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Prevalence of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*: First systematic review and meta-analysis from Iran

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ABSTRACT

Objectives: Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) have emerged as an important pathogen causing severe infections worldwide. Infections due to ESBL-KP are associated with high morbidity and mortality, especially in developing countries such as Iran. The aim of this study was to assess the pooled prevalence of ESBL-KP with different gene variants in Iran.

Methods: A literature search of Medline (via PubMed), Embase, Web of Science and Iranian Database was performed. A meta-analysis was conducted using Comprehensive Meta-Analysis Software (version 2.2, Biostat). A fixed- or random-effects model was used based on the heterogeneity test. Publication bias was determined using Begg's rank correlation and Egger's weighted regression methods.

Results: Among 783 articles identified, 43 studies met the eligibility criteria. The pooled prevalence of ESBL-KP was 43.5% (95% CI 39.3–47.9%) among clinical *K. pneumoniae* isolates. Among genes encoding ESBLs during 2000–2009, SHV, CTX-M and TEM were found with prevalences of 23.3%, 15.2% and 12.3%, respectively, whilst the prevalences of SHV, CTX-M, TEM and VEB were 24%, 28.1%, 25.2% and 8.3%, respectively, during the period 2010–2018.

Conclusion: The prevalence of ESBL-KP has increased steadily in recent years among clinical *K. pneumoniae* isolates in Iran. Thus, initial identification of ESBL-KP according to Clinical and Laboratory Standards Institute (CLSI) guidelines, proper molecular approaches, and implementation of antimicrobial stewardship programmes in Iranian hospitals together with comprehensive infection control measures are urgently needed to control the dissemination of these strains.

Contents

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1. Introduction

Klebsiella pneumoniae is a major cause of severe infections such as urinary tract infection, pneumonia, skin and soft-tissue infection, intra-abdominal infection, bloodstream infection,meningitis and pyogenic liver abscess both in community and hospital settings [1–3]. β-Lactam antimicrobials have been used to treat infections caused by *K. pneumoniae* [4]. One of the most important mechanisms of β-lactam resistance is production of extended-spectrum β-lactamases (ESBLs). ESBLs are diverse enzymes that are able to hydrolyse penicillin, oxyimino-cephalosporins such as third-generation cephalosporins, and monocyclic amide antibiotics such as aztreonam, but are inhibited by β-lactamase inhibitors such as tazobactam, sulbactam and clavulanic acid [4,5]. ESBL-producing *K. pneumoniae* (ESBL-KP) were initially reported in Europe in 1983 and in the USA in 1989 [5]. Infections due to ESBL-KP remain a clinical challenge because these strains are also resistant to other classes of antibiotics such as aminoglycosides, fluoroquinolones and trimethoprim/sulfamethoxazole; consequently, many of these organisms are multidrug-resistant [6]. More than 200 ESBL types have been identified in the Enterobacteriaceae family [7]. The most common and clinically relevant ESBL genes in ESBL-KP are CTX-M, TEM and SHV families [4]. These resistance genes are usually located on mobile genetic elements, such as plasmids, that can be easily transferred within and between bacterial species [8]. In the Middle East, where Iran is situated, studies show that the prevalence of ESBL-KP has increased over the past 10 years [9–12]. However, most of these studies have reported only local data, and a comprehensive study from various parts of Iran has not been performed. Thus, the aim of this study was to perform a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13] in order to determine the prevalence ESBL-KP with different gene variants in Iran (Supplementary Table S1).

