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ORIGINAL RESEARCH

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Tissue engineering in otorhinolaryngology: A knowledge-based analysis

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Abstract

Objective: To analyze the impact, performance, degree of specialization, and collaboration patterns of the worldwide scientific production on tissue engineering in otorhinolaryngology at the level of countries and institutions.

Methods: Two different techniques were used, performance and science mapping analyses, using as samples all the available documents regarding tissue engineering focused on otorhinolaryngology applications. The dataset was retrieved from the Core Collection of the Web of Science database from 1900 to 2020. Social structure was analyzed using science mapping analysis with VOSviewer software.

Results: The United States was the main producer, followed by Germany, and Japan. Malaysia and Germany had the highest Relative Specialization Index, indicating their greater relative interest in this area compared to other countries. The social structure analysis showed that the United States and Germany had significant co-authorship relationships with other countries. The University of California System, Kyoto University, and Harvard University were the leading institutions producing literature in this field. These latter two institutions showed the largest number of collaborations, although most of them were with institutions within their own country. There was a lack of connections between different communities of research.

Conclusion: The United States is the main country driving progress in this research area, housing the most notable institutions. However, significant collaborations between these research centers are currently lacking. Encouraging greater cooperation among these institutions and their researchers would promote the exchange of knowledge, ultimately facilitating and accelerating advancements in this field.

KEYWORDS

otorhinolaryngology, tissue engineering, global trends, knowledge-based analysis, science mapping analysis

1 | INTRODUCTION

Tissue engineering (TE) is a multidisciplinary field that applies the principles of engineering and life sciences toward the construction of biomimetic substitutes to replace absent or injured organs of the patient.[1] It constitutes a growing research area[2] and seminal milestones have been recognized in its recent history as a scientific field.[3,4] The development of TE products has remarkable benefits, by not requiring organ donation and preventing the immunological effects associated with organ transplantation.[1]

Particularly, in otorhinolaryngology, the morbidity derived from head and neck pathology, and the esthetic component associated, could be optimized by applying TE strategies.[5,6] The development of artificially created pinnae for the reconstruction of microtia or anotia is one of the most popular and well-known research topics in otorhinolaryngology,[7,8] with the milestone of the regeneration of a tissue-engineered human pinna in the back of a rat in 1997.[9] There are other consolidated lines of research, the most important are the closure of tympanic perforations[10] and the development of artificial cartilaginous tissue for use as a graft in nasal reconstructive surgery[11] or tracheal replacement.[12] Despite the fact that the objective is to obtain artificial constructs for use in humans, most of the work in the head and neck area has been limited to in vitro or animal model studies.[13] Future research in this field should build on and extend this work already completed in an effort to move toward its application in humans. The development of new medical approaches from advanced therapies as TE is considered a novel translational research field, with its own producers and leading institutions. However, an in-depth analysis of TE applications to otorhinolaryngology as a research area has not been performed.

A research field is a set of documents or other bibliometric units that define a research topic and an associated group of researchers who share an interest in the topic.[14] In that way, bibliometrics constitutes a robust methodology to perform a descriptive and quantitative analysis of TE documents in otorhinolaryngology, and it has been previously applied to identify leading countries, major producers, and institutions of reference in other health areas.[2,15,16] Evaluating and condensing international trends in the production of this research area will provide valuable insight into the future direction of TE in otorhinolaryngology.

Previous studies have attempted to characterize the advances of TE in otorhinolaryngology, analyzing its current concepts and eventual applications.[13,17] However, these papers have not performed an analysis of the global trends, so there is a lack of information on some relevant aspects such as which are the main countries or research centers, the knowledge flows established between them, or the impact of this field of research on the scientific community. Although recent studies have attempted to characterize the current state of TE based on its scientific production,[18,19] this type of analysis has not been carried out in the context of the specific scientific production for a medical specialty such as otorhinolaryngology, which would allow us to establish a contextual framework for its development.

This knowledge-based analysis may arise relevant information about the degree of development of TE in otorhinolaryngology. The bibliometric analysis helps to identify the leading countries and institutions in the scientific production of TE in otorhinolaryngology. It also helps to identify existing collaborations between different countries and institutions, which can promote collaboration and knowledge sharing in the field.[16,20] Scientific mapping analysis (SMA) is a useful tool that allows us to perform this type of analysis and can reveal the specific areas of TE that have received the most attention and research in otolaryngology. This can be used to identify research gaps and opportunities for future studies.[16,19,21]

In view of this background, the main objective of this work is to assess the worldwide scientific production and social structure of TE in otorhinolaryngology by knowledge-based analysis, to analyze the impact, performance, degree of specialization, and collaboration patterns of countries and institutions, providing valuable insights for researchers, policymakers, and institutions involved in the field.

