Original Article

Worldwide research trends on femur head necrosis (2000–2021): a bibliometrics analysis and suggestions for researchers

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Background: Osteonecrosis of the femoral head (ONFH) is a common and stubborn disease. The main causes are venous stasis of the femoral head, arterial blood supply damage, bone cell and bone marrow death, and bone tissue necrosis and subsequent repair obstacles. Over the past 22 years, the number of papers on ONFH has, overall, continued to increase.

Methods: Using bibliometrics, we investigated the trends, frontiers, and hotspots of global scientific output in the past 22 years. We searched Science Citation Index Expanded (SCIE) of the Web of Science Core Collection (WoSCC) and retrieved information associated with papers and records published between 2000 and 2021. We used VOSviewer and CiteSpace to conduct bibliometric analysis and visual analysis on the overall distribution of annual output, major countries, active institutions, journals, authors, commonly cited literature, and keywords. The impact and quality of the papers were assessed using the global citation score (GCS).

Results: We retrieved a total of 2006 articles and reviews. Over the past 22 years, the number of publications (NP) increased. China ranked first in terms of NP, while the United States had the highest h-index and the highest number of citations (NC). Shanghai Jiao Tong University and *International Orthopaedics* were the institution and periodical, respectively. The paper written by Mont *et al.* in 2006 had the highest total GCS score, at 379. The top three keywords were "ischemic necrosis", "osteonecrosis", and "hip joint". Although there was a fluctuation in publications associated with ONFH, overall, the NP increased. China was the most prolific in this area, while the United States was the most influential country. The top 3 authors in terms of NP were Zhang, Motomura, and Zhao. Areas of focus in ONFH over recent years include signal pathway, genetic differentiation, glucocorticoid-induced osteogenesis, induced ischemic necrosis and osteogenesis.

Conclusions: Our bibliometrics analysis revealed the research hotspots and rapid development trends of ONFH research in the past 22 years. The most critical indicators [researchers, countries, research institutions, and journals publishing osteonecrosis of the femoral head (ONFH) research] relevant to the research hotspots in the field of ONFH research were analyzed.

Keywords: Osteonecrosis of the femoral head (ONFH); bibliometric; VOSviewer; trends; CiteSpace

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Introduction

Osteonecrosis of the femoral head (ONFH) is a hip joint disease encountered in the field of orthopedic medicine and is difficult to treat. The main clinical features of ONFH are severe pain in the hip, claudication, and inconvenience to flexion and extension activities. ONFH often occurs in young and middle-aged people. If it is not treated in time, it will cause serious obstacles to the patient's joint function (1). Few necrotic femoral heads can heal spontaneously, and about 67% of asymptomatic patients and 85% of symptomatic patients will eventually experience collapse of the femoral head (2) and pain, and joint replacement surgery is often required in the late stage. It is caused by the injury of the femoral head blood supply system, causing the collapse or necrosis of the femoral head tissue (3). The disability rate of the disease is high (4), and there are more than 8 million patients with nontraumatic ONFH in China (5). Wideman *et al.* reported that necrosis of the femoral head occurs frequently between the age of 28 and 65 years, the male to female ratio is about 3.1:1, and more than 70% of patients have bilateral disease (6). Bone collapse in the late stage of femoral head necrosis is one of the main causes of hip disability in young people and tends to occur more frequently in younger people (7). At present, it is generally believed that vascular occlusion is the main pathogenesis of nontraumatic femoral head necrosis (8), but there is also a theory involving thrombosis (1). The application of steroids is one of the important pathogenic factors leading to nontraumatic necrosis of the femoral head (9). There is an abundance of literature and relating to femoral head necrosis. As the proposal of new concepts and the introduction of new technologies are great challenges for newer and older researchers in this field, a summary work is urgently needed.

Generally, the status of a field of research and its hotspots are summarized through literature review, but this method can easily be affected by subjective factors and has certain flaws. Bibliometrics is an interdisciplinary subject that uses mathematical and statistical methods to quantitatively analyze all knowledge carriers, especially scientific publications (10). Bibliometrics is a convenient method which can reveal the key research directions and estimate development trends through analyzing publication and database features. Moreover, it can guide funding decisions and experimental strategies by providing effective evidence (11). Over the years, fruits of bibliometric research have blossomed from a variety of fields, such as in gouty arthritis (12), traditional Chinese medicine in the field of ischemia-reperfusion injury (13), prenatal stress (14), artemisinin (11), polycystic ovary syndrome (15), the culinary heritage significance of Filipino kakanin (16), metformin (17), evidence-based nursing guidelines for preventing inpatient falls (18), and chimeric antigen receptor-based cell therapy (19). However, no bibliometric analyses of ONFH have been conducted. Thus, in this study, we completed a bibliometric analysis and a comprehensive review of ONFH research.

Highlight box

Key findings

- The most critical indicators [researchers, countries, research institutions, and journals publishing osteonecrosis of the femoral head (ONFH) research] relevant to the research hotpots in the field of ONFH research were analyzed.

What is known and what is new?

- Bibliometrics is a convenient method which can reveal key the research directions and estimate development trends through analyzing publication and database features.
- China is the main producer of literature on ONFH, but the United States has more influence in this area. The clinical research and molecular biology of ONFH have attracted extensive attention. The function of molecular pathways has become a potential hotspot in ONFH research.

What is the implication, and what should change now?

- The research into ONFH has good prospects. It is worth noting that studies on the efficacy of traditional Chinese medicine monomers in the treatment of ONFH should be carried out and expanded in the future.

Methods

Data sources and search methods

The literature database was compiled using the Web of Science Core Collection (WoSCC) of Thomson Reuters, which provides a set of comprehensive and standardized export data and has been widely used in the academic community (12), so we chose WOSCC as the data source. In consideration of the rapid updating of the database, a literature search was conducted within 1 day (July 8, 2022) to avoid bias. The search strategy for publications was as follows: [TS = ("osteonecrosis of the femoral head") OR TS = (ONFH) OR TS = (ANFH) OR TS = ("femur head necrosis") OR TS = ("ischemic necrosis femoris") OR TS = ("femoral head avascular necrosis") OR TS = ("avascular

Table 1 Topic search strategy

Procedure	Results	Search strategy
1	2,264	TS = ("osteonecrosis of the femoral head") OR TS = (ONFH) OR TS = (ANFH) OR TS = ("femur head necrosis") OR TS = ("ischemic necrosis femoris") OR TS = ("femoral head avascular necrosis") OR TS = ("avascular necrosis of femur head"). Indexes = SCIE. Refined by publication years: (2000 OR 2001 OR 2002 OR 2003 OR 2004 OR 2005 OR 2006 OR 2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021)
2	2,059	Articles or reviews
3	2,006	Refined by languages: English

TS, topic.

necrosis of femur head")]. Across various publications, only English-language articles and reviews were included. From 2000 to 2021, a total of 2006 articles were analyzed. The results of the thorough screening are shown in *Table 1*.

Data collection

Data on confirmed papers were obtained through the Science Citation Index Expanded (SCIE) database, which contains information on the number of papers and citations, countries/regions, authors, affiliations, journals, year of publication, h-index, keywords and references. We then used an online bioinformatics tool (http://www.bioinformatics.com.cn/), CiteSpace (v.6.1.R2), and VOSviewer (v.1.6.16.0; Leiden University's Centre for Science and Technology Studies) to further analyze the data.

Bibliometric analysis

The abovementioned tools were used to conduct the bibliometric analysis. The number of publications and citations commonly used to represent bibliographic materials is an example of bibliometric indicators. The number of published papers (NP) is often used to quantify production capacity, and the number of citations (NC) can indicate the impact. The h-index is mainly used to evaluate the academic contributions of researchers and predict future scientific achievements. The h-index unifies productivity and influence by determining the threshold linking NP and NC. If a researcher publishes h papers and each paper is cited at least h times, then his or her h-index is h. In addition, the h-index was designed to assess the academic performance of individuals. However, it can now also define the publication output of a country or region and the output of an institution or journal.

In addition, the impact factor (IF) calculated according to the latest issue of Journal Citation Reports (JCR; Clarivate Analytics) is widely considered to be of the most important indicators of the quality and influence of medical journals (20). The global citation score (GCS) is considered to be the NC of an article on a global scale. It is an important indicator of an article's contribution to the knowledge field. A high GCS indicates a high interest of scientists around the world (21). A polynomial model is used to predict the annual publication quantity and further explain the change of the annual publication quantity. The number of surveys per year is expressed by the variable f (x) and the year of publication is expressed by X.