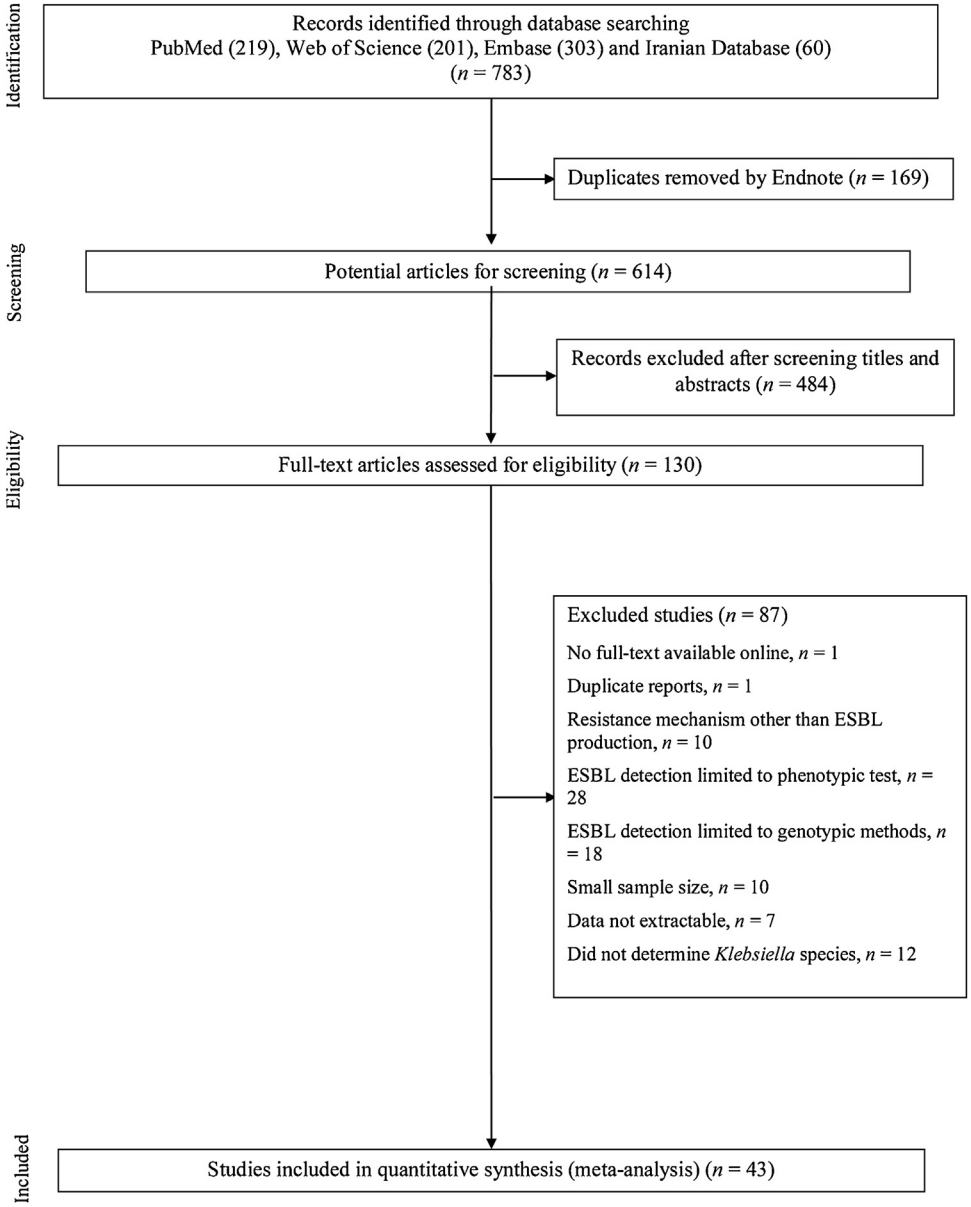


Fig. 1. Summary of the literature search and study selection. ESBL, extended-spectrum β-lactamase.

2. Methods

2.1. Search strategy and eligibility criteria

A comprehensive literature search was performed through the major electronic databases Medline (via PubMed), Embase, Web of Science and Iranian Database from January 2000 to April 2018 using the following terms: '*Klebsiella pneumoniae*' or '*K. pneumoniae*', 'extended-spectrum β-lactamases' or 'ESBLs' together with Iran. Searches were limited to English and Persian languages. The titles and abstracts of articles for possible inclusion in the review were independently screened by two reviewers. Eligible studies were selected in three steps: first, based upon the title; second, based upon the abstract; and third, based on the full-text publication. To be included in the meta-analysis, studies had to meet the following criteria: phenotypic detection of ESBL production (ESBL Etest, phenotypic confirmatory test or double-disk synergy test) according to Clinical and Laboratory Standards Institute (CLSI) guidelines [14]; detection of genes encoding ESBLs by molecular methods such as PCR; and studies that reported the number of ESBL-KP. Studies were excluded for one or more of the following reasons: studies using only phenotypic methods; studies that did not report ESBL-KP and ESBL gene prevalence; studies published in languages other than English or Persian; duplicate and overlapping studies; non-human studies; review articles; congress abstracts and meta-analyses or systematic reviews; and articles available only in abstract form.

Table 1
Characteristics of studies included in the meta-analysis.