2 | MATERIALS AND METHODS

2.1 | Sample

The metadata used in this study were obtained from the Core Collection of the Web of Science (WoS) database from Clarivate Analytics (London, United Kingdom). WoS is a collection of bibliographic reference and citation databases covering publications from 1900 to the present.[22] It consists of the Core Collection, which includes over 21,000 peer-reviewed, high-quality scholarly journals published worldwide (including Open Access journals) in over 250 disciplines in the science, social sciences, and humanities. Conference proceedings and book data are also available. It also includes analysis and evaluation tools, such as the Journal Citation Report and Essential Science Indicators. WoS is considered a reference by the scientific community as one of the most complete and reliable databases of scientific information.[23,24] However, while the WoS database is widely used in academic research, it has several limitations. These include language bias, which leads to incomplete and biased search results, particularly for researchers working in non-English speaking countries, and limited inclusion of certain types of publications, such as reports or gray literature (thesis dissertations, patents, or conference abstracts), which can be important sources of information in certain fields.[25]

A topic search was performed to retrieve all papers on TE with the search query "TS = ('tissue engineer*' OR 'tissue-engineer*') AND WC = Otorhinolaryngology" in the period between 1900 and 2020. This specific search query is a Boolean intersection between two components. First, the search strategy TS = ("tissue engineer*" OR "tissue-engineer*") was previously used to analyze all the literature published to date on TE.[2,19] Second, the query WC = Otorhinolaryngology allows us to ensure that the papers obtained have a clinical profile and are related to this medical specialty, thanks to the reliability of WoS in categorizing documents. It should be considered that there may be documents of interest in this area that are not included in this category. We have included in the study all the documents obtained by this search. Therefore, no filters or exclusion criteria were applied.

The characterization of scientific production consisted of an analysis to assess the relative specialization of each country in the area. The mean citation score (MCS) was considered as an index of the global impact of the country or institution's articles.[26] Finally, a SMA was performed to raise the social structure, that is, the main relationships between countries and institutions.

2.2 | Relative specialization analysis

The relative scientific production of different countries was assessed through the Relative Specialization Index (RSI) or Relative Activity Index.[27] The RSI assesses whether a country's share of world publication in a specific field is greater or less than its overall share of global publication. The calculation is based on the Thematic Specialization Index (TSI):

$$\mathrm{TSI} = \frac{a/b}{c/d},$$

where a = number of publications of country X in field Y; b = number of publications of country X in all fields; c = number of publications of all countries in field Y; d = number of publications of all countries in all fields. Then,

$$\mathrm{RSI} = \frac{\mathrm{TSI}-1}{\mathrm{TSI}+1}.$$

RSI can range from −1 to 1, with a value of 0 representing the average of the world. An RSI of less than 0 means that the country has a lower output rate than the average, while an RSI greater than 0 indicates higher-than-average activity.

Also, the Adjusted Index (AI) was also used,[28] which is calculated on the basis of GDP[29] per capita of each country.[30] This index is obtained by dividing the total number of documents in a country by its GDP per capita, multiplied by 100.

2.3 | Analysis of the social structure

The social framework of TE in ORL was assessed by using VOSviewer, a bibliometric software developed for the construction and visualization of scientific maps.[21] The construction of these maps is based on the notion of co-occurrence, that is, the joint appearance in a set of documents of a certain item (institutions and countries in our study). In the case of countries, the multiple country publication (MCP) ratio,[31] indicating the ratio between internal (inside the own country) and external (among other countries) collaboration, has been calculated and shown on the network map.

Briefly, the VOSviewer workflow consists of three phases: (1) construction of a similarity matrix; (2) application of the VOSviewer mapping technique; and finally, (3) translation, rotation, and reflection of the maps to obtain consistent results. The result is a map in which the items with the highest number of connections are located in the center and those with the lowest number of connections are located in the periphery. For a detailed description of the VosViewer, see Reference 21.

3 | RESULTS

3.1 | Sample

The result of the search for articles on TE and otorhinolaryngology retrieved 343 documents. This set of documents has been used for the analysis of relative priority, and social structure of TE in otorhinolaryngology.

3.2 | Country and institutions' performance and RSI analysis

In terms of the contribution of each country to the production of these documents, the United States is the main producer with a total of 166 documents (48.39% of the total). Other main producers are Germany with 59 documents (17.20%), Japan with 43 documents (12.53%), and South Korea with 18 (5.24%). Among the countries with more than 10 publications also appeared England (17 papers, 4.95%) and Canada (15 papers, 4.37%).

The RSI and AI were evaluated for those countries that produced five or more documents (Table 1). This table also includes the MCS of each country. To facilitate the visualization, Figure 1 shows a graphical representation of the correlation between the RSI and the AI of these 13 countries; Figure 2 shows the correlation between the RSI and the MCS of the same countries. The highest RSI is observed in Malaysia (4.39), Germany (2.97), and Austria (2.75). Other countries with an RSI higher than 1 are South Korea (2.61), Japan (2.25), and the United States (1.46), a value that indicates their higher relative interest than the rest of the countries. The countries with the highest AI were the United States (0.26), Germany (0.13), and Japan (0.11). However, the positions of Malaysia (0.07) and South Korea (0.06), which are ranked fourth and fifth, respectively, stood out.

