frontiers in Materials

ORIGINAL RESEARCH
published: 25 February 2022
doi: 10.3389/fmats.2022.834950

A Worldwide Bibliometric and Visualized Analysis in Publications of Research About Hydrogel in Cartilage Repair

Jieyu Lai[1,2†], *Dengjie Yu*[1,3†], *Changkai Ni*[2], *Aohan Zhang*[2], *Wenfeng Xiao*[1,3]* and *Yusheng Li*[1,3]*

[1]Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, China, [2]Xiangya School of Medicine, Central South University, Changsha, China, [3]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China

OPEN ACCESS

Edited by:
Mingqiang Li,
Sun Yat-sen University, China

Reviewed by:
Zhao Tingxiao,
Zhejiang Provincial People's Hospital, China
Bin Wang,
Second Hospital of Shanxi Medical University, China

***Correspondence:**
Yusheng Li
Liyusheng@csu.edu.cn
Wenfeng Xiao
Xiaowenfeng@csu.edu.cn

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Biomaterials, a section of the journal Frontiers in Materials

Received: 14 December 2021
Accepted: 04 February 2022
Published: 25 February 2022

Citation:
Lai J, Yu D, Ni C, Zhang A, Xiao W and Li Y (2022) A Worldwide Bibliometric and Visualized Analysis in Publications of Research About Hydrogel in Cartilage Repair. Front. Mater. 9:834950. doi: 10.3389/fmats.2022.834950

Background: Cartilage defect is a common joint disease. Hydrogels are widely used in the area of cartilage tissue engineering because of their ability to repair the defect cartilage. This study aimed to analyze published research on hydrogels in cartilage repair by using both bibliometric and visualized analysis.

Methods: The related articles about hydrogel in cartilage repair was extracted from the Web of Science Core Collection database. SPSS was used for the data analysis. Bibliographic coupling analysis, co-citation analysis, co-authorship analysis and co-occurrence analysis were conducted using VOSviewer. Burst detection conducted with CiteSpace helped to indicate the change of keywords.

Results: A total of 1,245 articles related to hydrogels in cartilage repair from 1997 to 2020 were identified and analyzed. Publication numbers grew steadily and reached 187 papers in 2020. The United States contributed the most to the research with the highest number of times cited, average citations and H-index. Over the studied period, *Acta Biomaterialia* published the most articles about hydrogels in cartilage repair, numbering 77. Johns Hopkins University was the institution that had the highest average citations per item, and Sichuan University, Harvard University, and Kyoto University were tied for the first by the H-index. Ranking first in the world were the National Institutes of Health, specifically the National Institute of Arthritis Musculoskeletal Skin Diseases, the National Institute of Biomedical Imaging and Engineering and the National Institute of Dental Craniofacial Research, which jointly sponsored 383 articles.

Conclusions: We provided the research trend of hydrogel in cartilage repair information for global researchers to better understand the facts and future development of research on hydrogels in cartilage repair. The number of publications on hydrogels in cartilage repair will probably still increase in the coming years according to the current trend.

Keywords: hydrogel, cartilage repair, bibliometric analysis, visualized analysis, cartilage

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative joint diseases. The cartilage defect is the original pathological change among the OA process, which is closely related to the cartilage degeneration as well as both the initiation and progression of osteoarthritis. Lymphocytes and macrophages in synovial tissue secrete inflammatory factors, which can gradually affect and damage cartilage (Goldring and Goldring, 2016; Maudens et al., 2018). Cartilage lacks blood supply and located in a low-density environment, so it is difficult for defected cartilage to regenerate quickly (Fan et al., 2022). In addition, once the cartilage impaired, mechanical pressure can cause a greater damage to the defected cartilage. What's more, defected cartilage fragments can be produced by the wear, which may induce inflammation. Damaged cartilage needs early repair to achieve efficient regeneration (Zhang et al., 2019). The high incidence of OA has caused a heavy burden for individuals, families and even society as a whole.

Currently, various of methods for cartilage repair have been developed. Among them, tissue engineering has attracted many attentions (Huang et al., 2018). Tissue engineering consists of seed cells, biological scaffolds and favorable growth factors. Hydrogels are cross-linked hydrophilic polymers with a 3D network and high water content, which is similar to the soft tissue structure in the human body (Wang et al., 2018). Therefore, it can be used to deliver seed cells, growth factors and nutrients. Seed cells can constantly proliferate and secrete the extracellular matrix, and growth factors can induce chondrocyte expression and chondroblast differentiation (Kudva et al., 2019), eventually forming tissues and achieving the purpose of repairing cartilage defects and reconstructing functions. In addition, the ideal biological scaffold should display biocompatibility and bioabsorption. With the rapid progression of bioengineering, a variety of improved hydrogels have shown excellent biocompatibility and bioabsorption for the application of biological scaffolds. In recent years, tissue engineering based on hydrogels has displayed great advantages. It can repair large tissue defects, avoid donor complications and it shows better cartilage repair effects (Kwon et al., 2019).

Bibliometric analysis is an important method to analyze related studies in various fields, and it has been increasingly used to assess research. More specifically, bibliometric analysis is excellent for the discovery of undiscovered public knowledge, and relational bibliometrics provide some of more thrilling modes of research (Zou et al., 2018; Iqbal et al., 2019). Bibliometric methods can be applied to examine many publications, and the research can be expanded from institutions to the world level. The main purpose of bibliometric analysis is to transform something intangible into a manageable entity (Wallin, 2005). The information extracted from the databases was analyzed *via* bibliometric methodology, which can provide researchers with vast quantities of intuitive information. With the help of bibliometric analysis, information about different authors, countries, journals and institutions can be compared, and the differences between them can be displayed as an intuitive graph. Moreover, the visualized analysis makes it easier to discover the relationships among authors, keywords, countries, institutions and journals. Because of these outstanding advantages, bibliometric analysis has been frequently applied in various fields, such as stem cells for osteoarthritis (Xing et al., 2018), spines (Jia et al., 2015) and neoplasms (Ugolini et al., 2007). However, the quantitative and qualitative characteristics of global research on hydrogels in cartilage repair have not been analyzed before. This study aims to evaluate the current trends and status of the publications.