VOSviewer v.1.6.16.0 was used to construct and visualize the network diagram of the literature metrology (22,23). This study used VOSviewer for co-occurrence and cocitation analysis. CiteSpace was used to perform timeline and cluster analysis of cited references and keyword bursts to help intuitively assess the knowledge areas and trends (24). Through cluster analysis, we were able to classify references and keywords and to find the basic research topics of ONFH.

Results

Summary of ONFH publications

We retrieved 2006 pieces of literature published in the past 22 years in the SCIE of WoSCC, including 1,836 articles and 170 reviews. The total citations of all publications was 22,764, and the average NC of each article was 18.24. The h-index of all publications was 75. *Figure 1A* depicts the geographical distribution of the total number of papers on ONFH research in all countries and regions. The top 10 countries accounted for more than 95% (97.56%) of

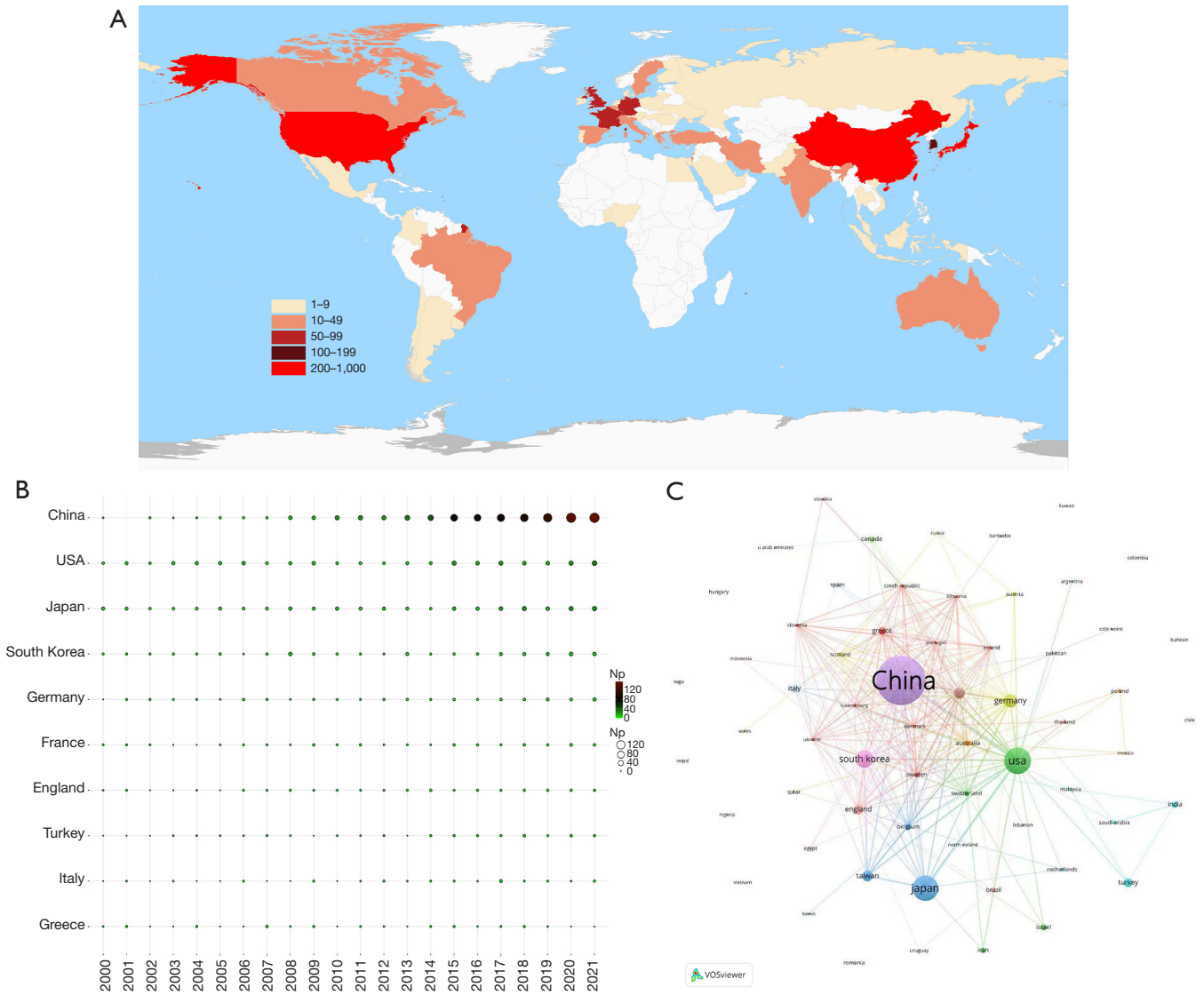


Figure 1 Countries/regions in ONFH research. (A) Geographical distribution of ONFH research publications from 2000 to 2021. (B) Top 10 countries according to annual publication number of ONFH research from 2000 to 2021. The size and color of the circle indicate the number of papers: the larger the circle, from green to red, the more articles published in that country. (C) The regional co-occurrence network. ONFH, osteonecrosis of the femoral head.

the total number of articles published in 2006. China was the country that published the most papers, followed by the United States, Japan, South Korea, and Germany. *Figure 1B* depicts the top 10 countries in annual publications of ONFH research from 2000 to 2021. China published the largest number of papers in 2020 (n=151) and 2021 (n=157), followed by the United States (2021, n=29) and Japan (2021, n=25). This indicates that China is still the country with the largest number of ONFH researchers. China published the most papers (NP =950, account 47.36% for the total number of publications), followed by the United States (NP =296, account 14.76% for the total number of publications) and Japan (NP =272, account 13.56% for the total number of publications). Papers from the United States were cited 8,818 times, accounting for 38.74% of the total citations, followed by Chinese papers (NC =8,360) and Japanese papers (NC =4,108). In addition, the United States had the highest h-index (h-index =55), followed by China (h-index

Table 2 The top 10 most productive countries/regions

Rank	Country	NP	NC	h-index
1	China	950	8,360	47
2	USA	296	8,818	55
3	Japan	272	4,108	36
4	South Korea	139	2,739	33
5	Germany	84	1,579	25
6	France	58	1,693	20
7	England	52	1,299	22
8	Turkey	40	433	11
9	Italy	35	715	17
10	Greece	31	923	19

NP, the number of publications; NC, the number of citations.

=47), and Japan (h-index =36) (*Table 2*). *Figure 1* shows the geographical distribution of the published literature around the world. The number of articles published by the top 10 countries each year is shown in *Figure 1B*. Among them, the number of articles issued by China is much higher than that of other countries. *Figure 1C* shows the co-occurrence relationship among countries, in which China is at the core, indicating that China has a high influence in this field.

Paper publication trends each year

As shown in *Figure 2A*, although there was a slight fluctuation in the past 10 years, there is a trend to more articles being published on the whole, with a correlation coefficient between the annual number of publications and the year is 0.9692 (*Figure 2A*). Overall, our data indicated that the study of ONFH has become a focus of interest and made rapid progress. *Figure 2B* shows the annual NPs associated with ONFH. The number of annual publications increased from 27 in 2000 to 249 in 2021, and the NP reached its peak in 2021.