First author [reference]	Study period	Year pf publication	Iranian Province	Isolate source	No. of *Klebsiella pneumoniae* isolates	Phenotypic method (no. ESBL-positive)	ESBL genes						
							CTX-M	SHV	TEM	OXA-48	PER	VEB	GES
Shahcheraghi [53]	2006	2007	Tehran	Clinical sample	145	PCT (50)	ND	39	18	ND	ND	ND	ND
Masjedian [54]	–	2007	Isfahan	Clinical sample	70	PCT (49)	ND	8	8	ND	ND	ND	ND
Feizabadi [52]	2006–2007	2010	Tehran	Clinical sample	104	PCT (75)	47	58	32	ND	ND	ND	ND
Feizabadi [12]	–	2010	Tehran	Clinical sample	89	PCT (62)	58	60	48	ND	ND	ND	ND
Khorshidi [49]	2007–2008	2011	Kashan	Clinical sample	100	PCT (32)	ND	16	12	ND	ND	ND	ND
Ghafourian [51]	2007–2008	2011	Ilam, Tabriz, Tehran	Clinical sample lavage	113	PCT (67)	16	63	11	ND	ND	ND	ND
Ghafourian [50]	2007–2008	2011	Tabriz	Clinical sample	103	PCT (44)	7	39	7	ND	ND	ND	ND
Nematzadeh [48]	2006–2009	2011	Tehran	Clinical sample	250	DDST (102)	73	ND	ND	ND	ND	ND	ND
Ghafourian [46]	2007–2008	2012	Ilam, Tabriz, Tehran	Urine	288	DDST (132)	22	104	17	ND	ND	ND	ND
Mansouri [45]	2007–2008	2012	Kerman	Clinical sample	75	PCT (31)	15	ND	ND	ND	ND	ND	ND
Zaniani [42]	2009–2010	2012	Mashhad	Clinical sample	78	PCT (32)	ND	6	5	ND	ND	ND	ND
Eftekhar [47]	2008	2012	Tehran	Urine	51	DDST (14)	7	10	6	ND	ND	ND	ND
Mohebi [44]	2008	2012	Ilam, Tabriz, Tehran	Clinical sample	576	PCT (258)	14	62	10	ND	ND	ND	ND
Pirouzi [43]	2009–2010	2012	Fars	Urine	144	DDST (38)	ND	11	13	ND	ND	ND	ND
Ghasemi [41]	2009–2010	2013	Shiraz	Clinical sample	60	PCT (36)	2	2	23	ND	ND	ND	ND
Taherpour [40]	2011–2012	2013	Tehran	Clinical sample	83	PCT (48)	28	30	24	ND	ND	ND	ND
Nobari [34]	2009–2012	2014	Tehran	Clinical sample	180	PCT (42)	29	25	15	N	7	N	N
Peerayeh [33]	2009–2010	2014	Tehran	Clinical sample (abscess)	200	PCT (72)	45	ND	ND	ND	ND	ND	ND
Zeighami [27]	2012–2013	2015	Zanjan	Clinical sample	149	PCT (58)	54	50	37	ND	ND	ND	ND
Hashemi [37]	2011–2012	2014	Tehran	Clinical sample	83	PCT (48)	30	ND	ND	2	ND	ND	ND
Mansouri [35]	2007–2008	2014	Kerman	Clinical sample	75	PCT (33)	16	ND	ND	ND	ND	ND	ND
Archin [39]	2010	2014	Shiraz	Clinical sample	60	DDST (36)	2	8	23	ND	ND	ND	ND
Gholipour [38]	2011–2012	2014	Isfahan	Urine	55	PCT (21)	ND	3	0	ND	ND	ND	ND
Lashgari [36]	2012	2014	Tehran	Clinical sample	100	PCT (26)	42	ND	ND	ND	ND	ND	ND
Mahmoudjanlou [29]	2010–2011	2015	Gorgan	Clinical sample	70	PCT (24)	15	ND	ND	ND	ND	ND	ND
Shams [28]	2013–2014	2015	Kashan	Clinical sample	185	DDST (87)	70	ND	ND	ND	ND	ND	ND
Eslami [32]	2014	2015	Kerman	Tracheal secretion	50	PCT (28)	ND	7	18	ND	ND	ND	ND
Hashemi [30]	2013–2014	2015	Tehran	Clinical sample	100	PCT (48)	28	30	24	ND	ND	ND	ND
Goudarzi [31]	2014–2015	2015	Tehran	Urine	310	DDST (247)	185	148	173	ND	ND	ND	ND
Peerayeh [9]	2009–2010	2016	Tehran	Clinical sample	127	PCT (59)	29	ND	35	ND	ND	ND	ND
Shahraki-Zahedani [19]	2011–2012	2016	Zahedan	Clinical sample	163	PCT (51)	51	ND	ND	ND	ND	ND	ND
Moradi [21]	2013	2016	Kerman	Clinical sample	111	PCT (59)	52	54	43	ND	ND	ND	ND
Asgari [26]	2013–2014	2016	Alborz	Urine	86	PCT (23)	ND	21	18	ND	ND	ND	ND
Ranjbar [20]	2015–2016	2016	Tehran	Urine	152	PCT (54)	40	ND	ND	ND	ND	ND	ND
Shahraki-Zahedani [18]	2012	2016	Zahedan	Clinical sample	170	PCT (55)	ND	51	40	ND	ND	ND	ND
Mansury [23]	2012–2013	2016	Shiraz	Clinical sample	144	Etest (38)	7	8	6	ND	ND	ND	ND
Bagheri-Nesami [25]	2014–2015	2016	Mazandaran	Clinical sample	75	DDST (24)	14	22	ND	ND	ND	4	4
Latifpour [10]	2013–2014	2016	Shahrekord	Urine	150	DDST (84)	ND	39	31	ND	ND	14	ND
Dadashi [24]	2012–2013	2016	Tehran	Clinical sample	100	DDST (48)	30	ND	ND	ND	ND	ND	ND
Mirzaee [22]	–	2016	Borujerd	Clinical sample	100	PCT (41)	ND	ND	31	ND	ND	ND	ND
Dehghan [17]	2014–2015	2017	–	Clinical sample	58	PCT (19)	34	ND	24	ND	N	5	ND
Ranjbar [16]	2015–2016	2017	Tehran	Clinical sample	76	PCT (31)	20	17	13	ND	ND	ND	ND
Maleki [15]	2015	2018	Isfahan	Urine	98	DDST (25)	23	ND	19	ND	ND	ND	ND

ESBL, extended-spectrum β-lactamase; PCT, phenotypic confirmatory test; ND, not detected; DDST, double-disk synergy test; N, negative.

