

Bibliometric Analysis of Publications in Clinical Trials on Knee Osteoarthritis Between 2001 and 2022

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Purpose: Clinical treatment of knee osteoarthritis has gained great interest, and numerous clinical studies have been reported. Few studies have described the detailed characterizations of clinical trials on knee osteoarthritis. This study is to identify, visualize, and characterize the clinical trials in knee osteoarthritis research.

Design and Methods: Articles published in recent two decades were extracted from the Web of Science core collection database using a query based on MeSH terms and topics of knee osteoarthritis and clinical trial. Basic characteristics of publications were analyzed based on the publication year, authors, institutions, counties, and keywords covered in the article. CiteSpace and VOS viewer were used for data visualization. The data were retrieved on May 28, 2022.

Results: A total of 1972 trials on knee osteoarthritis were identified. The number of publications has experienced rapid growth in the past two decades. America, England, and China had strong contributions in publication. *Osteoarthritis and Cartilage*, *Annals of the Rheumatic Diseases* and *American Journal of Sports Medicine* were highly cited and bellwether journals. Clustering mapping of the collaborative network, co-citation, and co-occurrence analyses showed that the research hotspots are mainly focused on disease-modifying medications, intra-articular injections, physical therapy for symptom control, lifestyle intervention, Chinese medicine treatment, and knee replacement.

Conclusion: Clinical treatments of knee OA are evolving. Pharmacologic therapy, intra-articular therapy, nonpharmacologic therapy including exercise or diet, self-management programs, Chinese medicine treatment, and knee replacement were highly represented in clinical trials of knee OA. Adjustment of combination therapy may be the next study focus in the future.

Keywords: knee osteoarthritis, treatment, clinical trial, bibliometric analysis, public health

Introduction

Osteoarthritis (OA) is the most common type of arthritis. Its pathological changes include synovial inflammation to varying degrees, degeneration of articular cartilage, formation of osteophytes, thickening of subchondral bone, degeneration of ligaments and meniscus of knee joint, and hypertrophy of joint capsule, affecting the entire joint structure.¹ The World Health Organization calls OA “the first disabling disease”, current medical means can only reduce the symptoms and signs of patients to a certain extent, delay the progress of the disease, it is difficult to treat the disease fundamentally.² The causes of OA involve inflammation, oxidative stress, joint damage, age and many other factors, and health care costs for OA reach \$303 billion a year.³

Osteoarthritis of the knee (knee OA) is the most common cause of articular pain in the elderly and features cartilage loss, synovial hypertrophy, osteophytes, and meniscal damage.⁴ Knee OA is a chronic aging disorder in the whole joint, increasing in incidence year on year due to the aging population. Symptoms of knee OA often involve joint pain, reduced functional motion, swelling, and stiffness.⁵ Many basic and clinical studies focusing on radiology,⁶ cytology,⁷ risk factors,⁸ medications,^{9,10} behavioral therapy,¹¹ and surgery¹² have been devoted to understanding the physiological and pathophysiological processes of knee OA and seeking effective treatments.^{13–15} However, there are still no effective therapeutic strategies that have been proven to

cure or delay symptom deterioration even with the huge economic cost to both individuals and society.¹⁶ However, this does not mean the researchers and clinicians would stop their steps to explore the best therapies for knee osteoarthritis. Targeted medical research is the key to achieving this goal.

Clinical trial, also commonly called randomized controlled trial (RCT) is a scientific research activity used to determine the safety and efficacy of therapies or drugs for use in patients. Clinical trial is characterized by rigorous study design, high levels of evidence, and more reliable results. Ever since clinical discovery of the treatment difficulty of knee osteoarthritis, more than 3000 clinical trials in this domain have already appeared in the scientific literature. Published articles covered a wide range of therapies, including but not limited to, physical therapy, pharmacological therapy, intra-articular injections, knee replacement, and combined treatment. Concurrently, these articles also revealed a wide range of dominant countries, journals, institutions, and authors that have made certain contributions in this field. Given the broad range of interests covered in these published works, it is of great necessity for scientific investigators to determine the precise study direction and relative challenges. Characterization of clinical trials for treating knee OA can aid researchers to tailor their study orientations and pursuit of associated interests.

Bibliometric analysis takes the publication system and characteristics as the research object, adopts mathematical and statistical methods to study the distribution structure, quantitative relationship and research topics of literature data, which can aid researchers to evaluate the publication trend and hotspots in a specific domain.¹⁷ Up to now, no bibliometric studies of clinical trials on knee OA have been conducted. Here, we aimed to identify the clinical trials focusing on the treatment of and to characterize these articles.

Materials and Methods

Articles Search and Selection

On May 28, 2022, we generated a series of published clinical trial studies related to the treatment of knee OA by utilizing the Web of Science Core Collection database. Here, we selected the Science Citation Index Expanded (SCI-EXPANDED), and Social Sciences Citation Index (SSCI) as the editions. Medical Subject Headings (MeSH) from the America National Library of Medicine was used to standardize the search terms due to the lack of subject term database in the Web of Science. Based on this, we used the following search terms and topics to retrieve publications in the database: (TS=(“Knee osteoarthr*”)) AND TS=(“Randomized Controlled Trial” OR “Randomised Controlled Trial” OR “clinical trial”). Next, we selected “Articles” for the file type and the publication period from January 1, 2001 to May 28, 2022, for the search and obtained 1972 original articles. All articles were published in English language. Through this flow, we finalized the clinical trial studies related to the treatment of knee OA for nearly two decades.

A clinical trial article related to the treatment of knee OA was defined as any research primarily focusing on surgical or nonsurgical treatment, drug or cell therapy, and combined management. Articles unrelated to our interests were excluded. Two reviewers (Jin-Yu Gu and Fei Han) performed independent article searching, identification, and analysis. The third senior reviewer (Qing Zhang) reassessed the fuzzy articles and discussed them until a consensus was reached.

Bibliometric Analysis

The basic characteristics of publications were described by using the intrinsic function of the Web of Science. Every article was reviewed for retrieval of the publication year, authors, institutions, counties, H-index, publication journal, journal citation reports (JCR), and keywords covered in the article. The H-index, widely considered a valuable measure of assessing academic productivity, has been studied in various medical and surgical specialties and has shown strong associations between higher h-indices and academic promotion, as well as with National Institutes of Health (NIH) awards.¹⁸

Data Visualization

Microsoft Office Excel and GraphPad Prism (8.3.0 version) were utilized to store data and visualize annual publications, institutional publications, and funding weightings, respectively. CiteSpace (version 6.1.R2) and VOS viewer (Leiden University, The Netherlands, version 1.6.18) were used for visualization of co-authorship, co-citation, and co-occurrence analysis. CiteSpace, a visual analysis software developed by Chaomei Chen, is most commonly used in bibliometric analysis. It analyses specific clusters of literature from multiple perspectives to explore and visualize research hotspots and trends in a particular field.¹⁹

Co-authorship analysis can be used to assess collaboration among countries, institutions and authors. Co-cited references (journals, authors) are two (or more) references (journals, authors) cited by one or more articles simultaneously.^{17,20} The centrality (betweenness centrality) of a node can present the significance of the position of the node in an interactive network.^{19,21} Its essence is a graph-theoretical property. The dual-map overlay of journals can well show the distribution of journals and the relationship between journals and cited journals (the color path represents the cited relationship).²² Clustering analysis of the co-authorship and co-citation results can indicate the research categories and directions of every study cluster. In addition, we used co-occurrence analysis (also known as keyword analysis) to cluster keywords from different studies to represent and predict research hotspots in the field.²⁰

Results

A total of 1972 original clinical trials on the treatment of knee OA were determined for further analysis. The number of annual publications for clinical trials on knee OA from 2001 to 2022 is shown in Figure 1. The number curve can be divided into three periods according to the increasing trend: slow growth period (P1, 2001–2010), accelerating growth period (P2, 2011–2018), and plateau period (P3, 2018–2021). The number of published clinical trials on the treatment of knee OA increased relatively rapidly after 2010, reaching a peak in 2018 with more than 200 publications per year, and then entered a plateau period. The top 15 study categories and funding of the total number of publications were also visualized in Figures 2 and 3, respectively. The research category with the highest number of publications was orthopedics, and the funding with the largest number of publications was United States Department of Health Human Services.

