

Identifying emerging trends in rheumatoid arthritis research: A scientometric analysis

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Abstract

Background Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized as chronic and progressive with acute inflammatory attacks. RA is highly prevalent across all societies and over the past two decades there has been substantial effort to improve diagnostics and therapeutics.

Methods We searched for pertinent studies using CiteSpace and created maps to understand the intellectual structure of RA research. Pertinent studies over the past two decades were retrieved from Web of Science. Scientometric analysis in this study includes time distribution, cluster analysis, time-zones and time-lines of keywords, as well as burst detection.

Results Our analysis has revealed a steady upward trend in publications from 2010 until 2018 which perhaps reflects growing global concern and investment. While the etiology of RA appears unknown, there is a plethora of studies into pathological mechanisms, diagnostics and drug development through one of the phases of basic and clinical research. RA pathogenesis has been shown to involve immune cells, including T cells, B cells, macrophages and synoviocytes which have a key role in invasive synovium and joint inflammation. X-rays and blood testing can support differential diagnostics, and there are a number of treatments available which are selected depending upon RA staging.

Conclusions TNF- α , apoptosis, pathogenesis, and NF- κ B are the most frequently used terms across this specialism in 2020. These terms represent the new theoretical understanding and necessitates further research because they may guide patient selection and more individualised RA care.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized as chronic and progressive with acute inflammatory attacks. Unfortunately, even with treatment RA can eventually lead to joint tenderness, loss of functioning, and is associated with an high rate of disability. RA usually affects [joints](#) but can also cause osteoporosis and is associated with cardiovascular disease, depression, and cognitive difficulties.^[1] While the etiology of this heterogeneous disease remains unclear, it is thought to manifest through a combination of [genetic](#), lifestyle and environmental factors.^[2] Geneticists have identified an higher risk of developing RA associated with HLA-DR4 and PTPN22.^[3,4] Likewise, smoking positively correlates and is considered a significant risk factor.^[5] Recently, air pollution has been identified as a trigger for innate immune responses and in raising levels of proinflammatory cytokines.^[6]

The three phases of RA progression are *initiation* due to non-specific inflammation, *amplification* which is due to [T cell](#) activation, and *chronic inflammation* with tissue injury caused generally by the [cytokines IL-1](#), [TNF- \$\alpha\$](#) and [IL-6](#).^[3] Diagnostics include blood tests (e.g., rheumatoid factor and ACPA) and x-rays,^[7] combined with a classification criterion for identifying those at high risk of developing RA to a chronic state.^[8] [Disease-modifying antirheumatic drugs](#) (DMARD) are generally considered as the first line

intervention for RA with methotrexate most commonly prescribed, followed by sulfasalazine and leflunomide.^[9]

Despite recent developments in our understanding, diagnostics and treatment of RA there are few systematic reviews which intercalate basic medical knowledge with clinical research. Bibliometrics is an increasingly popular text mining tool which can be used to quantitatively analyse literature published within specialisms.^[10] Scientometrics, as this combined approach is known, also enables researchers to observe trends and identify prospective areas for future consideration.^[11] As such, we used the literature measurement software to conduct visual research and social network analysis of RA studies over the past two decades. The overarching goal is to gain insight into the current knowledge and theories but also to provide evidence based guidance for future research.

1. Research Design

1.1 Method

We chose CiteSpace 5.6R2, which is a scientific document metrology automation software. This tool obtains and generates graphic representations of the knowledge structure in different research fields.^[12] Scientometric visualizations in this report include time distribution, cluster analysis, time-zones and a time-line of keywords, as well as burst detection.

1.2 Data collection

We obtained data from the Web of Science Core Collection. In order to collect pertinent literature, this research was conducted according to the following screening conditions: 1) Topic = rheumatoid arthritis; 2) Timespan = 2001-2020; and 3) Web of Science Categories = experimental medical research. Consequently, we retrieved a total of 4,472 publications. The retrieved entries were exported from databases in "Full text" format, on February 12, 2020 and records included information on authors, titles, abstracts and references. Deduplication processing was performed on source data using software. Deduplication data were obtained as next analysis objects.

