

Prevalence of bla_{CTX-M} Gene among Extended-Spectrum β -Lactamases Producing *Klebsiella pneumoniae* Clinical Isolates in Iran: A Meta-Analysis

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What's Known

- Several studies have examined the prevalence of CTX-Ms in ESBLs-producing *K. pneumoniae* clinical isolates in different geographical regions of Iran.
- The average rate of CTX-M enzymes among ESBLs-producing *K. pneumoniae* isolates has not been clearly identified in Iran.

What's New

- We reviewed published studies regarding the prevalence of bla_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates in Iran and presented an overall relative frequency (RF).
- The overall RF of bla_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates in Iran is 56.7%.

Abstract

Background: CTX-M-type extended-spectrum β -lactamases (ESBLs) are the most prevalent ESBLs in bacterial members of Enterobacteriaceae family including *Klebsiella pneumoniae*. The global spread of CTX-M-producing *K. pneumoniae* is a major concern in most countries including Iran. The aim of this meta-analysis was to determine the relative frequency (RF) of bla_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates in Iran and to report an overall prevalence.

Methods: A comprehensive literature search of studies published up to July 2016 was carried out. The keywords “Enterobacteriaceae”, “*Klebsiella pneumoniae*”, “ESBLs”, “CTX-M” and “Iran” were searched in PubMed, Scopus, EBSCO, Google Scholar, Scirus, SID and IranMedex in both English and Persian. Selected articles were published between July 2010 and July 2016 and all of them were in English. STATA SE version 11.0 was used for statistical analysis.

Results: Twenty-four articles/abstracts were included in this analysis. Selected studies were performed in Ahvaz, Arak, Ilam, Kashan, Kerman, Mashhad, Shiraz, Tabriz, Tehran, Zabol, and Zahedan. Our pooled evidence showed that the RF of bla_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates varied from 7.7% in Tabriz to 100% in Mashhad, Tehran, and Zahedan, with an overall RF of 56.7%.

Conclusion: Our meta-analysis revealed that the RF of CTX-M-type ESBLs-producing *K. pneumoniae* is diverse in different regions of Iran, and the central and eastern regions had higher prevalence rates compared to western regions.

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Keywords: • Extended-spectrum beta-lactamase • bla_{CTX-M} • *Klebsiella pneumoniae* • CTX-M

Introduction

Extended-spectrum β -lactamases (ESBLs) are bacterial enzymes that confer resistance to penicillins, broad-spectrum oxyimino-cephalosporins and aztreonam, but suppressed by serine-type β -lactamase inhibitors (e.g. clavulanic acid). ESBLs can be encoded through both chromosome and plasmid genes, and more than ten families have been so far documented to be associated with ESBLs, including CTX-M, SHV, TEM, PER, VEB, BES, GES, TLA, SFO, and OXA.¹⁻³ CTX-M-type ESBLs are plasmid-encoded

enzymes that have been detected in at least 26 bacterial species. CTX-Ms are the most prevalent ESBLs in Enterobacteriaceae particularly in *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.^{1,3-5} A member of the Enterobacteriaceae family, *K. pneumoniae* strains are ubiquitous in nature and exist specifically in natural environments and on mucosal surfaces of mammals. This microorganism is an opportunistic bacterial pathogen that commonly causes different infections in human.⁶⁻⁸ *K. pneumoniae* is one of the major ESBLs-producing bacteria. ESBLs-producing *K. pneumoniae* is more prevalent in Asia and South America,⁹ and has recently been listed as one of the six drug-resistant pathogens for which few potentially effective drugs are available.¹⁰ The worldwide spread of CTX-M-producing *K. pneumoniae* is a major concern in most continents such as Asia.¹¹⁻¹³ Recently, high rate of CTX-M enzymes (as high as 58.5%) among ESBLs-producing *K. pneumoniae* isolates have been reported in many countries including Brazil,¹² Spain,¹⁴ Korea,¹⁵ etc.

To date, several studies have examined the prevalence of CTX-Ms in ESBLs-producing *K. pneumoniae* clinical isolates in different geographical regions of Iran. Nevertheless, the average rate of CTX-M enzymes among ESBLs-producing *K. pneumoniae* isolates has not been clearly identified in Iran. Therefore, in this meta-analysis, we reviewed published studies regarding the prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates in Iran and presented an overall relative frequency (RF).

