. Finally, 20 studies were deemed eligible and included in the final meta-analysis, as shown in the PRISMA flow diagram (Fig. 1).

Characteristics of the studies included in the systematic review and meta-analysis

In this systematic review and meta-analysis, a total of 20 studies were included. Of these, 18 (90%) were cross-sectional studies, while the remaining two were case–control and longitudinal studies. Regarding sampling methods, 12 (60%) used convenience sampling, 6 (30%) used

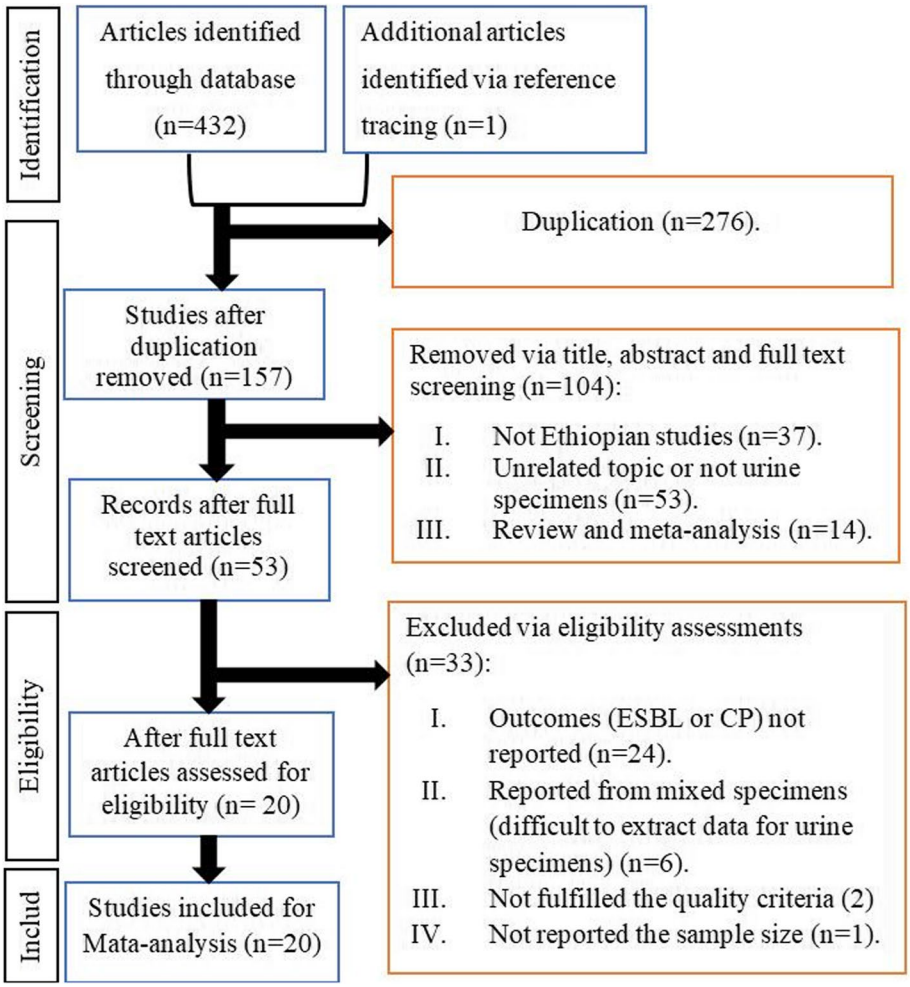

Fig. 1 A flow diagram of study selection for systematic review and meta-analysis of the prevalence of ESBL- and carbapenemase-producing Gram-negative bacteria related to UTIs in Ethiopia

Table 1 Characteristics of individual studies included in the meta-analysis of ESBL- and carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia

Study (Author, Year)	Study year	Study area	Study design	Sampling technique	Patient background	Patient status	sex	Mean age (Year)	Age group	Inve. m	Sample size	Study setting	ESBL methods	No tested isolates	No ESBL-producer N (%)
Eshetie et al., 2015 [28]	2014	Gondar	CS	Convenient	UTI-suspected patients	Infection	Both sex	37.1	All	P	442	Outpatient	CHROM agar	183	5 (2.73)
Abayneh et al., 2018 [29]	2016	Jimma	CS	Convenient	UTI-suspected patients	Infection	Both sex	35.07	Adult	P	226	Outpatient	DDST	49	9 (18.4)
											116	Inpatient	DDST	25	8 (32.0)
Gizachew et al., 2019 [30]	2016	Jimma	CS	Convenient	UTI-suspected patients	Infection	Female	29.6	Adult	P	424	Outpatient	DDST	92	53 (57.61)
Gebremariam et al., 2019 [31]	2017	Mekelle	CS	Convenient	UTI-suspected patients	Infection	Both sex	16–35	Adult	P	341	Outpatient	DDST	47	12 (25.53)
Endalamaw et al., 2020 [32]	2017	Gondar	CS	Systematic random	HIV-positive patients	Both infection & colonization	Both sex	37.9	All	P	387	Outpatient	DDST	42	9 (21.43)
Biset et al., 2020 [33]	2017	Gondar	CS	Systematic random	Pregnant women	Both infection & colonization	Female	26	Adult	P	384	Outpatient	CDT	33	6 (18.18)
Belete et al., 2020 [34]	2017	Dessie	CS	Convenient	Pregnant women	Infection	Female	26.7	Adult	P	323	Outpatient	CDT	20	3 (15.00)
Alemu et al., 2020 [35]	2018	Dessie	CS	Simple random	Diabetic patients	Both infection & colonization	Both sex	≥15	Adult	P	336	Outpatient	CDT	28	2 (18.21)
Agegnehu et al., 2020 [36]	2018	Hawassa	CS	Convenient	UTI-suspected patients	Infection	Both sex	≤14	Children	P	284	Outpatient	DDST	72	30 (41.67)
Getie et al., 2023 [27]	2018	Addis Ababa	CS	Convenient	Pregnant women	Both infection & colonization	Female	>20	Adult	P	177	Both in & outpatient	DDST	15	6 (40.00)
Fenta et al., 2020 [37]	2019	Bahir Dar	CS	Systematic random	UTI-suspected patients	Infection	Both sex	6 (1–15)	Children	P	299	Outpatient	DDST	44	6 (13.64)
Kasew et al., 2021 [38]	2019	Gondar	CS	Convenient	Urinary stone patients	Infection	Both sex	-	All	P	300	Outpatient	CDT	26	9 (34.62)
Ameshe et al., 2022 [39]	2019	Bahir Dar	CS	Simple random	UTI-suspected patients	Infection	Both sex	32	All	P	385	Outpatient	CDT	38	10 (26.32)
Gebremedhin et al., 2023 [40]	2020	Mekelle	CS	Convenient	UTI-suspected patients	Infection	Both sex	30	All	P	171	Outpatient	CDT	36	11 (30.6)
											126	Inpatient	CDT	31	28 (90.3)
Elale et al., 2023 [41]	2020–2021	Arba Minch	CS	Convenient	UTI-suspected patients	Infection	Both sex	-	Children	P	246	Outpatient	DDST	21	12 (57.14)