1.3 Research process

The analysis primarily includes an overview of literature analysis, research development analysis, and emerging research analysis which correspond to the intellectual base, academic structure, and research frontiers. We adopted a macro-to-micro strategy to analyse the field. Specifically, we first focused on publication trend analysis, co-citation clustering analysis and high-level literature summarisation to obtain an overview of the literature. Then, we analysed key word evolution stages and performed co-occurrence clustering analysis. Finally, we analysed keyword emergence in order to explore emerging areas in RA research.

2. Overview Of Research Base

2.1. The publishing trend of literature

As can be seen in Figure 1, the number of publications generally increased year-upon-year. However, this time-line can be divided into two distinct periods. From 2001 to 2010, the number of publications fluctuated with a gradual overall increase. This suggests that the interest RA research was relatively low with more limited funding. The second period from 2010 to 2018, suggests there was a rapid increase in funding which is represented by a substantial increase in RA-related research. More recently, there appears to be a dramatic decline since 2018 which maybe a cause for concern. This may mean researchers and contact research organisations feel we have reached the saturation threshold, although it may also suggest there has been a substantial decrease in global funding.

2.2. The analysis of co-citation cluster

To generate an understanding of the structure of this knowledge base, we analysed referencing through co-citation networking. Co-citations indicate that two articles appear together in the list of references within the third cited article.^[13]

The co-citation resulting network consisting of 400 nodes and 955 lines was constructed. The cluster map is provided below in Figure 2A. In the resulting clusters, our analysis determined there is a modularity Q of 0.8226 (>0.3) and a mean silhouette of 0.5295 (>0.5). This suggests that the knowledge structure strongly correlates and clustering information is valid.

As shown in Figure 2A, each cluster is rich in colour and closely related to other clusters which reveals a steadily increasing research trend during this period. Based on the clustering results, we further divided the cluster into three categories, as shown in the figure and described below.

(1) There are a lot of darker patches and clustering labels which reveals that most research in this category are in the early stages and involve several aspects within the This represents a broad exploration period of RA research.

(2) There is a small time interval between the first and second categories, and clustering results are closely distributed. The second level of clustering labels are mainly related to osteoarthritis treatment. As one can see from the enlarged intersection that there is an important link between the two categories. McInnes and Schett (2007) focused on the effect of cytokines in the pathogenesis of RA and found an imbalance between pro-and anti-inflammatory cytokine activities.^[14] They also uncovered cytokine-mediated articular destruction and connected RA treatment to the development of

(3) The colour patches of the third category are lighter and clustering labels are #5: fibroblast-like synoviocytes and #6: rheumatology. From this, we observed that synoviocytes are the focus of recent research. This is highlighted in the enlarged region which acts as a connection point between the first and the third categories. Singh et al. (2012) provided updated recommendations for the use of non-biologic and biologic treatments in RA and indicates that clinical treatments consist of DMARDs and biologic

agents.^[15] In this way, the treatment of RA is directly linked to the synoviocytes which suggests theoretical consistency across this field.

2.3. The analysis of key literature

Highly cited literature revealed what can be thought of as common knowledge in this field. Citation bursts on the other hand refer to suddenly increasing citation frequency which indicates that the report focuses on a key issue in the field.^[16]

Table 1. Top 10 references based on frequency

Frequency	First author	Year	Source
120	McInnes IB	2011	NEW ENGL J MED
95	Aletaha D	2010	ARTHRITIS RHEUM-US
60	Scott DL	2010	LANCET
57	Bartok B	2010	IMMUNOL REV
44	Smolen JS	2014	ANN RHEUM DIS
41	McInnes IB	2007	NAT REV IMMUNOL
40	Firestein GS	2003	NATURE
36	Bottini N	2013	NAT REV RHEUMATOL
34	Singh JA	2016	ARTHRITIS RHEUMATOL
29	Bombardier C	2000	NEW ENGL J MED

