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Worldwide prevalence of extended-spectrum β-lactamases-producing uropathogenic *Escherichia coli* isolates among kidney transplant patients: a systematic review and meta-analysis

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SUMMARY

A significant proportion of urinary tract infections (UTIs), typically affecting kidney transplant patients (KTPs), is attributed to the presence of extended-spectrum β-lactamases (ESBLs) and multi-drug resistance (MDR) in Escherichia coli strains. For this reason, the current meta-analysis was conducted to summarize the frequency of ESBL-producing UPEC among KTPs.

A systematic search was conducted to identify studies in the Web of Science, PubMed, Embase, and Scopus electronic databases between 2000 and 2021. Finally, 16 articles were selected for data extraction, and meta-analysis was performed using the metaprop command in the STATA (version 11) software.

From those studies, the pooled prevalence of ESBL-producing uropathogenic *E. coli* (UPEC) isolates was 40%. The subcategory analysis results based on continent indicated that Asian countries had the highest rate of ESBL-producing isolates with 45%, followed by 40%, 28%, and 16% in Europe, South America and North America, respectively.

Uncomfortably, high level of UPEC isolates in the current investigation was ESBL-producing isolates. These isolates pose a high serious threat to public health because they can contribute to the spread of antimicrobial resistance in the local population and hasten the ineffectiveness of the majority of commonly prescribed antibiotics for the treatment of UTI in KTPs and other patients.

Keywords: Uropathogenic *Escherichia coli*, kidney transplant patients, ESBL, KTP

INTRODUCTION

Urinary tract infections (UTIs) have been described to occur in 20% to 80% of kidney transplant patients (KTPs) in the first year after transplantation. In this period, UTIs are the most common cause of infectious consequences [1]. In a

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kidney transplant recipient, UTI can manifest as a fever, urosepsis, or an asymptomatic elevation in serum creatinine [2].

Different risk factors for UTIs following kidney transplant have been found, and they are likely to enhance the incidence of UTIs. These include age, diabetes, female gender, a history of acute renal failure, longer dialysis periods, medical manipulation during transplantation, urological disorders, as well as the immunosuppression level and severity [2-5].

The most common clinical isolates in UTI patients after Kidney transplantation (KTx) are *E. coli* isolates, notably the uropathogenic *E. coli* (UPEC) pathotype [6, 7]. UPEC strains adhere to epithelial cells in the bladder, causing pyelonephritis and cystitis. Pyelonephritis can also impact renal transplants, resulting in potentially fatal urosepsis [8, 9].

A substantial proportion of UTI usually impacting KTPs is caused by extended-spectrum β-lactamases (ESBLs) and multi-drug resistance (MDR) of *E. coli* strains [10]. ESBLs are a rapidly expanding category of plasmid enzymes that confer resistance to cephalosporins (first-, second-, and third-generation) penicillins, and aztreonam. The production of CTX-M, SHV, and TEM β-lactamases causes this occurrence [11]. The $bla_{CTX\text{-}M}$, bla_{SHV}, and bla_{TEM} genes are the most frequent ESBL-encoding genes, respectively [12]. Several findings indicate that CTX-M-type ESBLs are currently the most common plasmid-mediated β-lactamases worldwide [13, 14]. The term CTX refers to these β-lactamases' strong hydrolytic ability toward cefotaxime and are not very correlated to SHV or TEM β-lactamases [12]. β-lactamase inhibitors like tazobactam and clavulanic acid can inhibit ESBLs [15].

In some patients, antibiotic-resistant bacteria cause recurrent UTIs following transplantation [8]. UTIs induced by ESBL-producing *E. coli* are typically related to increased morbidity and death, as well as increased healthcare expenses [16]. Numerous studies have reported different frequency estimates and there has been no attempt to pool these findings to establish a reliable frequency approximation for ESBL-producing UPEC among KTPs. In 2017, a meta-analysis of observational studies found that 10% of KTPs experienced a UTI caused by Enterobacteriaceae that produces ESBL [17]. However, several original articles have been published since the release of that meta-analysis. Therefore, a complete meta-analysis summarizing all known findings in this field is required. As a result, the current meta-analysis was conducted to summarize current evidence on the frequency of ESBL-producing UPEC among KTPs in all ages.