Countries, Institutions and Authors

The articles covered 87 countries or regions, 2923 institutions, and 8967 authors. The majority of the publications were contributed by the United States ($n = 631$), distantly followed by Australia ($n=240$), China ($n=218$), England ($n=170$), and Canada ($n=143$) (Table 1). The top five countries mentioned above contributed 71% of the total publications. Considering the number of total citations and average citations (citation/publication ratio), the United States had 27,333 citations (43 average citations), far more than all other countries. The number of publications in England was relatively low, but its citation/publication ratio (44) was the highest among the 10 countries. China had many publications but a relatively fewer citation/publication ratio (26). Collaboration network analysis of countries visualized in Figure 4 shows that the US, England, China and Australia had relatively higher volume of outputs and closely cooperation networks with each other.

The top 10 institutions of the total number of publications are presented in Table 1. League of European Research Universities (LERU) published most clinical trials ($n=181$) with citation/publication ratio of 36, followed by the University of Melbourne (97 articles, 32 average citations), and the University of Sydney (89 articles, 32 average citations). Here, we specifically explored the collaborative networks and research direction clustering among institutions. As shown in Figure 5, institutions participating in the

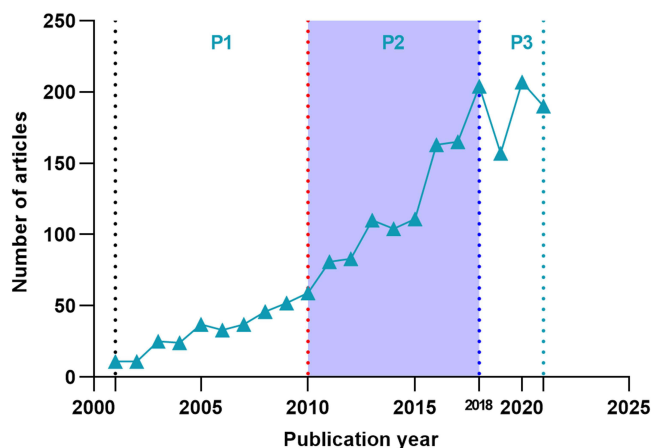


Figure 1 The number of annual publications during the past 22 years.

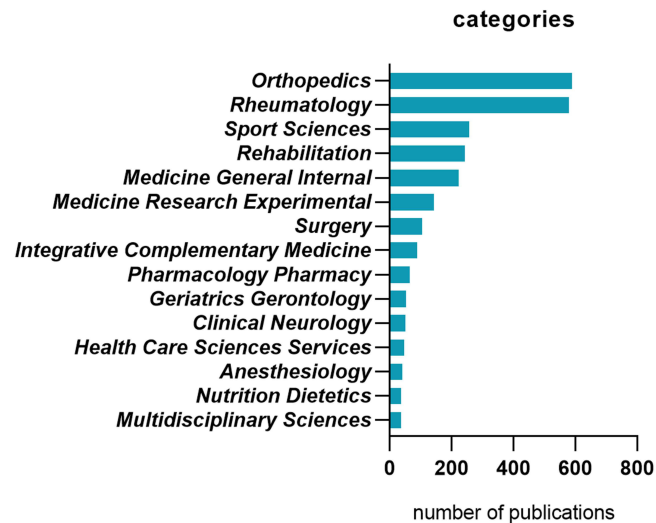


Figure 2 The top 15 study categories related to the clinical trials on knee osteoarthritis.



Figure 3 The top 15 study fundings related to the clinical trials on knee osteoarthritis.

publication of clinical trials on the treatment of knee OA were divided into nine clusters that respectively focused on different research orientations, such as Beijing University Chinese Medicine and its collaborative institutions (mainly focusing on manual acupuncture study), University of Ottawa and its collaborative institutions (mainly focusing on the efficacy of Hyalan G-F injection).

The top 10 authors of the total number of publications and the top 10 co-cited authors are presented in [Table 2](#). Bennell KL published the most trials ($n=73$), but the Messier SP had the highest citation/publication ratio (88), which indicated the high quality of his articles. Among the top 10 co-cited authors, Bellamy N had the highest number of citations ($n=901$). Correspondingly, visualization of collaborative networks and research direction clustering among authors is presented in [Figure 6](#). Here, we found that all authors can be classified into eight clusters according to their research networks. Details can be found in [Figure 6](#).

Journals and References

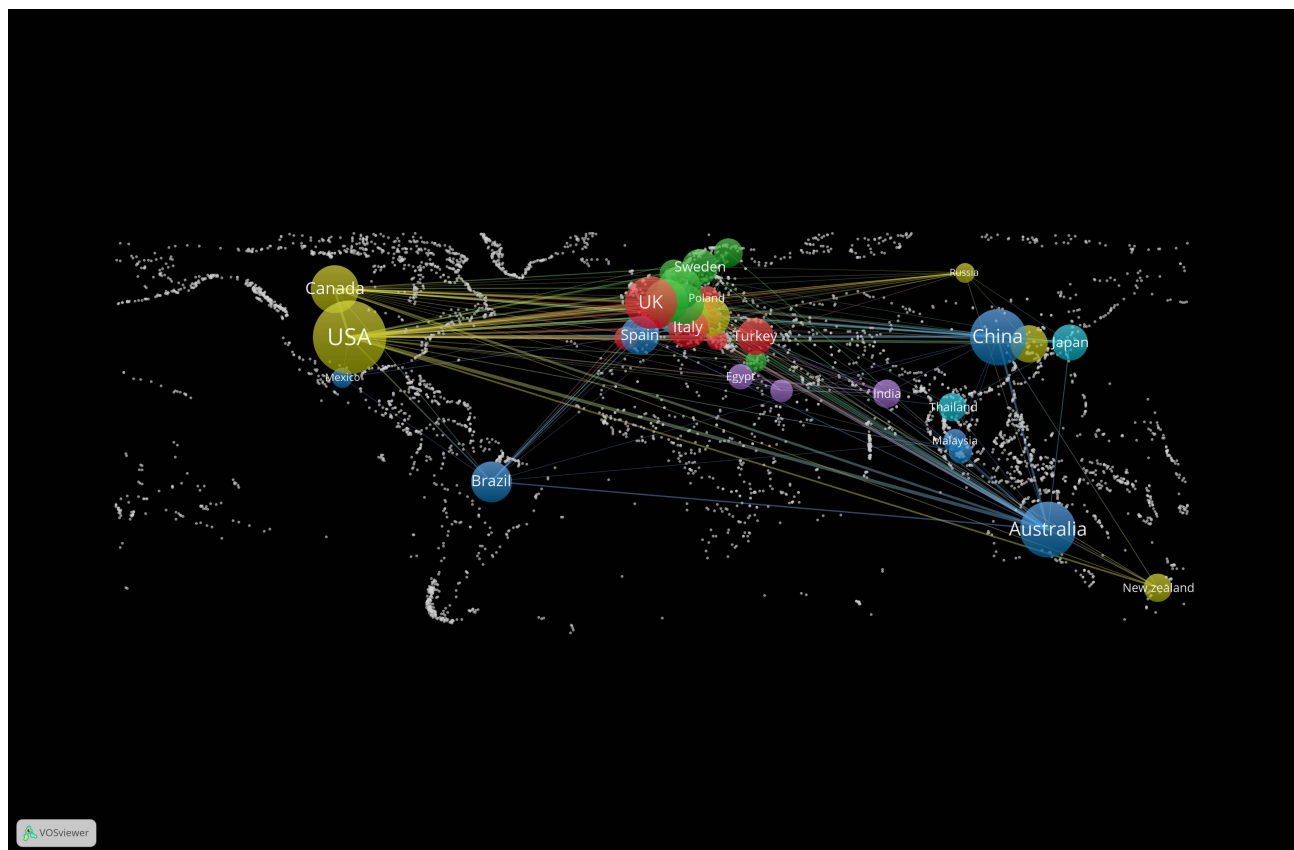
All of the clinical trials were published in 449 journals. The majority of the publications were contributed by *BMC Musculoskeletal Disorders* (147 articles, 15 average citations), followed by *Osteoarthritis and Cartilage* (240 articles, 32 average citations), *Trials* (73 articles, 7 average citations) ([Table 3](#)). It is worth noting that even though the *American Journal of Sports Medicine* (43 articles, 70 average citations) and *Annals of the Rheumatic Diseases* (40 articles, 77 average citations) did not have many published trials, they had a high citation/publication ratio. The highly cited articles were published in co-cited journals, led