Materials and Methods

Search Strategy

To identify all related published studies, we searched PubMed, Scopus, EBSCO, Embase, Google Scholar, Scirus and four Persian scientific search engines including IranMedex, IRANDOC, Magiran, and scientific information database (SID) in both English and Persian. The medical subject headings (MESH) and keywords used for the search were "Enterobacteriaceae" and "*Klebsiella pneumoniae* or *K. pneumoniae*" and "Extended-spectrum β -lactamases or ESBLs" and "CTX-M" and "Iran". The searched keywords were adapted to the primary language of the database. We also searched the references cited in these articles to find other relevant articles. Selected articles were published between July 2010 and July 2016 and all of them were in English.

Inclusion Criteria

Among obtained articles/abstracts, those with the following features were included in the study:

- Articles that have assessed the prevalence of *bla*_{CTX-M} gene
- Clinical isolates that were collected from Iranian hospitals
- Clinical isolates that were taken from patients (both inpatients and outpatients)
- Samples that only belonged to the genus *Klebsiella*, species *pneumoniae*
- Phenotypic confirmatory ESBL test (either combination disk test or double disc synergy test) which were used to detect ESBL production
- Only ESBLs-producing isolates which were confirmed by phenotypic ESBL test.

Exclusion Criteria

Studies with at least one of the following criteria were excluded from our study:

- Samples that were totally/partially selected from ESBLs collections
- The origin of samples (region or population) was not clear
- Unclear report of the results

Statistical Analysis

Statistical analysis was executed by the STATA software, version 11.0 (StataCorp, College Station, TX, USA). The overall RF of CTX-M in Iran was pooled by forest plot using the Meta-Analyst software. Heterogeneity among studies was assessed by Cochran's Q-test and I² measurement, which was interpreted as the proportion of total variation contributed among study variants. A P \leq 0.10 and an I² value \geq 50% shown significant heterogeneity. A random-effect model was applied in the incidence of significant heterogeneity; if not, a fixed-effect model was executed.

Results

According to heterogeneity test, random model methods were performed for meta-analysis tests (P $<$ 0.001). The I² $>$ 50% indicated the presence of heterogeneity in our pooled analysis.

Out of all papers found by the search of databases, 24 articles matched our inclusion criteria (20 full-text articles and 4 abstracts) selected for our pooled analysis¹⁶⁻³⁵ (table 1). A detailed flowchart showing the selection process is presented in figure 1. These studies were conducted in 10 provinces and 11 cities of Iran. The prevalence of ESBLs among *K. pneumoniae* clinical isolates varied from 28% in Kerman²¹ to 74% in Tehran,¹⁹ with the mean of 49%. The prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical

Table 1: Characteristics of studies included in meta-analysis

City	Hospitals name	Sample size	Number of isolates carrying the <i>bla</i> _{CTX-M} gene	Relative frequency of <i>bla</i> _{CTX-M} gene (%)	Study team (reference no.)	Year published
Ahvaz	Golestan, Razi	26	7	26.9	Khosravi et al. ¹⁶	2013
Arak	Educational hospitals of Medical University	41	36	87.8	Safari et al. ¹⁷	2013
Ilam	Emam Khomaini, Mostafa Khomaini, Ghaem	43	10	23.3	Ghafourian et al. ¹⁸	2012
Ilam	Emam Khomaini, Mostafa Khomaini, Ghaem	17	5	29.4	Ghafourian et al. ¹⁹	2011
Kashan	Hospitals in Kashan	35	28	80	Firoozeh et al. ²⁰	2014
Kerman	Afzali Poor, Kashani, Bahonar	33	16	48.5	Mansouri et al. ²¹	2014
Kerman	Hospitals in Kerman	31	6	20	Mansouri et al. ²²	2012 (abstract)
Mashhad	Qaem, 17-Shahrivar	9	9	100	Moghaddam et al. ²³	2014
Shiraz	Namazi	36	25	69.4	Ghasemi et al. ²⁴	2013
Tabriz	Emam Reza	45	7	15.5	Ghafourian et al. ²⁵	2011
Tabriz	Sina	45	26	57.8	Pormohammad et al. ²⁶	2014 (abstract)
Tabriz	Emam Reza	21	4	19	Ghafourian et al. ¹⁸	2012
Tabriz	Emam Reza	13	1	7.7	Ghafourian et al. ¹⁹	2011
Tehran	10 hospitals	102	73	71.6	Nematzadeh et al. ²⁷	2011
Tehran	3 general and 2 private hospitals	77	45	58.4	Nasehi et al. ²⁸	2010
Tehran	Hospitals in Tehran	72	45	62.5	Peerayeh et al. ²⁹	2014 (abstract)
Tehran	Milad	68	14	20.6	Ghafourian et al. ¹⁸	2012
Tehran	Taleghani, Mofid	48	30	62.5	Hashemi et al. ³⁰	2014
Tehran	Taleghani, Mofid	48	28	58.3	Taherpour et al. ³¹	2013
Tehran	Mofid	19	18	94.7	Karimi et al. ³²	2012
Tehran	Milad	37	10	27	Ghafourian et al. ¹⁹	2011
Tehran	Loghman-E Hakim, Imam Khomeini, Milad	17	17	100	Derakhshan et al. ³³	2014
Zabol	Amir Al-Momenin	20	13	65	Saeidi et al. ³⁴	2014
Zahedan	Ali ibn Abi Talib, Khatamal Anbiya, Buali	51	51	100	Shahraki-Zahedani et al. ³⁵	2016

