

Scientific Knowledge of Rheumatoid Arthritis: A Bibliometric Analysis from 2011 to 2020

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Background: Recently, research on rheumatoid arthritis (RA) has made rapid progress and grown rapidly. It is a challenge to comprehensively understand RA research and hotspots. The aim of this study was to explore the current status and research trends of RA through bibliometric analysis and to provide directions for future development.

Methods: Publications on RA from 2011 to 2020 were retrieved from the Web of Science Core Collection database (WoSCC). VOSviewer, CiteSpace and online bibliometric platform were used to analyze publication characteristics, including countries, institutions, journals, authors, core references, and keywords.

Results: A total of 17,037 publications were included. The publications steadily increased over the 10 years. The United States (3648 publications), with the largest proportion of publications and citations, was the largest contributor. Karolinska Institutet (508) and Annals of the Rheumatoid Disease (763) were the most active institution and journal, respectively. Emery P (193) and Tanaka Y (193) were the most prolific authors, and Smolen JS ranked first among the cited authors. The most cited reference focused on recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs. A co-occurrence network analysis revealed four highly connected clusters of keywords in RA research, including etiology, pathology, prognosis, biomarkers and treatment of RA.

Conclusion: The present study shows a systematic and comprehensive overview of the RA-related research in the past 10 years. Clinical trials on the long-term efficiency and safety of JAK inhibitors and other novel targeted drugs may be the potential research directions for future study in this field.

Keywords: rheumatoid arthritis, bibliometric analysis, pain, publications, research trends

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that affects approximately 0.5–1% of the general population worldwide and is characterized by joint swelling, pain and bone erosion.¹ Patients with RA suffer from ongoing pain in spite of disease remission.² Adults with early-stage RA indicated a 39% prevalence of work disability after 10 years.³ The ongoing pain and high disability rate of RA impose a severe economic cost and increased burdens on patients and society. It is vital to accurately grasp the research trends of RA. Given the rapid development and substantial growth of research on RA, a comprehensive understanding of RA research and hot spots is a challenge.

Bibliometrics is an important method to estimate the influence of publications and help evaluate emerging trends in the field of science.⁴ The bibliometric analysis can reveal detailed information about the collected publications, such as publication type, countries, institutions, journals, authors and keywords.^{5,6} Several articles on bibliometric analysis of RA have been reported. A bibliometric analysis of the field of RA-related depression was conducted by Wang et al.⁷ Zhang et al reported a bibliometric analysis of the RA-related interstitial lung disease.⁸ However, the bibliometric analysis of research hotspots and keywords related to RA is largely unknown.

In this study, we conduct a comprehensive scientific knowledge of RA-related publications within the past 10 years (from 2011 to 2020), focusing on the current status and research trends in RA. Our results also present prospects for the future development of the field.

Methods

Search Strategy and Data Collection

With more than 12,000 influential academic journals, Web of Science (WoS, Clarivate Analytics, Philadelphia, PA, USA) is regarded as the authoritative database to provide global academic information.⁹ WoS is widely accepted for bibliometric analysis in scientific fields. We retrieved and downloaded the data from the WoS Core Collection (WoSCC) database on Sep 20, 2021. The search strategy was as follows: TI = ("rheumatoid arthritis") AND PY = (2011–2020). The language type was limited to "English". Only articles and reviews were included. 17,044 publications were retrieved. Then, the full records and cited references of these publications were downloaded in.txt format and checked by two researchers independently. Finally, a total of 17,037 publications were included. And the up-to-date gross domestic product (GDP) and population information were retrieved from the Word Bank website (<https://data.worldbank.org.cn/>).