MATERIAL AND METHODS

Search strategies

The report of the present study followed the prescribed guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Supplementary Data). The electronic databases Web of Science, PubMed, Scopus, and Embase were used to conduct a systematic literature search. The search was limited to the articles published to the end of December 2021. The following terms, "*Escherichia coli*" OR "*E. coli*" OR "UPEC" OR "uropathogenic *E. coli*" OR "uropathogenic *Escherichia coli*" AND "ESBL" and "kidney transplant" OR "renal transplant" OR "renal failure "OR "kidney receivers", without country restriction, were searched as scientific keywords and phrases in the present survey.

Inclusion and exclusion criteria

To minimize the risk of errors and meet the inclusion criteria, two authors (S.N and M.H.) independently screened articles, considering relevant titles, abstracts, keywords, and full texts. Any discrepancies that emerged during this process were resolved by involving involving a third author.

This study reviewed the following articles: cross-sectional, retrospective, and cohort studies reporting the frequency or prevalence of ESBL in uropathogenic *E. coli* isolated from KTPs. We included only published articles worldwide with with English abstracts. Editorials, case report studies, letters to the editors, congress and meeting abstracts, studies with fewer than ten isolates, studies with samples from environmental or non-clinical sources, articles without full text, duplicate publications, and articles with unclear and missing data were excluded.

Quality assessment and data extraction

Joanna Briggs Institute references were used to extract five criteria for assessing worthiness and quality, and any discrepancies were resolved by consensus [18]. The data extracted from eligible studies were: author names, publication year, and

must be deleted time of testing, study location, characterization of the studied population, sample size, and prevalence or frequency of ESBL.

Statistical analysis

Analysis of data was carried out using the metaprop command in STATA statistical software, version 11.0 (Stata, College Station, TX) [19]. The pooled frequency of ESBL among KTPs with 95% confidence intervals (95% CIs) were estimated through the random effects model. The score method method was used to calculate the CIs for proportions in this meta-analysis. Based on Cochrane I2 and Cochrane Q, statistical heterogeneity between studies was calculated. A funnel plot, Begg's rank correlation test, and Egger's weighted regression test were used to evaluate potential publication biases [20]. Any asymmetry in the funnel plot or a $p<0.05$ in the test was indicative of statistically significant publication bias [20]. Meta-regression analysis was used to determine possible sources of heterogeneity, and subcategory analysis was accomplished based on the study's region (location) and patient types [21].

RESULTS

Based on our comprehensive search, a total of 16 cross-sectional hospital-based studies that met the eligibility criteria (as depicted in Figure 1) were included in the meta-analysis. These studies were conducted between the years 2006 and 2021 [1, 6, 7, 11, 16, 22-32].

Figure 1 presents the searching procedure to select eligible studies. Of the 16 included studies, 10 studies reported the prevalence of ESBL-producing isolates from adult patient. Moreover, six studies were performed on both groups of patients, adults and children.

These studies were from Spain (three studies), Iran, (two studies), Turkey (two studies), Portugal (one studies), Germany (one studies), Canada (one studies), UK (one studies), Pakistan (one studies), Brazil (one studies), China (one studies), and USA (one studies). The full characteristics of the involved studies are shown in Table 1. Also, the worldwide distribution of ESBL-producing UPEC isolates of the involved studies showed in Figure 2.

