

## Systematic Review

# An Overview of Tracheal Stenosis Research Trends and Hot Topics

Roya Farzanegan MD PhD<sup>1</sup>, Mansoureh Feizabadi PhD<sup>2</sup>, Fariba Ghorbani MD PhD<sup>1</sup>, Masoud Movassaghi MD<sup>3</sup>, Esmaeil Vaziri PhD<sup>4</sup>, Mahdi Zangi MD MPH<sup>1</sup>, Seyed Amirmohammad Lajevardi<sup>5</sup>, Mohammad Behgam Shadmehr MD<sup>1</sup>

**Abstract**

**Background:** Tracheal stenosis remains a challenge in the thoracic surgery field. Recognizing the hot topics and major concepts in this area would help the health policy makers to determine their own priorities and design the effective research plans. The present study analyzed and mapped the topics and trends of tracheal stenosis studies over time as well as authors' and countries' contributions.

**Materials and Methods:** Search results were obtained employing Bibexcel. To determine cold and hot topics, co-occurrence analysis was applied using three international databases 'Web of Science', 'PubMed' and 'Scopus'. Appropriately, different categories in the articles such as keywords, authors, and countries were explored via VOSviewer and NetDraw. Afterward, the trends of research topics were depicted in four time-intervals from 1945 to 2015 by ten co-occurrence terms.

**Results:** The majority of articles were limited to case series and retrospective studies. The studies had been conducted less frequently on prevention, risk factors and incidence determination but extensively on treatment and procedures. Based on the articles indexed in WOS, 45 countries and 8,260 authors have contributed to scientific progress in this field. The highest degree of cooperation occurred between the USA and England with 15 common papers.

**Conclusions:** Most of the published literature in tracheal stenosis research field was about surgical and non-surgical treatments. Conducting the screening and prevention studies would diminish the burden of this disease on the health system as well as the patients and their families' well-being.

**Keywords:** Intubation, scientometric, tracheal stenosis, visualization

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## Introduction

Although intubation has serious complications in ICU admitted patients, only a few studies have addressed these complications.<sup>1</sup> Intubation may cause mucosal damage and inflammation, granulation tissue formation, cartilage destruction, tracheomalacia and tracheal stenosis. Among these complications, post-intubation tracheal stenosis (PITS) as one of the worst complications, is the most common cause of tracheal reconstructive surgery.<sup>2-5</sup> While granulation tissue formation due to intubation could occur within hours,<sup>6</sup> tracheal stenosis usually takes more than five days to appear.<sup>7</sup> Esteller, et al. showed that 11% of patients who underwent intubation suffered from laryngotracheal injuries.<sup>8</sup> In another study, PITS was reported around 6% – 21%.<sup>9,10</sup> The literature showed that 10% of patients with benign stenosis may be undiagnosed for more than ten years or even incorrectly treated for asthma.<sup>11</sup> In a study performed in

London, the incidence rate of PITS was calculated as 926 new cases per one year.<sup>10</sup> This study demonstrated that four out of five patients did not receive the appropriate treatment due to incorrect diagnosis.<sup>12</sup> Early diagnosis of this complication may change the natural history of the disease.<sup>12,13</sup>

Unfortunately, because of the severity of symptoms, most of these patients undergo tracheostomy despite the fact that the main treatments for these patients are bronchoscopy and dilatation as well as airway resection and reconstruction at an appropriate time.<sup>14,15</sup>

The broad range of tracheal stenosis incidence rate in each country is due to local risk factors such as etiology prevalence, the expertise of the ICUs and emergency rooms staff, the quality of equipment and the number of ICUs. Our database for all patients with tracheal diseases (Alborz database), including more than 2300 patients in the previous two decades,<sup>16-18</sup> has shown that traffic accidents were the leading causes of hospitalization and intubation in most of our patients.<sup>19</sup> In Iran, one of the fatal injuries is traffic accidents which occur commonly among young population.<sup>20</sup> Peden, et al. in 2013 estimated a 65% increase of traffic injuries in developing countries in the next 20 years.<sup>21</sup> Therefore, it seems that the incidence rate of PITS in developing countries will be remarkable in the following years and one of the policies of the health system should be preventive methods after determining the risk factors of this iatrogenic complication. To accomplish that goal, it is required that all researches in this field are explored to clarify whether adequate studies have been conducted in relation to prevention along with treatment in the

**Authors' affiliations:** <sup>1</sup>Tracheal Diseases Research Center (TDRC), National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, <sup>2</sup>Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran, <sup>3</sup>Department of Pathology and Laboratory Medicine, UCLA, USA, <sup>4</sup>Department of Information Science and Knowledge Studies, Faculty of Humanities, University of Zabol, Zabol, Iran, <sup>5</sup>Faculty of Health, York University, Toronto, Canada.