Data Analysis

We analyzed multi-dimensional aspects of publications in RA research, including countries, institutions, journals, authors, keywords and hot spots. And we used kinds of indicators to assess the papers. Generally speaking, the article count reflects the productivity of agencies and the cited count represents the influence of papers.¹⁰ The Hirsch index (H-index) is uncritically regarded as an effective tool to measure the quality of science.¹¹ Impact factor (IF) obtained from the latest edition of Journal Citation Report (JCR) has been known as the leading method to assess the prestige of a journal.¹² As convenient tools, VOSviewer (Leiden University, Leiden, Netherlands) and CiteSpace (invented by Prof. Chaomei Chen) can visualize bibliometric information by colorful nodal networks and display the frontier of disciplinary development.¹³ We used VOSviewer 1.6.15 and CiteSpace 5.8.R2 to visualize bibliometric networks. An online bibliometric platform (<https://bibliometric.com/>) was also used to conduct the collaboration analysis of countries. Statistical analysis was performed using SPSS (IBM SPSS Statistics 24.0, Inc., Chicago, IL, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). Pearson's correlation was used to determine the strength of correlation between continuous variables, $P < 0.05$ was regarded as statistically significant.

Results

Publishing Trend

The overall flow of the study is summarized in Figure 1A. As shown in Figure 1B, the publications steadily increased in the 10-year period from 1310 in 2011 to 2126 in 2020, revealing that the research of RA gradually became a hot spot. The document counts displayed a linearly increasing trend ($R^2 = 0.9884$). The publishing trends of the top 5 productive countries were demonstrated by a bar chart (Figure 1C). The United States (USA) kept the largest proportion of publications from 2011 to 2019. There was a slight decrease in output from the Netherlands, a slight increase in output from the United Kingdom (UK) and Japan. The publications in China exponentially increased in recent 10 years ($R^2 = 0.9901$). Then, the collaboration network of countries is displayed in Figure 1D. The collaborative relationships among countries were mainly confined to American, European, and East Asian areas. The USA collaborated most closely with the UK, Netherlands and Canada.

Contribution of Countries

Among the publications, 123 different countries/regions participated in RA research over the past 10 years. The top 10 most contributive countries are listed in Table 1. Nine of them are developed countries. Among the countries, the USA represented the largest share of publications ($n = 3648$, 21.41%), followed by China ($n = 2497$, 14.65%) and the UK ($n = 2210$, 12.97%). For the cited counts, documents from the USA were cited 120,369 times, followed by the UK (65,664) and Netherlands (50,254). Also, the USA obtained the highest H-index (132), followed by the UK (107) and Netherlands (97).

