The Spread of Carbapenemase Genes in *Klebsiella pneumoniae* in Iran: a Systematic Review

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**Abstract**

**Introduction:** The emergence and global spread of carbapenemases produced by *Klebsiella pneumoniae* is a serious problem to health services worldwide. *K. pneumoniae*, belonging to the Enterobacteriaceae family, is commonly found in the human gastrointestinal tract and environment, especially in the hospital environment. Carbapenem is administered as the first treatment for severe infections created by multi-drug resistant *K. pneumoniae*. Despite the fact that the carbapenemase-producing *K. pneumoniae* has become more prevalent in Iran, few investigations have probed into the prevalence of different carbapenemase genes in Iran.

**Method:** The aim of this study was to examine the prevalence of carbapenemase genes in *K. pneumoniae* from 2010 to 2018 in Iran. PubMed and Scopus databases were searched for the articles published between 2010 and 2018 in Iran.

**Results:** A total of 25 papers published between 2012 and 2018 were selected. The highest frequency of *blaNDM*, *blaIMP*, *blaVIM*, *blaKPC* and, *blaOXA48* genes were related to cities of Shiraz in 2017 [23 (26.14%); Hamedan in 2017 [2 (50%); Babol in 2015 [15 (41.66%); Isfahan in 2013 [65 (44.83%); and, Isfahan in 2018 [90 (76.27%)], respectively. The results showed that the frequency of *blaNDM*, *blaOXA48*, and *blaIMP* genes increased in 2017 and 2018, and there was an increase in the frequency of the *blaVIM* gene in 2014 and 2015, and the *blaKPC* gene in 2013. The highest percentage of carbapenemases genes isolated in Iran were *blaNDM* [145 (37.08%)], *blaOXA48* [118 (30.18%)], and *blaNDM* [88 (22.51%)], and the lowest percentages were reported in *blaIMP* [4 (1.02%)], and *blaVIM* [36 (9.21%)], respectively.

**Conclusion:** The results of our review showed that *blaNDM* and *blaOXA48* carbapenemase genes have been increasing in Iran, and it seems that traveling is one of the most important factors in the transmission of carbapenemase genes.

**Keyword:** *Klebsiella pneumoniae*, Carbapenemase, NDM, VIM, IMP, KPC, OXA48

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**Introduction**

*Klebsiella pneumoniae* is usually found in the human gastrointestinal tract and environment, especially in the hospital environment.\(^{1,2}\) It can cause hospital infections, including pneumonia, blood infections, wound, and meningitis.\(^{3}\) These bacteria rapidly acquired antibiotic resistance, especially to carbapenem.\(^{4}\) Antibiotic resistance is a global health problem caused by increased antibiotic consumption in clinical and veterinary fields.\(^{5}\) Antibiotic resistance in gram-negative bacteria, especially Enterobacteriaceae, is one of the major causes of mortality and a serious health problem.\(^{6,7}\) Carbapenems are used as the first line of treatment for severe infections caused by multi-drug resistant *K. pneumoniae*.\(^{1,8}\) After extended-spectrum beta-lactamases, carbapenemases is another group of β-lactamases in which hydrolysis of carbapenem antibiotics, causes resistance to Gram-negative bacteria.\(^{9,10}\)

The most important carbapenemase genes include *blaNDM*, *blaKPC*, *blaOXA48*, *blaIMP*, and *blaVIM*. In 1996 for the first time, the *blaKPC* gene was reported in the United States\(^{11}\) followed by...
Puerto Rico, Colombia, Greece, Israel, and China.\textsuperscript{12,13} The \textit{bla}\textsubscript{IMP} gene was first reported in Japan in 1991\textsuperscript{14} and then spread around the world. This gene and \textit{bla}\textsubscript{IMP} gene are endemic in countries of Egypt, Taiwan, and Japan.\textsuperscript{15,16} The first report of the \textit{bla}\textsubscript{OXA-48} gene was in Turkey in 2003\textsuperscript{17}, followed by worldwide expansion in Africa, European countries, and the East and South of the Mediterranean Sea.\textsuperscript{18-20} \textit{bla}\textsubscript{NDM} gene was first reported in Sweden from an Indian patient in 2008 and then spread throughout the world.\textsuperscript{19} Also, there are a few reports of this gene in Canada and the United States, and the Balkans and the Middle East are believed to be the second reservoir of this gene.\textsuperscript{21,22} The first time the \textit{bla}\textsubscript{VIM} gene was discovered was in 1997 in Verona, Italy, after which it was reported in Greece and then spread around the world.\textsuperscript{23,24}

