

# Emergence of *Escherichia coli* ST131 Causing Urinary Tract Infection in Western Asia: A Systematic Review and Meta-Analysis

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*Escherichia coli* sequence type (ST) 131 is considered a high-risk pandemic clone and frequently extended-spectrum  $\beta$ -lactamase (ESBL)-producing clone that is strongly associated with the global dissemination of CTX-M-15 type. The emergence of ST131 has become a public health threat because this clonal group typically exhibits multiple virulence factors and antimicrobial resistance. Therefore, this study aimed to analyze the literature published on the estimation of the prevalence of clone ST131 among *E. coli* strains isolated from patients with urinary tract infections in western Asia. A systematic search was carried out to identify eligible articles in the Web of Science, PubMed, Scopus, Embase, and Google Scholar electronic databases from January 2010 to December 2018. Next, 13 articles meeting the inclusion criteria were selected for data extraction and analysis by Comprehensive Meta-Analysis Software. The included studies were conducted in Iran, Jordan, Kuwait, Pakistan, Saudi Arabia, Turkey, and Yemen. In all studies, the pooled prevalence of ST131 was 24.6% (95% CI: 13.5%–40.4%) in wild type isolates, 42.7% (95% CI: 32.5%–53.5%) among ESBLs-producing isolates, and 64.8% (95% CI: 36%–85.5%) among multiple-drug resistant (MDR) isolates. Moreover, the prevalence of ST131 isolates carrying CTX-M-15 type was 68% (95% CI: 48.4%–82.8%). Our study indicated the high prevalence of broadly disseminated ST131 clone among MDR and ESBLs isolates in western Asia. Moreover, O25b was the predominant ST131 clone type, which was mostly associated with CTX-M-15 type.

**Keywords:** *Escherichia coli*, ST131, ESBL, CTX-M-15, Asia

## Introduction

URINARY TRACT INFECTION (UTI) is one of the most prevalent bacterial infections in humans that is predominantly caused by extraintestinal pathogenic *Escherichia coli* (ExPEC).<sup>1</sup> It has become increasingly challenging to control *E. coli* caused by UTI due to the rapid spread of antibiotic resistance.<sup>2,3</sup> Of particular concern is the prevalence of extended-spectrum  $\beta$ -lactamase (ESBL)-producing *E. coli* across the world.<sup>2</sup> ESBLs are enzymes that confer resistance to several generations of  $\beta$ -lactam antibiotics, including penicillins, third-generation cephalosporins, and monobactams.<sup>3</sup> The most important groups associated with ESBLs are SHV, TEM, and CTX-M, of which CTX-M is currently the dominant type of ESBL in most regions of the world.<sup>4</sup> Today,

CTX-M-15 and CTX-M-14, more often carried by multiple-drug resistant (MDR) strains, are the most circulating CTX-M enzymes in both community and hospital settings.<sup>5</sup>

Since the 2000s, *E. coli* sequence type (ST) 131 has been identified as a high-risk ESBL-producing pandemic clone strongly associated with the widespread dissemination of CTX-M-15 type.<sup>6–8</sup> The emergence of ST131 has become a public health threat because this clonal group typically exhibits multiple virulence factors and antimicrobial resistance including fluoroquinolones and third- and fourth-generation cephalosporins.<sup>9,10</sup> In North America, ~50% of ESBL-producing and 20% of fluoroquinolone-resistant *E. coli* are associated with ST131.<sup>11</sup> Furthermore, studies conducted in Europe have reported the growing prevalence of ST131 clone among ESBL-producing strains.<sup>12</sup>

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The possible routes of gut colonization with ST131 are yet to be fully investigated, but foodborne origin has been recently proposed.<sup>13</sup> The wide use of antibiotics in livestock and poultry industry can cause the emergence of resistant strains.<sup>14</sup> There is compelling evidence that human cross-contamination with nonhuman bacterial strains can occur through occupational exposure or animal products.<sup>14</sup> In this regard, certain reports have shown that food supply is contaminated with ST131 strains.<sup>15,16</sup> Recently, ST131-H22 strains have been found in both retail poultry products and human clinical samples. The findings supported potential foodborne sources for human UTIs caused by ST131-H22 strains.<sup>14</sup>