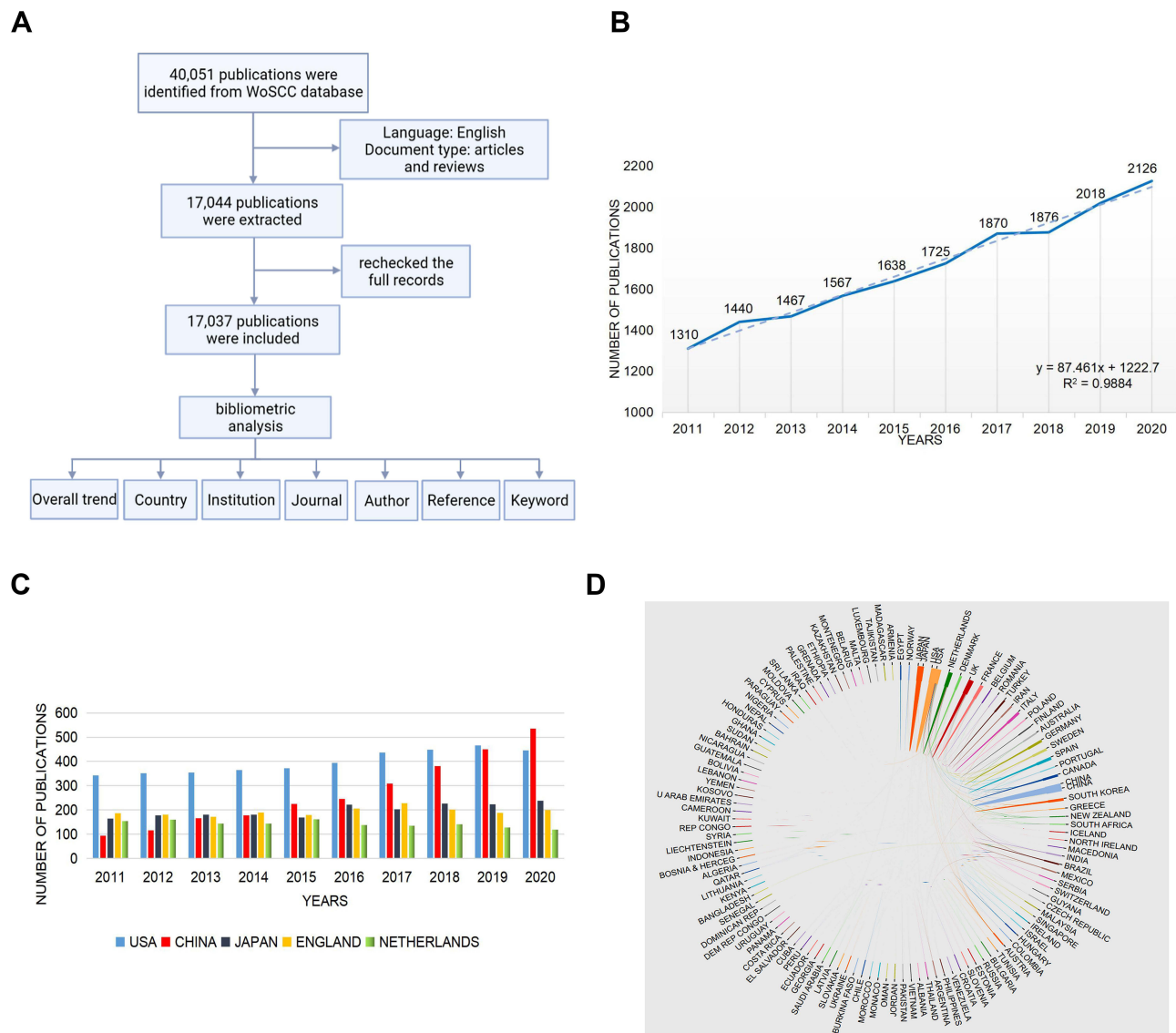


Figure 1 (A) Flow diagram of the publications selection and data analysis; (B) growth trends of publications on rheumatoid arthritis from 2011 to 2020. The increased frequency and r square were shown; (C) publishing trends of the top 5 productive countries; (D) the network map of cooperation between countries on rheumatoid arthritis.

The USA far exceeded the other countries in publication counts, cited counts and H-index. However, after standardization by GDP, Sweden ranked first with 1505.86 papers per trillion GDP. With 1449.89 papers per trillion GDP, the Netherlands occupied the second position. And the UK was in third place with 800.78 papers per trillion GDP. The Netherlands published the largest number of publications (75.97 papers) after standardization by population size, followed by Sweden (43.55 papers) and the UK (32.92 papers). In addition, the correlation analysis results showed that publication numbers were highly correlated to GDP ($r = 0.923$, $P < 0.001$), while publication counts for each country and their population counts had no significant correlation ($r = 0.536$, $P = 0.110$).

Distribution of Institutions

As shown in Table 2, all the most prolific institutions are located in the USA and Europe. Karolinska Institutet had the highest publication numbers (508) and H-index (74), whereas Leiden University had the highest cited counts (24,739). The co-authorship map of institutions is displayed in Figure 2. Co-authorship analysis can present similarity relationships among institutions based on the number of co-authored publications.¹⁴ The size of the nodes is determined by the citation

Table 1 The Top 10 Most Contributive Countries in Rheumatoid Arthritis from 2011 to 2020

Rank	Countries	Publication Counts	% of 17,037	Number of Papers per Trillion GDP	Number of Papers per Million People	Cited Counts	H-Index
1	USA	3648	21.41	174.10	11.07	120,369	132
2	China	2497	14.65	169.60	1.77	39,548	65
3	UK	2210	12.97	800.78	32.92	65,664	107
4	Japan	1800	10.56	355.89	14.30	33,530	70
5	Netherlands	1325	7.77	1449.88	75.97	50,254	97
6	Germany	927	5.44	241.00	11.14	37,372	85
7	Italy	852	5.00	451.25	14.31	24,334	64
8	France	829	4.87	315.17	12.30	32,148	78
9	Sweden	815	4.78	1505.86	43.55	30,792	78
10	South Korea	810	4.75	494.54	31.53	20,172	64