Considering the fact that several studies have been carried out on carbapenemases produced by \textit{K. pneumoniae} clinical isolates in different parts of Iran, but information on the mean prevalence of these enzymes is unclear. In this review, we examined the prevalence of carbapenemases produced by \textit{K. pneumoniae} clinical isolates.

\section*{Methods}

\subsection*{Searching the Databases}

To identify all the related published studies, we searched PubMed and Scopus in English. The medical subject headings (MESH) and keywords used for the search included "\textit{Klebsiella pneumoniae}" and "carbapenemases" and "Iran". We also selected the articles published between 2010 and 2018.

\subsection*{Study Selection Criteria}

In this study, only original articles were used. Inclusion criteria included the papers on \textit{K. pneumoniae} isolates from clinical specimens in different regions of Iran. Duplicate papers (n=10) on the two databases and two studies in which the clinical isolates included species other than \textit{K. pneumoniae} were excluded from the study.

Furthermore, in 2010 and 2011, there were no studies on carbapenemases produced by \textit{K. pneumoniae} on Scopus and PubMed databases.

\subsection*{Data Extraction}

The extracted data included the city in which the samples were collected, year, type of sample, type of carbapenemase described, Antibiotic resistance pattern and the references.

\subsection*{Results}

\subsection*{Study Selection}

The selection process and results are shown in \textbf{Figure 1}. A total of 37 articles were used from the PubMed database (n=21) and Scopus (n=16), of which 12 articles were excluded because ten articles were repeated in both Scopus and PubMed databases, and two articles (Scopus=1 and PubMed=1) evaluated species other than \textit{K. pneumoniae}. The remaining 25 studies were included in our final analysis, of which 20 were from the PubMed database and five from the Scopus database.

\subsection*{Study Characteristics}

The publication year of the studies was from 2012 to 2018. The majority of the articles were published in 2018 and the smallest number of studies was in 2016. The frequency and percentage of the related articles are shown in \textbf{Table 1}. In 2010 and 2011, no articles related to this study were published on the PubMed and Scopus databases. Most of the studies were in Tehran (n = 9) and Isfahan (n = 7) (\textbf{Figure 2}).

Frequency of clinical samples and number and percentage of these specimens are presented in \textbf{Table 2} and \textbf{Table 3}, respectively. The largest clinical samples are related to unknown [981 (35.10%)], urine [705 (25.22%)],

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The Process of Selection Articles Uses in This Study.}
\end{figure}
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and respiratory secretions [352 (12.77%)] samples, and the least frequent samples include cerebrospinal fluid (CSF) [15 (0.54%)], sputum [17 (0.61%)], feces [17 (1.97%)], blood [154 (5.50%)] and wound [214 (7.66%)] samples, respectively. Also, in these studies, the highest number of samples is related to the year 2017 [535 (23.67%)] and the lowest number of clinical specimens is in 2012 [48 (2.12%)].

Samples were collected from hospitalized patients in 20 articles [20 (80%)] and from outpatients in five articles [5 (20%)]. Furthermore, most specimens were collected from intensive care units (ICU) and burn wards.

The highest percentage of carbapenem resistance was related to ertapenem (63%), meropenem (62%), doripenem (62%), and imipenem (60%), respectively, as displayed in Table 3. In addition, the highest percentage of resistance to other antibiotics is illustrated in Figure 3, which is related to cefotaxime (48%), ceftazidime (44%), piperacillin (28%), azetronam (24%), ampicillin (16%), cefepime (16%), trimethoprim-sulfamethoxazole (12%) and ceftriaxone (12%), respectively.

