Bibliometric and visual analysis of mesenchymal stem cells in the treatment of osteoporosis based on CiteSpace software

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Abstract

Background: The focus of research in the treatment of osteoporosis (OP) has evolved from promoting bone formation and inhibiting bone resorption to current stem cell therapy. Due to their multipotent differentiation properties, mesenchymal stem cells (MSCs) can repair degenerated bones through transplantation, and have become a new method for the treatment of OP.

Methods: Relevant literatures included in the Web of Science database core collection database from 2012 to 2021 were retrieved. CiteSpace software was used to analyze the cooperative relationship among authors, journals, institutions, and countries, and to analyze the co-citation situation of the literature. And performed co-occurrence analysis, cluster analysis and burst analysis of keywords, draw visual maps and analyzed the results.

Results: A total of 2100 papers were included, and the number of papers published from 2012 to 2021 was on the rise. A total of 484 authors were included, and 176 authors published more than 3 papers. The high-yield authors were mainly represented by YAN JIN and BO GAO. A total of 99 journals were included, and the journal with the most publications was J BONE MINER RES. A total of 787 institutions were included, and the institution with the largest number of publications was Shanghai Jiao Tong University. A total of 65 countries were included. The country with the largest number of publications was China, and the United States had the highest centrality. The co-citation analysis of the literature found 2 articles with high citation frequency and high centrality. The main research direction was the mechanism of MSCs in the treatment of osteoporosis. A total of 133 keywords were included, and the hot keywords were osteogenic differentiation, expression, proliferation, bone marrow, etc.

Conclusions: The research hotspots in this field mainly focused on the mechanism of bone regeneration, proliferation and osteogenic differentiation of bone marrow MSCs, and the expression of osteogenic-related genes. The future research trends in this field are predicted to be the mechanism of action of microRNA and long non-coding RNA on MSCs and their relationship with OP; the mechanism of MSCs adipogenic and osteogenic differentiation, and tissue engineering scaffolds applications.

Abbreviations: MSCs = mesenchymal stem cells, OP = osteoporosis, WOSCC = the Web of Science database core collection.

Keywords: bibliometrics, CiteSpace, mesenchymal stem cells, osteoporosis, visualization analysis

1. Introduction

Osteoporosis (OP) is the most common chronic metabolic bone disease characterized by loss of bone strength due to an imbalance between bone resorption and bone formation mechanisms, leading to increased fragility and fractures. The pathophysiologial mechanism of this disease includes an insufficient formative response during the remodeling of bone formation, which is an important factor in the pathogenesis of OP.1-3 OP can generally be divided into two categories based on the known etiology. One is primary osteoporosis, which usually occurs in elderly and postmenopausal women, and is the most common type of OP. The second is secondary osteoporosis with a clear pathogenic mechanism.4 The spine, wrist, hip, and humeral head are the main sites of fractures caused by OP, and the negative impact of spine and hip fractures is greater, resulting in back pain, spinal deformity, loss of independence, and even death.3 At present, in the clinical treatment of OP, drug treatment is more common, mainly including bisphosphonates, estrogen, calcitonin and parathyroid hormone, etc., but these drugs have certain side effects.4 Therefore, it is very important to explore safer and more effective alternative therapies for the treatment of OP. Mesenchymal stem cells (MSCs) are pluripotent stromal cells that can self-renew and differentiate into mesoderm cells, such as bone, fat, and chondrocytes, and play an important role in the pathogenesis and treatment of OP.5 The mechanism by which MSCs treat OP is mainly attributed to the paracrine effect. By releasing a large number of functional molecules, MSCs are absorbed by damaged tissues or cells, thereby facilitating angiogenesis,
proliferation, inhibiting apoptosis and inflammation, and promoting osteogenesis.\[6\]

CiteSpace software was created by Professor Chen Chaomei of Drexel University in the United States. It is a knowledge management software for bibliometric analysis.\[7\] By generating a visual knowledge map, CiteSpace explores the research status, research hotspots, research fronts and evolution process of a scientific field, reveals research directions, research stages and frontier characteristics, and finally judges the development trend of this field.\[8\] So far, CiteSpace software has been used in various fields such as environmental science, education and public health.\[9\] In this paper, CiteSpace software was used to visually analyze the authors, countries, keywords and other data included in the literature, summarized the research hotspots and development trends in this research field, and provided support and reference for in-depth related research work.

