Bibliometric analysis and visualisation of research hotspots and frontiers in Takayasu's arteritis

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Abstract

Objective

Takayasu's arteritis (TAK) is an uncommon granulomatous large-vessel vasculitis associated with significant morbidity and mortality. This study endeavours to comprehend the research status and future frontiers through a bibliometric analysis.

Methods

Relevant original articles published in English were acquired from the Science Citation Index Expanded of the Web of Science Core Collection. Analysis of countries/regions, institutions, authors, co-cited references, and keywords were done using Citespace and VOSviewer software.

Results

The final analysis included 2215 documents contributed by 9091 scholars from 2053 institutions in 83 countries, with the United States being the largest contributor globally. Institutional and author collaboration analysis showed that collaborations are scattered and lack stable and intensive collaborative relationships. The journal 'Clinical and Experimental Rheumatology' was the most prolific journal. Anti-endothelial cell antibodies, interleukin-6, adalimumab, colour Doppler ultrasonography, and stents and prosthesis were the main research areas in TAK. Double-blind multicentre clinical trials, disease activity evaluation and cytokines were identified to be recent keyword bursts.

Conclusion

Although the area of TAK research is growing rapidly, intensive institutional and author collaboration has to be fostered in the future to fuel TAK research and information dissemination. Future research on TAK may revolve around cytokines, disease activity evaluation and clinical trials.

Key words

bibliometric, Takayasu's arteritis, cytokine, interleukin-6, clinical trial

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Introduction

Takayasu's arteritis (TAK) is an uncommon granulomatous large-vessel vasculitis that most frequently occurs in female patients before the age of 50 in Asia, the Middle East and Latin America (1). Although the exact etiopathogenesis for TAK remains unknown, studies suggest that infection, immunological disturbances and genetic factors all contribute to its development (2). TAK is histopathologically characterised by chronic inflammation of the aorta, its main branches, and pulmonary arteries that incur irreversible damages leading to vascular stenosis, occlusion or aneurysmal formation (3). The clinical manifestations of TAK are heterogeneous and non-specific, including fever, hypertension, claudication of extremities and ocular and renal abnormalities. Given the paucity of clinical symptoms and lack of specificity of laboratory test indicators, the diagnosis of TAK sometimes can be challenging. Consequently, disease activity assessment into "active", "remission" and "relapse" are often based on imaging findings, coupled with clinical manifestations and measurement of acute phase reactants (4). Currently, cardinal management strategies for TAK include both medical treatment and surgical procedures, in which the former constitutes glucocorticosteroids, immunosuppressives and biological agents. Outcomes for TAK have improved significantly due to recent advances in early diagnosis and availability of effective treatment; however, TAK is still associated with unacceptably high morbidity and mortality rate at long-term follow-up (5).

Bibliometrics is an interdisciplinary technique that reveals the cutting-edge knowledge developments and research frontiers by analysing the published literature both quantitatively and qualitatively using mathematical and statistical methods (6). The results of bibliometric analysis can provide a clear overview of current knowledge structure and research hotspots by visualising graphs vividly. Bibliometrics have been previously used in the field of rheumatology, such as gout, Behçet's disease, ankylosing spondylitis, rheumatoid arthritis and others (7-10).

The field of TAK has evolved and expanded significantly, rendering it increasingly difficult for researchers to capture the landscape of TAK research. In this sense, performing a bibliometric analysis instead of a traditional review would provide summary and insights into the knowledge gaps and trends in this field. We are aware that an earlier study had conducted analysis of highly cited publications in TAK (11). Thus, this study aimed to explore the research trends and hotspots of TAK that provides references for future studies using bibliometric analysis.

Methods

Data collection

The literature search was conducted using the comprehensive, multidisciplinary and continuously updated biomedical database Science Citation Index Expanded of the Web of Science Core Collection (SCIE-WOS, Clarivate Analytics) to retrieve relevant documents on August 6, 2023. The search strategy used was TS = ("Takayasu arteritis" OR "Takayasu's arteritis" OR "pulseless disease"), with language restricted to English and document type confined to articles. Documents meeting the eligibility criteria were downloaded with complete records and cited references in plain text for subsequent bibliometric analysis.