According to the reviewed articles for the detection of carbapenemases, only 4 used phenotypic methods [3 (12%)], 3 used genotypic methods [3 (12%)] and 19 studies used both phenotypic and genotypic methods [19 (76%)]. In the phenotypic methods, 22 studies [22 (88%)] used modified Hodge test (MHT) method, 4 studies used the method of E-test (Epsilometer test) with MHT [4 (16%)], 1 study used CHROMagar and 1 study used the kit (Rosco Diagnostica, Denmark). In addition, the number of clinical samples based on phenotypic and genotypic methods in the articles used in this study is presented in Table 4.

The highest percentage of carbapenemases isolated in Iran was related to \(\text{blaKPC} \) [145 (37.08%)], \(\text{blaOXA48} \) [118 (30.18%)], and \(\text{blaNDM} \) [88 (22.51%)], and the lowest percentages were in \(\text{blaIMP} \) [4 (1.02%)], and \(\text{blaVIM} \) [36 (9.21%)], respectively. Also, the largest number of carbapenemase genes is related to studies in Isfahan (57.43%), Tehran (11.03%), and Tabriz (10%), respectively (Table 4).

The results of the studies showed that the largest number of carbapenemases were reported from isolates of urine [101 (25.83%)], respiratory secretion [98 (25.06%)],
unknown [83 (21.23%)] and wound [43 (10.99%)], and the smallest number of carbapenemases was reported in blood [13 (3.32%)], sputum [6 (1.53%)], CSF [6 (1.53%)] and feces [39 (9.97%)], respectively.

The frequency of the carbapenemase genes based on the year of publication of the articles is shown in Figure 4. The highest prevalence of \(\text{blaNDM}, \text{blaIMP}, \text{blaVIM}, \text{blaKPC}\) and \(\text{blaOXA48}\) genes were observed in Shiraz in 2017 [23 (26.14%)], Hamedan in 2017 [2 (50%)], Babol in 2015 [15 (41.66%)], Isfahan in 2013 [65 (44.83%)] and Isfahan in 2018 [90 (76.27%)], respectively. In addition, the distribution of \(K.\ pneumoniae\) carbapenemase-produced in various geographical areas of Iran in the period 2012-2018 is displayed in Figure 5.

**Discussion**

Infections with multi-drug resistant bacteria as carbapenem-resistant \(K.\ pneumoniae\) are considered as a serious problem to global health.\(^5^\) The extensive dissemination of \(K.\ pneumoniae\) carbapenemases producer has led to the spread of this resistant pathogen worldwide.\(^5^,^6\) The present study was conducted to estimate the prevalence of carbapenemase genes in \(K.\ pneumoniae\) carbapenemase genes of \(K.\ pneumoniae\) in different cities of Iran. According to our findings, most studies have been conducted in Tehran [9 (36%)] and then in Isfahan [7 (28%)], because Tehran is the capital of Iran and enjoys more facilities, more research centers, more medical schools, and treatment centers. Isfahan is also one of the large and densely populated provinces of Iran and is close to Tehran. There were an almost equal number of studies in other Iranian cities.

The results of this review showed that the most clinical specimens were from urine and respiratory secretions due to the easy colonization of \(K.\ pneumoniae\) in the respiratory tract system and the urinary tract system. According to the results of this review, the rate of resistance to carbapenem antibiotics in \(K.\ pneumoniae\) varied from 5.6% to 63%, indicating a high range of resistance to these antibiotics and since they are the last line of treatment for severe infections, they should be administered with caution. Also, a recent report indicated that the rate of antibiotic resistance had increased in Portugal.\(^5^3\)