Table 2 The Top 10 Most Prolific Institutions in Rheumatoid Arthritis from 2011 to 2020

Institutions	Country	Publication Counts	Cited Counts	H-Index
Karolinska Institutet	Sweden	508	24,564	74
Leiden University	Netherlands	497	24,739	72
Harvard University	USA	490	21,619	70
LUMC	Netherlands	475	24,318	72
University of California System	USA	425	23,443	70
Brigham and Women's Hospital	USA	414	18,186	67
APHP	France	399	21,000	64
INSERM	France	383	13,647	53
University of Copenhagen	Denmark	343	10,635	48
The University of Manchester	England	337	17,784	61

Abbreviations: LUMC, Leids Universitair Medisch Centrum; APHP, Assistance Publique Hopitaux Paris; INSERM, Institut national de la santé et de la recherche médicale.

numbers of the publications. The more citations the institutions, the larger the nodes. The color bar in the bottom right corner of the visualization indicated the average appearing year of institutions. With a blue node, Harvard University was considered a relatively early participant in RA fields. In relative terms, researchers at the University of Copenhagen, marked with red color, were regarded as new entrants in this field.

Analysis of Journals

Table 3 lists the top 10 productive journals. Retrieved articles were published in 1682 journals. A total of 6047 publications (35.48%) were published in the top 10 journals. With the highest publications (763), cited counts (50,703) and IF (19.103), *Annals of the Rheumatoid Diseases* was the most contributive journal. Though *Rheumatology* did not rank in the top 3 in publication counts, the IF and H-index of the journal were far exceeded than the other 8 journals. Among these journals, 2 journals were belonged to Q1. The co-citation analysis of journals is shown in **Figure 3A**. The density map displayed journals with a minimum of 1000 citations. The color of each node denotes its frequency of co-citation. The redder the node is, the more co-citations in the journal. *Annals of the Rheumatoid Diseases* (68,541) ranked the first, followed by *Arthritis and Rheumatism* (39,774) and *Journal of Rheumatology* (28,256), suggesting that the articles published in these journals drew attention from researchers.

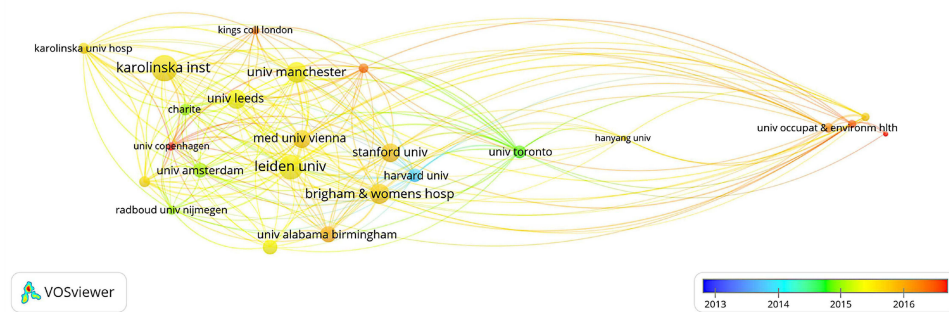


Figure 2 The co-authorship map of institutions.

Analysis of Authors

A total of 48,363 authors were filtered out in this study. The top 10 productive authors are displayed in Table 4. They reported 1640 articles, accounting for 9.63% of the total number of publications, making great achievements and academic values in the study of RA. Emery P and Tanaka Y had the highest publication numbers of 193. The articles of Smolen JS received the most citation of 14,651 and the highest H-index of 56, followed by Emery P (citation:13,747, H-index:55) and Van Der Heijde D (citation:11,280, H-index:45). Besides, Figure 3B demonstrates the co-authorship analysis of the authors. The size of the nodes is related to the publication numbers of the authors. The larger the nodes, the more productive the authors. Lines and distances between the nodes represent links. More lines and shorter distances stand for closer cooperation between the two authors. Emery P, Smolen JS and Van Der Heijde D had a deep collaboration. Also, diverse clusters were marked by different colors. Five clusters were presented in the network. Emery P, Smolen JS, Tanaka Y, Takeuchi T, Curtis JR, Crowson CS and Bae SC are core authors in these clusters, respectively.