Table 1 Top 10 Productive Countries and Institutions in the Clinical Trial on Knee Osteoarthritis Research

Countries	No.	Citation (per Citation)	H-Index	Institutions	No.	Citation (per Citation)	H-Index
USA	631	27,333 (43)	80	League of European Research Universities (LERU)	181	6551 (36)	44
Australia	240	7508 (31)	43	University of Melbourne	97	3057 (32)	29
China	218	2374 (11)	26	University of Sydney	89	2822 (32)	26
England	170	7439 (44)	44	Monash University	81	2103 (26)	23
Canada	143	4667 (33)	34	Harvard University	67	2229 (33)	27
Netherlands	107	2961 (28)	28	Boston University	59	3980 (67)	27
Denmark	102	3426 (34)	32	PCSHEP	58	3865 (67)	23
Brazil	87	1241 (14)	23	University of Southern Denmark	58	2022 (35)	21
Germany	86	3908 (45)	31	University of California System	52	3877 (75)	28
Italy	82	3484 (42)	27	US Department of Veterans Affairs	51	3539 (69)	22

Abbreviation: PCSHEP, Pennsylvania Commonwealth System of Higher Education PCSHE.

by *Osteoarthritis and Cartilage* (5175 citations) and *Annals of the Rheumatic Diseases* (3712 citations). The impact factors and JCR category of journals and co-cited journals are also summarized in Table 3. Visualization of co-cited analysis of journals and corresponding clusters based on research direction is presented in Figure 7. All of these cited journals were divided into 14

**Figure 4** Collaboration network analysis of countries associated with the clinical trials on knee osteoarthritis.

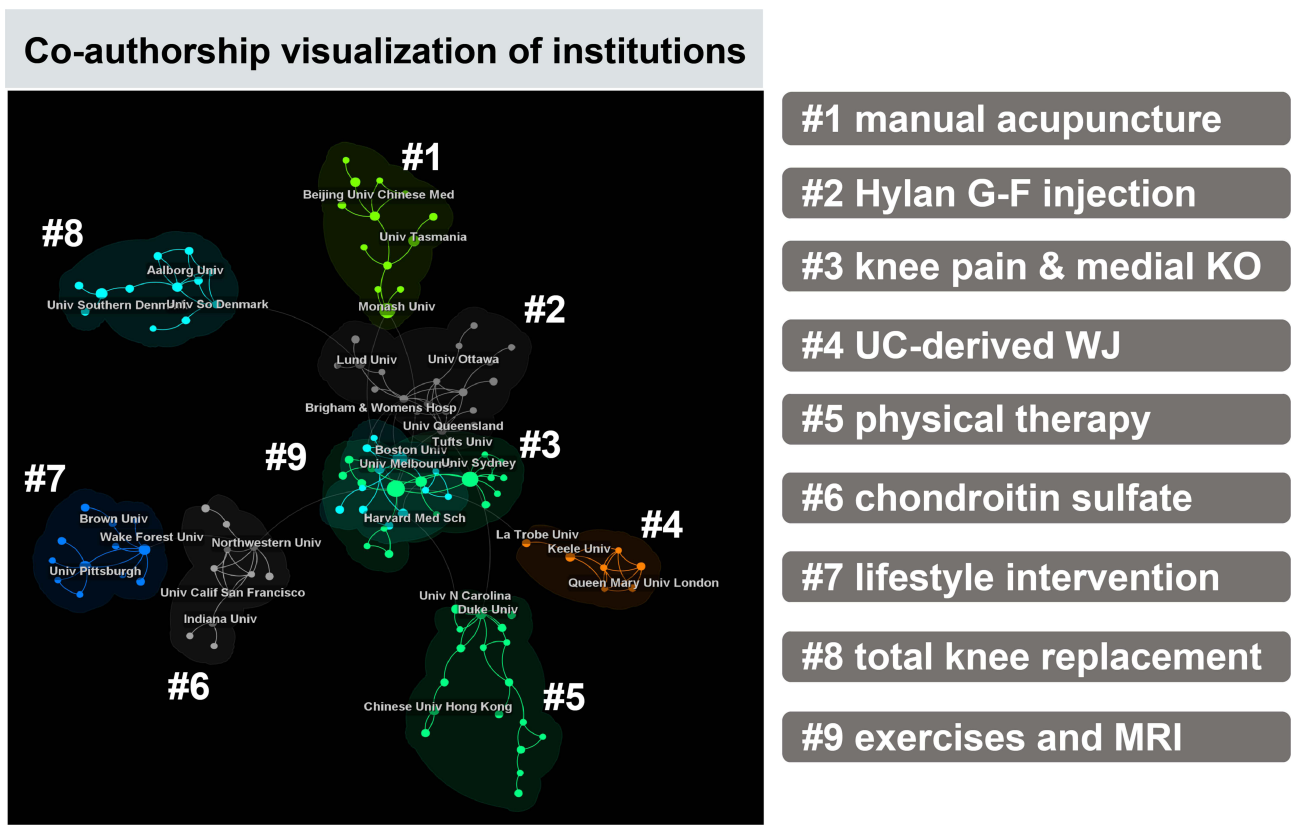


Figure 5 Collaboration network analysis of institutions associated with the clinical trials on knee osteoarthritis.

categories with research preferences that covered diverse treatment options used in the clinical setting. Furthermore, we also used the journal burst analysis in CiteSpace to detect emerging journals in a specific period to determine the advancement of research in this domain. The top 30 cited journals with the strongest citation bursts (burst intensity) are presented in [Figure 8](#).

Table 2 Top 10 Productive Authors and Co-Cited Authors Related to Clinical Trial on Knee Osteoarthritis

Author	No.	Citation (per Citation)	H-Index	Co-Cited Authors	Citation	Centrality
Bennell KL	73	2318 (32)	24	Bellamy N	901	0.01
Hinman RS	64	2123 (33)	22	Altman R	554	0.03
Hunter DJ	52	1802 (35)	20	Felson DT	550	0.05
Roos EM	35	2036 (58)	20	Zhang W	524	0.01
Kasza J	30	388 (13)	11	Altman RD	472	0.03
Messier SP	30	2651 (88)	18	Kellgren JH	464	0.02
Bliddal H	28	893 (32)	13	Bennell KL	428	0.03
Bierma-Zeinstra SMA	26	445 (17)	11	Fransen M	413	0.06
Wrigley TV	26	834 (32)	12	Mcalindon TE	379	0.08
Guermazi A	25	1430 (57)	13	Hochberg MC	354	0.03
Jones G	25	663 (27)	14	Messier SP	328	0.08