Table 1 (continued)

Study (Author, Year)	Study year	Study area	Study design	Sampling technique	Patient background	Patient status	sex	Mean age (Year)	Age group	Inve. m	Sample size	Study setting	ESBL methods	No tested isolates	No ESBL-producer N (%)
Simeneh et al., 2022 [42]	2021	Arba Minch	CS	Systematic random	HIV-positive patients	Infection	Both sex	42.9	Adult	P	251	Outpatient	DDST	32	9 (28.63)
Seid et al., 2023 [6]	2021	Arba Minch	CC	Systematic random	UTI-suspected patients	Both infection & colonization	Female	20.8	Adult	P	296	Outpatient	DDST	47	26 (55.32)
Teferi et al., 2023 [43]	2021	Jimma	CS	Convenient	Patients admitted for gynecological cases	Both infection & colonization	Female	31.9	Adult	P	386	Both in & outpatient	DDST	77	16 (20.78)
Asmare et al., 2024 [44]	2022	Bahir Dar	LC	Convenient	Patients had indwelling urinary catheter	Infection	Both sex	38	All	P	363	Inpatient	CDT	52	10 (19.23)
	Carbapenemase-producing Gram-negative bacteria												**CP-method**	**No of isolates**	**CP-producer** N (%)
Eshetie et al., 2015 [28]	2014	Gondar	CS	Convenient	UTI-suspected patients	Infection	Both sex	37	All	P	442	outpatient	CHROM agar, KPC agar	183	5 (2.7)
Gizachew et al., 2019 [30]	2016	Jimma	CS	Convenient	UTI-suspected patients	Infection	Female	30	Adult	P	424	outpatient	MHT	92	41 (45)
Mitiku et al., 2022 [45]	2020	Arba Minch	CS	Systematic random	UTI-suspected patients	Infection	Both sex	40	Adult	P	422		mCIM	131	11 (8.4)
Gebremedhin et al., 2023 [40]	2020	Mekelle	CS	Convenient	UTI-suspected patients	Infection	Both sex	30	All	P	171	outpatient	MHT	36	0 (0)
											126	Inpatient	MHT	31	7 (22.6)
Simeneh et al., 2022 [42]	2021	Arba Minch	CS	Systematic random	HIV-positive patients	Infection	Both sex	43	Adult	P	251	outpatient	mCIM	32	5 (16)
Asmare et al., 2024 [44]	2022	Bahir Dar	LC	Convenient	Patients had indwelling urinary catheter	Infection	Both sex	38	All	P	363	Inpatient	mCIM	52	3 (5.8)

ESBL methods: methods of confirmation, *Inve. M* Investigation methods, *P* Phenotype, *CS* Cross-sectional, *CC* Case–control, *LC* Longitudinal cohort, *UTI* Urinary tract infection, *ESBL* Extended-spectrum beta-lactamases, *CP* Carbapenemase, *CP-method* Carbapenemase confirmation methods, *No* Number, *HIV* Human immunodeficiency virus, *CDT* Combined disk test, *DDST* Double disk synergy test, *MHT* Modified carbapenem inactivation method, *MHT* Modified Hodge test

systematic random sampling, and 2 (10%) used simple random sampling. Fifteen (75%) of the studies were conducted between 2020 and 2024. In terms of age groups, 3 (15%) studies focused on children, 10 (50%) on adults, and 7 (35%) included participants of all age groups.

Among these studies, 14 investigated ESBL-producing isolates, 5 focused on both ESBL- and carbapenemase-producing isolates, and 1 study examined carbapenemase-producing isolates exclusively. All the studies included in this review were conducted in five regions and one city administration (Addis Ababa) in Ethiopia. Of the 20 studies, 9 (45%) were from the Amhara region, 4 (20%) from southern Ethiopia, 3 (15%) from Oromia, 2 (10%) from Tigray, and 1 (5%) each from Addis Ababa and Sidama (Table 1).

Eleven (57.9%) of the reviewed articles used the double disk synergy test (DDST), 7 (36.8%) used the combined disk test (CDT), and the remaining 1 (5.3%) article used CHROM agar for the detection of ESBL phenotypes. All of these studies were performed phenotypically. Among the 6 studies reviewed for carbapenemase activity, 3 (50%) used the modified carbapenem inactivation method (mCIM), 2 (33%) used the modified Hodge test (MHT), and 1 used CHROM agar or KPC agar methods for the detection of carbapenemase. In total, 1010 and 557 Gram-negative bacterial isolates from 6263 and 2199 urine samples for ESBL and carbapenemase, respectively, were included. The minimum and maximum sample sizes were 177 [27] and 442 [28], respectively (Table 1).

