

# Knowledge Mapping of Global Status and Trends for Thromboangiitis Obliterans: A Bibliometrics and Visual Analysis

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**Objective:** Thromboangiitis obliterans (TAO) is a segmental nonatherosclerotic inflammatory vascular disease characterized by recurrent progressive inflammatory reactions and thrombosis in the small and medium-sized arteries and veins of the extremities. However, there are few bibliometric studies on TAO. Therefore, this study was employed to generalize the research status, hotspots and development trends of TAO-related research.

**Methods:** The data from 1999 to 2022 were collected from the Web of Science core collection database, and analyzed through bibliometrics software. VOSviewer was utilized to carry out academic collaboration between different countries/regions, institutions, and authors, visualization map of co-cited authors, journals, reference, and co-occurring keywords. CiteSpace was used to analyze the dual-map of journals, keyword bursts, and timeline of keywords. Bar and pie charts in this study were statistically analyzed and graphed through Microsoft Excel 2021. Scimago Graphica was applied to map the academic collaboration between different countries/regions.

**Results:** A total of 553 literatures were involved in this study. Japan at the leading global position not only in the number of publications, but also total citations, average citations and H-index. Institution with the major contribution to TAO research is Mashhad University of Medical Sciences, and Nagoya University. *Annals of Vascular Surgery*, *Angiology*, *Journal of Vascular Surgery* are the main publication channel for articles related to TAO. Fazeli, B., Iwai, T., and Kihara, Y. are major contributors in this field. The studies on TAO keywords could be grouped into four clusters: Etiology, Mechanism, Cell therapy and Clinical therapy.

**Conclusion:** Although the number of TAO publications has fluctuated over the past 20 years, it has generally shown a steady upward trend. Etiology and treatment research on TAO and some keywords such as trail, therapy, outcome, management, stem cells, angioplasty, and activation will become a hot spot in the future.

**Keywords:** thromboangiitis obliterans, Buerger's disease, bibliometrics analysis, visual analysis, web of science, CiteSpace, VOSviewer, scimago graphica

## Introduction

Thromboangiitis obliterans (TAO) is a segmental nonatherosclerotic inflammatory vascular disease characterized by recurrent progressive inflammatory reactions and thrombosis in the small and medium-sized arteries and veins of the extremities.<sup>1</sup> TAO is also known as Buerger's disease because Leo Buerger published an article in 1908 detailing the vessels pathological outcome in patients with this disease.<sup>2</sup> TAO is characterized by regional distribution, which is common in the Far East, Middle East, South-East Asia, South America, and Eastern Europe. And the disease frequently happens to men younger than 45 years of age with a history of excessive smoking.<sup>3</sup> According to Choi B. et al's report, the prevalence and incidence of TAO in Korea in 2017 were approximately 9 and 4 per 100,000 population, respectively.<sup>4</sup> The prevalence of TAO in all patients with peripheral artery disease is as low as 0.5 to 5.6% in Western Europe, as high

as 16% to 66% in Korea and Japan, up to 45% to 63% in India, and up to 80% among Ashkenazi Jews.<sup>5</sup> The etiology of TAO is unknown, but it involves genetic susceptibility, immunity, coagulation reactions, and tobacco exposure.<sup>6</sup> The course of TAO is divided into three stages (acute, subacute, and chronic stages). In the acute phase, patients present with typical rest pain.<sup>7</sup> As for the treatment of TAO, scientists have studied many treatment methods, including drug treatment, interventional therapy, surgical treatment, stem cell therapy and so on. So far, researchers have conducted many studies on TAO, including etiology, pathology, epidemiology and treatment. But how to better use and mine the existing literature to provide us with new clinical and scientific research ideas?

Bibliometrics is an interdisciplinary subject that combines statistics and bibliography to quantitatively analyze all knowledge carriers through statistical means, so as to discover research hotspots and development trends. A bibliometrics analysis would be helpful to scientists' objective and comprehensive understanding of the development law and future trend. To the best of our knowledge, few studies summarized TAO's existing findings from a bibliometric perspective. Therefore, our study aims to explore the research progress of TAO from the perspective of visual analysis and bibliometrics, to clarify the future orientation and constructive information in the field.

## Materials and Methods

### Data Sources and Search Strategy

Web of Science Core Collection (WoSCC) database is regularly used in bibliometric analysis, which includes the Science Citation Index–Expanded (SCI-Expanded), Arts & Humanities Citation Index (AHCI), Social Science Citation Index (SSCI), Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), Conference Proceedings Citation Index – Science (CPCI-S), Current Chemical Reactions - Expanded (CCR-Expanded), Index of Copernicus (IC) and Emerging Sources Citations Index (ESCI).

All publications were retrieved in WoSCC on April, 2023. The search formula was: (TS=thromboangiitis obliterans OR Buerger's disease). The literatures which published between January 1, 1999 and December 31, 2022 were included. Article types were restricted to “article” and “review”. Types of research excluded include Letter, Meeting Abstract, Editorial Material, Proceeding Paper, Early Access, Correction, Book Chapters, Biographical-Item, and News Item. In addition, the language was limited to English, which indicates that the study only covered literature in English, and several large populations was therefore excluded (eg, French, Spanish, Arabic etc).

### Data Collection and Analysis

Full records and cited references (eg, titles, authors, years of publications, nationalities, institutions of authors, journals of publications, keywords, total citations, etc) were extracted from the WoSCC database for bibliometric analysis. The relevant information was imported into VOSviewer (v.1.6.18), CiteSpace (v.6.1.R2), Microsoft Excel 2021, and Scimago Graphica for analysis.

VOSviewer (v.1.6.18) was utilized to carry out academic collaboration between different countries/regions, institutions, and authors; visualization map of co-cited authors, journals, reference, and co-occurring keywords.

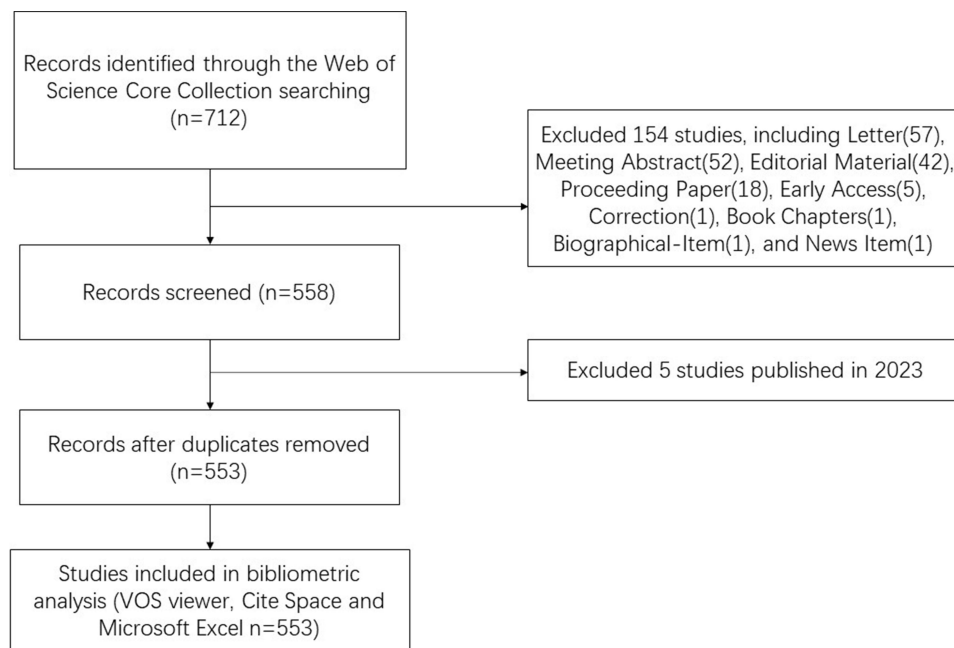
CiteSpace (v.6.1.R2) was used to analyze the dual-map of journals, keyword bursts, and timeline of keywords. The settings were as follows: timespan (1999–2022), years per slice (1), scale factor  $k=25$ , selection criteria (Top  $N=50$ ), cluster labels were extracted by the log-likelihood ratio (LLR) algorithm, and other parameter settings follow the initial software settings.

Bar and pie charts in this study were statistically analyzed and graphed through Microsoft Excel 2021. Scimago Graphica was applied to map the academic collaboration between different countries/regions. Additionally, all the information in the following tables were extracted from the citation report in the WoSCC database.

## Results

### Trends of Publications and Citations Over Time

A total of 553 TAO-related literatures published between 1999 and 2022 was included in our study. Figure 1 shows the process of inclusion and exclusion. The 553 included papers came from 2693 authors from 772 institutions in 53



**Figure 1** The process of study selection.

countries, which were published in 302 journals. These articles have been divided into the following research areas by WOS: peripheral vascular disease, surgery, medicine general internal, cardiac cardiovascular systems, pharmacology pharmacy, medicine research experimental, rheumatology, hematology, dermatology, radiology nuclear medicine medical imaging (Figure 2). In the past 23 years, the number of citations about TAO has generally shown a steady upward trend, and the number of publications shows a state of fluctuation. In 2021, the number of citations and publications of TAO-related literatures reached peaked at 897 and 46 (Figure 3).