Table 2
Meta-analysis of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) and genes encoding extended-spectrum β-lactamases (ESBLs).

Subgroup	Study period	No. of studies	Prevalence (95% CI)	n/N[a]	Statistical model	Heterogeneity test		Begg's test	Egger's test
						I^2 (%)	*P*-value		
ESBL-KP	2000–2018	43	43.5 (39.3–47.9)	2451/5556	Random	89.7	<0.001	0.8	0.7
ESBL genes									
CTX-M	2000–2009	10	15.2 (7.3–29)	261/1079	Random	96.3	<0.001	0.4	0.1
	2010–2018	22	28.1 (22.6–34.5)	844/2699	Random	90	0.00	0.01	0.0007
SHV	2000–2009	13	23.3 (14.5–35.3)	478/1921	Random	95	<0.001	0.1	0.4
	2010–2018	15	24 (18–31.2)	513/1799	Random	90	0.00	0.01	0.0003
TEM	2000–2009	13	12.3 (6.7–21.3)	210/1921	Random	94	0.00	0.3	0.04
	2010–2018	17	25.2 (19–32.7)	574/2052	Random	91	0.00	0.2	0.0006
VEB	2010–2018	3	8.3 (5.6–12.2)	23/283	Fixed	20	0.5	0.4	0.3

CI, confidence interval.
[a] n = number of events (ESBL-KP or ESBL gene); N = total number of *K. pneumoniae* isolated from patients.

2.2. Data extraction and definitions

For all studies, the following details were extracted: first author's name; study period; year of publication; city in which the study was conducted; sample size; and prevalence of ESBL-KP and genes encoding ESBLs.

2.3. Quality assessment of studies

Quality assessment was performed independently by two authors using a checklist provided by the Joanna Briggs Institute (JBI) [13]. Any disagreements were resolved through discussion with a third author. The checklist consists of 10 questions to which the reviewers responded individually for each study. A 'Yes' answer for each question received a point. Scores ranged from 0–10, and studies that attained >7 points were entered into the review.

2.4. Statistical analysis

Comprehensive Meta-Analysis v.2.2 (Biostat, Englewood, NJ) was used for the meta-analyses. Based on heterogeneity between different studies, fixed- or random-effects models were used. Statistical heterogeneity among the included studies was assessed via Cochran's Q and the inconsistency I^2 test. In cases of significant heterogeneity ($P < 0.1$ or $I^2 > 50\%$), the random-effects model was applied; otherwise, the fixed-effects model ($P > 0.1$ and $I^2 < 50\%$) was used. Funnel plots, Begg's test and Egger's test were used to detect publication bias, and $P < 0.05$ was regarded as statistically significant.

3. Results

3.1. Risk of bias assessment

Results of the critical appraisal (JBI checklist) of included studies are presented in Supplementary Table S1. Forty-three studies presented a low risk of bias (quality assessment score >7).

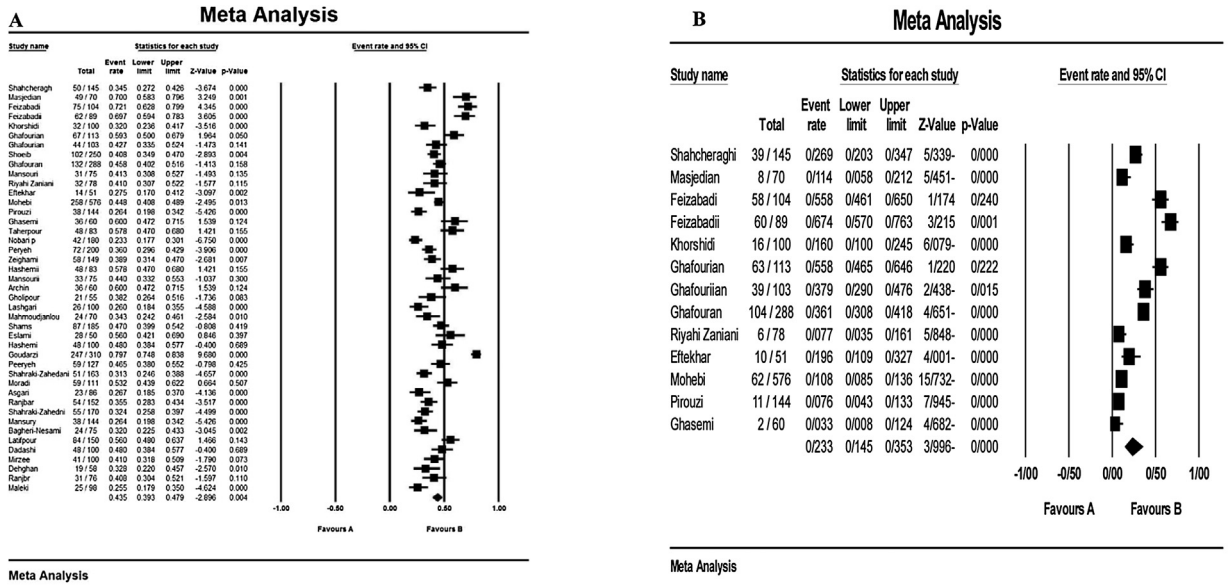
A total of 783 articles were initially identified, of which 614 remained after duplicates were removed. In the next stage, 484 records were excluded after screening the titles and abstracts. Thus, 130 articles remained for further full-text assessment. Based on the inclusion and exclusion criteria detailed in Section 2.1, 87 articles were excluded and 43 articles met the inclusion criteria. The process of study selection and reasons for exclusion are shown in Fig. 1, and the main characteristics of the selected studies are provided in Table 1 [9,10,12,15–54]. The pooled prevalence of ESBL-KP was 43.5% [95% confidence interval (CI) 39.3–47.9%] by phenotypic methods in clinical isolates of *K. pneumoniae*. Among the genes encoding ESBLs during 2000–2009, SHV, CTX-M and TEM were found with prevalences of 23.3% (95% CI 14.5–35.3%), 15.2% (95% CI 7.3–29%) and 12.3% (95% CI 6.7–21.3%), respectively (Table 2), whilst the prevalences of SHV, CTX-M, TEM and VEB were 24% (95% CI 18–31.2%), 28.1% (95% CI 22.6–34.5%), 25.2% (95% CI 19–32.7%) and 8.3% (95% CI 5.6–12.2%), respectively, during the period 2010–2018.

