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Molecular & Cellular Biomechanics 2025, 22(4), 1272.
https://doi.org/10.62617/mcb1272

Article

Global trends of bone marrow mesenchymal stem cells in tissue engineering: A bibliometric analysis

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CITATION

Wang X, Chen H, Xu M, et al. Global trends of bone marrow mesenchymal stem cells in tissue engineering: A bibliometric analysis. Molecular & Cellular Biomechanics. 2025; 22(4): 1272. https://doi.org/10.62617/mcb1272

ARTICLE INFO

Received: 30 December 2024
Accepted: 27 January 2025
Available online: 28 February 2025

Abstract: Bone marrow mesenchymal stem cells (BMSCs) tissue engineering has been an emerging field of research in recent years. Given the increasing global interest, we utilized a bibliometric analysis and visualization of studies on BMSCs in the field of tissue engineering published from 2004 to 2023 to explore research progress and identify future research directions. Data was collected from the Web of Science Core Collection (WoSCC), and in-depth analysis was conducted using various bibliometric tools, including CiteSpace, VOSviewer, and R-Bibliometrix. Our study revealed the historical development and evolution of active topics in BMSCs in terms of temporal dynamics, covering 2967 publications, 65 countries, 2454 academic institutions, and 605 journals, with significant growth observed over the last 20 years. China and the United States dominate the global research landscape. Shanghai Jiao Tong University is one of the most significant contributors to the field. In terms of co-citation analysis, Biomaterials was identified as a key journal. Our analysis also revealed current trends such as extracellular vesicles, exosomes, 3D printing, hydrogels, and nanomaterials. These findings provide a clear perspective for future research on the tissue engineering of BMSCs. This study fills a gap in the field of bibliometrics, enabling researchers to identify popular research areas and providing a comprehensive perspective and broad outlook on this emerging field of research.

Keywords: bone marrow mesenchymal stem cells; tissue engineering; bibliometrics; CiteSpace; VOSviewer

1. Introduction

Tissue engineering is an interdisciplinary field with the potential to repair, maintain, improve, and replace tissue functions. It integrates engineering and life sciences [1]. Currently, the main method for repairing or reconstructing tissue defects involves implanting functional cells into scaffolds with good biocompatibility and degradability, culturing them in vitro for a while, and then implanting them in vivo after they have matured [2]. Seed cells are a crucial component in the successful construction of tissue-engineered scaffolds. Due to their ease of obtainment, autologous origin, strong self-renewal ability, lack of immune rejection problems during transplantation, and better compatibility [3], bone marrow mesenchymal stem cells (BMSCs) are a valuable tool in tissue engineering for treating clinically relevant diseases. Their ability to be expanded in vitro on a large scale and differentiated in the

desired direction by artificially imposing various intervening conditions is a significant advantage [4,5]. Bruder first proposed the use of autologous BMSCs for musculoskeletal tissue repair in 1994 [6]. Since then, this idea has undergone over 20 years of development and has encountered several challenges. These included ensuring the survival of sufficient quantities of BMSCs after transplantation [7], matching the rate of degradation and uptake of biomaterials with the rate of tissue or organ regeneration [8,9], and ensuring the stability and reproducibility of the tissue construct [10]. Researchers have shown that BMSCs can repair and regenerate a range of human tissues and organs, including bone [11], cartilage [12], tendon [13], skin, nerve [14], bladder [15], and liver [16]. The application of BMSCs in regenerative medicine and tissue engineering has made significant progress and breakthroughs due to the deepening of basic and clinical research and the interdisciplinary intersection of materials science, bioengineering, and computer science [17]. The rise of 3D printing technology [18], the application of 3D new material scaffolds, the research of extracellular vesicle technology [19], and the rise of nanotechnology and hydrogel technology have created opportunities for the application of BMSCs in tissue engineering [20]. Bone tissue engineering is generally considered the earliest and fastest developing field of research. Skin tissue engineering, on the other hand, is a more technically mature field. Neural tissue engineering has experienced rapid development in recent years, and myocardial tissue engineering is currently receiving more attention [21]. Research is also booming in the area of repairing and regenerating muscular tissue injuries or dysfunctions, such as those affecting the esophagus [22], bladder [15], urethra [23], intestines [24], and uterus [25]. Therefore, analyzing and summarizing the development, current status, and future trends is significant.

Over the past two decades, the field of BMSCs has experienced significant growth in published literature, with about 3000 papers in disciplines such as materials science and biomedicine. However, keeping up with the latest trends and advances in the field has become a time-consuming and labor-intensive task for researchers due to the sheer volume of literature. Therefore, to address the aforementioned issues, a quantitative approach based on reviewing and surveying the existing literature in a given field can be employed, such as bibliometric analysis. Bibliometrics was first introduced in the early 20th century and has since become a separate discipline, widely used in literature analysis [26]. The premise is that the published literature in a field reflects knowledge in that field. Bibliometric analyses can provide statistical descriptions of publications, which can be used to explore the productivity of researchers, institutions, and countries within specific subject areas. These methods have also been used to examine research trends and priorities across disciplines and guide policy decisions [27]. Computer analysis techniques are used to extract data from the Web of Science Core Collection (WoSCC) by analyzing individual publications [28]. Many researchers have accepted the WoSCC as a high-quality database of digital literature resources, making it the most suitable database for bibliometric analysis. The records were analyzed for their spatiotemporal distribution, authorship, subject categories, topics, references, and keywords using R-Bibliometrix, CiteSpace, and VOSviewer. R-Bibliometrix [29], CiteSpace [30], and VOSviewer [27] are bibliometric analysis tools that offer a range of functions, including citation analysis, author collaboration networks, topic evolution analysis, and visualization

tools such as heat maps, keyword collaborative networks, and author collaboration networks. By employing bibliometric analysis, researchers can identify emerging trends, transformative research, and new technologies in their respective fields. This approach allows biomedical scientists to have a better grasp of the bibliometric structure and knowledge structure of their research field. Here, we perform a bibliometric analysis and visualization of studies on BMSCs in the field of tissue engineering published from 2004 to 2023 to explore research progress and identify future research directions. The graphic abstract is shown in **Figure 1**.

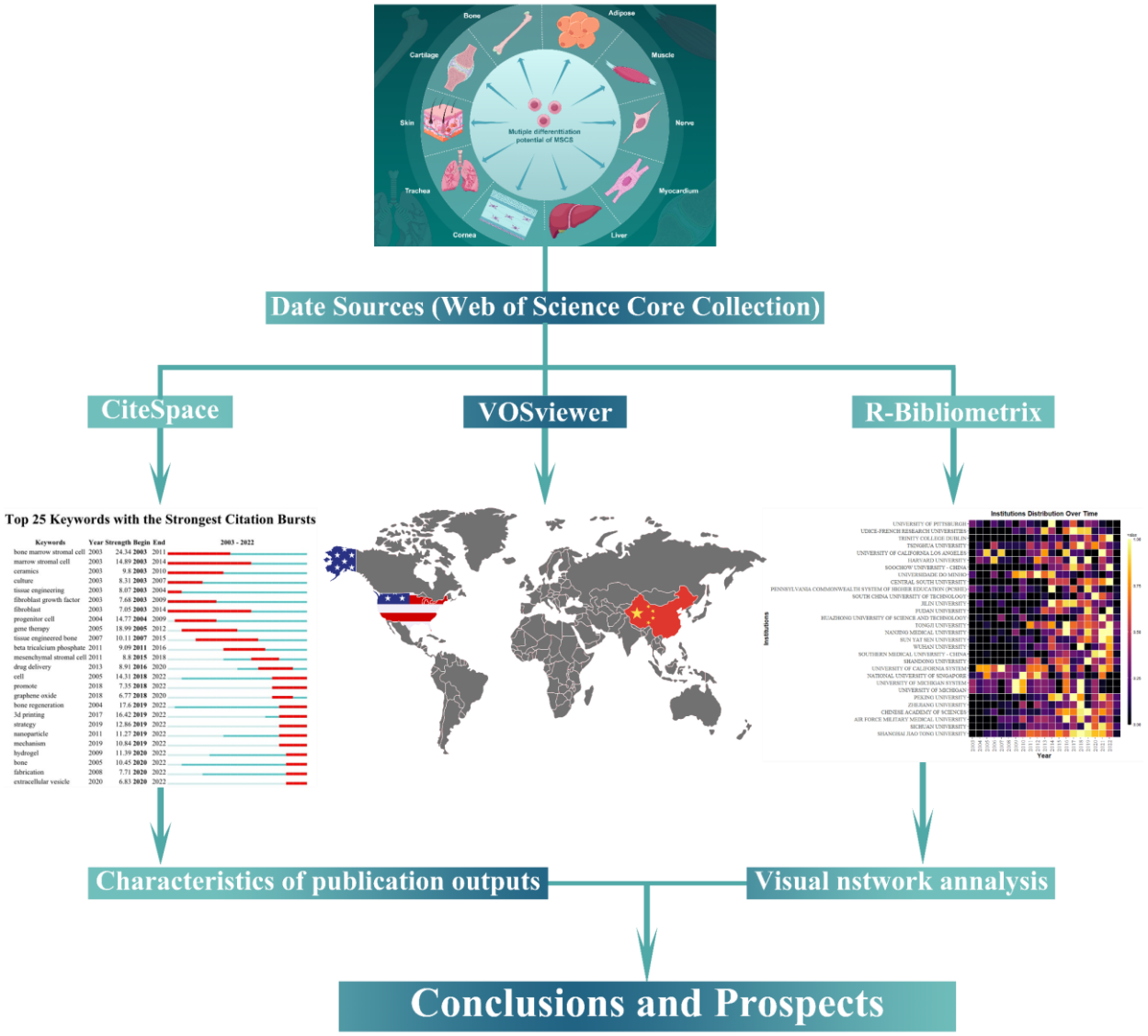


Figure 1. Schematic illustration of global trends of bone marrow mesenchymal stem cells in tissue engineering.