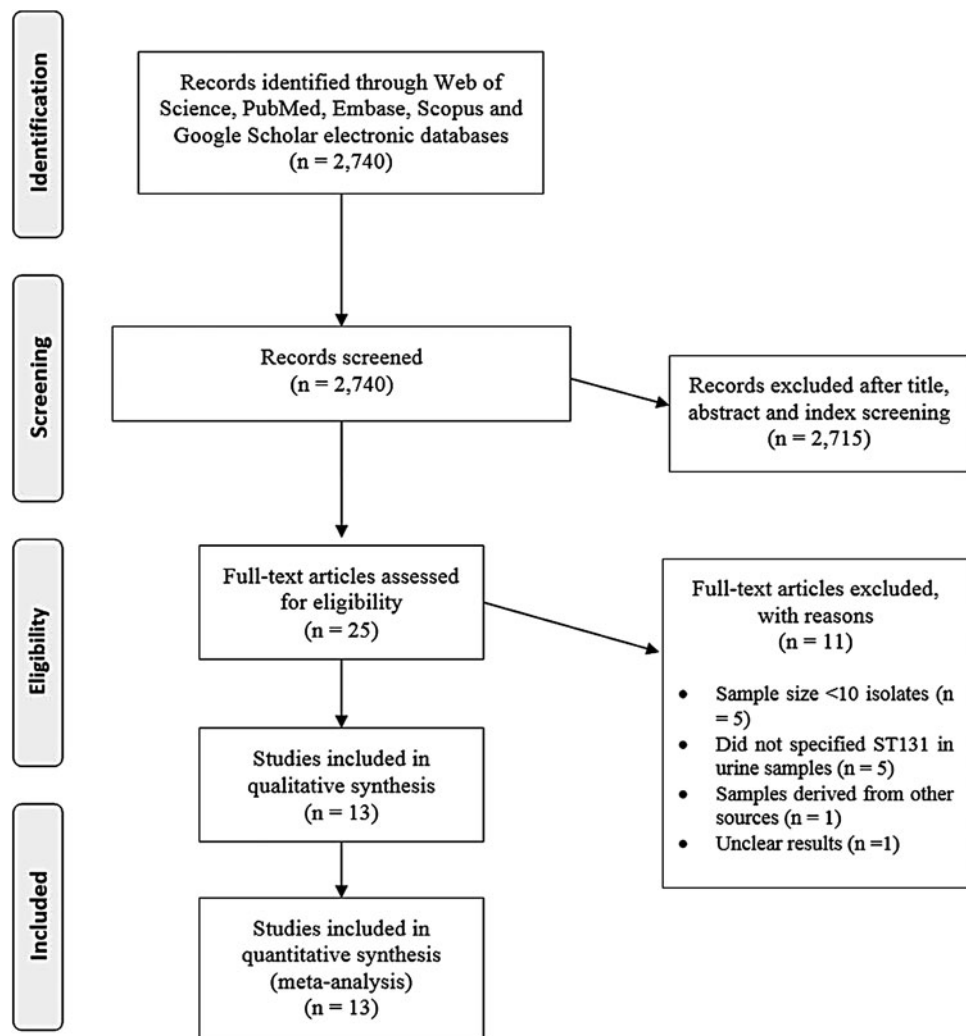
In recent years, consistent with worldwide reports, clone ST131 has emerged in Asian countries<sup>11,17,18</sup>; however, there is limited information on the distribution and characteristics of this clone of *E. coli* isolated from UTIs in western Asia where self-medication with antibiotics is high.<sup>19</sup> Accordingly, the objective of this study was to analyze the published literature to estimate the prevalence of ST131 clone among *E. coli* strains isolated from patients with UTIs in western Asia. These data can contribute to successful management and treatment of UTIs caused by *E. coli*.