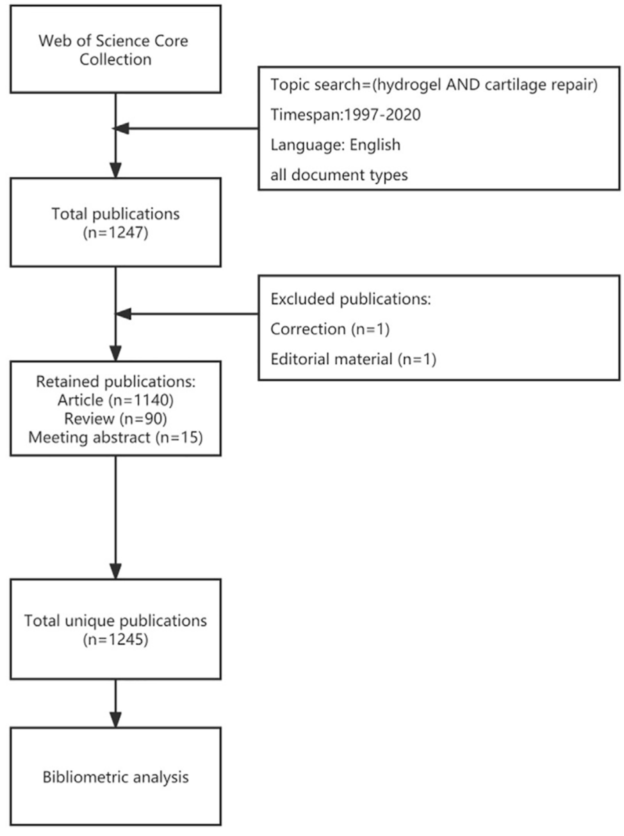

Figure 1 | Flowchart of literature selection

MATERIALS AND METHODS

Data Collection

Literature was extracted on 4 September 2021 from the Web of Science Core Collection. The search strategy are as follows: [TS = (hydrogel AND cartilage repair) AND PY = (1997-2020)] and English (Languages). A total of 1,247 publications from the Web of Science Core Collection were collected. We excluded invalid documents, including correction and editorial material. Articles, reviews, book chapters, proceedings papers and meeting abstracts were included (See **Figure 1**). Finally, a total of 1,245 publications were selected for our study. All data from the Web of Science Core Collection, which included titles, abstracts, author names, journals, publishers and countries, was saved as a TXT file.

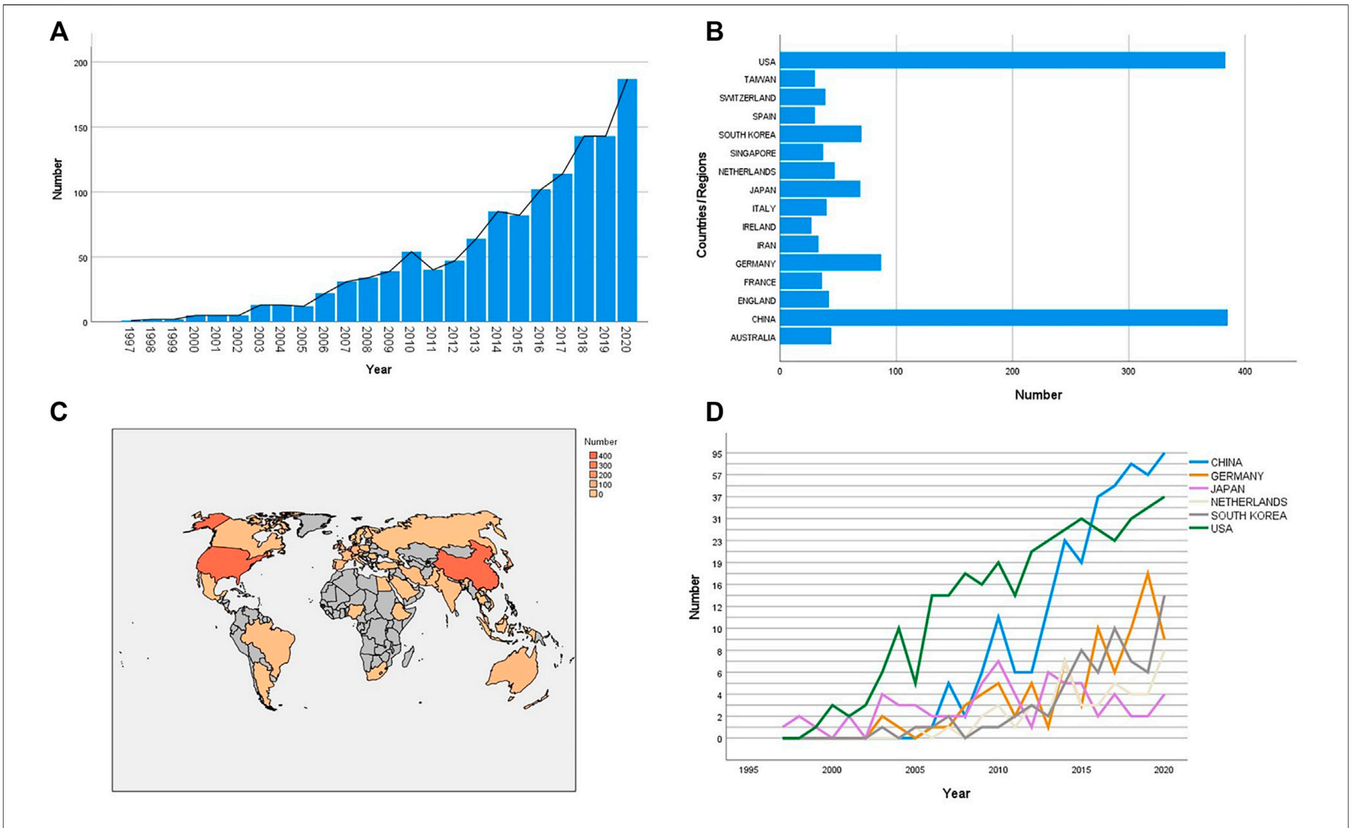

Figure 2 | Global trends and countries contributing to research of hydrogel in Cartilage repair **(A)** The Annual number of publications related to research of hydrogel in cartilage repair. **(B)** The sum of publications about research of hydrogel in cartilage repair from the top 16 countries. **(C)** The Worldwide heat map showing the contribution of different countries to research of hydrogel in cartilage repair.The area with the darker color contributes more to researches. **(D)** The Number of publications from top 6 countries over time.

Data Analysis

All data extracted from Web of Science Core Collection were converted into SPSS, VOSviewer, and CiteSpace to perform visual analysis. SPSS software (v.28.0, IBM) was used to analyze the data. The number of papers published globally and in different countries or regions every year, the heat map of studies worldwide and indicators of the quality of a country's papers, including total times of citation, average citation per item and H-index, were all protracted in graphs by SPSS. Meanwhile, by using VOSviewer (v.1.6.17.0), bibliographic coupling analysis, co-authorship analysis, co-citation analysis and co-occurrence analysis were finished, and visualized maps were produced. Burst detection performed by CiteSpace (5.8.2.0) also played an important role in the analysis of keywords. The trends in the number of publications from the top six countries over time were analyzed using linear regression, and statistical significance was considered when p values were less than 0.05.

RESULTS

Analysis of Global Publications

Changes in the number of publications can reflect the development of this field. The future trend of research can be shown directly by carrying out data analysis and drawing charts. There were a total of 1,245 articles derived from the WOS databases from 1997 to 2020. It is clear that the number of studied related to hydrogels in cartilage repair grew steadily over this period, and the literature published in the last five years (2016-2020) made up a large part in the sum of publications, accounting for 55.3% of the total publications (**Figure 2A**). **Figure 2B** showed different countries' contributions to worldwide research. China had the most contributions with 385 articles (30.9%), followed by the United States (383 articles, 30.8%), Germany (87 articles, 7.0%), South Korea (70 articles, 5.6%) and Japan (69 articles, 5.5%). Meanwhile, the top 16 countries jointly made great contributions to global research on hydrogels in cartilage repair. Shown in **Figure 2C**, the world heat map effectively showed the contributions of different countries. The areas covered by a darker color contribute more to worldwide research. Compared with countries in developing areas, countries in developed areas published more papers from 1997 to 2020. From **Figure 2D**, it is easy to see that the publications of each top country also increased annually: China ($R^2 = 0.695$, $p < 0.001$), the United States ($R^2 = 0.943$, $p < 0.001$), Germany ($R^2 = 0.663$, $p < 0.001$), South Korea ($R^2 = 0.695$, $p < 0.001$), Japan ($R^2 = 0.206$, $p < 0.05$) and Netherlands ($R^2 = 0.701$, $p < 0.001$).

