Original Article

The interplay between the nerves and skeleton: a 30-year bibliometric analysis

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Background: The mechanisms and effects of the interplay between the nerves and skeleton remain a popular research topic. This study aimed to analyze and evaluate publications on nerve-bone interactions using bibliometrics and to identify the state of the art of current research, hotspots, and future directions.

Methods: This study included 1989 articles and reviews from the Web of Science Core Collection (WoSCC) published from January 1, 1991, to June 22, 2022. The Bibliometrix package of R 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria) was used to analyze basic information about the publications, including the annual number of publications, institution analysis, author influence analysis, journal analysis, and the national cooperation network. We also used CiteSpace 5.8.R3 for bibliometric analysis, including co-occurrence, co-citation, and cluster analysis.

Results: We discovered a significant increase in the number of articles on nerve-bone interactions published over the last 10 years. The most active country and institution were the United States and the University of Minnesota, respectively. In terms of journals and cocited journals, *Bone* was ranked highest with respect to the number of publications, while *Journal of Bone and Mineral Research* was ranked highest among cited journals. Wang Lei was the author with the most publications, and Bjurholm A was the most cited author. The analysis of references and keywords revealed that the impact of nerve- and neuromodulation-related factors on stem cell differentiation was a persistently hot topic. Osteoarthritis, neuropeptide Y, and osteoclastogenic process are likely to be the next era of research hotspots. The neurovascular crosstalk within bone has received great attention, especially in skeletal diseases, which may provide potential targets for future treatments.

Conclusions: We used a bibliometric method to provide an efficient, objective, and comprehensive assessment of existing research about the interplay between the skeletal and nervous systems and to accurately identify hotspots and research frontiers, providing valuable information for future research.

Keywords: Skeleton; bibliometric analysis; nerve; Web of Science Core Collection (WoSCC); knowledge map

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Introduction

The interplay of the skeletal and nervous systems is considered an important regulatory mechanism for bone development, turnover, and regeneration (1). Nerve fibers are the first to be detected in the bone microenvironment during skeletal development, particularly in ossification centers (2). Cells adjacent to centers of incipient ossification can secrete nerve growth factor (NGF), increase innervation of bone surfaces, promote vascular invasion of the primary and secondary ossification centers, and increase femoral length and volume (3). Furthermore, in skeletal pathophysiologies, such as fractures, bone cancer, heterotopic ossification, bone defects, or osteoporosis, dysregulation of bone homeostasis is often accompanied by significant alterations in the density and distribution of nerve fibers (4,5). The consistency of the distribution of nerves with the area of ossification centers during bone regeneration suggests a nerve-guided self-healing process in skeletal diseases, including for bone defects (6-8). In addition, soft tissue trauma induces perivascular NGF expression, which mediates nerve axonal invasion and subsequently triggers heterotopic ossification within the soft tissue (9). Thus, nerves regulate bone homeostasis both in developmental and pathological states.

Bibliometrics, a quantitative and qualitative analysis method for published academic literature, is commonly used to track the development of a given research field within a defined time frame, which is important for evaluating scientific activities in the field (10). Through focusing on the impact of publications, contributions of individuals/institutions/countries, patterns of authorship, and future research direction, bibliometrics reflects the current status and research trends in a scientific and comprehensive manner. CiteSpace, a valuable Java-based application for bibliometrics, developed by Prof. Chaomei Chen, is widely used to analyze and visualize the author/institution/country collaboration, author/literature cocitation relationship, and keyword co-occurrence relationship of academic literature (11). This approach has been applied in various disciplines, such as oncology, hypertension, and periodontology (12-14). However, to date, no bibliometric analyses of the global literature on interactions between the skeletal and nervous systems have been conducted.

Based on the complexity and importance of nerve-skeleton interactions, a bibliometric analysis can show the lineage and trends of the field, which would provide a reference for further research. Bibliometric analysis can provide information about the main contributing journals, seminal articles, active institutions and research teams, and recent hotpots in the field of nerve-skeleton interaction. This paper provides a bibliometric analysis for research on the interplay between the nerves and skeleton from 1991 to 2022. We aim to provide a panoramic picture of the current research and predict future research hotspots.

Highlight box

Key findings

- This paper summarizes the research thread and research frontier in the field of nerve-skeleton interaction using bibliometrics method.

What is known and what is new?

- We concluded that the most active country and institution were the United States and the University of Minnesota, respectively. In terms of journals and cocited journals, *Bone* was ranked highest with respect to the number of publications, while *Journal of Bone and Mineral Research* was ranked highest among cited journals. Wang Lei was the author with the most publications, and Bjurholm A was the most cited author.
- We conclude that the current research frontier will focus on osteoarthritis, neuropeptide Y, and osteoclastogenic process.

What is the implication, and what should change now?

- The research in the field of nerve-skeleton interaction should pay more attention to sympathetic nerve, osteoarthritis, osteoclastogenic process, and the crosstalk among nerves, bones and blood vessels.

Methods

Data acquisition and search strategy

All data were obtained from the Web of Science Core Collection (WoSCC) on June 22, 2022. The search strategy used for this study was as follows: "(TS = (Osteoblasts OR Osteocytes OR Osteoclasts OR Osteogenesis OR Osteolysis OR Biomineralization)) AND TS = (innervation OR neurons OR nerve)" (TS = Topics). The timespan was from January 1, 1991, to June 22, 2022, which yielded a total of 2,127 papers. The overall workflow is shown in *Figure 1*. All data were independently searched by the 2 authors and stored in text format. Publications with little value, such as conference papers and letters, were filtered out. Only 1,989 articles and reviews were used for subsequent analysis. The data were downloaded from public databases, and no medical ethics issues were involved.

Data analysis

The Bibliometrix package of R 4.2.0 (The R Foundation for

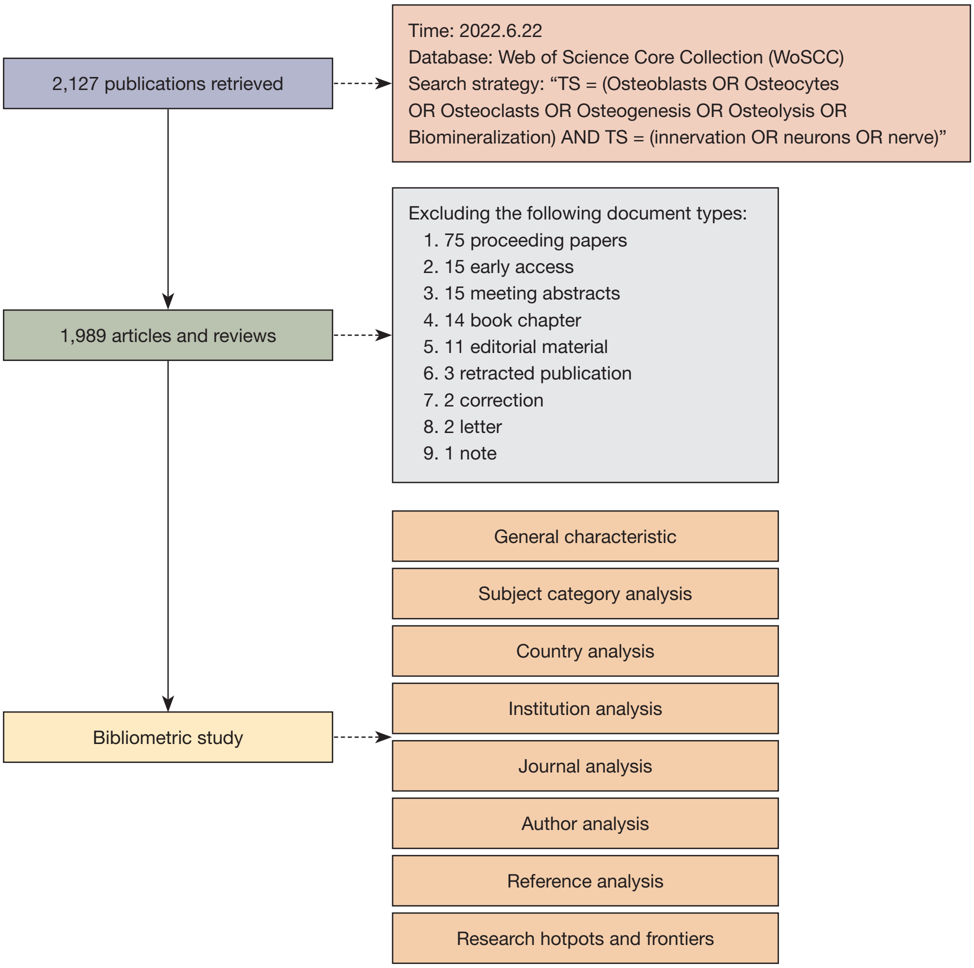

Figure 1 Workflow of this study. TS, topics.