2. Materials and methods

2.1. Data source and retrieval strategy

2.1.1. Data source. The Web of Science database core collection (WOSCC).

2.1.2. Search strategy. The retrieval strategy was “TS = (osteoporosis* OR OP) AND TS = (‘mesenchymal stem cell*’ OR MSC).” The time span was set to 2012 to 2021. The document type was limited to “Article.” The language type was set to “English.” The last search date was 2022-04-20, and a total of 2100 related literatures were obtained.

2.2. Methods

The retrieved literature was exported in the format of “full record and cited references” and “plain text,” a total of 2586 articles, named “download_XXX.txt.” After deduplication by Citespac5.8.R3 software, no duplicate literature was found. By manually excluding conference papers, books and other unrelated literature, 2100 articles were finally included. In CiteSpace5.8.R3 software parameter settings, set the time span to 2012-2021, the time division to 1 year, the threshold item to select “Top N” (the value is set to 50), selected “Pathfinder” and “Pruning sliced” networks” as a cut connection method to simplify the network structure and highlight important features. The node type selected authors, institutions, countries, journals, cited documents and keywords for visual analysis, and drew knowledge graphs. The size of each node represents the number of documents. The purple outer circle of a node indicates that the node has high centrality and may be a turning point or key point in the field. The connection between nodes indicates co-occurrence or co-citation relationship, and the thicker the connection is, the closer the connection is.\[10\] Nodes of centrality are often considered to be turning points or pivot points in a field.\[10\]

3. Results

3.1. Annual publications

In the end, 2100 papers were included, and a line chart was drawn with the year as the abscissa and the annual number of publications as the ordinate (Fig. 1). As shown in the figure, the number of published papers in this field in general had a steady upward trend from 2012 to 2021. The number of papers published in 2021 is about 3.7 times that of 2012, indicating that research in this field had continued to develop in the past 10 years and had good prospects for development.

3.2. Authors

By analyzing the cooperation network of authors in this field, a knowledge graph consisting of 484 nodes and 976 connections was obtained, as shown in Figure 2. The authors with the highest number of published papers were YAN JIN (24 papers), YAN ZHANG (19 papers), LEI YANG (16 papers), BO GAO (16 papers) and LI LIAO (14 papers), etc. The author with the highest centrality was BO GAO (0.02) of the Institute of Orthopaedic Surgery, Xijing Hospital, Fourth Military Medical University. Most of the authors with the highest number of publications and centrality were from China, indicating that Chinese scholars’ research in this field has a great influence on the world.

3.3. Journals

By analyzing the journal cooperation network in this field, a knowledge graph consisting of 99 nodes and 229 connections was obtained, as shown in Figure 3. The top journals in terms of publication volume were J BONE MINER RES (1371 papers), BONE (1316 papers), J BIOL CHEM (988 papers), PLOS ONE (943 papers) and J CELL BIOCHEM (877 papers), etc.; The top journals were J BONE MINER RES (0.48), BONE (0.36), SCI REP-UK (0.16), CELL (0.15) and J BIOL CHEM (0.14), etc.

![Figure 1](image_url) The annual number of publications.
3.4. Institutions

By analyzing the cooperation network of institutions in this field, a knowledge graph consisting of 787 nodes and 1455 connections was obtained, as shown in Figure 4. The top institutions in terms of published papers were Shanghai Jiaotong University (109 papers), Fourth Military Medical University (65 papers), Sichuan University (50 papers), Chinese Academy of Sciences (48 papers) and Southern Medical University (45 papers), etc. The top institutions for centrality were Chinese Academy of Sciences (0.13), Fourth Military Medical University (0.1), Sun Yat-sen University (0.09), Shanghai Jiaotong University (0.08) and Southern Medical University (0.08), etc. It can be seen from the results that most of the institutions with the highest publication volume and centrality are Chinese institutions of higher learning, indicating that Chinese scholars have ranked first in the world in terms of publication volume in the past 10 years, and domestic institutions had been closely cooperating.