Regarding the distribution of institutional centers, the University of California System (USA) (12.75%), Kyoto University (Japan) (8.69%), and Harvard University (USA) (6.37%) are the three main institutions producing articles. The role of Berlin, Germany, where three universities, Humboldt University, the Charité Medical University, and the Free University of Berlin, together account for 12.45% of the affiliations, is noteworthy (Table 2). The RSI and the MCS of each institution are included to provide more information on the dedication to this field of research by institutions and the impact they have (Figure 3).

3.3 | Analysis of the social structure of tissue engineering in otorhinolaryngology

The corresponding map of the analysis by country of production and social structure is shown in Figure 4. In terms of the number of papers

TABLE 1 Countries with the total number of published papers on tissue engineering in otorhinolaryngology, global scientific output, with their relative specialization index (RSI) and adjusted index (AI) according to their GDP per capita (GDP), and the main citation score (MCS) of each country is shown.

Country	Docs	%	Global production	RSI	RSI rank	GDP (US$)	AI	AI rank	MCS
United States	166	48.39	22,930,732	1.47	#6	63,543.60	0.26	#1	22.27
Germany	59	17.20	4,018,609	2.98	#2	46,208.40	0.13	#2	10.15
Japan	43	12.53	3,875,651	2.25	#5	39,538.90	0.11	#3	19.67
South Korea	18	5.24	1,397,507	2.61	#4	31,489.10	0.06	#5	13.56
England	17	4.95	5,172,947	0.67	#10	40,284.60	0.04	#6	26.88
Canada	15	4.37	3,044,941	1.00	#7	43,258.20	0.03	#7	12.20
Austria	8	2.33	589,805	2.75	#3	48,327.60	0.02	#8	14.25
Italy	8	2.33	2,558,488	0.63	#11	31,676.20	0.03	#7	11.13
Malaysia	7	2.04	323,292	4.39	#1	10,401.80	0.07	#4	25.71
France	6	1.74	3,205,304	0.38	#12	39,020.40	0.02	#8	5.50
People's Republic of China	6	1.74	6,589,676	0.18	#13	10,500.40	0.06	#5	25.50
The Netherlands	5	1.45	1,492,644	0.68	#8	52,397.10	0.01	#9	11.80
Sweden	5	1.45	1,032,192	0.98	#9	52,259.30	0.01	#9	4.60