Statistical Computing, Vienna, Austria) was used to extract and analyze the basic information about the publications, including the annual number of publications, institution analysis, author analysis (including H index, G index, M index, and publication overtime), journal analysis, and the national cooperation network. The H index refers to authors who have published at least H papers, with each paper being cited at least H times (6). Given a set of articles ranked in decreasing order of the number of citations they have received, the G index is the largest number such that the top G article has received at least G^2 citations (15). The M index refers to the author's H index divided by the author's academic age (academic age was measured as the number of years since the first published paper in the research area) (6). The H index, G index, and M index were used to characterize the output of each researcher.

To further show the relationship between the publications mentioned above, we used CiteSpace 5.8.R3 for bibliometric analysis. CiteSpace is a Java-based citation visualization tool developed by Professor Chaomei Chen that can show the structure, patterns, and distribution of scientific knowledge (16,17). CiteSpace has 5 main functions:

(I) Co-occurrence analysis (including authors, institutions, countries, and keywords), which showed the cooperation and clustering relationships of individual nodes.
(II) Cocitation analysis (including references and cited authors), which showed the relevance and clustering relationship of each node, with document cocitation referring to the relationship between paper A and paper B when paper A and paper B are both cocited by paper C (18,19).
(III) Cluster identification, in which the cluster labels

were based on the "title term" of each article.

(IV) Timeline construction, in which the specific publications/keywords in each cluster were arranged by publication time, showing the time period and relationship of the publications of each cluster.

(V) Parameter identification, in which burst, centrality, and sigma were analyzed for each node (including references, authors, and institutions), with burst indicating the sudden change of the node in the whole network, centrality indicating the importance of the node in the whole cocitation or cooccurrence network, and sigma indicating the combination of burst and centrality.

Statistical analysis

This study is a descriptive study using numbers, frequencies, and percentages to describe the indicators statistically. There was no difference analysis involved, and there was no need to set a test level. R 4.2.0 and CiteSpace 5.8.R3 were used to extract indicators and generate graphs.

Results

General characteristics of publications

The annual distribution of 1,989 publications (only articles and reviews) is shown in *Figure 2A*. The year 2009 was a very clear cutoff point in terms of annual publications. From 1991 to 2008, this field underwent a development period, with a total of 620 publications over 17 years. From 2009 to 2022, there was a qualitative leap, with 1,369 articles published during the 14 years, nearly twice the number as that of the previous period. These findings indicated that the interplay between nerves and the skeleton had become a popular research topic.

Subject category analysis

A category co-occurrence analysis revealed that publications mainly focused on "cell biology" [393], followed by "biochemistry & molecular biology" [230], "surgery" [223], "neurosciences & neurology" [205], "endocrinology & metabolism" [198], "research & experimental medicine" [161], "medicine, research & experimental" [161], and "dentistry, oral surgery & medicine" [159] (*Figure 2B*). These categories indicated that research about the interplay of skeletal and nervous systems was multifaceted and multilayered, including cellular physiological and biochemical research, as well as clinical application research, such as for drugs and clinical treatments. Notably, dentistry-related research played an integral role in the field.

Country analysis

Research on nerve-bone interactions was conducted in 72 countries. Among the top 10 countries, there were 2 North American countries, 3 Asian countries, 4 European countries, and 1 Oceanian county (Australia) (*Figure 2C*; Table S1). With 1,552 papers, the United States published most of the publications, followed by China [1,237] and Japan [602]. These 3 countries were also the global centers of cooperation (*Figure 2D*), leading the research on nerve-bone interplay. Notably, the burst analysis showed a spike in post-2018 publications in China (*Figure 2E*).

Institution analysis

All publications were from 2043 institutions, indicating a broad interest in crosstalk between nerves and the skeleton. Among the top 20 institutions, 9 were from the United States, 7 were from China, 3 were from Japan, and 1 was from Portugal (*Figure 2F*; Table S2). The University of Minnesota was the most active institution (*Figure 2F*). Institution cooperation analysis showed that the Fourth Military Medical University (frequency =31), Shanghai Jiao Tong University (frequency =28), and Sichuan University (frequency =24) were collaborating extensively with other institutions. Articles from these institutions were mainly published after 2008, showing when Chinese institutions emerged in this field (*Figure 2G*).

Author analysis

A total of 8,598 authors published articles about the interplay between nerves and the skeleton. The academic output of these authors was assessed based on the H index, and the top 20 authors are shown in *Figure 3A*. Analysis of the H index showed the 5 most important authors were Elefteriou F, Mantyh PW, Wang L, Togari A, and Karsenty G. Additional information for the top 20 authors, including the G index and M index, is listed in Table S3.

Author cooperation analysis showed that cooperation across the field was not very close. The research team centered on Mantyh PW published more in the early years,