Performance of affiliations

Table 3 lists the top 10 affiliations with the highest number of ONFH papers. The highest ranking belongs to Shanghai Jiao Tong University (87 points), Guangzhou University of Traditional Chinese Medicine (60 points) is close behind, followed by Kyushu University (58 points). Shanghai Jiao Tong University had the highest NC (n=1,253) and the highest h-index (h-index =20). More than half of the branches were located in China. This indicates that an increasing number of institutions in China are paying attention to ONFH research. Although the NP of Guangzhou University of traditional Chinese medicine ranked second, its NC ranked second from the bottom, indicating that the unit should strengthen the depth of research and improve the quality of research. The top 10 units were all from Asia, indicating that Asia is in a leading position in this field. Osaka University ranked third from the bottom in NP, but its h-index ranked second. As shown by the visual international cooperation network, there was close cooperation among the subsidiary bodies (*Figure 3A*). Shanghai Jiao Tong University, Kyushu University, Osaka University, Stanford University, and others (purple or green) performed the earlier research in this area than compared to other affiliated universities (yellow) (*Figure 3B*). *Figure 3C* shows the top 25 representative burst affiliations. At present, Wuhan University is the most influential institution. *Figure 3D* shows the clustering time span diagram of affiliations. Among the top 20 clusters was osteonecrosis of the femoral head, delphi, geographic distribution, population-based cohort study, trans trochanteric rotational osteotomy, microstructure, and single-nucleotide polymorphism, among others. The clusters with the highest current popularity were osteonecrosis of the femoral head, delphi, geographic distribution, population-based cohort study, trans trochanteric rotational osteotomy, and single-

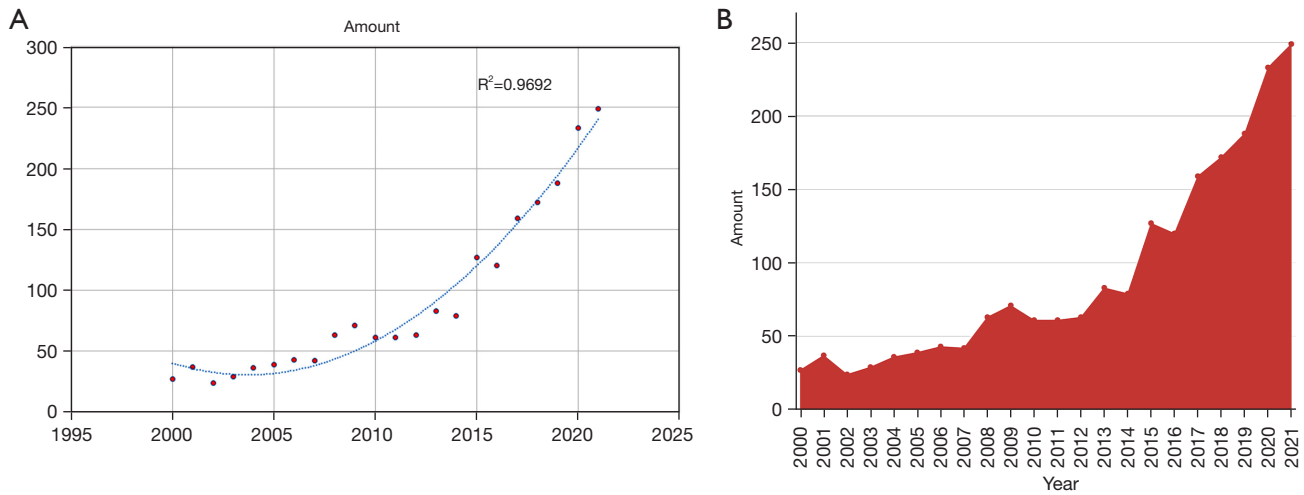


Figure 2 Annual publication statistics. (A) Curve fitting between annual publication each year (R^2=0.9692); (B) the annual number of publications over the past 22 years.

Table 3 The top 10 most productive affiliations

Rank	Affiliation	Country	NP	NC	h-index
1	Shanghai Jiao Tong University	China	87	1,253	20
2	Guangzhou University of Chinese Medicine	China	60	566	14
3	Kyushu University	Japan	58	644	17
4	China-Japan Friendship Hospital	China	56	779	18
5	Xi'An Jiaotong University	China	49	588	14
6	Chinese Academy of Medical Sciences Peking Union Medical College	China	48	689	17
7	Dalian University	China	48	944	15
8	Osaka University	Japan	47	900	19
9	Peking Union Medical College	China	43	608	17
10	Peking University	China	40	552	14

NP, the number of publications; NC, the number of citations.

nucleotide polymorphism.

Analysis of authors

The 10 most prolific authors are listed in *Table 4*. In total, there were 398 papers published, which accounted for 19.8% of all contributions. Zhang (NP =49) from Shanghai Jiao Tong University, China, published the most ONFH papers, followed by Motomura (NP =46) from Kyushu University and Zhao (NP =44). Zhao had the highest citations (NC =932). In addition, the top 10 authors in research of ONFH are all from China and Japan. This indicates that there are more excellent researchers in ONFH from in China and Japan, and they will focus on ONFH research. *Figure 4A* shows the co-occurrence relationship among the authors. Due to the large number of authors, only those with a minimum of 7 published papers were included, leaving 166 authors. He, Zhao, Sun, Wulang, and Yamamoto had the largest nodes, which indicates that these authors had a large number of papers and high influence in this field. *Figure 4B* shows the VOSviewer classification of all authors according to color and their average publication

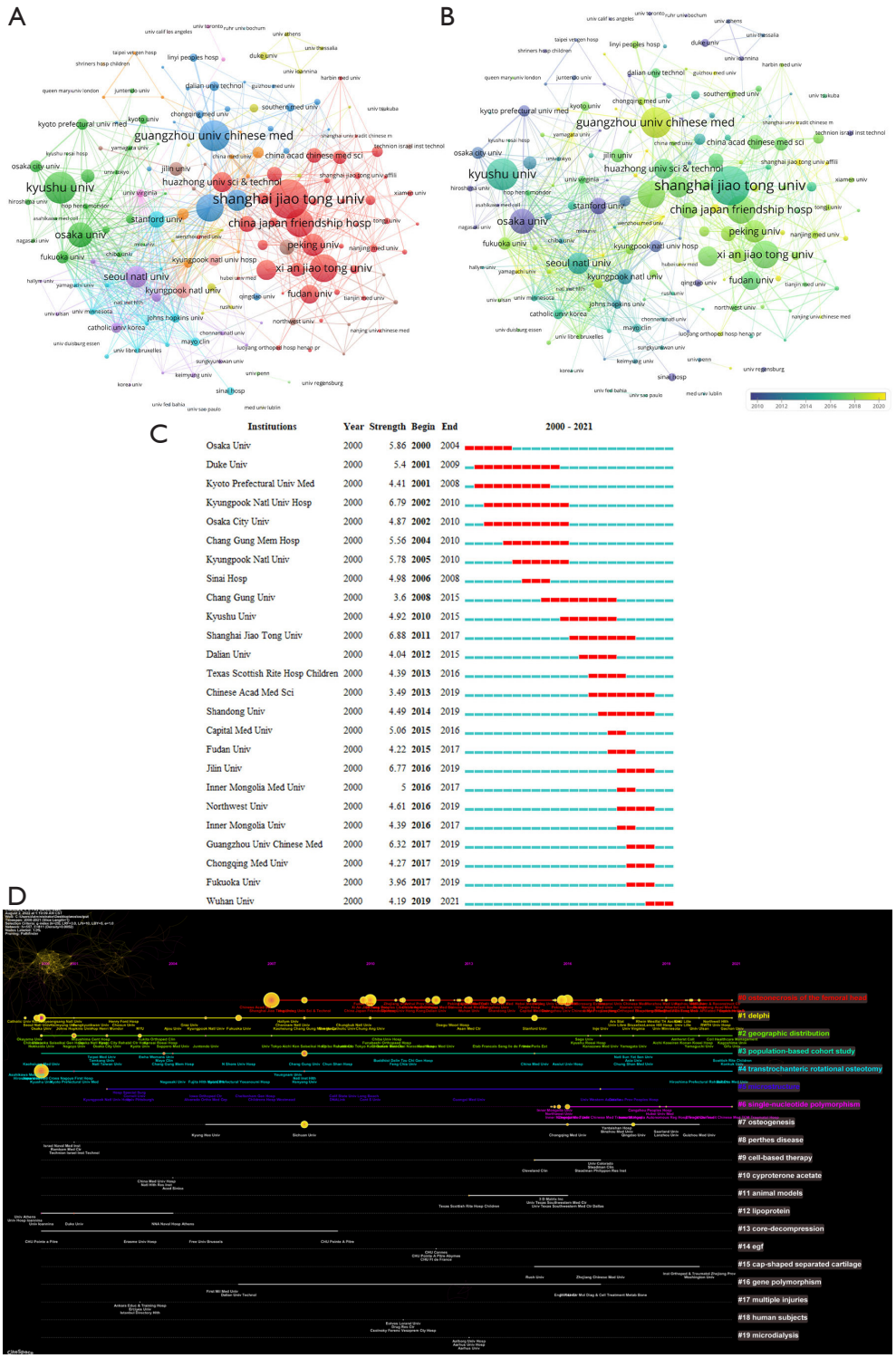


Figure 3 Affiliations in ONFH research. (A) Visualization of cooperation among affiliations; (B) network of affiliations based on APY; (C) top 25 representative burst affiliations; (D) timeline visualization among affiliations. ONFH, osteonecrosis of the femoral head; APY, average publication year.