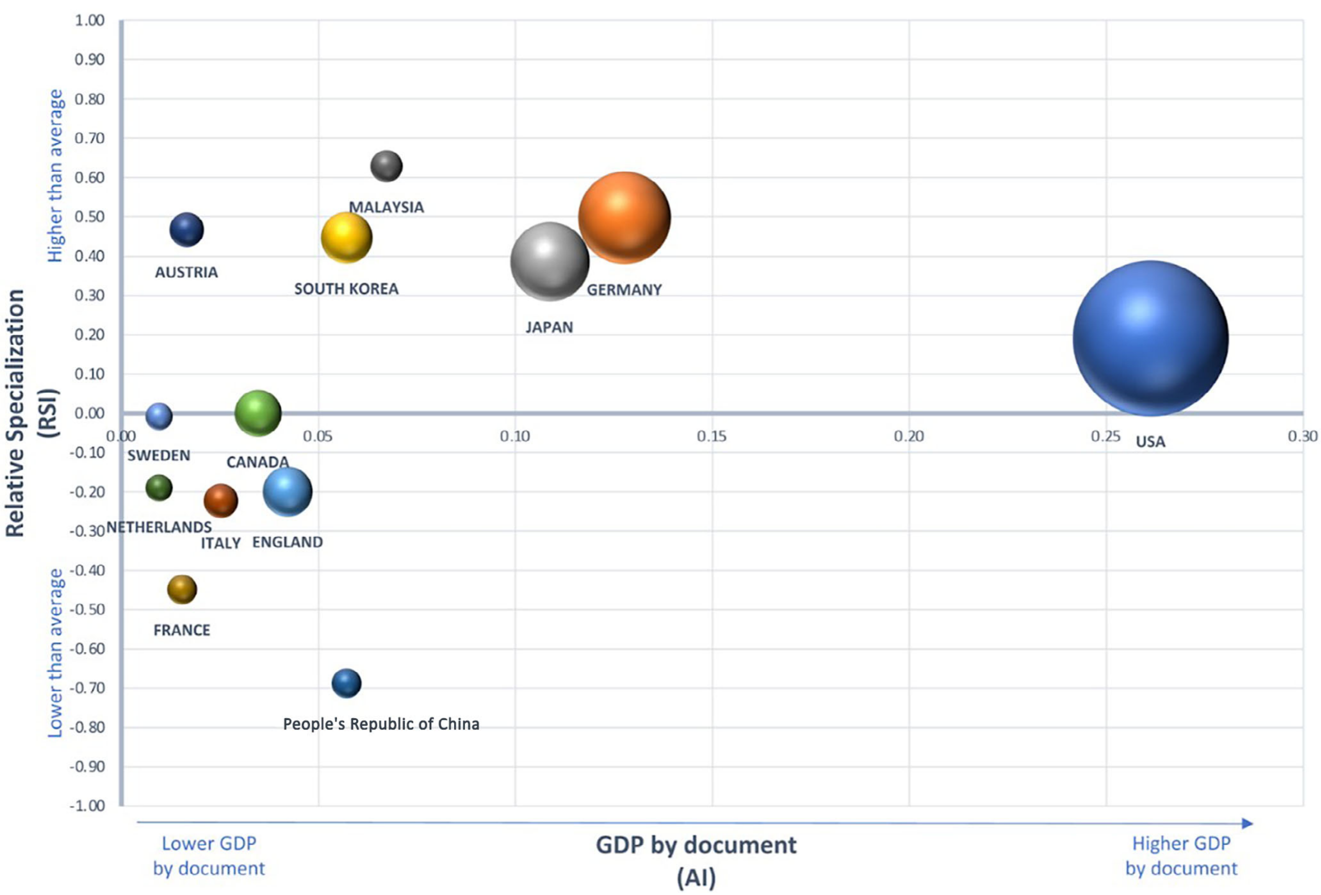

FIGURE 1 Correlation between the Relative Specialization Index (RSI) of the 13 main producing countries and their Adjusted Index for GDP per capita.

published, the graphic highlights the United States as the main producer as it appears in the central part of the map, next to Japan. European countries appear in the upper part, centered on Germany. Countries such as China and Malaysia are isolated to the right of the map. This map also shows the co-authorship relationships of these countries, with the main nodes of

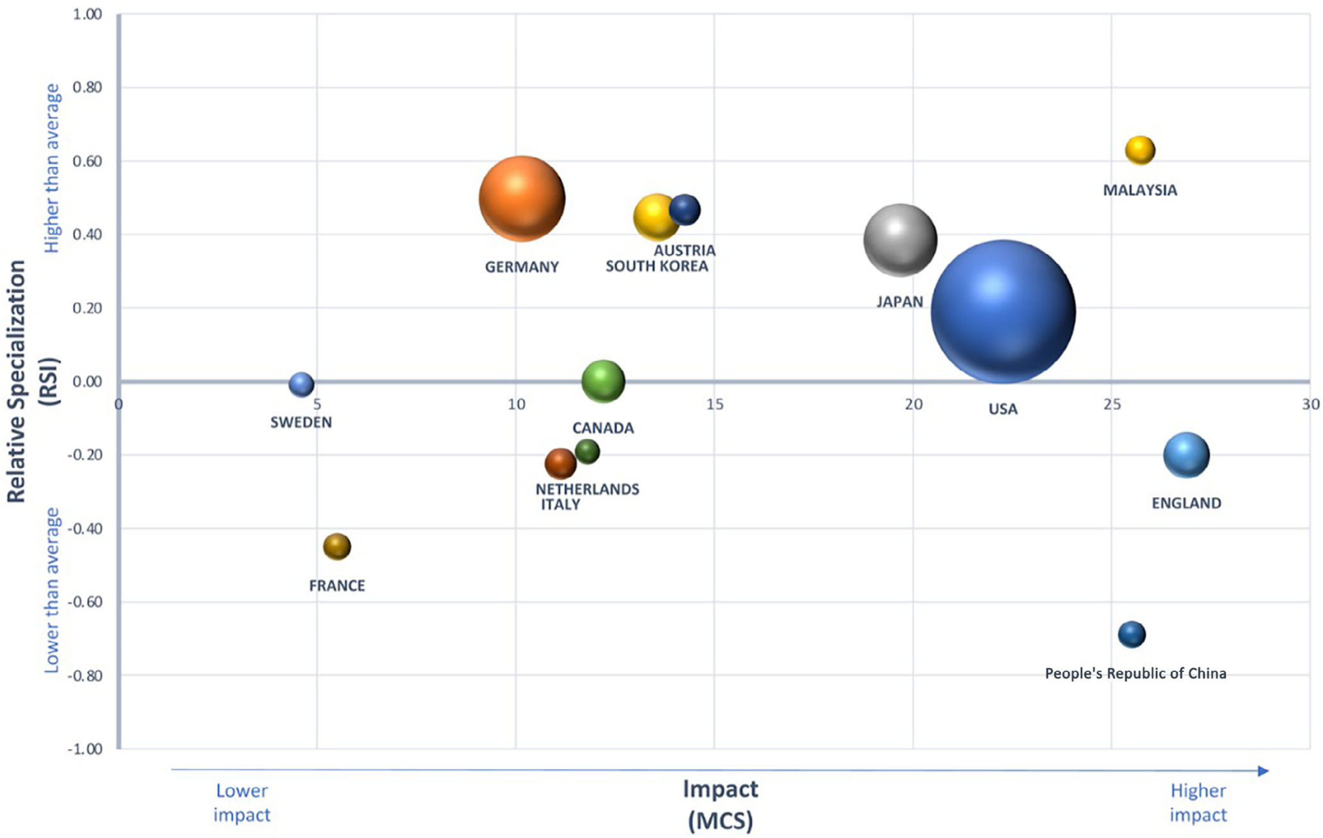

FIGURE 2 Correlation between the Relative Specialization Index (RSI) of the 13 main producing countries and their main citation score (MCS).

TABLE 2 Analysis of tissue engineering production in otorhinolaryngology by institution of origin, their Relative Specialization Index (RSI), and their impact measured by their main citation score (MCS).