Table 2. Top 10 references based on bursts

Burst	Author	Year	Source
40.9	McInnes IB	2011	NEW ENGL J MED
35.17	Aletaha D	2010	ARTHRITIS RHEUM-US
20.64	Bartok B	2010	IMMUNOL REV
20.46	Scott DL	2010	LANCET
17.75	Smolen JS	2014	ANN RHEUM DIS
15.08	Singh JA	2016	ARTHRITIS RHEUMATOL
14.46	Bottini N	2013	NAT REV RHEUMATOL
14.42	McInnes IB	2007	NAT REV IMMUNOL
14.08	Firestein GS	2003	NATURE
13.66	Smolen JS	2016	LANCET

Notes: For analytical consistency Figure 2B is combined with Table 1 which lists the top 10 references in RA literature published via the Web of Science Core Collection over the past 20 years. Table 2 shows references and corresponding information for the top 10 strongest citation bursts.

After 2010, RA studies have gradually increased. Combining Tables 1 and 2, we found that highly cited publications and those that experience citation bursts are aligned. For further analysis, we divided them into three categories, as described below:

(1) Literature within this analytical category focuses on RA McInnes et al. (2011) reveals that RA pathogenesis includes environmental triggers, activation of the innate immune system and cartilage damage.^[17] Bartok and Firestein (2010) suggest that fibroblast-like synoviocytes (FLS) in the synovial intimal lining also play a key role by producing cytokines.^[18]

(2) Publications in this category introduce pharmaceutical interventions for Based on T-cell-mediated antigen-specific responses of rheumatoid synovium, Firestein (2003) recommended that specific therapeutic interventions can be designed to inhibit synovial inflammation and joint destruction in rheumatoid arthritis.^[19] Smolen et al. (2013) updated the management of RA with synthetic and biological disease-modifying antirheumatic drugs.^[20] Bottin et al. (2013) found that FLS from patients with RA also display unique aggressive features, indicating that therapies targeting FLS could be complementary to immune-targeting therapies in the treatment of RA.^[21] In addition to the RA treatment above, Singh et al. (2016) and Bombardier et al. (2000) determined that targeted therapy should be carried out for patients with other diseases at the same time.^[22, 23] Scott et al. (2010) and Smolen et al. (2016) found that early diagnosis and genetic factors are important for optimal therapeutic success.^[3]

(3) In addition to publications on RA pathogenesis and pharmaceutical treatment recommendations, another important category focuses on RA disease classification and diagnostics. Aletaha et al. (2010) created a new classification system, redefining the current paradigm of RA by focusing on early symptoms of the disease.^[8]

3. The Development Of Ra Research

The evolution of keyword usage can reveal the underlying structure and characteristics of the field. By analysing the occurrence frequency of keywords in different time periods, the trends in RA-related research can be obtained.^[24] Keywords used at a higher frequency can represent the focus within the RA specialism and provide insight into issues which need to be addressed and determine the level of urgency. Keywords co-occurrence analysis used here employs two analytical maps, time-zones and time-lines to analyse the evolution of RA research on a macro-to-micro scale.

3.1. The evolution stages of keywords

As shown in Figure 3A, RA research can be divided into the following stages:

(1) The timespan across the time-zone was mapped from 2001-2020. This is when the literature on RA medical research was first published. "Rheumatoid arthritis" (e., purple node) is in the centre and connects to most keywords. Please see Figure 3A, which indicates that RA has attracted increasing attention for many years.

(2) There were fewer research keywords from 2003 to 2008, which suggests that there were fewer RA-related studies during this time period, and keywords appeared less frequently.