Table 4 The top 10 most productive authors

Rank	Author	Affiliation	Country	NP	NC	h-index
1	Zhang, Changqing	Shanghai Jiao Tong University	China	49	830	16
2	Motomura, Goro	Kyushu University	Japan	46	402	14
3	Zhao, Dewei	Dalian University	China	44	932	15
4	Sugano, Nobuhiko	Osaka University	Japan	43	812	19
5	Yamamoto, Takuaki	Kyushu University	Japan	40	520	16
6	Nakashima, Yasuharu	Kyushu University	Japan	37	357	13
7	Sun, Wei	China-Japan Friendship Hospital	China	36	544	15
8	Gao, You-Shui	Shanghai Jiao Tong University	China	35	357	12
9	Ikemura, Satoshi	Kyushu University	Japan	34	364	14
10	Iwamoto, Yukihide	Kyushu University	Japan	34	581	17

NP, the number of publications; NC, the number of citations.

year (APY). The above-mentioned authors who had a large number of number articles also tended to have published earlier. *Figure 4C* shows the top 25 most influential authors, but these authors have lost their influence over the past 2 years, which indicates that research in this field should cultivate new talents. In addition, the topics of polymorphism, femoral head necrosis, case-control study, rotary osteotomy, internal fixation, glucocorticoids (GCs), have long been the focus of ONFH research (*Figure 4D*).

Performance of journals

As shown in *Table 5*, *International Orthopaedics* (93 papers; IF: 3.479) published the most studies on femoral head necrosis and was followed by *Clinical Orthopaedics and Related Research* (74 articles; IF: 4.755) and the *Journal of Bone and Joint Surgery* (American volume; 67 articles, IF: 6.558). About 30% of publications searched were published in the top 10 journals (n=555, 28.67%). Only the *Journal of Bone and Joint Surgery* (American volume) had a high IF (defined as >5.000). Thus, it appears that the quality of papers needs to be improved in the future and number of published works maintained.

GCS analysis

Figure 5 shows the annual citations of publications with a high GCS. The paper of Mont *et al.* published in 2006 ranked the first in terms of GCS. Mont *et al.* proposed that there might be a genetic basis to the etiology of hip osteonecrosis. Interactions of genetic predisposition and certain risk factors could determine the disease development. For collapsed femoral heads, joint-sparing surgery is less satisfactory than is total hip arthroplasty. New pharmacological measures and use of differentiation and growth factors to prevent and treat the disease might ultimately change the approach to treatment (25). In the study of Hernigou *et al.*, 116 cases (189 hips) were reported. Postoperative follow-up ranged from 5 to 10 years, and results depended on the change of Harris hip score, the progress of radiological staging, and the need of hip replacement. The most common site was the anterior part of the iliac bone, and the extracted bone marrow was reduced. As patients underwent surgery before collapse (stage I and stage II), 9 of 145 hips underwent hip replacement. Total hip arthroplasty (stage III and IV) was required in 25 of the 44 hips after collapse. To measure the amount of transplanted progenitor cells, they made use of fibroblast colony-forming units as indicators of stromal cell activity. Patients with more hematopoietic progenitor cells transplanted in the hip joint had a better prognosis (26). In another study, data on 121 patients with sickle cell disease (121 hips) were collected, and these patients were identified as having asymptomatic ONFH on the opposite side of the hip joint, with the symptoms always appearing before the collapse (27). Gangji *et al.* reported 13 patients (18 hips) with stage I or II ONFH studied according to the research system of the Orthopaedic Association (28), and it provided

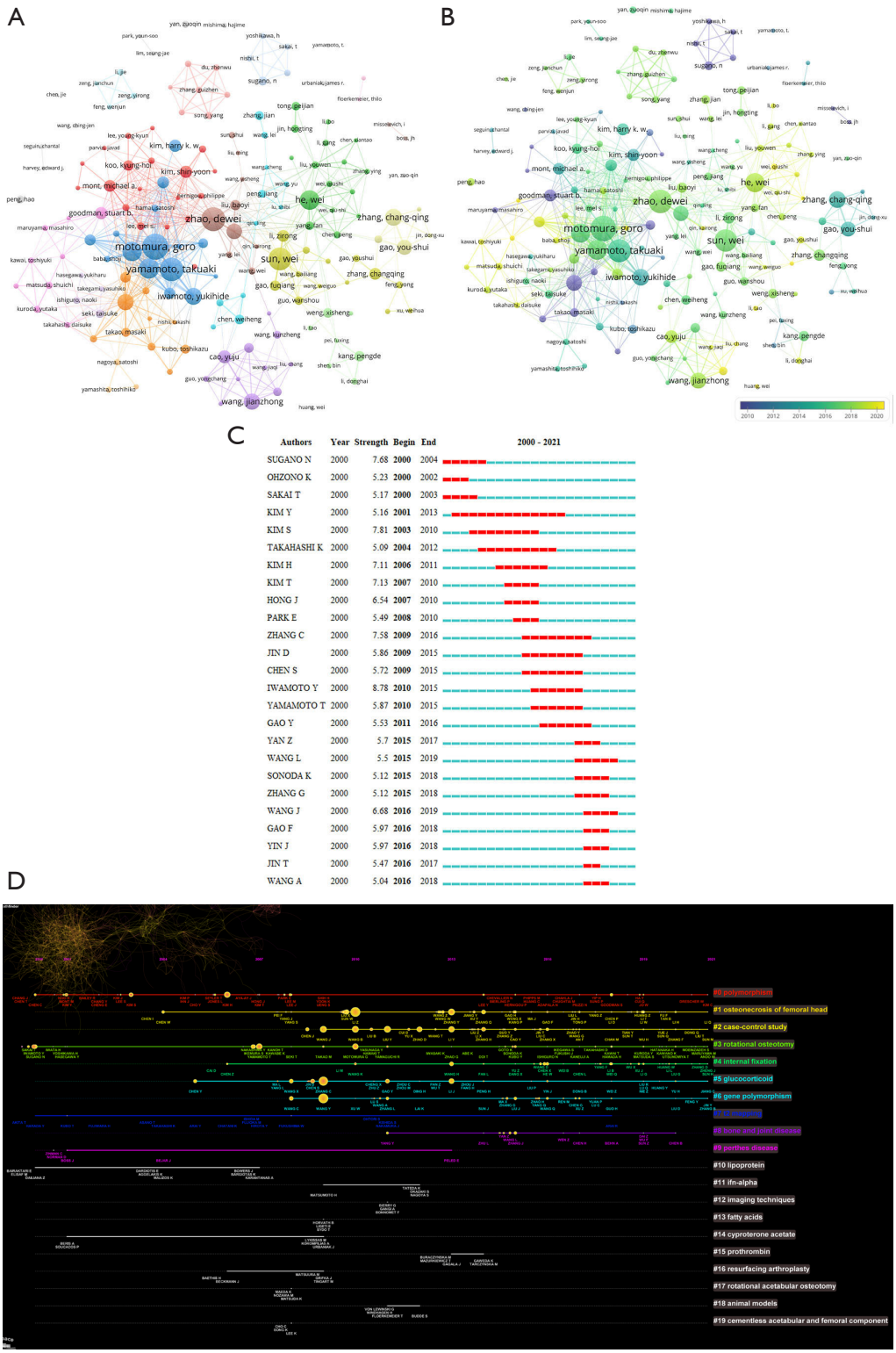


Figure 4 Authors in ONFH research. (A) Visualization of cooperation among authors; (B) network of authors based on APY; (C) top 25 representative burst authors; (D) timeline visualization among authors. ONFH, osteonecrosis of the femoral head; APY, average publication year.

Table 5 The top 10 most productive journals

Rank	Journal	IF [2021]	NP	NC	h-index
1	*International Orthopaedics*	3.479	93	1,703	24
2	*Clinical Orthopaedics and Related Research*	4.755	74	3,364	36
3	*Journal of Bone and Joint Surgery American Volume*	6.558	67	4,977	39
4	*Journal of Arthroplasty*	4.435	64	1,304	21
5	*Journal of Orthopaedic Surgery and Research*	2.677	56	253	9
6	*Archives of Orthopaedic and Trauma Surgery*	2.928	50	822	18
7	*BMC Musculoskeletal Disorders*	2.562	40	372	12
8	*Journal of Orthopaedic Science*	1.805	40	595	15
9	*Medicine*	1.817	36	208	10
10	*Hip International*	1.756	35	262	10

IF, impact factor; NP, the number of publications; NC, the number of citations.