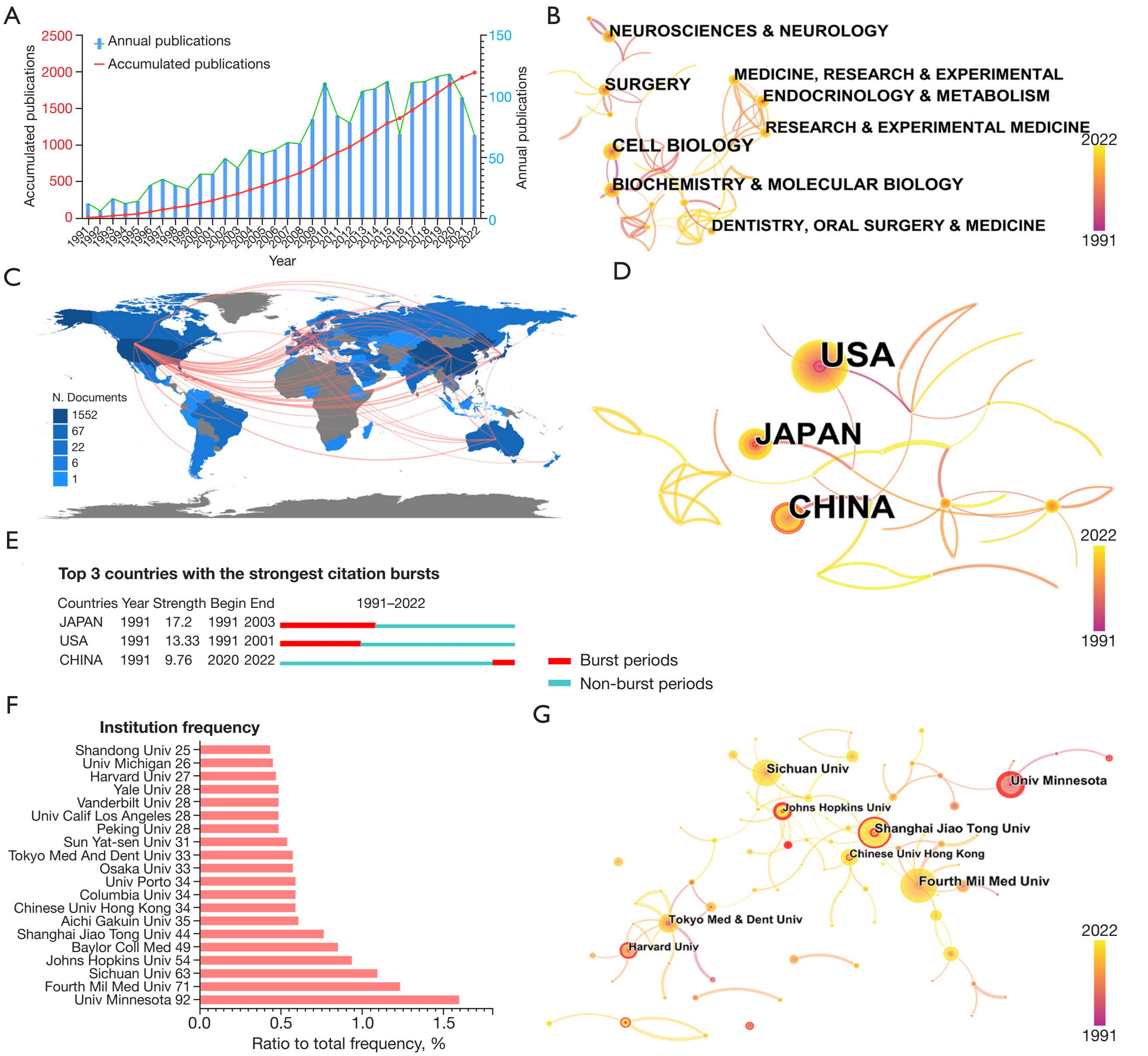

Figure 2 Time, subject category, institution, and country distribution of publications. (A) Annual publications and accumulated publications from 1991 to 2022. (B) Subject categories distribution and co-occurrence analysis. (C) Geographic distribution of countries on nerve-bone interactions publications between 1991 and 2022. The shade of the color represents the number of publications issued by the country, and the thickness of the red line represents the frequency and intensity of cooperation between countries. (D) Country distribution and co-occurrence analysis. (E) Burst analysis for countries. (F) The top 20 institutions related to publications on nerve-bone interactions from 1991 to 2022. The frequencies are listed after the names of the institutions. (G) Institution distribution and co-occurrence analysis. For (B,C,G), each node represents a category/country/institution, and the size of the ring denotes the number of publications in the category/country/institution in a given year. The color of the connecting line represents the co-occurrence time, and the shade represents the strength of the association. The CiteSpace parameters were as follows: link retaining factor (LRF =3), look back years (LBY =8), e for top n (e=2; n=50), timespan [1991–2022], and years per slice [1].

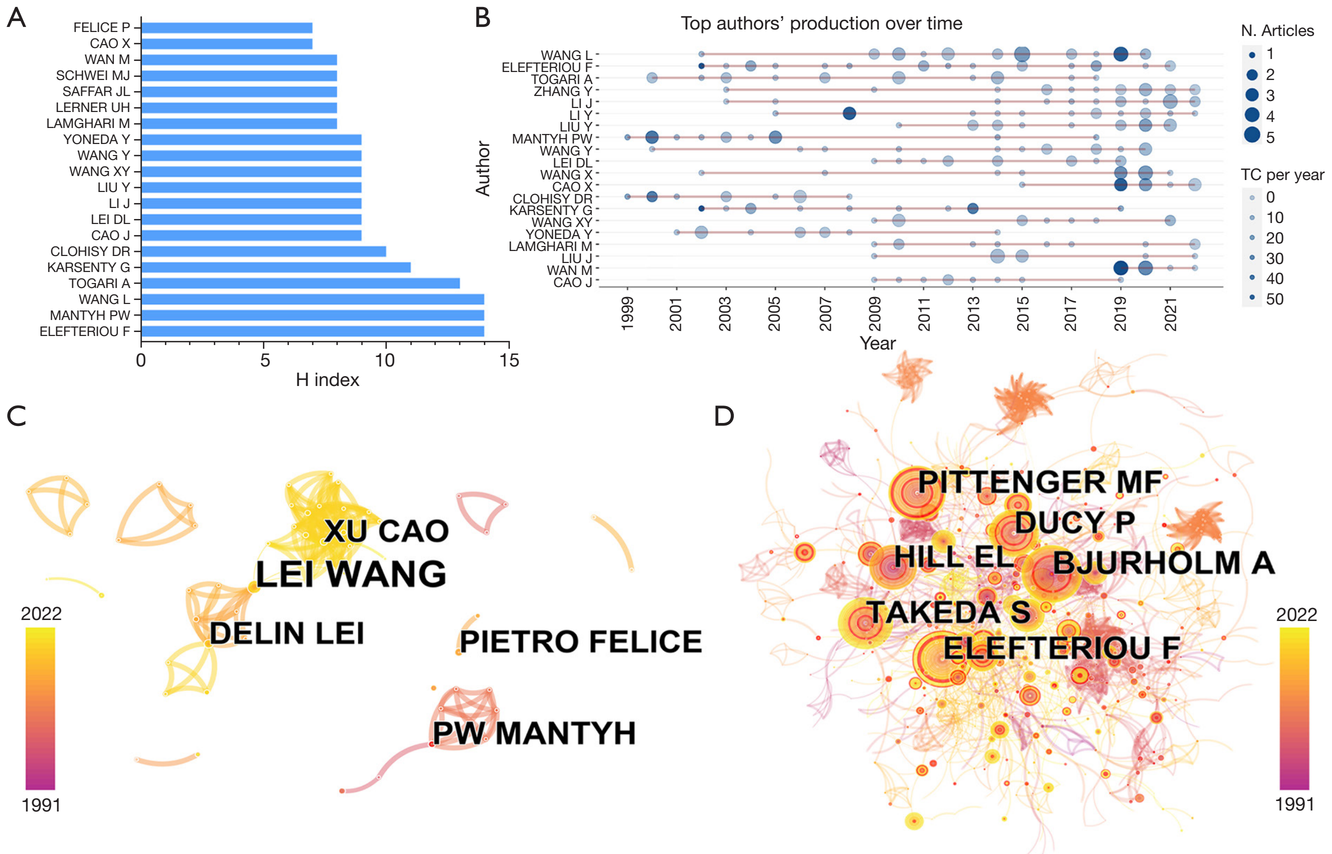

Figure 3 Author analysis. (A) The top 20 authors according to the H index. The H index is defined as authors who have published at least H papers, with each paper been cited at least H times. (B) The top 20 authors' production over time. The size of the node represents the number of articles published, and the shade of the color represents the total number of citations (TC). (C) Author co-occurrence network. (D) Author cocitation network. For (C,D), each node represents an author/cited author, and the size of the ring denotes the number of publications of the author/cited author in a given year. The color of the connecting line represents the co-occurrence/cocitation time, and the shade represents the strength of the association. The CiteSpace parameters were as follows: link retaining factor (LRF =3), look back years (LBY =8), e for top n (e=2; n=50), timespan [1991–2022], and years per slice [1].

mostly around the year 2000. The Wang Lei-centered team was more active around the year 2012. The Cao Xu-centered team was more active around the year 2019 (*Figure 3B,3C* and Table S4). Wang Lei was the most active researcher (*Figure 3C*), whose research focused on the mechanisms and clinical applications of peripheral nerves in the field of bone defects, especially the role of the inferior alveolar nerve and nerve-related factors in distraction osteogenesis (20-24). The top 20 authors in terms of author cooperation are listed in Table S4.

The author cocitation analysis showed that Bjurholm A was the most cited author with 143 citations, followed by Elefteriou F [132], Pittenger MF [127], and Takeda S [124] (*Figure 3D*; Table S5).

Journal analysis

In order to obtain a picture of the journals publishing literature about the interplay of the skeletal and nervous systems, we analyzed the publication volume of journals. The top 10 journals in terms of publication volume are shown in *Figure 4A*, with the top 3 being *Bone* (IF =4.398), *PLoS ONE* (IF =3.240), and *Journal of Bone and Mineral Research* (IF =6.471). These journals were excellent choices for researchers to submit their manuscripts.