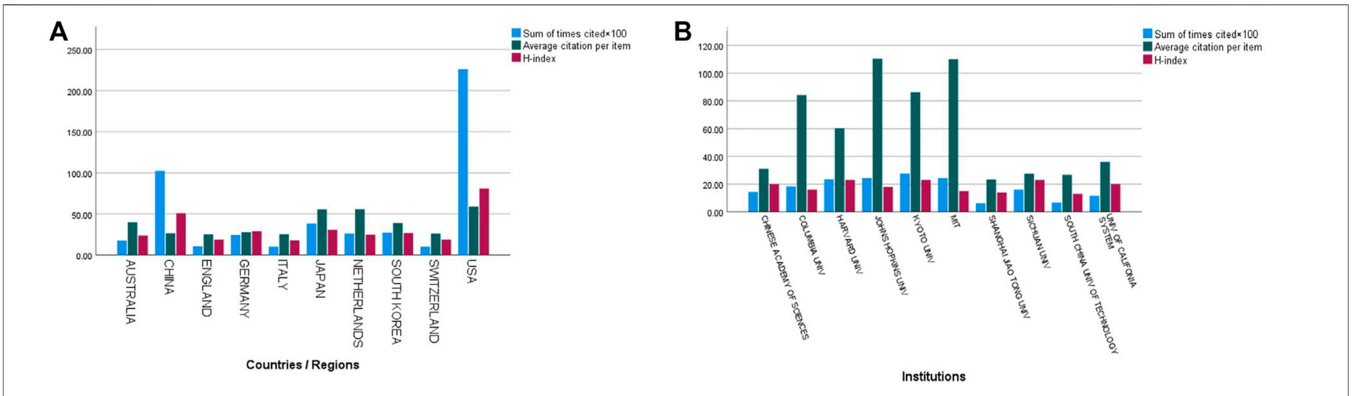

Figure 3 | Analysis of citation and H-index of different countries/regions and institutions.**(A)** Sum of times cited average citation per item and H-index of top 10 countries or regions.**(B)** Sum of times cited average citation per item and H-index of top 10 institutions MIT; Massachusetts Institute Of Technology.

Analysis of Citation and H-Index

Figure 3A shows the sum of times cited, average citation of each item and H-index of the top 10 countries/regions worldwide. Among them, with 22,589 citations, 58.98 average citations per item and an H-index of 81, the United States undoubtedly played a leading role in this field, ranking first in these three aspects. The total number of citations, average citations per item and H-index of the top 10 institutions are included in **Figure 3B**. Sichuan University, Harvard University, and Kyoto University were tied for the first in the world in regard to H-index (23). Johns Hopkins University had the highest average citations per item (110.45), and Kyoto University's total number of citations was the highest in the world (2,758). In addition, there were six other top institutions: Chinese Academy of Sciences (20 H-index), University of California system (20 H-index), Columbia University (16 H-index), Shanghai Jiao Tong University (14 H-index), University of Colorado system (14 H-index) and South China University of Technology (13 H-index).

Study Category and Article Type Analysis

Globally, studies about hydrogels in cartilage repair were categorized into 78 study types. As is shown in **Figure 4A**, materials science biomaterials with 525 articles (42.169%) were observed most frequently. followed by engineering biomedical with 481 articles (38.635%), cell tissue engineering with 178 articles (14.297%), cell biology with 159 articles (12.771%), polymer science with 134 articles (10.763%) and orthopedics with 128 articles (10.281%). Additionally, 1,114 articles (89.478%), 90 review articles (7.229%), 44 proceeding articles (3.534%), 24 book chapters (1.928%) and 15 meeting abstracts (1.205%) were published in this field (**Figure 4B**). The number of publications of articles and review articles from China are respectively 350 and 30, which both exceeded that of any other country.

Journals and Funding Agency Analysis

In total, 352 journals published papers related to hydrogels in cartilage repair. The top 10 journals that published the most papers are presented in **Figure 5A**. Among them, *Acta Biomaterialia* made the greatest contribution to global research related to hydrogels in cartilage repair, with 77 articles (6.2%), followed by *Biomaterials* (67, 5.4%), *Tissue Engineering Part A* (55, 4.4%), *Journal of Biomedical Materials Research Part A* (41, 3.3%) and *Materials Science Engineering C Materials for Biological Applications* (33, 2.7%).

As **Figure 5B** shows, the NIH United States, NIAMS, NIBIB and NIDCR jointly sponsored 383 articles (30.8%), making the greatest contribution to related research worldwide. NSFC was also an active contributor and ranked second worldwide by sponsoring 267 articles (21.4%).

Bibliographic Coupling Analysis

By analyzing the sum of the reference items used together, bibliographic coupling analysis can help to discover the relatedness of items. The resulting maps of primary authors, institutions and countries directly displayed the connection network among them in research on hydrogels in cartilage repair. As **Figure 6** shows, an author, institution or country is represented by a point, and the line between any two points symbolizes their collaborations. The thickness of the line is called the link strength, and the thicker the line is, the stronger the collaboration. The same applies to co-authorship analysis, co-citation analysis and co-occurrence analysis.

According to the total link strength (TLS), 114 authors are presented in **Figure 6A**. Moreover, in **Figure 6A**, the larger the dots are, the stronger the power of the author in global hydrogel cartilage repair research. Based on papers with a minimum number of documents of an author greater than 5, the top 5 authors were Zhang Xingdong (TLS = 14,341), Mauck Robert L (TLS = 9,734), Kitamura Nobuto (TLS = 9,709), Yasuda Kazunori (TLS = 9,709), Gong Jianping (TLS = 8,872) and Kurokawa Takayuki (TLS = 8,853). There were 123 institutions in **Figure 6B** based on the minimum number of documents of an institution of more than 5. The top 5 institutions with the most TLSs were listed: Chinese Academy Sciences (TLS = 22,786), Sichuan University (TLS = 22,167), Massachusetts Institute of Technology (TLS = 14,897), Utrecht University (TLS = 14,337) and Pennsylvania University. (TLS = 14,284). The top 5 countries

Figure 4 | Analysis of study category and article type related to research on hydrogels in cartilage repair. **(A)** Study categories of research on hydrogels in cartilage repair. **(B)** Article types of research on hydrogels in cartilage repair.

based on the minimum number of documents of a university greater than 5 included the United States (TLS = 141,965), China (TLS = 116,108), Germany (TLS = 38,981), Netherlands (TLS = 32,763) and South Korea (TLS = 32,271) (**Figure 6C**).