Analysis of References

The basic information of the top 10 articles with the maximum citations is shown in Table 5. These articles were published between 2010 and 2017 and were mainly reported in *Annals of The Rheumatic Diseases*, which was the most influential journal in the period. Most of these articles were related to recommendations for the management of RA. All the citations of articles were more than 300 times, while only one article was more than 700 times (Smolen JS 2014). The most cited article was written by Smolen et al on recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs published in 2014.

Table 3 The Top 10 Productive Journals in Rheumatoid Arthritis

Rank	Journal	Publication Counts	Cited Counts	H-Index	IF (2020)	JCR
1	Ann Rheum Dis	763	50,703	109	19.103	Q1
2	Clin Rheumatol	724	7637	34	2.980	Q3
3	Arthritis Res Ther	713	18,498	60	5.156	Q2
4	Rheumatology	618	17,174	61	7.580	Q1
5	Rheumatol Int	616	7678	37	2.631	Q4
6	J Rheumatol	591	13,133	52	4.666	Q2
7	Mod Rheumatol	542	5622	33	3.023	Q3
8	Clin Exp Rheumatol	526	6856	34	4.473	Q2
9	Arthrit Care Res	519	15,838	56	4.794	Q2
10	PLoS One	435	8864	43	3.240	Q2

Abbreviations: Ann Rheum Dis, Annals of the Rheumatic Diseases; Clin Rheumatol, Clinical Rheumatology; Arthritis Res Ther, Arthritis Research & Therapy; Rheumatol Int, Rheumatology International; J Rheumatol, Journal of Rheumatology; Mod Rheumatol, Modern Rheumatology; Clin Exp Rheumatol, Clinical and Experimental Rheumatology; Arthrit Care Res, Arthritis Care and Research.

Table 4 Authors Contributed to Publications on Rheumatoid Arthritis from 2011 to 2020

Authors	Country	Publication Counts	Cited Counts	H-Index
Emery P	England	193	13,747	55
Tanaka Y	Japan	193	5914	42
Takeuchi T	Japan	188	7101	42
Huizinga TWJ	Netherlands	166	8767	46
Bae SC	South Korea	165	4669	29
Yamanaka H	Japan	162	5039	36
Curtis JR	USA	158	8380	42
Smolen JS	Austria	155	14,651	56
Ostergaard M	Denmark	135	4211	34
Van Der Heijde D	Netherlands	125	11,280	45

Table 5 The Top 10 Most Cited Articles in Rheumatoid Arthritis

No.	First Author	Title	Cited Times	Journal	Year
1	Smolen JS ¹⁵	EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.	780	Ann Rheum Dis	2014
2	Smolen JS ¹⁶	EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update.	679	Ann Rheum Dis	2017
3	Singh JA ¹⁷	2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.	557	Arthritis Rheumatol	2016
4	Aletaha D ¹⁸	2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.	554	Arthritis Rheum	2010
5	Smolen JS ¹⁹	EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs.	476	Ann Rheum Dis	2010
6	Singh JA ²⁰	2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis.	462	Arthritis Care Res	2012
7	McInnes IB ²¹	The pathogenesis of rheumatoid arthritis.	455	N Engl J Med	2011
8	Smolen JS ²²	Treating rheumatoid arthritis to target: recommendations of an international task force.	428	Ann Rheum Dis	2010
9	Aletaha D ²³	2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.	362	Ann Rheum Dis	2010
10	Smolen JS ²⁴	Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force.	325	Ann Rheum Dis	2016

Abbreviations: Ann Rheum Dis, Annals of the Rheumatic Diseases; Clin Rheumatol, Clinical Rheumatology; Arthritis Res Ther, Arthritis Research & Therapy; Rheumatol Int, Rheumatology International; J Rheumatol, Journal of Rheumatology; Mod Rheumatol, Modern Rheumatology; Clin Exp Rheumatol, Clinical and Experimental Rheumatology; Arthritis Care Res, Arthritis Care and Research.