2. Material and methods

2.1. Search strategies and data acquisition

The WoSCC is widely chosen as the primary data source for bibliometric studies due to its comprehensive coverage of high-quality, peer-reviewed literature across various scientific disciplines. It provides robust citation data, enabling detailed

analyses of citation relationships, research trends, and collaborations. WoSCC's rigorous indexing standards ensure the reliability and accuracy of bibliometric results, making it a preferred choice over other databases [31]. Additionally, its advanced search and filtering capabilities enhance data precision, which is critical for effective bibliometric research [32]. The documents retrieve from this database ensure the reliability and authority of the conclusions. The WoSCC comprises numerous databases. For research on bone marrow mesenchymal stem cells in tissue engineering, we have chosen two relevant databases: SCI-EXPANDED and SSCI. We conducted a comprehensive search of the WoSCC database to identify publications related to BMSCs in tissue engineering. The search strategy was refined through an iterative process: Initial keywords included "bone marrow mesenchymal stem cells," "tissue engineering," and related terms. A preliminary search was reviewed manually to identify additional relevant synonyms, such as "stem cell-based tissue engineering" and the abbreviation "BMSCs," while excluding irrelevant terms. Boolean operators were used to broaden the search. Specifically, combinations such as "BMSCs" AND "tissue engineering" and "mesenchymal stem cells" were applied to enhance the coverage of relevant publications. The final search terms were refined to balance comprehensiveness and specificity, ensuring that both widely cited foundational articles and recent publications were captured. This approach provided a robust dataset for bibliometric analysis, allowing us to investigate research trends, collaborations, and emerging themes in the field [33,34]. The search terms were TS = ("bone marrow mesenchymal stem cell*" OR "bone marrow stromal stem cell*" OR "bone marrow stem cell*" OR "bone marrow stromal cell*" OR BMSC* OR BM-MSC*) AND TS = "Tissue engineering". The period was set from 2004 to 2023. A total of 3206 records comprising nine types were obtained. The language type was set to "English" and the documents type was limited to "Article" and "Review Article". A total of 2967 records were exported in the form of "Full Record and Cited References" in the format of "Plain Text". The flow of the search process is shown in **Figure 2**. The data was analyzed separately by three investigators, with any conflicts being resolved by enlisting the assistance of a senior specialist (CF).

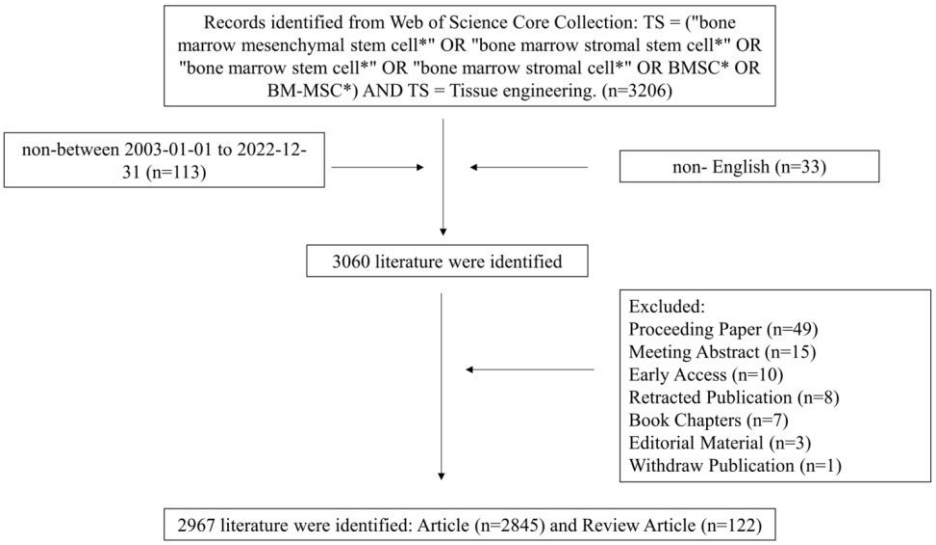


Figure 2. Flow diagram illustrating the process of identifying and including studies.

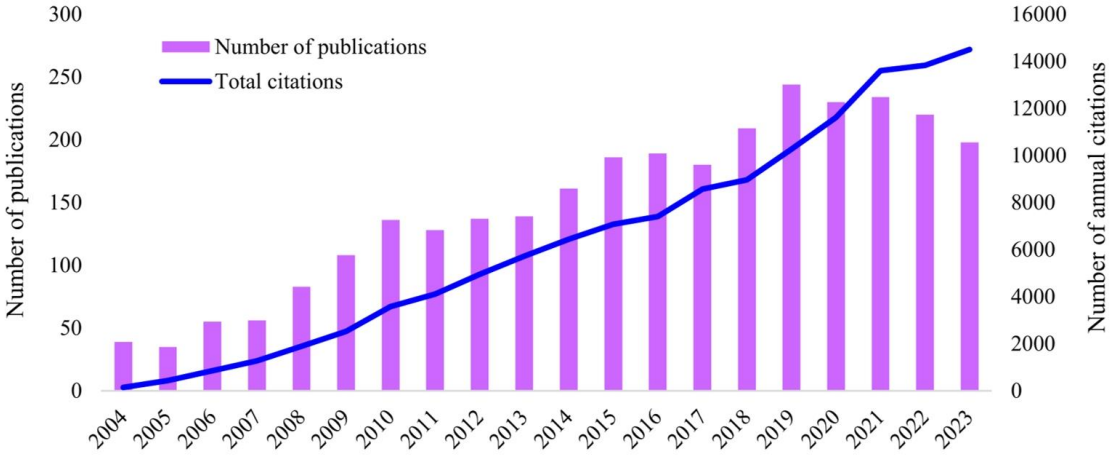
2.2. Data analysis and visualization

The WoSCC dataset comprised text data, which included fundamental information such as the title, abstract, keywords, country, institution, journal, author, and co-cited articles. All valid data were imported to Microsoft Office Excel 2021, VOSviewer (version 1.6.19), Citespace (version 6.1.R2), and Bibliometrix (https://bibliometric.com/) 4.1.0 Packages based on the R language to perform visual analysis for the research on BMSCs and tissue engineering. Descriptive statistical analyses of annual outputs and growth trends, as well as statistics on the frequency of occurrence of countries, institutions, journal authors, and references, were performed using Microsoft Office Excel 2021. The study employed the Bibliometrix package in R software to analyze trends in keyword changes and national/regional collaborations. VOSviewer is a web application for building knowledge maps developed by Dr. Ness Jan van Eck and Dr. Walterman of Leiden University, the Netherlands [27]. It has a simple operator interface and can be used to build collaborative networks that identify countries, production institutions, journals, authors, and cited references. Additionally, it allows for co-occurrence analysis, which can be grouped into clusters and represented by different colors to predict collaboration trends. The VOSviewer visualization network displays connections that reveal relationships between countries/regions, institutions, and journals. The size of each node represented the number of studies or frequency of co-occurrence. The connections between nodes indicated co-occurrence relationships, with the thickness of the connection indicating the frequency of co-occurrence. CiteSpace, developed by Chao-Mei Chen at Drexel University in the USA, is the most widely used bibliometric analysis software. It was used in this study to identify keywords and documents with the strongest citation outbreaks and to construct a visual network of co-cited documents and clusters [35]. It is important to note that different nodes on the CiteSpace visualization network represent different analyzed individuals, with larger nodes indicating a higher frequency of occurrence. We conducted centrality analysis using CiteSpace software. The centrality score indicates the importance of the node. VOSviewer and CiteSpace complement each other, enabling mutual validation to ensure the trustworthiness of the data. Journal Citation Report 2022 provides impact factor, h-index, and category ranking quartiles. The h-index is a useful metric for describing the scientific output of a journal or researcher. We chose CiteSpace and VOSviewer due to their complementary strengths in bibliometric and network visualization analyses: CiteSpace specializes in detecting emerging trends, citation bursts, and co-citation patterns, making it ideal for identifying research frontiers and evolving knowledge structures in the field. VOSviewer offers advanced visualization capabilities for creating co-authorship, keyword co-occurrence, and institutional collaboration networks, providing an intuitive and interactive mapping of complex relationships. These tools, when combined, enable a comprehensive analysis that captures both temporal dynamics and structural connections, enhancing the depth and breadth of bibliometric insights.