Bibliometric analysis

The Java-based bibliometric analysis software CiteSpace was used to analyse the collaboration of institutions and authors, cluster analysis of co-cited references, and keyword co-occurrence, clustering and keyword burst analysis. The nodes in the map created by CiteSpace are proportional to the number of publications, and inter-nodal lines are closely related to the degree of collaborations. In congruence with prior reports, nodes with intermediary centrality >0.1 are considered to be crucial points (12). In the cluster analysis, a mean silhouette value >0.7 and modularity value >0.3 suggested strong clustering results and strong node grouping, respectively. Another common bibliometric software, VOSviewer (Leiden University Centre for Science

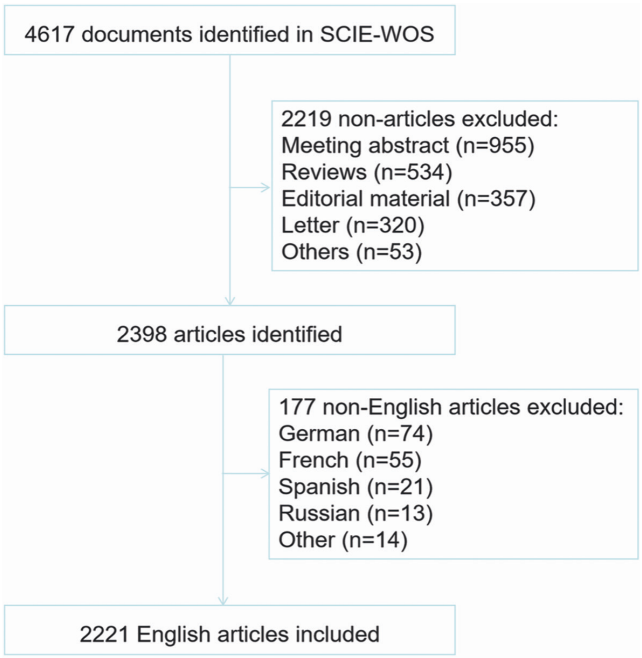

Fig. 1. Study flow chart.

and Technology Studies), was applied to analyse cooperation among countries. The Microsoft Excel programme was used to estimate the number of scientific outputs in the future years by fitting an exponential smooth curve based on data from previous publications.

Results

Analysis of annual publication outputs

Study flow chart is presented in Figure 1. In total, 2221 original articles published from 1975 to August 6, 2023 were finally included and analysed. The annual number of global publications was shown in Figure 2, in which an exponential growth pattern can be observed. The number of publications before 1990 were very small, with less than 10 original articles published each year. According to the prediction curve, the total number of original articles for TAK will be 172 in 2030.

Contributions from countries/regions, institutions and authors

9091 scholars from 2053 institutions in 83 countries/regions contributed to the included literature. Country cooperation analysis (Fig. 3A) demonstrated that the USA (n=372) ranked the first in terms of number of outputs, followed by Japan (n=358), China (n=333), India (n=161) and Turkey (n=153), totally accounting for 62.0% of all scientific outputs. England (centrality=0.21) and USA (centrality=0.17) were determined to be crucial points by CiteSpace, as indicated by intermediary centrality > 0.1.

The leading 5 institutions with the largest number of publications were Chinese Academy of Medical Sciences-Peking Union Medical College (n=124), Peking Union Medical College (n=114), Capital Medical University (n=77), UDICE-French Research Universities (n=72) and Fu Wai Hospital-CAMS (n=69). Institution collaboration analysis (Fig. 3B) showed distinct patterns, in which the Chinese institutions cooperated predominantly with only Chinese institutions. Moreover, the intermediary centrality score for all the institutions were <0.1, suggesting a lack of widespread inter-institutional cooperation.