## Materials and Methods

### Search strategies

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This was done through searching multiple electronic bibliographic databases, including Web of Science, PubMed, Embase, Scopus, and Google Scholar from January 2000 to December 2018 to find relevant studies. The search for keywords was done in the title or abstract or within the full text of the articles. For this purpose, we used a combination of predefined keywords, including “*Escherichia coli*” AND “Extended-spectrum  $\beta$ -lactamase OR ESBL” AND “Multiple-drug resistant OR MDR” AND “CTX-M” AND “Sequence type 131 OR ST131” AND “Urine” AND “Urinary tract infection OR UTI” AND “UPEC” AND “ExPEC” AND “Clinical sample” AND “Country name [Afghanistan OR Armenia OR Azerbaijan OR Bahrain OR Georgia OR Iran OR Iraq OR Jordan OR Kuwait OR Lebanon OR Oman OR Pakistan OR Qatar OR Saudi Arabia OR Syria OR Turkey OR Yemen OR United Arab Emirates]” in the titles, abstracts, and keywords fields.

**FIG. 1.** Flowchart of the literature search strategy and study selection.



*Selection criteria and quality assessment*

Two reviewers independently checked the search results in the databases with relevant keywords and analyzed the titles, abstracts, and full texts to apply eligibility for inclusion, and discrepancies were resolved through discussion. There was no limitation regarding the language of publication, but the abstract had to be available in English. The study was limited to cross-sectional articles indexed in the Web of Science or PubMed or Scopus. Articles with the following criteria were then included in the study: (1) sample collection from the urine of patients with UTI and (2) distribution of ST131 clone among wild type (WT) or ESBL or MDR isolates. Meanwhile, the exclusion criteria were a sample size of <10 isolates and ST131 unspecified in urine samples. Review articles, case reports, and congress abstracts with no necessary information were further excluded. The reference lists of all related studies were also reviewed for any other related publications.

*Quality assessment and data extraction*

Two researchers separately assessed the quality using the nine-point Joanna Briggs Institute critical appraisal checklist for studies reporting the prevalence data, and any disagreement was resolved by consensus.<sup>20</sup> Studies fulfilling more than half of the quality assessment parameters were included. Afterward, the following data were extracted from eligible studies by two researchers: authors' names, publi-