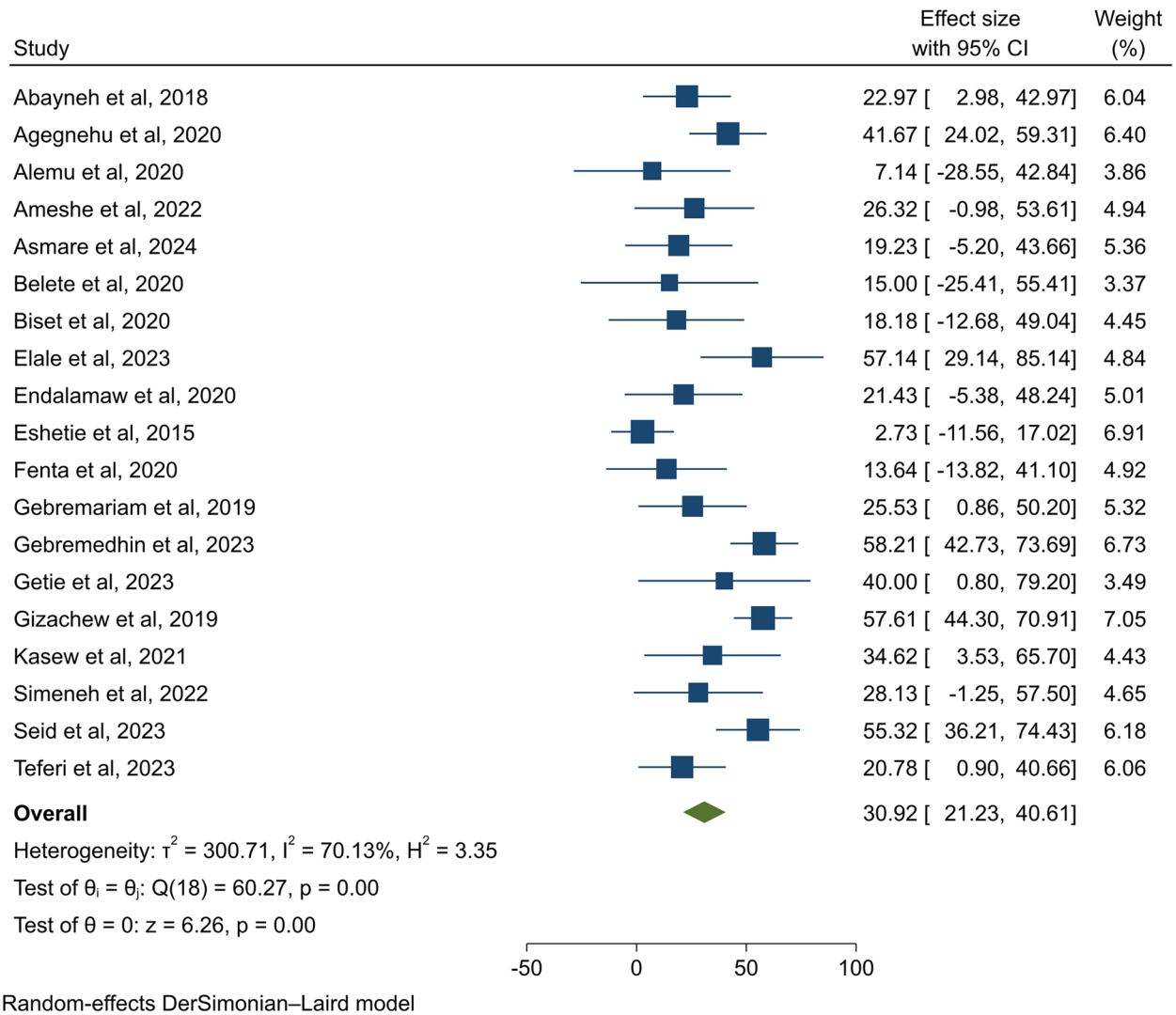

Fig. 2 Forest plot for ESBL-producing Gram-negative bacteria among UTIs in Ethiopia

Pooled estimate of ESBL- and carbapenemase-producing uropathogens

The pooled rates of ESBL- and carbapenemase-producing Gram-negative bacteria were determined for 1010 and 557 tested isolates, respectively. Accordingly, the overall pooled estimate of ESBL-producing Gram-negative bacteria was 30.92% (95% CI: 21.23–40.61, $P<0.001$), with a moderate level of heterogeneity ($I^2=70.13\%$), as indicated in (Fig. 2). The pooled estimate of carbapenemase-producing Gram-negative bacteria was 15.12% (95% CI: -0.28–30.52, $P<0.001$), with a significant level of heterogeneity ($I^2=72.95\%$), as demonstrated in (Fig. 3). The predominant ESBL producer was *Klebsiella* spp., 43.91% (95% CI: 30.63–57.18, $P<0.001$), followed by *E. coli*, 31.14% (95% CI: 21.27–41.01, $P<0.001$) (Figs. 4 and 5), respectively.

Among the different species, the ESBL production proportion were 36.98% (98/265) for *Klebsiella* spp., 31.82% (14/44) for *Proteus* spp., 25.99% (151/581) for *E. coli*, 17.65% (9/51) for *Enterobacter* spp., and 13.89% (5/36) for *Citrobacter* spp. (Table 2). Similarly, the predominant carbapenemase producer was *Klebsiella* spp., 17.78% (24/135), followed by *E. coli*, 11.42% (33/289), as shown in (Table 2).

Publication bias

Publication bias was assessed to determine bias related to published and unpublished studies. The analysis of both ESBLs and carbapenamases revealed an unequal visual distribution of study effect sizes in the funnel plot (Figs. 6 and 7), respectively. However, Egger's test revealed a non-significant publication bias ($P=0.212$ and $P=0.760$) for the ESBL- and carbapenemase-producing isolates, as presented in Tables 3 and 4, respectively.

Sensitivity analysis

According to the random effects model, there were no studies that excessively influenced the overall pooled estimates of the rates of ESBL- and carbapenemase-producing Gram-negative bacteria among UTIs (Table 5).

Subgroup analysis of ESBL- and carbapenemase-producing isolates

Subgroup analysis for ESBL- and carbapenemase-producing isolates was performed across the administrative regions of the country, study year, age group, sex and methods of detecting ESBL. Therefore, the highest pooled estimate of ESBL producers was observed in South Ethiopia (48.91%), followed by Tigray (43.34%), whereas the lowest pooled estimate was reported in Amhara (14.07%). When subgroup analysis was performed by study year, the pooled prevalence of ESBL producers was greater in studies conducted from 2019–2022 (35.99%) than in those conducted from 2014–2018 (26.27%). Additionally, the highest prevalence rate of ESBL was reported in children (37.85%), followed by adults (31.65%), and the highest pooled estimate of ESBL was recorded in females (37.59%) compared with other sexes (28.09%), as indicated in Table 6. Regarding patient status and study settings, the highest pooled prevalence of ESBL-producing isolates were reported in cases of infection (33.64%; 16.90–50.38) compared to both infection and colonization (28.74%; 12.93–44.55). Similarly, the prevalence was higher among inpatients (48.34%; -3.61–100.29) than

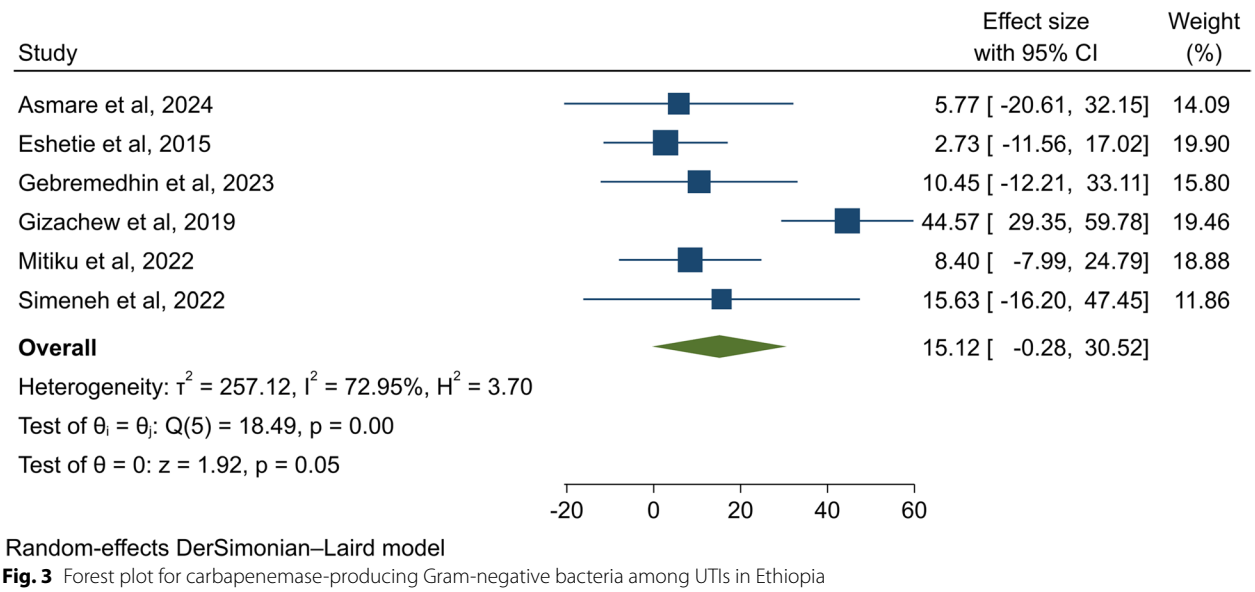

Fig. 3 Forest plot for carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia

