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Original Article

Epidemiology of Multidrug Resistant Uropathogenic *Escherichia coli* in Iran: a Systematic Review and Meta-Analysis

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SUMMARY: Urinary tract infection (UTI) is one of the most common infections in humans. It is primarily caused by uropathogenic *Escherichia coli* (UPEC), which has a high multidrug resistance (MDR). In consideration of the prevalence of MDR-UPEC strains, the aims of the present study were to systematically review the published data about the prevalence rate of MDR-UPEC from different parts of Iran and to establish the overall relative frequency (RF) of these strains in Iran. We searched several databases including PubMed, ISI Web of Science, Scopus, Google Scholar, IranMedex, and Iranian Scientific Information Database by using the following keywords: ''*Escherichia coli*'', ''multidrug resistant'', ''MDR'', ''urinary tract infections'', ''UTI'', ''uropathogenic''. and ''Iran''. Articles or abstracts that reported the prevalence of MDR-UPEC were included in this review. We found 15 articles suitable for inclusion in this study. A pooled estimation of 10,247 UPEC strains showed that 49.4% (95% confidence interval = 48.0–50.7%) of the stranis were MDR positive. The RF of MDR-UPEC in different studies varied from 10.5% to 79.2% in the Kashan and Hamedan provinces, respectively. According to the results of the present study, the RF of MDR-UPEC in Iran is high. Thus, measures should be taken to keep the emergence and transmission of these strains to a minimum.

INTRODUCTION

Escherichia coli trains are a very diverse species of bacteria found naturally in the intestinal tract of all humans and many other animal species. A subset of *E. coli* is capable of causing enteric/diarrheal diseases and a different cluster causes extra-intestinal infections, including urinary tract infection (UTI) (1). Uropathogenic *E. coli* (UPEC), a gram negative bacillus, is the main etiologic agent and predominant microorganism causing UTIs (in 50–80%) (2–4). UTI is the most common bacterial infectious disease encountered in clinical practice, accounting for considerable morbidity rates and high medical costs (4). UTIs are one of the most prevalent and significant community-acquired and nosocomial infections, with 150 million cases of this extra-intestinal infection occurring annually worldwide (5,6). Moreover, UTI has become a global public health problem especially in hospitals owing to its high mortality rate in humans, and complications including hypertension, chronic renal failures, chronic pyelonephritis, and dramatically increased drug resistance (7,8). The severity of UTI produced by *E. coli* is due to the expression of a wide spectrum of antimicrobial resistance genes. The level of resistance to different antibiotics, and even that of spontaneous resistance to several antibiotics in *E. coli* strains are growing. This increased rate of drug resistance has induced the emergence of multiple drug resistance (MDR) in UPEC strains. MDR was described as the non-susceptibility to at least one agent in 3 or more antimicrobial classes (9). Resistant *E. coli* strains are emerging globally as a threat to the favorable outcome of common infections in community and hospital settings. These conditions are increasing particularly in developing or third-world countries that frequently use antibiotic agents in both animals and humans, where people consume antibiotics without the supervision or prescription of a physician (10,11). Inappropriate antibacterial treatment and misuse of antibiotics have contributed to the emergence of antibacterial-resistant bacteria (12). The rate of MDR among UTI isolates changes across different geographic regions. For example, the prevalence of MDR-UPEC was reported to be 92% in India (13), whereas the prevalences in the United States and Slovenia were 7.1% and 42%, respectively (14,15). Although, several studies have presented local information about the rate of MDR-UPEC in different cities of Iran, the average rate of MDR UPEC in Iranian hospitals is still

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unknown (16).

In the present study, we aimed to systematically the review the published data about the prevalence rate of MDR-UPEC from different parts of Iran and to establish the overall relative frequency (RF) for Iran by using meta-analysis.