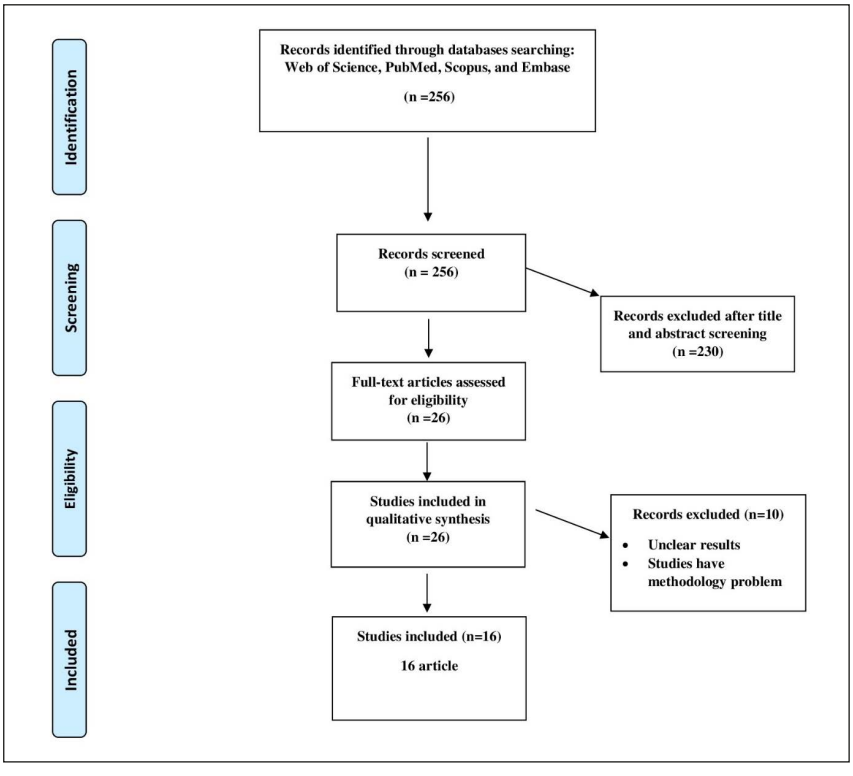

Figure 1
Flow chart of the study selection.

Table 1 - Key characteristics of studies included in the meta-analysis

Author	*Year of publication*	*Country*	*Type of patients*	*Number of patients evaluated*	*No. UPEC*	*ESBL*
Valera et al.	2006	Spain	Children, Adults	–	41	10
Parapiboon et al.	2012	Thailand	Adults	74	19	10
Vidal et al.	2012	Spain	Adults	206	118	31
Ak et al.	2013	Turkey	Children, Adults	–	43	25
Azap et al.	2013	Turkey	Adults		407	96
Bodro et al.	2015	Spain	Adults	174	66	13
Espinar et al.	2015	Portugal	Adults	98	50	32
Brakemeier et al.	2017	Germany	Adults	93	63	52
Delmas-Frenette et al.	2017	Canada	Adults	147	90	7
Al Midani et al.	2018	UK	Children, Adults	198	94	24
Halaji et al.	2020	Iran	Children, Adults	–	46	20
Najafi khah et al.	2020	Iran	Children, Adults	–	60	20
Hamid et al.	2020	Pakistan	Adults	72	32	7
Freire et al.	2020	Brazil	Adults	787	165	47
Wang et al.	2021	China	Adults	510	64	47
Velioglu et al.	2021	USA	Adults	102	52	33

UPEC: uropathogenic *Escherichia coli*; ESBL: extended-spectrum β-lactamases.