## Quality Analysis of Global Publications

### Country

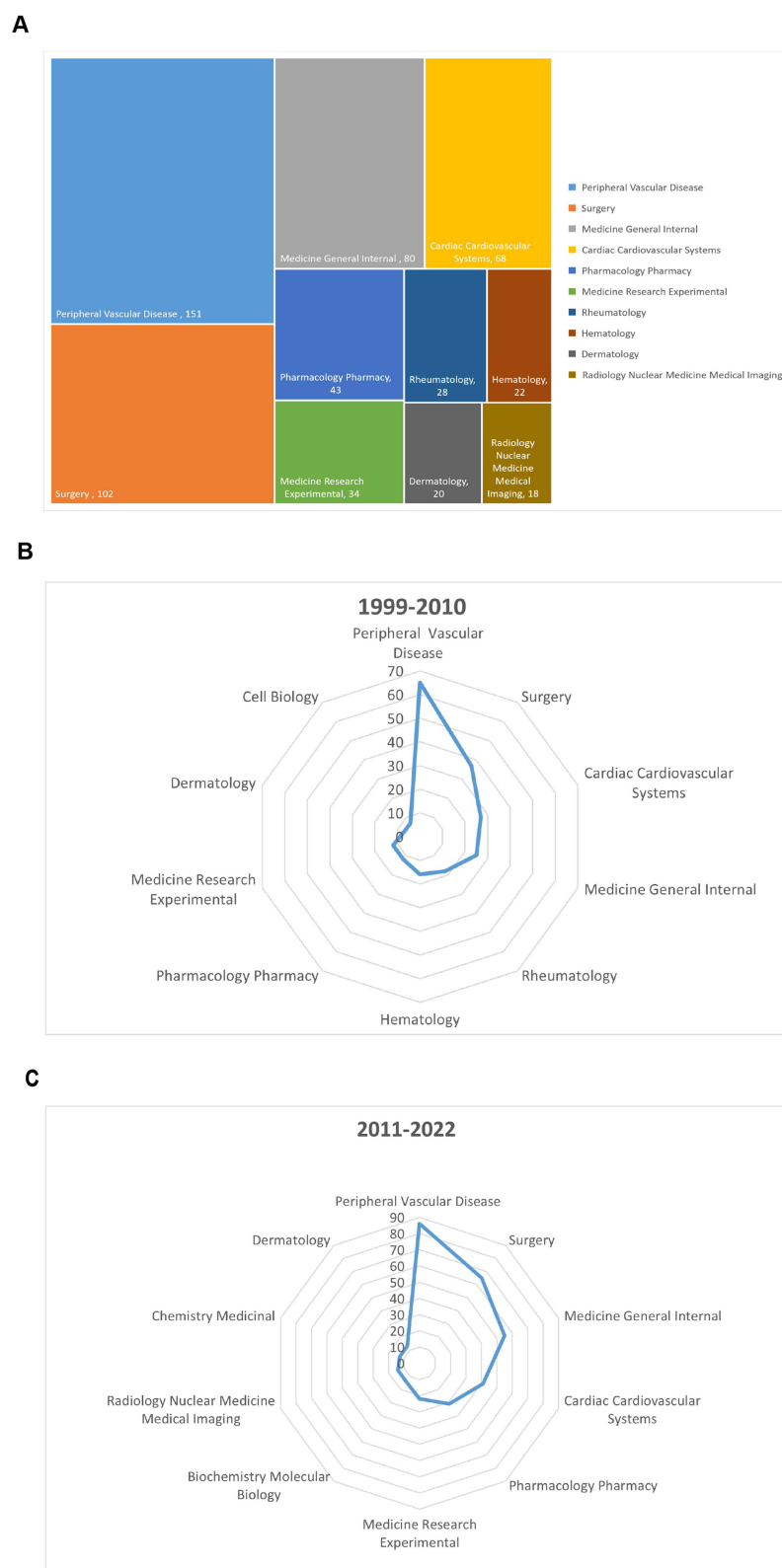
In terms of the number of publications about TAO by country (Table 1), Japan publishes the most relevant articles (91 articles, 16.46%), followed by China (74 articles, 13.38%), the United States (71 articles, 12.84%), Turkey (54 articles, 9.76%), Iran (45 articles, 8.14%), India (39 articles, 7.05%), Italy (31 articles, 5.61%), France (26 articles, 4.70%), Germany (26 articles, 4.70%), and South Korea (24 articles, 4.34%). A pie chart about top 10 countries vividly shown in Figure 4. Notably, Japan ranks first not only in the number of publications, but also total citations, average citations and H-index.

### Institution

Table 2 shows the top 10 most contributing institutions over the world: Mashhad University of Medical Sciences (35 articles), Udice-French Research Universities (17 articles), Assistance Publique Hopitaux Paris (16 articles), Nagoya University (14 articles), Tokyo Medical and Dental University (12 articles), Christian Medical College & Hospital (11 articles), Tehran University of Medical Sciences (11 articles), Istanbul University (9 articles), Seoul National University (9 articles), Wroclaw Medical University (9 articles). Institution with the largest contribution to TAO research is Nagoya University (H-index=11) which keeps the highest total citation and average citation.

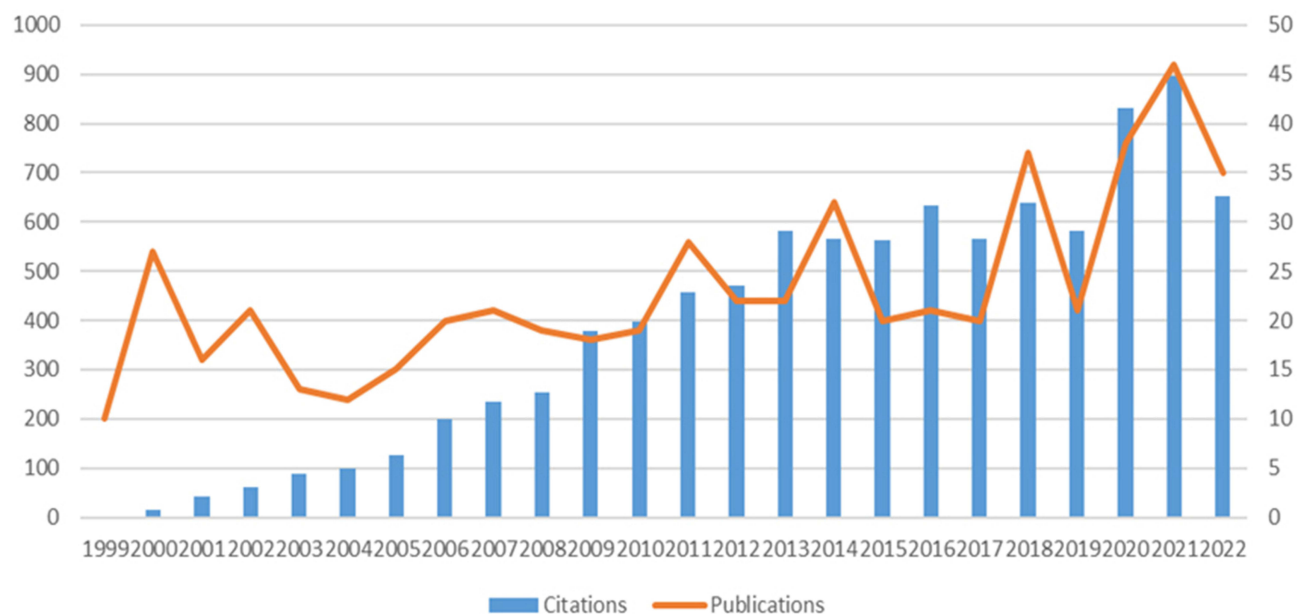
### Author

As shown in Table 3, the top 10 authors are almost divided between Iran and Japan. The number of publications: Fazeli, B. (26 articles), Ravari, H. (10 articles), Iwai, T. (10 articles), Kihara, Y. (7 articles), Sharebani, H. (7 articles), Komori, K. (6 articles), Modagheh, M.H.S. (6 articles), Agarwal, S. (6 articles), Taheri, H. (6 articles), Higashi, Y. (5 articles). Specifically,



**Figure 2** The research area analysis of global publications in thromboangiitis obliterans. **(A)** Research areas in TAO. **(B)** Radar map of research areas in TAO during 1999–2010. **(C)** Radar map of research areas in TAO during 2011–2022.