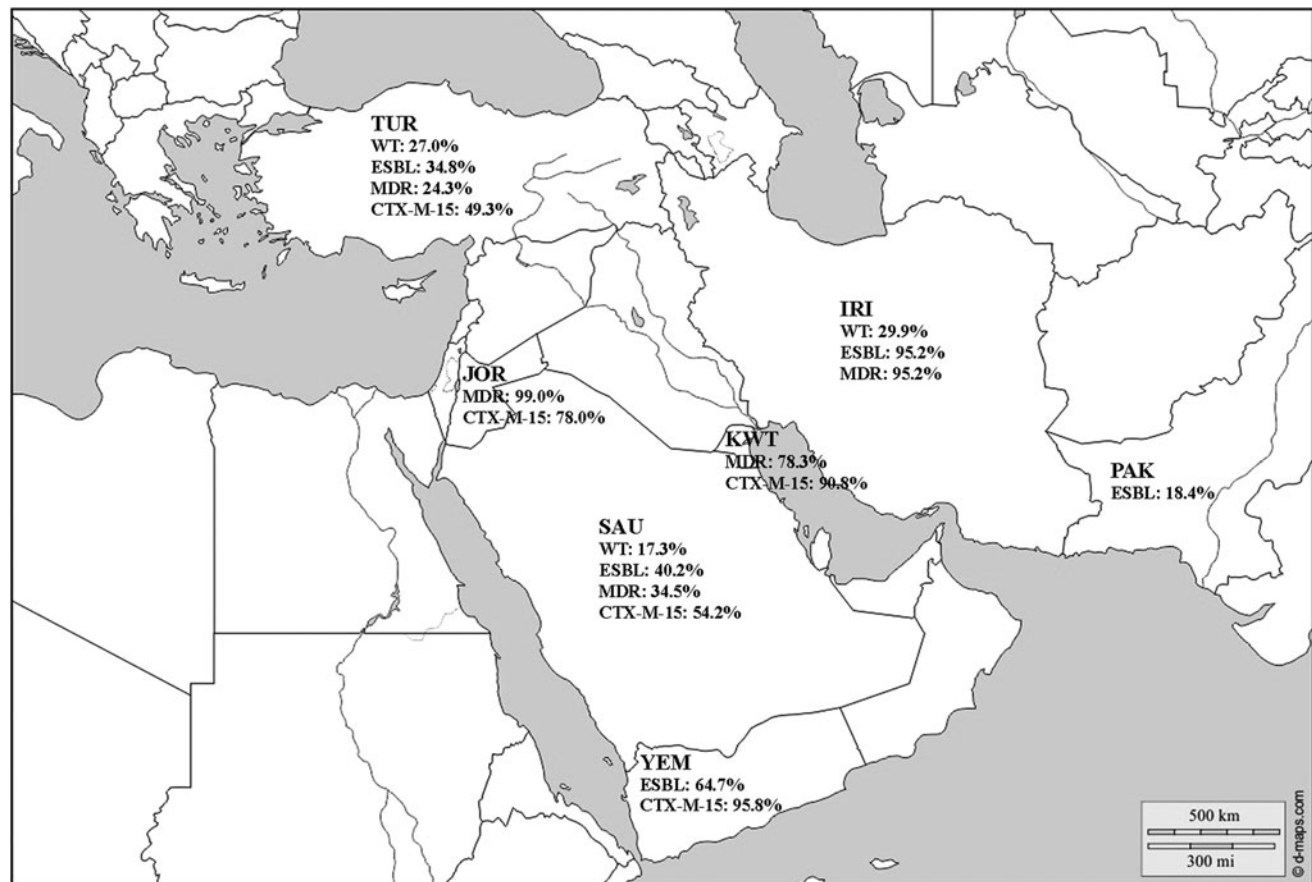
cation time, time of conducting the research, geographical distribution, sample size, and distribution of ST131 clone. To reach consensus, the inconsistencies between the researchers were further discussed.

*Statistical analysis*

Meta-analysis was performed using the random effects model to estimate the pooled prevalence and corresponding 95% confidence interval (CI). Heterogeneity between studies was assessed using the Cochran's Q statistic and *I*-square (*I*<sup>2</sup>) test. Publication bias was graphically evaluated by a funnel plot and mathematically assessed through the use of the Begg's rank correlation and Egger's weighted regression test (*p*<0.05 was considered as statistically significant publication bias). A meta-regression using the random-effect model (method of moments) was performed to determine whether the prevalence of ST131 clone was modulated by time (performed years). Meta-regression coefficients (slopes of the meta-regression line) indicate the estimated increase in the log events rate per unit increase in the covariate. Analysis of data and construction of graphs were done by Comprehensive Meta-Analysis Software Version 2.2 (Biostat).

**Results**

Our comprehensive search identified 13 studies reporting the prevalence of *E. coli* ST131 clone among UTI patients.<sup>8,21-32</sup> Fig. 1 presents a flow diagram of the literature search and



**FIG. 2.** Geographical distribution of ST131 isolates in western Asia (Photograph by www.d-maps.com).

study selection. The included articles had been carried out in Iran, Jordan, Kuwait, Pakistan, Saudi Arabia, Turkey, and Yemen. (Fig. 2). The main characteristics of each study registered in the meta-analysis are summarized in Table 1.