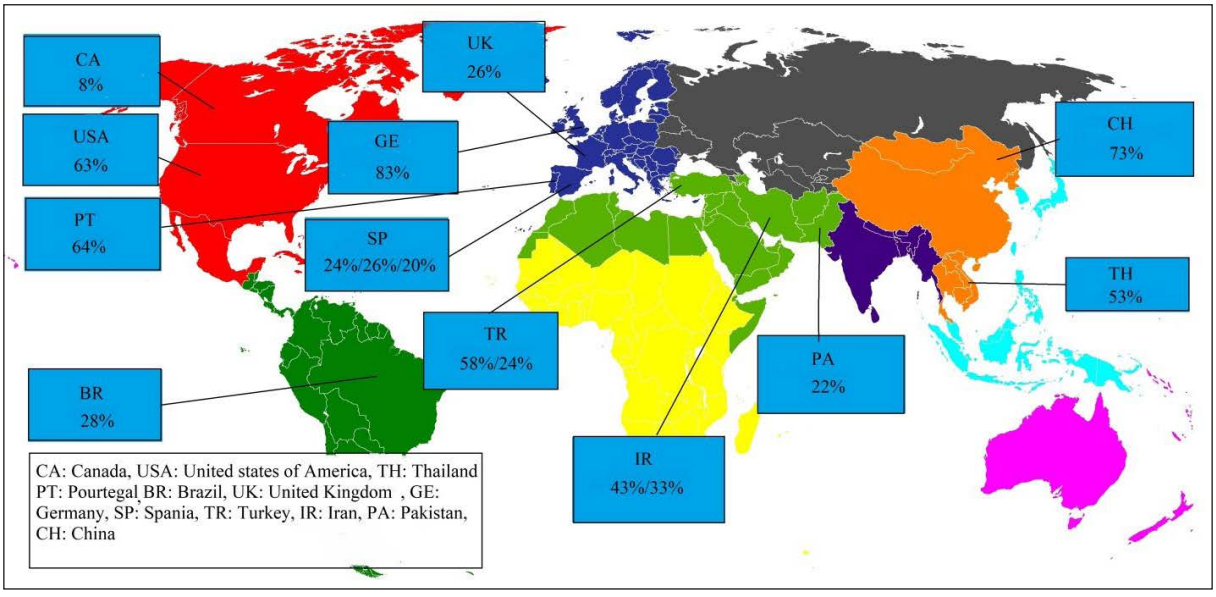

Figure 2 - The worldwide distribution of ESBL-producing UPEC isolates of the involved studies.

Prevalence of ESBL-producing UPEC isolates among KTP

From those studies, the pooled prevalence of ESBL-producing UPEC isolates were 40% (95% CI: 29–51) (Figure 3). There was significant heterogeneity among the 16 studies (χ^2=333.38, I2=95.5%, p<0.001). The publishing bias funnel plot did not reveal any asymmetry. Additionally, the publication bias was statistically assessed using Begg's and Egger's tests.

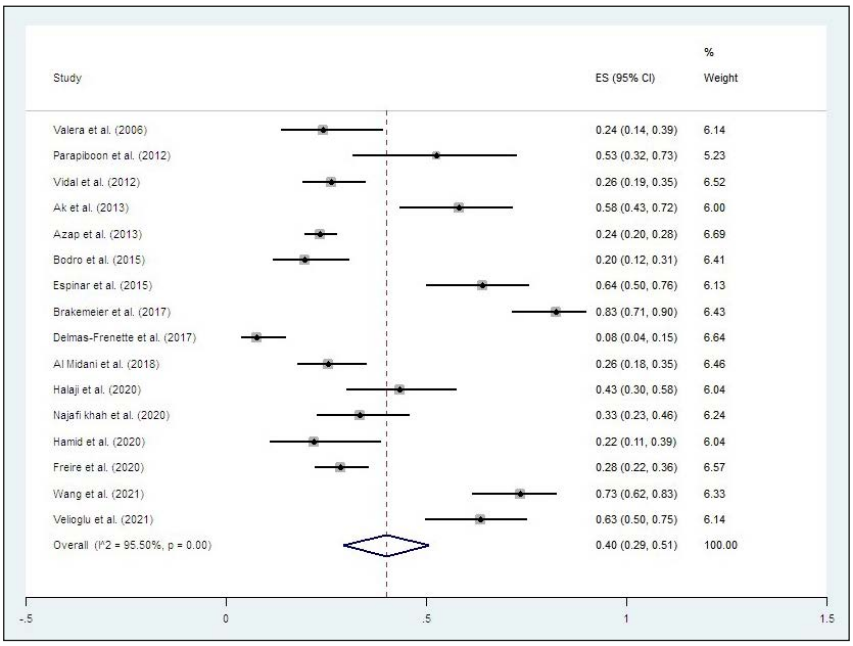

Figure 3
Forest plot of the pooled frequency in ESBL-producing UPEC among KTP.

There was no significant publication bias, as shown by the results of Begg's (z=1.49, p=0.13) and Egger's tests (t=2.46, p=0.02) (Figure 4).

Subgroup analysis of prevalence of ESBL-producing UPEC isolates

The subcategory analysis results based on continent indicated that Asian countries had the highest rate of ESBL-producing isolates with 45% (95% CI: 25-65), followed by 40% (95% CI: 25-56), 28% (95% CI: 22-36) and 16% (95% CI: 11-21) in Europe, South America and North America, respectively.

Studies performed in Asia (χ^2=40.27; p<0.001; I2=90.07%) and Europe (χ^2=173.58; p<0.001; I2=96.97%) showed significant heterogeneity based on the Q statistic and I2 (Figure 5).