### Table 3. The Frequency of Carbapenems Resistance Based on the Articles Used in This Study

| Author Name              | Number of Isolates | Imipenem Percentage | Meropenem Percentage | Ertapenem Percentage | Doripenem Percentage | Reference |
|--------------------------|--------------------|---------------------|----------------------|----------------------|----------------------|-----------|
| Shoja et al              | 170                | 5.9%                | 6.5%                 | 8.2%                 | 7.6%                 | 25        |
| Agha-Seyed Hosseini et al| 181                | 19.9%               | 20.4%                | 5.6%                 | 7.2%                 | 26        |
| Kiaei et al              | 30                 | 23.3%               | 26.7%                | 30%                  | N                    | 27        |
| Fazeli et al             | 112                | 42%                 | 41.1%                | N                    | N                    | 28        |
| Shokri et al             | 120                | 60%                 | 62%                  | 63%                  | 62%                  | 29        |
| Khorvash et al           | 29                 | 29%                 | 29%                  | N                    | N                    | 30        |
| Gheitani et al           | 100                | N                   | N                    | 50%                  | N                    | 31        |
| Hosseinzadeh et al       | 112                | 13.7%               | 13.7%                | N                    | N                    | 32        |
| Shahcheraghi et al       | 45                 | 6.6%                | 28.8%                | 20%                  | N                    | 33        |
| Rastegar et al           | 29                 | 54%                 | N                    | N                    | N                    | 34        |
| Japoni Nejad et al       | 100                | 8%                  | 12%                  | N                    | N                    | 35        |
| Nobari et al             | 180                | 7.7%                | 23.3%                | 16.1%                | N                    | 36        |
| Bina et al               | 270                | 13.9%               | 14.5%                | 15.5%                | N                    | 37        |
| Rajabnia et al           | 50                 | 52%                 | N                    | N                    | N                    | 38        |
| Eftekhar and Naseh        | 55                 | 20%                 | 20%                  | N                    | N                    | 39        |
| Shokri et al             | 128                | 55%                 | 58%                  | N                    | N                    | 40        |
| Akhi et al               | 63                 | N                   | N                    | 34.9%                | N                    | 41        |
| Ghotaslou et al          | 57                 | 19.9%               | 24%                  | 28.6%                | N                    | 42        |
| Tavakoly et al           | 118                | 4.9%                | N                    | N                    | N                    | 43        |
Table 4. The Frequency of Carbapenemase Genes Found in Studied Cities