As shown in Figure 3C, the network diagram of authors was consisted of

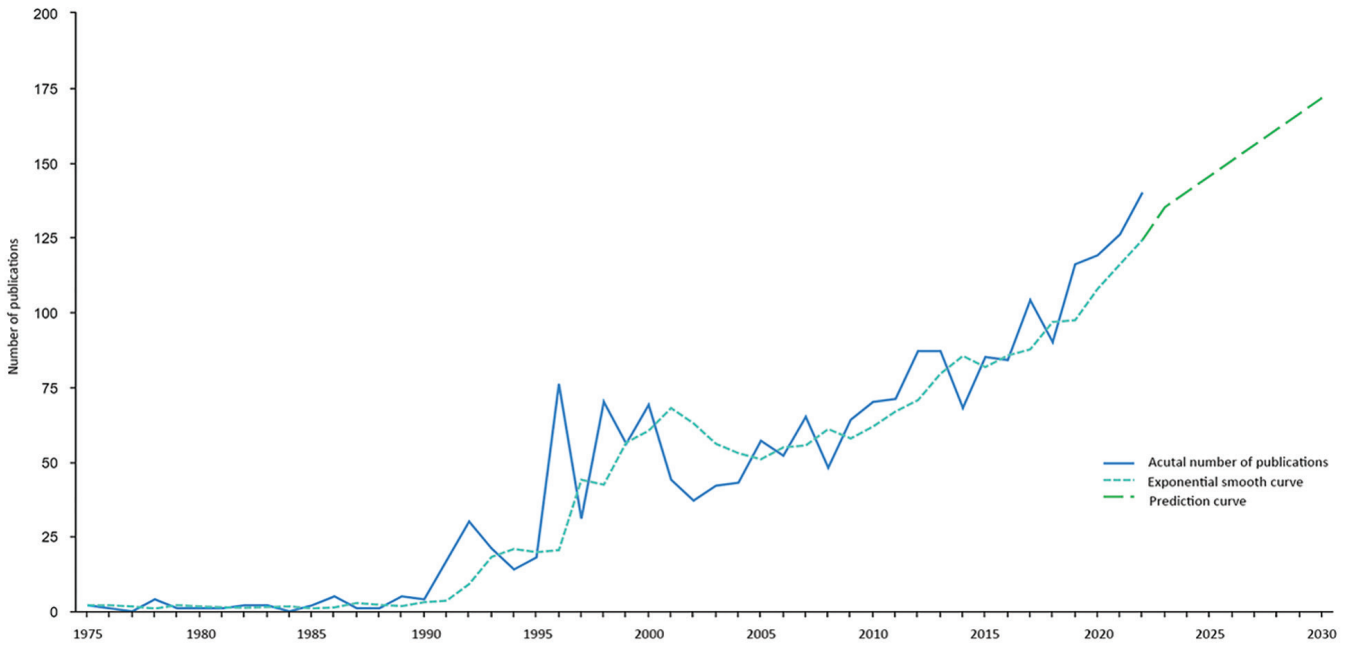

Fig. 2. Diagram showing the changes of annual number of publications. The curve was fitted with the exponential smooth estimation model.