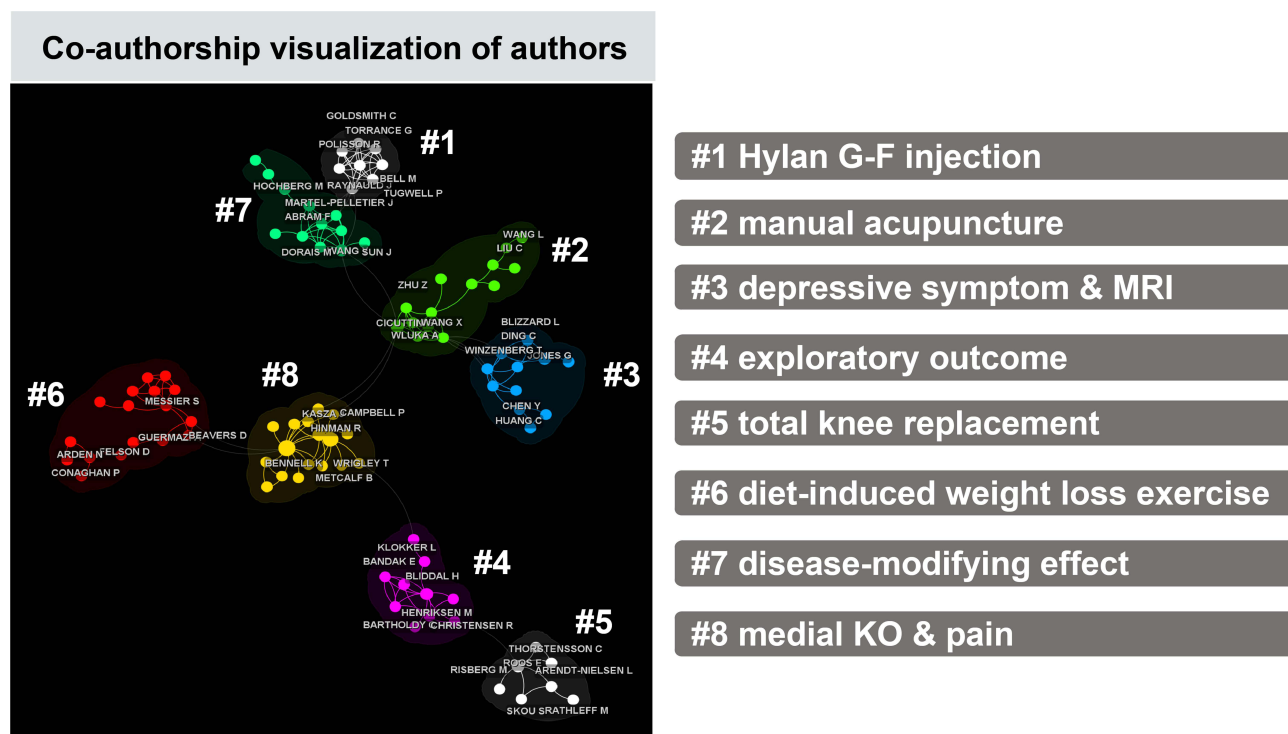


Figure 6 Collaboration network analysis of authors associated with the clinical trials on knee osteoarthritis.

Dual-map overlay of journals identified two main colored reference pathways in Figure 9 indicating that articles published in *Molecular, Biology, Genetics, Health, Nursing, Medicine, and Sports, Rehabilitation, Sport* journals were often cited in articles published in *Medicine, Medical, Clinical and Neurology, Sports, Ophthalmology* journals.

The top five most frequently co-cited references involved Mcalindon TE (2014),¹⁰ Hochberg MC (2012),²³ Bannuru RR (2019),²⁴ Zhang W (2010),²⁵ and Zhang W (2018).²⁶ Clustering analysis based on research directions and detailed characterizations of co-cited references were summarized in Figure 10. The top 30 references with the strongest citation bursts (burst intensity) are presented in Figure 11.^{9,10,16,23–49}

Table 3 Top 10 Productive Journals and Co-Cited Journals Related to Clinical Trials on Knee Osteoarthritis

Journal	Number	Citation (per Citation)	IF (2021)	Quartile	Co-Cited Journal	Citation	IF (2021)	Quartile
<i>BMC Musculoskeletal Disorders</i>	147	2200 (15)	2.562	Q3	<i>Osteoarthritis and Cartilage</i>	5175	7.507	Q1
<i>Osteoarthritis and Cartilage</i>	122	3057 (32)	7.507	Q1	<i>Annals of the Rheumatic Diseases</i>	3712	27.973	Q1
<i>Trials</i>	73	510 (7)	2.728	Q4	<i>Journal of Rheumatology</i>	2803	N/A	N/A
<i>Arthritis Care Research</i>	48	1295 (27)	5.178	Q2	<i>Arthritis & Rheumatology</i>	1993	15.483	Q1
<i>Clinical Rehabilitation</i>	48	993 (21)	2.884	Q1	<i>Arthritis and Rheumatism</i>	1746	N/A	N/A
<i>American Journal of Sports Medicine</i>	43	3024 (70)	7.010	Q1	<i>American Journal of Sports Medicine</i>	1581	7.010	Q1
<i>Annals of the Rheumatic Diseases</i>	40	3094 (77)	27.973	Q1	<i>Arthritis Care & Research</i>	1424	5.178	Q2
<i>BMJ Open</i>	35	151 (4)	3.009	Q2	<i>Arthritis Rheum-Arthr</i>	1348	4.152	Q2
<i>Physical Therapy</i>	26	1040 (40)	3.021	Q2	<i>BMC Musculoskeletal Disorders</i>	1130	2.562	Q3
<i>Archives of Physical Medicine and Rehabilitation</i>	24	1049 (44)	4.060	Q1	<i>Pain</i>	1100	7.926	Q1

Abbreviation: N/A, not available.

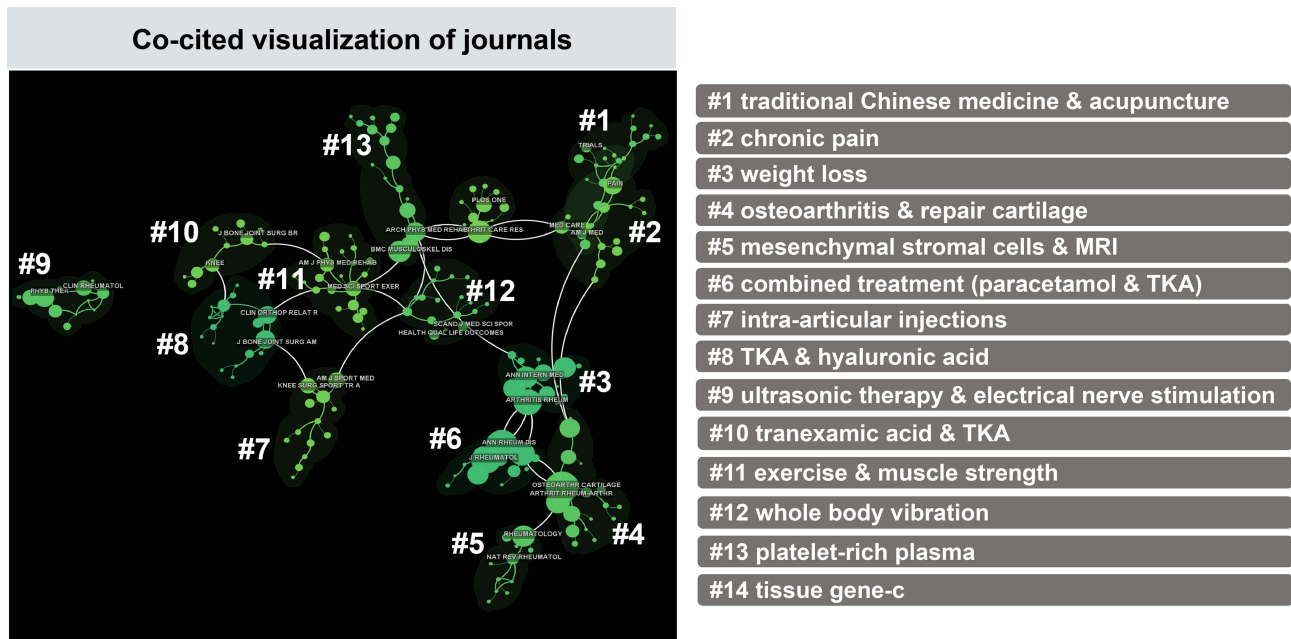


Figure 7 A cluster diagram of co-cited analysis of journals associated with the clinical trials on knee osteoarthritis.