Co-authorship Analysis

By analyzing the sum of co-authored documents, co-authorship analysis can help to discover the relatedness of items. The resulting maps of primary authors, institutions and countries directly displayed the connection network among them in research on hydrogels in cartilage repair. Valuable information can guide researchers in finding authors to cooperate with, institutions to making the acquaintance of other institutions, and countries to developing cooperation at the world level. After analyzing the data in VOSviewer, there were 44 authors, 118 institutions and 28 countries in the resulting maps. Authors, institutions and countries were all based on the minimum number of documents of an author, an institution or a country of no less than 5. Zhang Xingdong had the most TLSs (94), followed by Fan Yujiang (TLS = 59), Kitamura Nobuto (TLS = 36), Yasuda Kazunori (TLS = 36) and Kurokawa Takayuki (TLS = 34) (**Figure 7A**). In terms of TLS, the top 5 institutions were Chinese Academy Science (TLS = 62), Harvard University (TLS = 35), Sichuan

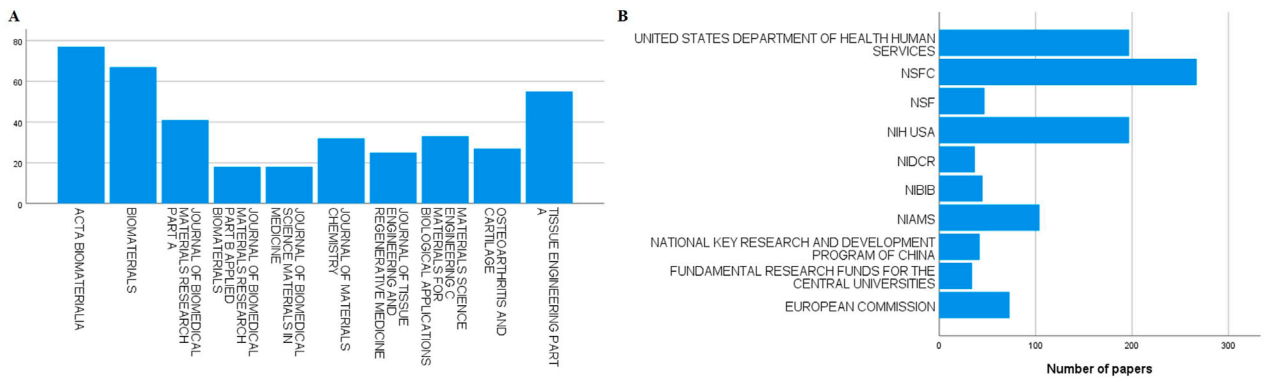

Figure 5 | Analysis of journals and fundings agency related to researches of hydrogel in cartilage repair. **(A)** The number of papers published by the top 10 journals. **(B)** Top 10 funding agency Contributing to the global research hydrogel in cartilage repair. NSFC, National Institute of Dental Carniofacial Research; NIBIB, National Institute of Biomedical Imaging Bioengineering; NIAMS, National Institute Of Arthritis Musculoskeletal Skin Diseases.

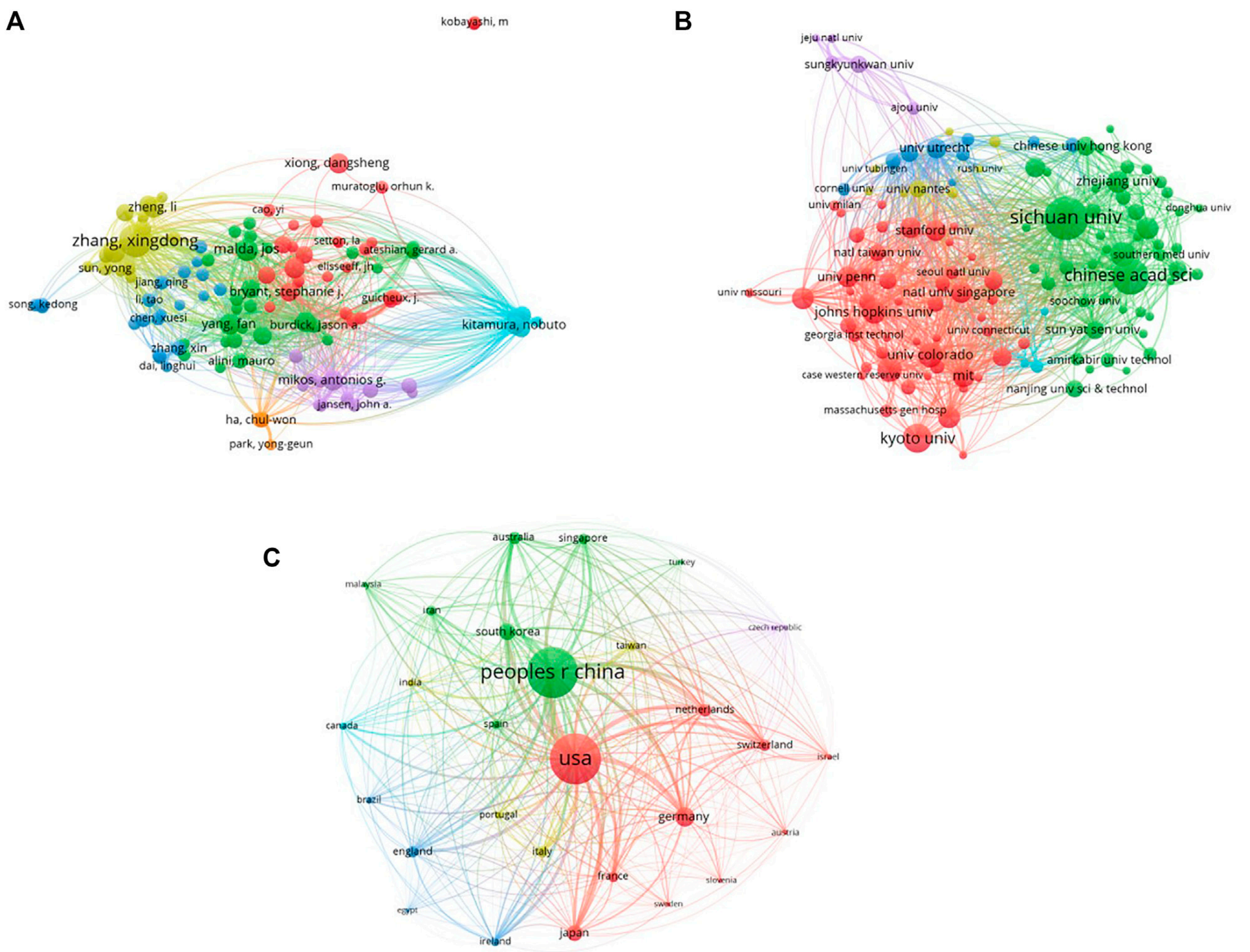

Figure 6 | Bibliographic coupling analysis of research on hydrogels in cartilage repair. **(A)** Map of 113 authors related to research on hydrogels in cartilage repair. **(B)** Map of 123 institutions related to research on hydrogels in cartilage repair. **(C)** Map of 29 countries related to research on hydrogels in cartilage repair. The thicker the connecting line the stronger the relationship between two dots.