**Figure 3** The trends in publications and citations of thromboangiitis obliterans.

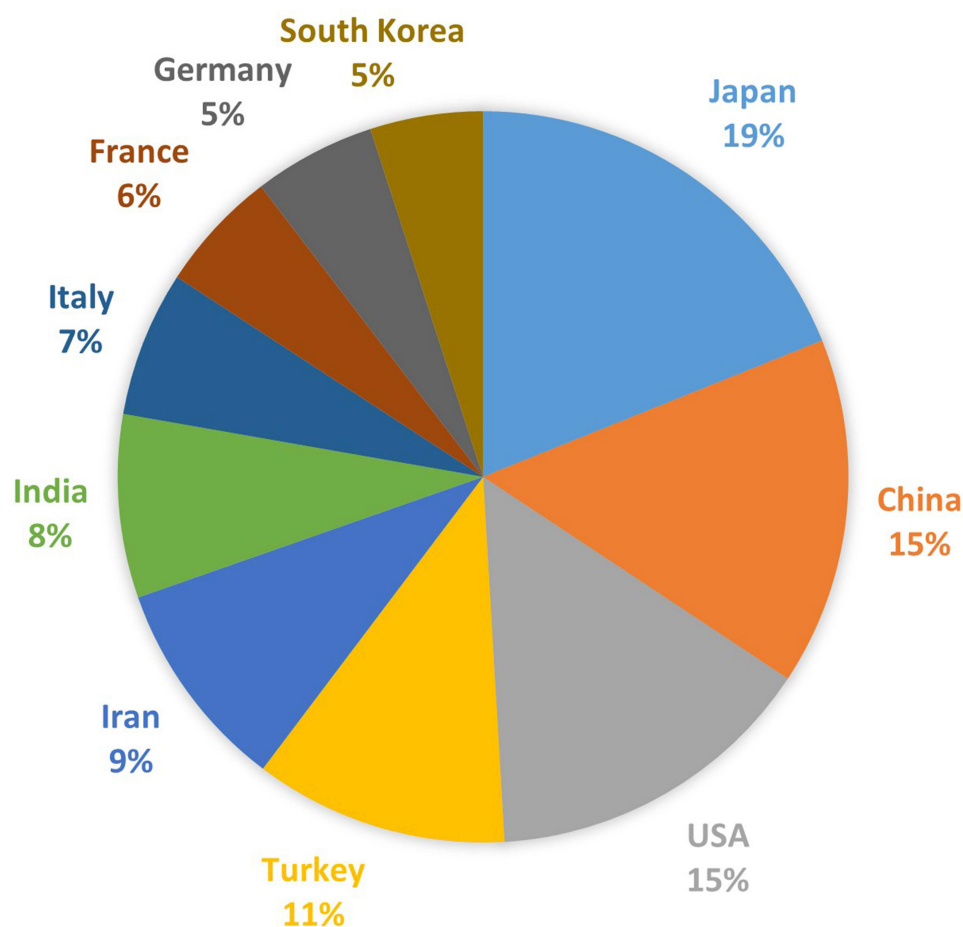
Fazeli, B. from Mashhad University of Medical Science keeps the highest H-index. Iwai, T. from Tokyo Medical and Dental University has the highest total citations. Kihara, Y. from Kobe City Medical Center General Hospital has the highest average citations.

### Journal

Table 4 shows the top 10 journals that publish the most TAO-related articles. The impact factor (IF) and journal quartile were taken from Journal Citation Reports 2022. The top 10 most-published journals are *Annals of Vascular Surgery* (21 articles), *Angiology* (20 articles), *Journal of Vascular Surgery* (16 articles), *Vascular* (14 articles), *Circulation Journal* (10 articles), *European Journal of Vascular and Endovascular Surgery* (9 articles), *International Angiology* (9 articles), *International Journal of Cardiology* (8 articles), *Atherosclerosis* (7 articles), *Clinical and Applied Thrombosis-Hemostasis* (7 articles). *Journal of Vascular Surgery* (IF=4.86) keeps the highest total citation and H-index. However, *Clinical and Applied Thrombosis-Hemostasis* (IF=3.512) has the highest average citations. Figure 5 shows the dual-map overlay of journals on TAO. The cited journals are on the right, the citing journals are on the left, and the colored path represents the citation relationship. One main path can be easily found out: from medicine/medical/clinical to health/nursing/medicine.

**Table I** The Top 10 Countries by Publications

Rank	Country	Publications	% of 553	Total Citations	Average Citations	H-Index
1	Japan	91	16.46	2476	27.21	26
2	China	74	13.38	499	6.74	13
3	United States	71	12.84	1435	20.21	19
4	Turkey	54	9.76	661	12.24	12
5	Iran	45	8.14	372	8.27	11
6	India	39	7.05	220	5.64	7
7	Italy	31	5.61	588	18.97	10
8	France	26	4.70	562	21.62	15
9	Germany	26	4.70	431	16.58	13
10	South Korea	24	4.34	646	26.92	11



**Figure 4** The total number and percentage of publications among the top ten countries.

## Academic Collaboration

Academic cooperation and exchanges between various countries/regions, institutions and authors are of great importance to advancing the in-depth academic research. In [Figure 6A](#), each node stands for a different country. Node colors represent different clusters (research topics). The node connection line represents the collaborative relationship. The thicker the connection line, the closer the cooperation between the two. The size of the node stands for the number of published literatures that results from their collaboration. This graph lists the collaboration between the 21 most-connected countries (the

**Table 2** The Top 10 Institutions Distributed by Publications

Rank	Institution	Publications	Total Citations	Average Citations	H-index	Original Country
1	Mashhad University of Medical Sciences	35	302	8.63	10	Iran
2	Udice-French Research Universities	17	384	22.59	11	French
3	Assistance Publique Hopitaux Paris	16	364	22.75	11	French
4	Nagoya University	14	714	51	11	Japan
5	Tokyo Medical and Dental University	12	443	36.92	9	Japan
6	Christian Medical College & Hospital	11	59	5.36	3	India
7	Tehran University of Medical Sciences	11	49	4.45	4	Iran
8	Istanbul University	9	122	13.56	5	Turkey
9	Seoul National University	9	386	42.89	7	South Korea
10	Wroclaw Medical University	9	119	13.22	5	Poland

**Table 3** The Top 10 Authors Distributed by Publications

Rank	Author	Publications	Total Citations	Average Citations	Country	Institution	H-Index
1	Fazeli, B	26	260	10	Iran	Mashhad University of Medical Science	10
2	Ravari, H	10	100	10	Iran	Mashhad University of Medical Science	8
3	Iwai, T	10	350	35	Japan	Tokyo Medical and Dental University	7
4	Kihara, Y	7	323	46.14	Japan	Kobe City Medical Center General Hospital	5
5	Sharebiani, H	7	25	3.57	Iran	Mashhad University of Medical Science	3
6	Komori, K	6	198	33	Japan	Nagoya University	5
7	Modaghegh, MHS	6	45	7.5	Iran	Mashhad University of Medical Science	4
8	Agarwal, S	6	11	1.83	India	Christian Medical College & Hospital	2
9	Taheri, H	6	13	2.17	Iran	Tehran University of Medical Sciences	2
10	Higashi, Y	5	144	28.8	Japan	Hiroshima University	5

**Table 4** The Top 10 Journals Distributed by Publications

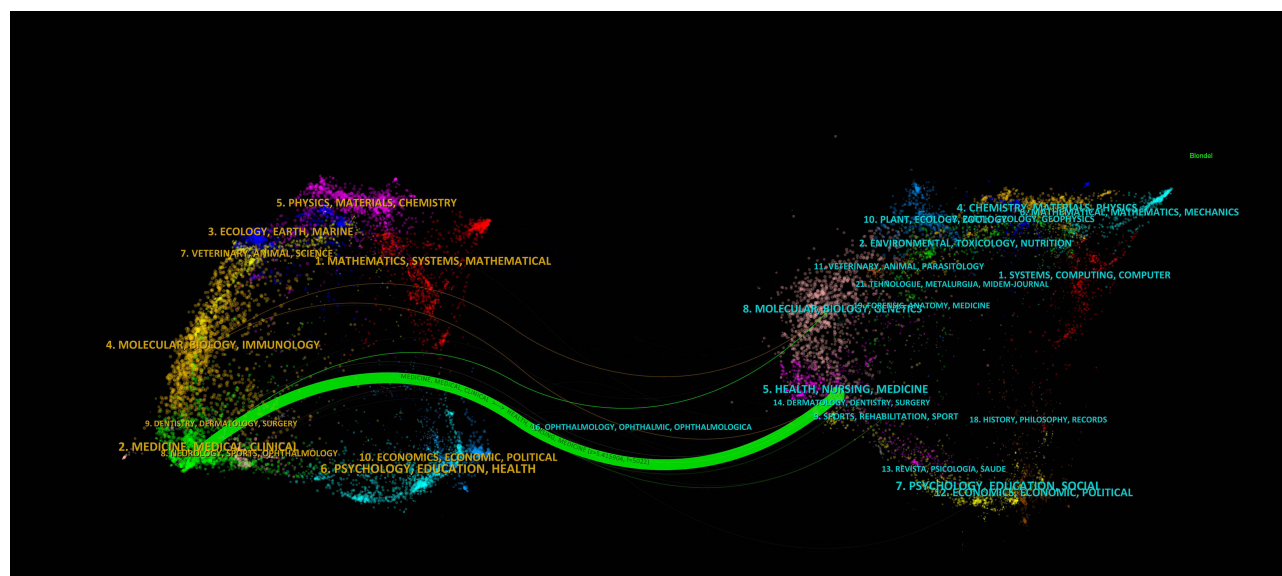
Rank	Journal	Publications	Total Citation	Average Citations	H-index	Impact Factors	JIF Quartile
1	Annals of Vascular Surgery	21	279	13.29	9	1.607	Q4
2	Angiology	20	276	13.8	9	3.299	Q3
3	Journal of Vascular Surgery	16	730	45.63	12	4.860	Q1
4	Vascular	14	122	8.71	6	1.105	Q4
5	Circulation Journal	10	555	55.5	8	3.350	Q3
6	European Journal of Vascular and Endovascular Surgery	9	160	17.78	7	6.427	Q1
7	International Angiology	9	132	14.67	6	2.103	Q4
8	International Journal of Cardiology	8	221	26.38	8	4.039	Q2
9	Atherosclerosis	7	403	57.57	7	6.851	Q1
10	Clinical and Applied Thrombosis-Hemostasis	7	79	77.29	6	3.512	Q3