Of all the included articles, four reported the prevalence of ST131 among WT isolates (Fig. 3). In these studies, the pooled prevalence of ST131 was 24.6% (95% CI: 13.5%–40.4%), and there was a high heterogeneity ( $I^2=93.248$ ,  $p<0.001$ ) yet no significant publication bias (Table 2). Based on subgroup analysis, the overall occurrence of ST131 (All O-serogroups) among WT-*E. coli* was 30.4% (95% CI: 17%–48.3%), whereas the occurrence of O25b-ST131 was 11.9% (95% CI: 3.6%–32.8%) (Supplementary Figs. S1–S15).

The prevalence of ST131 among ESBL-producing isolates was investigated in 10 studies (Fig. 4), of which the pooled prevalence of ST131 was 42.7% (95% CI: 32.5%–53.5%). Subgroup analysis showed that the overall occurrence of ST131 (All O-serogroups) among ESBLs was 50.4% (95% CI: 32.1%–68.6%), whereas the occurrence of O25b-ST131 was 38.7% (95% CI: 25.3%–54.1%) (Supplementary Figs. S1–S15). Iranian patients experienced the highest prevalence of ESBL-ST131 isolates with a pooled prevalence of 95.2% (95% CI: 84.5%–98.7%), whereas Pakistan had the lowest prevalence with 18.4% (95% CI: 9.3%–33.0%) (Supplementary Figs. S1–S15).

The prevalence of ST131 clone among MDR isolates was reported in six studies (Fig. 5), of which the pooled prevalence of ST131 was 64.8% (95% CI: 36%–85.5%). The occurrence of ST131 (all O-serogroups) and O25b-ST131 in MDR isolates was 74.7% (95% CI: 23.4%–96.6%) and 61% (95% CI: 23.1%–89.1%), respectively (Supplementary Figs. S1–S15). Iran and Turkey had the highest (95.2% [95% CI: 86.2%–98.5%]) and the lowest (24.3% [95% CI: 19%–30.5%]) prevalence of MDR-ST131 isolates, respectively (Supplementary Figs. S1–S15).

The association of CTX-M-15 with ST131 isolates was investigated in eight studies (Fig. 6), where the prevalence of ST131 isolates harboring CTX-M-15  $\beta$ -lactamase was 68% (95% CI: 48.4%–82.8%). According to subgroup analysis, the overall prevalence of ST131 (all O-serogroups) and O25b-ST131 isolates containing CTX-M-15 was 47.3% (95% CI: 14.9%–82.3%) and 76.4% (95% CI: 52.6%–90.4%), respectively (Supplementary Figs. S1–S15).

Meta-regression results revealed that the occurrence of ST131 among MDR isolates significantly increased annually, with a coefficient of 0.64402 (95% CI: 0.08615–1.20189,  $p<0.02$ ) (Supplementary Figs. S1–S15). However, the overall occurrence of ST131 (coefficient: 0.20013, 95% CI: –0.19951 to 0.59977,  $p=0.33$ ), ESBL-ST131 (coefficient: 0.14019, 95% CI: –0.04606 to 0.32643,  $p=0.14$ ), and CTX-M-15-positive isolates (Coefficient: 0.04622, 95% CI: –0.38373 to 0.47617,  $p=0.83$ ) was not affected by year.

## Discussion

The worldwide emergence of *E. coli* ST131 clone as a novel multidrug-resistant extraintestinal pathogen has recently posed a significant public health threat.<sup>33</sup> The increasing recovery of ST131 is associated with the global increase in the antimicrobial resistance of *E. coli*.<sup>33,34</sup> Understanding the international distribution of *E. coli* ST131

TABLE 1. THE MAIN CHARACTERISTICS OF STUDIES INCLUDED IN THE META-ANALYSIS (RESULTS PRESENTED AS NUMBER OF EVENTS)