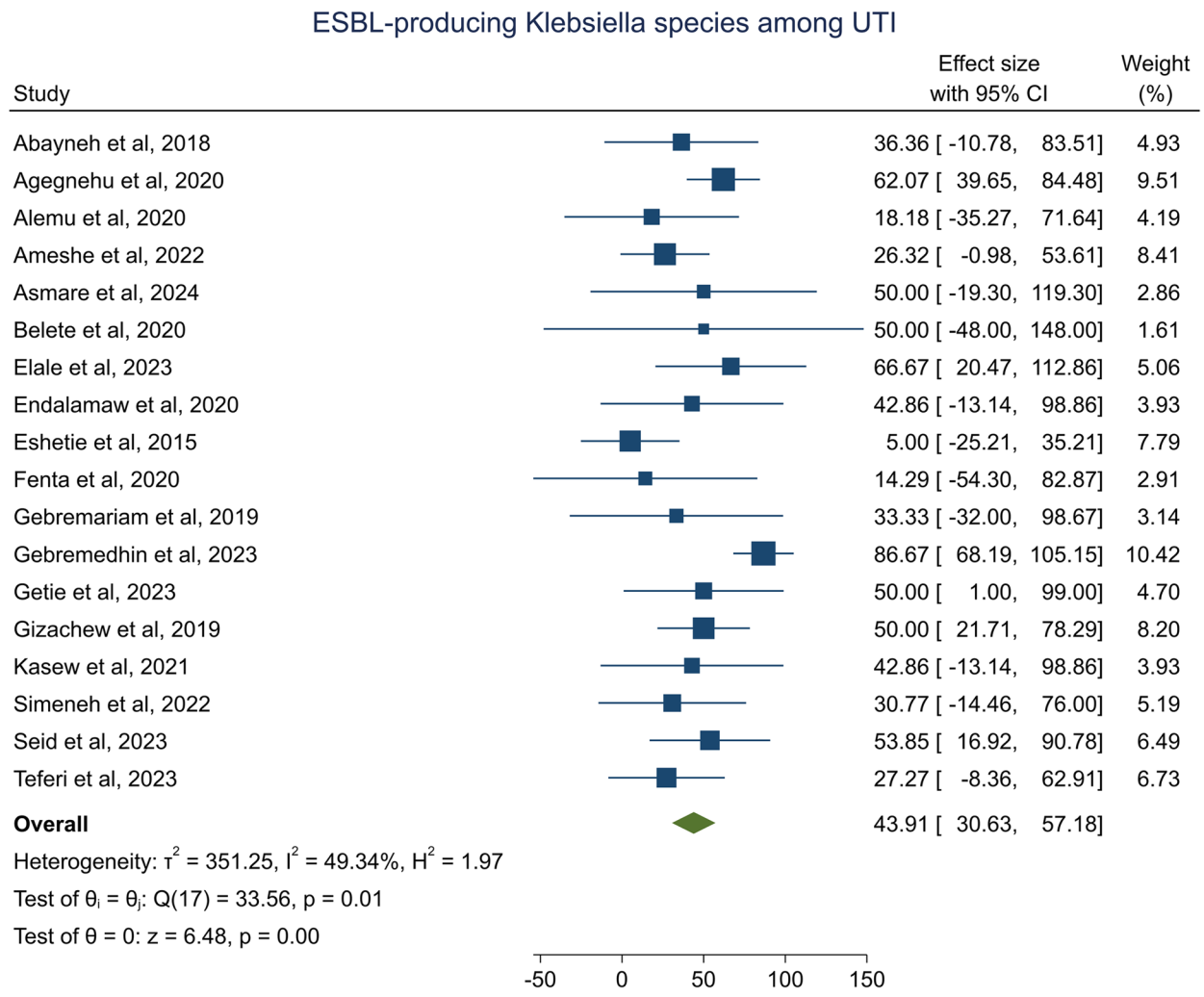

Fig. 4 Forest plot for ESBL-producing *Klebsiella* spp. among UTIs in Ethiopia

among outpatients (29.58%; 18.89–40.26) (Table 6). Similarly, the highest prevalence of carbapenemase-producing isolates was reported in the Oromia (44.57%) regional state (48.91%), followed by Tigray (10.45%), and the lowest pooled estimate was recorded in the Amhara regional state (3.42%) (Table 6).

Discussion

Owing to their high burden and resistance to treatments, carbapenemase-producing and ESBL-producing Gram-negative bacteria are critical pathogens [46]. In our systematic review and meta-analysis, the overall pooled prevalence rates of ESBL- and carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia were 30.92% (95% CI: 21.23–40.61, $P < 0.001$) and 15.12% (95% CI: -0.28–30.52, $P < 0.001$), respectively.

The prevalence of ESBL-producing isolates in this systematic review and meta-analysis is similar to that reported in a systematic review in Africa (22.8%) [47], and a study in Kenya (26.4%) [48], but higher than the 18% pooled prevalence found by Kiros et al. from various specimens in Ethiopia [49]. It also exceeds the global pediatric UTI systematic review, which reported a pooled ESBL prevalence of 14% [50]. Additionally, the prevalence of carbapenemase-producing isolates in this study is higher than the 5.44% reported in an Ethiopian systematic review from various specimens [51], and the 1% to 5% range reported in global surveillance data for UTIs caused by carbapenemase producers [52].