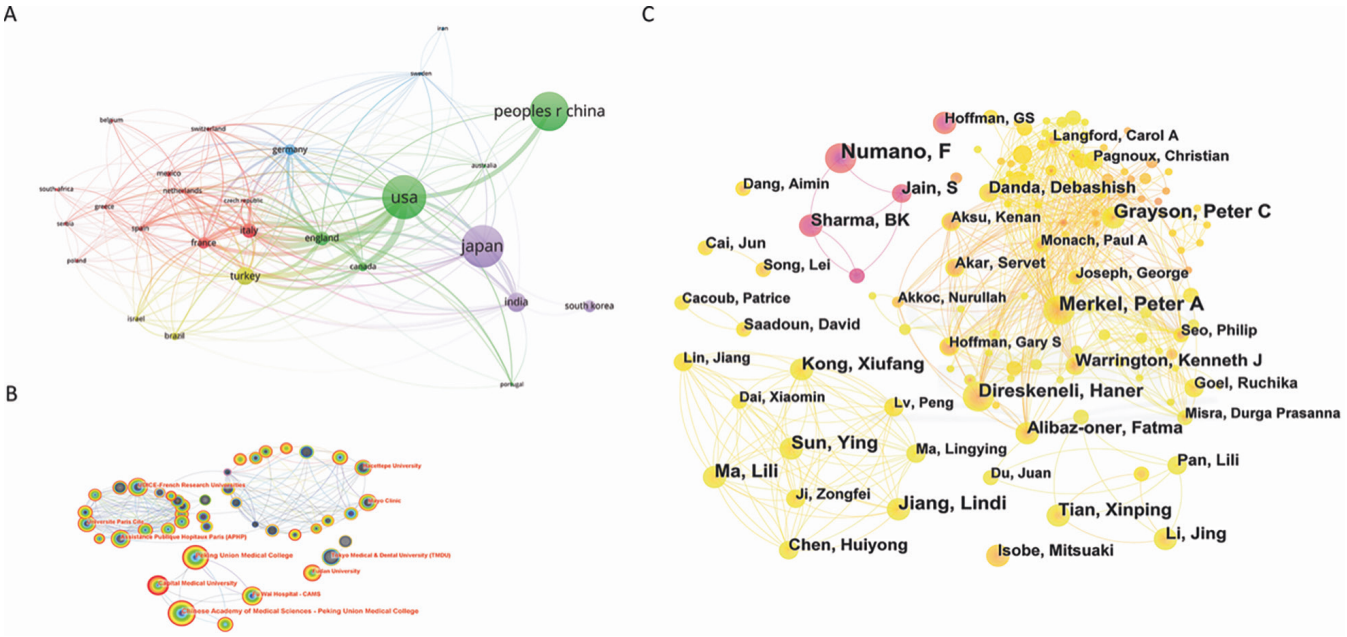

Fig. 3. A: Network diagram of cooperative relationships between countries. **B**: Institution cooperation network. The nodes in the map represent the institutions. The larger the nodes, the larger the scientific output. **C**: Author cooperation network. The nodes in the map represent authors and the lines between nodes denote the collaborative relationships.

891 nodes and 1937 links with a density of 0.0049. Widespread intensive author collaborations have not formed, as indicated by the findings that the intermediary centrality for almost all authors were zero. Author analysis demonstrated that Numano (Tokyo Medical & Dental University) contributed the most in this field, with a total of 38 articles, followed by Merkel (University of Pennsylvania, n=31), and Jiang (Fudan University, n=29).

Productive journals

These 2221 original articles were published in 571 academic journals, of which 95 journals published ≥5 papers and 18 journals published ≥20 papers. The journal with the most publications in the field of TAK is *Clinical and Experimental Rheumatology* (n=102), followed by *International Journal of Cardiology* (n=96), *Clinical Rheumatology* (n=79), *Journal of Rheumatology* (n=66) and *Rheumatology* (n=52).

Highly cited documents

Citation analysis showed that 1068 documents have been cited ≥10 times and 98 have been cited ≥100 times. The top 10 highly cited literature were listed in Table I, with the highest and lowest number of citations of 1593 and 291, respectively. Of note, the top 3 most highly-cited articles were related to the classification criteria and disease activity assessment of TAK.

Co-cited references

Co-citation, defined as the simultaneous appearance of two related articles in the reference list of a third article, may provide insight into the most important and influential work in a given field. The included 2221 documents cited 26588 references in all, and the top 10 co-cited references were presented in Table II.

The cluster analysis of co-cited references (Fig. 4) showed that these references can be categorised into 5 informative clusters, including interleukin-6 (no. 1), adalimumab (no. 3), colour Doppler ultrasonography (no. 4), stents and prosthesis (no. 6) and anti-endothelial cell antibodies (no. 7), in addition to the apparent clusters of large-vessel vasculitis (no. 0), aorta (no. 2), TAK (#5) and aortic arch arteritis (no. 8).

Analysis of keyword occurrence, clustering and bursts

Keywords serve as thematic summary of an article, and analysis of keywords would decipher document central ideas. Keyword co-occurrence analysis (Fig. 5A) created by the CiteSpace suggested hypertension, disease activity, inflammation, tocilizumab, aneurysm, angiography, magnetic resonance imaging, angioplasty, children, epidemiology, and pregnancy were keywords with frequency over 20. Cluster analysis (Fig. 5B) showed that the high-frequency keywords can be grouped into 10 significant clusters, with a modularity Q score of 0.5375 and the weighted mean silhouette value of 0.8752. The research directions of TAK can be summarised with cluster no. 0, cluster no. 1, cluster no. 2, cluster no. 3 and cluster no. 8 suggesting TAK itself; cluster no. 4 was related to the manifestation and complication of TAK; cluster no. 5 and cluster no. 9 were classified as the imaging diagnosis and treatment for TAK; cluster no. 6 and cluster no. 7 were related to the pathogenesis and disease activity of TAK.