MATERIALS AND METHODS

Search strategy: PubMed, ISI Web of Science, Scopus, and Google Scholar were searched (up to March 2015) by using the following keywords: ''*Escherichia coli*'', ''multi drug resistant'', ''MDR'', ''urinary tract infections'', ''UTI'', ''uropathogenic'', and ''Iran''. In addition to articles published in English, 2 Persian scientific search engines, Iranian Scientific Information Database <www.sid.ir> (SID), and IranMedex <www.iranmedex.ir> were also searched for relevant articles. No limitation was used in the search of the databases. The references lists of all related studies were also reviewed for any other related publications. The search was restricted to original articles/abstracts published in English and in Persian that reported the prevalence of MDR-UPEC measured by using disk diffusion method in Iran. All these steps were done by 4 authors (MS, MM, SH, and RR), and any disagreements concerning article selection were resolved through a discussion. The corresponding author (MS) was available to resolve any disagreement.

Inclusion criteria: Among the English and Persian articles/abstracts found with the above strategies, those with the following features were included in the study: (i) UPEC samples were collected from Iranian hospitals because this review study is limited to Iran, and its purpose was to measure the prevalence of MDR-UPEC strains in this country alone; (ii) the clinical specimens were taken from patients. If there were specimens from hospital personnel, the personal results were not included in the analysis because those samples were collected from patients with repetitive sampling and therefore not valid. Therefore, all of the studies that have been included in this survey have been conducted on clinical samples from patients; (iii) the disk diffusion method (Kirby-Bauer) was used to find the MDR-UPEC strains because this method is the standard phenotypic assay used in most studies on antibiotic resistance patterns and in studies demonstrating the MDR of bacterial strains.

Exclusion criteria: Articles were excluded from the review if (i) the samples were partially/totally selected from UPEC collections (i.e., UPEC samples collected and stored previously); (ii) other phenotypic methods instead of Kirby-Bauer were used for the identification of MDR-UPEC strains; (iii) the origin of the samples was unclear, (i.e., the reviewer(s) could not determine which region or population [for example, inpatients, personnel, or outpatients] the specimens were gathered from); and (iv) the review articles, congress abstracts, or studies were reported in languages other than English or Persian, as well as if the article/abstracts were from a meta-analysis or systematic reviews, or a duplicate publication of the same study (or a study published both in English and in Persian). Concerning the duplicate publications, the study with a bigger sample size or with more detailed results were chosen for our systematic review.

Data collection: For all studies, the following data were extracted: last name of the first author, publication date, sample size, study setting, study enrollment time, number of participants with MDR-UPEC, the RF of MDR-UPEC strains, drug resistance status (MDR), and research location. Two authors independently extracted the data from all of the included studies. Inconsistencies between the reviewers were discussed to reach consensus.

Statistical analysis: The total number of participants and the number of participants with MDR-UPEC isolates were used to estimate the RF which was then converted to log RF and its standard error (SE) to be included in the meta-analysis (17). Summary effects were derived by using a random effects model, which takes between-study variation into account (18). Between study heterogeneities were assessed by using a Cochran's Q-test and the I-square (I^2) test (17). A sensitivity analysis was used to examine the extent to which the overall summary effect might depend on a particular study or a group of publications. Publication bias was checked by using Begg's funnel plots (19) and asymmetry tests including Egger's regression test and Begg's adjusted rank correlation test (18). All statistical analyses were conducted by using STATA version 11.2 (STATA Corp, College Station, TX, USA). P values <0.05 were considered statistically significant.

RESULTS

A total of 7,431 articles were retrieved through the database search. The summary of the literature search and study selection is shown in Fig. 1. In a secondary screening process, 3,277 of the publications were excluded based on an evaluation of the titles and abstracts, and 279 articles were retained for a detailed full-text evaluation. After the full-text evaluation, 15 articles (abstract with full-text articles) describing the prevalence of MDR-UPEC in Iran were selected for analysis and are presented in Table 1. In the studies that we investigated, the samples included infectious urine specimens taken from outpatients and hospitalized patients, both man and woman and across different ages. Most of the studies were conducted in central and west Iran, followed by south Iran. Fig. 2 shows the distribution of MDR-UPEC across different regions of Iran.

The status of MDR-UPEC strains in Iran is shown in Table 2. From the random-effects model, the prevalence of MDR-UPEC strains was found to be 49.4% (95% confidence interval [CI]: 48.0–50.7%). However, an evident heterogeneity of MDR-UPEC RF was observed among studies (Cochran's Q test, $P < 0.001$, $I^2 = 98\%$). Fig. 3 shows the forest plot of the meta-analysis of MDR-UPEC. As shown in Fig. 4, although a slight asymmetry was seen in Begg's funnel plot, this was not confirmed by statistical asymmetry tests ($P = 0.447$ for Begg's rank correlation analysis; $P = 0.625$ for Egger's weighted regression analysis).