(3) In 2009, "Inflammation" first appeared as a keyword in the RA field (frequency of occurrence >15), and has become an highly central keyword (e., the purple node). Most of the keywords are connected to this word which suggests that, "inflammation" serves as a the interconnecting theme. Since 2009, the number of keywords has increased and additional keywords include: systemic lupus erythematosus, NF-κB (nf

kappa b in Fig. 3A), apoptosis, etc. This suggests that in last 10 years, RA research has focused on autoimmune diseases more generally, in terms of cytokines, and damaged joints, etc.

(4) This stage ends on February 12, 2020. The research focus of 2019 can represent the more recent research interests within this field, such as the focus on TNF- α inhibition (e., inflammatory inhibition), osteoporosis, etc.

3.2. Analysis of co-occurrence cluster

Keyword co-occurrence clustering analysis is an effective way to identify the evolution of research topics because this analysis can potentially highlight knowledge links between different keywords.

From Figure 3B, we can see that the largest node is rheumatoid arthritis. Looking at the time horizontally, RA research has continued for many years without interruption. There are essentially 20 clusters, which indicates that researchers have explored many different areas in search of answers. Conversely, some clusters have had only relatively short durations, which may be because researchers have explored new research pathways and transitioned to another research topic. In addition, the map provides us with the evolutionary relationship between keywords. Using the first cluster as an example, we labelled the relationship between osteoarthritis with other keywords in Figure 3B and utilised this to generate Figure 3C.

Adalimumab has been shown to be an effective management for RA.^[25] As can be seen in cluster #0 adalimumab in Figure 3C, osteoarthritis, a joint disease mainly characterized by degeneration of articular cartilage that displays similar clinical symptoms to those of RA, and has the highest frequency of co-occurrence.^[26] Since 2001, there have been 207 publications about osteoarthritis in the RA research field.

One of the most influential studies is from Diarra et al. (2007), who found that inhibiting Dickkopf-1 (DKK-1), a regulatory molecule of the Wnt pathway, is able to reverse the bone-destroying pattern of a mouse model of rheumatoid arthritis to the bone-forming pattern of osteoarthritis.^[27] Their article, which has been cited 839 times, suggests that the Wnt pathway is a key regulator of joint remodelling.

According to Figure 3C, osteoarthritis in the #0 cluster is closely related to the following keywords: chronic synovitiiti, cyclooxygenase, trial, and knee osteoarthritis. In addition, the related keywords also include: double blind (cluster #14), cartilage (cluster #17), suppressed (cluster #20). After searching citation histories, we found that osteoarthritis and chronic synovitiiti appear to co-occur according to the Harald et al. (2005) article on radiosynoviorthesis (RSO). Their work states that RSO, though slightly more effective in RA, represents an effective treatment option for osteoarthritis and other disorders with concomitant synovitis.^[28]

Osteoarthritis and cartilage appear together as keywords in 22 articles, of which the most highly cited publications included work from Lefèvre et al. ,^[29] the work from Aida et al. on the role of interleukin-1 on altering cartilage matrix turnover,^[30] and a clinical trial from Gruenwald et al. on glucosamine sulfate.^[31]

In particular, Gruenwald et al (2009) states osteoarthritis symptoms (e.g., morning stiffness, pain in hips and knees) were reduced at the end of the study by combining glucosamine and omega-3 fatty acids compared to glucosamine sulfate alone. These clinical results may assist drug development and highlight the need for dietary changes.

4. The Analysis Of The Foci

We know that keywords with an high degree of bursting represent a common interest for researchers over a period of time. Changes in the frequency of emergent words can be used to determine the frontiers and trends of the research field. This last burst in the term “RA” from 2016 to 2020 indicates that “contract management” may represent an emerging topic trend for future RA research.