**\*Corresponding author and reprints:** Mohammad Behgam Shadmehr MD, Tracheal Diseases Research Center, Shahid Beheshti University of Medical Sciences, Massih Daneshvari Hospital, Shahid Bahonar Ave., Darabad, Tehran, 19558-41452, Iran. Tel: +98-21-27122163, Fax: +982126108753, E-mail: mbshadmehr@sbmu.ac.ir.

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countries. Although airway stenosis may be a small research area, it is a life-threatening condition. The current study provides an overview of quantitative perspective of the tracheal stenosis field by mapping subject terms, developments and dynamics of science, authors, and countries which could yield a new insight on science policy and decision-making in this area.

## Materials and Methods

### Strategy of search

Co-word and cluster analyses techniques were used to map the tracheal stenosis research field published in Web of Science (WOS), PubMed, and Scopus indexing databases by the end of 2015. Moreover, four time-periods (before 2000, 2001 – 2005, 2006 – 2010, and 2010 – 2015) were considered to investigate the dynamics of science within this research area. For the sake of uniformity and better understanding of terms used in the retrieved articles, their keywords were uniformed using Medical Subject Heading (MeSH). For instance, the query used for WOS database was as follows: [TS = (“Tracheal stenosis” OR “Tracheal stricture” OR “airway stenosis” OR “Laryngotracheal Stenosis” OR “Endotracheal stenosis” OR “Intratracheal stenosis” OR “subglottic stenosis”)].

### Research population

The study population included 2,756 articles indexed in the Web of Science, 4,246 articles indexed in PubMed, and 8515 articles indexed in Scopus. In the first stage, after extraction of all articles based on query strategy, the bibliographic information of all items was fed into Bibexcel software. The required pre-processing was conducted on the retrieved articles. After removal of the vague terms, a file containing the words co-occurred in topics, as well as keywords, authors, and countries information was generated, and their network file was also prepared. Then, VOSviewer and Pajek were used to create the maps.<sup>22</sup>

## Methods

Co-word and cluster analyses techniques were used to distinguish the most frequent research subjects in this field. Then, through network analysis methods, the linkages between these words and, co-word pairs were explored. Articles obtained from WOS were used to analyze the trend of subjects and to measure scientific cooperation among authors and countries. The analysis of the dynamics of subjects was carried out by analyzing the appearances, disappearances as well as alterations of keywords in the different clusters.<sup>23–25</sup> To confirm the data obtained from the database above, keywords and topics used in articles, indexed in PubMed and Scopus, were also studied.

The pre-process and extraction of data were done with Bibexcel software. Also, VOSviewer 1.6.1 was used to create density and label maps and determine the clusters that constitute a network of keywords and terms used in the topics of articles. This software uses distance-based techniques to create maps. In VOSviewer generated maps, the distance between concepts provides an indication of linkage among them; in addition, the size of circles indicates the number of articles on that idea.<sup>25</sup> In general, the larger the number of co-occurrence of terms and subjects, the smaller the distance between them. To investigate scientific cooperation, related maps were created at the level of authors

and countries, using Pajek software. A co-authorship network is a map of common nodes or co-authorship communications within a research community.<sup>26</sup> It would be said that two peer authors communicate scientifically if they jointly wrote an article. Investigation into such networks provides an inside view of the social structure of research communities.<sup>25,27</sup> In other words, this type of network reveals which author in a co-authorship relationship has a central role in the process of communication within the network.

### Scientific maps

In label maps of keywords network created by VOSviewer, every concept was represented by a colored circle. The size of the font and circle indicates the weight of that concept or the frequency or co-occurrence of that idea. In each cluster, a concept with the greatest frequency or weight was displayed with a larger circle and was considered as the primary group.<sup>22</sup> To study the research trend and the growth of science in tracheal stenosis area over time, density maps were prepared based on keywords used in articles in five-year periods.<sup>28,29</sup> Using density view allowed us to observe important subjects and areas in the currently active maps.<sup>22,27,30</sup> The color spectrum displayed in these maps indicated the importance and density of these terms and subjects. Red, followed by yellow, showed the highest density and frequency of relevant articles.