In this systematic review and meta-analysis, the estimated rates of ESBL-producing Gram-negative bacteria in UTIs were lower than those reported in a previous systematic review of ESBL-producing Enterobacteriaceae

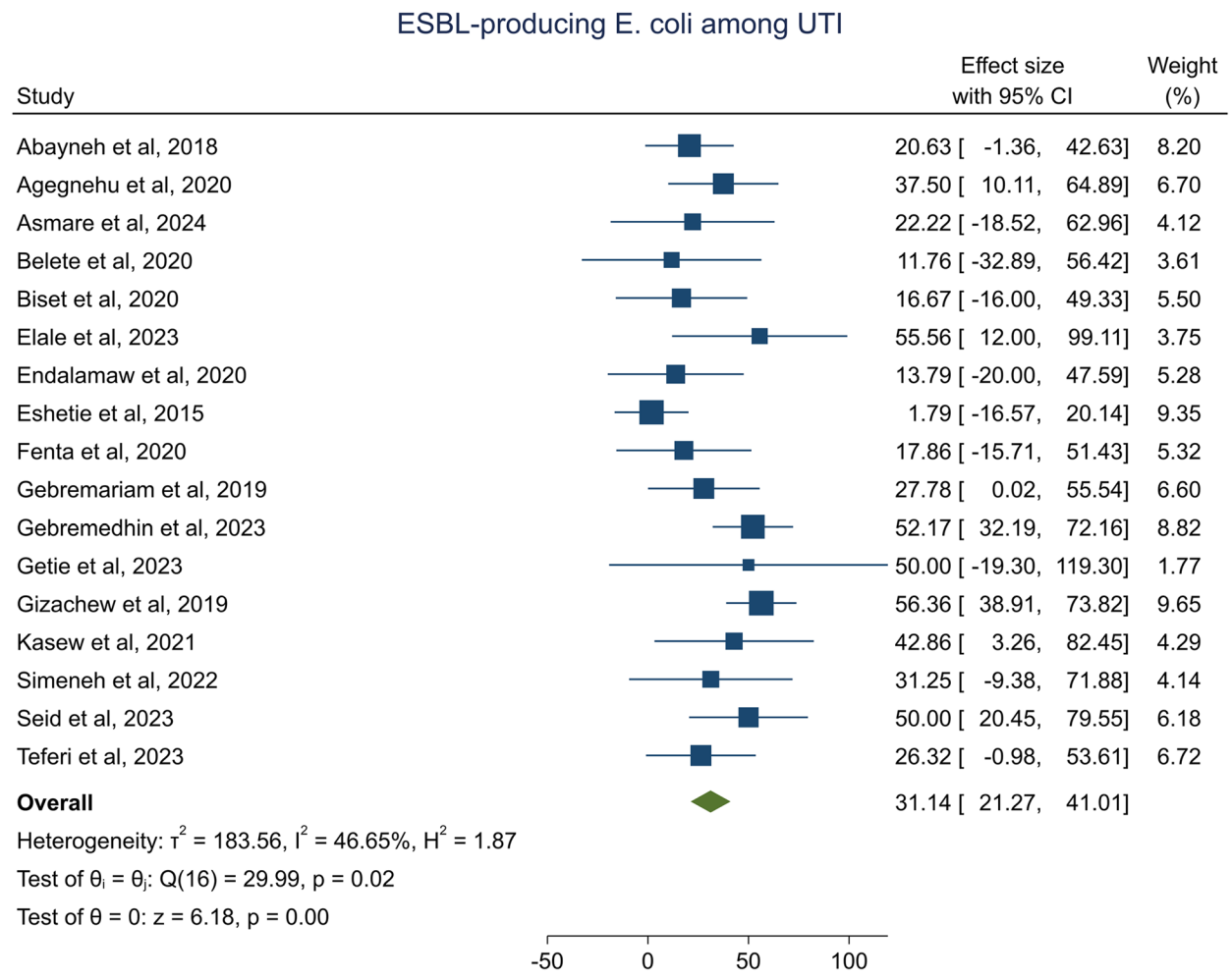

Fig. 5 Forest plot for ESBL-producing *E. coli* among UTIs in Ethiopia

from various clinical specimens in Ethiopia (49% and 50%, respectively) [53, 54]. The rates were also lower than those found in studies from Cameroon (55%) [55], Nepal (55.2%) [56], Italy (42.9%) [57], and India (40.2%) [58], and (39.31%) [59], which analyzed urine specimens. This variation may be due to differences in study periods, geographic locations, antibiotic policies, and infection prevention practices.

Furthermore, the high prevalence of ESBL- and carbapenemase-producing Gram-negative bacteria in UTIs may be linked to the proximity of the gastrointestinal and urinary tracts, facilitating bacterial transfer. Bacteria from the gastrointestinal tract can ascend to infect the urinary tract [60]; as the gastrointestinal tract is the primary reservoir for ESBL- and carbapenemase-producing Gram-negative bacteria [18, 61, 62]. Additionally, as most hospitalized patients use urinary catheters [8], the abiotic surface of the catheter plays a significant role in biofilm formation, which often resists antibiotic penetration. Consequently, catheter biofilms may harbor ESBL- and carbapenemase-producing uropathogens [63].

In the current systematic review and meta-analysis, the predominant ESBL-producing pathogens were *Klebsiella* spp. and *E. coli*, with pooled prevalence estimates of 43.91% and 31.14%, respectively. Similarly, the predominant carbapenemase producer was *Klebsiella* spp. (17.78%), followed by *E. coli* (11.42%). These findings are consistent with those of other reported systematic review of ESBL- and carbapenemase-producing Gram-negative bacteria in Ethiopia [53, 54]. Additionally, they are comparable to meta-analyses conducted on pediatric UTIs globally [50], as well as in Thailand [64], Nepal [56], India [58, 59], Turkey [65], and Italy [57], which reported that *K. pneumoniae* and *E. coli* were the predominant ESBL-producing pathogens among Gram-negative bacteria in urine.

Table 2 Species distribution of the proportion of ESBL- and carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia

Gram-negative bacteria	No. of studies	No. of tested isolates	No. of ESBL-producer	Rate of ESBL-producer (95% CI)
E. coli	18	581	151	25.99 (18.99–32.98)
Klebsiella spp.	19	265	98	36.98 (27.42- 46.54)
Enterobacter spp.	7	51	9	17.65 (-7.26–42.55)
Citrobacter spp.	2	36	5	13.89 (-16.42–44.20)
Proteus spp.	4	44	14	31.82 (7.42-.56.22)
P. aeruginosa	2	18	3	16.67 (-25.51–58.84)
Others[a]	-	15	0	-
Total	-	1010	280	28.70 (22.64–34.77)
Carbapenamase-producing species			No. of CP producer	Rate CP producer (95% CI)
E. coli	6	289	33	11.42 (0.57–22.27)
Klebsiella spp.	6	135	24	17.78 (2.48–33.07)
Others[b]	6	133	15	11.28 (-4.73–27.29)
Total	-	557	72	13.02 (5.27–20.76)

[a] Other: *A. boumanii* (4 isolates), *Serratia* spp. (3 isolates), *Providencia* spp. (5 isolates), *Morganella morganii* (3 isolates), ESBL: Extended-spectrum beta-lactamases CP: Carbapenemase

[b] Other: *P. aeruginosa* (5 CP from 27 isolates), *Enterobacter* spp. (4 CP from 34 isolates), *Citrobacter* spp. (2 CP from 20 isolates), *Proteus* spp. (4 CP from 45 isolates), *A. boumanii* (0 from 3 isolates), *Serratia* spp. (0 CP from 3 isolates), and *Morganella morganii* (0 CP from 1 isolate)