Figure 5 Annual global citation number of papers with high GCS. GCS, global citation score.

a new idea for the treatment of femoral head necrosis. Mont *et al.* reviewed different treatment methods of femoral head necrosis. They reported that various nonsurgical treatment options have been evaluated to treat precollapse disease. he results of semiresurfacing and total resurfacing are not satisfactory, and these procedures limit the indications for patients with femoral head necrosis (29). Lai *et al.* reported alendronate appeared to prevent early collapse of the hip femoral head in patients with Steinberg stage II or III nontraumatic osteonecrosis (30). Kerachian *et al.* indicated that the use of GCs has a strong association with FH, but its underlying mechanism is unclear. The direct effect of GCs is to inhibit the production of osteoblasts and osteoclast precursors, and it can also increase the apoptosis of osteoblasts and osteocytes while prolonging the life of osteoclasts and the apoptosis of vascular endothelial cells (ECs). High-dose GC administration can also reduce tissue plasminogen activator (T-PA) activity and enhance the procoagulant effect of GCs. It may also lead to blocked angiogenesis, bone repair, and altered nitric oxide metabolism. In addition, GC treatment modulates other vasoactive substances such as endothelin-1, norepinephrine, and bradykinin. Therefore, GC administration can regulate the reactivity of vasoactive substances to blood vessels. Vasoconstriction caused by the femoral head artery in the bone leads to femoral head ischemia. GCs also cause ischemia by increasing intraosseous pressure, which in turn reduces blood flow to the femoral head through endothelial apoptosis, and increases lipogenesis and lipohypertrophy levels in the bone marrow. It is difficult to predict what disease will develop in patients receiving a given dose of GCs, suggesting that there may be individual differences in hormone sensitivity and other mechanisms. Although more efforts are needed to better understand the role of GC in ONFH, recent data on the effects of GCs on endothelial cells and theories of local endothelial bed dysfunction shed new light on specific GC mechanisms. A better understanding of the GC-related pathogenesis could lead to better treatment options (31). In the study by Mont *et al.*, they determined the incidence of developing symptomatic disease and/or collapse of the femoral head. Next, results were stratified according to lesion size, lesion location, radiological stage, associated risk factors and/or disease, and level of study evidence. A total of 16 studies (including 664 hips) were available for outcome analysis. Results varied according to the size of the lesion, the location of the lesion, and the radiological stage at diagnosis. Small lesions located in the middle had the best prognosis, with a collapse rate of less than 10%, although the small lesions in the middle have a very low progression rate. Therefore, it may be beneficial to consider joint-sparing surgical treatment in asymptomatic patients with moderate or large and/or lateral lesions (32). In the study by Zhao *et al.*, 100 patients with early ONFH were randomly assigned to either a bone mesenchymal stem cells (BMSC) therapy or core decompression (CD) therapy. Autologous subtrochanteric bone marrow cells (2×10^6) and *in vitro* expanded bone marrow mesenchymal stem cells were implanted. X-ray stage of Femoral head (FH), Harris hip score (HHS), and volume of necrotic foci or low-signal areas (LowsiZ) were assessed before surgery and at 6, 12, 24, and 60 months after surgery. The results indicated that at 60 months after surgery, only 2 of 53 hips underwent bone marrow mesenchymal stem cell transplantation and received vascularized bone graft. In the CD group, 7 hips were lost during follow-up, 10 of the remaining 44 hips progressed, and 5 hips underwent vascularized bone grafts or total hip replacement. Compared with the CD group, the BMMSC-treated group had significantly improved HHS of the hip joint and reduced femoral head hypovolemia (33). Haidukewych *et al.* reported that of 82 patients treated with internal fixation from 1975 to 2000, 83 had femoral neck fractures and were between 15 and 50 years of age. Two patients died and eight patients were lost to follow-up. Moreover, 73 fractures were followed up until the fracture healed and until the patients were converted to hip replacement, or at least 2 years, and the mean follow-up time was 6.6 years. Of the 73 fractures, 51 were displaced and 22 were not. Among 57 patients (58 fractures) who did not undergo early joint replacement, the mean follow-up time was 8.1 years. Of 73 fractures, 53 (73%) healed after 1 operation without signs of femoral head necrosis; 17 fractures (23%) were complicated with osteonecrosis, and 6 (8%) were complicated with nonunion; 4 of the 6 nonunions healed after the second operation. At the last follow-up, 13 patients underwent total hip arthroplasty due to osteonecrosis (11 cases), nonunion (1 case), or both (1 case). Of the 51 displaced fractures, 5 (9.8%) had nonunion and 14 (27%) had osteonecrosis. Of the 22 nondisplaced fractures, 3 (14%) were associated with osteonecrosis and 1 (4.5%) was associated with nonunion. Of the 46 displaced fractures, 11 (24%) had excellent reduction, 11 (24%) had osteonecrosis, and 2 (4%) had

nonunion. Of the 5 displaced fractures, 4 had good or poor reduction (34).

Analysis of hotspots

In addition to retrieval terms, VOSviewer and CiteSpace also evaluated keywords in abstracts and titles of 2006 papers. In *Figure 6A*, cluster 1 (red) focuses on basic research for exploring the pathogenesis of ONFH; cluster 2 (green) mainly focuses on clinical research for exploring the treatment and prognosis of patients with ONFH; the cluster 3 (blue) focuses on the epidemiological characteristics of ONFH; cluster 4 (yellow) mainly relates to the treatment and diagnostic methods; cluster 5 (purple) mainly focuses on drugs for the treatment of ONFH. The most frequent keywords are "ischemic necrosis", "osteonecrosis", "hip", "femoral head necrosis", and "nucleus pulposus decompression", which indicates that research associated with ONFH principally focuses on disease phenotype and treatment. In *Figure 6B*, all keywords are classified by colors into different clusters according to APY by VOSviewer. The newest keyword was "glucocorticoid-induced osteonecrosis" [cluster 1; APY: 2019.16 (the degree of timing of publication)], others were "pathway" (cluster 1; APY: 2018.74), and the keywords were all closely related to femoral head necrosis. In addition, "signal pathway", "osteogenic differentiation", "glucocorticoid-induced osteonecrosis", "induced ischemic necrosis", "pathway", and "osteogenesis" have been constantly focused upon in ONFH research, as shown in *Figure 6C*. We further found that "apoptosis", "total hip replacement", "femoral neck fracture", "risk factors", "core decompression", "gene polymorphism", and "mesenchymal stem cells" were the hot keywords of the past 3 years in *Figure 6D*. In the future, more literature on the basic research of ONFH will be published, and an increasing number of scholars will explore the pathogenesis and treatment mechanism of ONFH through animal experiments and thus open more possibilities for treating ONFH.

Analysis of cocitation

Cocitation analysis is a quantitative information research method and one of the main citation analysis methods. It mainly studies the relationship between documents by analyzing situations in which 2 documents are cited by other documents at the same time. This method is widely used in many fields, such as scientific evaluation and scientific and technological management.