In the global co-authorship network, each node indicates an individual country. Moreover, the links and relationships between the countries show scientific cooperation among them. The size of circles demonstrates the number of articles in a particular country, and the thickness of links indicates the degree of scientific cooperation between two countries.

The study should be validated by correlation the metric results with the judgment of the experts regarding the relevance of the publications and comparing the retrieved results and knowledge discovery between the databases. Therefore, the maps were separately interpreted and investigated by two experts who had worked on the management and treatment of tracheal stenosis and its research field for many years.

## Results

### Global status of scientific products

In total, 2,756 articles on tracheal stenosis have been published in WOS by the end of 2015. Investigation into these articles by publication year shows that 1,106 (40%) of them were published until 2000. In addition, 459 (16%), 578 (21%), and 613 (22%) articles were issued within 2001 – 2005, 2006 – 2010, and 2010 – 2015, respectively.

Of 2,756 articles retrieved from WOS, 7,329 keywords were extracted. Among 988 highly frequent keywords, the map of 90 terms with minimum link strength of 40 was created. Meanwhile, terms with co-occurrence rates of less than 40 in small areas were removed from the analysis. In this way, the number of undervalued terms was reduced in the map.

Figure 1 shows the label map of keywords from WOS. The main concepts of the clusters were Laryngostenosis, Tracheal Stenosis, Trachea, Tracheotomy, Laryngotracheal Stenosis, and Bronchoscopy. In this map, each cluster was shown with a separate color.

To demonstrate the strength of link among keywords with the greatest co-occurrence rate, the network map of keywords with





**Table 1.** Twenty frequent terms in four-time intervals from 1945 to 2015.

Number	Four-time intervals			
	1945–2000	2001–2005	2006–2010	2011–2015
1	Tracheal Stenosis	Tracheal Stenosis	Tracheal Stenosis	Tracheal Stenosis
2	Laryngostenosis	Laryngostenosis	Laryngostenosis	Laryngostenosis
3	Tracheotomy	Tracheotomy	Tracheotomy	Laryngotracheal Resection-reconstruction
4	Laryngotracheal Resection-reconstruction	stents	Bronchoscopy	Laryngotracheal stenosis
5	Child	Laryngotracheal Resection-reconstruction	Stents	Tracheotomy
6	Trachea	Bronchoscopy	Laryngotracheal Resection-reconstruction	Bronchoscopy
7	Laryngotracheal Stenosis	Child	Laryngotracheal Stenosis	Trachea
8	Stents	Trachea	Trachea	Stents
9	Bronchoscopy	Stenosis	Stenosis	Granulomatosis with Polyangiitis
10	Percutaneous Tracheostomy	Complications	Resection AND End-To End Anastomosis	Child
11	Intubation	Airway Obstruction	Child	Larynx
12	Airway Obstruction	Endoscopy	Airway Obstruction	Airway
13	Laser Therapy	Larynx	Granulomatosis with Polyangiitis	Resection AND End-To-End Anastomosis
14	Infant	Laryngotracheal stenosis	Complications	Balloon Dilatation
15	Tracheoplasty	Tracheomalacia	Airway	Pediatrics
16	Congenital Tracheal Stenosis	Tracheal-Esophageal Fistula	Trachea-abnormalities	Complications
17	Complications	Granulomatosis with Polyangiitis	Pediatrics	Intubation
18	Gastroesophageal	Gastroesophageal	Mitomycin-C	Tracheomalacia
19	Tracheomalacia	Tracheal Surgery	Ventilation	Congenital Tracheal Stenosis
20	Endoscopy	Laser Therapy	Stridor	Gastroesophageal Reflux

Stents had the highest rate of co-occurrence in all periods above. Regarding the small number of scientific products within 1945 – 2000, all of them were placed in the category of before the year 2000.

To analyze the trend of research on tracheal stenosis, those articles retrieved from the PubMed were also reviewed, and their map was created. Figure 5a shows the density map of highly frequent terms (with co-occurrence rate of more than 40 used in articles extracted from PubMed). The most common terms with co-occurrence rate of at least 40 were Stenosis and Tracheal (633), Subglottic and Stenosis (394), and Stenosis and Management (174). Other terms located in hot spots (orange and yellow colour zone) were illustrated in Figure 5b.