As the impact of journals was measured by the number

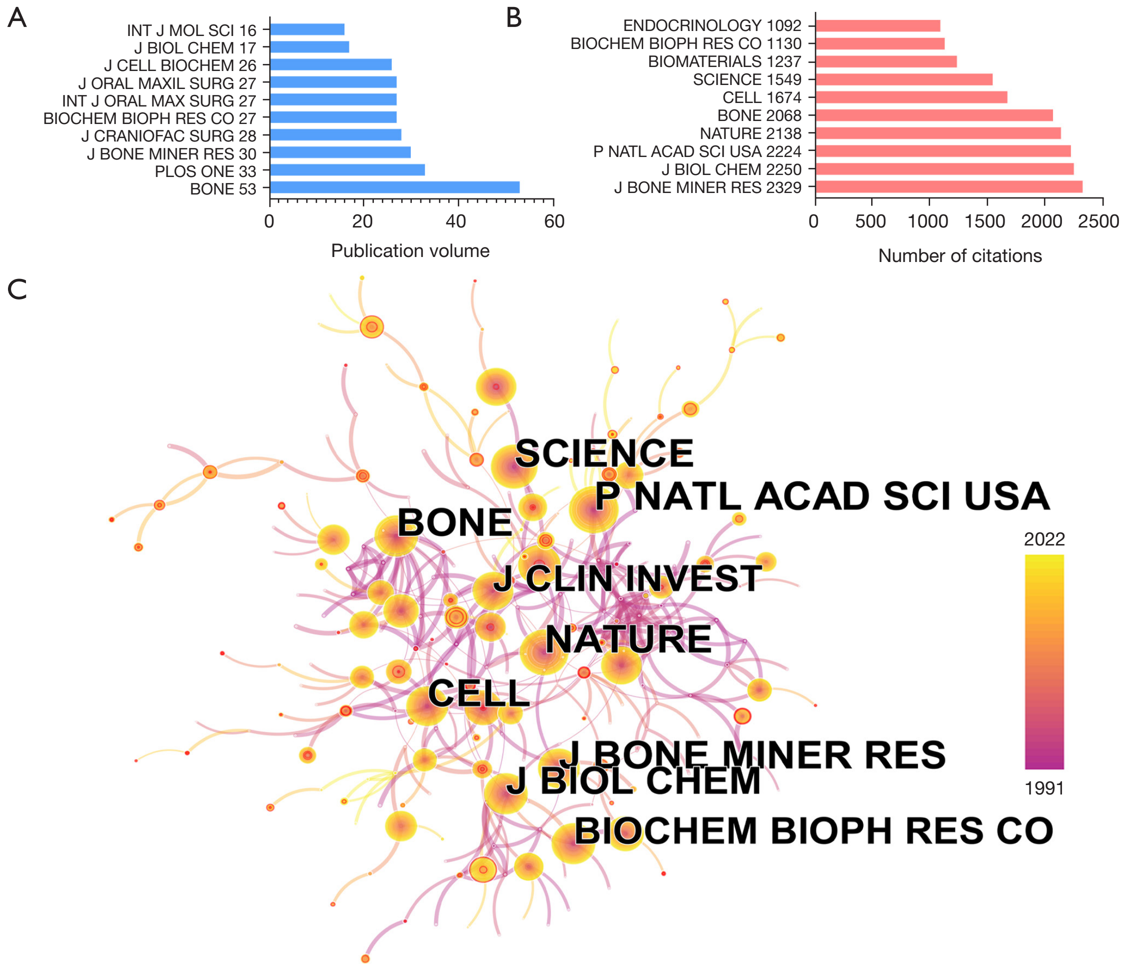

Figure 4 Journal analysis. (A) The top 10 journals by publication volume. (B) The top 10 journals by citation number. (C) The journal cocitation network. Each node represents a journal, and the size of the ring denotes the number of publications of the journal in a given year. The color of the connecting line represents the cocitation time, and the shade represents the strength of the association. The CiteSpace parameters were as follows: link retaining factor (LRF =3), look back years (LBY =8), e for top n (e=2; n=50), timespan [1991–2022], and years per slice [1].

of citations, we listed the top 10 journals with the highest number of citations (*Figure 4B*). Furthermore, we conducted a journal cocitation analysis (*Figure 4C*) and identified the top 20 journals based on citation frequency (Table S6). Seven journals were identified as seminal journals with high-quality articles, which included *Journal of Biological Chemistry* (IF =5.157), *Proceedings of the National Academy of Sciences of the United States of America* (IF =11.205), *Nature* (IF =49.962), *Science* (IF =48.728), *Cell* (IF =41.582), *The Journal of Bone and Mineral Research* (IF =6.741), and *Bone* (IF =4.398). If readers need to gain a comprehensive and in-depth understanding of the field, they should primarily target articles from these journals.

Reference analysis

We performed a 30-year reference cocitation analysis of these publications. We found that the article entitled "Leptin regulates bone formation via the sympathetic nervous system" in *Cell* by Takeda *et al.* (25) was the most frequently cited article, followed by the articles entitled "*Multilineage potential of adult human mesenchymal stem cells*" (26), "*Sema3A regulates bone-mass accrual through sensory innervations*" (27), and "*Leptin regulation of bone resorption by the sympathetic nervous system and CART*" (28) (Figure S1). Furthermore, we conducted a 10-year reference cocitation analysis. The article entitled "*Sema3A regulates bone-mass accrual through sensory innervations*" (27) was found