3. Results

3.1. Temporal distribution map of the literature

The number of publications over time can reflect the pace and trends of research in the field. A total of 2845 original research articles and 122 reviews associated with BMSCs and tissue engineering. Curve fitting analysis (**Figure 3A**) indicated an overall increasing trend in the annual number of publications on BMSCs and tissue engineering for nearly two decades, and the annual growth rate was 13.81%. Between 2004 and 2008, less than 100 papers were published each year, but the average number of years from 2009 to 2010 was the largest increase in the number of papers. In 2019, a total of 244 papers were published, making it the year with the highest number of publications in the past two decades. Over the past two decades, the number of annual citations has continued to grow, indicating that interest in the field continues to grow. China's research influence has been far ahead in the past two decades (**Figure 3B**), followed by the USA, Japan, and Germany.



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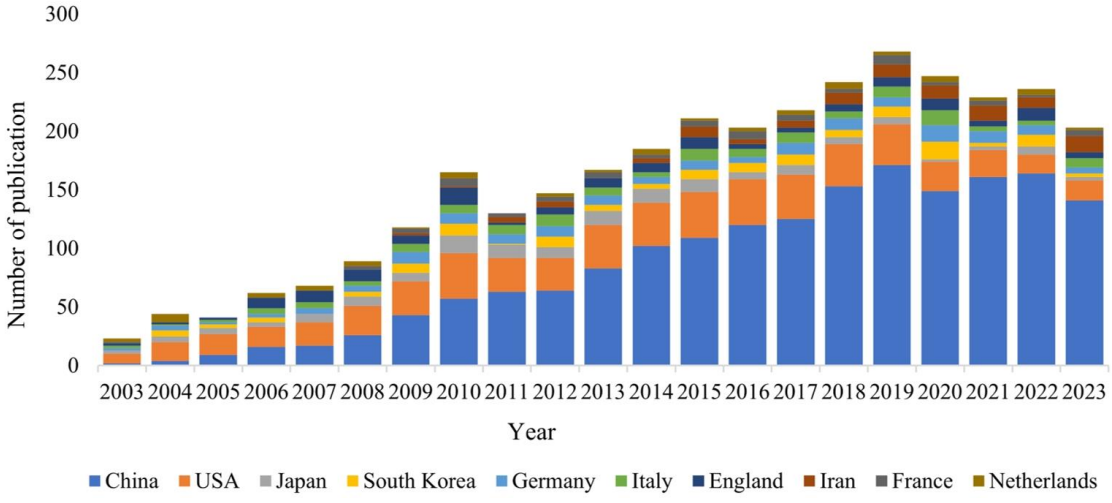
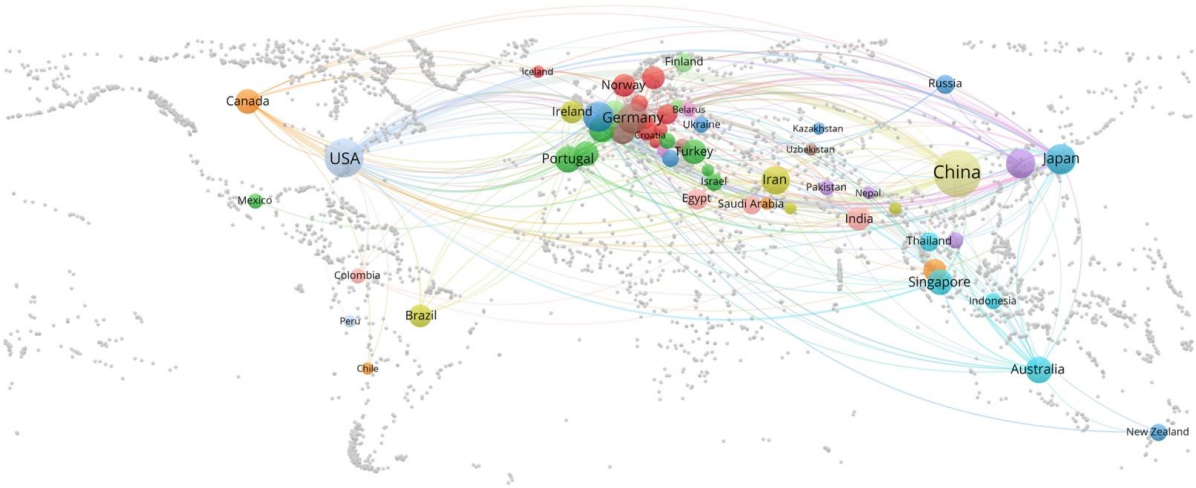


(B)

Figure 3. The overall distribution of publication outputs on BMSCs and tissue engineering research. **(A)** The annual number of publications and citations (Purple bar: Number of annual publications; Blue line: Number of citations); **(B)** Annual output trend of top 10 productive countries.

3.2. Distribution of countries/regions

To identify the major contributors and collaborative dynamics in the fields of BMSCs and tissue engineering, we analyzed country-based contributions using VOSviewer and CiteSpace. Between 2004 and 2023, 65 countries published research in this domain. The global distribution of publications is illustrated, and the connection between countries in **Figure 4A,B**, while **Table 1** lists the top 10 countries by publication frequency, centrality, and h-index. China led with 1597 publications, followed by the USA. The USA's centrality score of 0.41 indicates a prominent role in international collaborations, compared to China's score of 0.27. Germany ranked third, and although Japan placed fourth in publications, it showed minimal international cooperation with a low centrality score. This finding highlights the dominant influence of China and the USA in shaping research developments through extensive collaborations, while other countries, despite active contributions, engage in fewer international partnerships.



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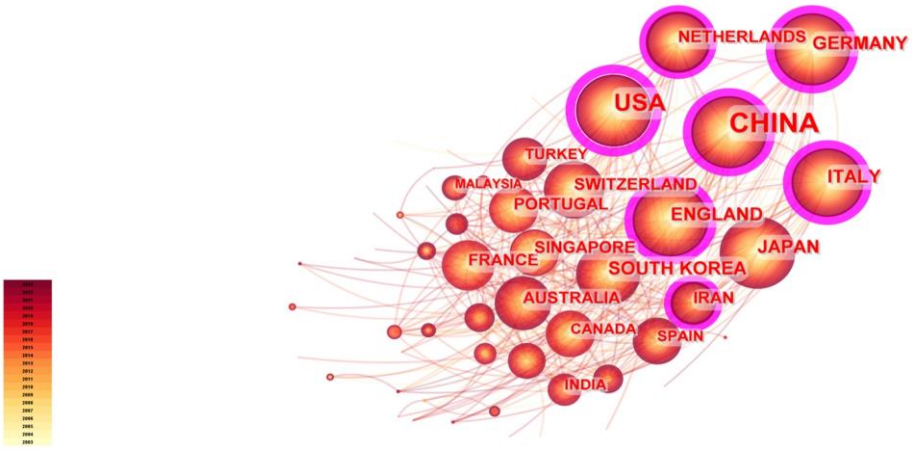


(B)

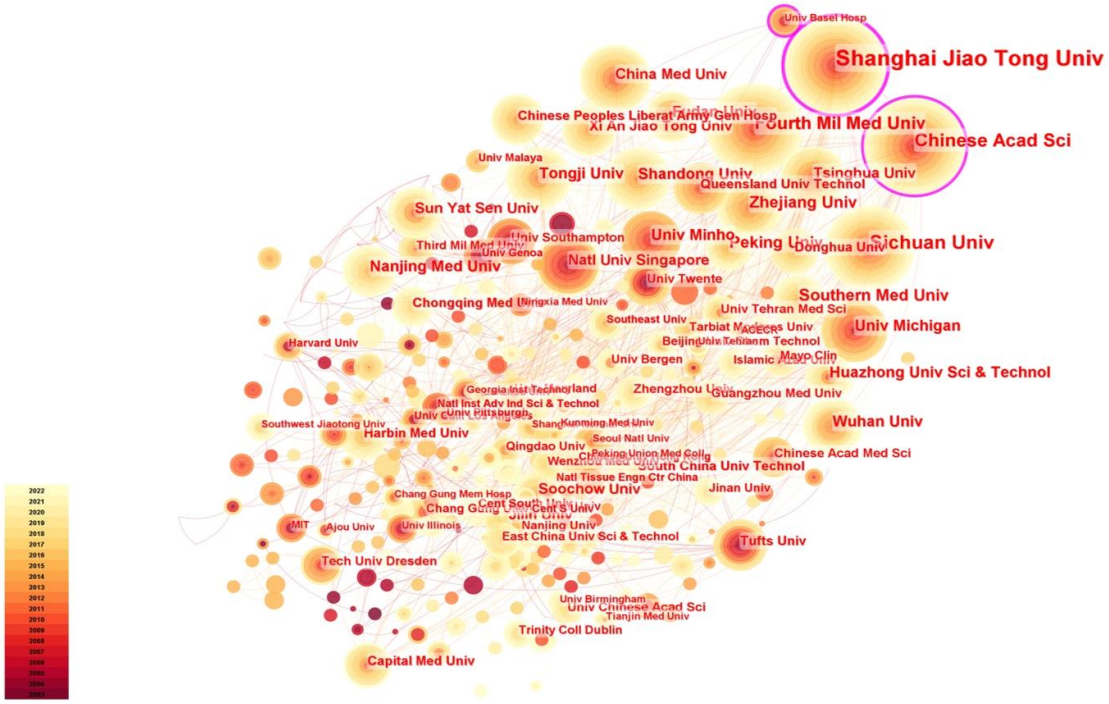
Figure 4. Country/region publication characteristics. **(A)** Production and collaboration map of countries and regions (The nodes' colors represent various countries, with larger nodes indicating more publications and connecting lines indicating collaboration.); **(B)** Contributed to publications on BMSCs and tissue engineering research from 2004 to 2023 (The nodes represent countries and the node's size represents the frequency. Darker colors indicate earlier studies. Purple rings outside the nodes indicate their centrality is greater than 0.1.).