First author, publication date	Performed time	Country	ESBL detection method	WT ST131- positive/total	MDR ST131- positive/total	ESBL ST131- positive/total	CTX-M-15 CTX-M positive/ST131 Total	Detected clone	Ref
Habeeb, 2014	2005, 2009–2010	Pakistan	DDS	ND	ND	18/98	ND	O25b-B2	21
Al-Agamy, 2014	2010–2011	Saudi Arabia	DDS	ND	ND	17/24	17/17	O25b-B2	22
Dashui, 2014	2010–2012	Kuwait	DDS	ND	65/83	ND	59/65	O25b-B2	23
Can, 2016	2011	Turkey	PCR	ND	26/107	18/59	12/26	O25b-B2	24
Can, 2015	2011	Turkey	DDS	35/294	26/107	21/70	13/35	O25b-B2	25
Alghoribi, 2015	2012–2013	Saudi Arabia	Vitek®	35/202	ND	21/71	11/35	All	26
Alyamani, 2017	2014–2015	Saudi Arabia	Vitek®	ND	20/58	20/58	ND	All	27
Aktas, 2017	2015–2016	Turkey	DDS	ND	ND	81/203	51/81	All	8
Hojabri, 2017	2015–2016	Iran	DDS	63/211	60/63	60/63	ND	All	28
Atac, 2018	2010–2013	Turkey	DDS	21/41	ND	ND	ND	All	29
Alisharapy, 2018	2013	Yemen	DDS	ND	ND	11/17	11/11	O25b-B2	30
Nairoukh, 2018	2016	Jordan	ND	ND	50/50	ND	39/50	O25b-B2	31
Cizmeci, 2018	2016–2017	Turkey	DDS	ND	ND	91/251	ND	O25b-B2	32

DDS, double disk synergy; PCR, polymerase chain reaction; ND, no data; WT, wild type; MDR, multiple-drug resistant; ESBL, extended-spectrum  $\beta$ -lactamase.

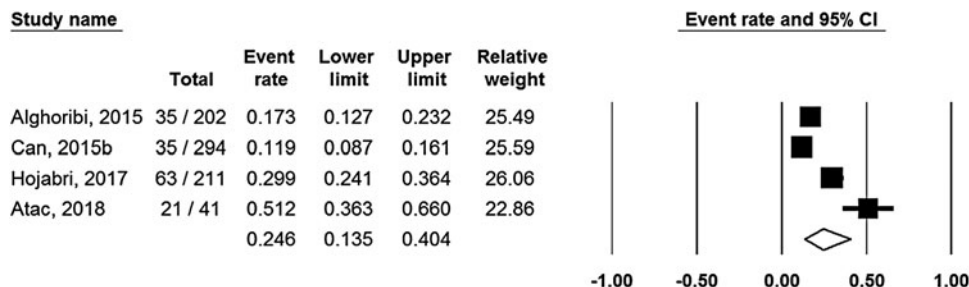


FIG. 3. Forest plots of the overall prevalence of ST131 in western Asia.

TABLE 2. THE COMPLETE RESULTS OF HETEROGENEITY AND PUBLICATION BIAS EXAMINATION

Variable (Prevalence of ST131 among)	Number of report/s	Pooled prevalence %	95% CI		Heterogeneity			Begg's rank correlation		Egger's regression	
			Lower limit %	Upper limit %	$\chi^2$	p value	$I^2$	p value	z value	p value	t value
WT	4	24.6	13.5	40.4	44.430	<0.001	93.248	0.734	0.340	0.618	0.585
ESBL	10	42.7	32.5	53.5	69.188	<0.001	86.992	0.152	1.143	0.199	1.400
MDR	6	64.8	36.0	85.8	107.282	<0.001	95.339	0.348	0.939	0.135	1.869
CTX-M-15	8	68.0	48.4	82.8	53.886	<0.001	87.010	0.711	0.371	0.366	0.978