minimum number of documents per country is greater than five). Three clusters are formed in the figure Iran (total link strength=37), Japan (total link strength=23), USA (total link strength=16) has the highest total link strength in each cluster. In [Figure 6B](#), institutions with a frequency of two or more are included. Mashhad University of Medical Sciences (total link strength=24) has the highest total link strength. Using VOSviewer software, 265 authors whose publication more than or equal to two are selected. Some of the 265 authors are not associated with others. The largest set of connected countries include 55 items ([Figure 6C](#)). Kihara, Y. (total link strength=63) has the highest total link strength.

## Co-Citation Analysis

### Co-Cited Authors

Co-citation analysis stands for a method of expressing the correlation between items based on the number of simultaneous citations. Co-citation analysis shows a total of 9931 authors in the TAO field. Olin, J.W. (387 citations, total link strength=4498) has the most citations, followed by Shionoya, S. (249 citations, total link strength=3063) and Fazeli, B. (177 citations, total link strength=2090). Our data found that 88 authors have 20 citations or more than that. After clustering these researchers, 5 major clusters were formed ([Figure 7A](#)).



**Figure 5** The dual-map overlay of journals on thromboangiitis obliterans. The “yellow” text represents the cited journals, the “blue” text indicates the citing journal, whereas the “green” path refers to the citation relationship.

### Co-Cited Journals

Figure 7B shows the relationship among the 155 identified journals (one journal with a minimum citation count of 20 or more than that). The top three journals by citations are as follows: Journal of Vascular Surgery (791 citations, total link strength=27,156), Circulation Journal (702 citations, total link strength=24,361), The New England Journal of Medicine (457 citations, total link strength=15,096).

### Co-Cited References

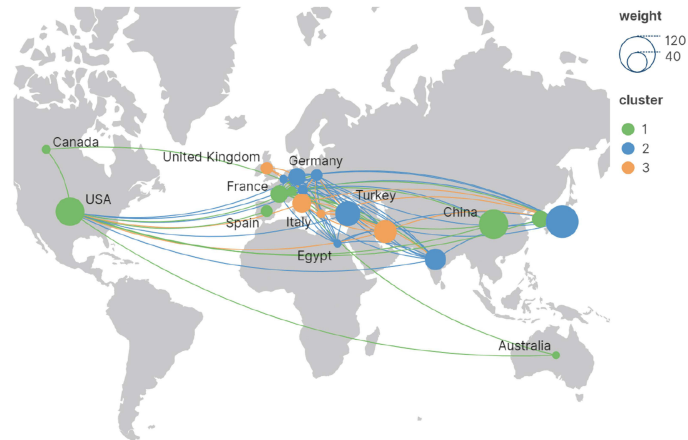
The clustering of co-cited references reflects the direction of the research field to a certain extent. A total of 66 references with a minimum number of 20 citations are shown in Figure 7C.<sup>3,8–20</sup> The top 3 co-cited references refer to: “Thromboangiitis obliterans (Buerger’s disease)”<sup>21</sup> (182 citations, total link strength=1212), “The changing clinical spectrum of thromboangiitis obliterans (Buerger’s disease)”<sup>13</sup> (94 citations, total link strength=865) and “Diagnostic criteria of Buerger’s disease”<sup>22</sup> (115 citations, total link strength=840). These articles all deal with the clinical aspects of TAO, which illustrates the central role of clinical aspects in TAO research.

### Analysis of Highly Cited Articles and Hot Spot

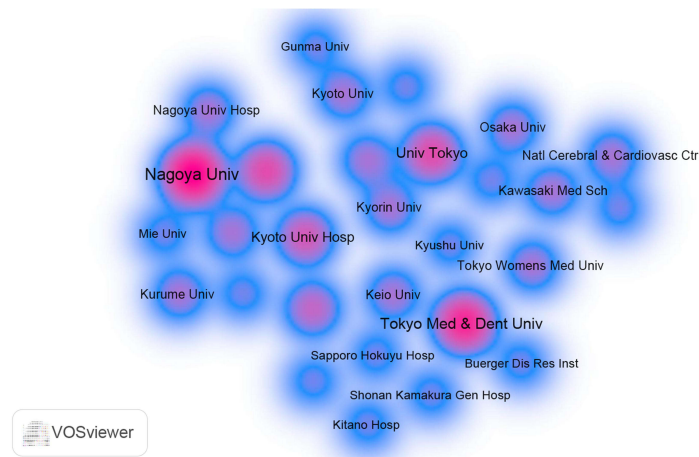
The top 10 most-cited articles are shown in Table 5. The first one refers to Olin, J.W.,<sup>21</sup> they summarized the latest progress of TAO from four aspects: cause and pathogenesis, pathological findings, clinical features, treatment. The second one is written by Flammer, J. et al.<sup>23</sup> They discussed the role of vasospasm in the pathogenesis of the disease. The third one refers to Matoba, S. et al. They conducted a randomized controlled trial (Therapeutic Angiogenesis by Cell Transplantation) to testify the feasibility of bone marrow mononuclear cells injection in patients with critical limb ischemia.

Keywords stand for the essence and core of a paper, which reflect the research hotspots in the field. The top 5 keywords ranked in this study and their frequencies are thromboangiitis obliterans (177), thromboangiitis-obliterans (151), buerger’s disease (150), buergers-disease (115), critical limb ischemia (60). By clustering the keywords with frequency more than or equal to 10, a total of 71 qualified keywords were obtained and grouped into four clusters (Figure 8A). Green clusters represent “Cell therapy study”, mainly about endothelial progenitor cell; blue clusters represent “Mechanism study”, mainly about inflammation; red clusters represent “Etiology study”, mainly about smoking; yellow clusters represent studies on “Clinical therapy study”, mainly about sympathectomy. Figure 8B shows the map of co-occurring keywords over time. In this figure, different colors indicate the relevant year of

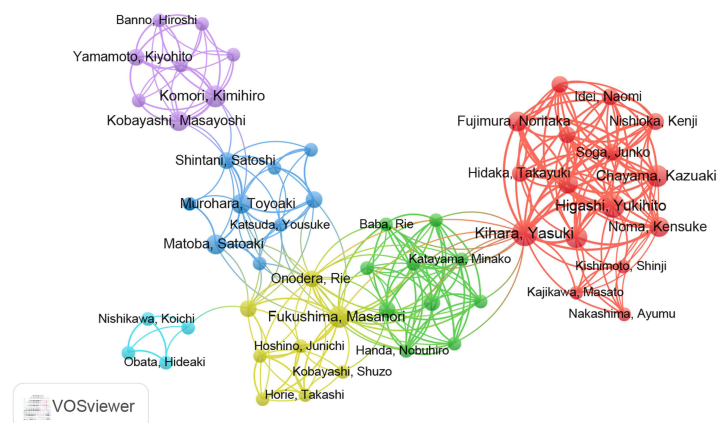
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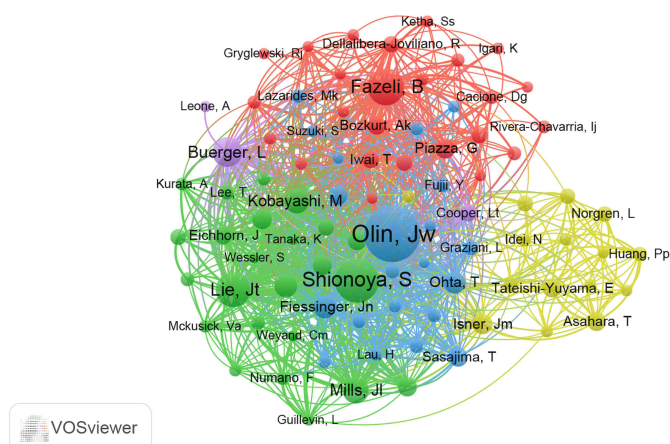
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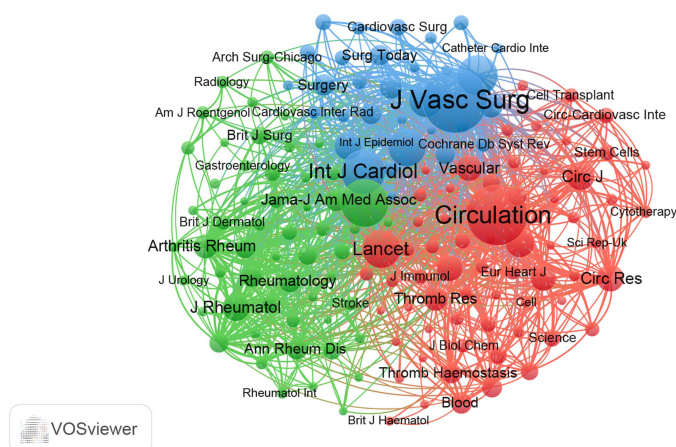
**Figure 6 (A)** The academic collaboration between different countries/regions. Each node stands for a different country. Node colors represent different clusters (research topics). The node connection line represents the collaborative relationship. The thicker the connection line, the closer the cooperation between the two. The size of the node stands for the number of published literatures that results from their collaboration. **(B)** The collaboration between different institutions. **(C)** The collaboration between different authors.