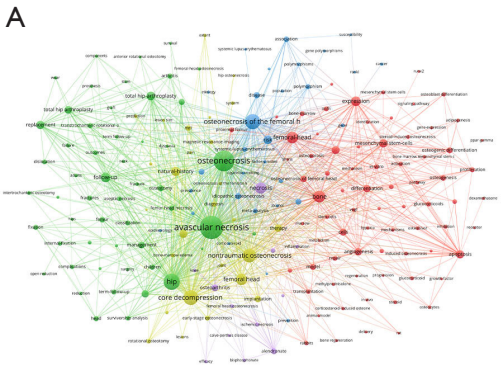
Cocitation reference analysis

A cocitation network involves research topics closely associated with certain fields, which is different from GCS. Considering the large amount of references, the minimum number of citations needed for inclusion in the network for a document was 30. Of the 32,155 articles retrieved, 207 were selected for cocitation analysis. In addition, the paper was also divided into multiple clusters using different node colors as shown in *Figure 7A*: the cluster 1 (red) includes 67 references and focuses on the pathogenic factors, treatment, and prevention of ONFH; cluster 2 (green) focuses on the clinical treatment of ONFH; cluster 3 (blue) mainly focuses on the effects of ONFH on the body and the corresponding treatment strategies; cluster 4 (yellow) focuses on the adverse reactions after treatment and the degree of bone death of ONFH; cluster 5 (purple) focuses on the prediction and diagnosis of ONFH; and cluster 6 (light blue) describes the drug treatment research of nonalcoholic macular degeneration. On the basis of cluster, it can be found that majority of studies focused on the pathogenesis and epidemiology of ONFH. *Figure 7B* shows the density of the cocited literature, and *Figure 7C* depicts the top 25 cocitated literatures with the highest number of citations. Mont *et al.* had a high intensity of citations (15.17). Their article describes the etiology of the development of osteonecrosis of the femoral head has not been elucidated. But damage to circulation in specific areas, and eventually necrosis of the femoral head, is involved. Joint preservation surgery is used to treat precollapse disease, and some studies have shown successful results in medium - and long-term follow-up. Studies of total joint replacement after femoral head collapse have described favorable results over 10 years of follow-up, which is a significant advance and has led to a paradigm shift in the treatment of these patients (29). As shown in *Figure 7D*, the commonly cited reference clusters that still have good effects are "femoral head necrosis", "icariin", and "urine-derived stem cells".

Analysis of bibliographic coupling

Bibliographic coupling refers to 2 papers quoting 1 or more identical documents. Usually, the statistical connection degree between 2 documents can be measured quantitatively by the citation coupling number. The greater the citation coupling is, the stronger the correlation between the 2

A



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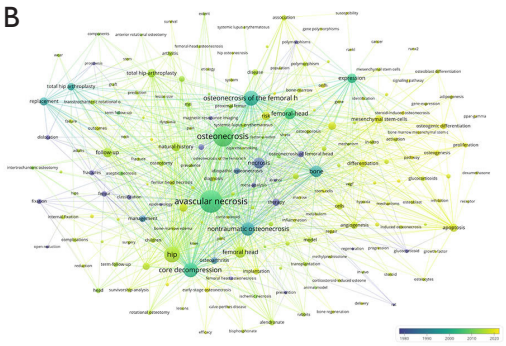


C

Keywords	Year	Strength	Begin	End	2000 - 2021
avascular necrosis	2000	13.66	2000	2007	
aseptic necrosis	2000	9.92	2000	2009	
term follow up	2000	13.21	2001	2011	
hypofibrinolysis	2000	5.58	2001	2013	
replacement	2000	5.77	2003	2006	
ischemic necrosis	2000	5.24	2003	2011	
intertrochanteric osteotomy	2000	5.77	2004	2011	
cement	2000	4.51	2005	2006	
nontraumatic avascular necrosis	2000	7.09	2006	2010	
alendronate	2000	5.59	2007	2010	
factor v leiden	2000	4.97	2008	2015	
systemic lupus erythematosus	2000	4.75	2008	2015	
model	2000	6.04	2010	2016	
rabbit	2000	8.06	2011	2017	
transplantation	2000	5.06	2011	2015	
osteoporosis	2000	4.58	2014	2018	
in vitro	2000	5.56	2015	2018	
gene polymorphism	2000	6.92	2016	2017	
signaling pathway	2000	4.47	2017	2021	
osteogenic differentiation	2000	6.13	2018	2021	
glucocorticoid induced osteonecrosis	2000	5.84	2018	2021	
induced avascular necrosis	2000	5.79	2018	2021	
prediction	2000	4.62	2018	2019	
osteogenesis	2000	6.43	2019	2021	
pathway	2000	5.8	2019	2021	

D

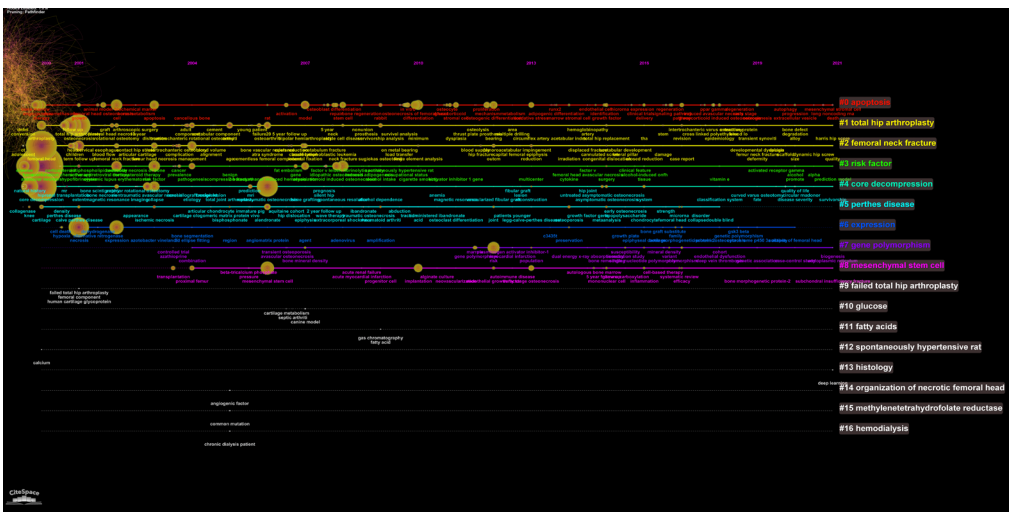
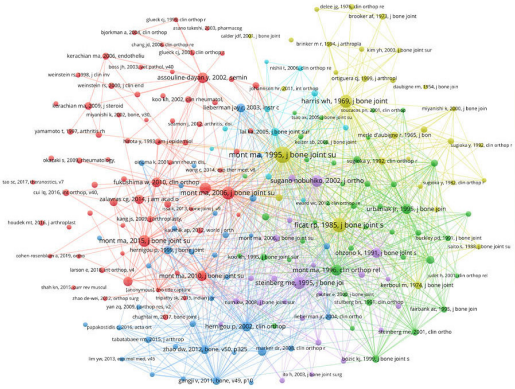


Figure 6 Keywords in ONFH research. (A) Visualization of keywords; (B) network of keywords according to APY; (C) top 25 representative burst keywords; (D) timeline visualization among keywords. ONFH, osteonecrosis of the femoral head; APY, average publication year.

A



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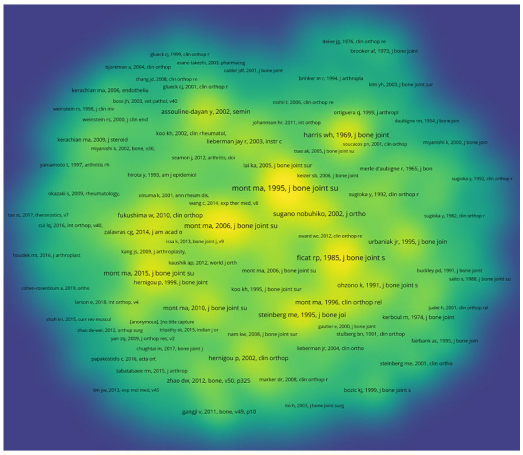