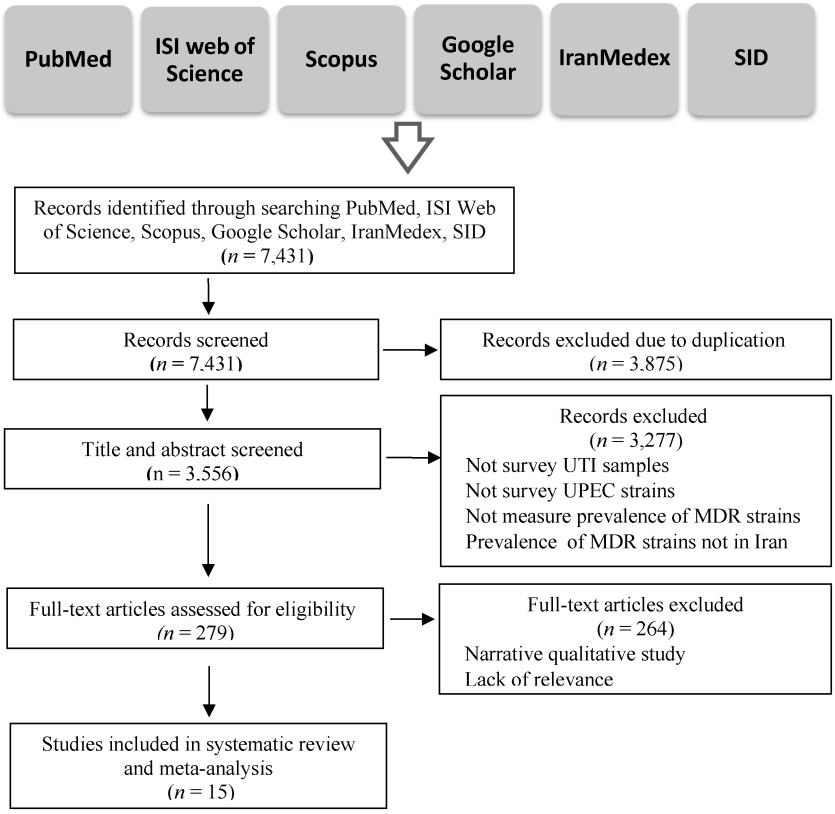

Fig. 1. Flowchart for literature search and study selection.

Table 1. Characteristics of studies included in the systematic review and meta-analysis after full evaluation

First author	Publication year	Enrollment period	Location	Total No. of samples	Rate of MDR (%)	Ref.
Kazemnia et al.	2014	2012	Urmia	235	27.7	(20)
Iranpour et al.	2015	2013	Bushehr	6,406	39.33	(21)
Fallah et al.	2012	2012	Tehran	200	77.5	(22)
Shams et al.	2014	2013	East Azerbayejan	134	53	(23)
Shams et al.	2015	2014	East Azerbayejan	234	64.1	(24)
Erdem et al.	2013	2012	Multi-center[1)]	62	28.8	(25)
Mirzarazi et al.	2013	2012	Isfahan	702	68	(26)
Ahangarzadeh et al.	2011	2009	East Azerbayejan	140	50	(27)
Sharifi et al.	2013	2011–2012	Kashan	1,041	71.9	(28)
Mamani et al.	2015	2012–2013	Hamedan	154	79.2	(29)
Moniri et al.	2003	2001	Kashan	220	10.9	(30)
Mansouri et al.	2002	2000	Kerman	500	41.8	(31)
Farshad et al.	2008	2007	Fars	96	48	(32)
Farshad et al.	2010	2009	Fars	90	77	(33)
Babaei-Hemmati et al.	2015	2012	North of Iran	33	55	(16)

[1)]: Multi-center of Iran including Shiraz, Kerman, Kashan, Yazd, Bandar Abbas, Rasht, and Sanandaj cities.