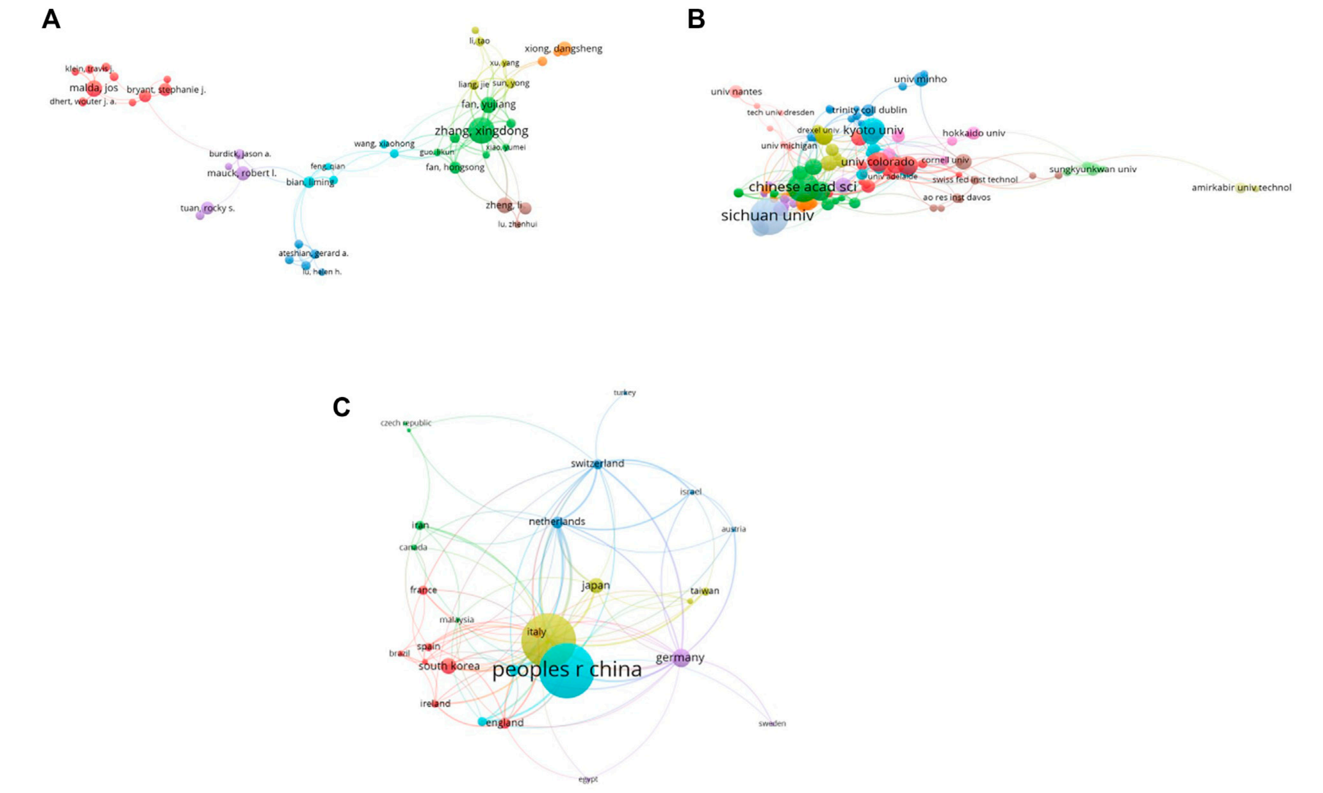

Figure 7 | Co-authorship analysis of researches about hydrogel in cartilage repair. **(A)** Map 44 authors related to researches about hydrogel in cartilage repair. **(B)** map of 118 institutions related to researches about hydrogel in cartilage repair. **(C)** Map of 28 countries related to researches about hydrogel in cartilage repair. The frequency is represented by the size of the dots and the cooperation between two authors/institutions/countries is represented by the line between two dots. The thicker the connecting line, the stronger the relationship between two dots.

University (TLS = 32), Chinese University Hong Kong (TLS = 31) and Utrecht University (TLS = 31) (**Figure 7B**). Similarly, the United States (TLS = 169), China (TLS = 108), Netherlands (TLS = 63), Germany (TLS = 59) and Australia (TLS = 47 times) were the top 5 countries with the most TLSs (**Figure 7C**).

Co-citation Analysis

By analyzing the number of times items are cited together, co-citation analysis can help to discover the relatedness of the items. Significant information can be rapidly and conveniently obtained from a very large number of cited papers. Moreover, the resulting maps will show the relevance of items intuitively. A total of 186 references were analyzed *via* VOSviewer with the minimum number of citations of a cited reference of no less than 20, and the top 5 were as follows (**Figure 8A**): *The New England Journal of Medicine*.1994 OCT; 331(14):889-905 (TLS = 897), *Osteoarthritis And Cartilage* (Brittberg et al., 1994). 2002 JUL; 10(7):564-572 (TLS = 823) *Science*. 1999 (Hunziker, 2002), APR; 284(5,411): 143-147 (TLS = 688), *Science*. 2012 NOV (Pittenger et al., 1999); 338(6,109):917-921 (TLS = 671) and *Biomaterials*. 2011 DEC (Huey et al., 2012); 32(34):8,771-8,782 (TLS = 612) (Kim et al., 2011). Based on papers with the minimum number of citations of a source, more than 30, 260 sources are shown in **Figure 8B**. *Biomaterials* (TLS = 368,025), *Acta Biomaterialia* (TLS = 130,985), *Osteoarthritis Cartilage* (TLS = 106,674), *Journal of Biomedical Materials Research Part A* (TLS = 94,737) and *Tissue Engineering Part A* (TLS = 93,501) were the top 5 journals with the largest TLS. Similarly, 214 authors with papers of the minimum number of citations of an author more than 30 were analyzed through the VOSviewer, and the top 5 authors with largest TLS were listed (See **Figure 8C**): Hunziker EB (TLS = 4,236), Bryant SJ (TLS = 3,945), Mauck RL (TLS = 3,545), Chung C (TLS = 3,448) and Park H (TLS = 3,227).

Co-occurrence Analysis

By analyzing the number of papers in which items occur together, co-occurrence analysis aims to discover the relatedness of items and to show the internal relationship of a certain scientific field. From the resulting maps of keywords, it is also easier to obtain advanced information in this field. Popular topics were demonstrated in keyword maps *via* co-occurrence analysis, which can help researchers follow up on the development of domain research. Keywords based on the minimum number of occurrences greater than 4 from 1988 to 2000 are included in **Figure 9A**. There were only 3 keywords: articular cartilage, tissue and hydrogel. **Figure 9B** shows 76 keywords with a minimum number of occurrences greater than 10 for 2010. Research on hydrogels in cartilage repair has expanded to the protein level and