(1070) and “remission” (791), and in cluster 4, the high-associated keywords were “methotrexate” (1887), “therapy” (1678), “double-blind” (1514), “modifying antirheumatic drugs” (1091), and “efficacy” (937).

The keyword bursts were analyzed using Citespace (Figure 4B). The red line segments indicated the burst time of a subject, the blue line represented relative unpopularity. During the period from 2011 to 2020, “revised criteria” had the strongest citation bursts (22.14), followed by “trial” (13.9) and “microRNA” (13.72). “revised criteria” became important from 2011 to 2014. “Juvenile Idiopathic Arthritis” and “mRNA” were the keywords with the most extended duration (5 years). In 2020, ten keywords kept drawing attention.

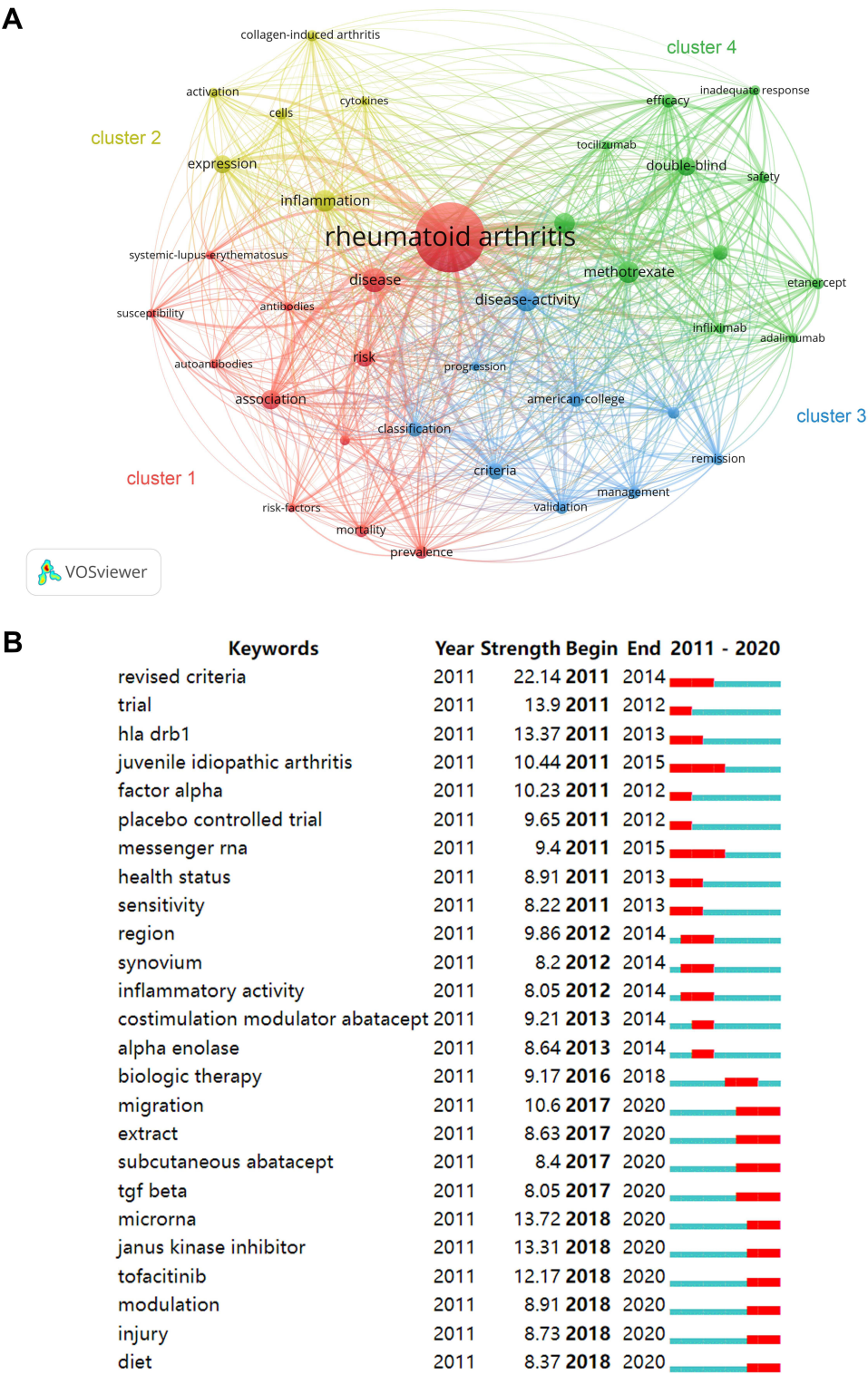


Figure 4 (A) The co-occurrence network of keywords. Different color nodes belonged to diverse clusters. **(B)** The top 25 keywords with the strongest citation bursts.

Discussion

RA is a worldwide chronic inflammatory disease. Several studies have presented the characteristics of research in RA field. Zhong et al conducted a bibliometric analysis focused on prolific countries and journals to reveal the research productivity in RA between 2017 and 2019.²⁵ Yin et al analyzed the top 100 cited articles in RA from 1985 to 2017.²⁶

The present study extracts publications on RA from 2011 to 2020 and systematically summarizes the current status and hotspots in RA. In total, 17,037 publications on RA were retrieved. The number of annual global publications on RA research was steadily increased.

With the largest publications and citations, the USA made a great contribution in RA research, as mentioned in the previous study.²⁵ GDP is the most commonly used indicator to measure the economic activity of a country. The USA had the highest GDP in the world.²⁷ In addition, Sweden is the most productive country after normalization by the GDP and population counts. According to World Health Organization, health care expenditure as a share of GDP was 11.37% in Sweden in 2020 (<https://www.who.int/>). Based on our correlation results between publication counts and GDP, sufficient fund is a powerful guarantee of scientific study. Of note, the papers in China increased at a very rapid speed and the number of papers exceeded that in the USA in 2020. However, China still had a wide gap in the centrality of publications.