Table 3. Burst keywords from 2016 to 2020

Keyword	Burst	Burst Begin	Burst End
disease activity	15.3033	2015	2018
TNF- α	13.5977	2018	2020
association	13.3991	2015	2018
double blind	13.1196	2016	2018
apoptosis	12.44	2016	2020
risk	12.0203	2015	2018
pathogenesis	10.8606	2016	2020
NF- κ B	10.8606	2016	2020
arthritis	10.8606	2016	2020
mechanism	9.9524	2018	2020

After preparing Table 3, we researched emergent keywords and found that they can be divided into the following categories:

- (1) Disease process: disease activity, association, risk;
- (2) RA mechanism: TNF α , apoptosis, pathogenesis, NF- κ B, arthritis, mechanism;
- (3) Clinical Trials: double blind, risk

The keywords above represent foci of recent RA research, which suggests that researchers are devoting an increasing amount of attention to these areas in the next research phase. In particular, TNF- α , apoptosis, pathogenesis, NF- κ B, arthritis, and mechanism are still burst keywords in 2020.

5. Discussion

In this study, we performed a comprehensive analysis of worldwide research outputs in the RA field over the past two decades. According to the aforementioned analysis, we generated a summary figure for consideration. As can be seen below in Figure 4, RA research is not merely associated with the development of pharmacological interventions, but is an interdisciplinary field involving RA pathology, diagnostics, pharmacology, clinical research and drug safety evaluations. Interestingly, a considerable

number of studies have found that the clinical drug treatment options for RA are more complex because each drug recommendation is made after considering the balance of relative benefits and harms.

Various hypotheses have attempted to explain RA over the past half century might be reinterpreted in order to appreciate the complexity of the disease and the multiple mechanisms of synovial inflammation. RA pathogenesis has been shown to involve certain types of immune cells, including T cells, B cells, macrophages, and synoviocytes which have a key role in invasive synovium and joint inflammation. Fibroblast-like synoviocytes (FLS) are typical synovium cells and therefore we tried to take FLS as an example to analyse frontier research (Figure 4):

(1) Reduced FLS apoptosis appears to promote hyperplastic rheumatoid pannus formation which characterizes synovia in RA;

(2) FLS also appears to mediate invasion and destruction of cartilage by balancing the extracellular matrix (ECM) and matrix metalloproteinases (MMPs) in accordance with their ability to secrete TNF-related activation-induced cytokine;

(3) FLS secrete various types of cytokines thereby causing inflammation in an arthritic joint. In FLS, the NF- κ B pathway, which is activated by TNF and IL, appears to be the dominant signalling pathway, and performs immunoregulatory functions.

Research into RA has been ongoing and we can see that research has expanded to many fields, even including somewhat peculiarly into soy sauce. Combined with the scientometric analysis, we would recommend following the 2015 ACR RA treatment guidelines. The guidelines advocate the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early and established RA, and the use of various treatment approaches according to the most commonly encountered clinical scenarios, including treat-to-target, switching between therapies, tapering therapies, the use of biologics and DMARDs in high-risk RA patients. There is also a growing interest in vaccinations in patients with RA receiving DMARDs or biologics, TB screening with biologics or tofacitinib, and laboratory monitoring with DMARDs.

This study represents the first detailed scientometric analysis around the pathogenesis and treatment of rheumatoid arthritis. There are very few researchers who have used scientometric analysis for RA medical research. Analysis by Schöffel et al. (2010) revealed single areas of interest, as well as the most prolific journals, authors, and institutions in the RA field.^[32] However, their research lacks a content summary of RA research which we provided in detail. As has been described, we have confirmed the feasibility and effectiveness of bibliometrics. However, the amount of data involved was large, and due to space issues, we cannot focus on each and every detail. Therefore, this study cannot adequately convey all the information related to RA research. Although, evidence seems to suggest that there is a need to conduct a more comprehensive systematic review, combining basic medical research with clinical knowledge. Using our work as a guide, we may be able to develop research projects which individualise RA interventions according to biomarkers.