isolates varied from 7.7% in Tabriz¹⁹ to 100% in Mashhad, Tehran and Zahedan,^{23,33,35} with the mean of 56.7%. In Tehran, the capital city of Iran, the prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates varied from 20.6% to 100%, with the mean of 61.7%.^{18,19,27-33} Pooled estimation of *K. pneumoniae* samples revealed that 55.9% (95% CI=43.0-68.9) of strains are CTX-M positive. Figure 2 demonstrates the forest plot of the relative frequency of *bla*_{CTX-M} gene among different studies performed in Iran.

Discussion

In recent years, numerous studies by Iranian researchers have been conducted to identify *bla*_{CTX-M} gene variants among ESBLs-producing

K. pneumoniae clinical isolates. Based on these studies, this review presented a meta-analysis to show the prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates in Iran. Based on our results, the CTX-M-type ESBLs-producing *K. pneumoniae* is less frequent in western cities compared to central and eastern cities. The mean prevalence of ESBLs among *K. pneumoniae* clinical isolates in Iran was 49% that, on average, 56.7% of these isolates (ESBLs-producing isolates) possessed *bla*_{CTX-M} gene. Lee et al.,¹¹ in their study on *K. pneumoniae* clinical isolates in 9 Asian countries have shown that ESBLs-production rates differed amongst the studied countries. The percentage of ESBLs-producers was low in Hong Kong and Taiwan (7.7% and 8.3%, respectively), but was high in South Korea,

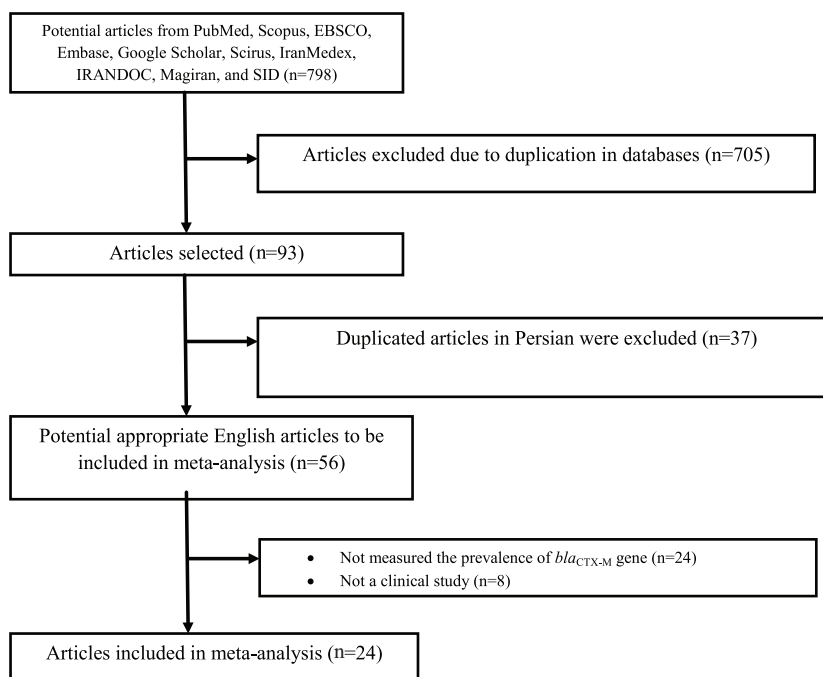


Figure 1: Flowchart of the study selection process.