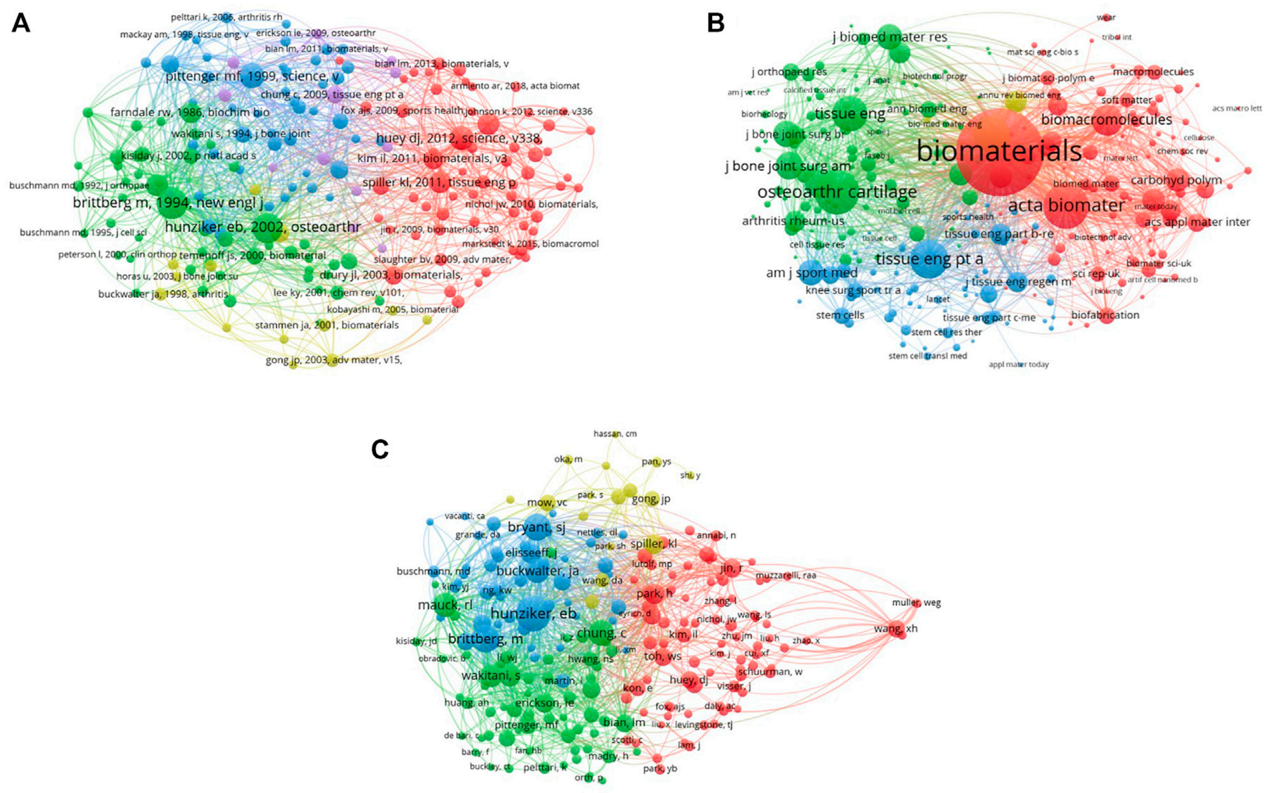

Figure 8 | Co-citation analysis of researches about hydrogel in cartilage repair. **(A)** Map of co-cited reference related to researches about hydrogel in cartilage repair. **(B)** Map of co-cited journals related to researches about hydrogel in cartilage repair. **(C)** map of co-cited authors related to researches about hydrogel in cartilage repair. The citation frequency is represented by the size of the dots and the line between two represents that the two were cited in a same paper/journal. Shorter the line, stringer the link between two dots.

added new topics, such as mesenchymal stem cells, growth factors, collagen type, viability, scaffolds and tissue engineering. Most studies have been carried out *in vitro* or *in vivo* in animals, and the mechanism of cartilage damage and repair has been recognized and gradually explained. Moreover, new materials have been applied to improve the composition of hydrogels (Miljkovic et al., 2009). For 2020, keywords with the minimum number of occurrences greater than 10 increased rapidly to 371 (**Figure 9C**). Some keywords that appeared before were also included, such as mesenchymal stem cells and articular cartilage. In addition, there were also some new keywords, such as engineering, bioprinting, polymers, osteochondral defect, implantation and transplantation. At this time, some studies were carried out *in vivo* in humans. In addition, new methods have been applied to treat cartilage damage, such as tissue engineering and 3D bioprinting (Duchi et al., 2020).

Figure 9D shows the burst detection of the top 10 keywords. From the burst time, implant was the earliest keyword to emerge (1998) in this field and lasted the longest (12 years), which indicates that implantation was likely the ideal therapy for cartilage damage in the early years. In addition, regeneration became a popular topic from 2017 to 2018, indicating that the direction of therapy changed from inserting new cells in patients from the outside to helping patients' cells regenerate.

DISCUSSION

Trends of Papers of Researches About Hydrogel in Cartilage Repair

By bibliometric analysis and visualized analysis, this study aimed to evaluate the trends and predict the development of research on hydrogels in cartilage repair. From 1997 to 2020, the sum of publications increased steadily, and it is easy to predict the growth of publications in coming years. Articular cartilage will be damaged to varying degrees in cases of acute trauma and chronic wear. With the aging and increasing obesity of the world population, there is a large increase in the demand for clinical treatment of osteoarthritis (Cross et al., 2014). Tissue engineering is a promising way to treat cartilage damage caused by osteoarthritis and hydrogels are considered as the ideal materials for tissue engineering, which can explain the growth of publications in the field of hydrogels in cartilage repair to some extent. Meanwhile, hydrogel has shown its promising prospect in acute cartilage defects. Jeong et al. demonstrated a injectable hyaluronate hydrogel, which successfully repaired *in situ* cartilage defect (Jeong et al., 2020). It

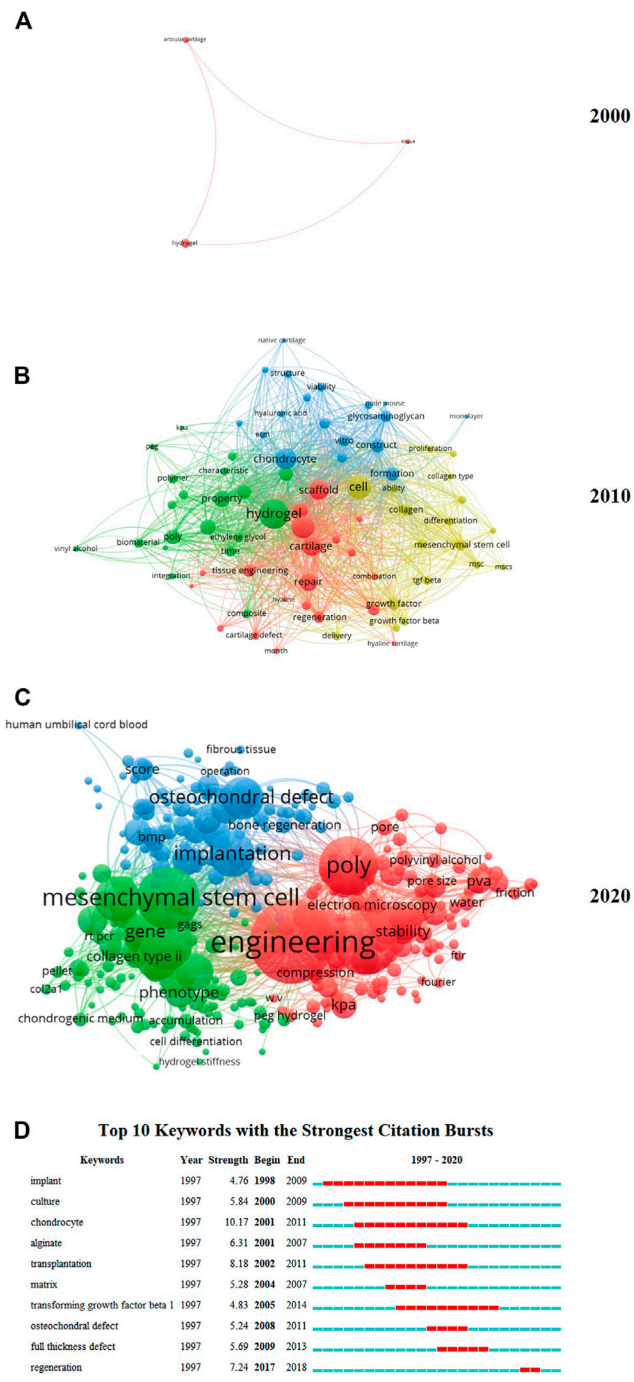

Figure 9 | Co-occurrence analysis of researches about hydrogel in cartilage repair. **(A)** Map of keywords of researches about hydrogel in cartilage repair from 1988 to 2000. **(B)** map of researches about hydrogel in cartilage repair from 1988 to 2010. **(C)** map of keywords is represented by a dot and the size of the dot represents the number of publications in this dot. The line between two dotsa shows the collaboration and co-occurrence. The Larger the number of publications for which two dots are both found, the stronger the relationship between the dots. **(D)** Burst detections of top 10 keywords with the strongest citation bursts.

showed the potential in treating early cartilage defect caused by athletic injury and preventing occurrence and development of osteoarthritis in the future. There were 27 countries or regions that had published papers related to hydrogels in cartilage repair. The top six countries or regions, which published the most documents, all made great progress in the number of publications in recent years. Popular topics and promising research orientations were also shown in our study. Compared with traditional drug therapy, tissue engineering is a better choice for clinical treatment and hydrogels are considered as suitable scaffolds for the transplantation of mesenchymal stem cells (He et al., 2017). Treated by tissue engineering, the patients who have cartilage damage will have less complications and better cartilage repair effects. Researchers can study in a more specific field and further study can be carried out for promising and significant applications.