Table 2. Status of MDR-UPEC strains among included studies

Status	No. of studies	Point estimation[1)]	95% CI[2)]	*P*	Test for heterogeneity	
					I^2	*P*
Multidrug	15	0.494	0.480:0.507	<0.001	98	<0.001

[1)]: Random-effects model.
[2)]: 95% confidence interval.

DISCUSSION

The high prevalence of UPEC infections across different ages and in different parts of the country, especially in hospitals, as well as the increasing antibiotic resistance of this pathogen, led us to undertake this meta-analysis and systematic review. The present study was designed to estimate the prevalence and distribution of MDR-UPEC in the Iranian population according to available data from articles collected from different parts of the country by Iranian researchers.

Furthermore, on the basis of these studies, we provided a map to display the epidemiology of MDR-UPEC in Iran. During recent years, efforts to detect MDR-UPEC strains have become a current trend among Iranian researchers. In the 15 articles evaluated in this study, the prevalence of MDR in UPEC strains was follows: 27.7%, 39.33%, 77.5%, 53%, 64.1%, 28.8%, 68%, 50%, 71.9%, 79.2%, 10.9%, 41.8%, 48%, 77%, and 55%, in the studies of Kazemnia et al., Iranpour et al., Fallah et al., Shams et al., (2014, 2015), Erdem et al., Mirzarazi et al., Ahangarzadeh et al., Sharifi et al., Mamani et al., Moniri et al., Mansouri et al., Farshad et al. (2008, 2010), and Babaei-Hemmati et al., respectively (16,20–33). According to our study, the mean prevalence of MDR-UPEC in Iran was 49.4% and was >50% in most Iranian cities. We tried to compare our study with several studies carried out in different countries worldwide.

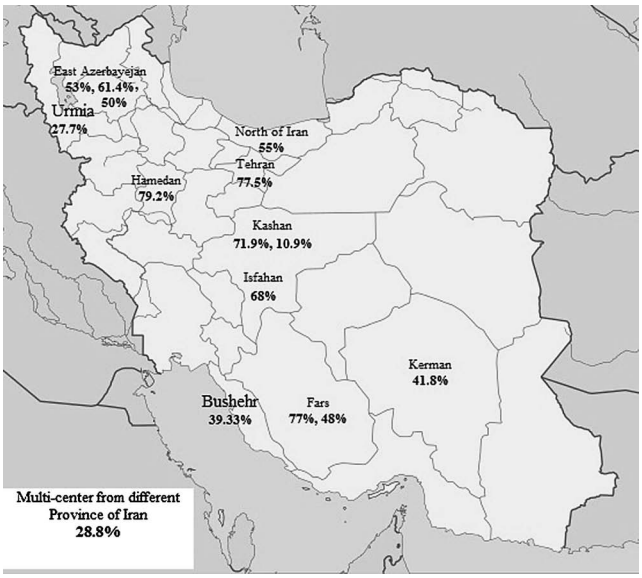

Fig. 2. Distribution of MDR-UPEC in different regions of Iran. (Multi-center of Iran including Shiraz, Kerman, Kashan, Yazd, Bandar Abbas, Rasht, and Sanandaj cities)

Most of the recent studies investigating MDR-UPEC strains have been done in India. In the study by Akram et al. in 2007, the rate of MDR strains among UPEC isolates was 92% (5). In a study done by Hasan et al. in 2007, the prevalence of MDR-UPEC was 52.9% (34). A study by Mathai et al. in 2008 showed that 8.4% of UPEC strains were MDR (35). In the study carried out by Hassan et al. in 2011, all 100 isolates of UPEC (100%) were MDR (36). The findings of the study conducted by Dash et al. in 2012 demonstrated that all 20 UPEC strains (100%) investigated by authors were MDR (37). In the study carried out by Mukherjee et al. in 2013, 37 (92.5%) out of the 40 UPEC isolates (92.5%) were MDR (38). In the study carried out by Niranjan et al. in 2014 of 119 UPEC isolates, 91 (76.51%) were MDR (39). In another study conducted by Annapurna et al. in 2014, all 15 UPEC isolates (100%) were identified as MDR strains (40). In the study carried out by Ranjini et al. in 2015, 148 of 179 UPEC strains (82.68%) were MDR (41).