#### Role and contribution of countries in producing scientific papers on tracheal stenosis

In general, 45 countries have published a total of 2,756 articles on tracheal stenosis in WOS. The ten leading countries in developing research articles on tracheal stenosis were the USA (1003 articles), England (190 articles), Germany (184 articles), Japan (159 articles), France (111 articles), Canada (80 articles), South Korea (72 articles), China (70 articles), Turkey (67 articles), and Italy (64 articles). Regarding cooperation between countries in publishing articles, the highest degree of cooperation occurred between the USA and England with 15 common papers, followed by the USA and France as well as the USA and Germany with eight joint papers. The scientific cooperation in the field of tracheal stenosis among the 30 leading countries has been shown in Figure 6a.

#### Role of co-authorship in publication of articles on tracheal stenosis

According to research findings in WOS, the 2,756 articles were written by 8,260 authors, among whom Dr. Robin T. Cotton with 58 articles, Dr. Lauren D. Holinger with 33 articles, and Dr. Micheal J. Rutter with 32 articles had the highest number of scientific contributions in this field. Analysis of co-authorship showed that the greatest degree of cooperation was between Dr. S.A. Reza. Nouraei and Dr. Guri S. Sandhu with 20 articles and Dr. S. A. Nouraei and Dr. David J. Howard with 13 articles.

Figure 6b shows 20 authors with at least five joint articles with other organizations and countries on tracheal stenosis (domestic cooperation was not considered). A total of 19 articles, indexed in WOS from Iran, were written by 109 authors, of which 79 authors had an affiliation from Iran.

#### Discussion

Co-word and cluster analyses techniques could be used for identification of the most important research subjects or concepts in every research field.<sup>24,27,31,32</sup> In this study, the intellectual and conceptual structures governing the scientific productions in the field of tracheal stenosis were analyzed and visualized by word co-occurrence analysis of keywords and topics. The results showed a continuous increase in scientific productions and also the dynamic development of thematic areas structure in the field of "tracheal stenosis" over time. As indicated on the survey map of keywords in WOS, Scopus and reviewed titles in PubMed, the majority of articles were in the field of surgical treatments, while some other



areas such as prevention require more studies and attention. The evaluation of scientific maps in different time intervals showed that some keywords were repeated in the all-time periods, whereas some keywords appeared or disappeared over time. The titles map in PubMed from 1945 to 2015, showed studies on tracheal stenosis and laryngotracheal stenosis in the form of "case series", "case reports" and "reviews of the literature". "Follow-up studies" such as incidence studies and determination of risk factors related to tracheal stenosis were in the cold (blue) area of the map. As prevention is the best treatment,<sup>8</sup> it is recommended that the researchers conduct more studies on detection of risk factors and prevention of post-intubation tracheal stenosis.

The incidence rate of PITS has been determined in some countries through retrospective studies which resulted in an underestimation.<sup>12</sup> The incidence may differ in various countries. The high incidence could be seen in the countries with high ICU bed occupancy and large population at risk. The patients after critical care should be screened for airway injuries. To our knowledge, there are few outpatient follow-up clinics to assess the patients discharged from the ICU with a history of prolonged intubation.<sup>33</sup> Consequently, the patients are not referred to the specialists after ICU discharge to evaluate the adverse effects of intubation such as tracheal stenosis in a timely manner. If this complication is not diagnosed, it can be life-threatening and lead to a major impairment of the quality-of-life.<sup>12,34</sup> To prevent further PITS, each country should assess its local risk factors and establish an evidence-based ICU guideline. The screening programs should also be planned for its timely diagnosis and management.<sup>33,35</sup> Regarding the risk factors of PITS, some studies have demonstrated prolonged intubation (more than 24 hours), endotracheal tube material, over-inflation of its cuff, trauma during intubation and tube displacement after intubation.<sup>36,37</sup> Among the risk factors, cuffed endotracheal and tracheostomy tubes have been studied more extensively.<sup>38</sup> Cuff pressure changes with the movement of the head and neck during surgeries lasting more than four hours,<sup>39</sup> body temperature,<sup>40</sup> and spread of nitrogen oxide gas into the cuff during surgery.<sup>39</sup> Moreover, designing the tubes with high volume and low-pressure cuffs, low volume and low pressure, and, in more recent years, taper-shaped cuffs that reduce the cuff pressure on tracheal wall mucosa are included.<sup>38,41</sup> Other studied risk factors include the duration of intubation,<sup>42</sup> endotracheal tube size, and the methods of caring the intubated patients in critical care centers.<sup>43</sup> The researchers have also considered the role of reflux in developing mucosal damage in patients who were intubated for less than 24 hours, regardless of intubation tube movements in an area of the trachea above the cuff.<sup>44,45</sup> The severity of respiratory failure, patient's cardiovascular condition during the intubation, patient's sex and age were described, as well.<sup>36,37</sup> Although analyses of "prevention" and "experimental" studies were also performed, the numbers were not high enough during these years to be placed in the hot area of the map (yellow and orange). Thus, conducting these types of studies to decrease the incidence rate of tracheal stenosis should be considered in future studies.