Top 30 Cited Journals with the Strongest Citation Bursts

Cited Journals	Year	Strength	Begin	End	2001 - 2022
ARCH INTERN MED	2001	38.19	2001	2012	██████████ ██████████
BRIT J RHEUMATOL	2001	35.51	2001	2013	██████████ ██████████
J RHEUMATOL	2001	34.73	2001	2009	██████████ ██████████
ARTHRITIS RHEUM	2001	33.76	2001	2010	██████████ ██████████
BRIT MED J	2001	19.36	2001	2011	██████████ ██████████
CLIN THER	2001	18.65	2001	2008	██████████ ██████████
JAMA-J AM MED ASSOC	2001	18.41	2001	2008	██████████ ██████████
AM J PUBLIC HEALTH	2001	12.52	2001	2013	██████████ ██████████
AM J MED	2001	21.54	2003	2011	██████████ ██████████
CURR MED RES OPIN	2001	12.61	2003	2011	██████████ ██████████
OSTEOARTHRITIS CARTILAGE	2001	17.45	2004	2010	██████████ ██████████
J ORTHOPAED RES	2001	11.39	2005	2015	██████████ ██████████
NEW ENGL J MED	2001	12.51	2007	2009	██████████ ██████████
HEALTH TECHNOL ASSES	2001	12.17	2007	2013	██████████ ██████████
AUST J PHYSIOTHER	2001	11.5	2010	2016	██████████ ██████████
BMJ OPEN	2001	24.99	2018	2022	██████████ ██████████
SCI REP-UK	2001	20.81	2018	2022	██████████ ██████████
PLOS ONE	2001	20.34	2018	2022	██████████ ██████████
J ORTHOP SURG RES	2001	15.86	2018	2022	██████████ ██████████
INT J RHEUM DIS	2001	15.53	2018	2022	██████████ ██████████
THER ADV MUSCULOSKEL	2001	10.48	2018	2019	██████████ ██████████
J PAIN RES	2001	21.01	2019	2022	██████████ ██████████
J ARTHROPLASTY	2001	15.02	2019	2022	██████████ ██████████
CARTILAGE	2001	12.17	2019	2022	██████████ ██████████
J BACK MUSCULOSKELET	2001	10.72	2019	2022	██████████ ██████████
ARTHRITIS RHEUMATOL	2001	25.13	2020	2022	██████████ ██████████
MEDICINE	2001	20.19	2020	2022	██████████ ██████████
QUAL LIFE RES	2001	14.42	2020	2022	██████████ ██████████
ANN PHYS REHABIL MED	2001	12.22	2020	2022	██████████ ██████████
BIOMED RES INT	2001	12.05	2020	2022	██████████ ██████████

Figure 8 The top 30 journal with the most burstiness related to clinical trials on knee osteoarthritis. Years in blue indicate that the journal is less influential, and years in red indicate that the journal is more influential.

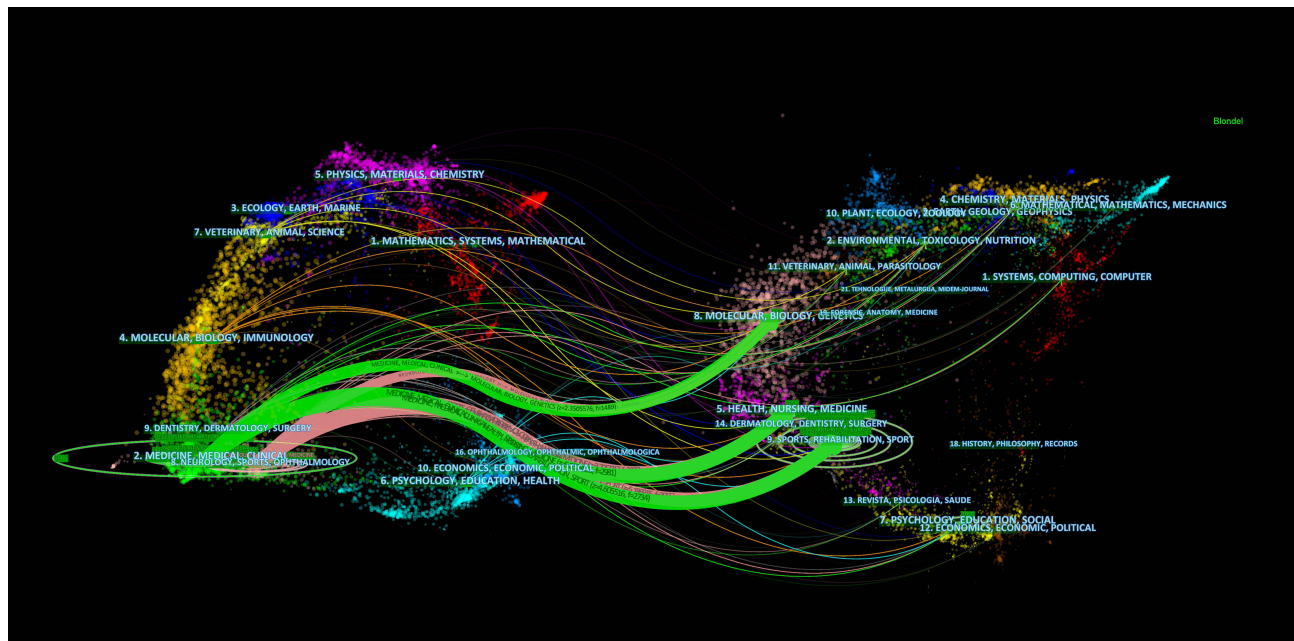


Figure 9 The dual map overlay of journals associated with the clinical trials on knee osteoarthritis. The cited journals are located on the right, and the citing journals are located on the left. The colored path represents cited association.

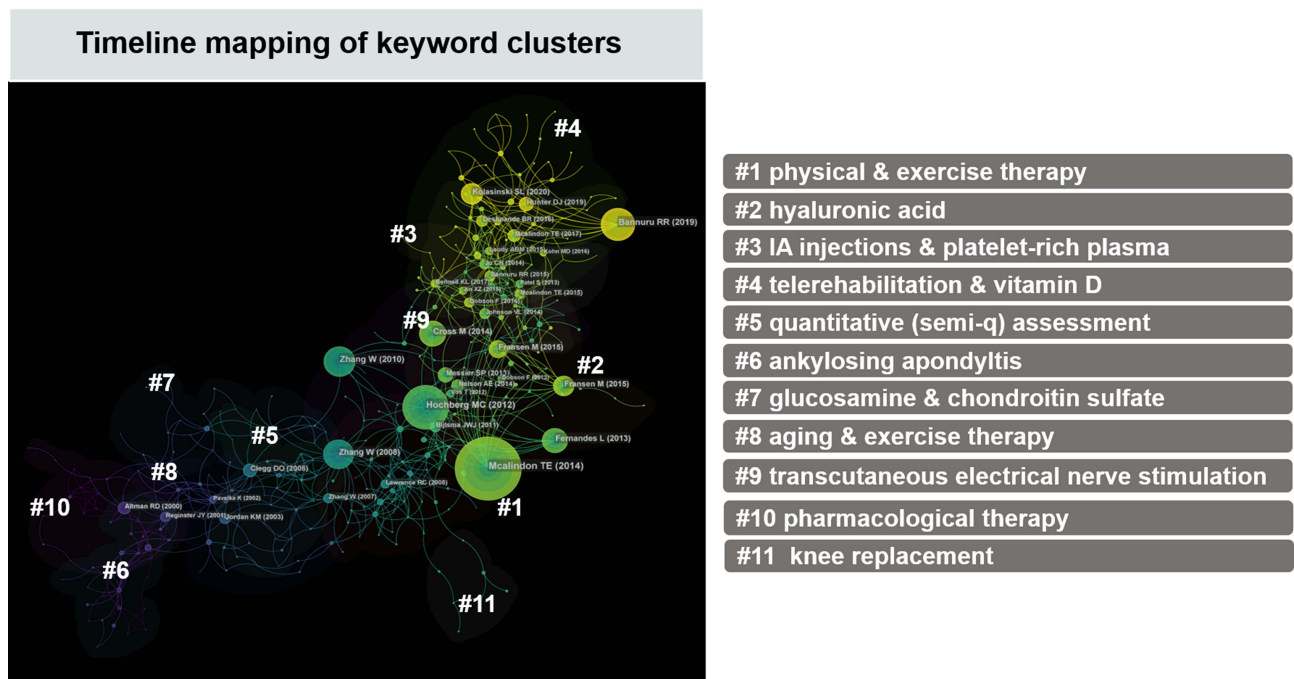


Figure 10 A cluster diagram of co-cited references associated with the clinical trials on knee osteoarthritis.