| Author Name          | City           | Date  | No. of Sample | No. of MHT Positive Isolate (%) | Type of Method for Identification Carbapenemase Gene | No. of \( \text{blaNDM} \) | No. of \( \text{blaNDM1} \) | No. of \( \text{blaNDM7} \) | No. of \( \text{blaIMP} \) | No. of \( \text{blaIMP1} \) | No. of \( \text{blaVIM} \) | No. of \( \text{blaVIM1} \) | No. of \( \text{blaKPC} \) | No. of \( \text{blaKPC2} \) | No. of \( \text{blaOXA48} \) | Reference |
|----------------------|----------------|-------|---------------|---------------------------------|------------------------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Shoja et al          | Bandar-abbas   | 2017  | 170           | 4 (2.35%)                       | Phenotypic and genotypic                               | -                           | 4                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 25                          |
| Shahcheraghi et al   | Hamadan        | 2017  | 65            | 29 (44.62%)                     | Phenotypic and genotypic                               | 1                           | -                           | 2                           | 2                           | -                           | -                           | -                           | -                           | -                           | 1                           | 44                          |
| Agha-Seyed Hosseini et al | Kashan   | 2016  | 181           | N                               | Genotypic                                             | -                           | -                           | -                           | -                           | -                           | 21                          | -                           | -                           | -                           | -                           | 26                          |
| Kiaei et al          | Kerman         | 2018  | 30            | 5 (16.66%)                      | Phenotypic and genotypic                               | 9                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 27                          |
| Fazeli et al         | Isfahan        | 2015  | 112           | 6 (5.36%) + E-test\(^a\)        | Phenotypic and genotypic                               | 6                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 28                          |
| Shokri et al         | Isfahan        | 2018  | 80            | 0 (0%) + E-test\(^a\)           | Phenotypic and genotypic                               | 18                          | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 29                          |
| Mobbadampour et al   | Isfahan        | 2018  | 80            | 0 (0%) + E-test\(^a\)           | Phenotypic and genotypic                               | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 45                          |
| Khorvash et al       | Isfahan        | 2018  | 29            | N                               | Genotypic                                             | -                           | -                           | 1                           | 3                           | -                           | -                           | -                           | -                           | -                           | -                           | 1                           | 30                          |
| Solgi et al          | Isfahan        | 2018  | 96            | 77 (80.21%)                     | Phenotypic and genotypic                               | 6                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 90                          |
| Gheitani et al       | Isfahan        | 2018  | 100           | 68 (68%)                        | Phenotypic and genotypic                               | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 31                          |
| Hosseinzadeh et al   | Shiraz         | 2017  | 112           | 27 (24.11%)                     | Phenotypic and genotypic                               | 23                          | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 2                           | 32                          |
| Azimi et al          | Tehran         | 2012  | 3             | 3 (100%) (KPC\(^b\))           | Phenotypic                                             | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 10                          | -                           | 47                          |
| Shahcheraghi et al   | Tehran         | 2012  | 45            | 0 (0%)                         | Phenotypic and genotypic                               | 1                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 33                          |
| Rastegar et al       | Tehran         | 2013  | 29            | 19 (65.52%) (KPC\(^b\))        | Phenotypic                                             | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 34                          |
| Japoni Nejad et al   | Tehran         | 2014  | 100           | 68 (68%) + E-test\(^a\)        | Phenotypic and genotypic                               | -                           | -                           | -                           | -                           | -                           | 10                          | -                           | -                           | -                           | -                           | 35                          |
| Nobari et al         | Tehran         | 2014  | 180           | 24 (13.33%) + E-test\(^a\)     | Phenotypic and genotypic                               | 3                           | -                           | -                           | -                           | -                           | 5                           | 1                           | -                           | -                           | -                           | 36                          |
| Bina et al           | Tehran         | 2015  | 270           | 41 (15.18%)                    | Phenotypic and genotypic                               | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | -                           | 33                          |

\(^a\) E-test method for phenotypic testing. \(^b\) KPC method for genotypic testing.
| Author Name         | City       | Date | No. of Sample | No. of MHT Positive Isolate (%) | Type of Method for Identification Carbanapenemase Gene | No. of blaNDM | No. of blaNDM1 | No. of blaNDM7 | No. of blaIMP | No. of blaIMP1 | No. of blaVIM | No. of blaVIM1 | No. of blaKPC | No. of blaKPC2 | No. of blaOXA48 | Reference |
|---------------------|------------|------|---------------|-------------------------------|------------------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|--------------|-------------|
| Rajabnia et al      | Babol      | 2015 | 50            | 10 (20%)                     | Phenotypic and genotypic                              | -             | -             | -             | -             | -             | -             | -             | -             | -             | -             | Rajabnia et al |
| Eftekhari and Naseh | Tehran     | 2015 | 55            | 4 (7.27%)                    | Phenotypic and genotypic                              | -             | -             | -             | -             | -             | -             | -             | -             | -             | Eftekhari and Naseh |
| Solgi et al         | Tabriz     | 2017 | 33            | CHROMagar phenotypic method 29 (87.8%) | Phenotypic and genotypic                              | 17            | -             | -             | -             | -             | -             | -             | -             | -             | Solgi et al |
| Shokri et al        | Isfahan    | 2013 | 128           | 65 (50.78%) (KPC)            | Phenotypic                                           | -             | -             | -             | -             | -             | -             | -             | -             | -             | Shokri et al |
| Akhi et al          | Tabriz     | 2014 | 63            | 20 (31.75%)                  | Phenotypic and genotypic                              | -             | -             | -             | -             | -             | -             | -             | -             | -             | Akhi et al |
| Solgi et al         | Tehran     | 2017 | 35            | 17 (48.57%)                  | Phenotypic and genotypic                              | -             | -             | 1             | -             | -             | -             | -             | -             | -             | Solgi et al |
| Ghotaslou et al     | Other      | 2018 | 57            | N                            | Genotypic (Kit)                                      | -             | -             | -             | -             | -             | -             | -             | -             | -             | Ghotaslou et al |
| Tavakoly et al      | Other      | 2018 | 118           | 7 (5.93%)                    | Phenotypic and genotypic                              | -             | -             | -             | -             | -             | -             | -             | -             | -             | Tavakoly et al |