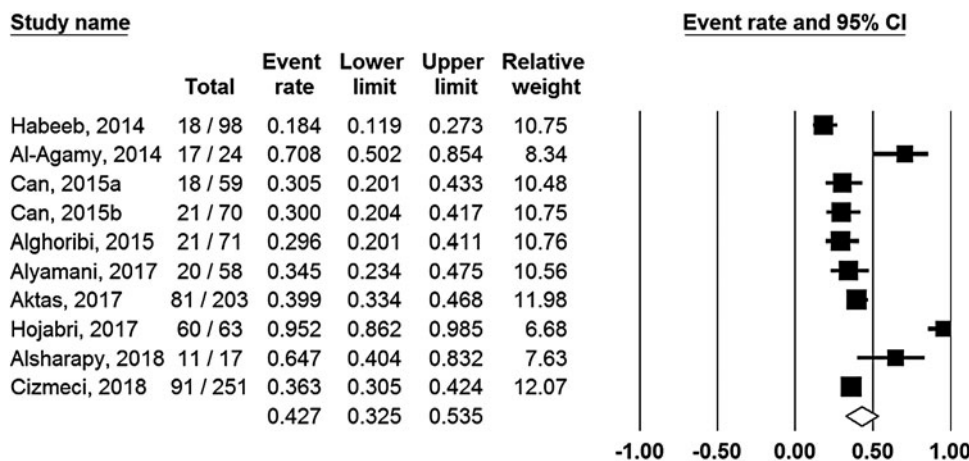


FIG. 4. Forest plots of the prevalence of ST131 in ESBLs-producing isolates. ESBL, extended-spectrum  $\beta$ -lactamase.

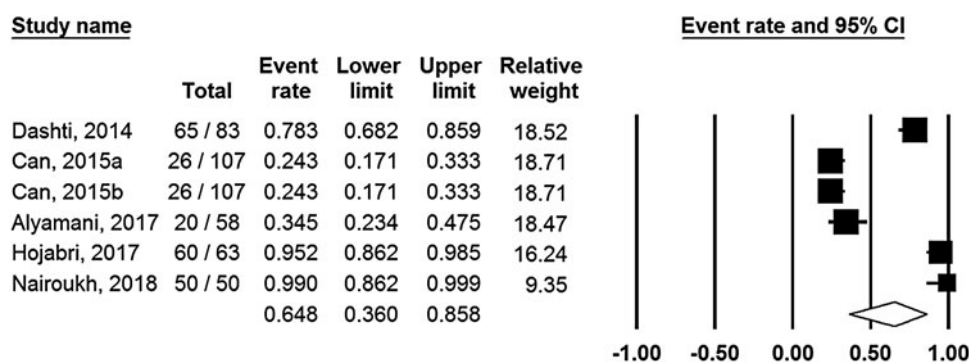


FIG. 5. Forest plots of the prevalence of ST131 in MDR isolates. MDR, multiple-drug resistant.

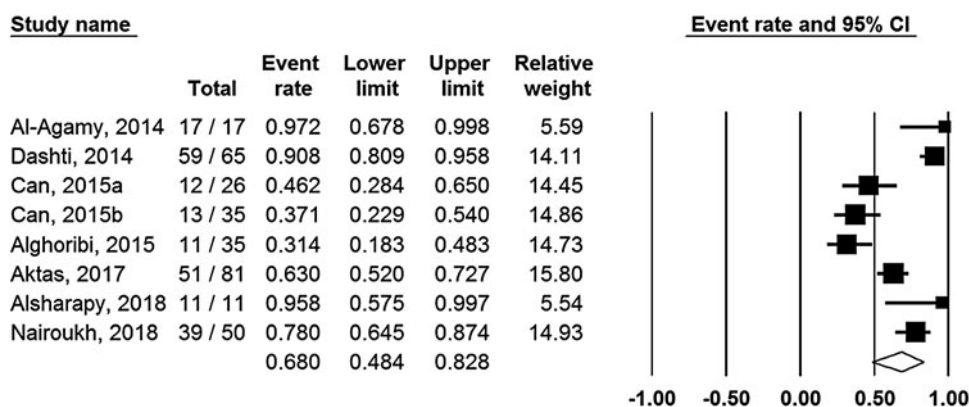


FIG. 6. Forest plots of the prevalence of ST131 isolates carrying CTX-M-15.

could be conducive to preventing the incidence of hospital and community outbreaks.