Heterogeneity between studies ($I^2 = 89.7$, $P < 0.001$ for ESBL-KP; $I^2 = 95$, $P < 0.001$ for SHV, $I^2 = 96.3$, $P < 0.001$ for CTX-M, and $I^2 = 94$, $P = 0.00$ for TEM during the period 2000–2009; and $I^2 = 90$, $P = 0.00$ for SHV and CTX-M, and $I^2 = 91$, $P = 0.00$ for TEM during the period 2010–2018) was observed, therefore the random-effects model was used for meta-analysis (Table 2). However, the fixed-effects model was used for the VEB gene ($I^2 = 20$, $P = 0.5$). As shown in Table 2, some evidence of publication bias was detected by Begg's and Egger's tests (SHV, Begg's test, $P = 0.01$, Egger's test, $P = 0.0003$; and CTX-M, Begg's test, $P = 0.01$, Egger test, $P = 0.0007$ during the period 2010–2018), but was not found for ESBL-KP (Begg's test, $P = 0.8$, Egger's test, $P = 0.7$), SHV (Begg's test, $P = 0.1$, Egger's test, $P = 0.4$ during the period 2000–2009), CTX-M (Begg's test, $P = 0.4$, Egger's test, $P = 0.1$ during the period 2000–2009) and VEB (Begg's test, $P = 0.4$, Egger's test, $P = 0.3$ during the period 2010–2018). Publication bias was observed by Egger's test for TEM ($P = 0.04$ during the period 2000–2009; $P = 0.0006$ during the period 2010–2018), but was not observed by Begg's test for TEM ($P = 0.3$ during the period 2000–2009; $P = 0.2$ during the period 2010–2018). Fig. 2 shows forest plots for the prevalence rate of ESBL-KP as well as SHV, CTX-M, TEM and VEB genes. The asymmetric shape of the funnel plots (Fig. 3) displays some evidence of publication bias among the evaluated papers.

4. Discussion

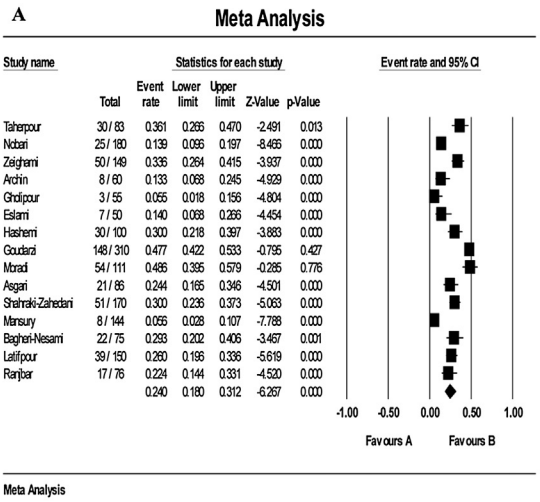
To the best of our knowledge, here we provide the first systematic review and meta-analysis on the prevalence of ESBL-KP and the ESBL genes in Iran. Based on the findings, phenotypic detection demonstrated a high rate of ESBLs (43.5%; 95% CI 39.3–47.9%) in Iran. This issue is of great concern, particularly in low-income countries such as Iran, as infections due to ESBL-KP are associated with significant morbidity, mortality, length of hospital stay and medical costs [55,56].