a Studies that used the E-test in addition to the MTH test.
b Genes that identified using phenotypic tests.
-: reported gene.
in European countries shows that the mean percentage of resistance against third-generation cephalosporins antibiotics (ceftazidime, cefotaxime) is 30.3%. The highest antibiotic resistance in *K. pneumoniae* in 10 years based on the articles used in this study was related to the cephalosporins antibiotics.

The results showed that the most common carbapenemase genes were related to *blaKPC* [145 (37.08%)], *blaOXA48* [118 (30.18%)], and *blaNDM* [88 (22.51%)].

*blaNDM* is the most common carbapenemase in Europe, India, North America, Pakistan, Australia and other parts of Asia. The *blaNDM* gene increased slightly in 2014 and 2015 but increased significantly in 2017 and 2018 based on the findings of the present study. *blaIMP* and *blaVIM* were reported in South America, North America, Asia, Australia, and Europe. The results of our study also demonstrated that the frequency of the *blaIMP* gene increased only in 2017 and the *blaVIM* gene became more prevalent in 2017 but decreased gradually in 2018. *blaKPC* was reported to be the most common carbapenemase in the United States and *blaOXA* was reported in Europe, Turkey, northern Africa and the Middle East.

In our study, the *blaOXA48* gene increased gradually only in 2017 and 2018 and *blaKPC* gene increased in 2013 and then decreased gradually until 2018.

The results of this review during 2010-2018 showed that the *blaNDM*, *blaOXA48* and *blaIMP* genes increased in 2017 and 2018 more than in eight years ago and the *blaVIM* gene in 2014 and 2015 and the *blaKPC* gene in 2013 increased and then declined, respectively. This increase is due to the easy dissemination of these genes by plasmids among Enterobacteriaceae bacteria, and on the other hand, the importance of studying resistance to carbapenems as a treatment for severe infections.

Nahid et al collected 356 clinical isolates of the hospitals. Out of a total of 356 isolates, 160 displayed imipenem resistance and 131 showed MBLs production. In MBL positive isolates, 31 isolates reported harboring the *blaNDM-1* gene out of which 13 (41.93%) were *K. pneumoniae*. In 2016, Khan et al reported that the prevalence of the *blaNDM* gene was 78%, which indicates the high prevalence of this gene in Pakistan. This high prevalence is because the primary source of the *blaNDM* genes was in India and Pakistan. Also, the high prevalence of this gene in the study in Kerman, Iran, as one of the cities close to the border with Pakistan, can be due to people coming from the bordering countries for trade or treatment.
In Turkey, the prevalence of the blaNDM gene was reported to be 19% in 2013 and 52.9% in 2016, respectively.61,62 According to the studies in Turkey, the high prevalence of the blaNDM gene in Tabriz may be because of the trade and treatment of people coming from the bordering countries in this city.

Limitations of the Study
In this study, Persian databases such as Scientific Information Database (SID) and Magiran were not used and only articles in English were examined.

Conclusion
Whereas information from all cities of Iran is still limited, this systematic review provides a picture of the prevalence of carbapenemase genes in K. pneumoniae in Iran. The findings showed that resistant genes of carbapenemases like the blaNDM and blaOXA48 genes are becoming more prevalent in Iran, and worldwide, which is worrying and alarming. Traveling is probably one of the main reasons for the transmission of carbapenemase genes. Also, physicians should be careful about the correct use of antibiotics.

Authors’ Contribution
ASD designed the study, performed the searching of databases, and wrote the manuscript. NS performed the searching of databases and revised the manuscript.

Ethical Approval
Not applicable.

Competing Interests
No conflict of interest was reported by the authors.

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