In conclusion, our analysis provides evidence around the direction of modern RA research and will be an important asset as researchers continue to study this currently incurable disease. There appears to be a dramatic decline in published research within this field over the past two year which may reflect financial disengagement although this requires further research. TNF- α , apoptosis and NF- κ B are at the forefront of research in this field although future research surely demands clinical researchers intercalate these measures into trials in order to add sophistication to this evolving evidence base.

List Of Abbreviations

RA: Rheumatoid arthritis; DMARD: [Disease-modifying antirheumatic drugs](#); FLS: fibroblast-like synoviocytes; DKK-1: Dickkopf-1; RSO: radiosynoviorthesis; ECM: extracellular matrix; MMPs: matrix metalloproteinases.

Declarations

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are available in the Web of Science repository, <https://apps.webofknowledge.com>.

Competing interests

All authors approved this manuscript and no author has financial or other contractual agreements that might cause conflicts of interest.

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Authors' contributions

Xiang Li and Gong Chen designed the study. Xiang Li, Gong Chen, Zhehui Zhao, Haijing Zhang, Ying Peng collected and analysed the data. Xiang Li, Gong Chen and Samuel Seery interpreted findings, drafted and edited the report. Lianqiu Wu examined and verified the study. All authors made substantial contributions and approve the final manuscript.