Current Situation and Quality of Global Publications

China made the greatest contribution to the global publications according to the graph of contributions of countries/regions. For journals, *Acta Biomaterialia* published the most papers. In terms of funding agencies, NIH United States, NIAMS, NIBIB and NIDCR jointly ranked first in the world by sponsoring a great number of publications. The sum of citation times, average citation per item and H-index were the criteria for judging the quantity and quality of the papers of a country, a region and an institution. With the highest number of citations, average citations per item and H-index, the United States can be considered the leading country for and best contributor to global research associated with hydrogels in cartilage repair. The average citations per item and H-index are both recommended criteria for judging the quality of papers published by a country, a region or an institution, and they can represent the academic impact of a country, a region or an institution. The average citations per item are in accord with the H-index because the United States ranked first in both aspects. In terms of institutions, some universities in the United States also made great contributions. For instance, Johns Hopkins University had the highest average citation per item, and its H-index ranked 6th in all institutions worldwide. Meanwhile, with the largest H-index, Harvard University took a lead globally. Also, Sichuan University and Kyoto University, also had the largest H-index and contributed greatly to this field.

Bibliographic coupling means two publications cite the same third publications in their references. In this study, through bibliographic coupling analysis, the internal relationship of a great number of authors, institutions and countries was demonstrated and illustrated. The authors shown in **Figure 6A** probably contributed most to the research on hydrogels in cartilage repair. Their latest publications and research should receive more attention, and they are likely to have significantly advanced discoveries in this field. In **Figure 6B**, the top 2 institutions with the most TLSs were from China and are Sichuan University and Chinese Academy Sciences respectively. This proved that China played an important role in this field by creating excellent institutions at the world level. As **Figure 6C** showed, the United States is the country that contributed most to global research. In addition, China also made great contributions to research, which echoed the bibliographic coupling analysis results of institutions. Co-authoring can help researchers innovate and obtain new information. By co-authorship analysis, the collaboration among different authors, institutions and countries was assessed and demonstrated. Authors, institutions and countries with higher TLSs were more willing to cooperate with others, which provided directions for research to find partners. Therefore, Zhang Xingdong, Chinese Academy Sciences and the United States may be ideal choices for researchers to collaborate with. Through counting times that papers were cited together, co-citation analysis can also evaluate the influence of studies. In **Figure 8A**, a variety of frequently cited references were included. Biomaterials was the journal with the largest frequency of citations, and Hunziker EB, Bryant SJ and Mauck RL had great achievements in this domain.

Researches Concentrated on Hydrogel in Cartilage Repair

Keywords from titles and abstracts of all extracted publications were analyzed by co-occurrence analysis. Keywords for 2000, 2010 and 2020 were shown in **Figure 9**. The yearly sum of the keywords increased from 4 in 2000 to 371 in 2020, which indicates that the content of this field was enriched. Moreover, popular topics were also represented in the resulting maps. Tissue engineering, polymers, collagen and human mesenchymal stem cells were all hotspots in this research field. Articular cartilage was an important keyword from 2000 to 2020, which indicated that studies of hydrogels in cartilage repair were related to osteoarthritis. Plolymers, such as polyethylene glycol (PEG) hydrogels, are a new type of chemical hydrogels, which characterize in its 3D network and are similar with soft tissue structure in human body. Mesenchymal stem cells, as the ideal seed cells for tissue engineering, have many advantages. Compared with chondrocytes, it is easy to obtain mesenchymal stem cells and mesenchymal stem cells have the ability to differentiate into other cell types (Ferrand et al., 2011), which can explain the popularity of mesenchymal stem cells in researches of hydrogels in cartilage repair. Most studies were original articles and many of them concentrated on the materials science biomaterials and engineering biomedical fields. The studies were mainly carried out *in vitro* or *in vivo* in animals while *in vivo* studies in humans were gradually carried out.

Advantages and Limitations

Publications of research on hydrogels in cartilage repair were all extracted from the Web of Science Core Collection. In addition, the current situation and quality of studies were analyzed *via* bibliometric analysis and visualized analysis so that the study is relatively comprehensive and objective. Nevertheless, there were still some limitations in this study. Publications published in 2021 were not included in this study, and non-English papers were also excluded. Thus, further study should introduce newly published papers and non-English papers.

CONCLUSION

This study presented the current global situation and trends in research on hydrogels in cartilage repair. The United States was the best contributor to research and took a lead in worldwide research over the examined period. *Acta Biomaterialia* had the most publications related to hydrogels in cartilage repair. What is most remarkable is that there is likely to be an increasing number of publications in the future. Tissue engineering and mesenchymal stem cells are popular topics in this field. Because of the promising biocompatibility and bioabsorption of hydrogels, tissue engineering based on hydrogels shows unique advantages, including better cartilage repair and the decrease of donor complications. Mesenchymal stem cell, as the ideal seed cell in tissue engineering because of its great potential for differentiation, is also a hot spot. Therefore, an increasing number of researchers will pay attention to these fields, which may lead to great achievements in the coming years. With the development of medical technology, the experiments of hydrogels in cartilage repair have been carried out *in vivo*. In addition, tissue engineering has already been used to treat cartilage repair in clinic.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

This article was written by JL and DY. Data was collected and analyzed by CN and AZ. WX and YL designed and revised this study. All authors consent to the final vision of the manuscript and are willing to take responsibility for the content of all works provided.

FUNDING

This work was supported by National Natural Science Foundation of China (No. 81874030, 82072506), National Key R&D Program of China (2019YFA0111900), National Clinical Research Center for Geriatric Disorders (Xiangya Hospital,Grant No. 2021KFJJ02), National Clinical Research Center for Orthopedics, Sports Medicine and Rehabilitation (2021-NCRC-CXJJ-PY-40), Science and Technology Innovation Program of Hunan Province (No. 2021RC3025), Provincial Natural Science Foundation of Hunan (No. 2020JJ3060), Provincial Clinical Medical Technology Innovation Project of Hunan (No. 2020SK53709), the Administration of Traditional Chinese Medicine of Hunan Province (No. 2021075), Innovation-Driven Project of Central South university (No. 2020CX045), Wu Jieping Medical Foundation (320.6750.2020-03-14), CMA Young and Middle-aged Doctors Outstanding Development Program – Osteoporosis Specialized Scientific Research Fund Project (G-X-2019-1107-12) and the Independent Exploration and Innovation Project for Postgraduate Students of Central South University (No. 2021XQLH041).