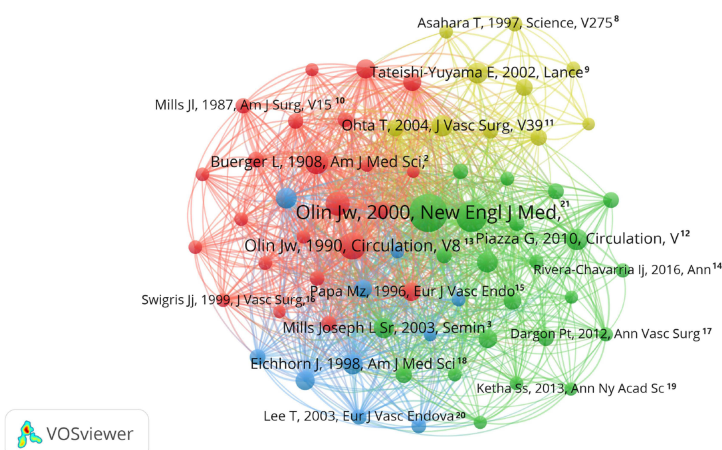
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**Figure 7 (A)** The VOSviewer visualization map of co-cited authors devoted to thromboangiitis obliterans research. Our data found that 88 authors have 20 citations or more than that. After clustering these researchers, 5 major clusters were formed. Different colored nodes represent different clusters. **(B)** The VOSviewer visualization map of co-cited journals devoted to thromboangiitis obliterans research. **(C)** The VOSviewer visualization map of co-cited references devoted to thromboangiitis obliterans research.



**Table 5** The Top 10 Cited Articles

Rank	Author	Title	Total Citations	Journal
1	Olin, JW <sup>21</sup>	Current Concepts: Thromboangiitis Obliterans (Buerger's Disease)	326	The New England Journal of Medicine
2	Flammer, J <sup>23</sup>	Vasospasm, its Role in the Pathogenesis of Diseases with Particular Reference to The Eye	287	Progress In Retinal and Eye Research
3	Matoba, S <sup>24</sup>	Long-term Clinical Outcome after Intramuscular Implantation of Bone Marrow Mononuclear Cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] Trial) in Patients with Chronic Limb Ischemia	225	American Heart Journal
4	Fadini, GP <sup>25</sup>	Autologous Stem Cell Therapy for Peripheral Arterial Disease Meta-analysis and Systematic Review of the Literature	189	Atherosclerosis
5	Lee, HC <sup>26</sup>	Safety and Effect of Adipose Tissue-Derived Stem Cell Implantation in Patients With Critical Limb Ischemia - A Pilot Study	188	Circulation Journal
6	Kawamoto, A <sup>27</sup>	Intramuscular Transplantation of G-CSF-Mobilized CD34(+) Cells in Patients With Critical Limb Ischemia: A Phase I/IIa, Multicenter, Single-Blinded, Dose-Escalation Clinical Trial	176	Stem Cells
7	Kim, SW <sup>28</sup>	Successful Stem Cell Therapy Using Umbilical Cord Blood-derived Multipotent Stem Cells for Buerger's Disease and Ischemic Limb Disease Animal Model	175	Stem Cells
8	Aksu, K <sup>29</sup>	Inflammation-Induced Thrombosis: Mechanisms, Disease Associations and Management	174	Current Pharmaceutical Design
9	Kajiguchi, M <sup>30</sup>	Safety and Efficacy of Autologous Progenitor Cell Transplantation for Therapeutic Angiogenesis in Patients with Critical Limb Ischemia	128	Circulation Journal
10	Lawall, H <sup>31</sup>	Treatment of Peripheral Arterial Disease Using Stem and Progenitor Cell Therapy Challenges for Clinical Use	115	Journal of Vascular Surgery Development

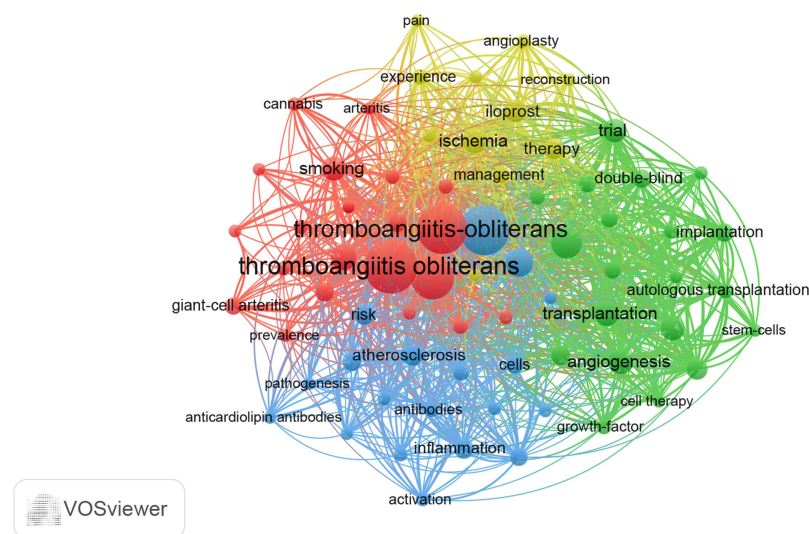
publication. Yellow keywords came later than blue keywords. In addition, a burst keyword means the word that occur frequently within a specific time period. It shows the evolution of research hotspots over time, which indicates the research trends recently and foreshadow future trends (Figure 9). The burst keyword with highest strength is endothelial progenitor cells. However, trial, therapy, outcome, and management have received much attention in recent years. Timeline of keywords on TAO (Figure 10) forms 10 clusters over time: #0 (thromboangiitis obliterans), #1 (buerger's disease), #2 (peripheral arterial disease), #3 (c-reactive protein), #4 (adhesion molecules), #5 (critical limb ischemia), #6 (endovascular procedure), #7 (diabetes mellitus), #8 (peripheral artery disease), #9 (paracrine action).

## Discussion

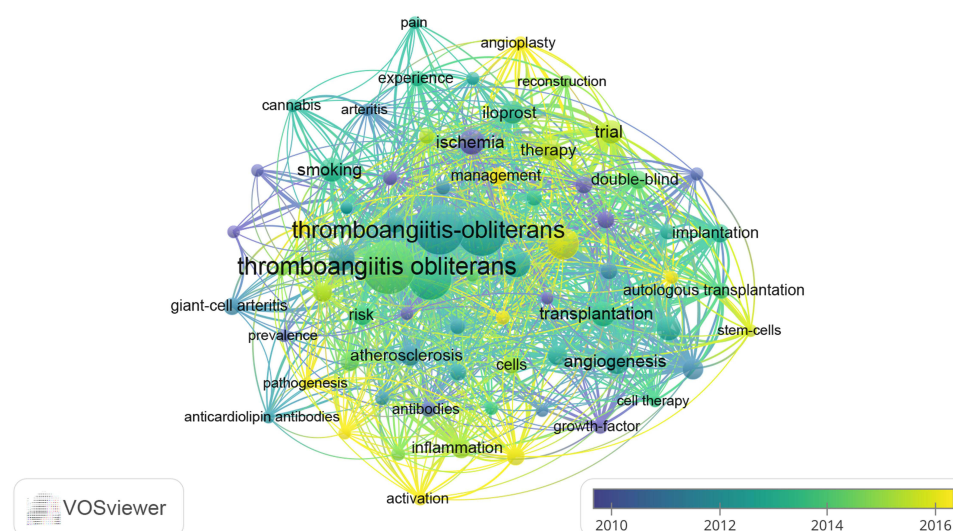
To the best of our knowledge, our study is the first bibliometric research on TAO. Bibliometrics analysis has already become a powerful tool to summarize the current status and predict the future vision. We utilized bibliometric techniques to analyze countries/regions, authors, institutions, journals, references, and keywords, summarizing knowledge networks and forecasting emerging topics related to TAO. A total of 553 TAO-related literatures, including 469 original articles and 84 review articles published in 1999–2022 period, were included in our study. Figure 3 shows that although the number of publications fluctuates from year to year, the number of citations shows a steady upward trend every year. This indicates that TAO, as a kind of immune disease, has received increasingly attention from researchers. Therefore, it can be predicted that TAO-related researches will continue to increase globally and more researchers will participate in TAO's research in coming years. As for the fluctuation of publication volume, it may be due to some practical reasons, such as the 2019 pandemic caused the publication volume to plummet in 2019.