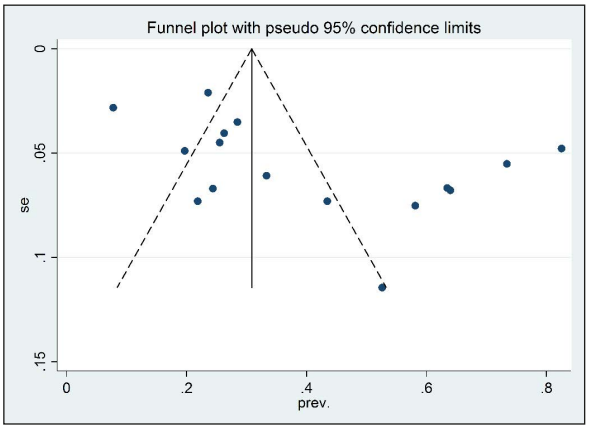

Figure 4 - Funnel plot for evaluation of publication bias.

Metaregression

Metaregression results indicated that the frequency of ESBL-producing UPEC among KTP was not significantly associated with year, coefficients: 0.14436 (95% CI: 0.0009254-0.029798, p=0.08) (Figure 6). Additionally, no substantial increasing trend was observed over time on the estimated pooled frequency of ESBL-producing UPEC isolates in the included studies.

DISCUSSION

Despite significant advancements in surgical methods and immunosuppressive medication following kidney transplantation, UTI remains the most common complication in KTPs, and the primary cause of UTI in KTPs is UPEC [31, 33].

Although β-lactam antibiotics are typically used to treat infections brought on by *E. coli* strains, a hazard to public health has emerged in recent years due to establishment of antibiotic resistance

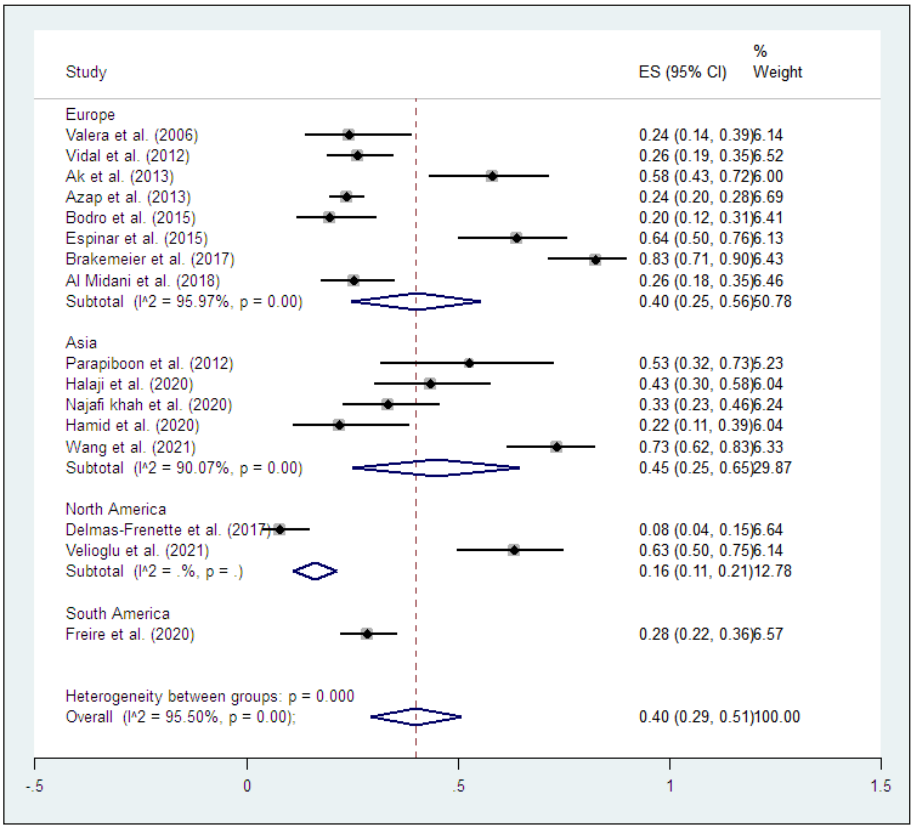

Figure 5
Forest plots of the overall frequency of ESBL-producing UPEC among KTP.