Keyword bursts refer to a significant increase in the frequency of keywords and thus attention within a certain period and can be considered as indicators of research frontiers. As outlined in Figure 5C, a total of 48 keyword bursts were detected. In the 1990-2015, research on TAK were predominantly focused on the histologic changes, imaging diagnosis and evaluation, and treatment with steroid or necrosis fac-

Table I. Top 10 highly-cited articles in the field of Takayasu's arteritis.

Rank	Author	Year	Article title	Journal	Citations
1	Arend *et al*.	1990	The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis	Arthritis Rheum	1593
2	Kerr *et al*.	1994	Takayasu arteritis	Ann Intern Med	1356
3	Ozen *et al*.	2010	EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria	Ann Rheum Dis	797
4	Hall *et al*.	1985	Takayasu arteritis. A study of 32 North American patients	Medicine (Baltimore)	547
5	Ozen *et al*.	2006	EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides	Ann Rheum Dis	498
6	Hata *et al*.	1996	Angiographic findings of Takayasu arteritis: new classification	Int J Cardiol	386
7	Hoffman *et al*.	2002	A multicentre, randomised, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis	Arthritis Rheum	374
8	Meller *et al*.	2003	Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI	Eur J Nucl Med Mol Imaging	328
9	Maksimowicz-mckinnon *et al*.	2007	Limitations of therapy and a guarded prognosis in an American cohort of Takayasu's arteritis patients	Arthritis Rheum	327
10	Hoffman *et al*.	2004	Anti-tumour necrosis factor therapy in patients with difficult to treat Takayasu's arteritis	Arthritis Rheum	291

Table II. Top 10 co-cited references in the field of Takayasu's arteritis.

Rank	Author	Year	Article title	Journal	Citations
1	Arend *et al*.	1990	The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis	Arthritis Rheum	857
2	Kerr *et al*.	1994	Takayasu arteritis	Ann Intern Med	742
3	Lupiherrera *et al*.	1977	Takayasu's arteritis. Clinical study of 107 cases	Am Heart J	332
4	Hata *et al*.	1996	Angiographic findings of Takayasu arteritis: new classification	Int J Cardiol	267
5	Hall *et al*.	1985	Takayasu arteritis. A study of 32 North American patients	Medicine (Baltimore)	241
5	Johnston *et al*.	2002	Takayasu arteritis: a review	J Clin Pathol	194
6	Maksimowicz-mckinnon *et al*.	2007	Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients	Arthritis Rheum	187
7	Jennette *et al*.	2013	2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides	Arthritis Rheum	185
8	Hunder *et al*.	1990	The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis	Arthritis Rheum	152
9	Subramanyan *et al*.	1989	Natural history of aortoarteritis (Takayasu's disease)	Circulation	143
10	Misra *et al*.	2013	Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010)	Rheumatology (Oxford)	136

tor. By comparison, the research frontiers evolved toward double-blind multicentre clinical trials, disease activity evaluation and cytokines in the latest 3–5 years in the field of TAK.

Discussion

This bibliometric study comprehensively analysed the research status, hotspots and future frontiers in the field of TAK. The absolute number of annual publications showed discernible rapid increase after year 1990, which may be related to the fact that the criteria for the classification of TAK established by the American College of Rheumatology has been released (13). This classification criteria have laid solid foundations for the study of TAK and fuelled ongoing researches.

Of note, analysis of countries showed that the USA lead the research of TAK in terms of centrality and total publication outputs, despite TAK incidence in the USA is relatively much smaller than the Silk Road countries, such as China, Japan and Turkey (14). Although 4 of the top 5 leading institutions were based in China, their external collaborations with alien institutions were