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Figures

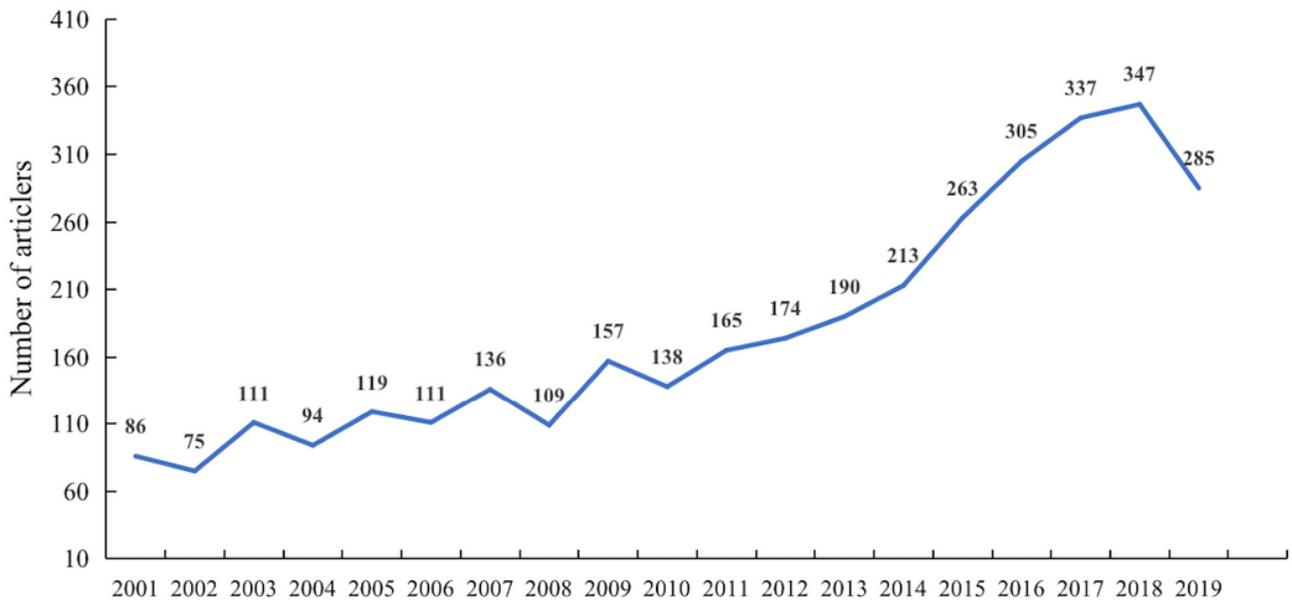


Figure 1

Number of published RA articles

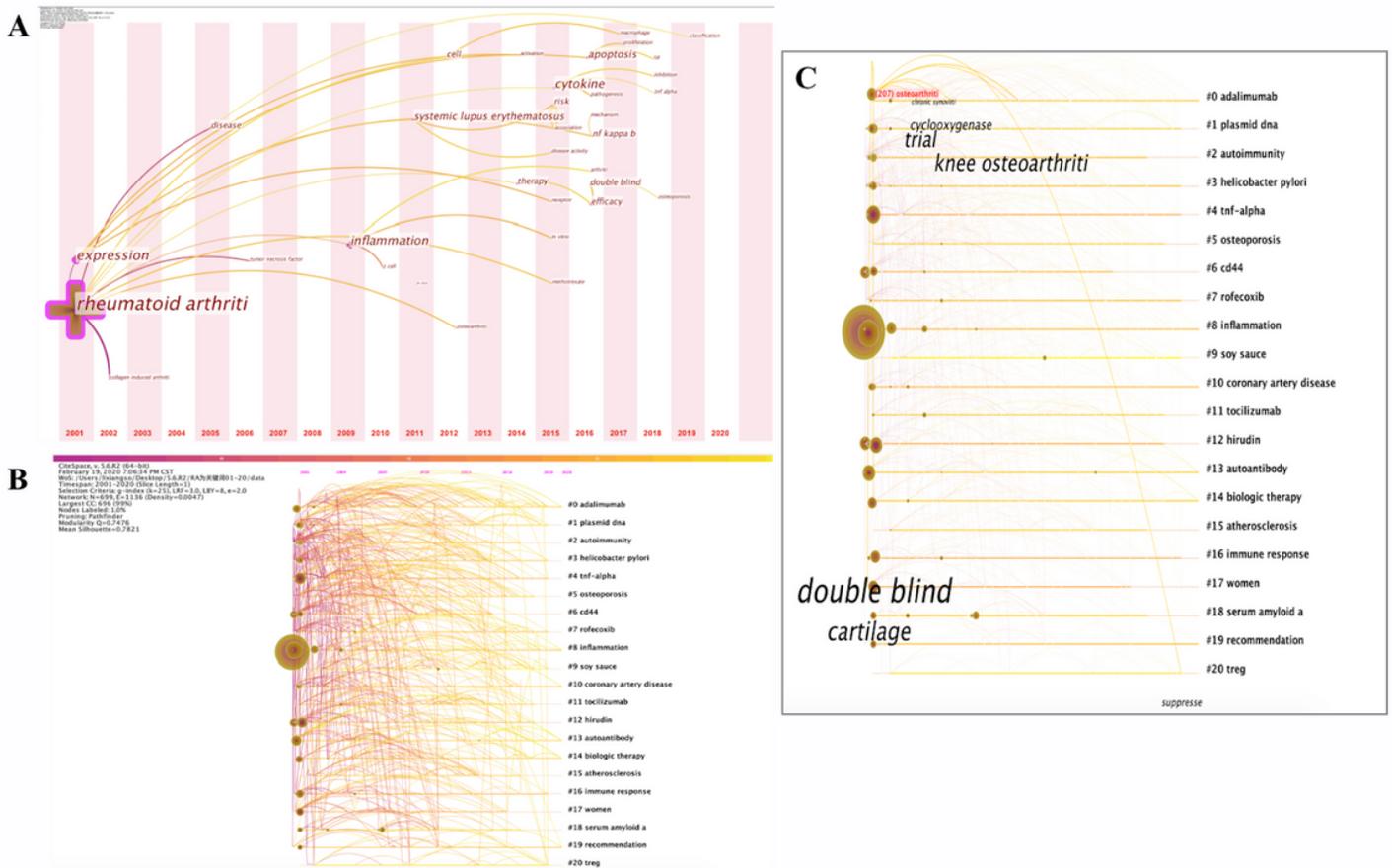


Figure 3

A Time-zone mapping of the keyword network Note: The X-axis, where the node is located, represents the year when the keyword first appeared. The font size of each node label is proportional to keyword frequency. Connections between nodes represents the inheritance relationship between keywords. B Time-line mapping of key words network Note: Keywords are marked above each of the nodes. The size of each nodes and node labels is proportional to the co-occurrence frequency of keywords. A