The largest number of articles pertained to the area of treatment, especially surgical procedures such as resection and anastomosis in tracheal stenosis or laryngotracheal resection for subglottic stenosis, in which specialists reported their experiences in surgical techniques and management of complications in their patients.<sup>10,18,46-48</sup> Some studies on the use of T-Tube and silicone or metal stents have also been published. Studying tracheal

stenosis in PubMed and Scopus review articles showed that it had been considered separately in infants, children, and adults.<sup>49-51</sup> The researchers have also paid more attention to tracheotomy by conducting many studies on the following issues: tracheal stenosis as a complication of using cuffed tracheostomy tube, tracheal cuff caring and designing, comparing tracheostomy tubes with endotracheal tubes in causing tracheal stenosis, the time of tracheostomy in patients who have been on mechanical ventilation for more than seven days, the tracheotomy procedure, and comparing percutaneous tracheotomy with open tracheotomy regarding complications.<sup>8,36,38,52-54</sup>

Resectional airway surgery is almost impossible for lesions more than one-half of the length of the trachea in adults or one-third in children.<sup>32</sup> Other factors such as age, regional anatomy pathology, and previous treatments may also limit surgical treatment. In the field of tracheal reconstruction, some researches addressed implantation of artificial conduits. A wide range of alternatives from autologous tissue flaps as well as synthetic stents compose the spectrum of tracheal replacements. These substitutes have been assessed in both clinical and experimental studies. The animal models used for tracheal research vary widely including dog, pig, sheep, rat, mouse, and rabbit. Tissue engineered grafts opened a new horizon in 1994, and the first human artificial trachea was transplanted in 2008.<sup>55</sup> Although researchers have conducted some studies to provide tracheal replacements, an appropriate scaffold has not been reported yet.<sup>32</sup> In the investigators' view in tissue engineering field, simultaneously considering strong points of synthetic and biological scaffolds could lead to a developed structure in future studies.

#### Thematic Commentary of the keywords in four-time intervals

In the all mentioned time intervals, the most repeated words were tracheotomy, bronchoscopy, resection, airway reconstruction, and children, which showed that tracheal stenosis in children, surgical treatments, and bronchoscopy (considered to be an important diagnostic and therapeutic method) were highly applied keywords. The phrase "laser therapy" started in the second interval, which was observed as the most repeated word among the first twenty words; however, it was repeated more in the third interval and appeared on the map and continued to remain in the fourth interval.

#### 1945–2000

The tracheal stenosis issue focused on children and infants, mainly regarding resectional surgery, laryngotracheal and cricotracheal reconstruction, and postoperative complications. One of the most repeated phrases during this period was "percutaneous tracheostomy", which was proposed as a new method in the 1980s.<sup>56,57</sup> As a result, physicians and researchers published their experiences regarding percutaneous tracheostomies, such as comparisons between tracheal stenosis via percutaneous tracheostomy and regular tracheostomy.

Gastroesophageal reflux and tracheoesophageal fistula were other topics that have been studied during these years. Case reports of congenital diseases, which have been associated with tracheal stenoses, such as Down syndrome and Pfeiffer syndrome were seen on the map (before 2000).<sup>58,59</sup> The incidence of tracheal stenosis in patients with congenital heart problems was reported to be 1.2%, while its incidence was reported to be 40% in patients with Down syndrome.<sup>59</sup> In this period, diagnostic and treatment

methods have also been investigated. Among diagnostic methods, the keywords "CT scan" and "spirometry" appeared on the map;<sup>60</sup> these studies suggest the pattern of the flow-volume loop may indicate a tracheal obstruction. However, the sensitivity of this method to detect tracheal stenosis has been reported to be 50%.<sup>60</sup>