Klebsiella spp., particularly, *Klebsiella pneumoniae* poses a significant public health threat as a common, severe MDR pathogen in the ESKAPE group, alongside *Enterococcus*, *S. aureus*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species [66]. Currently, those pathogens are common in both developed [67], and developing countries [68]. Cephalosporins and carbapenems, vital for treating Gram-negative bacterial infections, including those from *Klebsiella* spp. and *E. coli*, have lost efficacy due to widespread resistance genes like ESBLs and carbapenemases. The predominance of ESBL- and carbapenemase-producing *Klebsiella* spp. and *E. coli* in this systematic review and meta-analysis and many other systematic review may be because these pathogens are

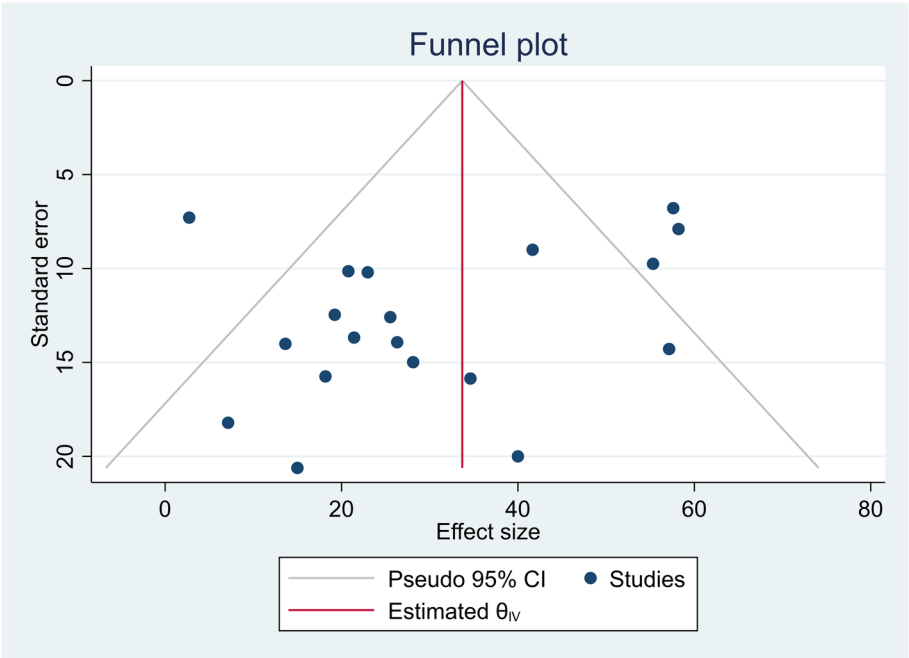

Fig. 6 Funnel plot showing publication bias for ESBL-producing Gram-negative bacteria among UTIs in Ethiopia

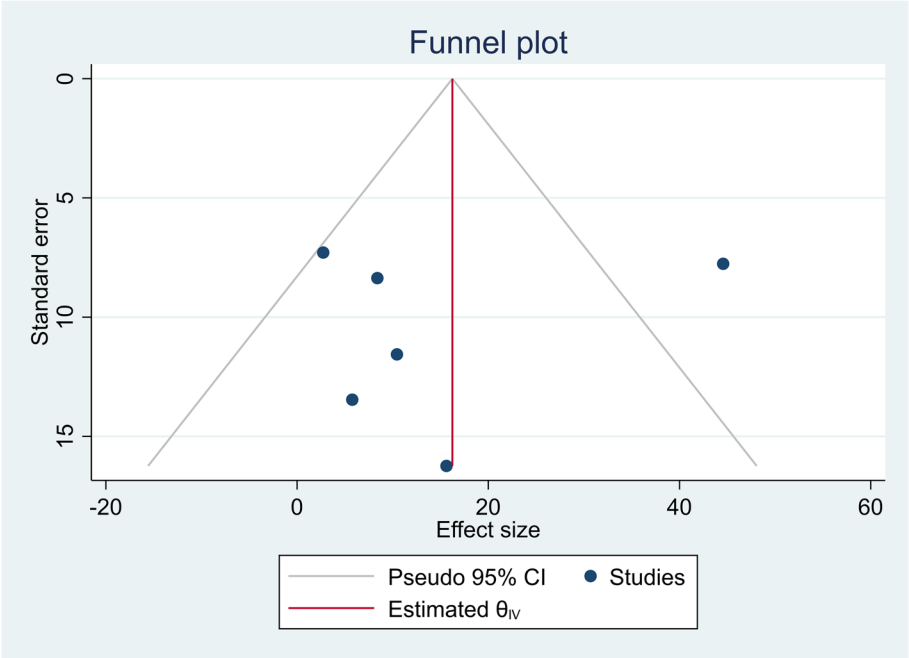

Fig. 7 Funnel plot showing publication bias for carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia

Table 3 Egger's test for ESBL-producing Gram-negative bacteria among UTIs in Ethiopia

Number of studies = 19					**Root MSE = 1.796**	
Std _Eff	**Coefficient**	**Std. err**	**t**	***P*>|t|**	**[95% conf. interval]**	
slope bias	51.61653	14.56884	3.54	0.003	20.87896	82.35411
	-1.691692	1.304425	-1.30	0.212	-4.443787	1.060404
Test of HO: no samall-study effects			P = 0.212			

Table 4 Egger's test for carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia

Number of studies = 6					**Root MSE = 2.122.796**	
Std _Eff	Coefficient	Std. err	t	*P*>|t|	[95% conf. interval]	
slope bias	25.7794	30.2938	0.85	0.443	-58.32967	109.8885
	-1.042968	3.189339	-0.33	0.760	-9.897992	7.812057

mostly multidrug resistant because of the production of those enzymes [46]. Those pathogens are ubiquitous and considered "One Health" pathogens, associated with various types of infections in humans and different animal species, including dogs, cats [69], and chickens [70].

In the present systematic review and meta-analysis, the heterogeneity between studies was moderate ($I^2 = 70.13\%$ and 72.95%) for the prevalence of ESBL-producing and carbapenemase-producing isolates, respectively. Therefore, subgroup meta-analysis was carried out by region, and the highest pooled estimate of ESBL-producers was reported in South Ethiopia (48.91%), followed by Tigray (43.34%), whereas the lowest pooled estimate was reported in Amhara (14.07%). Similarly, the highest prevalence of carbapenemase-producing isolates was reported in the Oromia (44.57%) regional state (48.91%), followed by Tigray (10.45%), and the lowest pooled estimate was recorded in the Amhara regional state (3.42%). This difference might be due to the number of studies, which has their own effect on the pooled estimates during stratification. For example, 2, 3, and 7 studies involved Tigray, southern Ethiopia, and Amhara regional

Table 5 Sensitivity analysis of ESBL- and carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia, 2024