Institution	Docs.	% Total	RSI	MCS
University of California System	44	12.75	−0.49	20.34
Kyoto University	30	8.69	0.26	28.23
Harvard University	22	6.37	−0.50	42.59
Fukushima Medical University	19	5.50	0.91	28.00
Humboldt University of Berlin	15	4.34	0.08	22.47
Massachusetts Eye Ear Infirmary	15	4.34	0.86	43.20
University of Michigan System	15	4.34	−0.32	23.87
Charite Universitatsmedizin Berlin	14	4.05	0.25	20.21
Free University of Berlin	14	4.05	−0.02	20.21
University of Wisconsin System	12	3.47	−0.37	21.67
University of Munich	11	3.18	−0.15	20.36
US Department of Veterans Affairs	11	3.18	−0.34	11.91

collaboration in the United States and Germany, the last one surrounded and connected with the rest of the European countries. The absence of collaboration between China and Malaysia with the rest of the countries is also striking.

The social map regarding collaborations among institutions and reference centers is shown in Figure 5. The different institutions are distributed following a heterogeneous pattern, with two institutions standing out: Harvard University and Kyoto University. Although these two universities have the largest number of collaborations, most of them are with other centers in the same country, being less frequent with foreign institutions. Small clusters of collaboration between different institutions can be observed, but there is no link between these clusters.

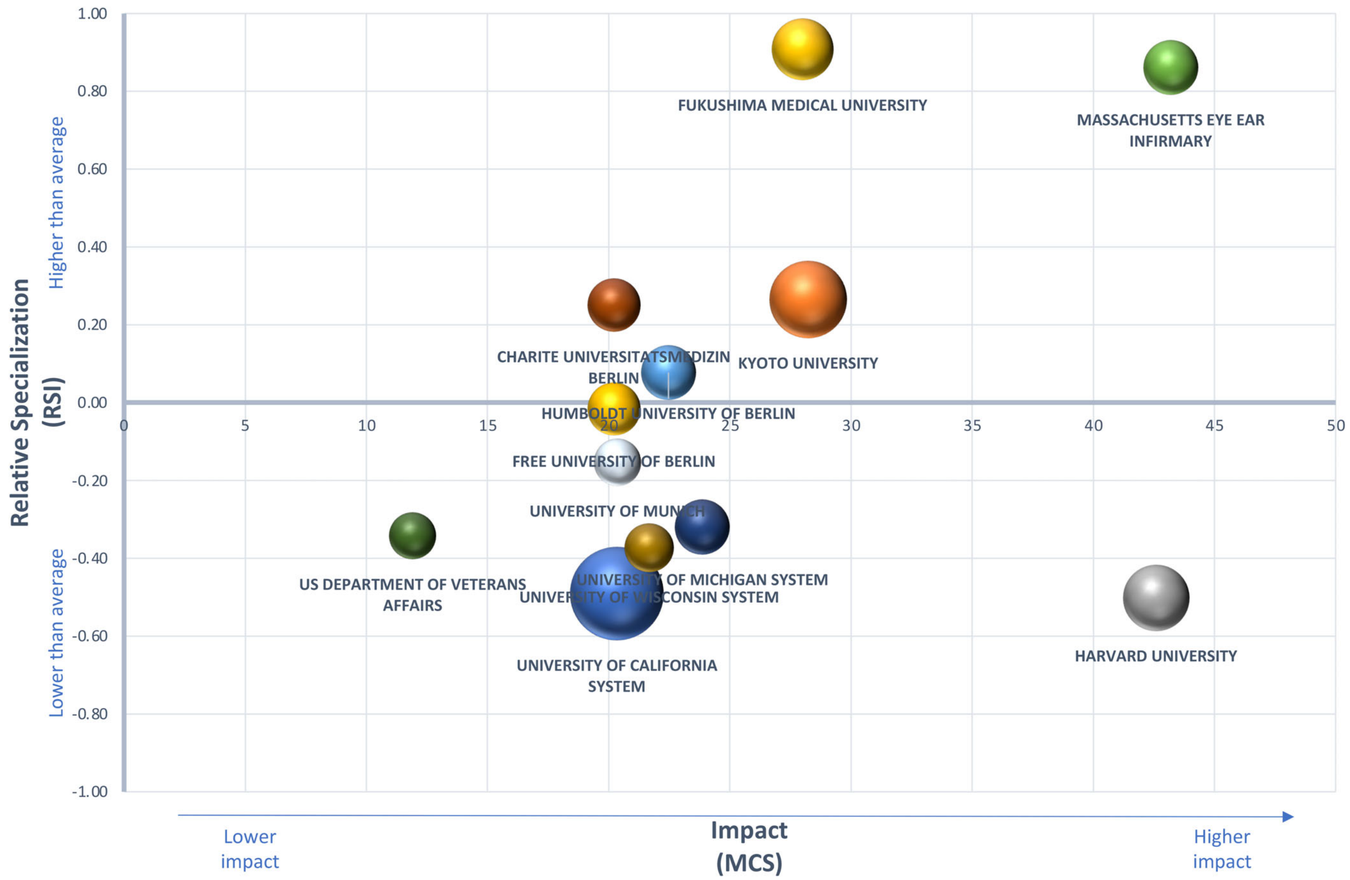

FIGURE 3 Correlation between the Relative Specialization Index (RSI) of the main producing institutions and their main citation score (MCS).