Table 1. The top 10 countries contributing to publications in BMSCs and tissue engineering research.

Country	Counts	Centrality	Citations	Average citation number	% of 3131	H-index	Total link strength
China	1597	0.27	50,920	28.87	51.262	133	307
USA	492	0.41	34,968	68.58	17.854	128	302
Germany	137	0.19	6540	33.83	4.759	59	55
Japan	136	0.03	7486	53.57	4.663	70	112
England	129	0.19	7750	68.33	4.216	71	101
Italy	116	0.19	5938	44.22	3.96	65	85
South Korea	111	0.08	5162	36.15	3.897	58	50
Iran	98	0.15	2164	22.98	3.002	53	40
Australia	67	0.11	3266	53.33	2.204	45	61
Netherlands	65	0.10	4989	82.06	2.172	46	72

3.3. Distribution of institutions

Institutional collaborations were mapped using CiteSpace, revealing 570 nodes and 1174 links, where purple-circled nodes signify high centrality (**Figure 5A**). Shanghai Jiao Tong University emerged as the most prolific institution (263 publications). However, despite Sichuan University's ranking second in productivity (126 publications), the Chinese Academy of Sciences demonstrated greater citation influence and collaboration intensity **(Table 2)**. Using a co-authorship analysis with a 15-publication threshold (**Figure 5B**), we identified 18 major collaboration clusters. Institutions such as the University of California have maintained a long-term presence in this field, contributing to foundational and recent advancements. The heatmap in **Figure 5C** indicates a growing concentration of institutional contributions over the last eight years, suggesting a sustained increase in research productivity.



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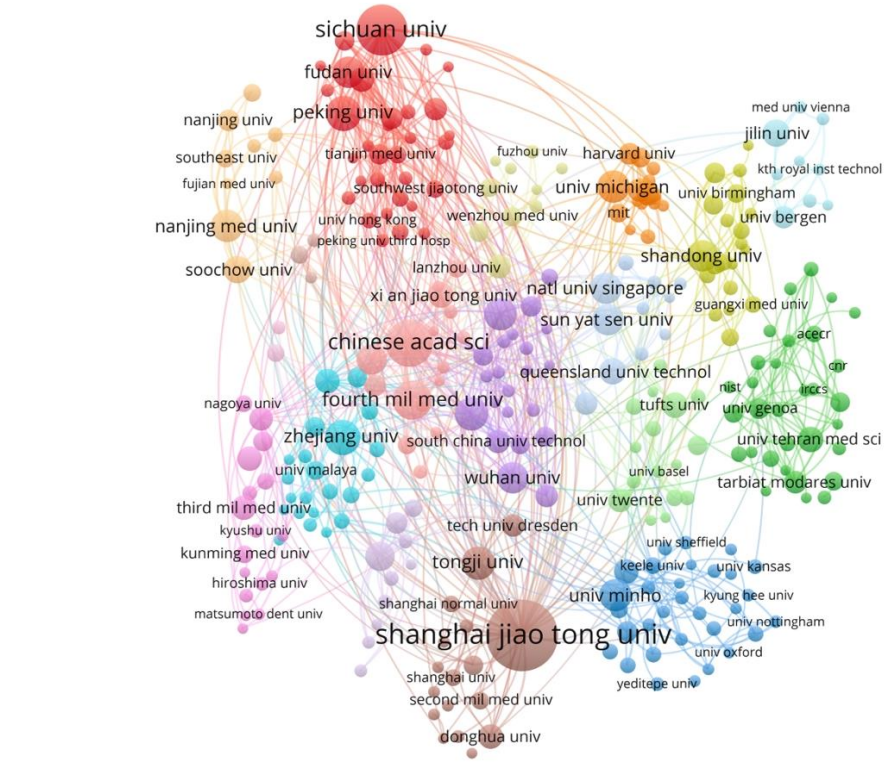

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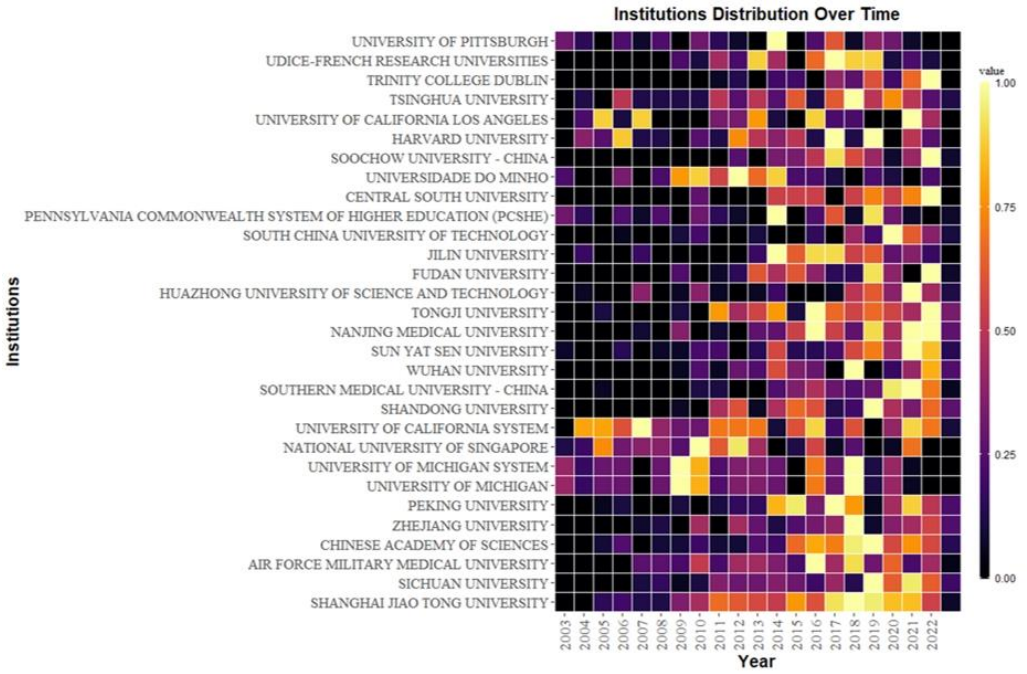


(C)

Figure 5. Contribution of institutions and academic collaboration in BMSCs and tissue engineering research. **(A)** The network map of institutions related to BMSCs and tissue engineering (The nodes represent academic institutions, and the size of the nodes represents the frequency. Lighter colors indicate earlier studies. Purple rings outside the nodes indicate their centrality is greater than 0.1.); **(B)** cooperation network map of academic institutions (The graph displays academic institutions as nodes, with each node's size indicating the collaboration frequency. Clusters of the same color indicate more active collaboration, while connecting lines represent the collaborations themselves.); **(C)** heat map analysis of academic institutions.

Table 2. Publications of the top 10 global academic institutions.