Sensitivity analysis of ESBL-producing isolates			Sensitivity analysis of carbapenamase-producing isolates		
Study omitted	**Estimate**	**95% Confidence Interval**	**Study omitted**	**Estimate**	**95% Confidence Interval**
Eshetie et al., 2015	33.66	25.01–42.30	Eshetie et al., 2015	18.14	0.57–35.72
Abayneh et al., 2018	31.38	21.15–41.60	Gizachew et al., 2019	6.83	-1.95–15.60
Gizachew et al., 2019	28.99	19.65–38.33	Simeneh et al., 2022	16.51	-2.61–35.63
Gebremariam et al., 2019	31.18	21.01–41.34	Mitiku et al., 2022	14.98	-2.45–32.41
Agegnehu et al., 2020	30.12	19.78–40.46	Gebremedhin et al., 2023	15.91	-2.34–34.16
Alemu et al., 2020	31.88	22.02–41.75	Asmare et al., 2024	16.62	-0.97–34.21
Belete et al., 2020	31.46	21.53–41.39	**Combined**	**15.12**	**-0.28–30.52**
Biset et al., 2020	31.49	21.48–41.51	-	-	-
Endalamaw et al., 2020	31.39	21.30–41.48	-	-	-
Fenta et al., 2020	31.81	21.83–41.78	-	-	-
Kasew et al., 2021	30.71	20.61–40.80	-	-	-
Simeneh et al., 2022	31.02	20.91–41.13	-	-	-
Ameshe et al., 2022	31.12	20.99–41.25	-	-	-
Elale et al., 2023	29.59	19.68–39.58	-	-	-
Elale et al., 2023	29.59	19.68–39.58	-	-	-
Gebremedhin et al., 2023	29.03	19.46–38.50	-	-	-
Getie et al., 2023	30.56	20.56–40.80	-	-	-
Getie et al., 2023	30.56	20.56–40.80	-	-	-
Seid et al., 2023	29.34	19.43–39.24	-	-	-
Teferi et al., 2023	31.53	21.34–41.71	-	-	-
Asmare et al., 2024	31.55	21.46–40.65	-	-	-
Combined	**30.92**	**21.23–40.61**	-	-	-

states for analysis. Moreover, the discrepancy might be due to differences in people's lifestyles and health care-seeking behavior.

According to the subgroup analysis by age group, the pooled prevalence of ESBL- and carbapenemase-producing Gram-negative bacteria was greater in children (37.85%) than in other age groups (31.65%). Owing to the poor hygienic conditions for both sexes of children and the less acidic pH of the vaginal surface for female children, the number of normal vaginal flora, such as *Lactobacillus* spp., is low, as different *Lactobacillus* spp. strains exhibit probiotic effects and protect against other pathogenic bacteria in women of reproductive age [71].

Additionally, the highest prevalence rate of ESBL- and *carbapenemase*-producing Gram-negative bacteria was recorded in females (37.59%) compared with other sexes (28.09%). This variation may be due to anatomical differences in the urinary tract, as women's urinary anatomy, particularly a short and wide urethra with proximity to the perianal area, increases the chances of contamination with fecal microbes [72]. This is due to the commensal nature of Gram-negative bacteria from the gastrointestinal system. For example, *E. coli* is one of the most common normal flora of the gastrointestinal system and has the inherent ability to adhere to the urinary tract in females moving from perianal areas [73].

When we stratified ESBL-producing uropathogens by study period, the highest pooled estimate of ESBL was recorded from studies conducted and published after 2018 and 2020, respectively. This gap may be because the emergence of multidrug-resistant bacteria has increased over time, and recently studied papers may provide a high number of ESBL-producing uropathogens [74].

Furthermore, the increase in ESBL- and carbapenemase-producing Gram-negative bacteria observed in this systematic review and meta-analysis, may be attributed to immunosuppression, as most studies included in our meta-analysis involved HIV-positive patients, pregnant women, and diabetic patients. The pooled prevalence of ESBL-producing Gram-negative bacteria was 24.47% (4.67–44.27) for HIV-positive patients, 23.48% (2.69–44.27) for pregnant women, and 19.23% (-5.20–43.66) for diabetic patients, respectively. The major factor is a decreased immune system due to

Table 6 Subgroup analysis of ESBL- and carbapenemase-producing isolates from UTIs in Ethiopia, 2024

Subgroup analysis for ESBL-producing isolates							
Characteristics	**No. of Studies**	**No. of study participants**	**No. of tested isolates**	**No. of ESBL-producer**	**Pooled prevalence of ESBL-producer (95% CI)**	**Heterogeneity**	
						I^2 (%)	**P value**
Region							
South Ethiopia	3	793	100	47	48.91 (32.37- 65.45)	25.3	0.262
Tigray	2	638	114	59	43.34 11.45–75.23)	79.3	0.028
Oromia	3	1152	243	86	34.68 (8.73- 60.64)	84.7	0.001
Sidama	1	284	72	30	41.67 (24.02- 59.31)	NA	NA
Addis Ababa	1	177	15	6	40.00 (0.80–79.20)	NA	NA
Amhara	9	3219	466	60	14.07 (5.65–22.48)	0.0	0.698
Study year							
2014–2018	10	3440	606	143	26.27 (11.75–40.79)	75.1	< 0.001
2019–2022	9	2823	404	137	35.99 (23.27–48.71)	61.5	0.008
Publication year							
2015–2019	4	1549	396	87	27.38 (2.40–52.37)	87.3	< 0.001
2020–2024	15	4714	614	193	33.63 (18.05–49.21	84.8	< 0.001
Study design							
Cross-sectional	17	5604	911	244	31.39 (16.95–45.82	86.9	< 0.001
Case–control	1	296	47	26	19.23 (-5.20–43.66	0.0	< 0.001
Longitudinal cohort	1	363	52	10	55.32 (36.21–45.28	0.0	< 0.001
Study setting							
Outpatient	16	5095	810	112	29.58 (18.89–40.26	68.5	< 0.001
Inpatient	3	605	108	46	48.34 (-3.61–100.29)	94.2	< 0.001
Both in & Outpatient	2	563	92	22	24.71 (6.98–42.44)	0.0	0.391
Patient status							
Infection	13	4297	768	215	33.64 (16.90–50.38)	89.5	< 0.001
Both infection & colonization	6	1966	242	65	28.74 (12.93–44.55)	51.5	0.067
Patient background							
UTI-suspected patients	10	3356	685	210	38.26 (19.67–56.85)	90.7	< 0.001
Diabetic patients	1	336	28	2	7.14 (-28.55–42.84)	0.0	< 0.001
HIV-positive patients	2	638	74	18	24.47 (4.67–44.27)	0.0	0.741
Patients with urinary catheter	1	363	52	10	19.23 (-5.20–43.66)	0.0	< 0.001
Pregnant women	3	884	68	15	23.48 (2.69–44.27)	0.0	0.617
Patients with urinary stone	1	300	26	9	34.62 (3.53–65.70)	0.0	< 0.001
Patients with gynecological cases	1	386	77	16	20.78 (0.90–40.66)	0.0	< 0.001
Methods of ESBL-detection							
CDT	7	2388	264	79	28.39 (11.87–44.92)	60.1	0.020
CHROM agar	1	442	183	5	2.73 (-11.56–1702)	NA	NA
DDST	11	3433	563	196	36.02 (25.46–46.58)	58.9	0.007
Age group							
Adult	10	3260	465	150	31.65 (19.05–44.25)	61.9	0.005
Children	3	829	137	48	37.85 (15.92–59.77)	59.8	0.083
All age	6	2174	408	82	27.09 (6.40–47.77)	81.8	< 0.001