For the analysis of countries distribution, we can see that Japan with the highest H-index ranks first in Table 1, followed by China, United States, Turkey, Iran, India, Italy, France, Germany, South Korea. In addition to this, according to Figure 6A, Japan and the United States have the most communication and cooperation with other countries. Therefore, our results suggest that Japan is the top country for global TAO research and has an international perspective. We

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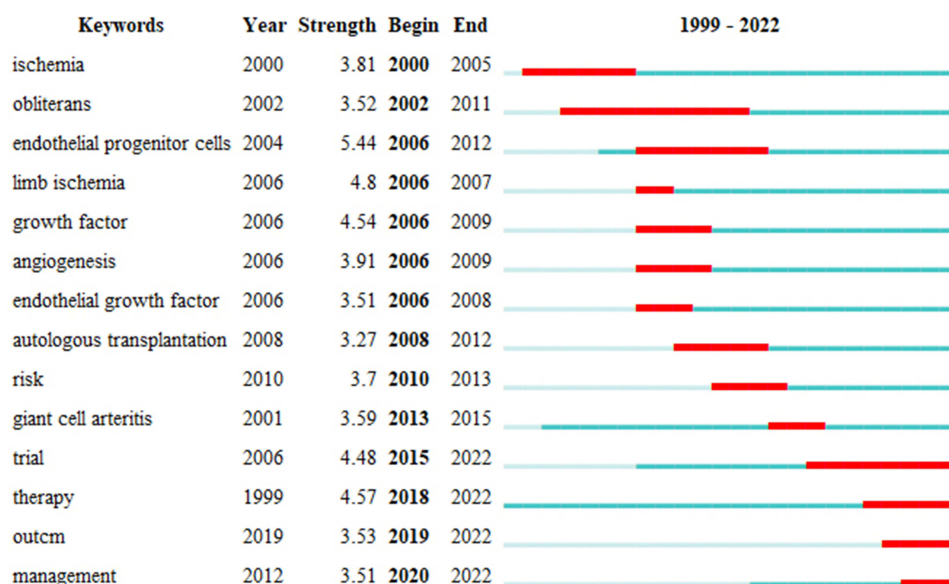
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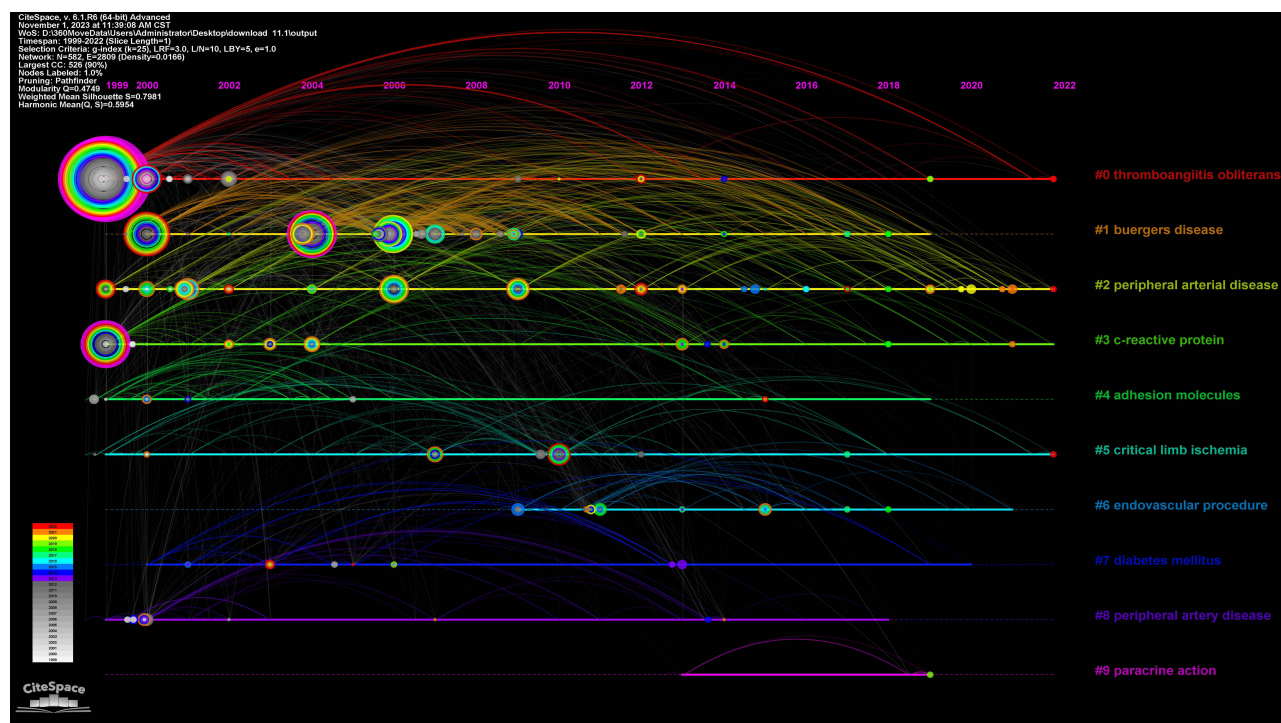
**Figure 8** The VOSviewer visualization map of co-occurring keywords. **(A)** Keyword maps in the past 23 years. **(B)** Distribution of keywords according to their time of appearance. The size of the nodes indicates occurrence frequency. The different colors indicate the relevant year of publication. Yellow keywords came later than blue keywords.

observed that as a developing country, China has surpassed the United States in the number of publications on TAO to take second place, indicating that with the rapid development of China's economy and the increase in public demand for medical and health care, the country's investment and funding in this area is also gradually increasing. However, we also observed that China has a lower number of citations and an H-index compared to other countries. This may be due to the fact that although China's economy is growing rapidly, it has developed relatively late in the TAO field and its foundation is not yet solid. In order to solve this problem, China should strengthen cooperation and exchanges with other countries to achieve high-quality TAO research. Interestingly, more than half of the top 10 countries are from Asia, which may be due to the large number of smokers and the low criteria for diagnosing TAO.<sup>32</sup>

From the perspective of institutions, the first place is Mashhad Medical University in terms of publications. But in terms of citations, the first place is Nagoya University, because it has good exchanges and cooperation with other schools



**Figure 9** The top 14 keywords with the strongest citation bursts of thromboangiitis obliterans. The “Year” represents the time when the keyword appears, the “Strength” represents the relative intensity of the keyword citation burstiness, the bolded “Begin” represents the year in which the keyword begins to burst, and the “End” represents the year in which the keyword ends burstiness. The years between “Begin” and “End” represent the period when the keyword was more influential. The dark green years indicate that the keyword is less influential, whereas the red years indicate that the keyword is more influential.



**Figure 10** The timeline of keywords on thromboangiitis obliterans. The timeline of keywords on amputation shows the top 3 high-frequency keywords in each cluster over time.

(Figure 6B). Table 3 shows that four of the top 10 authors are from Mashhad Medical University, which proves the university’s leading position in TAO research. Additionally, most of the top 10 institutions are universities, which revealed that researches from universities have made great contributions to TAO-related scientific research.

As shown in Table 3, Fazeli, B had the most articles published on TAO research and had highest H-index. Thus, Fazeli, B was the most productive author. In terms of total citation, Iwai, T have the highest total citation. However, Kihara, Y have the highest average citation. What's more, Kihara, Y. (total link strength=63) has the highest total link strength in Figure 6C. Therefore, the most cooperative author refers to Kihara, Y. and he can be regarded as leading experts in TAO research. Besides, almost the top 10 authors are all from the top 10 institutions, which reveals the complementary role between distinguished scholars and first-class research platforms.

The journals that publish the most articles related to TAO are *Annals of Vascular Surgery*, which means its leading position in this field (Table 4). However, *Journal of Vascular Surgery* has the highest H-index and total citations, and judging from the co-citation analysis of Figure 7B, this journal is also very popular for TAO research around the world. Furthermore, it is difficult to ignore the outstanding performance of the *Circulation Journal* in Figure 7B, and it also has a top ranking in publications, total citations, and average citations, which reveals its important role in advancing TAO research. It is not difficult to find that most of these journals are pertinent to TAO's research field (medicine, medical and clinical in Figure 5), and these journals are included in SCI with relatively efficient and professional characteristics, which is might be the reason for their popularity among researchers.