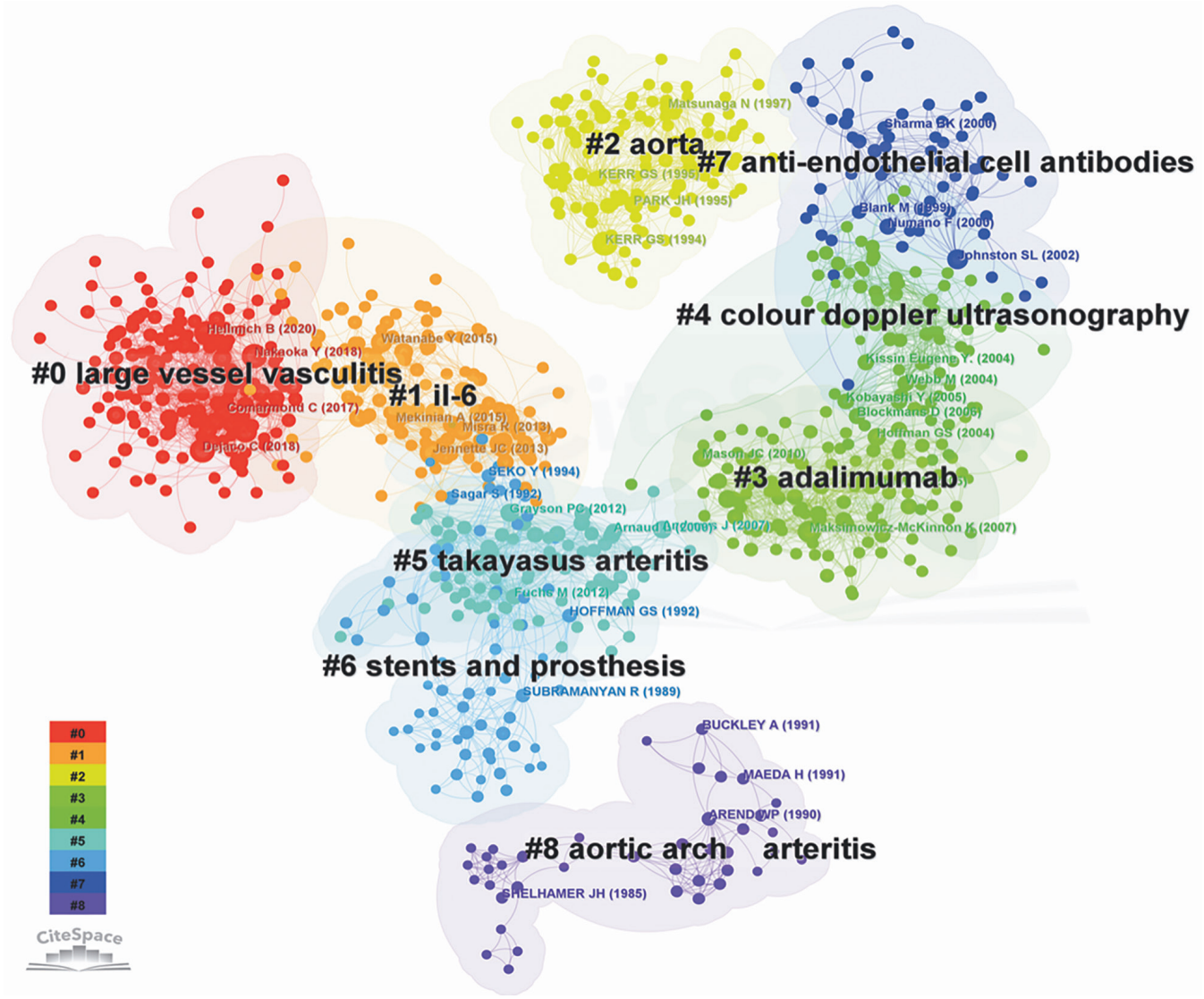

Fig. 4. Cluster analysis of co-cited references by CiteSpace. Those with similar themes were clustered into the same group.

scarce. This finding was also supported by author analysis demonstrating that diverse research groups are active in this field and no widespread author collaborations have formed. Therefore, strengthening international cooperation remains imperative to further promote the development of TAK research.

Most of the TAK researches were published in rheumatology journals and only a minority were in cardiology and vascular journals. Therefore, potential contributors are advised to pay attention to these journals for manuscript submission. In the evaluation of publications on the overall number of citations, the study that received the most citations was determined to be that published by Arend *et al*. (13), in which the classification criteria of TAK was proposed. Specifically, 3 of the 6 criteria, including age at onset ≤40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference >10 mmHg, bruit over the aorta or the subclavian artery, and arteriogram abnormalities, were required for a diagnosis of TAK. This article has also been shown to be the most highly co-cited document, suggesting it is a core literature in this field. Notably, the second most cited and co-cited document tend to be the same article by Kerr *et al*. (15), in which the authors proposed that patients with fulfilment of ≥2 of the following 4 criteria, including 1) fever and arthralgia, 2) elevated erythrocyte sedimentation rate, 3) typical angiographic findings, and 4) clinical manifestations of vascular ischemia and inflammation, should be categorised as "active".