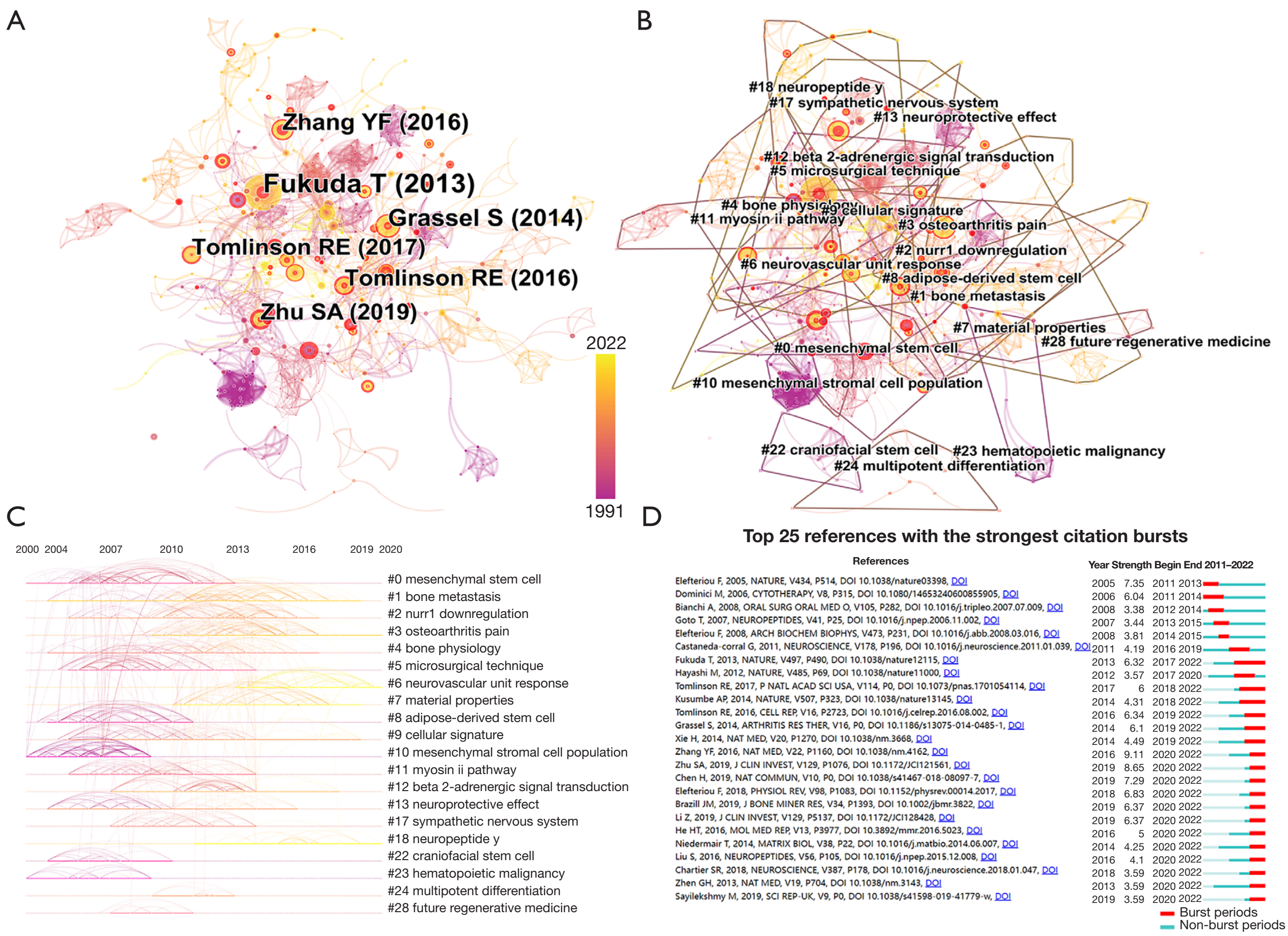

Figure 5 The 10-year reference analysis. (A) A 10-year reference cocitation analysis. Each node represents a reference, and the size of the ring denotes citations of the reference. The color of the connecting line represents the cocitation time, and the shade represents the strength of the association. (B) Cluster analysis for 10 years of references. Different color blocks represent different clusters. The color of the block represents the publication time period of references in the cluster, and the labels are marked to reflect the topic of the respective cluster. (C) Time distribution of articles in different clusters. (D) The top 25 references with the strongest citation bursts. The CiteSpace parameters were as follows: link retaining factor (LRF =3), look back years (LBY =8), e for top n (e=2; n=50), timespan [2011–2022], and years per slice [1].

to be the most frequently cited piece of literature in the last 10 years, followed by the articles entitled "*The role of peripheral nerve fibers and their neurotransmitters in cartilage and bone physiology and pathophysiology*" (29) and "*Implant-derived magnesium induces local neuronal production of calcitonin gene-related peptide (CGRP) to improve bone-fracture healing in rats*" (30) (*Figure 5A*). Cluster analysis of publications revealed that osteoarthritis pain, neurovascular unit response, and neuropeptide Y (NPY) subject clusters had been the research hotspots since 2015 (*Figure 5B,5C*). In addition, the mesenchymal stem cell, mesenchymal stromal cell population, multipotent differentiation, and adipose-derived stem cell subject clusters indicated that stem cell research remained an important part of the field (*Figure 5C*). The article entitled "*Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats*" (30) was the most emergent article (burstness strength =9.11), followed by the articles entitled "*Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain*" (31) (burstness strength =8.65) and "*Leptin regulation of bone resorption by the sympathetic nervous system and CART*" (28) (burstness strength =7.35; *Figure 5D*).

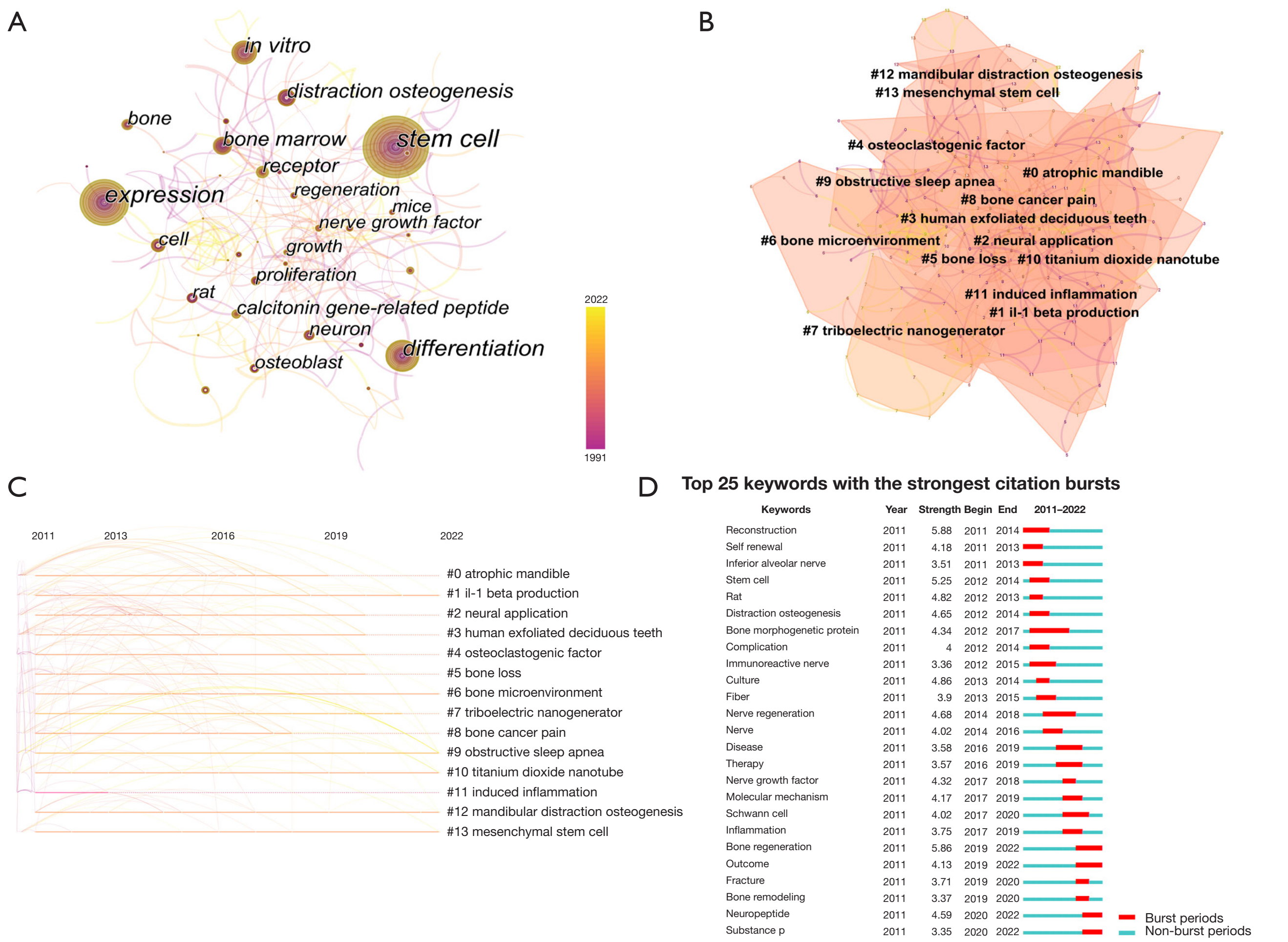

Figure 6 The 10-year keywords analysis. (A) The 10-year keyword co-occurrence analysis. Each node represents a keyword, and the size of the ring denotes the frequency of the keyword. The color of the connecting line represents the co-occurrence time, and the shade represents the strength of the association. (B) Cluster analysis for 10 years of keywords. Different color blocks represent different clusters. The labels are marked to reflect the topic of the respective cluster. (C) Time distribution of keywords in different clusters. (D) The top 25 keywords with the strongest occurrence burst. The CiteSpace parameters were as follows: link retaining factor (LRF =3), look back years (LBY =8), e for top n (e=2; n=50), timespan [2011–2022], and years per slice [1].

Research hotpots and frontier

We further conducted a 10-year keyword co-occurrence analysis for publications from 2011 to 2022 and found that "expression", "differentiation", "cell", and "mesenchymal stem cell" were the most frequent keywords (*Figure 6A*). These top keywords were consistent with the results of the 30-year keyword co-occurrence analysis (Figure S2A). We further conducted a cluster analysis of 10-year keywords and found that there were 13 clusters, including bone cancer pain, osteoclastogenic factor, mesenchymal stem cell, bone loss, bone microenvironment, and mandibular distraction osteogenesis clusters (*Figure 6B,6C*). The 30-year keywords cluster analysis provided more information for hotpots from 1991 to 2022 (Figure S2B,S2C).