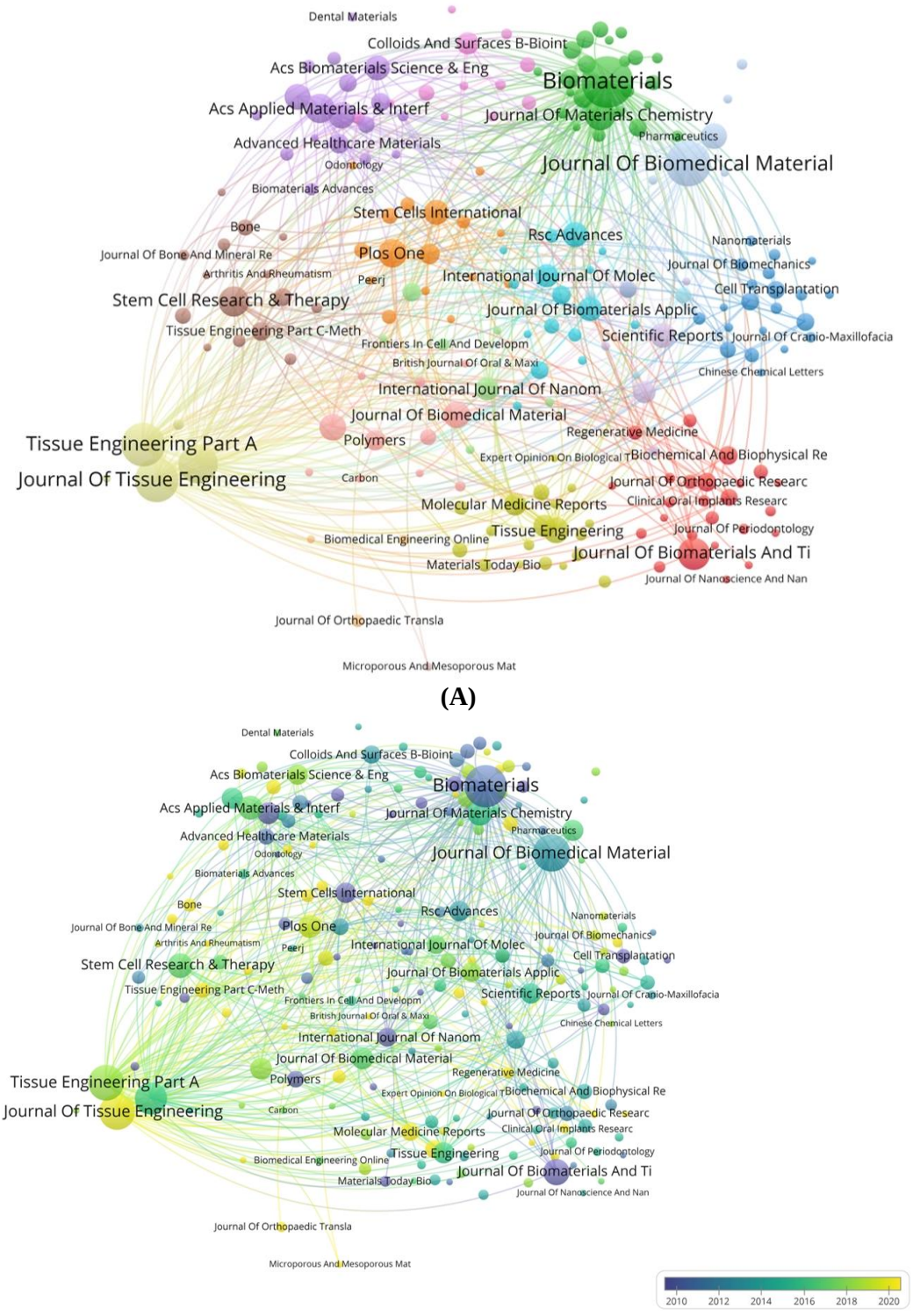
Affiliations	Counts	Centrality	Citations	Total link strength
Shanghai Jiao Tong University	263	0.30	9313	298
Sichuan University	126	0.09	3676	97
Chinese Academy of Sciences	116	0.20	6802	154
Air Force Military Medical University	80	0.07	3125	62
Southern Medical University China	66	0.06	1107	60
Peking University	65	0.05	2342	58
Zhejiang University	60	0.03	2103	29
Tongji University	52	0.02	2886	63
Fudan University	50	0.06	1053	46
Universidade Do Minho	50	0.07	3067	54

3.4. Distribution of journal

Our analysis identified 605 journals publishing BMSC and tissue engineering research. **Table 3** lists the top 10 journals by publication count, citation impact, and h-index. “Biomaterials” leads in all metrics, followed by “Journal of Biomedical Materials Research Part A” and “Tissue Engineering Part A”. Most high-impact journals are based in the USA and England, reflecting a concentration of influential research in these regions. Cluster analysis (**Figure 6A**) categorizes related journals into 12 groups and **Figure 6B** showed the distribution of journals in order of their appearance, providing insights into their interconnected focus areas.

Table 3. Ranking of top-10 journals for the number of articles published in BMSCs and tissue engineering research from 2004 to 2023.

Journal	Counts	IF	JCR	H-index	Citations	Total link strength	Country/region
Biomaterials	153	14.0	Q1	82.0	17,059	1047	Netherlands
Journal of Biomedical Materials Research Part A	117	4.9	Q2	40.0	5652	367	USA
Tissue Engineering Part A	107	4.1	Q2	40.0	4401	441	USA
Journal of Tissue Engineering and Regenerative Medicine	105	3.3	Q2	31.0	3030	334	England
Acta Biomaterialia	82	9.7	Q1	45.0	5189	307	England
Journal of Biomaterials and Tissue Engineering	55	0.2	Q4	7.0	205	78	USA
Stem Cell Research &Therapy	48	8.0	Q1	24.0	1642	161	England
Journal of Materials Chemistry B	47	7.0	Q1	22.0	1202	151	England
Acs Applied Materials & Interfaces	45	9.5	Q1	27.0	2542	168	USA
Plos One	41	3.8	Q2	24.0	1578	150	USA



(A)

(**B**)

Figure 6. Co-cited network of journals. **(A)** Mapping of journals in the research field (The frequency of occurrence is represented by the size of the nodes. The journal articles were classified into 12 categories based on their respective research fields.); **(B)** Distribution of journals according to the chronological order of appearance (Yellow indicates late emergence, while blue indicates early emergence.).

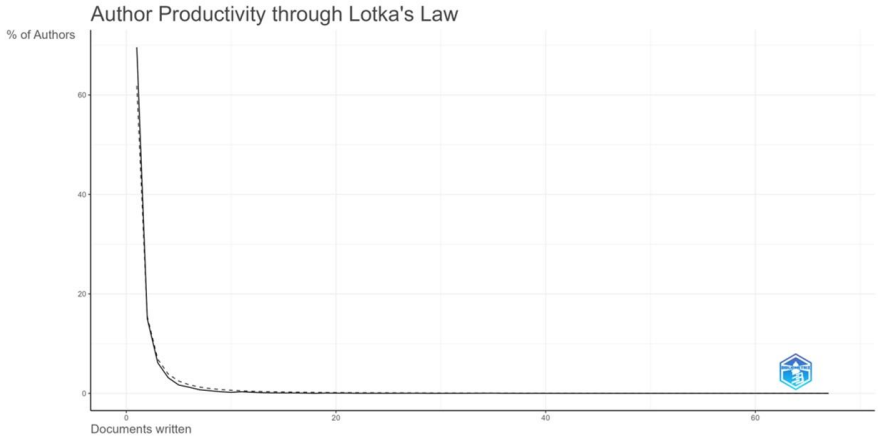
3.5. Distribution of authors

Lotka's law describes the relationship between authors and the number of papers they write. The number of authors who write N papers is about $1/n^2$ of the number of authors who write one paper. According to Lotka's law, the number of authors who write two papers (1750) is approximately one-fourth of the number of authors who write one paper (8116). Applying Lotka's law, we classified authors in the field of BMSCs and tissue engineering research according to productivity, and the results were shown in **Table 4**. The total number of authors was 11,659, with an average number of 3.72 authors per document. The TI (transience index) of 69.61% indicates that the majority of authors contributed only one paper (**Figure 7A**), making them "small producers". The number of "large producers" with more than 10 articles to their credit was 187, which accounts for 1.60% of the total number of authors. VOSviewer was used for visualizing authors (**Figure 7B**). **Table 5** revealed the top 10 large producers: Liu Yang (65 articles, 3340 citations) was the most prolific author, followed by Jiang Xianquan (47 articles, 1853 citations) and Reis Roil (44 articles, 2206 citations); among the top ten authors, nine were from China. The author collaboration network was constructed for "large producers" (**Figure 7B**), and the highest total link strength (175) was found for Jiang Xinquan, who has successively collaborated with 26 authors. In addition, as can be seen by the cluster color, numerous tight-knit research teams have formed within this field.

Table 4. Classification of authors based on productivity.

	PI ≥ 1 (10 or more articles)	**0 < PI < 1 (2–9 articles)**	**PI = 0 (1 articles)**	**Total**
Number of authors	187	3355	8116	11,659
% authors	1.60	28.79	69.61	100

Note: PI = 0 (small producers); 0 < PI < 1 (medium-sized producers); PI ≥ 1 (large producers). PI, productivity index.



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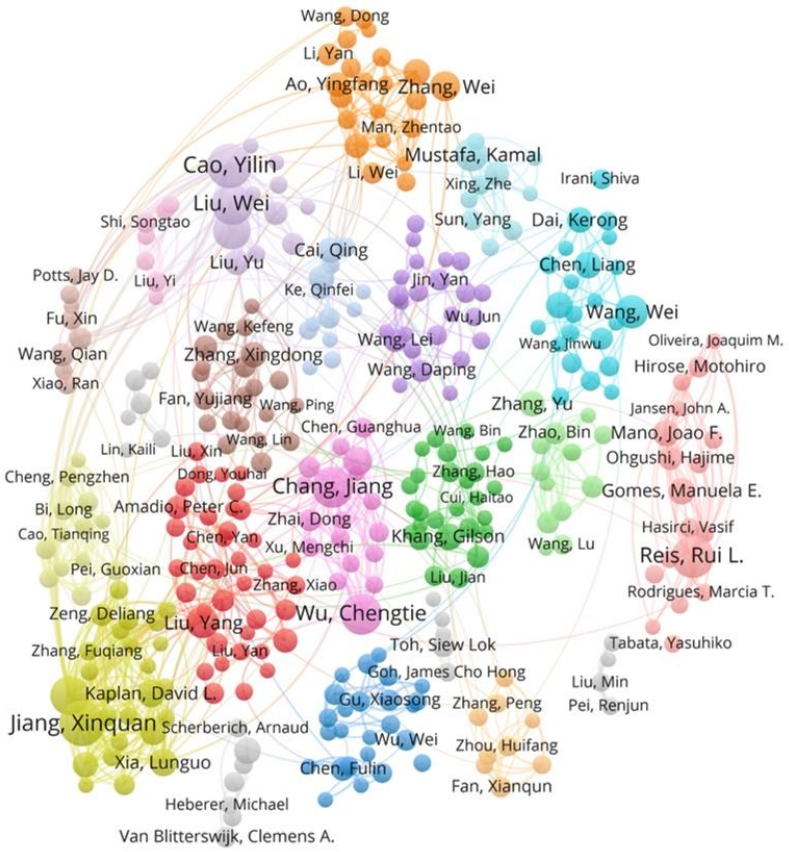


(B)

Figure 7. Authors and co-author analysis. **(A)** Author's Lotka's law; **(B)** Mapping of the co-cited authors related to this field.