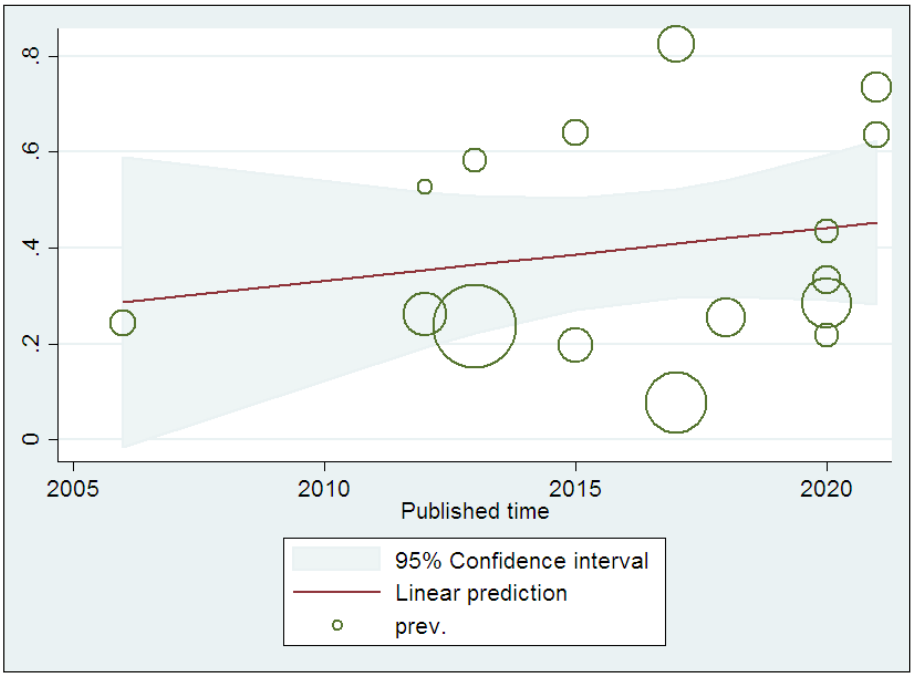

Figure 6
Metaregression of the log-event rates by year.

and the dissemination of MDR- and ESBL-producing UPEC isolates [34-36].

The incidence of ESBL-producing UPEC among KTPs examined from urine samples ranged from 8% to 83% in international research, according to the current analysis. Additionally, the study reported a pooled prevalence of 40% for ESBL-producing UPEC. These findings strongly suggest that ESBL-producing UPEC is widely distributed in KTPs, potentially compromising the effectiveness of antibiotics in these patients.

According to the meta-analysis study conducted by Garousi et al, patients with UTI had a pooled frequency of 37.9% for ESBL-producing *E. coli* [36]. In another study conducted by Sadeghi et al. in the north of Iran, the frequency of isolates that produced ESBL was found to be 46%. This was determined on the antibiotic resistance results of *E. coli* isolates obtained from UTI patients [37]. In a study conducted in Iran, Naziri et al. showed that among 78 UPEC isolates, 27 (34.6%) were detected as ESBL producer isolates [38].

In the present meta-analysis, two studies from Iran were included, which reported the frequency of ESBL-producing UPEC isolates among KTPs with UTIs as 33% and 43%. These percentages were found to be very similar to the results reported in other studies.

In a study, Belas et al. examined the frequency of ESBL-producing *E. coli* that cause UTIs in non-related companion animals (35 isolates) and humans (85 isolates). The results of their study showed that out of the 35 companion animal isolates, 14 isolates (40%) carried ESBL encoding genes, while out of the 85 human isolates, 80 isolates (94.1%) carried ESBL encoding genes [39].

Probably, one of the reasons for the high frequency of ESBL-producing UPEC in this study is the method used to identify these isolates. The PCR method was employed instead of the DDST method, as molecular techniques have been shown to possess higher sensitivity and specificity compared to phenotypic tests.

Furthermore, the frequency of ESBL-producing isolates in other pathotypes of *E. coli* has also been investigated. For example, Bezabih et al. performed a systematic review that included 133 articles published between January 1, 2000, and April 22, 2021.

The findings of their investigation revealed that 17.6% of healthy people worldwide and 21.1% of inpatients in healthcare settings harbored ESBL-producing *E. coli* in their intestines. The global carriage rate in healthcare settings increased threefold, from 7% in 2001-2005 to 25.7% in 2016-2020. Additionally, in community settings, the carriage rate increased tenfold, rising from 2.6% to 26.4% over the same time period [40].