3.5. Countries

The national cooperation network in this field was analyzed, and a knowledge graph consisting of 65 nodes and 154 connections was obtained, as shown in Figure 5. The countries with the highest number of published articles were China (1247 articles), the United States (392 articles), South Korea (102 articles), Germany (80 articles) and Japan (68 articles), etc. The countries
with the highest centrality ranking were United States (0.59), China (0.22), Italy (0.18), United Kingdom (0.16) and Germany (0.12). China led other countries in the number of published papers, but there was still a certain gap between the centrality and the United States.

3.6. Co-citations references
After analyzing the total citations of the literature in this field, a knowledge graph consisting of 719 nodes and 1889 connections was obtained, as shown in Figure 6. The specific information of the top 10 literatures ranked by citation frequency and centrality was shown in Table 1. Co-citation means that two articles are cited by the same citing document. The larger the node, the more citations. The thicker the line between the two nodes means the greater the co-citation strength. The higher the number of citations, the more common research topic. Through visual analysis, two articles with high citation frequency and high centralitv were found. Li et al. found that miR-188 was a key regulator of MSCs switching between age-related osteogenesis and adipogenesis, and may be a potential target for the treatment of age-related bone loss. Wang et al. found through experiments that these data suggest that miR-214 has an important role in inhibiting osteogenesis, and inhibiting miR-214 in osteoblasts may be a potential anabolic strategy for improving OP.

3.7. Keywords
3.7.1. Co-occurrence analysis. After analyzing the keywords in this field, a knowledge graph consisting of 133 nodes and 526 connections was obtained, as shown in Figure 7. Remove the subject words “mesenchymal stem cell,” “osteoporosis,” etc. related to the retrieval strategy, “differentiation” had the highest frequency with 413 times; “osteogenic differentiation” had the highest centrality with a value of 0.15. The specific information of the top 10 keywords with frequency and centrality was shown in Table 2. Keywords with high centrality and frequency...
represent research hotspots in a certain field in this time period.[13] After analyzing the keywords, it is found that the research hotspots in this field mainly focus on the proliferation and osteogenic differentiation of MSCs,[16–18] osteogenesis-related genes expression, and so on.[19–21]

3.7.2. Cluster analysis. The log-likelihood ratio (LLR) algorithm was applied to perform cluster analysis on the keywords, as shown in Figure 8. The silhouette value of cluster groups was 0.73, indicating that the clustering result was credible. A total of 6 clusters were obtained, which were #0 bone regeneration, #1 osteogenic differentiation, #2 bone marrow, #3 parathyroid hormone, # 4 mechanism, #5 osteoclastogenesis. The details of the clustering were shown in Table 3, and the time-line diagram of the clustering is shown in Figure 9.

3.7.3. Burst analysis. Burst words are keywords with high frequency change rate in a certain period of time, which can show the development trend of a certain research field to a certain extent.[22] Burst analysis was performed on the keywords, and the top 25 burst word maps of the emergent intensity were obtained, as shown in Figure 10. According to the analysis results, the research in this field can be divided into three stages. The first stage was from 2012 to 2015, mainly focusing on transcription factors,[23] adipocyte differentiation,[24] bone morphogenetic proteins,[25] parathyroid hormone,[26] and other mechanisms that lead to the occurrence of OP and the pathogenesis of senile OP.[27] The second stage is from 2015 to 2018, mainly focusing on the role of NF-KB (nuclear factor kappa-B, NF-KB) and other signaling pathways in OP,[28,29] and the therapeutic effect of bisphosphonates and estrogen on OP[30,31] and related studies of postmenopausal OP in women.[21] The third stage was from 2018 to 2021, focusing on the mechanism of action of microRNA and long non-coding RNA on OP,[32,33] the regulatory mechanism of MSCs osteogenic and adipogenic differentiation on OP,[24,34,35] and The application of stents in the treatment of OP.[36]
4. Discussion