total of 20 RA research clusters are labelled on the right, which are arranged vertically in descending order according to scale. The colour of connections between nodes also indicates the year in which the two keywords occurred together in an article, and follows a distribution from dark to light, with light representing recent co-occurrences. Because of the software's automated screening, we manually filtered uninformative keywords, including "expression", "disease", and "cell", and then labelled the top 10 keywords in the figure. C Time-line mapping of "osteoarthritis" network

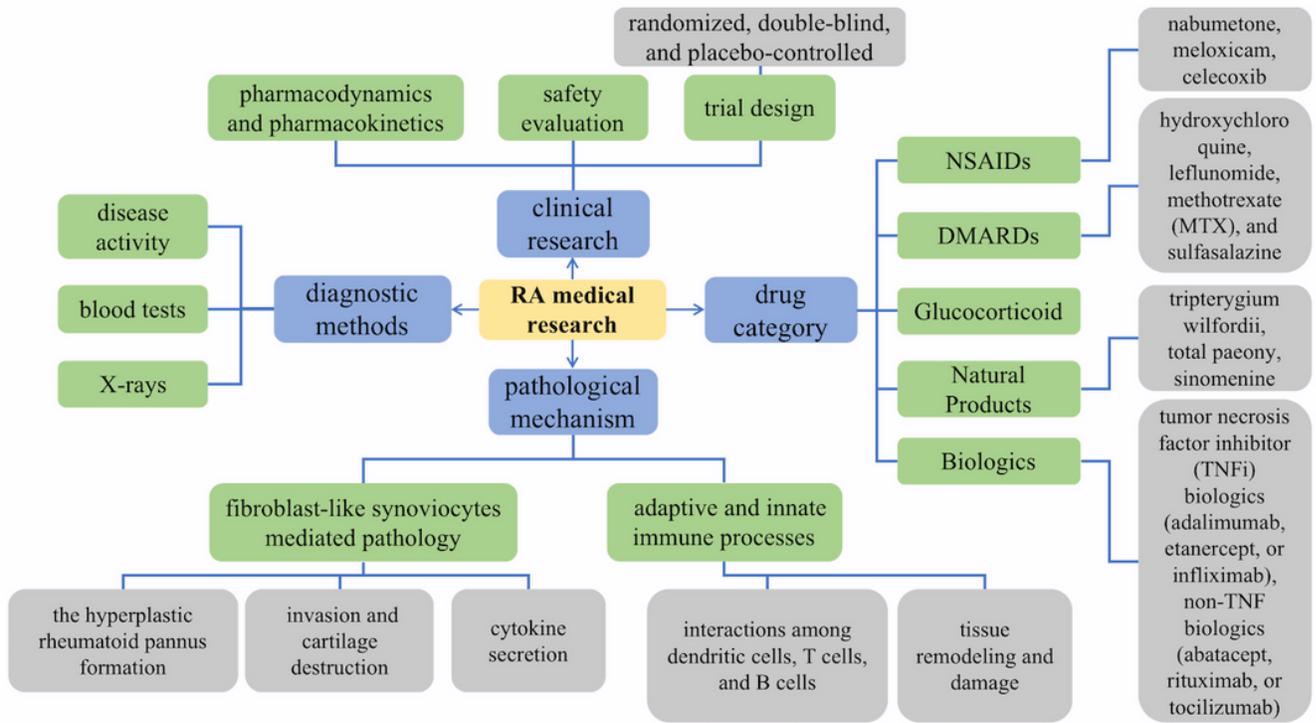


Figure 4

Systematization of RA medical research