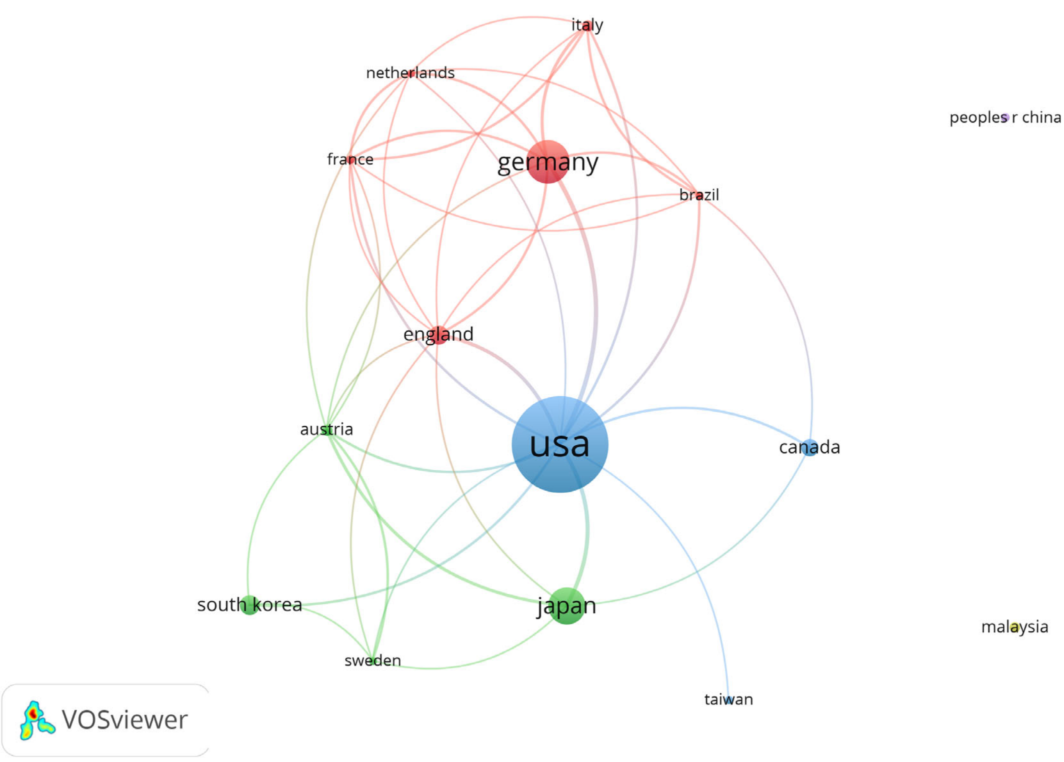

FIGURE 4 Production and co-authorship network of countries whose authors have published at least four articles related to tissue engineering and otorhinolaryngology.