In terms of institutions, the majority of the productive institutions were universities and medical centers located in the USA and Europe, revealing that these institutions are the main forms of research groups. As for journals, *Annals of the Rheumatoid Diseases*, with IF of 19.103, publication numbers of 763 and citations of 50,703, was absolutely the most contributive journal. For author analysis, Emery P and Smolen JS could be regarded as authorities in the field of RA. As exhibited in Figure 3B, these 2 excellent authors kept cooperating with each other. Though the publication counts in China ranked second in the world, no Chinese authors moved into the top 10. It is suggested that strengthening the communication and cooperation between the authors may be a viable method to improve the quality of study in China.

Yin et al reported the top 100 cited articles in RA from 1985 to 2017.²⁶ According to their work, most of the top 10 cited articles were clinical studies from 1988 to 2010. In our work, the top 10 cited articles mainly focused on the recommendations for the treatment and management of RA from American College of Rheumatology (ACR) or the European League Against Rheumatism (EULAR). A possible reason for the difference between the two studies may be related to the different time span of retrieved publications. Also, the quick update of recommendations suggested that the research of RA developed rapidly in the last decade. The highly frequent citation of recommendations also indicated that the treatment of RA made great progression, such as the invention of janus kinase (JAK) inhibitors.

Four highly connected research clusters were screened as the main research topics in this domain. In cluster 1 (epidemiology research), except for “rheumatoid arthritis” and “disease”, the main keywords were “association”, “risk”, “classification”, “prevalence”, and “mortality”. To date, the exact etiology of RA remains uncertain. Genetic and environmental factors are the potential cause of RA. More than 100 polymorphisms conferring disease risks have been identified in genetic studies, confirming the strong association of RA with MHC class II alleles and adaptive immunity.²⁸ Relevant environmental risk factors for RA are smoking, silica exposure, dust exposure, working in the cold, periodontitis and microbiota in the gut or lung.²⁹ In recent years, epigenetic modifications are considered as important factors of RA, including DNA methylation, histone modifications and noncoding RNA.³⁰