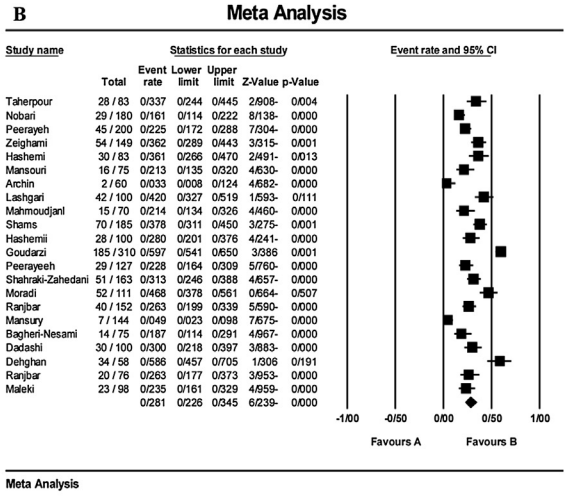
The prevalence of ESBLs in Iran is higher than in developed countries. In a study from Sweden in 2018, Vading et al. reported that only 2% of *K. pneumoniae* isolates produced ESBLs [57]. In Spain, the prevalence of ESBL-KP in 2017 was 7.2% [58]. In a similar study conducted in Canada in 2010–2012, Karlowsky et al. reported that the prevalence of ESBL-producers was 3.6% among

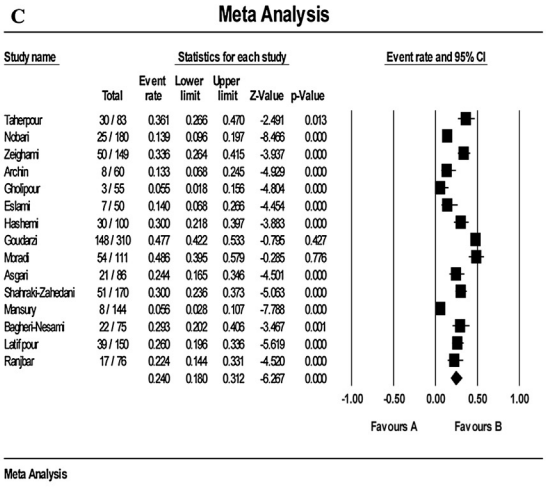


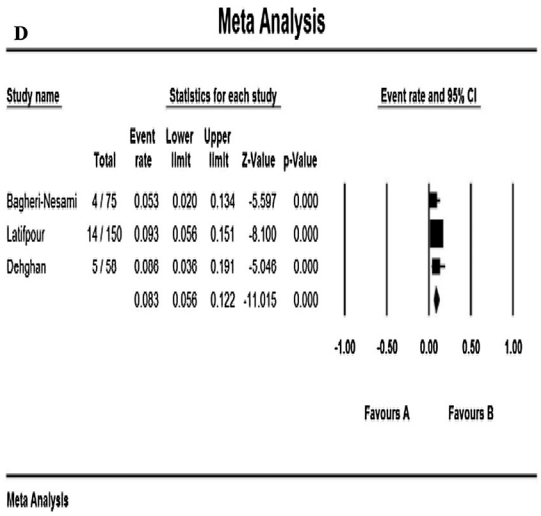
(a)

Fig. 2. (a) Forest plot of studies included in the meta-analysis for the period 2000–2009 in Iran: prevalence of (A) extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP), (B) the SHV gene among ESBL-KP, (C) the CTX-M gene among ESBL-KP and (D) the TEM gene among ESBL-KP. (b) Forest plot of studies included in the meta-analysis for the period 2010–2018 in Iran: prevalence of (A) SHV gene, (B) CTX-M gene, (C) TEM gene and (D) VEB gene among ESBL-KP.









(b)

Fig. 2. (Continued)

K. pneumoniae isolates [59]. On the other hand, high rates of ESBL-KP have been documented from developing countries. For example, studies in Saudi Arabia, United Arab Emirates and Tunisia between 2009 to 2018 revealed a prevalence of ESBL-KP between 38% and 55% in different community setting and hospitals [60–62]. Recently, a systematic review and meta-analysis conducted by Abrar et al. revealed that the prevalence of ESBL-producing Enterobacteriaceae was high (40%) in Pakistan in 2018 [63]. A possible explanation for this variation is that in developing countries such as Iran, misuse and excessive use of broad-spectrum antibiotics is still common, whilst in developed countries policies have been implemented to restrict the use of antibiotics [64–66].