In this study, 24.6% (95% CI: 13.5%–40.4%) was the pooled prevalence of ST131 clone among WT isolates over the past decade in western Asia. The prevalence reported in our review was closest to those reported among patients with UTI in the United States (29.4%),<sup>35</sup> Brazil (24.07%),<sup>36</sup> and Canada (23.1%)<sup>37</sup>; however, it was lower than those reported from China (15.4%),<sup>18</sup> Korea (13.2%),<sup>38</sup> the United Kingdom (7%),<sup>39</sup> and the Netherlands (4%).<sup>40</sup>

Our findings suggest that ST131 clone occurrence among ESBL-producing *E. coli* is 42.7% (95% CI: 32.5%–53.5%). These results are comparable with the studies performed in India (69.6%),<sup>41</sup> Taiwan (65%),<sup>42</sup> Spain (54%),<sup>43</sup> Korea (50%),<sup>38</sup> and Canada (46%).<sup>44</sup> The observed disparities were mostly originated from the differences in the study population, sample size, or detected O-serogroups. The higher rates of resistance and virulence profile related to ST131 isolates give them a competitive advantage over non-ST131 isolates regarding the promotion of clonal expansion and dominance.<sup>33</sup> Therefore, the prevalence of this clone might be a potential explanation for the increased prevalence of ESBL-producing isolates in both community and hospital settings.<sup>34</sup> However, some authors have suggested that ST131 isolates owe their success to the ESBL phenotype.<sup>40</sup>

In western Asia, a high proportion of ST131 isolates was found to be CTX-M-15 positive (68%; 95% CI: 48.4%–82.8%), mostly associated with O25b-ST131 isolates (76.4%; 95% CI: 52.6%–90.4%). Our findings are in line with the studies reporting CTX-M-15 as the dominant CTX-M type among *E. coli* ST131 isolates from India (100%)<sup>41</sup> and Spain (95%).<sup>43</sup> However, it has been proposed that ST131 can also be associated with other CTX-M types or even lack them.<sup>18,37,45</sup> IncF plasmids, particularly IncFII, are responsible for the global dissemination of CTX-M-15.<sup>46,47</sup> The presence of *bla*<sub>CTX-M-15</sub> could be a predictor of treatment failure because in addition to  $\beta$ -lactamases, a wide range of antimicrobial resistance genes may be integrated into IncF plasmids.<sup>48</sup> Moreover, the abundance of ST131 among ESBL-producing isolates (highly associated with IncF plasmids) may be attributed to the increased prevalence of fluoroquinolone resistance in western Asia.<sup>49,50</sup>

This study encountered certain limitations. First, most of the available data were limited to few regions, so the results may not reflect the actual epidemiology in western Asia. Furthermore, in most studies, only the prevalence of O25b-ST131 was investigated; therefore, the overall prevalence of ST131 isolates might be overlooked.

Despite these limitations, our study demonstrated a high prevalence of broadly disseminated ST131 clone among MDR and ESBLs in western Asia. Moreover, O25b was the predominant ST131 clone type, which was mostly associated with CTX-M-15 type. Owing to the rapid spread of ST131 clone, it is indispensable to identify risk factors, reservoirs, transmission routes, and precautionary measures.

#### Disclosure Statement

No competing financial interests exist.

#### Funding Information

No funding was received for this study.

#### Supplementary Material

Supplementary Figure S1  
 Supplementary Figure S2  
 Supplementary Figure S3  
 Supplementary Figure S4  
 Supplementary Figure S5  
 Supplementary Figure S6  
 Supplementary Figure S7  
 Supplementary Figure S8  
 Supplementary Figure S9  
 Supplementary Figure S10  
 Supplementary Figure S11  
 Supplementary Figure S12  
 Supplementary Figure S13  
 Supplementary Figure S14  
 Supplementary Figure S15

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