In Pakistan, 4 studies had been done. In the study conducted by Bashir et al. in 2011, all 59 UPEC isolates (100%) were MDR (10). In the study by Tanvir et al. in 2012 among 310 UPEC strains, 203 (65.5%) were considered MDR isolates (42). Ali et al. reported in 2014 that the prevalence of MDR strains among 80 UPEC strains isolated from non-hospitalized patients was 77.5%. All the screened isolates were resistant to 3 or more of the tested antibiotics (13). Sabir et al. had done one study in 2014 on *E. coli* strains isolated from community- and hospital-acquired UTI cases in Pakistan and demonstrated that of 321 UPEC strains, 261 (81%) were MDR (43).

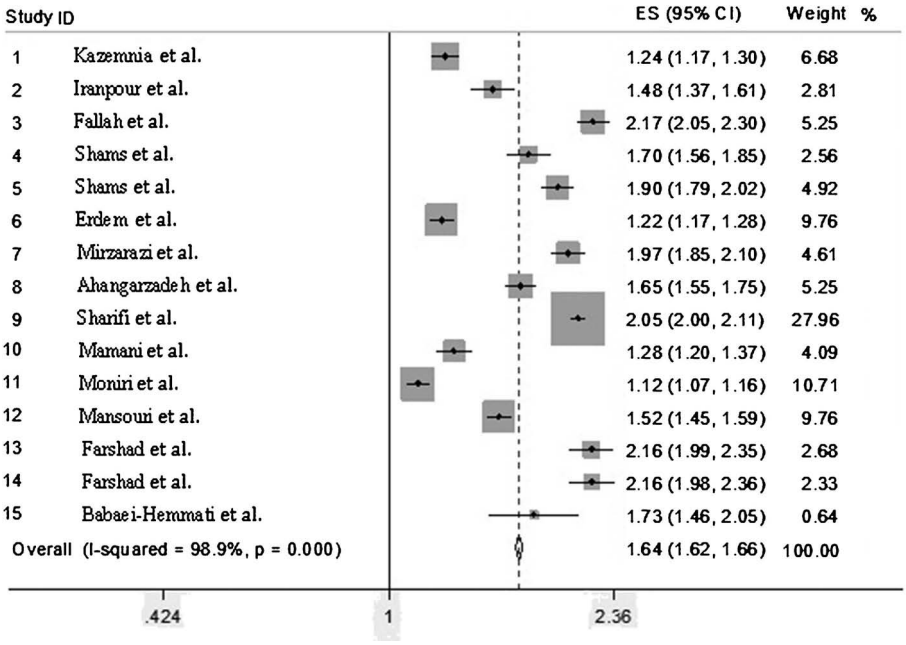

Fig. 3. Forest plot of meta-analysis on log prevalence of MDR-UPEC with 95% CI (illustration of weighted relative frequency using random effects model for assessing overall prevalence of positive MDR-UPEC samples).

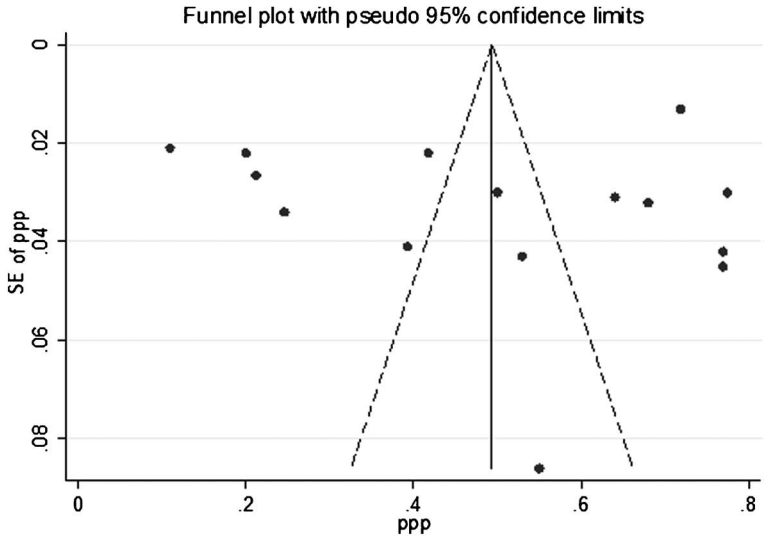

Fig. 4. Funnel plot of the relative frequencies (RFs) versus the standard errors (SE) of the Framingham risks in studies that evaluated the positive MDR-UPEC samples in Iranian patients (with pseudo 95% confidence limits).