Table 5. The top 10 most productive authors.

Authors	Counts	% of 3131	H-index	Citations	Total link strength
Liu Y	65	2.08	27	601	55
Jiang XQ	47	1.50	27	1853	175
Reis RL	44	1.41	31	2206	75
Zhang Y	42	1.34	21	322	11
Cao YL	39	1.25	23	1822	135
Zhang WJ	39	1.25	24	1315	137
Li J	37	1.18	19	491	19
Chen L	36	1.15	20	92	18
Wang L	36	1.15	21	760	16
Zhang X	36	1.15	20	387	58

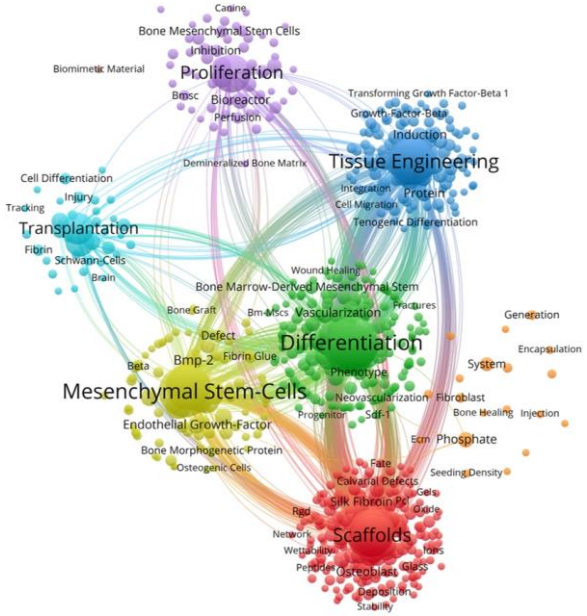
3.6. Keyword clustering analysis

The keywords were analyzed using VOSviewer. **Figure 8A** showed that keywords with similar topics were grouped into the same category, with 7 main clusters: scaffolds, mesenchymal stem cells, differentiation, tissue engineering, transplantation, proliferation, and fibroblast. This reflected several research directions of BMSCs in the field of tissue engineering. The red cluster encompasses keywords

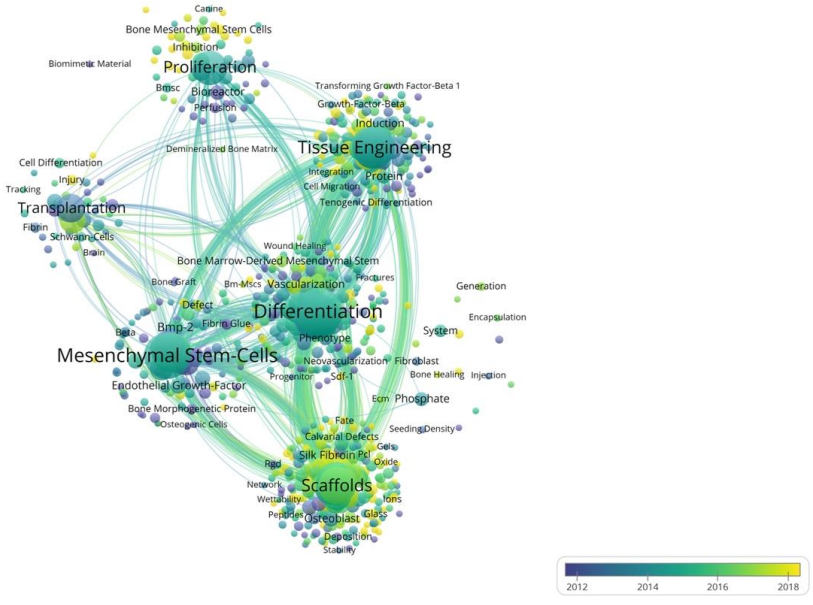
related to biological materials (such as scaffolds, hydrogels, extracellular matrix, cell sheet, and 3D printing). The green cluster encompasses keywords related to differentiation (including differentiation, osteogenic, chondrogenic, tendon, and liver). The blue and yellow cluster was dedicated to keywords focused on tissues and cells (including stromal cells, in vivo, exosome, and cytokine). Lastly, the purple and light blue cluster encompasses keywords related to proliferation and transplantation (such as heart, liver, and bone). Furthermore, the VOSviewer utilizes color coding to distinguish keywords based on how often they appear in all published papers (**Figure 8B**). The color blue indicated early appearance, whereas yellow signified late appearance. It is worth noting that 3D cell printing, extracellular matrix, cell sheets, and exosomes have been the focus of considerable research attention in recent times.

3.7. Research frontier analysis

In this study, the keywords with a high frequency of occurrence over time were analyzed using the Bibliometric package based on the R language. As can be seen in **Figure 8C**, most of the keywords were in a yearly increasing trend until 2018; however, the frequency of most of the keyword occurrences was in a yearly decreasing trend during the period 2019–2023. Noteworthy was that the frequency of stent appearances was increasing year by year and ranked first in frequency among all keywords in 2022. This phenomenon served as a warning to us that research on scaffolds for MSCs is starting to heat (**Figure 8D**). Taking advantage of short-term keyword bursts can be a valuable tool for tracking and analyzing research hotspots. Researchers can stay up-to-date on the latest research frontiers by pinpointing the most recent breaking keywords. To perform this analysis, Citespace provided a keyword burst graph that depicts the intensity of each burst and the year it began and ended (**Figure 8E**). Among the top 25 keywords from 2004 to 2023, the earliest keywords, such as “bone marrow stromal cells”, “cytokine”, “progenitor cell”, “transplantation”, “fibroblast growth factor” and “implants” mainly focused on the function of BMSCs, of which “marrow stromal cells” had the highest intensity of 16.73. In contrast, the increase in keyword diversity gained in recent years reflects the maturity of this field of study. Researchers are now exploring fields such as “3D printing”, “hydrogel”, “extracellular vesicles”, and “nanoparticle”.


Canine
Bone Mesenchymal Stem Cells
Inhibition
Biomimetic Material
Proliferation
Bmsc
Bioreactor
Perfusion
Transforming Growth Factor-Beta 1
Growth-Factor-Beta
Induction
Demineralized Bone Matrix
Tissue Engineering
Cell Differentiation
Injury
Tracking
Integration
Protein
Cell Migration
Tenogenic Differentiation
Transplantation
Fibrin
Schwann-Cells
Brain
Wound Healing
Bone Marrow-Derived Mesenchymal Stem
Bone Graft
Bm-Mscs
Vascularization
Fractures
Generation
Defect
Differentiation
Encapsulation
Bmp-2
Fibrin Glue
Beta
Phenotype
System
Mesenchymal Stem-Cells
Neovascularization
Fibroblast
Progenitor
Sdf-1
Bone Healing
Injection
Endothelial Growth-Factor
Ecm
Phosphate
Bone Morphogenetic Protein
Fate
Osteogenic Cells
Seeding Density
Calvarial Defects
Gels
Silk Fibroin Psl
Rad
Oxide
Network
Scaffolds
Wettability
Ions
Peptides
Osteoblast
Glass
Deposition
Stability

(A)


Canine
Bone Mesenchymal Stem Cells
Inhibition
Biomimetic Material
Proliferation
Bmsc
Bioreactor
Perfusion
Transforming Growth Factor-Beta 1
Growth-Factor-Beta
Induction
Demineralized Bone Matrix
Tissue Engineering
Cell Differentiation
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Vascularization
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Mesenchymal Stem-Cells
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Fate
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Seeding Density
Calvarial Defects
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Scaffolds
Wettability
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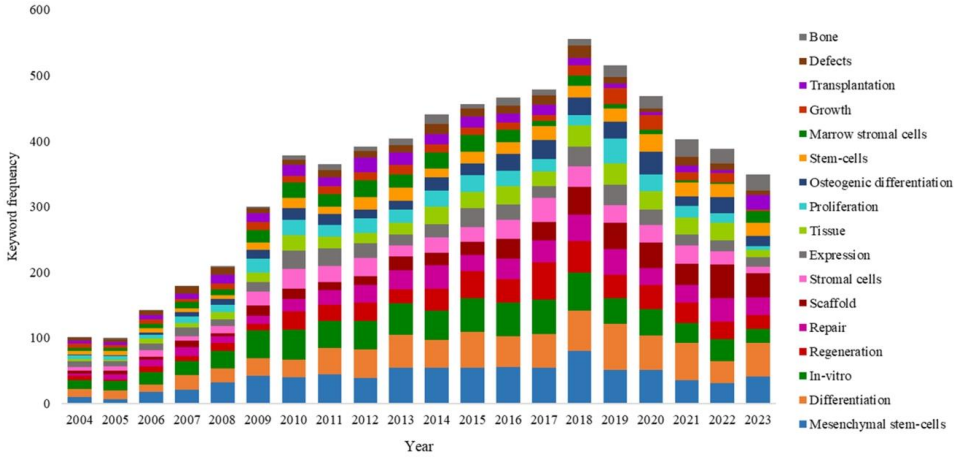
Osteoblast
Glass
Deposition
Stability
2012
2014
2016
2018