4.1. Research status and development trend

The research in this paper shows that from 2012 to 2021, the number of published papers in this field has grown steadily, which can be divided into three stages. From 2012 to 2014, the growth rate was small, and the upward trend was not obvious. From 2014 to 2016, the number of published articles increased sharply, showing a rapid development trend. From 2016 to 2021, the annual growth rate remained stable, showing a steady upward trend. The average annual publication volume was 210, which showed that the research prospect in this field is good and the development space is broad. From the analysis of the author’s cooperation network, the author with the most publications was YAN JIN, whose main research direction was the effects of tumor necrosis factor and autophagy on MSCs and OP.\(^{37,38}\) The author with the highest centrality was BO GAO, whose main research direction was the regulation of Wnt signaling pathway and melatonin on MSCs and the effect on OP.\(^{39–41}\) The analysis found that the author centrality in this field is generally low, and the authors with no centrality > 0.1, to a certain extent, indicated that the research in this field was still in the exploratory stage. From the analysis of the journal cooperation network, the publication volume and centrality of J BONE MINER RES ranked first, and the influence was greater. From the perspective of institutional cooperation network analysis, the institution with the largest number of publications was Shanghai Jiaotong University. The institution with the highest centrality was the Chinese Academy of Sciences. From the analysis of the national cooperation network, China and the United States ranked first and second respectively in the number of documents published, and the number of documents published by China far exceeded that of the United States and other countries. However, the centrality of the United States was the highest, indicating that the United States had more in-depth research in this field and had academic influence.

Through the keyword co-occurrence analysis, it could be seen that differentiation, expression, osteogenic differentiation, in vitro, proliferation, osteoblast differentiation, osteoblast bone cells, bone, bone formation, activation and other keywords were hot keywords in this field. Through keyword clustering analysis, a total of 6 clusters were obtained. The smaller the cluster number, the more keywords the cluster contains.

### Table 2

| Rank | Frequency | Keywords               | Rank | Centrality | Keywords               |
|------|-----------|------------------------|------|------------|------------------------|
| 1    | 413       | differentiation         | 1    | 0.15       | osteogenic differentiation |
| 2    | 412       | expression             | 2    | 0.12       | bone marrow            |
| 3    | 394       | osteogenic differentiation | 3    | 0.11       | fracture               |
| 4    | 250       | in vitro               | 4    | 0.1        | in vitro               |
| 5    | 239       | proliferation          | 5    | 0.09       | bone                   |
| 6    | 232       | osteoblast differentiation | 6    | 0.09       | bone formation          |
| 7    | 185       | osteoblast             | 7    | 0.09       | activation             |
| 8    | 165       | bone                   | 8    | 0.08       | differentiation         |
| 9    | 158       | bone formation          | 9    | 0.08       | stromal cell            |
| 10   | 153       | activation             | 10   | 0.08       | tissue                 |

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regeneration, #2 osteogenic differentiation, #3 bone marrow, #4 parathyroid hormone, #5 mechanism, #6 osteoclastogenesis, a total of 6 clusters were the research hotspots in this field. Combined with the keyword clustering timeline diagram, it can be seen that bone regeneration, osteogenic differentiation, bone marrow and mechanism will remain the research hotspots in 2021. Therefore, the research hotspots of MSCs in the treatment of OP mainly focused on the mechanism of bone regeneration, proliferation and osteogenic differentiation of bone marrow MSCs, and the expression of osteogenic-related genes.

According to the burst analysis of keywords, the development trend of this field can be inferred. From 2018 to 2021, there are 7 burst words, namely: microRNA, repair, promote, scaffold, long noncoding RNA, cancer, adipogenic differentiation. Therefore, the future development trend in this field mainly focuses on the mechanism of microRNA and long non-coding RNA on MSCs.
and their relationship with OP, the mechanism of MSCs adipogenic and osteogenic differentiation, and the application of tissue engineering scaffolds.

4.2. Limitations
This paper analyzed the relevant content of this field through the application of CiteSpace software, and understood the overall research situation in this field. However, this paper only analyzed the literature from WOSCC database, and didn’t analyze other databases, and the analysis results had certain limitations.

4.3. The significance of the research
This article included the recent 2012 to 2021 literature on the treatment of OP with MSCs in the WOSCC database. The application of CiteSpace software for bibliometric and visual analysis could help scholars understand the research status, hotspots and development trends in this field, and provide some reference for their research on the application of MSCs in the treatment of OP.

Author contributions
Data curation: Yueying Wang.
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Figure 10. Top 25 keywords with the strongest citation bursts.
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