In Nepal, 4 studies were conducted. In one study carried out by Ansari et al. in 2015, of 200 clinical isolates of *E. coli*, 156 isolates (78%) were MDR (44); however, a higher rate of MDR-UPEC strains (90.8%) was reported by Sharma et al. in 2013 (45). On the other hand, Khanal et al. in 2013 reported a lower rate of MDR-UPEC isolates (50%) (46), and, similarly, Baral et al. in 2012 showed that 38.2% of UPEC strains were MDR positive (47).

Two studies had been done in the United States. In one study carried out by Sahm et al. in 2001, 38,835 urinary isolates of *E. coli* were investigated. Of these isolates, 2,763 (7.1%) were considered MDR (48). In another study carried out by Linder et al. in 2005, the rate of MDR-UPEC strains was 7.1% (49). In the study by van der Donk et al. in 2012 conducted in different parts of Europe (the Netherlands, Germany, and Belgium). MDR was observed in 74 of 421 (17.5%) UPEC isolates collected from urine samples from urology services (50).

A high prevalence of MDR-UPEC was observed in various geographic regions. In the study carried out by Salem et al. in 2010 in Egypt, the prevalence of MDR-UPEC isolates was 87% (51). A high incidence of MDR *E. coli* (92.2%) was also observed in Sudan by Ibrahim et al. in 2012 (52). In the study carried out by Kibret et al. in 2011 in Ethiopia, the prevalence of MDR-UPEC isolates was 74.6% (53). In the study by Ngwai et al. in 2010 in Nigeria, the prevalence of MDR among UPEC isolates were 83.9% (54). In the study by Bilal et al. in 2001 in Saudi Arabia, the prevalence of MDR among UPEC isolates was 74% (55). In the study by Mowla et al. in 2011, in Bangladesh, 72% of the UPEC strains were MDR (56). In the study by Rijavec et al. in 2006 in Slovenia, 42% of the UPEC isolates were MDR (15). Finally, in the study by Oteo et al. in 2005 in Spain, the prevalence of MDR among UPEC isolates was 20.6% (57).

Iran clearly has a lower prevalence of MDR-UPEC than other Asian countries (India, Pakistan, Nepal, Saudi Arabia, and Bangladesh) and also has a lower prevalence than African countries (Egypt, Sudan, Ethiopia, and Nigeria). In contrast, Iran has a higher prevalence of MDR-UPEC than European countries (the Netherlands, Germany, and Belgium) and the United States. Taking these results together, although the presence of MDR strains in Iranian UPEC isolates is less than those in Asian and African isolates, the rate is relatively high compared with some other countries. This finding indicates that the prevalence and distribution of MDR isolates in developing countries is much greater than those in developed countries, and that physicians and health-care centers may face difficulties in treating half of UTI cases due to UPEC infections in Iran.

This meta-analysis has several limitations that should be considered. First, non-English literature could not be reviewed because of the language barrier. Second, this study cannot fully represent Iran because there were no data on MDR-UPEC from many parts of the country (e.g., east, northeast, and southeast Iran). Third, owing to limited access to in-press articles and theses, some studies might have been missed, which was also suggested by the statistical analysis. Fourth, heterogeneity exists among the included studies. Although the random-effects model allows for the presence of heterogeneity, there may still be some controversy about combining study estimates in its presence. Finally, as with any systematic review, limitations associated with potential publication bias should be considered. In comparison with similar studies, the RF of MDR-UPEC in Iran is moderately high; thus, measures should be taken to keep the emergence and transmission of these strains to a minimum. Careful monitoring of MDR strains and early detection of these isolates by using phenotypic and genotypic laboratory methods are recommended for the prevention and control of MDR-UPEC in Iran. Guidelines for physicians and personnel are needed to prevent the spread of these strains in hospitals.

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Conflict of interest None to declare.

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