Keywords

In total, 5429 keywords were extracted from all of the clinical trials and were classified into 11 clusters (Figure 12) based on co-occurrence analysis in CiteSpace: structure-modifying drug, platelet-rich plasma injection, bone marrow, total knee arthroplasty, sham acupuncture, exercise therapy, behavioral management, strengthening muscles, multicenter, anterior cruciate ligament reconstruction, and medial compartment osteoarthritis studies. The larger the circle in the graph, the more frequently the keyword appears. Furthermore, we visualized the keywords based on the timeline of their occurrence, as detailed in Figure 13. The position

Top 30 References with the Strongest Citation Bursts

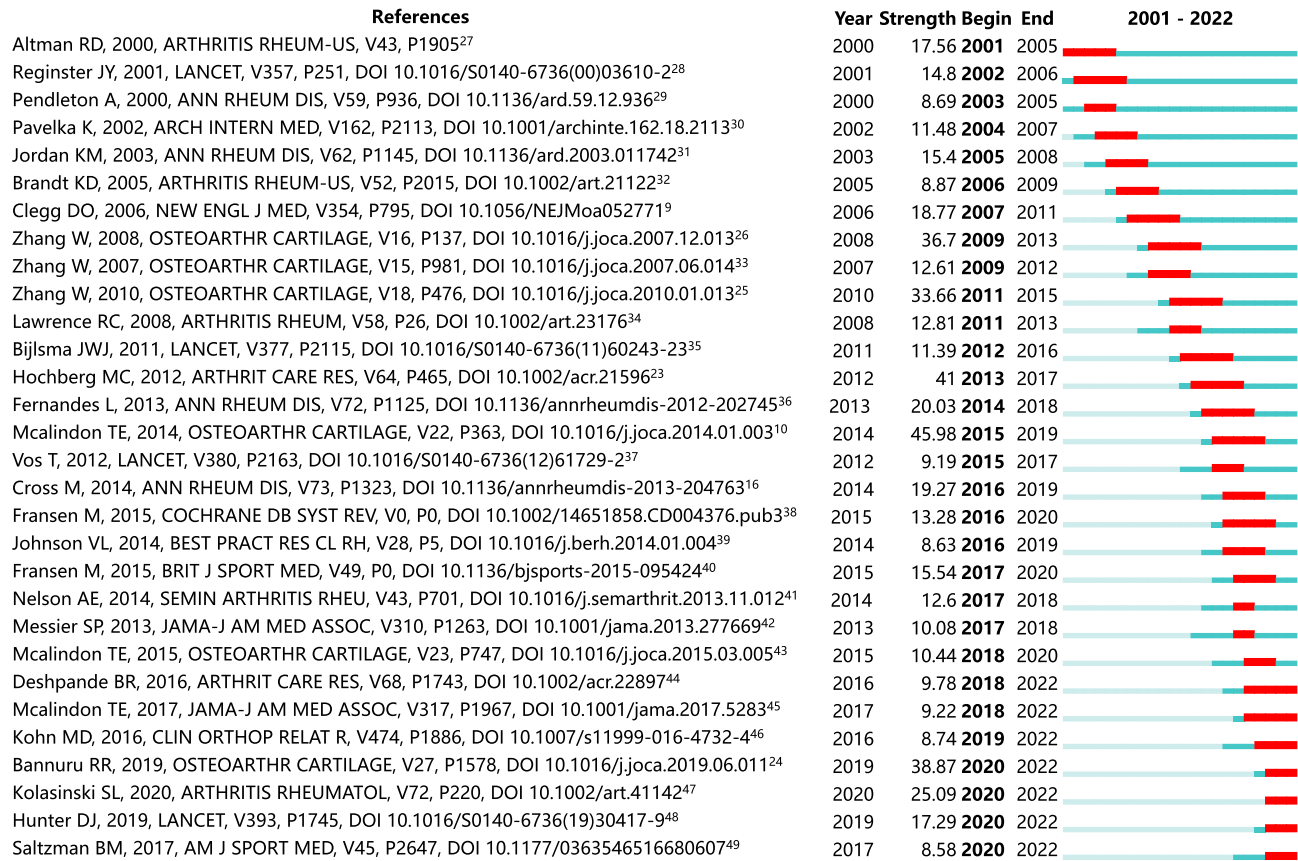


Figure 11 The top 30 co-cited references with the most burstiness related to clinical trials on knee osteoarthritis. The bolded type in the graph represents the point in time when the number of citations to an article increases significantly, indicating that the relevant research direction receives progressively more attention after that point in time.

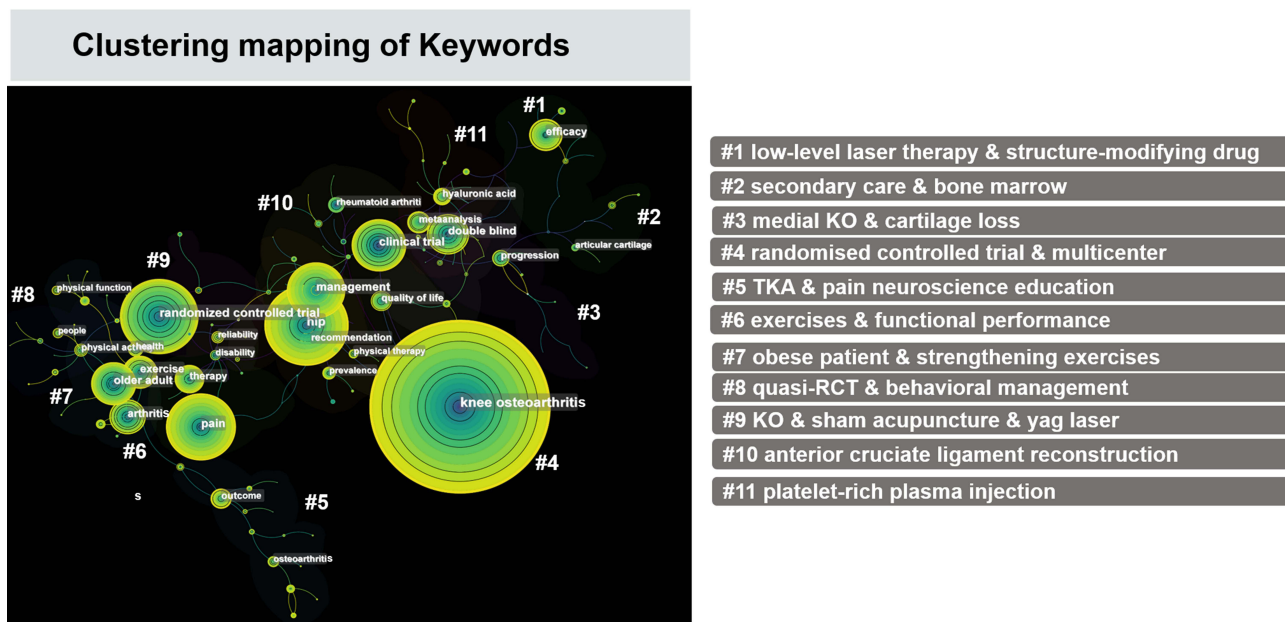


Figure 12 Mapping of keyword clusters associated with the clinical trials on knee osteoarthritis.