In burns, tracheal stenosis complication occurs first after inhalation injury, which causes inflammation and airway adhesion. Then, it occurs following prolonged intubation or tracheostomy.<sup>61</sup>

#### 2001–2005

In this time period, the keyword "tracheomalacia" appeared on the map, mainly due to the performance of posterior cricoidotomies and use of rib graft. Moreover, tracheotomy, comparisons of the complications of endotracheal tubes with tracheostomy and evaluations of the right time to change the endotracheal tube with a tracheostomy tube in patients who require mechanical ventilation were studied.<sup>8,38,53,54</sup>

#### 2006–2010

There was a greater variety of studies. In this period, there were larger numbers of studies on interventional bronchoscopy and laser therapy in treatment of some types of tracheal stenosis.<sup>62</sup> The keyword "Mitomycin-C" appeared on the map in this period with regard to treatment of tracheal stenosis and continued in the following years. The researchers claimed that Mitomycin-C reduces the recurrence rate of tracheal stenosis. They have also published the results of using Mitomycin-C when performing bronchoscopy in patients with tracheal stenosis.<sup>62</sup>

#### 2011–2015

In this time interval, while the published articles still focused on laryngo-tracheobronchial stenosis in infants and children, topics related to stenosis after intubation were also observed on the map and indicated a larger number of studies regarding those topics in this period. However, tracheal resection and anastomosis in treatment of tracheal stenosis and use of stents for tracheomalacia have been studied more extensively. Spirometry was still studied for diagnosis of tracheal stenosis.<sup>63</sup>

The comparison between the scientific maps of keywords in WOS and the most repeated words in the titles of articles in PubMed and keywords in Scopus revealed a consistency between the published subjects.

We found that the developing countries should increase their products in this field. Despite the efforts of all Iranian experts in this area, for example recording the information of our own center (more than 2,300 patients with tracheal diseases) in Alborz database during the past 20 years and publication of our experiences in this area,<sup>16,18,46,64–66</sup> there are still a lot of research areas to address, hopefully, to increase the number of studies and published articles in internationally recognized journals and develop our international cooperation.

Although researchers and specialists have paid more attention to tracheal stenosis regarding etiology, surgical, and non-surgical treatments, more attention still needs to be paid to studies such as the incidence, risk factors, cost, genetics, prevention and quality of life. In addition, it should be possible to allocate more funds to these research topics. The health policymakers can achieve the practical research planning through the current review study to prevent this underestimated complication of intensive care as the best policy.

## Strengths and limitations

This study could map the different concepts, subject terms, authors and countries in the tracheal stenosis research field based on the evidence from the literature. Instead of seeking the views of a fairly small number of experts, the present study discovered the whole topic areas as well as keywords, and the linkages among them. The validity of the data was guaranteed by using WOS and confirmed by Pubmed and Scopus databases. Thus, the policymakers can easily make decisions about allocation of funds to the studies which are needed to be addressed. The availability and validity of the data played a key role in this study. So, although we chose the databases in which the science articles were well-represented, some research outputs such as patents were poorly documented. Moreover, to decrease the bias of interpretation of the maps, the experts in the related field inferred the results.

In conclusion, as airway resection and anastomosis besides other methods of treatment have been improved and published, it is expected that tracheal stenosis is considered in other aspects, as well. However, prevention of acquired tracheal stenosis could lead to health promotion for people at risk in the community. This study could help the countries' health policy makers to determine their own priorities and design epidemiological studies for assessing the incidence rate and risk factors.

## Authors' contribution

*Roya Farzanegan: Reviewing the literature, designing the study, interpretation of the results, writing the first draft, final approval of the paper; Mansoureh Feizabadi: Designing the study, preparing the data, data analysis, final approval of the paper; Fariba Ghorbani: Reviewing the literature, interpretation of the results, revising the manuscript, final approval of the paper; Masoud Movassaghi: Revising the article, final approval of the paper; Esmaeil Vaziri: Gathering the data, data analysis, revising and final approval of the paper; Seyedamirmohammad Lajevardi: Gathering the data, data analysis and final approval of the paper; Mahdi Zangi, Reviewing the literature, final approval of the paper; Mohammad Behgam Shadmehr: Providing critical revision of the article and final approval of the paper.*

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