We also performed a 10-year keyword burst analysis. The burst strength of "reconstruction" was found to be the highest, followed by "bone regeneration" and "stem cell" (*Figure 6D*). The subjects of neuropeptides and substance P were hot topics from 2020 to 2022. The 30-year keywords burst analysis suggested that the top 3 keywords in terms of burst strength were "immunoreactive nerve", "messenger RNA" and "osteogenic differentiation" (burst strength =15.25, 12.33, and 10.15, respectively). Osteogenic differentiation, scaffold, bone regeneration, and fracture remained the burst topics from 2010 to now (Figure S2D).

Discussion

We analyzed the highly cited articles reporting on the interplay of the skeletal and nervous systems based on 30-year and 10-year reference cocitation analysis. This analysis provided a comprehensive picture of the development of research examining crosstalk between the nerves and skeleton across a 30-year timeframe. Before 1999, highly cited articles focused on the distribution of nerves within the bone (32). After 2000, research fell into 2 main directions. On the one hand, publications in *Nature* in 2005 (28), *Journal of Clinical Investigation* in 2002 (33), and *Cell* in 2000 (34) and 2002 (25) all focused on leptin, an important hormone that activates the sympathetic release of neuropeptides to participate in bone remodeling, inhibiting osteogenesis and promoting osteoclastic process. These articles became the seminal literature on the neural regulation of bone homeostasis. Meanwhile, around the year 2000, a series of articles discovered that mesenchymal stem cells (MSCs) could differentiate into ectodermal neuronal cells (26,35,36). This groundbreaking discovery provided the theoretical basis for subsequent tissue engineering and neuroscience research. Later, highly cited publications from 2011 to 2022 focused on sensory nerves after Fukuda *et al.* (27) identified that sensory innervation can regulate bone mass. This discovery allowed for the understanding that two clinical symptoms—pain and bone remodeling—are mechanistically coupled in skeletal disorders. Some osteoarthritis research focused on osteoclasts, which can secrete factors to induce sensory nerve axonal growth and cause osteoarthritis pain (31,37). This confirmed that bone tissue could lead to a different effect on the germination and atrophy of sensory nerves in the pathological state, a discovery which expands the understanding of the interplay between nerves and the skeleton (38).

Using cluster analysis and burst analysis, we identified 4 molecules as “star molecules” during the interplay between the skeletal and nervous systems; these were CGRP, NPY, semaphorin 3A (Sema3A), and NGF. CGRP has been a key topic in this field since 1991 (39) and has been proven to be involved in bone formation and skeletal diseases (40). Since the year 2000, CGRP has gradually become a marker of sensory nerves or an indicator of sensory nerve activity. NPY is an extremely important neurological factor in the sympathetic nervous system, which started to be a hot topic in 2012. The role of NPY in bone metabolism is multifaceted (41). On the one hand, NPY can lead to a decrease in bone mass by combining with Y1 receptors (42,43). On the other hand, NPY exhibits an osteoprotective effect by directly promoting the proliferation and osteogenic differentiation of MSCs (44-47) and combining Y1 receptors in macrophages to maintain the activity of stem cells (18). Sema3A is an axon repellant about which an explosion of studies emerged beginning in 2012 (48). Sensory nerve-derived Sema3A functions as an osteoprotective factor and plays an important role in bone development and remodeling (27). An explosion of articles related to NGF began to appear after 2017. NGF secreted by osteoblasts, stem cells, and macrophages can combine with the tropomyosin receptor kinase A (TrkA) receptor on sensory nerves to guide sensory nerve growth, promoting angiogenesis and bone tissue formation. NGF plays an indispensable role in bone formation (3), osteoarthritis (49,50), bone fracture (8), mechanical loading (51), bone defects (7), and rare bone disease (including heterotopic ossification) (9). These star molecules are currently hot topics in the study of nerve-bone interaction due to their extremely important roles.

Our results also show the current research hotspots and frontiers. Among clinical disorders, osteoarthritis is a highly prevalent and debilitating joint disorder without effective medical therapy because of a limited understanding of its pathogenesis (27,47). The clinical issue of osteoarthritis pain has received widespread attention (49,52,53). Among clinical symptoms, sympathetic and sensory nerves play an important role in nerve-bone interactions (53). Among bone remodeling, the osteoclastic process has gained increasing attention from researchers. Osteoclasts can secrete various factors involved in bone remodeling and affect the growth of nerve axons, leading to nociceptive hypersensitivity in osteoarthritis (31,54,55). Among cells in bone, osteocytes have received increasing attention (56). Several studies have confirmed that osteocytes can also secrete neuromodulation-related factors such as NPY and Sema3A to participate in bone remodeling (57,58), which may be regulated by nerves (57).

The cluster analysis of publications revealed that “neurovascular unit response” has been a popular research topic since 2015, which suggests that a deeper examination of the crosstalk between nerves and blood vessels during skeletal development and pathophysiology is needed. In skeletal development, sensory nerves are first distributed around capillaries surrounding bone trabeculae, especially in areas with high osteogenic and chondrogenic activity (2). In turn, innervation induces vascular invasion of primary and secondary ossification centers in the skeleton, which ultimately mediates bone growth (59). Notably, although the phenomenon of neurovascular crosstalk in skeletal development has been extensively studied, the functional coupling of nerves, vessels, and skeleton in skeletal pathophysiology can provide more information for the treatment of related diseases. Some bone-related rare diseases, such as fibrodysplasia ossificans and heterotopic ossification, have become typical models for bone homeostasis imbalance (60). Heterotopic ossification is caused by severe soft tissue trauma and characterized by extraskeletal pathological cartilage and bone formation (61,62). Several clinical symptoms, including pain and a high prevalence around large peripheral nerves, suggest the important role of nerves in the initiation and development of heterotopic ossification (63). A further study confirmed that vascular smooth muscle cells and pericytes could secrete NGF to mediate axon innervation (9). Nerve injury, in turn, affects the formation of blood vessels, thereby delaying ossification (64). The same nerve-vessel crosstalk was found in osteoarthritis, another skeletal disease characterized by pain. In the early stage of osteoarthritis, increased osteoclast activity in the subchondral bone leads to the release of transforming growth factor- β1 (TGF-β1) to precipitate angiogenesis and the secretion of netrin-1 to induce innervation (31). The nerves grow into the cartilage along the blood vessels, triggering osteoarthritis pain. During the late stage of osteoarthritis, NGF secretion by preosteoclasts and prostaglandin E2 (PGE2) secretion by osteoblasts mediate persistent nerve germination (49,65). The neurovascular crosstalk within bone has received great attention, especially in skeletal diseases, which may provide potential targets for future treatments.

Conclusions

This article surveyed the global scientific output of research into the interplay between the skeletal and nervous systems from January 1, 1991, to June 22, 2022. We found a significant increase in the number of articles published over the last 10 years. In terms of countries, the United States, China, and Japan were leading research centers and dominated global research collaborations. In terms of institutions, the University of Minnesota was the leader in the field. In terms of authors, Wang Lei was the most active researcher, while Bjurholm A produced the most prolific and widely cited outputs. In terms of journals, *Bone* and *Journal of Bone and Mineral Research* were the most prominent sources for research on nerve-bone interactions. The impact of nerve- and neuromodulation-related factors on stem cell differentiation was a persistently hot topic. Osteoarthritis, neuropeptide, and osteoclastogenic processes will likely emerge as hotspots in the next era of research.