TAO-related articles published between 1999 and 2022 are divided into 68 different WOS research areas. However, in order to show the changes in research areas over time more easily and clearly, we ended up selecting 10 research areas. Figure 2A describes these research areas and the corresponding number of TAO-related articles, of which the field of peripheral vascular disease has received the most attention (151, 27.31%). Figure 2B shows the distribution of TAO-related research fields of 1999–2010 and 2011–2022 periods, from which we can visually see the changes in TAO-related research fields. Peripheral vascular disease and surgery have always been the most concerned research areas. Over time, the study of medicine general internal, pharmacology pharmacy, and medicine research experimental has steadily increased rheumatology, hematology and cell biology were replaced by chemistry medicinal, biochemistry molecular biology, radiology nuclear medicine medical imaging.

It is undeniable that vasodilator drugs, antiplatelet drugs, anticoagulant drugs, and thrombolytic drugs play a certain alleviating effect on the treatment of TAO, but these drugs will also change the body's blood indicators and affect the body's metabolism.<sup>33</sup> In recent years, some traditional Chinese medicines have gradually been studied for TAO treatment. For example, Chu Y. J. et al found that the active ingredients of Mailuo shutong pills (magnoflorine chloride, paeoniflorin, albiflorin, and 4-methoxycinnamic acid) positively correlated with the synergistic mechanism of TAO.<sup>34</sup> Zou C. et al concluded that Baiying qingmai formulation improves TAO by inhibiting activation of JNK, ERK, p38 MAPK, and HMGB1/RAGE/NF- $\kappa$ B signaling pathways.<sup>35</sup> As for rheumatology: there are 12.5% of patients with TAO who had joint problems in the pre-occlusive stage, they presented with recurrent episodes of large joints with signs of local inflammation (swelling due to stasis edema). At this stage, patients are likely to consult rheumatologists, so the differential diagnosis between TAO and rheumatism is very important.<sup>36,37</sup> Moreover, the increased research in radiology nuclear medicine medical imaging may be related to TAO's increasingly sophisticated interventional therapy. Interventional therapy has the advantages of accurate targeting, direct procedure, small trauma, integration of diagnosis and treatment, and repeatability.<sup>38</sup>

Table 5 shows the top 10 cited articles, of which the first article is a review, published in *The New England Journal of Medicine*, which detailly describes the cause and pathogenesis, pathological findings, clinical features, and treatment of TAO.<sup>21</sup> Interestingly, this article and the author has the strongest co-citation relationships with others in Figure 7A and C, indicating its insurmountable academic impact worldwide. The second and eighth articles mainly analyze TAO from the pathogenesis aspect, while the remaining 7 articles study TAO from a therapeutic perspective, including implantation of bone marrow mononuclear cells,<sup>24</sup> implantation of adipose tissue-derived stem cells,<sup>26</sup> implantation of G-CSF-mobilized CD34(+) cells,<sup>27</sup> implantation of umbilical cord blood-derived multipotent stem cells,<sup>28</sup> and autologous progenitor cell transplantation ect.<sup>30</sup>

Figure 8A shows a visualization map of co-occurring keywords through VOSviewer. The most frequently-used keywords in "Cell therapy study" cluster are stem-cells, endothelial progenitor cell, autologous transplantation, and therapeutic angiogenesis. The most commonly-used terms in "Mechanism study" cluster are activation, anticardiolipin antibodies, oxidative stress, thrombosis, and inflammation. Moreover, prevalence, tobacco, cannabis, smoking are often-used keywords in "Etiology



study” cluster. The primary keywords in “Clinical therapy study” cluster are iloprost, bypass, revascularization, sympathectomy. Figure 8B is composed according to the time when the keyword appears. The different colors indicate the relevant year of publication. Yellow keywords came later than blue keywords. By overlapping the results of the two plots, we can see that etiology and treatment research will be the future trend of TAO research. To go into more detail, there is still a lot of room for research into key items such as stem cells, angioplasty, and activation. For example, Cacione D. G. et al conducted a randomized controlled trial demonstrating that bone marrow-derived stem cells may have an effect on ulcer healing and improving painless walking distance in patients with Buerger’s disease.<sup>39</sup> A prospective pilot study was conducted by Yang L. et al to prove ideal effect of laser-assisted angioplasty (LA) combined with radiofrequency ablation (RFA) on TAO.<sup>40</sup> In addition to this, the therapy of transverse tibial bone transport can enhance distraction osteogenesis and vascularization to treat TAO, achieve the effect of limb salvage, and improve the pain and numbness symptoms of patients. However, there is a certain recurrence rate after surgery, and patients still need to actively control their tobacco addiction throughout the course of the disease.<sup>41,42</sup> As for the pathogenesis of TAO, Li M. D. et al concluded that it is related to complex factors such as oxidative stress, immunity, hemodynamic changes, and inflammation. Clinical research and exploration should be carried out, and valuable things in various studies should be synthesized, and further summarized to better clarify the mechanism of its pathogenesis.<sup>43</sup> Figure 9 shows the period of concentrated outbreaks for the top 14 projects and how hot spots changed over time from 1999 to 2022. As you can see, trail, therapy, outcome, and management have continued to explode in recent years. Based on the previous inferences, it can be concluded that the future research directions are: randomized controlled trials, cell therapy, and personalized management. The interrelationships between the keyword clusters and the change of each keyword over time are shown in Figure 10. A total of 10 clusters of keywords have been formed in this study, among which the following are still under study: #0 (thromboangiitis obliterans), #1 (buerger’s disease), #2 (peripheral arterial disease), #3 (c-reactive protein), #5 (critical limb ischemia). Nevertheless, c-reactive protein (a reliable indicator of inflammation) is widely used in various TAO-related studies.<sup>44,45</sup> All in all, further global collaborative research is urgently needed for a comprehensive understanding of TAO.

## Strengths and Limitations

To the best of our current knowledge, few studies have extensively investigated the research status and trends in TAO. Our study is the first bibliometrics and visual analysis of TAO. We used VOSviewer, CiteSpace, Scimago Graphica, and other software to visualize countries, journals, authors, and institutions ect. Our study provides useful information for scientists in this field to better understand the changing process of TAO research, and also provides new research ideas and perspectives for exploring the frontiers of TAO research.

However, the limitations should also be acknowledged. We restricted our search to articles published in English language, and the potentially valuable articles may be missed. Nevertheless, English articles in WoSCC are the most commonly used data source in bibliometrics research and represent the majority of information. Influenced by the WoSCC database, this study only included articles from 1999 to 2022.

## Conclusion

We present the global status and trends of TAO-related publications from 1999 to 2022. Although the number of TAO publications has fluctuated over the past 20 years, it has generally shown a steady upward trend. Japan has the leading global position not only in the number of publications, but also total citations, average citations and H-index. Institution with the major contribution to TAO research is Mashhad University of Medical Sciences, and Nagoya University. *Annals of Vascular Surgery*, *Angiology*, *Journal of Vascular Surgery* are the main publication channel for articles related to TAO. Fazeli, B., Iwai, T., and Kihara, Y. are major contributors in this field. In addition, etiology and treatment research on TAO will become a hot spot in the future. Specifically, trail, therapy, outcome, management, stem cells, angioplasty, and activation have received much attention from researchers in recent years.

## Data Sharing Statement

The data is accessible from the Web of Science repository, and the corresponding author can also be contacted for further information.

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## Disclosure

The authors report no conflicts of interest in this work.