Co-cited references are an analysis of document coupling that provides insight into the key concepts, methods or experiments in a discipline. The cluster analysis of co-cited references in TAK demonstrated that anti-endothelial cell antibodies, interleukin-6, adalimumab, colour doppler ultrasonography, and stents and prosthesis were the main clusters. Although the exact etiopathogenesis of TAK remains unknown, studies have shown that 18 out of the 19 TAK patients were tested positive for anti-endothelial cell antibodies (16). Recent studies suggested that the endothelial protein C receptor and scavenger receptor class B type 1 are the novel endothelial autoantigens in anti-endothelial cell

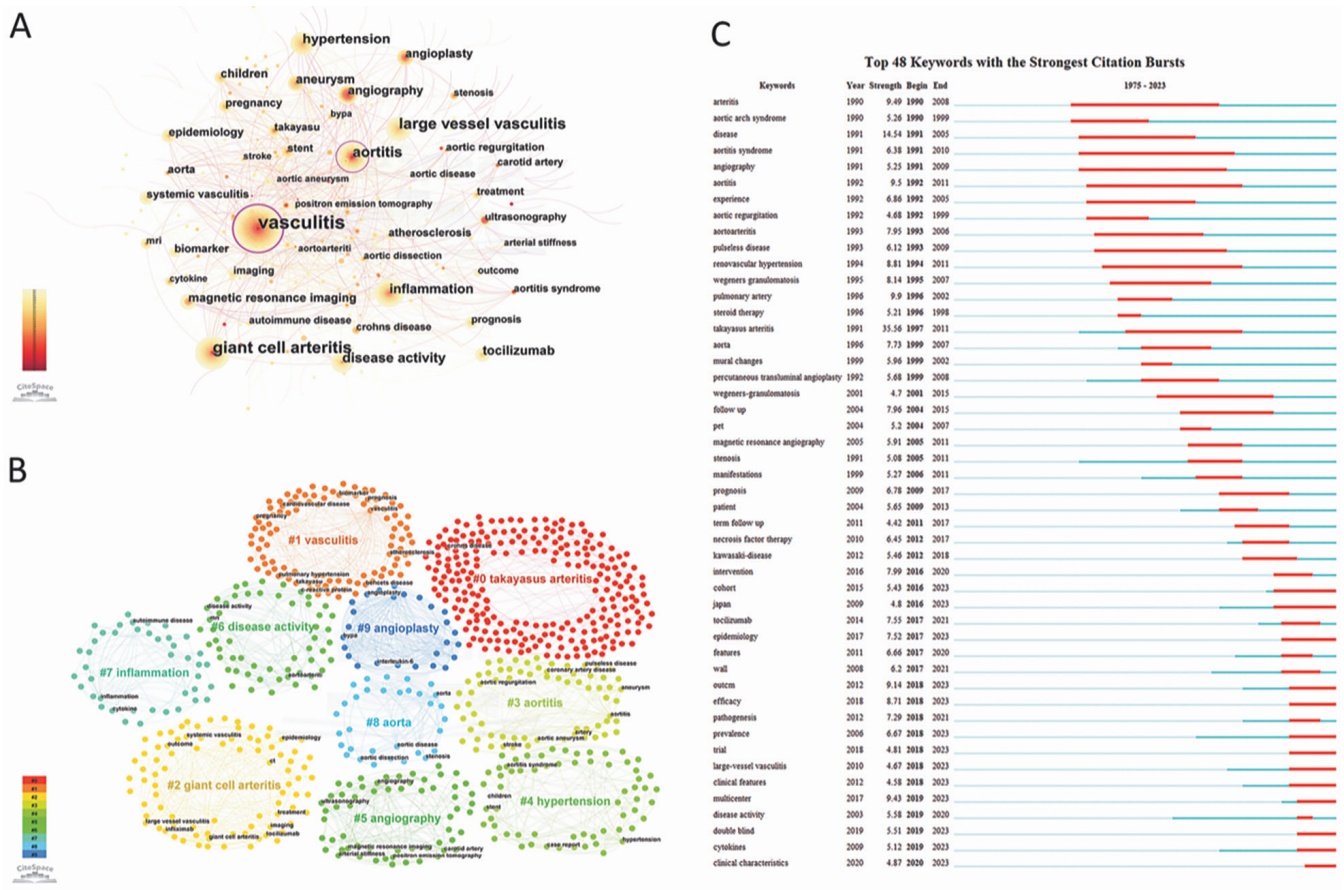

Fig. 5. A: Keyword co-occurrence network diagram. The size of the node is positively correlated with the keyword frequency and those with purple ring are considered to be pivotal points. **B**: Keywords with similar themes were clustered into various groups. **C**: Keyword burst detection.

antibodies-associated TAK by inducing vasculopathy (17). The cytokine interleukin-6 has been implicated in the pathogenesis of TAK by promoting inflammation and vascular fibrosis (18). Consequently, there are fervent interests in the rheumatology community to apply tocilizumab, an interleukin-6 inhibitor, for treating TAK. An earlier multi-centre study investigating tocilizumab in 46 TAK found that tocilizumab is superior to disease-modifying anti-rheumatic drugs in terms of efficiency to prevent TAK relapse (19). A recent meta-analysis that comprised 19 studies with 466 TAK patients suggested that tocilizumab would significantly reduce blood inflammatory biomarkers, decrease steroid use and improve clinical outcomes with minimal side effects (20).

Adalimumab is a monoclonal antibody targeting tumour necrosis factor-, which has been demonstrated to be elevated in patients with TAK and implicated in its pathogenesis (21). The reported efficacy of adalimumab for TAK are consistent, with almost all reported studies found it could induce and sustain remission, and it had equivalent efficacy, relapse and drug retention rate with interleukin-6 inhibitors (22-25). In addition, some even reported that adalimumab combined with glucocorticosteroids and methotrexate might be efficacious than tocilizumab combined with glucocorticosteroids and methotrexate in patients with severely active TAK (26). Colour doppler ultrasonography and stents/prosthesis belongs to the category of TAK diagnosis and treatment. An analysis of 116 TAK patients showed that the 5-year and 10-year vascular primary patency rate for open surgery were 70.5% and 48.8%, which is comparable to 57.5%, and 31.8% in the endovascular treatment group (27).