REFERENCES

Brittberg, M., Lindahl, A., Nilsson, A., Ohlsson, C., Isaksson, O., and Peterson, L. (1994). Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation. *N. Engl. J. Med.* 331, 889–895. doi:10.1056/nejm199410063311401

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., et al. (2014). The Global burden of Hip and Knee Osteoarthritis: Estimates from the Global burden of Disease 2010 Study. *Ann. Rheum. Dis.* 73, 1323–1330. doi:10.1136/annrheumdis-2013-204763

Duchi, S., Onofrillo, C., O'Connell, C., Wallace, G. G., Choong, P., and Di Bella, C. (2020). "Bioprinting Stem Cells in Hydrogel for *In Situ* Surgical Application: A Case for Articular Cartilage, *Methods Mol. Biol.*, 2140, 145–157. doi:10.1007/978-1-0716-0520-2_9

Fan, X., Wu, X., Trevisan Franca De Lima, L., Stehbens, S., Punyadeera, C., Webb, R., et al. (2022). The Deterioration of Calcified Cartilage Integrity Reflects the Severity of Osteoarthritis-A Structural, Molecular, and Biochemical Analysis. *Faseb J.* 36. doi:10.1096/fj.202101449r

Ferrand, J., Noël, D., Lehours, P., Prochazkova-Carlotti, M., Chambonnier, L., Ménard, A., et al. (2011). Human Bone Marrow-Derived Stem Cells Acquire Epithelial Characteristics through Fusion with Gastrointestinal Epithelial Cells. *PLoS One* 6, e19569e19569. doi:10.1371/journal.pone.0019569

Goldring, S. R., and Goldring, M. B. (2016). Changes in the Osteochondral Unit during Osteoarthritis: Structure, Function and Cartilage-Bone Crosstalk. *Nat. Rev. Rheumatol.* 12, 632–644. doi:10.1038/nrrheum.2016.148

He, Z., Wang, B., Hu, C., and Zhao, J. (2017). An Overview of Hydrogel-Based Intra-articular Drug Delivery for the Treatment of Osteoarthritis. *Colloids Surf. B: Biointerfaces* 154, 33–39. doi:10.1016/j.colsurfb.2017.03.003

Huang, K., Li, Q., Li, Y., Yao, Z., Luo, D., Rao, P., et al. (2018). Cartilage Tissue Regeneration: The Roles of Cells, Stimulating Factors and Scaffolds. *Cscr* 13, 547–567. doi:10.2174/1574888x12666170608080722

Huey, D. J., Hu, J. C., and Athanasiou, K. A. (2012). Unlike Bone, Cartilage Regeneration Remains Elusive. *Science* 338, 917–921. doi:10.1126/science.1222454

Hunziker, E. B. (2002). Articular Cartilage Repair: Basic Science and Clinical Progress. A Review of the Current Status and Prospects. *Osteoarthritis and Cartilage* 10, 432–463. doi:10.1053/joca.2002.0801

Iqbal, U., Rehan, A., Akmal, M., Jamali, M., Iqbal, A., Khan, B. A., et al. (2019). Top 100 Most Influential Articles in the Field of Myeloid Neoplasms: A Bibliometric Study. *Acta Haematol.* 141, 68–78. doi:10.1159/000493251

Jeong, S. H., Kim, M., Kim, T. Y., Kim, H., Ju, J. H., and Hahn, S. K. (2020). Supramolecular Injectable Hyaluronate Hydrogels for Cartilage Tissue Regeneration. *ACS Appl. Bio Mater.* 3, 5040–5047. doi:10.1021/acsabm.0c00537

Jia, Z. W., Wu, Y. H., Li, H., Li, H. F., Zhao, X. Y., Tang, Y., et al. (2015). Growing Trend of China's Contribution to the Field of Spine: a 10-year Survey of the Literature. *Eur. Spine J.* 24, 1806–1812. doi:10.1007/s00586-015-4030-y

Kim, I. L., Mauck, R. L., and Burdick, J. A. (2011). Hydrogel Design for Cartilage Tissue Engineering: a Case Study with Hyaluronic Acid. *Biomaterials* 32, 8771–8782. doi:10.1016/j.biomaterials.2011.08.073

Kudva, A. K., Dikina, A. D., Luyten, F. P., Alsberg, E., and Patterson, J. (2019). Gelatin Microspheres Releasing Transforming Growth Factor Drive *In Vitro* Chondrogenesis of Human Periosteum Derived Cells in Micromass Culture. *Acta Biomater.* 90, 287–299. doi:10.1016/j.actbio.2019.03.039

Kwon, H., Brown, W. E., Lee, C. A., Wang, D., Paschos, N., Hu, J. C., et al. (2019). Surgical and Tissue Engineering Strategies for Articular Cartilage and Meniscus Repair. *Nat. Rev. Rheumatol.* 15, 550–570. doi:10.1038/s41584-019-0255-1

Maudens, P., Jordan, O., and Allémann, E. (2018). Recent Advances in Intra-articular Drug Delivery Systems for Osteoarthritis Therapy. *Drug Discov. Today* 23, 1761–1775. doi:10.1016/j.drudis.2018.05.023

Miljkovic, N. D., Lin, Y.-C., Cherubino, M., Minteer, D., and Marra, K. G. (2009). A Novel Injectable Hydrogel in Combination with a Surgical Sealant in a Rat Knee Osteochondral Defect Model. *Knee Surg. Sports Traumatol. Arthrosc.* 17, 1326–1331. doi:10.1007/s00167-009-0881-2

Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., et al. (1999). Multilineage Potential of Adult Human Mesenchymal Stem Cells. *Science* 284, 143–147. doi:10.1126/science.284.5411.143

Ugolini, D., Puntoni, R., Perera, F. P., Schulte, P. A., and Bonassi, S. (2007). A Bibliometric Analysis of Scientific Production in Cancer Molecular Epidemiology. *Carcinogenesis* 28, 1774–1779. doi:10.1093/carcin/bgm129

Wallin, J. A. (2005). Bibliometric Methods: Pitfalls and Possibilities. *Basic Clin. Pharmacol. Toxicol.* 97, 261–275. doi:10.1111/j.1742-7843.2005.pto_139.x

Wang, L., Huang, J., Huang, C., Li, Q., Liu, L., Luo, S., et al. (2018). Adult Stem Cells and Hydrogels for Cartilage Regeneration. *Cscr* 13, 533–546. doi:10.2174/1574888x12666170511142917

Xing, D., Zhao, Y., Dong, S., and Lin, J. (2018). Global Research Trends in Stem Cells for Osteoarthritis: a Bibliometric and Visualized Study. *Int. J. Rheum. Dis.* 21, 1372–1384. doi:10.1111/1756-185x.13327

Zhang, Y., Liu, S., Guo, W., Hao, C., Wang, M., Li, X., et al. (2019). Coculture of hWJMSCs and pACs in Oriented Scaffold Enhances Hyaline Cartilage Regeneration *In Vitro*. *Stem Cell Int.* 2019, 5130152. doi:10.1155/2019/5130152

Zou, X., Yue, W. L., and Vu, H. L. (2018). Visualization and Analysis of Mapping Knowledge Domain of Road Safety Studies. *Accid. Anal. Prev.* 118, 131–145. doi:10.1016/j.aap.2018.06.010

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.