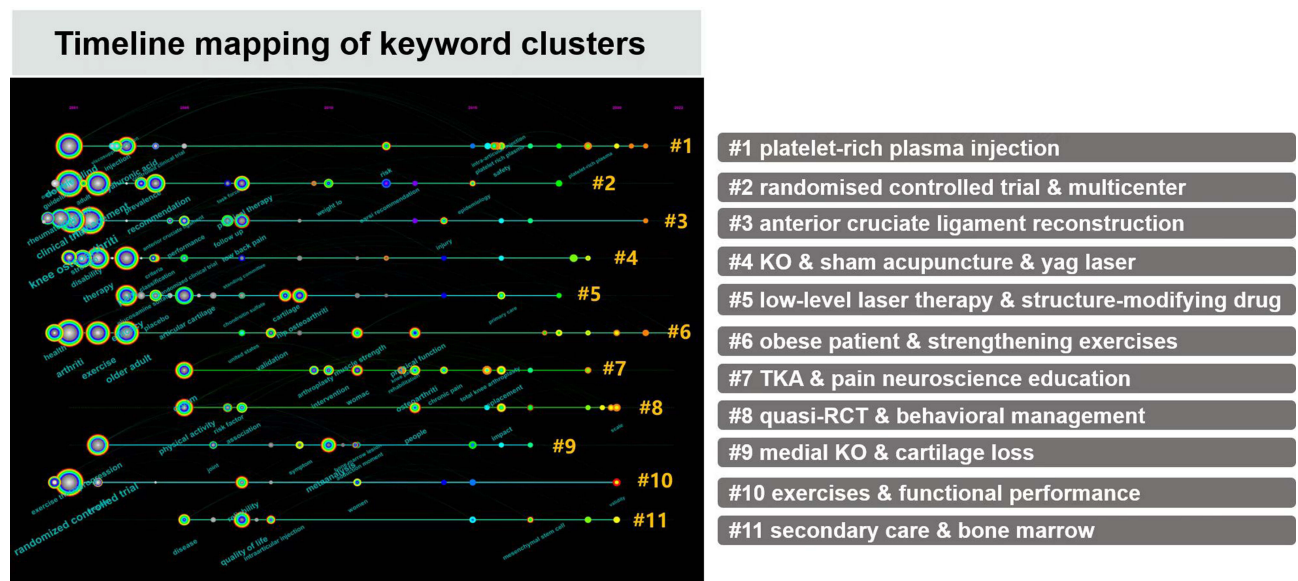


Figure 13 Keyword cluster analysis on timeline distribution associated with the clinical trials on knee osteoarthritis.

where the circle appears represents the time of the first appearance of the keyword, and the size of the circle represents the cumulative number of appearances. In addition, the top 30 keywords with the strongest citation bursts (burst intensity) are presented in [Figure 14](#).

Highly Cited Clinical Trials

Publications with a high number of citations are considered central in a specific domain.⁵⁰ We also characterized the influential clinical trials with the most total citations related to the treatment of knee OA. The number of subjects, intervention measures, delivery methods, duration, primary outcome measures, and National Clinical Trial (NCT) number are summarized in [Table 4](#). Medications such as glucosamine sulphate and behavioral intervention such as diet for losing weight, depression care and exercise treatments were previously evaluated in randomized controlled trials, and then investigators began to focus on the intra-articular injection therapies such as mesenchymal stem cells and platelet-rich plasma. Primary clinical measures of the majority of these clinical trials were the extent of pain decrease and physical performance of the knee. Although these treatments did not achieve joint complete pain relief and function, the results of these influential clinical trials were encouraging and published in international top journals. A combination of multiple interventions may be more effective. Large and long-term clinical trials are ongoing.

Discussion

Here, we first utilized bibliometric analysis in an attempt to characterize the clinical trials on the clinical management of knee OA. Results of randomized controlled trials have a decisive impact on clinical treatment. Since the industry noticed the difficulties in the therapy of knee OA, clinical trials of diverse therapeutic measures have flourished. Identification and understanding of the publication trend and hotspots of these clinical trials are of great interest to scientific researchers, clinicians, and the public. First, scientific researchers would find clear study orientations and current challenges that they must face thereby effectively adjusting interventions. They also can determine the influential institutions or authors that specialize in one subspecialty and cooperate with them. Furthermore, with the aid of the information that our study provides, clinicians can guide patients with knee OA to manage their distressing symptoms reasonably. Third, the public also can capture some specific information such as topics covered in clinical trials, which might be helpful for compliance with informed clinical and daily prevention treatments.

Top 30 Keywords with the Strongest Citation Bursts

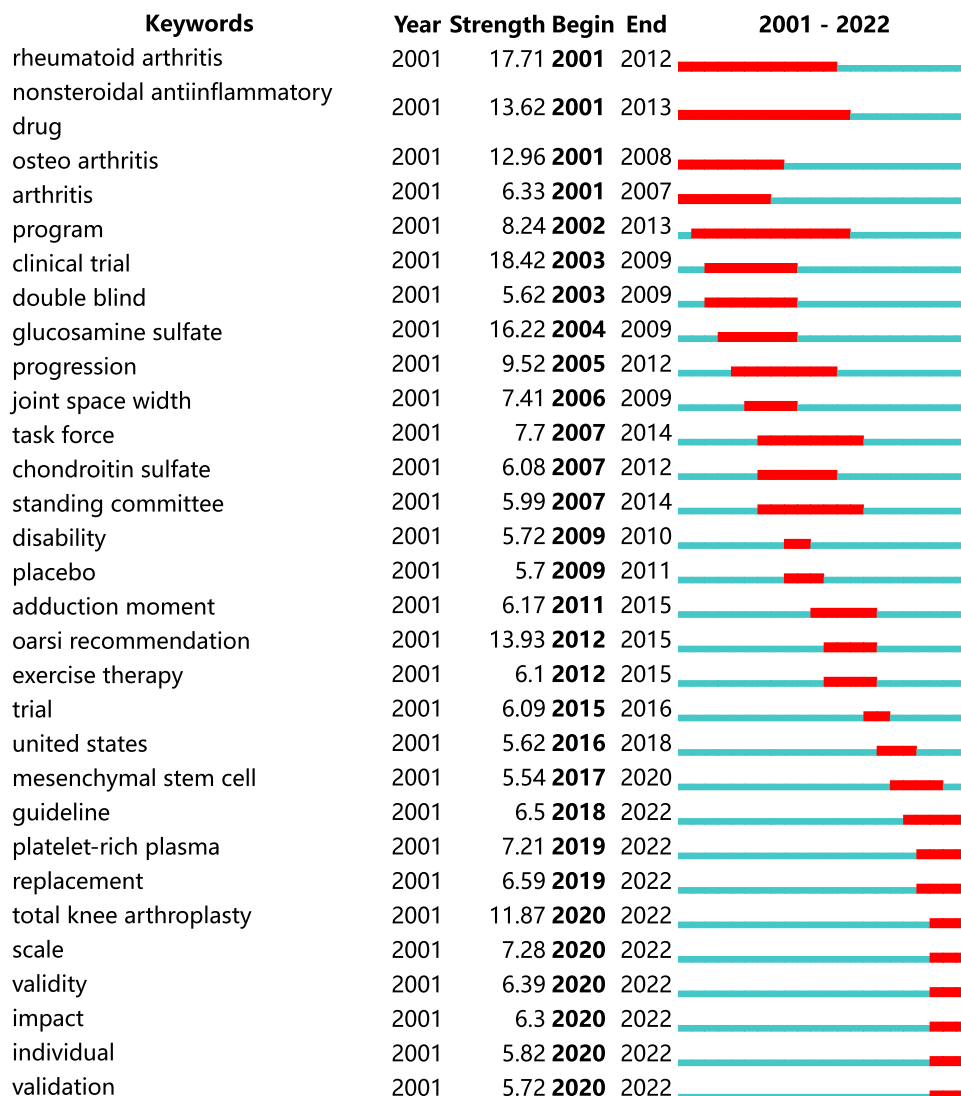


Figure 14 The top 30 keywords with the largest bursts related to clinical trials on knee osteoarthritis. The bolded type in the graph represents the point in time when the number of citations to an article increases significantly, indicating that the relevant research direction receives progressively more attention after that point in time.