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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-22-3323/coif). All authors report that this work was supported by the National Natural Science Foundation of China (Nos. 31971240 and 31670951) and the Clinical Research Project of West China Hospital of Stomatology, Sichuan University (No. LCYJ2019-22). The authors have no other 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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Supplementary

Table S1 Top 20 active countries in nerve–bone interaction publications from 1991 to 2022

Country	Number of publications	Location
USA	1552	North America
China	1237	Asia
Japan	602	Asia
Germany	296	Europe
Italy	268	Europe
UK	206	Europe
France	195	Europe
South Korea	187	Asia
Australia	109	Australia
Canada	99	North America
Iran	93	Asia
Sweden	84	Europe
Netherlands	83	Europe
Spain	70	Europe
Brazil	69	South America
Switzerland	63	Europe
Belgium	60	Europe
Israel	59	Asia
Turkey	57	Europe
Portugal	51	Europe

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Table S2 Top 20 active institutions in nerve–bone interaction publications from 1991 to 2022

Institution	Number of publications	Country
University of Minnesota	92	USA
Air Force Medical University	71	China
Sichuan University	63	China
Johns Hopkins University	54	USA
Baylor College of Medicine	49	USA
Shanghai Jiao Tong University	44	China
Aichi Gakuin University	35	Japan
The Chinese University of Hong Kong	34	China
Columbia University	34	USA
University of Porto	34	Portugal
Osaka University	33	Japan
Tokyo Medical and Dental University	33	Japan
Sun Yat-sen University	31	China
Peking University	28	China
University of California, Los Angeles	28	USA
Vanderbilt University	28	USA
Yale University	28	USA
Harvard University	27	USA
University of Michigan	26	USA
Shandong University	25	China

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Table S3 G index, M index, total citation, and number of publications of the top 20 authors in nerve–bone interaction publications from 1991 to 2022

Authors	G index	M index	Total citation	Number of publications	PY start
Elefteriou F	19	0.667	2242	19	2002
Mantyh PW	14	0.583	2416	14	1999
Wang L	26	0.667	820	26	2002
Togari A	17	0.565	586	17	2000
Karsenty G	11	0.524	2213	11	2002
Clohisy Dr	11	0.417	1562	11	1999
Cao J	9	0.643	169	9	2009
Lei DL	12	0.643	170	12	2009
Li J	12	0.45	186	12	2003
Liu Y	13	0.692	201	13	2010
Wang XY	11	0.643	123	11	2009
Wang Y	14	0.391	268	14	2000
Yoneda Y	10	0.409	305	10	2001
Lamghari M	8	0.571	177	8	2009
Lerner UH	8	0.333	285	8	1999
Saffar JL	8	0.32	309	8	1998
Schwei MJ	8	0.333	1975	8	1999
Wan M	9	2	331	9	2019
Cao X	9	0.875	295	9	2015
Felice P	8	0.5	290	8	2009

G index means that, given a set of articles ranked in decreasing order of the number of citations they received, the G index is the largest number such that the top G articles received at least G^2 citations. The M index was the author's H index divided by the author's academic age (academic age was measured as the number of years since the first published paper in the research area). PY: Year Publication.

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Table S4 Top 20 active authors in author cooperation related to nerve–bone interaction publications from 1991 to 2022

Rank	Freq.	Burst	Degree	Centrality	Sigma	Author	Year
1	14		9	0	1	Lei Wang	2012
2	9		16	0	1	Xu Cao	2019
3	9	4.54	10	0	1	PW Mantyh	2000
4	8	3.56	9	0	1	Pietro Felice	2009
5	8		9	0	1	Delin Lei	2012
6	7		5	0	1	DR Clohisy	2000
7	7		3	0	1	Akifumi Togari	2007
8	6		13	0	1	Gang Li	2020
9	6		2	0	1	Florent Elefteriou	2011
10	6		14	0	1	Mei Wan	2019
11	6		14	0	1	Gehua Zhen	2019
12	5		2	0	1	Ping Gong	2019
13	5		9	0	1	Xiao Wang	2019
14	4		3	0	1	Xudong Wang	2019
15	4		6	0	1	Zhaojie Du	2012
16	4		0	0	1	Hiroki Wakabayashi	2017
17	4		2	0	1	Roberto Pistilli	2012
18	4		2	0	1	A Togari	2000
19	4		5	0	1	Meriem Lamghari	2010
20	4		8	0	1	Yusheng Li	2019

The CiteSpace parameters were as follows: link retaining factor (LRF = 3), look back years (LBY = 8), e for top n (e=2; n=50), timespan (1991 to 2022), and years per slice (1). Burst measures a sudden change of items or citations. Centrality quantifies the importance of the node's position in the network. Sigma is a combination of burst and centrality.

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Table S5 Top 20 cocited authors in nerve–bone interaction publications from 1991 to 2022

Rank	Freq.	Burst	Degree	Centrality	Sigma	Author	Year
1	143	13.15	12	0	1	Bjurholm A	1991
2	132	8.16	13	0	1	Elefteriou F	2006
3	127	15.38	7	0	1	Pittenger MF	2001
4	124	5.99	9	0	1	Takeda S	2003
5	112	12.17	15	0	1	Hill EL	1993
6	112	5.67	7	0	1	Ducy P	2000
7	87	5.19	9	0	1	Hukkanen M	1996
8	80	5.54	12	0	1	Togari A	2000
9	69	11	6	0	1	[anonymous]	2008
10	66	11.22	6	0	1	Gronthos S	2005
11	65	11.45	7	0	1	Wang L	2010
12	64	–	24	0	1	Li Y	1999
13	63	–	13	0	1	Lerner UH	1996
14	62	4.6	17	0	1	Mccarthy JG	1997
15	60	4.89	11	0	1	Mach DB	2003
16	58	10.04	16	0	1	Zaidi M	1993
17	56	12.97	15	0	1	Zuk PA	2003
18	56	5.65	11	0	1	Ilizarov GA	1996
19	56	10.75	8	0	1	Dominici M	2009
20	54	12.3	19	0	1	Hohmann EL	1994

The CiteSpace parameters were as follows: link retaining factor (LRF = 3), look back years (LBY = 8), e for top n (e=2; n=50), timespan (1991 to 2022), and years per slice (1). Burst measures a sudden change of items or citations. Centrality quantifies the importance of the node's position in the network. Sigma is a combination of burst and centrality

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Table S6 Top 20 cocited journals in nerve–bone interaction publications from 1991 to 2022 and impact factor (IF) published in June 2021

Rank	Freq.	Burst	Centrality	Sigma	Journal	IF 2021
1	535		0	1	*P Natl Acad Sci U S A*	11.205
2	492		0	1	*Plos One*	3.24
3	490		0	1	*Nature*	49.962
4	485		0	1	*Bone*	4.398
5	455		0	1	*J Bone Miner Res*	6.741
6	420		0	1	*Cell*	41.582
7	416		0	1	*Science*	47.728
8	403		0	1	*J Biol Chem*	5.157
9	340		0	1	*Biochem Bioph Res Co*	3.575
10	294		0	1	*J Clin Invest*	14.808
11	257		0	1	*J Neurosci*	6.167
12	255		0	1	*Biomaterials*	12.479
13	255		0	1	*Stem Cells*	6.277
14	252		0	1	*J Cell Physiol*	6.384
15	249		0	1	*J Cell Biochem*	4.429
16	242		0	1	*Nat Med*	53.44
17	223		0	1	*Clin Orthop Relat R*	4.176
18	205		0	1	*J Orthop Res*	3.494
19	201	45.1	0	1	*Sci Rep-Uk*	4.379
20	199		0	1	*Neuroscience*	3.359

IF, impact factor. The CiteSpace parameters were as follows: link retaining factor (LRF = 3), look back years (LBY = 8), e for top n (e=2; n=50), timespan (1991 to 2022), and years per slice (1). Burst measures a sudden change of items or citations. Centrality quantifies the importance of the node's position in the network. Sigma is a combination of burst and centrality.