A comparison of the results of our study with this meta-analysis reveals the following:

1) The pooled frequency of ESBL-producing isolates among intestinal *E. coli* strains is lower than that among UPEC strains.
2) Over time, the frequency of ESBL-producing isolates has increased, which is in line with our finding.

In our meta-analysis, the oldest study was published in 2006 by Valera et al., and the most recent studies were published in 2021 by Velioglu et al. and Wang et al., who reported the frequency of ESBL-producing UPEC isolates as 24, 63, and 73%, respectively. Based on these results, the frequency of ESBL-producing isolates shows an upward trend.

In the United States, two meta-analysis studies were conducted by Flokas et al. These studies investigated the frequency of ESBL-producing *Enterobacteriaceae* (ESBL-PE) in pediatric patients with UTI and bloodstream infection. The pooled frequency of ESBL-PE was reported as 14% and 9%, respectively [41-43].

These results demonstrate that the frequency of ESBL-PE in pediatric UTI is higher than that in blood infections. Additionally, a study conducted on pediatric UTI indicated the following pooled rates: 76% in Africa, 37% in Asia, 12% in Europe, 7% in the Western Pacific, 5% in the Eastern Mediterranean, and 2% in the Americas.

Furthermore, Onduru et al. and Diriba et al. conducted two meta-analysis studies investigating the pooled frequency of ESBL-PE in Africa. The pooled rates were reported as 38% and 49%, respectively [43, 44]. One of the most significant reasons for the variation in the frequency of ESBL-PE in these studies is the disparity in geographical location and healthcare levels between developing and developed countries. Additionally, in our study, subgroup analysis by continent revealed that Asian countries had the highest ESBL-production rate at 45%, followed by Europe at 40%, South America at 28%, and North America at 16%. Consistent with our findings, Bezabih et al. report-

ed the highest rate of ESBL-producing isolates in Asia (27%) [42].
Our meta-analysis has certain limitations. Firstly, the majority of the studies we examined were conducted in a limited number of regions, which may hinder the accurate representation of global epidemiology. Secondly, the included studies did not provide sufficient data on the antibiotic susceptibility patterns of ESBL-positive isolates. Thirdly, heterogeneity was observed among the included studies, prompting us to conduct subgroup analysis and metaregression. However, it is crucial to interpret the results cautiously due to variations in sample sizes and significant heterogeneity.

CONCLUSION

Unfortunately, 40% of the UPECs in the current investigation were identified as ESBL-producing isolates. These isolates present a significant public health concern as they can facilitate the dissemination of antimicrobial resistance within the local population and accelerate the ineffectiveness of commonly prescribed antibiotics for UTI treatment in KTPs and other patients. In light of these findings, ongoing regional screening of ESBL producers is crucial, particularly in developing nations, to account for variations in the characteristics of UPEC strains across different geographical locations and their evolutionary changes over time. This need is particularly pronounced in developing countries.

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Ethics approval
This study was approved by the research ethics committee of Babol University of Medical Sciences; Babol, Iran with number code IR.MUBABOL.HRI.REC.1401.199.

Availability of data and materials
Data available on request from the authors.

Authors' contributions
TM, HSh, MH and MR conceived and designed the experiments. Performed the experiments: AF, SN, MH and AP. Performed statistical and spatial analyses and interpreted all the results: HSh, MH and MR. Contributed to the writing of the manuscript and revised the final version manuscript: MH, AP, AF and MR. All authors read and approved the final manuscript.

Conflict of interest
The authors report no conflicts of interest in this work

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Supplementary Material - S1 Checklist: PRISMA checklist

Section/topic	#	*Checklist item*	*Reported on page #*
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (*e.g.*, Web address), and, if available, provide registration information including registration number.	10
Eligibility criteria	6	Specify study characteristics (*e.g.*, PICOS, length of follow-up) and report characteristics (*e.g.*, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (*e.g.*, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (*e.g.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (*e.g.*, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (*e.g.*, PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (*e.g.*, risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g.*, I^2) for each meta-analysis.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (*e.g.*, publication bias, selective reporting within studies).	6