C

References	Year	Strength	Begin	End	2000 - 2021
Scully S, 1998, J BONE JOINT SURG AM, V80A, P1270, DOI 10.2106/00004623-199809000-00004, DOI	1998	6.57	2000	2003	
Mont M, 1996, CLIN ORTHOP RELAT R, V0, P0, DOI 10.1097/00003086-199603000-00020, DOI	1996	5.16	2000	2001	
Sakamoto M, 1997, J BONE JOINT SURG BR, V79B, P213, DOI 10.1302/0301-620X.79B2.7179, DOI	1997	4.99	2000	2002	
Steinberg M, 1999, CLIN ORTHOP RELAT R, V367, P262	1999	5.57	2001	2003	
Assouline-dayan Y, 2002, SEMIN ARTHRITIS RHEU, V32, P94, DOI 10.1053/sarh.2002.33724, DOI	2002	7.27	2003	2007	
Mont M, 2000, INSTR COURSE LECT, V49, P169	2000	5.11	2003	2004	
Mont M, 2001, J ARTHROPLASTY, V16, P134, DOI 10.1054/arth.2001.28722, DOI	2001	5.73	2004	2006	
Kim Y, 2003, J BONE JOINT SURG AM, V85A, P675, DOI 10.2106/00004623-200304000-00014, DOI	2003	9.11	2005	2008	
Steinberg M, 2001, CLIN ORTHOP RELAT R, V0, P71	2001	6.03	2005	2006	
Lai K, 2005, J BONE JOINT SURG AM, V87A, P2155, DOI 10.2106/JBJS.D.02959, DOI	2005	8.04	2006	2009	
Gangji V, 2004, J BONE JOINT SURG AM, V86A, P1153, DOI 10.2106/00004623-200406000-00006, DOI	2004	8.04	2006	2009	
Agarwala S, 2005, RHEUMATOLOGY, V44, P352, DOI 10.1093/rheumatology/keh481, DOI	2005	7.09	2006	2009	
Mont M, 2006, J BONE JOINT SURG AM, V88A, P1117, DOI 10.2106/JBJS.E.01041, DOI	2006	11.72	2007	2011	
Nishii T, 2006, CLIN ORTHOP RELAT R, V0, P0, DOI 10.1097/01.blo.0000194078.32776.31, DOI	2006	5.52	2007	2009	
Petrigliano F, 2007, CLIN ORTHOP RELAT R, V0, P0, DOI 10.1097/BLO.0b013e3181591c92, DOI	2007	6.76	2009	2012	
Seamon J, 2012, ARTHRITIS, V0, P0, DOI 10.1155/2012/601763, DOI	2012	7.6	2013	2017	
Gangji V, 2011, BONE, V49, P1005, DOI 10.1016/j.bone.2011.07.032, DOI	2011	5.21	2014	2016	
Mont M, 2015, J BONE JOINT SURG AM, V97A, P1604, DOI 10.2106/JBJS.O.00071, DOI	2015	15.17	2017	2021	
Moya-angeler J, 2015, WORLD J ORTHOP, V6, P590, DOI 10.5312/wjo.v6.i8.590, DOI	2015	8.19	2017	2021	
Zalavras C, 2014, J AM ACAD ORTHOP SUR, V22, P455, DOI 10.5435/JAAOS-22-07-455, DOI	2014	7.54	2017	2019	
Tabatabaee R, 2015, J ARTHROPLASTY, V30, P11, DOI 10.1016/j.arth.2015.06.022, DOI	2015	6.12	2017	2019	
Zhao D, 2015, CHINESE MED J-PEKING, V128, P2843, DOI 10.4103/0366-6999.168017, DOI	2015	6.12	2019	2021	
Larson E, 2018, INT ORTHOP, V42, P1723, DOI 10.1007/s00264-018-3917-8, DOI	2018	5.64	2019	2021	
Pepke W, 2016, ORTHOP REV, V8, P5, DOI 10.4081/or.2016.6162, DOI	2016	5.64	2019	2021	
Cui L, 2016, INT ORTHOP, V40, P267, DOI 10.1007/s00264-015-3061-7, DOI	2016	5.6	2019	2021	

D

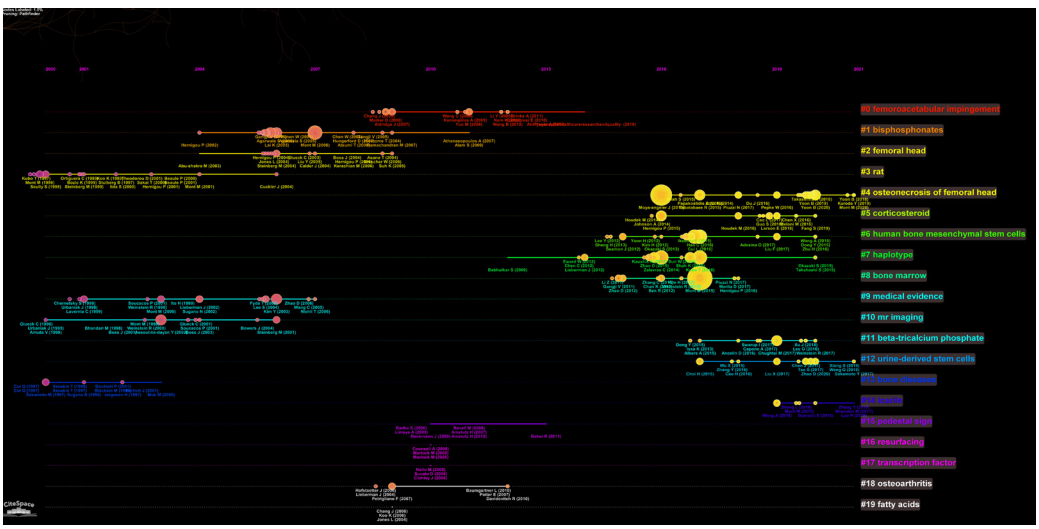

Figure 7 Cocited references in ONFH research. (A) Visualization of cocited references. (B) Density network of cocited references. (C) Top 25 representative cocited references. (D) Timeline visualization of cocited references. ONFH, osteonecrosis of the femoral head.

documents. The analysis on bibliographic coupling is shown in *Figure 8* and is based on the total connection strength. The top 10 countries are China [365,369], the USA [246,785], Japan [169,302], South Korea [110,447], Germany [82,744], France [54,628], England [44,352], Turkey [32,540], Greece [31,930], and Italy [29,238]. The top 10 affiliations are Dalian University [72,303], Stanford University [71,031], Osaka University [66,578], Kyushu University [53,795], Seoul National University [52,846], China-Japan Friendship Hospital [52,528], Guangzhou University of Traditional Chinese Medicine [52020], John Hopkins University [51,897], Shanghai Jiao Tong University [50,368], and Fukuoka University [45,396]. The top 10 documents were Mont *et al.* 2006b [1,305] (25), Mont *et al.* 2006a [1,056] (35), Tripathy *et al.* 2015 [959] (36), Marker *et al.* 2008a [946] (37), Marker *et al.* 2008 [790] (38), Mont *et al.* 2020 [704] (39), Mont *et al.* 2015 [701] (29), Chughtai *et al.* 2017 [606] (40), Malizos *et al.* 2007 [548] (41), and Seyler *et al.* 2008 [536] (42). The top 10 journals are *International Orthopaedics* [57,566], *Clinical Orthopaedics and Related Research* [57,181], *Journal of Bone And Joint Surgery* [American volume; 55,399], *Journal of Arthroplasty* [42,889], *Journal of Orthopaedic Surgery and Research* [33,140], *Archives of Orthopaedic and Trauma Surgery* [29,900], *BMC Musculoskeletal Disorders* [25,327], *Journal of Bone and Joint Surgery* [British volume; 22,624], *Journal of Orthopaedic Science* [21,005], and *Biomed Research International* [18,915]. The top 10 authors are Yamamoto [57,778], Zhao [54,873], Mont [54,198], Motomura [51,834], Sugano [48,261], Goodman, [45,284], Nakashima [39,930], Ikemura [39,642], Jones [36,596], and Sun [35,493]. The bliographic coupling diagram is shown in *Figure 8*.

Discussion

ONFH is a common and refractory disease in orthopedic medicine. The early symptoms are not obvious. With the progress of the disease, the symptoms and signs such as hip pain, flexion, and obviously limited abduction and external rotation function (43). In the later stage, the pain is aggravated, and the affected limb is shortened and lame, which seriously affects the quality of life. The basic causes of femoral head necrosis mainly include trauma to the patient's hip, use of a large amount of GCs, and long-term alcoholism. If the condition is accompanied by sickle cell anemia or systemic lupus erythematosus or other diseases, the possibility of femoral head necrosis may also arise (44). Our study is the first bibliometric study on ONFH research worldwide. The purpose of this study was to conduct bibliometric analysis on the developing trends and research hotspots in ONFH by using the WoSCC database, VOSviewer, and the SCIE extension of CiteSpace. We retrieved 2006 papers published between 2000 and 2021. Based on the polynomial fitting curve, although the amount of papers published in the past 22 years fluctuated slightly, there was a general trend of an increasing number of papers. This also shows that a growing number of researchers are interested in the topic of ONFH. Publications are distributed globally, but productivity is not high in many regions. *Figure 1A* shows the geographical distribution of publications related to ONFH. China ranked first in terms of publications (n=950), followed by the United States (n=950), Japan (n=272), and South Korea (n=139). Among the top 10 countries/regions, China ranks first in terms of NP, indicating that China is a very productive country in ONFH research. The top 10 authors and affiliations are from China and Japan, which indicates that these 2 countries have the most professional researchers and affiliations. Compared with China, United States had a relatively high h-index. In addition, the United States has conducted more in-depth research on this topic than have other countries in. This suggests that Chinese scholars and academic branches should improve the academic quality of their studies.