Table 6 (continued)

Subgroup analysis for ESBL-producing isolates							
Characteristics	**No. of Studies**	**No. of study participants**	**No. of tested isolates**	**No. of ESBL-producer**	**Pooled prevalence of ESBL-producer (95% CI)**	**Heterogeneity**	
						I^2 (%)	**P value**
Sex							
Female	6	1990	284	110	37.56 (20.47–54.64)	67.4	0.009
Both sex	13	4273	726	170	28.09 (16.85–39.33)	67.3	< 0.001
Subgroup analysis for carbapenemase -producing isolates							
Characteristics	No. of Studies	No. of study participants	No. of tested isolates	No. of CP-producer	Pooled prevalence of CP-producer (95% CI)	I^2 (%)	P value
Region							
South Ethiopia	2	673	163	16	9.91 (-4.66– 24.68)	0.0	0.692
Tigray	1	297	67	7	10.45 (-12.21–33.11)	NA	NA
Oromia	1	424	92	41	44.57 (29.35–59.78)	NA	NA
Amhara	2	805	235	8	3.42 (-9.14–15.99)	0.0	0.843
Study year							
2014–2018	2	866	275	46	23.56 (-17.43–64.56)	75.1	< 0.001
2019–2022	4	1333	282	26	9.31 (-1.81–20.42)	61.5	0.008
Study design							
Cross-sectional	5	1836	505	69	18.73 (0.37–37.09)	77.2	0.002
Longitudinal cohort	1	363	52	3	5.77 (-20.61–32.15)	0.0	< 0.001
Sampling technique							
Convenient	6	1526	394	56	19.27 (-4.44–42.98)	82.1	< 0.001
Systematic random	2	673	163	16	9.91 (-4.66–24.48)	0.0	0.692
Study setting							
Outpatient	4	1710	474	62	18.01 (-3.51–39.53)	82.8	< 0.001
Inpatient	2	489	83	10	12.84 (-7.25–32.92)	0.0	0.418
Patient background							
UTI-suspected patients	4	1585	473	64	19.31 (-2.13–40.76)	82.8	< 0.001
HIV-positive patients	1	251	32	5	15.63 (-16.20–47.45)	0.0	< 0.001
Patients with urinary catheter	1	363	52	3	5.77 (-20.61–32.15)	0.0	< 0.001
Methods of CP detection							
mCIM	3	1036	215	19	8.94 (-3.81–21.70)	0.0	0.892
CHROM agar	1	442	183	5	2.73 (-11.56–17.02)	NA	NA
MHT	2	721	159	48	28.58 (-4.79–61.95	83.3	0.014
Age group							
Adult	3	1097	255	57	23.77 (-2.41–49.96)	81.0	0.005
All age	3	1102	302	15	5.07 (-5.92–16.06)	0.0	0.851
Sex							
Female	1	424	92	41	44.57 (29.35–59.78)	NA	NA
Both sex	5	1775	465	31	6.83 (-1.95–15.60)	0.0	0.945

methods *UTI* Urinary tract infection, *ESBL* Extended-spectrum beta-lactamases, *CP* Carbapenemase, *CP-method* Carbapenemase confirmation methods, *No* Number, *HIV* Human immunodeficiency virus, *CDT* Combined disk test, *DDST* Double disk synergy test, *MHT* Modified carbapenem inactivation method, *MHT* Modified Hodge test

the reduced number and ability of white blood cells to fight infections in HIV-positive and diabetic patients, respectively. Researchers agree that diabetes is mostly associated with poor circulation and that poor contraction of the bladder leads to bladder dysfunction [75]. Furthermore, the above-listed populations are more likely to have contact with healthcare facilities that may be exposed to antibiotic-resistant strains. In particular, for HIV-positive patients, the use of antibiotic prophylaxis, such as sulfamethoxazole-trimethoprim, for the prevention of opportunistic infections may contribute to the multidrug resistance of pathogens [76, 77].

Limitations

Data on risk factors for the prevalence of ESBL- and carbapenemase-producing isolates among UTIs, the identification of genes encoding ESBLs and carbapenemases in Gram-negative bacteria from UTI patients are lacking. Additionally, mortality data to assess differences in outcomes between UTIs caused by ESBL- and carbapenemase-producing isolates are also insufficient. The antibiotic resistance results for ESBL-producing and non-ESBL-producing isolates, as well as for carbapenemase-producing and non-carbapenemase-producing isolates, were also insufficient.

Conclusion and recommendations

This study highlighted a significant prevalence of ESBL- and carbapenemase-producing Gram-negative bacteria among UTIs in Ethiopia, with *Klebsiella* spp. and *E. coli* being the dominant ESBL and carbapenemase producers. The highest prevalence of ESBL- and carbapenemase-producing isolates was observed in the South Ethiopia Regional State, followed by the Tigray Regional State. The highest prevalence of carbapenemase-producing isolates was reported in the Oromia Regional State, followed by the Tigray Regional State. Regarding age groups and study settings, the highest prevalence of ESBL-producing isolates was recorded among children and inpatients, respectively. The ESBL- and carbapenemase-producing uropathogens should be considered in the development of empiric treatment protocols and antibiotic stewardship programs. It is better to collect and analyze data on antibiotic susceptibility tests for ESBL-producing isolates and non-ESBL-producing isolates, as well as for carbapenemase-producing isolates and non-carbapenemase-producing isolates, separately. Furthermore, researchers should identify the predominant ESBL and carbapenemase genes in Ethiopia to better understand resistance mechanisms. Mortality data should also be incorporated to evaluate differences in outcomes between UTIs caused by ESBL- and carbapenemase-producing isolates.

Abbreviations

CDT	Combination disk test
CI	Confidence intervals
DDST	Double-disk synergy test
ESBL	Extended-spectrum beta-lactamase
mCIM	Modified carbapenem inactivation method
MHT	Modified Hodge test
HIV	Human immunodeficiency virus
MDR	Multidrug resistance
UTI	Urinary tract infection

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

MT: conception, designation, data extraction, data analysis, data interpretation, drafting, and finalization of the manuscript for publication; MA: conception, assisted in data extraction, data interpretation, and manuscript revision; GA: assisted in data extraction, data analysis, data interpretation, and manuscript revision; LD, YG, and KT: assisted in data extraction and reviewed the initial and final manuscript revision. All the authors reviewed the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

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Not needed.

Consent for publication

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Competing interests

The authors declare no competing interests.

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