(B)


Keyword frequency
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400
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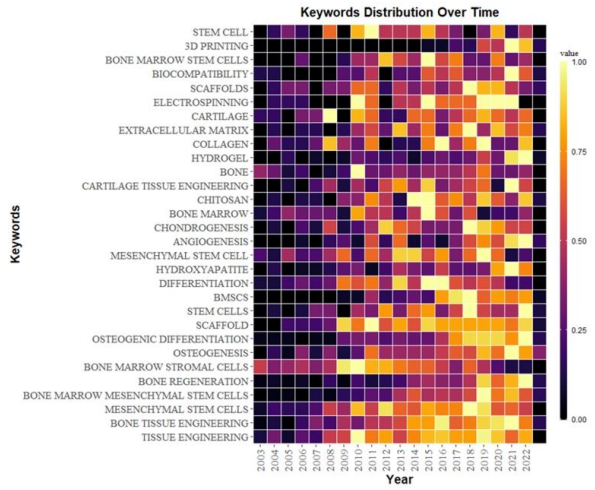
2020
2021
2022
2023
Year
Bone
Defects
Transplantation
Growth
Marrow stromal cells
Stem-cells
Osteogenic differentiation
Proliferation
Tissue
Expression
Stromal cells
Scaffold
Repair
Regeneration
In-vitro
Differentiation
Mesenchymal stem-cells

(C)



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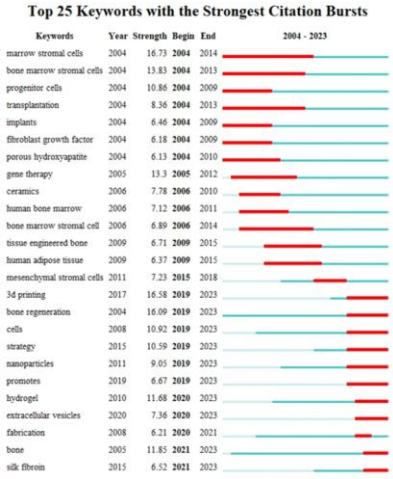


(E)

Figure 8. The visualization of keyword co-occurrence analysis with a focus on BMSCs and tissue engineering. **(A)** The keywords mapped in the context of ASCTE research have been visually represented, with point size indicating their frequency of occurrence. The research area has been segmented into five categories based on the colors assigned to each keyword cluster; **(B)** the visual presentation of the keyword distribution shows yellow for the later appearance of the keyword and blue for its earlier appearance; **(C)** annual output trends of keywords; **(D)** heat map analysis of keywords; **(E)** the top 25 keywords with the strongest citation bursts.

3.8. Co-cited references analysis

3.8.1. Most co-cited references

The bibliometric method was mainly composed of citation analysis, which was the source of impact factors. Papers with a high number of citations were considered central to the research. Therefore, top and highly cited papers provide evidence and information about research trends and scientific progress in a specific field. First of all, we used VOSviewer to visually analyze 270 co-cited references (set the minimum number of cited references to 20) (**Figure 9A,B**). The top 5 co-cited articles with the highest total link strength included Pittenger MF, 1999, Science, v284, p143, (link strength: 2611); Langer R, 1993, Science, v260, p920, (link strength: 806); Dominici M, 2006, Cytotherapy, v8, p315; Quarto R, 2001, The New England journal of medicine, v344, p385, (link strength: 769); Petite H, 2000, Nature biotechnology, v18, p959, (link strength: 766). To some extent, the number of citations serves as an indicator of the importance of reference within a given field. **Table 6** listed the top 10 co-cited articles. The study published by Pittenger MF in Science was the most cited (482 citations), followed by the study published by Langer R in Science (176 citations) and the study published by Dominici M in Cytotherapy (174 citations). Afterwards, 81,124 cited references, including 3131 articles, were analyzed for co-citation using CiteSpace, with **Figure 9C** revealing the authors and publication years of the burst articles that have experienced an increase in citation frequency. Each node represented a cited article. The size of the node represented the total number of articles cited. The links between nodes indicated how often the same reference was cited. These nodes with a purple ring could be used to connect the growth stages of a field.

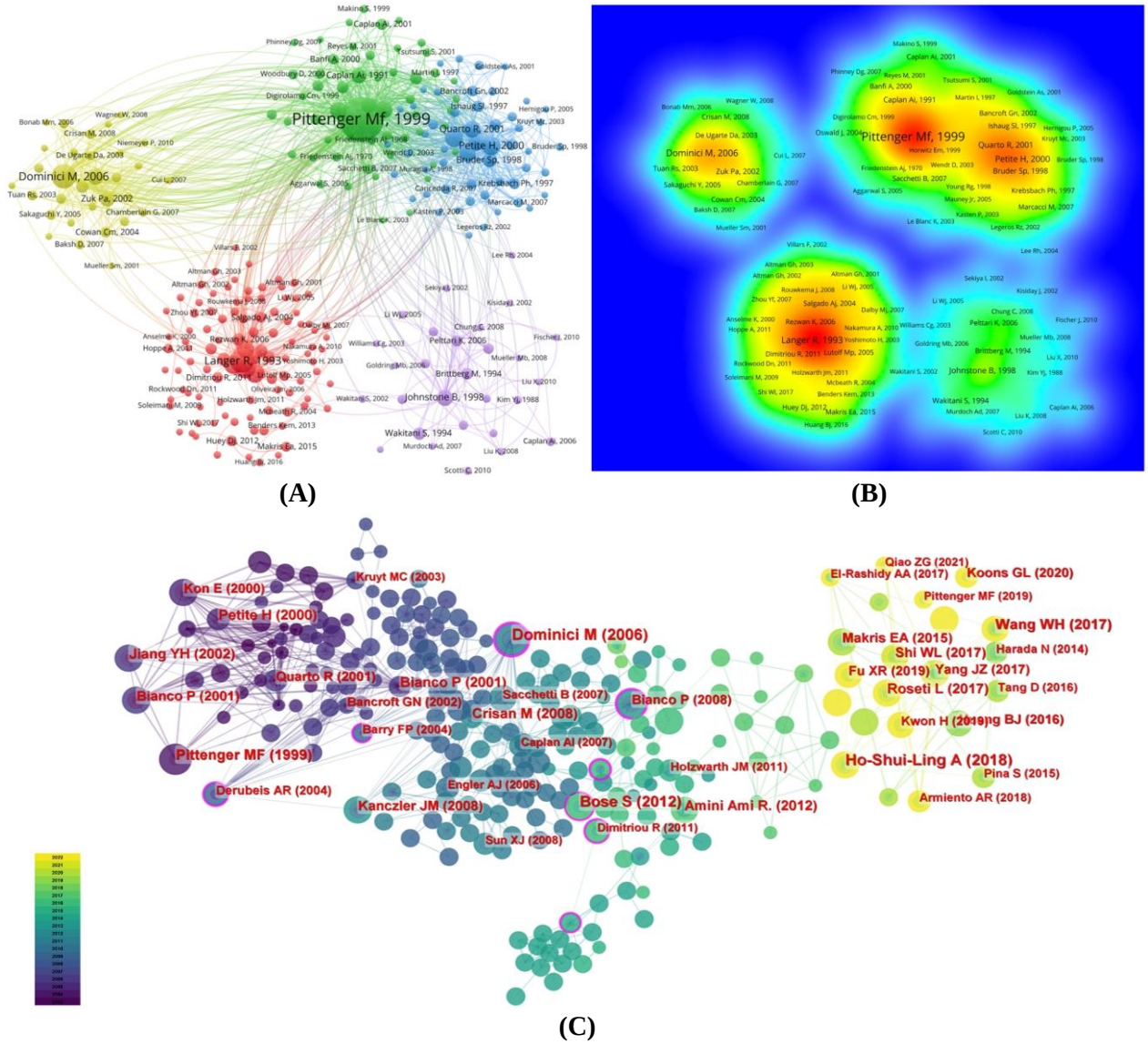


Figure 9. Clustering and burst citation analysis of references. **(A)** Visual network of co-cited references in BMSCs and tissue engineering research. Point sizes represent citation frequencies, and the line between points indicates that they were cited in one paper. The shorter the line between two points, the closer the link between the two papers. The same color indicates the same research area; **(B)** co-occurrence density visualization map of reference; **(C)** co-cited references map on BMSCs and tissue engineering research from 2004 to 2023. The node's size is proportional to the number of co-citations, while different colors indicate the timeline.