Another explanation for the high incidence of ESBL-KP in Iran is lack of good microbiological laboratory capacity [66–68]. Most clinical microbiology laboratories were unfamiliar with the importance of ESBL-producing organisms and phenotypic methods for their detection. Thus, physicians face serious problems in choosing effective antimicrobial agents against ESBL-producing

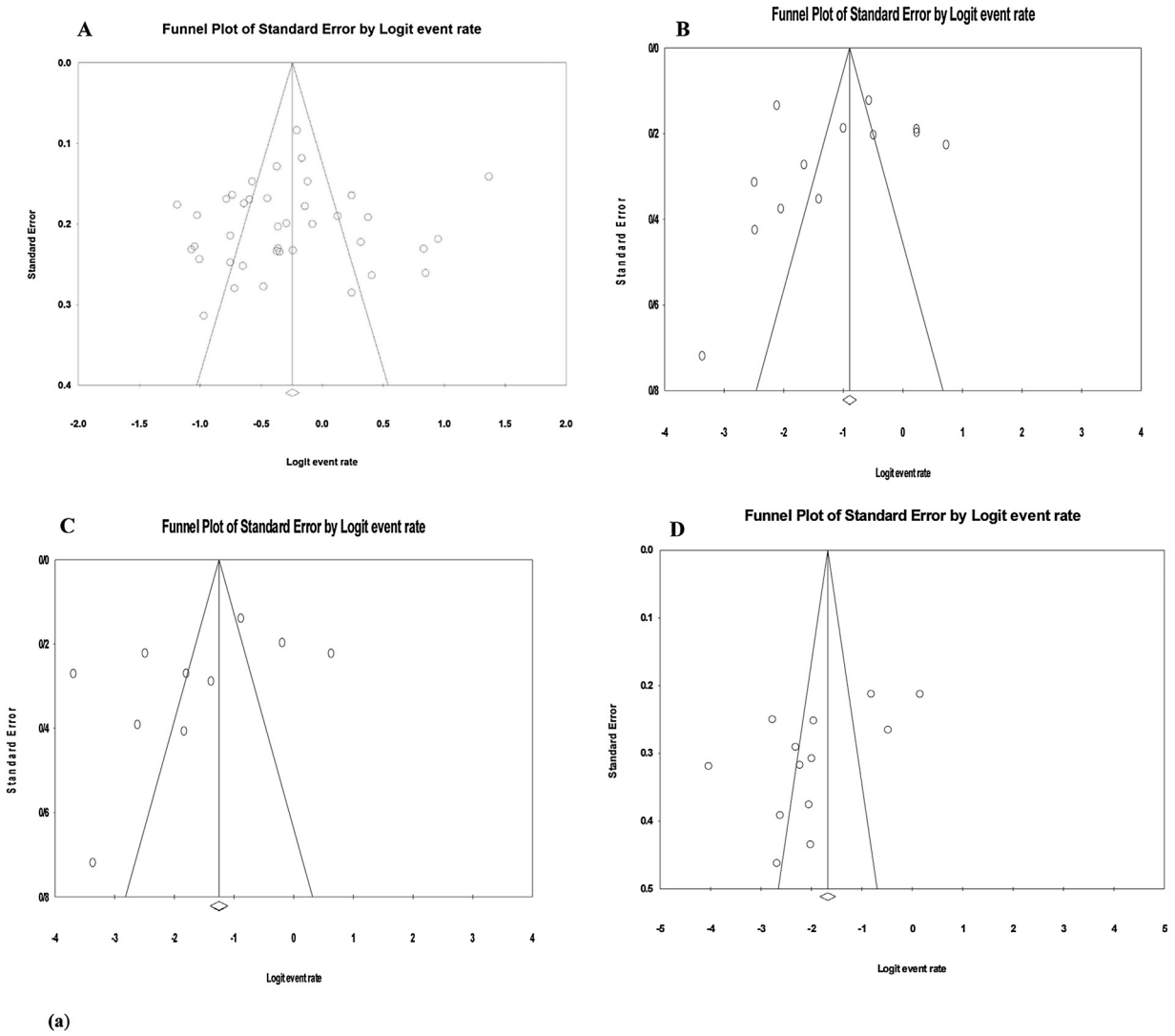


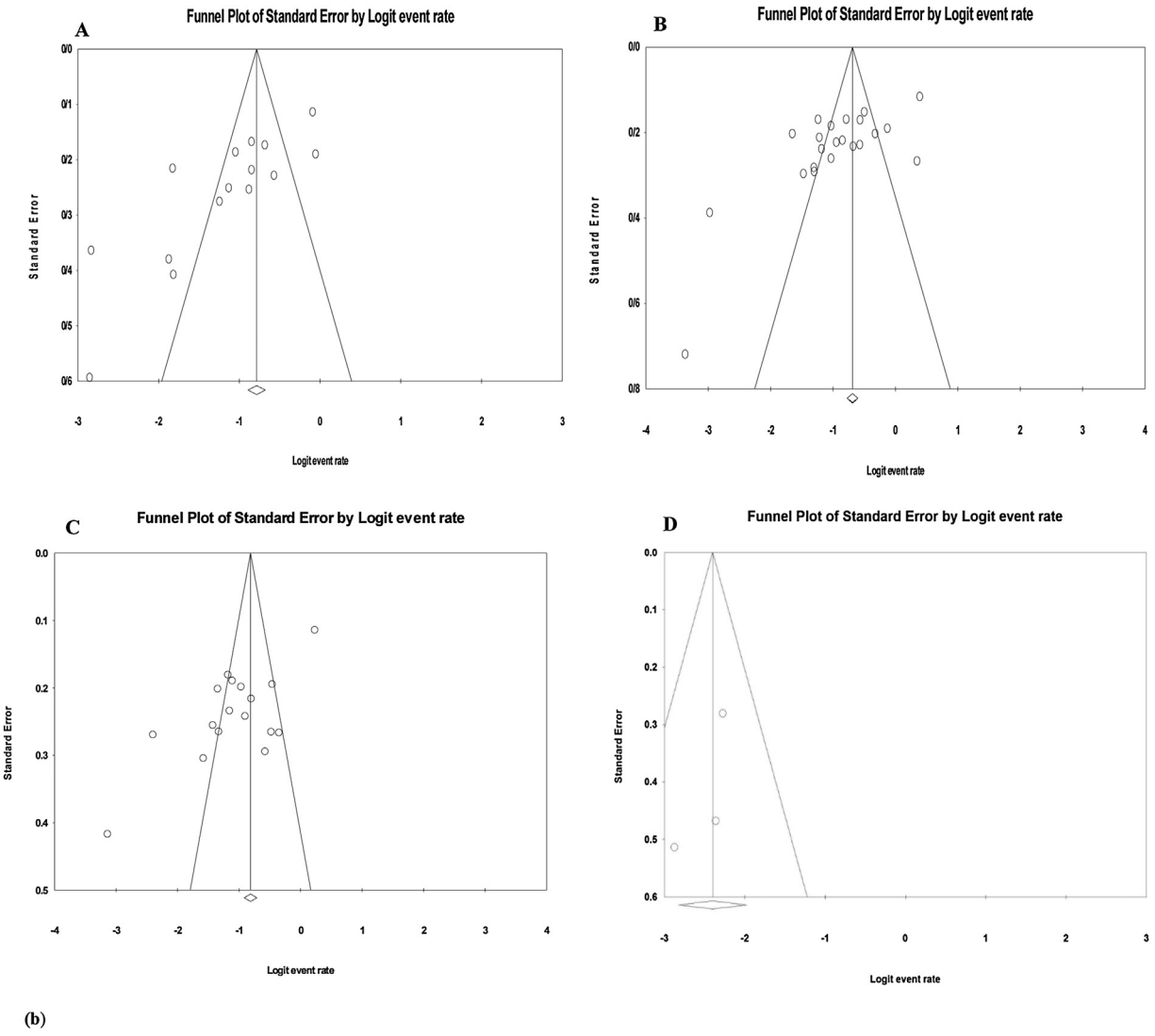
Fig. 3. (a) Funnel plot of publication bias for the included studies for the period 2000–2009 in Iran: prevalence of (A) extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP), (B) the SHV gene among ESBL-KP, (C) the CTX-M gene among ESBL-KP and (D) the TEM gene among ESBL-KP. The asymmetric shape of the funnel plots indicates bias in the meta-analysis. Each study is represented by a circle. (b) Funnel plot of publication bias for the included studies for the period 2010–2018 in Iran: prevalence of (A) SHV gene, (B) CTX-M gene, (C) TEM gene and (D) VEB gene among ESBL-KP. The asymmetric shape of funnel plots indicates bias in the meta-analysis. Each study is represented by a circle.

bacteria. Consequently, treatment failures occur in patients who receive inappropriate antibiotics [67].

Poor infection control practice in hand hygiene, lack of education and training of healthcare workers, and low use of personal protective equipment combined with poor antimicrobial stewardship programmes can contribute to amplify and disseminate ESBL-producing bacteria in Iranian hospitals [65,66,68–71].