Characterizations of Published Trials

The number of publications related to the clinical treatment of knee OA has experienced rapid growth in the past two decades (nearly 20-fold since 2001). Three different increased periods clarified the quantity and clinical importance of scientific research related to the clinical trials on knee OA. Clinical efficacy observations and understanding of knee OA before 2009 contributed to the burst research activity of the clinical trials during 2010–2018.^{51,52} There was a decrease in clinical trial studies in 2019, which may be due to COVID-19. COVID-19 lockdown has a significant impact on end-stage knee OA patients in many ways, such as physical activity and function, joint function, pain, etc.⁵³

International collaborative network analysis revealed the majority of clinical trials were conducted in developed countries such as America, England, Australia, and their domestic influential institutions. The dominant position of publications of China in developing countries is firmly established (Table 1 and Figure 4). This trend demonstrates that more effective interventions are urgently needed in these areas. In this study, we also explored in particular the directions

Table 4 Influential Published Clinical Trials Investigating the Safety and Efficacy of Diverse Treatment Measures for Knee Osteoarthritis

Year	Total Citations (Average)	No. of Subjects	Intervention & Design	Delivery Methods	Duration (M)	Primary Outcome Measures	Journal	[Ref.] NCT
2001	839 (38.14)	212	Glucosamine sulphate vs placebo	Oral	36	Mean joint-space width and WOMAC symptoms index; safety evaluation	<i>Lancet</i>	N/A ²⁸
2014	783 (87)	1635	Physical activity vs health education	-	30	Major mobility disability objectively defined by loss of ability to walk 400 m	<i>JAMA</i>	01072500 ⁶⁰
2006	777 (45.71)	1583	Glucosamine, chondroitin sulfate, and combination	Oral	6	20% decrease in knee pain from baseline to week 24	<i>NEJM</i>	00032890 ⁹
2004	687 (36.16)	316	Diet only, exercise only, and diet plus exercise vs healthy	-	18	Self-reported physical function as measured with the WOMAC	<i>Arthritis and Rheumatism</i>	N/A ⁵⁶
2011	620 (51.67)	93	Weight loss, exercise, or both	-	12	Change in score on the modified Physical Performance Test	<i>NEJM</i>	00146107 ⁵¹
2014	515 (57.22)	18	Mesenchymal stem cells	IA	6	Safety and the WOMAC index at 6 months.	<i>Stem Cells</i>	N/A ⁶¹
2018	443 (88.6)	240	Opioid vs nonopioid medications	Oral	12	Pain-related function ([BPI] interference scale) over 12 months	<i>JAMA</i>	01583985 ⁵²
2013	434 (43.4)	399	≥10% reduction in body weight (by diet), with or without exercise	-	18	Knee joint compressive force and plasma IL-6 levels	<i>JAMA</i>	00381290 ⁴²
2013	411 (41.1)	78	Platelet-rich plasma	IA	6	Evaluation of pain by WOMAC and VAS, satisfaction and complications	<i>AJSM</i>	N/A ⁶²
2003	407 (20.35)	1801	Enhancing care for depression	-	12	Depression, pain, health status and quality of life outcomes	<i>JAMA</i>	N/A ⁵⁸

Abbreviations: WOMAC index, Western Ontario and McMaster Universities osteoarthritis index; *JAMA*, *Journal of the American Medical Association*; BPI, Brief Pain Inventory; *NEJM*, *New England Journal of Medicine*; *AJSM*, *American Journal of Sports Medicine*; IA, Intra-articular injection; VAS, visual analog scale; N/A, not available.

of collaboration and research frontiers of different institutions and authors (Figures 5 and 6). Visualization results showed that the therapeutic measures or research hotspots in this field are mainly focused on manual acupuncture, intra-articular injection such as Hylan G-F injection, physical therapy, medications for disease-modifying such as chondroitin sulfate, lifestyle intervention such as diet, knee replacement, and pain management.

The journal *BMC Musculoskeletal Disorders* and *Osteoarthritis and Cartilage* published the majority of clinical trials on the treatment of knee OA, while the highly cited journals focusing on the cartilage, rheumatic diseases, and rehabilitation mainly include the journals *Osteoarthritis and Cartilage*, *Annals of the Rheumatic Diseases*, and *American Journal of Sports Medicine* (Table 3). These journals are bellwether in the domain of orthopedics, rheumatology, and sports sciences. The co-citation visualization (Figure 7) and top-cited trials illustrated that Mcalindon TE, Hochberg MC, Bannuru RR, and Zhang W were the game changers on the current concept of the clinical treatment of knee OA. Their future research may have a substantial impact on the development in this field and should be closely monitored to grasp the latest advancement. The same therapeutic focuses obtained in the cooperative network clustering analysis were roughly found in the co-cited visualization of references and journals. Noteworthy, finer research subcategories yielded in the co-cited visualization of references and journals demonstrated that there is a growing consensus among clinicians on the management concept of a thorough understanding of the treatment mechanism and precise control of symptoms.

The high-frequency keywords involving osteoarthritis, clinical trial, pain, management, exercise, older adult, and hip in the clinical trials on the treatment of knee OA were classified into 11 clusters (Figure 12). This indicates that clinical trials in this area are becoming more mature and precise in treatment. We were also able to clarify from the analysis the main current research directions and clinical strategies. Furthermore, the TimeLine mapping of these clusters (Figure 13) illustrated that these studies have been carried out for almost 20 years and are still ongoing. Burst detection analysis of top keywords showed that clinical trial,

rheumatoid arthritis, nonsteroidal anti-inflammatory, OA, glucosamine sulfate, oral recommendation, and total knee arthroplasty attracted relatively higher attention from researchers and clinicians during the past two decades (Figure 14). Additionally, mesenchymal stem cell, platelet-rich plasma, total knee arthroplasty, individual therapy, and treatment validation were among the new emerging since 2017. Therefore, the research foci in the clinical medication treatment of knee OA seem to have shifted from nonsteroidal anti-inflammatory drugs to intra-articular injection therapy. Arthroplasty is gradually becoming more acceptable to patients. In general, researchers are placing more emphasis on clinical efficacy and pursuing individualized precision medicine.

Treatment Findings and Areas of Uncertainty

In the past two decades, there has been a shift from pharmacologic treatment to nonpharmacologic therapy due to the limited efficacy of symptom relief and daily activity of the former.⁵⁴ Choice of effective medications for the base treatment of knee OA is uncertain. Pharmacological treatment is also gradually shifting from non-steroidal anti-inflammatory drugs (NSAIDs) to intra-articular injection therapy, especially mesenchymal stem cells.⁵⁵ Nonpharmacologic treatments mainly include exercise, diet therapy, self-efficacy and self-management program, Chinese medicine treatment such as manual acupuncture, and surgery. Clinical trials have proved that therapeutic exercise in patients with knee OA can significantly alleviate pain and improve joint function and quality of life.^{51,56,57} However, how to achieve reasonable physical exercise is still unclear. In overweight or obese patients, weight loss is urgently needed.¹¹ Clinicians could add exercise therapy as needed.⁵¹ Self-management programs include education, pain management, practice, and behavioral control such as fear, depression, and anxiety.^{11,58} In patients with advanced knee OA and uncontrolled pain with other nonsurgical therapies, knee arthroplasty should be considered.⁵⁹ More clinical data on the performance comparison between monotherapy and combination therapy are still needed. Large clinical trials are ongoing.

Limitations

Compared with reviews that cannot analyze massive heterogeneous articles, the present study based on bibliometric and visualized analyses provides a deep insight into the global status and trends of studies about the treatment of knee OA. However, our study has limitations. First, database bias. We searched only the Web of Science database that might differ from other databases such as PubMed, Scopus, and Embase to determine the relative studies. Second, the abbreviated forms and the plural forms of the same author, institution, country, and keywords might need to be merged during the analysis making the process cumbersome. Finally, we used the Medical Subject Headings (MeSH) that Web of Science does not have to standardize the search formula, which may lead to incomplete retrieval of publications.

Conclusion

Clinical trials on knee OA have flourished and matured after over 20 years of research. Bibliometric visualization in our study identified and characterized the publication trends and hotspots in this domain. Pharmacologic therapy including oral NSAIDs, glucosamine or chondroitin sulfate, intra-articular therapy including glucocorticoid and mesenchymal stem cells injections, nonpharmacologic therapy including exercise or diet, self-management programs and pain-coping skills training, Chinese medicine treatment such as manual acupuncture, and knee replacement were highly represented in the clinical trials on the clinical treatments of knee OA. Relevant results have been published in influential journals. Combination therapy may be the study foci in the future. The trends concluded from this cohort of articles furnish substantial confidence for future therapeutics for knee OA.

Abbreviations

Knee OA, osteoarthritis of the knee; RCT, randomized controlled trial; NCT, National Clinical Trial.

Data Sharing Statement

Data yielded in our study will be made available by the corresponding author to any qualified researchers.

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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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