Keyword analysis showed that "signaling pathway", "genetic differentiation", "glucocorticoid-induced osteogenesis", "induced avascular necrosis", and "osteogenesis" have high influence at present. Multiple signaling pathways have been confirmed to be involved in the pathogenesis of ONFH including Wnt/β-catenin, MARK signaling pathway, and OPG/RANKL/RANK signaling pathway. A previous study has found that the JAK/STAT signaling pathway is also involved in the pathological process of femoral head necrosis (45). The Wnt/β-catenin signaling pathway is one of the key pathways that regulate the development of the skeletal system and participates in the early stage of ONFH (46). A study has found that mir-122-5p can improve bone density, trabecular volume, and the average trabecular plate thickness of the femoral head; promote bone repair; and prevent ONFH by activating the MAPK signaling pathway (47). In the pathological process of femoral head necrosis, bone necrosis and repair coexist. Osteoblasts play an important role in the whole process of bone metabolism. They are important functional cells that participate in bone formation. They are important for bone development and the stability of the

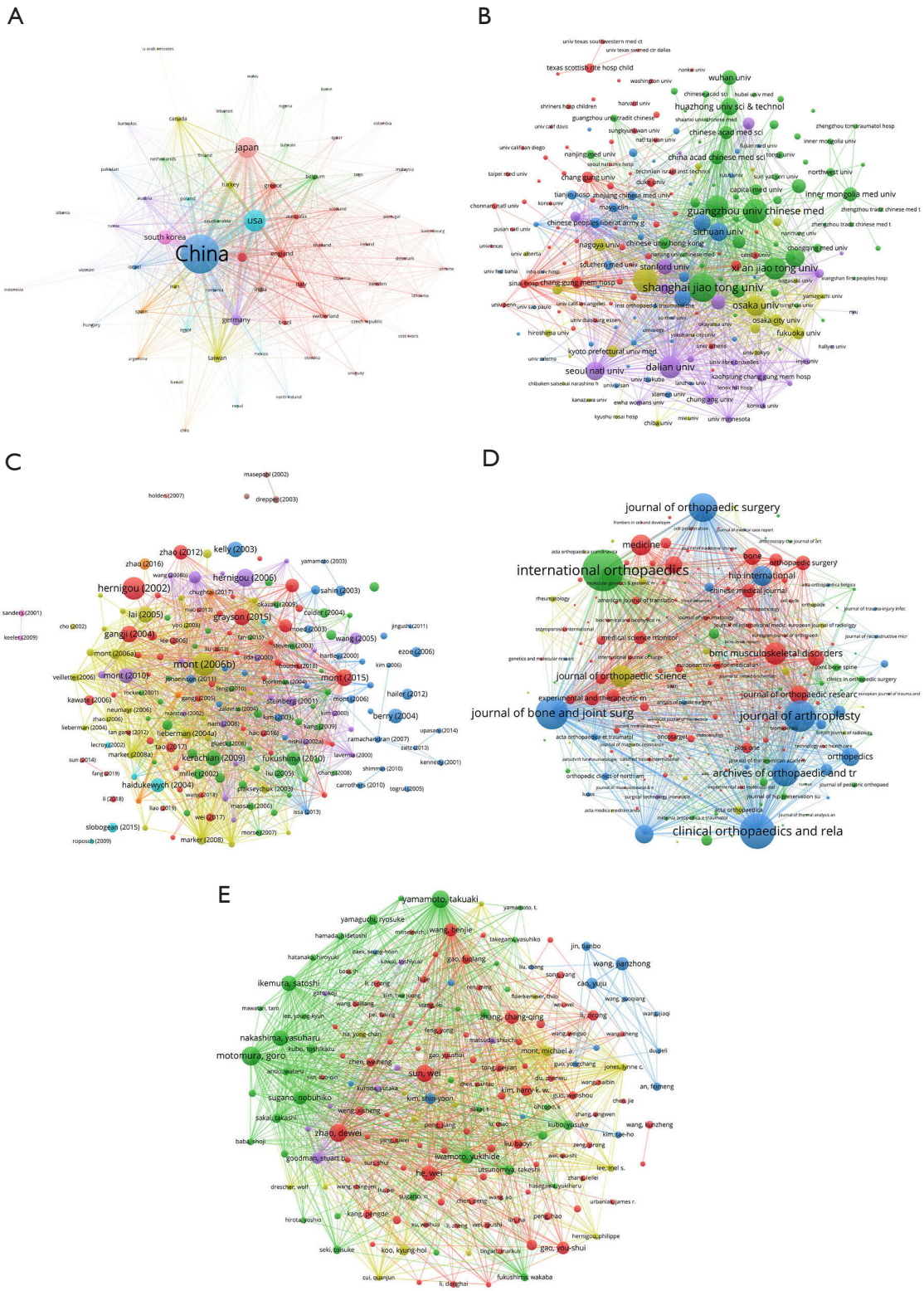

Figure 8 Bibliographic coupling analysis. (A) Common network of countries; (B) network of co-occurring relationships; (C) documents appearing on the network at the same time; (D) network of joint publishing between journals; (E) author co-occurrence network.

internal environment of new bone. They also participate in the regulation of the osteogenic process and the bone resorption function of osteoclasts (48). A study on a rabbit model of steroid-induced necrosis of the femoral head found that the expression of ERK1 and ERK2 significantly decreased while the expression of JNK and p38 significantly increased after avascular necrosis of the femoral head. By regulating the phosphorylation levels of ERK, p38, and JNK, the related pathways of MAPK are activated or inhibited, thus inhibiting the bone necrosis in the medullary cavity of the femoral head, promoting the proliferation and differentiation of osteoblasts, accelerating the bone repair in the necrotic area, and thus exerting a certain therapeutic effect in the necrosis of the femoral head (48). Inflammatory pathway is also the core link leading to the onset of ONFH. Adverse factors such as hormones and alcohol cause ischemic injury of the femoral head, the TLR4/NF-κB inflammatory pathway is activated, and the abnormal immune response makes interleukin (IL-1, IL-3, IL-6, IL-12) and tumor necrosis factor-α (TNF-α), with other inflammatory factors also being highly expressed (45). Avascular necrosis of the femoral head is a common and refractory disease in the orthopedic field. It is mainly caused by venous stasis of the femoral head and impaired arterial blood supply, which causes the death of bone cells and bone marrow, resulting in bone tissue necrosis and subsequent repair obstacles, resulting in structural changes and collapse of the femoral head (49).

In summary, femoral head necrosis has been a research hotspot for a long time, and there are many scholars and research teams engaged in this field. The research institutions are mainly traditional Chinese medicine research institutions, with China being in the leading position in this field. International research is mainly based on the combination of basic research and clinical research. On the basis of this study, clinical research should be combined with the results of this study in future studies to promote the development of this field. Using tissue engineering and biomaterials, seed cells, growth factors and scaffold materials were transplanted into the bone defect site to provide good structural support and promote bone tissue regeneration, so as to complete the repair of bone and blood vessels in the necrotic area, which is conducive to the treatment of ONFH, Besides, with the continuous development of materials science, great progress has been made in the treatment of femoral head necrosis by tissue engineering technology, including the application of 3D printing and nanotechnology in scaffold materials, the repair of osteonecrosis by different kinds of genetically modified mesenchymal stem cells, and the relationship between the expression of growth factors and femoral head necrosis. However, most of these studies are still in the animal experimental stage, and the commonly used animal models include rat models, rabbit models, sheep models, pig models and chicken models, etc. With the rapid development of nanotechnology, biomaterials and tissue engineering, it is expected to develop artificial biomimetic materials with good performance to replace bone grafting materials and promote the treatment of femoral head necrosis, and the role of H-type blood vessels in ONFH should be further studied (50).

Conclusions

This bibliometric analysis showed that the number of papers published in ONFH research has fluctuated slightly over the past 22 years. The general trend, however, is the publication of a greater number of articles over time, and thus the research into ONFH has good prospects. China has published the most articles, while the United States has more influence in this area. The clinical research and molecular biology of ONFH have attracted considerable attention, with the function of molecular pathways having become a potential hotspot in ONFH research. It is worth noting that studies on the efficacy of traditional Chinese medicine monomers in the treatment of ONFH should be carried out and expanded in the future. Our research may be beneficial.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-303/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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