In cluster 2 (pathogenesis research), the frequently used keywords were “inflammation”, “expression”, “cells”, “collagen-induced arthritis”, and “activation”. As we all known, synovial inflammation is the hallmark of RA. Two pathogenetic changes in synovium occur in RA. First, a widespread influx of immune system cells infiltrate the synovial sub-lining.²¹ Synovial dendritic cells are activated by TLR ligands and migrate to lymph nodes. Then, mass naive T cells are stimulated and differentiated towards Th1 cells there, home to inflamed synovial tissue.³¹ Secondly, the tissue-resident macrophages and fibroblasts in the intimal lining are greatly increased.²¹ The macrophage-like synoviocytes produce a variety of pro-inflammatory cytokines, chemokines, reactive oxygen species or angiogenic factor.³² Fibroblast-like synoviocytes are promoted by the chemokines and invade to the cartilage surface.³³

In cluster 3 (diagnosis research), the prominent keywords were “disease-activity”, “criteria”, “classification”, “American-college” and “remission”, which indicated that the prognosis and management of RA was one of the research hot spots. In 2010, the ACR and EULAR updated the classification criteria for RA. In contrast to the criteria in 1987, newly characterized antibodies and acute-phase reactant levels were incorporated. The new version was more specific and adapted to the patients with early RA. Up to now, the goal of RA therapy is remission in a treat-to-target approach.¹⁶

In cluster 4 (clinical research), the high-associated keywords were “methotrexate”, “therapy”, “double-blind”, “modifying antirheumatic drugs”, and “efficacy”. The clinical research of RA is related to the treatment. Large amounts of double-blind randomized controlled trials (RCT) about drugs were reported in recent years. As the first-line therapy

for RA, methotrexate (MTX) is commonly used as controlled or combined drug in RCTs.³⁴ “Etanercept”, “infliximab”, and “adalimumab” frequently appear in the keywords. These biological agents with MTX were associated with statistically significant and relative clinically meaningful benefits in the outcomes (ACR50, HAQ scores, and RA remission rates) compared with MTX alone.³⁵

Keywords represent immediate information and potentially detect trending research themes in articles. We utilized keywords burst to track the research. An obvious boundary occurred in 2016. Before 2016, research concentrated on “revised criteria”, “trial” and “HLA-DB1”. The recent research place emphasis on “mircoRNA”, “JAKs inhibitor” and “tofacitinib”. The research trend of RA has been transformed from genetic factors and bDMARDs to epigenetic factors and targeted synthetic DMARDs the biological agents. Tofacitinib and Baricitinib are the first-generation JAK inhibitors. Preclinical studies showed that tofacitinib alleviated inflammation by attenuated JAK1/JAK3-mediated signaling of lots of pro-inflammatory cytokines.³⁶ Baricitinib selectively inhibits JAK1 and JAK2. Baricitinib inhibits the differentiation of B cells to plasmablasts, differentiation of naive CD4⁺T cells, and the phosphorylation of STAT transcription factors on T cells.³⁷ The invention of JAK inhibitors was the latest breakthrough in the treatment of RA. Whereas, more clinical trials are needed to explore the long-term efficiency and safety of JAK inhibitors and other novel targeted drugs.

However, our study has some limitations. First, due to the limitation of online bibliometric platform, we only extracted publications from WoSCC database. It may lead to publication bias. Second, papers from 2011 to 2020 were included in the present study. With the continuous updating of the publications, the findings of this study may have a certain lag.

Conclusion

This study summarizes the current status of RA-related publications from 2011 to 2020 through bibliometric methods. Clinical trials on the long-term efficiency and safety of JAK inhibitors and other novel targeted drugs may be the potential research directions for future study. Our findings can help scholars make sense of major research hot spots in RA and provide referential directions for RA research in the future.

Data Sharing Statement

The raw data can be directly obtained from the WoSCC and the Word Bank website.

Ethics Approval and Informed Consent

This study did not include any patient information. Thus, the requirement for ethics approval was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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