As a result of cluster analysis in the evaluation of keywords, 4 categories related to TAK manifestation and complication, imaging diagnosis and treatment, pathogenesis and disease activity were noted. Therefore, the current studies in TAK research are diverse, advanced and encompass almost all the aspects. Among the 48 identified keyword bursts, we found that the current research frontiers were double-blind multi-centre clinical trials and cytokines. Given that TAK is a rare disease, cooperation between institutions is often necessary for clinical trials. Recently, the result of a multi-centre clinical trial that assessed the efficacy and safety of Janus kinase inhibitors in TAK has been reported (28). Another research frontier in TAK would be cytokines, which have been proposed as serum biomarkers or predictors for disease pathogenesis, relapse and treatment outcomes (29-30). More importantly, biological agents targeting cytokines have been increasing tested for the treatment of TAK. For instance, ustekinumab (monoclonal antibody targeting the subunit common to interleukin-12 and interleukin-23) and secukinumab (a fully human monoclonal antibody that selectively targets

interleukin-17A) are being currently investigated in patients with TAK with overall promising results (31-32).

The current study suffers from several limitations that should be acknowledged. First, only articles published in English were retrieved from the sole source of SCIE-WOS. However, the PubMed database is not suitable for citation and co-citation analysis, and the Scopus database does not index some journals. Second, the continuously updated indexation would probably lead to changes in the results. At last, the documents were not individually assessed for content quality.

In conclusion, this bibliometric analysis showed that chronologically the area of TAK research is growing rapidly. The USA is determined to be the leader in research on the subject of TAK. Widespread institutional and author collaboration has to be fostered in the future to fuel TAK research and information dissemination. Moreover, anti-endothelial cell antibodies, interleukin-6, adalimumab, colour doppler ultrasonography, and stents and prosthesis were the main research areas in TAK. Double-blind multicentre clinical trials, disease activity evaluation and cytokines were at the forefront of TAK research. These findings provide insight into the current research status and guide future directions for TAK research.

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