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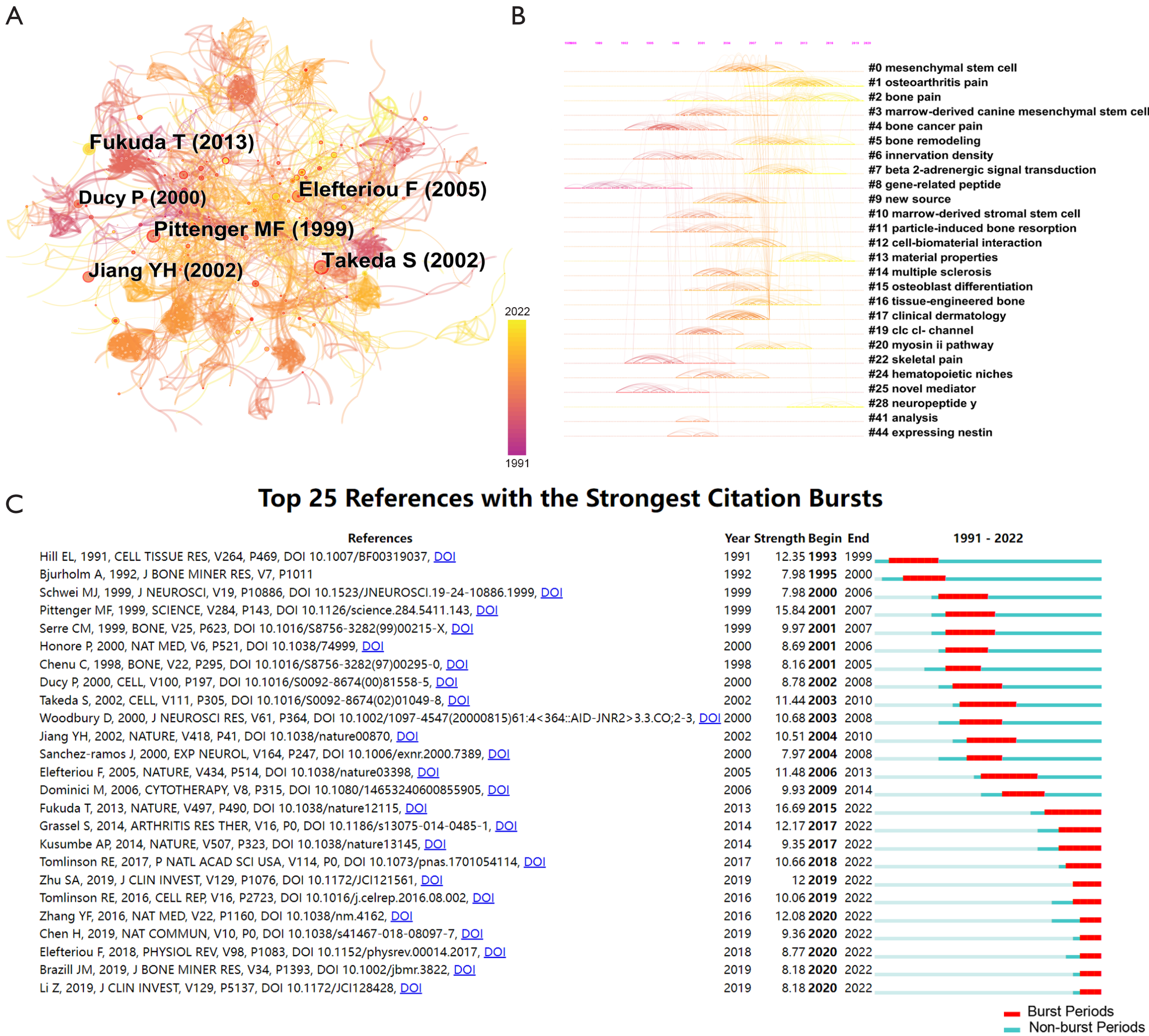

Figure S1 The 30-year reference analysis. (A) The 30-year reference co-citation analysis. Each node represents a reference, and the size of the ring denotes the number of citations of the reference. The color of the connecting line represents the cocitation time, and the shade represents the strength of the association. (B) Time distribution of the literature in different clusters. (C) The top 25 references with the strongest citation bursts. The CiteSpace parameters were as follows: link retaining factor (LRF = 3), look back years (LBY = 8), e for top n (e=2; n=50), timespan (1991–2022), and years per slice (1).

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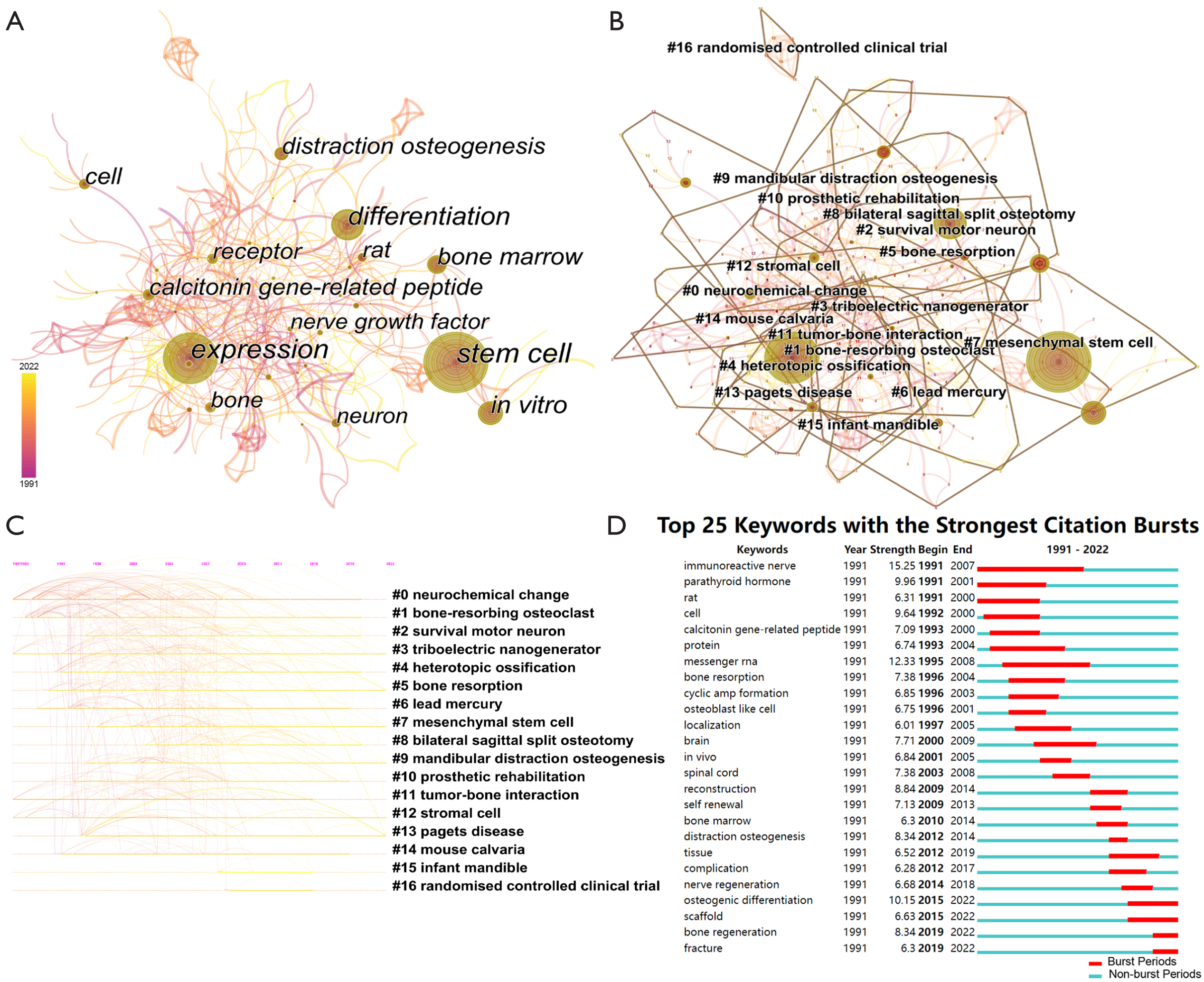

Figure S2 The 30-year keyword analysis. (A) The 30-year keyword co-occurrence analysis. Each node represents a keyword, and the size of the ring denotes the frequency of the keyword. The color of the connecting line represents the co-occurrence time, and the shade represents the strength of the association. (B) Cluster analysis for the 30-year keyword analysis. Different color blocks represent different clusters. The labels are marked to reflect the topic of the respective cluster. (C) Time distribution of keywords in different clusters. (D) The top 25 keywords with the strongest occurrence bursts. The CiteSpace parameters were as follows: link retaining factor (LRF = 3), look back years (LBY = 8), e for top n (e=2; n=50), timespan (1991–2022), and years per slice (1).

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