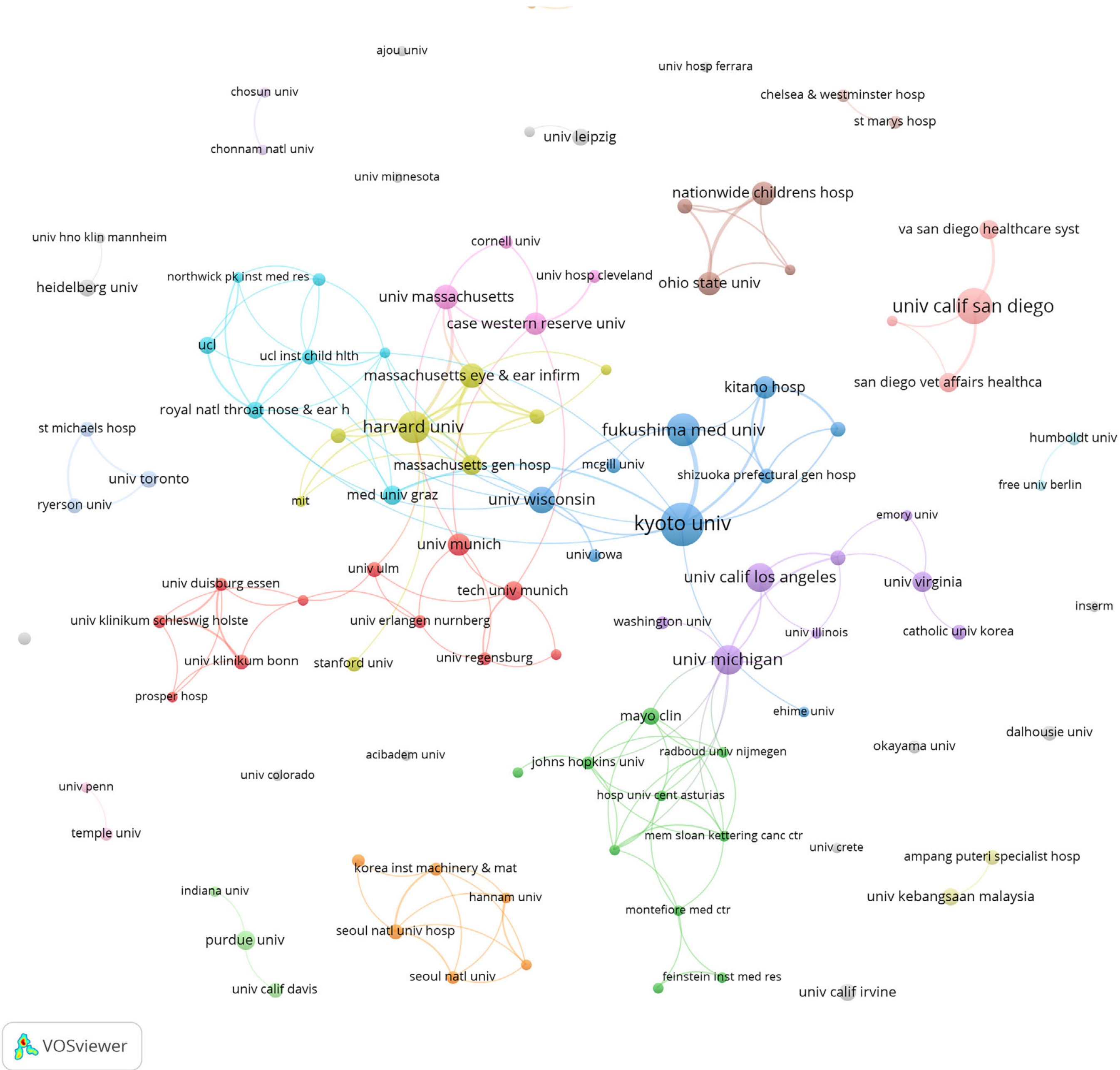

FIGURE 5 Co-authorship network of institutions whose authors have published at least two articles related to tissue engineering and otorhinolaryngology.

4 | DISCUSSION

Tissue engineering is an area of research aimed at developing artificial tissues and organs that can restore, maintain, or even improve the anatomical and/or functional integrity of damaged tissues.[1] Although it is a relatively young discipline, recent studies have shown a trend toward its consolidation through the bibliometric analysis of its scientific production.[2,18,19] The main aim of this study was to assess, using bibliometric techniques, which countries or institutions are the main producers, their relative interest as well as the scientific impact and the pattern of collaborations underlying in the TE documents applied to otorhinolaryngology.

The presented results provide valuable insights into the production and social structure of TE research in otorhinolaryngology. The analysis of country performance highlights the United States as the main producer of research articles in this field, followed by Germany, and Japan. Furthermore, it can be seen that the most productive institutions are located in these three countries, indicating their relevance in driving progress and contributing to the knowledge base of TE in otorhinolaryngology. Previous studies have shown that these countries are also the main producers of total scientific TE production,[2] and the leading producers in the otorhinolaryngology category.[32] However, China, which had been reported to be is the second largest producer of TE documents[2] and a significant producer in the otorhinolaryngology field,[32] was not among the top countries in this results, indicating that the development of applied TE in otorhinolaryngology is not as relevant as in other countries. This hypothesis could be confirmed by the fact that China showed a very low RSI, a result that would indicate that this country's share of publications in this specific field is relatively smaller compared to its overall share of global publications.

However, some considerations regarding the production of each country should be considered. First, although the United States has a higher number of published documents when the RSI is evaluated, other countries make a greater relative effort in research and production in this field, such as Malaysia and Austria. In this regard, Malaysia and Austria, unlike Germany, are not among the five most productive countries in terms of scientific publications. Looking at our results, this could be due to the presence of two research groups at the University Kebangsaan of Malaysia and the Medical University of Graz, working on the development of auricular or tracheal cartilage[33] and vocal fold regeneration,[34,35] respectively. Nevertheless, these findings must be interpreted with caution, as it could be a consequence of the relatively small sample analyzed in this study. When analyzing a small number of documents, the existence of research groups specialized in the topic analyzed may highlight the role of the whole country. As the production will increase in the coming years, these countries will have to make greater efforts to maintain their status.

However, when the GDP per capita was considered for the adjustment of priority, the United States, Germany, and Japan led the ranking, which correlates directly with the main producers of articles. These three countries have the best correlation between the RSI and the AI. This result provides further evidence of the correlation between the wealth (GDP per capita) of a country and its scientific production, which has also been confirmed in previous studies.[36,37] Again, Malaysia and South Korea stood out as countries with a high level of TE research in the field of otorhinolaryngology, despite having a lower GDP per capita than the other countries, suggesting that these countries have a particular interest in the otorhinolaryngological translation of TE.