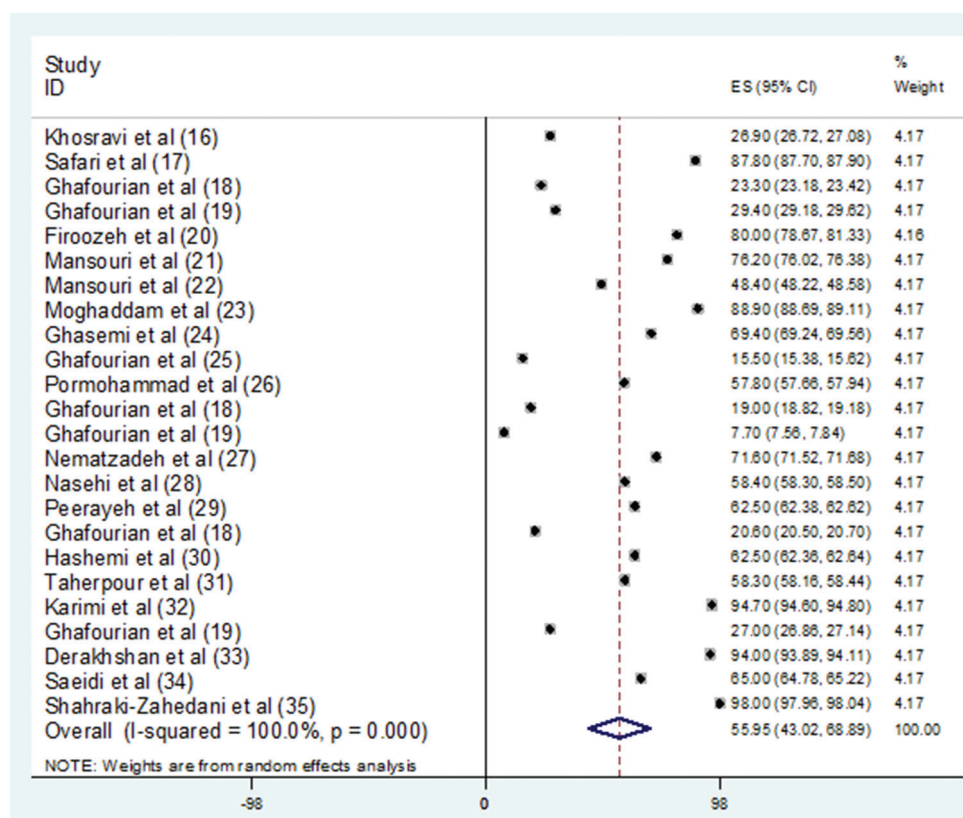


Figure 2: Forest plot of the current relative frequency of *bla*_{CTX-M} gene among ESBLs-producing *Klebsiella pneumoniae* clinical isolates in different Iranian studies.

India, and Thailand (66.7%, 57.1%, and 55.3%, respectively). Moreover, they showed that 72.8% of ESBLs-producing isolates were possessed *bla*_{CTX-M} gene which amongst, *bla*_{CTX-M-15} was the major variant. Similarly, in Iran, the sequencing

results in some studies demonstrated that the major variants of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates are *bla*_{CTX-M-15}^{23,26,29,30,32,35-37} followed by *bla*_{CTX-M-8}^{35,36}, *bla*_{CTX-M-3} and *bla*_{CTX-M-22}²⁶. From a regional

stand, Iran has a higher mean prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates compared to reports from neighboring countries including Turkey (30%),^{38,39} Saudi Arabia (35.3%),^{40,41} Iraq (45.2%),^{42,43} and Bahrain (10%)⁴⁴ as well as lower mean prevalence compared to Pakistan (96.9%),^{45,46} Kuwait (100%),⁴⁷ and United Arab Emirates (64.4%).⁴⁸ In a continental perspective, Iran has a lower mean prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates compared to reports from East Asian countries (78.8%).^{11,49} At the international level, mean prevalence of *bla*_{CTX-M} gene among ESBLs-producing *K. pneumoniae* clinical isolates in Iran is higher than USA (26.4%),⁵⁰ Russia (34.9%),⁵¹ and South Africa (7.4%)³⁹ as well as lower than Brazil (62.1%)^{12,52} and Argentina (61.1%)³⁹ in Latin America and some European countries (84.5%).^{9,53-56}

Our study had some limitations, including lack of published data from certain regions of Iran and the unavailability of some in-press articles that were excluded from our study.

Conclusion

In conclusion, this study showed that the prevalence of CTX-M-type ESBLs-producing *K. pneumoniae* is diverse in different regions of Iran, and the central and eastern regions have higher RF compared to western regions.

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Conflict of Interest: None declared.

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