According to the statistical analysis, during 2000–2009 the predominant ESBL genes were SHV (23.3%), CTX-M (15.2%) and TEM (12.3%), but during 2010–2018 this situation has changed dramatically and the prevalence of CTX-M, TEM, SHV and VEB reached 28.1%, 25.2%, 24% and 8.3%, respectively. This displacement may be associated with transmission of CTX-M genes by mobile genetic elements such as plasmids and transposons [72,73]. Evidence shows that horizontal gene transfer via IncF-type plasmids plays an important role in the dissemination of CTX-M genes among *K. pneumoniae* [72–74]. Another reason for this increase is probably related to clonal spread. Several studies have shown that clonal spread has contributed to the dissemination of CTX-M ESBLs [73–76].

This review has some limitations. First, the studies could not fully show the prevalence of ESBL-KP in Iran because the magnitude of the issue has not yet been determined in various areas of the country. Second, only articles published in English and Persian languages were considered in the current meta-analysis, thus language bias may be included. Third, the phenotypic methods used to detect ESBLs differed between studies. Fourth, heterogeneity was observed among the included studies. In conclusion, this systematic review indicated that the prevalence of ESBL-KP is high in Iran. Therefore, initial identification of ESBL-KP, careful monitoring of these organisms, proper molecular approaches, implementation of strict antimicrobial stewardship and comprehensive infection control measures are recommended strategies for the prevention and spread of these strains.



(b)

Fig. 3. (Continued)

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Competing interest

None declared.

Ethical approval

Not required.

Availability of data and materials

The data and material in this review are authentic and are available from the author upon reasonable request.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jgar.2019.01.020.

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