## References

- Olin JW. Thromboangiitis obliterans. *Curr Opin Rheumatol*. 1994;6(1):44–49. doi:10.1097/00002281-199401000-00008
- Buerger L. Landmark publication from the American Journal of the Medical Sciences, ‘Thrombo-angiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene’. 1908. *Am J Med Sci*. 2009;337(4):274–284. doi:10.1097/MAJ.0b013e31818c8bc9
- Mills JL. Buerger’s disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg*. 2003;16(3):179–189. doi:10.1016/s0895-7967(03)00023-1
- Choi B, Jang SY, Kim S-K, et al. The incidence, prevalence, and survival rate of thromboangiitis obliterans in Korea: a retrospective population-based study. *Cardiovasc Diagn Ther*. 2020;10(5):1238–1244. doi:10.21037/cdt-20-582
- Arkkila PE. Thromboangiitis obliterans (Buerger’s disease). *Orphanet J Rare Dis*. 2006;1(1):14. doi:10.1186/1750-1172-1-14
- Cacione DG, Macedo CR, Do Carmo Novaes F, Baptista-Silva JC. Pharmacological treatment for Buerger’s disease. *Cochrane Database Syst Rev*. 2020;5(5):Cd011033. doi:10.1002/14651858.CD011033.pub4
- Pu H. Endovascular Excimer Laser-Assisted Balloon Angioplasty for Infrapopliteal Arteries in Thromboangiitis Obliterans: a Treatment for Acute-Phase TAO. *Front Cardiovasc Med*. 2022;9:831340. doi:10.3389/fcvm.2022.831340
- Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science*. 1997;275(5302):964–967. doi:10.1126/science.275.5302.964
- Tateishi-Yuyama E. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet*. 2002;360:427–435. doi:10.1016/s0140-6736(02)09670-8
- Mills JL, Taylor LM, Porter JM. Buerger’s disease in the modern era. *Am J Surg*. 1987;154(1):123–129. doi:10.1016/0002-9610(87)90301-1
- Ohta T, Ishioashi H, Hosaka M, Sugimoto I. Clinical and social consequences of Buerger disease. *J Vasc Surg*. 2004;39(1):176–180. doi:10.1016/j.jvs.2003.08.006
- Piazza G, Creager MA. Thromboangiitis obliterans. *Circulation*. 2010;121(16):1858–1861. doi:10.1161/circulationaha.110.942383
- Olin JW, Young JR, Graor RA, Ruschhaupt WF, Bartholomew JR. The changing clinical spectrum of thromboangiitis obliterans (Buerger’s disease). *Circulation*. 1990;82:1v3–8.
- Rivera-Chavarría IJ, Brenes-Gutiérrez JD. Thromboangiitis obliterans (Buerger’s disease). *Ann Med Surg*. 2016;7:79–82. doi:10.1016/j.amsu.2016.03.028
- Papa MZ, Rabi I, Adar R. A point scoring system for the clinical diagnosis of Buerger’s disease. *Eur J Vasc Endovasc Surg*. 1996;11(3):335–339. doi:10.1016/s1078-5884(96)80081-5
- Swigris JJ, Olin JW, Mekhail NA. Implantable spinal cord stimulator to treat the ischemic manifestations of thromboangiitis obliterans (Buerger’s disease). *J Vasc Surg*. 1999;29(5):928–935. doi:10.1016/s0741-5214(99)70221-1
- Dargon PT, Landry GJ. Buerger’s disease. *Ann Vasc Surg*. 2012;26(6):871–880. doi:10.1016/j.avsg.2011.11.005
- Eichhorn J, Sima D, Lindschau C, et al. Antiendothelial cell antibodies in thromboangiitis obliterans. *Am J Med Sci*. 1998;315(1):17–23. doi:10.1097/00000441-199801000-00004
- Ketha SS, Cooper LT. The role of autoimmunity in thromboangiitis obliterans (Buerger’s disease). *Ann N Y Acad Sci*. 2013;1285(1):15–25. doi:10.1111/nyas.12048
- Lee T, Seo JW, Sumpio BE, Kim SJ. Immunobiologic analysis of arterial tissue in Buerger’s disease. *Eur J Vasc Endovasc Surg*. 2003;25(5):451–457. doi:10.1053/ejvs.2002.1869
- Olin JW. Thromboangiitis obliterans (Buerger’s disease). *N Engl J Med*. 2000;343(12):864–869. doi:10.1056/nejm200009213431207
- Shionoya S. Diagnostic criteria of Buerger’s disease. *Int J Cardiol*. 1998;66(Suppl 1):S243–245. doi:10.1016/s0167-5273(98)00175-2
- Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. *Prog Retin Eye Res*. 2001;20(3):319–349. doi:10.1016/s1350-9462(00)00028-8
- Matoba S, Tatsumi T, Murohara T, et al. Long-term clinical outcome after intramuscular implantation of bone marrow mononuclear cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] trial) in patients with chronic limb ischemia. *Am Heart J*. 2008;156(5):1010–1018. doi:10.1016/j.ahj.2008.06.025
- Fadini GP, Agostini C, Avogaro A. Autologous stem cell therapy for peripheral arterial disease meta-analysis and systematic review of the literature. *Atherosclerosis*. 2010;209(1):10–17. doi:10.1016/j.atherosclerosis.2009.08.033
- Lee HC, An SG, Lee HW, et al. Safety and effect of adipose tissue-derived stem cell implantation in patients with critical limb ischemia: a pilot study. *Circ J*. 2012;76(7):1750–1760. doi:10.1253/circj.11-1135
- Kawamoto A, Katayama M, Handa N, et al. Intramuscular transplantation of G-CSF-mobilized CD34(+) cells in patients with critical limb ischemia: a phase I/IIa, multicenter, single-blinded, dose-escalation clinical trial. *Stem Cells*. 2009;27(11):2857–2864. doi:10.1002/stem.207



28. Kim SW, Han H, Chae G-T, et al. Successful stem cell therapy using umbilical cord blood-derived multipotent stem cells for Buerger's disease and ischemic limb disease animal model. *Stem Cells*. 2006;24(6):1620–1626. doi:10.1634/stemcells.2005-0365
29. Aksu K, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. *Curr Pharm Des*. 2012;18(11):1478–1493. doi:10.2174/138161212799504731
30. Kajiguchi M, Kondo T, Izawa H, et al. Safety and efficacy of autologous progenitor cell transplantation for therapeutic angiogenesis in patients with critical limb ischemia. *Circ J*. 2007;71(2):196–201. doi:10.1253/circj.71.196
31. Lawall H, Bramlage P, Amann B. Treatment of peripheral arterial disease using stem and progenitor cell therapy. *J Vasc Surg*. 2011;53(2):445–453. doi:10.1016/j.jvs.2010.08.060
32. Lie JT. The rise and fall and resurgence of thromboangiitis obliterans (Buerger's disease). *Acta Pathol Jpn*. 1989;39(3):153–158. doi:10.1111/j.1440-1827.1989.tb01494.x
33. Gao J, Huang L, Wang J. Outcomes of Anticoagulant Therapy with Low-Molecular-Weight Heparin (LMWH) and Warfarin for Thromboangiitis Obliterans (TAO). *Curr Vasc Pharmacol*. 2021;19(6):655–662. doi:10.2174/1570161119666210118125424
34. Wang X-B, Wang M-L, Chu Y-J, et al. Integrated pharmacokinetics and pharmacometabolomics to reveal the synergistic mechanism of a multicomponent Chinese patent medicine, Mailuo Shutong pills against thromboangiitis obliterans. *Phytomedicine*. 2023;112:154709. doi:10.1016/j.phymed.2023.154709
35. Zou C, Liu L, Huang C, Hu S. Baiying qingmai formulation ameliorates thromboangiitis obliterans by inhibiting HMGB1/RAGE/NF-κB signaling pathways. *Front Pharmacol*. 2022;13:1018438. doi:10.3389/fphar.2022.1018438
36. Puéchal X, Fiessinger JN, Kahan A, Menkès CJ. Rheumatic manifestations in patients with thromboangiitis obliterans (Buerger's disease). *J Rheumatol*. 1999;26(8):1764–1768.
37. Puechal X, Fiessinger JN. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. *Rheumatology*. 2007;46(2):192–199. doi:10.1093/rheumatology/ke1388
38. O'Sullivan GJ. The role of interventional radiology in the management of deep venous thrombosis: advanced therapy. *Cardiovasc Intervent Radiol*. 2011;34(3):445–461. doi:10.1007/s00270-010-9977-9
39. Cacione DG, Do Carmo Novaes F, Moreno DH. Stem cell therapy for treatment of thromboangiitis obliterans (Buerger's disease). *Cochrane Database Syst Rev*. 2018;10(10):CD012794. doi:10.1002/14651858.CD012794.pub2
40. Yang L, Tang J, Tian Y, et al. The Preliminary Outcome of Laser-Assisted Angioplasty Combined with Endovascular Radiofrequency Ablation for Thromboangiitis Obliterans. *Adv Ther*. 2021;38(12):5700–5709. doi:10.1007/s12325-021-01945-x
41. Qu L, Wang A, Tang F. The therapy of transverse tibial bone transport and vessel regeneration operation on thromboangiitis obliterans. *Zhonghua Yi Xue Za Zhi*. 2001;81(10):622–624.
42. Wang D, Zhang Y, He G, Zhang X, Qin S. Clinical study on treatment of chronic infection of foot and ankle with lower extremity ischemic diseases by tibial transverse transport combined with antibiotic embedded bone cement. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2020;34(8):979–984. doi:10.7507/1002-1892.202003098
43. Li MD, Wang YF, Yang MW, Hong FF, Yang SL. Risk Factors, Mechanisms and Treatments of Thromboangiitis Obliterans: an Overview of Recent Research. *Curr Med Chem*. 2020;27(35):6057–6072. doi:10.2174/0929867326666190816233042
44. Joras M, Poredos P, Fras Z. Endothelial dysfunction in Buerger's disease and its relation to markers of inflammation. *Eur J Clin Invest*. 2006;36(6):376–382. doi:10.1111/j.1365-2362.2006.01646.x
45. Kim D-H, Ko Y-G, Ahn C-M, et al. Immediate and late outcomes of endovascular therapy for lower extremity arteries in Buerger disease. *J Vasc Surg*. 2018;67(6):1769–1777. doi:10.1016/j.jvs.2017.09.020

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