Concerning the institutions, recent studies have reported Harvard University, the University of California System, and the Massachusetts Institute of Technology, all in the United States, as the institutions producing the largest number of articles based on TE.[2] However, in the specific field of TE in otorhinolaryngology, Kyoto University has emerged as one of the leading institutions. This Japanese university has relevant lines of investigation about the closure of tympanic perforations by tissue-engineered products.[10] Despite the fact that the University of California System is the main producer of documents, Harvard Medical School, and in particular its affiliate the Massachusetts Eye and Ear Infirmary (MEEI), renowned for its expertise in ophthalmology, otorhinolaryngology, and related fields, has shown the greatest impact, as it presents the highest MCS. This suggests that their work is recognized and referenced by other researchers, indicating their importance and influence within the academic community. In fact, researchers at Harvard Medical School and its affiliated hospitals have made notable contributions to the field, in particular, advances in tissue-engineered cartilage.[38,39] In terms of specialization, the MEEI also emerged as one of the institutions with the highest RSI, which places it as the institution with the best correlation between specialization and impact. Fukushima Medical University, which has many of its most relevant publications related to laryngotracheal regeneration, also emerged as an institution with a high degree of specialization.[40,41]

When analyzing the social structure through the maps generated by the VOSviewer, we can see the hegemony of these three countries (United States, Germany, and Japan) in terms of production and the relationship they establish among themselves and with other less productive countries. It is previously known that, although the growth in international research collaboration involves all sciences, the pattern of collaboration differs according to scientific fields,[42] reflecting the differences between basic and more applied sciences.[43] The United States establishes a collaborative network with most of the countries, while Germany is mainly limited to other European countries. The position of China and Malaysia is striking, as they are outside any co-authorship connection with another country, which indicates that their production is generated almost exclusively by researchers of their own nationality.[19] Malaysia has not even collaborated with other nations. Furthermore, another Asian country, South Korea, only has a co-authorship network with only three countries: Austria, Sweden, and the United States. This indicates that the scientific production of these countries is more difficult to export, with lines of work and the advances obtained being locked up in the same research groups. This lack of collaboration may be due to many factors, including political and cultural differences, limited economic or financial resources, or a lack of effective communication and coordination mechanisms between the different research centers or institutions. With respect to the production of each institution in these countries, we observe a radial distribution with no university or central institution establishing networks with the rest. We observe small clusters of collaboration between different universities, with Kyoto University and Harvard University being the ones that establish the largest collaborative networks with other institutions.

In view of the previous discussion, some aspects could be highlighted. The development of TE in otorhinolaryngology is crucial for advancing treatment options or enabling personalized medicine. Researchers and clinicians can exploit the full potential of TE for the benefit of patients with otorhinolaryngology-related conditions. Otorhinolaryngology specialists are involved in a significant number of studies focused on TE and their work is published in different journals, although most are basic science journals, which may influence the dissemination of advances in TE among clinical otorhinolaryngologists.[13] The results of this study have allowed us to meet the objective of identifying which countries or centers are leading the development of TE in otorhinolaryngology. Social mapping analysis is a potential tool that could be useful for the identification of the most collaborative centers, which are prone to be considered a reference not only for research but also education and training of novel clinicians and researchers. Even, it has been recently reported that collaborative patterns are associated with a higher scientific impact as well as other benefits.[44] In this sense, it is important not only to raise the most productive centers but those who are more collaborative.[45] This type of study presents relevant implications for clinical practice as allows the identification of reference research centers to collaborate or work on research in this area, to consider the development of clinical trials, and for the centers themselves to justify grants and funding. For future research, this bibliometric approach can be used to analyze the degree of translation of TE in otorhinolaryngology and the impact of this work on clinical practice. The promotion of international collaboration and knowledge exchange could enhance research outcomes and accelerate progress in TE in the context of otorhinolaryngology, boosting translational research and, thus, generating new advanced therapies that improve the clinical outcomes of current treatments for head and neck injuries and diseases.

Despite the useful findings, our study has some limitations that need to be considered. The first is that it is based on documents and information obtained from a database, which may give a partial view of the subject under analysis due to search bias and results. The sample obtained is small, due to the recentness of this field of research, so the patterns of production and collaboration will change in the near future. There are articles with different affiliations, which may lead to overestimation of the relevance of some actors. Nevertheless, to the extent of our knowledge, this is the first article that analyzes and highlights the initial development of this new discipline that is TE in otorhinolaryngology and provides a very useful perspective for those who want to get started in it.

5 | CONCLUSION

TE is a consolidated area of research, although its production in specific clinical medical areas is still growing. In the case of otorhinolaryngology, there has been an exponential increase in production and citations received recently, indicating a growing interest from the scientific community in this field of research. The distribution of scientific production according to country and institution follows an irregular distribution, the most productive being the University of California System and Harvard University in the United States, and Kyoto University in Japan. The analysis of the social structure shows us the isolation of the different production clusters from each other, as there are no large networks of collaboration, which hinder the flow of knowledge between the different groups of works that exist. This can be seen in the different levels of production, from collaboration between countries or institutions, where this lack of diversity of collaborative links is more accentuated. The findings highlight the importance of promoting international collaboration and knowledge exchange to further advance the field. Encouraging interdisciplinary collaborations and bridging the gaps between clusters could enhance research outcomes and accelerate progress in TE within the context of otorhinolaryngology.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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