Table 6. Top 10 most co-cited references in BMSCs and tissue engineering research from 2004 to 2023.

Rank	Title	First author	Year	Journal	Cite frequency
1	Multilineage potential of adult human mesenchymal stem cells	Pittenger MF	1999	Science	482
2	Tissue engineering	Langer R	1992	Science	176
3	Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement	Dominici M	2006	Cytotherapy	174
4	Porosity of 3D biomaterial scaffolds and osteogenesis	Karageorgiou V	2005	Biomaterials	129
5	Tissue-engineered bone regeneration	Petite H	2000	Nature Biotechnology	111

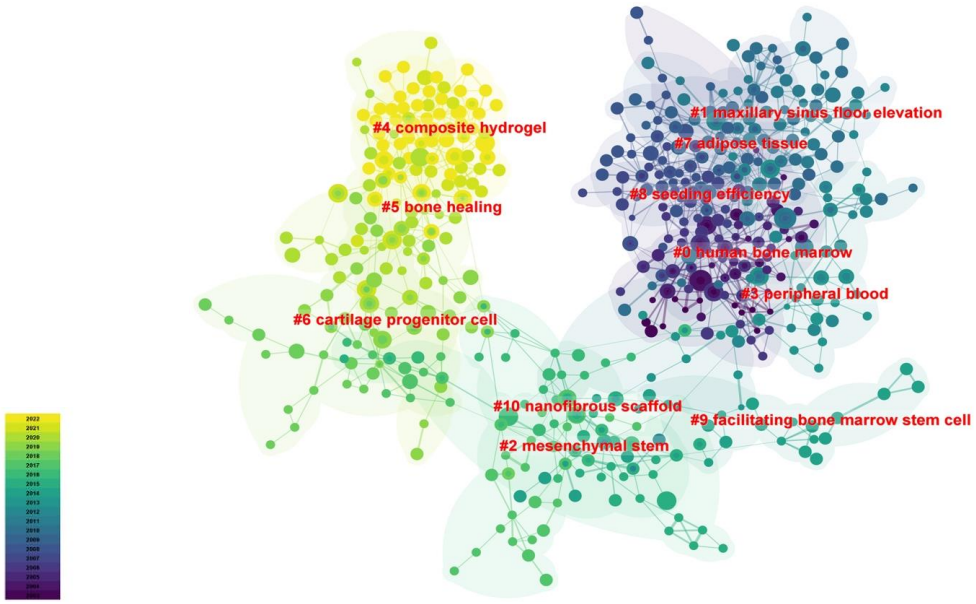
Table 6. (*Continued*).

Rank	Title	First author	Year	Journal	Cite frequency
6	Matrix elasticity directs stem cell lineage specification	Engler AJ	2006	Cell	108
7	Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method	Livak KJ	2001	Methods	107
8	Bone formation in vitro by stromal cells obtained from bone marrow of young adult rats	Maniatopoulos C	1988	Cell and Tissue Research	107
9	Scaffolds in tissue engineering bone and cartilage	Hutmacher DW	2000	Biomaterials	98
10	Marrow stromal cells as stem cells for nonhematopoietic tissues	Prockop	1997	Science	94

3.8.2. Analysis of reference

Figure 10A showed the clustering information of co-cited references, divided into 12 categories. From the tags of these categories, the hot point of the research can be read out. Based on the colors of the nodes it is possible to predict which themes are emerging, which are classic, and which are outdated. Early research in this field was cluster #0 (human bone marrow), #1 (maxillary sinus floor elevation), #3 (peripheral blood), #7 (adipose tissue), and #8 (seeding efficiency), which appeared from 1998 to 2009. Cluster #2 (mesenchymal stem), #9 (facilitating bone marrow stem cell), and #10 (nanofibrous scaffold) were intensively studied from 2010 to 2015 and these studies are closely related to each other. Subsequently, since 2016, there have been clustered #4 (composite hydrogel), #5 (bone healing), and #6 (cartilage progenitor cell).

The citation bursts were regarded as the heightened attention and interest shown by experts within a specific field towards a particular reference during a specific period [36]. According to **Figure 10B**, we analyzed the top 25 references displaying the strongest citation bursts. Notable was Roseti published in 2017 in Materials Science and Engineering C, which experienced a strong citation burst lasting 5 years and with an intensity of 9.33. Another noteworthy reference was that of Jiang in 2002, published in Nature, which underwent a significant citation explosion recently lasting 3 years and having a strength of 11.04. The highest strength was Bose in 2012, published in Trends in Biotechnology at 12.98. The above three papers provide insight into the current status and emerging research directions in which the pluripotency of MSCs allows them to be used to generate or repair a multitude of tissues in tissue engineering and skeletal scaffolds used to support cell growth and tissue formation in bone tissue engineering. Consequently, it is possible to gain an understanding of the current state of the art in the field of tissue engineering, the latest research advances, as well as future challenges and opportunities.



(A)

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2004 - 2023
Jiang YH, 2002, NATURE, V418, P41, DOI 10.1038/nature00870, DOI	2002	11.04	2004	2006	
Bianco P, 2001, NATURE, V414, P118, DOI 10.1038/35102181, DOI	2001	9.29	2004	2006	
Petite H, 2000, NAT BIOTECHNOL, V18, P959, DOI 10.1038/79449, DOI	2000	8.12	2004	2005	
Kruyt MC, 2003, TISSUE ENG, V9, P327, DOI 10.1089/107632703764664792, DOI	2003	6.55	2004	2008	
Arinzeh TL, 2003, J BONE JOINT SURG AM, V85A, P1927, DOI 10.2106/00004623-200310000-00010, DOI	2003	7.05	2005	2008	
Cowan CM, 2004, NAT BIOTECHNOL, V22, P560, DOI 10.1038/nbt958, DOI	2004	6.73	2006	2009	
Dominici M, 2006, CYTOTHERAPY, V8, P315, DOI 10.1080/14653240600855905, DOI	2006	11.79	2009	2011	
Kanczler JM, 2008, EUR CELLS MATER, V15, P100, DOI 10.22203/eCM.v015a08, DOI	2008	6.42	2009	2013	
Crisan M, 2008, CELL STEM CELL, V3, P301, DOI 10.1016/j.stem.2008.07.003, DOI	2008	8.77	2010	2013	
Holzwarth JM, 2011, BIOMATERIALS, V32, P9622, DOI 10.1016/j.biomaterials.2011.09.009, DOI	2011	7.43	2013	2015	
Bose S, 2012, TRENDS BIOTECHNOL, V30, P546, DOI 10.1016/j.tibtech.2012.07.005, DOI	2012	12.98	2014	2017	
Amini Ami R., 2012, CRITICAL REVIEWS IN BIOMEDICAL ENGINEERING, V40, P363	2012	9.84	2014	2017	
Roseti L, 2017, MAT SCI ENG C-MATER, V78, P1246, DOI 10.1016/j.msec.2017.05.017, DOI	2017	9.33	2018	2023	
Huang BJ, 2016, BIOMATERIALS, V98, P1, DOI 10.1016/j.biomaterials.2016.04.018, DOI	2016	7.6	2018	2019	
Makris EA, 2015, NAT REV RHEUMATOL, V11, P21, DOI 10.1038/nrrheum.2014.157, DOI	2015	7.33	2018	2020	
Wang WH, 2017, BIOACT MATER, V2, P224, DOI 10.1016/j.bioactmat.2017.05.007, DOI	2017	8.75	2019	2023	
Shi WL, 2017, ADV MATER, V29, P0, DOI 10.1002/adma.201701089, DOI	2017	7.91	2019	2023	
Kang HW, 2016, NAT BIOTECHNOL, V34, P312, DOI 10.1038/nbt.3413, DOI	2016	6.88	2019	2021	
Tang D, 2016, BIOMATERIALS, V83, P363, DOI 10.1016/j.biomaterials.2016.01.024, DOI	2016	6.8	2019	2020	
Yao QQ, 2017, BIOMATERIALS, V115, P115, DOI 10.1016/j.biomaterials.2016.11.018, DOI	2017	6.38	2019	2021	
Ho-Shui-Ling A, 2018, BIOMATERIALS, V180, P143, DOI 10.1016/j.biomaterials.2018.07.017, DOI	2018	12.84	2020	2023	
Armiento AR, 2018, ACTA BIOMATER, V65, P1, DOI 10.1016/j.actbio.2017.11.021, DOI	2018	6.77	2020	2023	
Fu XR, 2019, CELLS-BASEL, V8, P0, DOI 10.3390/cells8080784, DOI	2019	9.96	2021	2023	
Koons GL, 2020, NAT REV MATER, V5, P584, DOI 10.1038/s41578-020-0204-2, DOI	2020	9	2021	2023	
Kwon H, 2019, NAT REV RHEUMATOL, V15, P550, DOI 10.1038/s41584-019-0255-1, DOI	2019	8.17	2021	2023	

(B)

Figure 10. Clustering and burst citation analysis of references. **(A)** Reference clustering was based on the similarity between references; **(B)** the references with citation bursts at different periods.

4. Discussion

4.1. General information

The objective of this investigation was to employ bibliometric methods to analyze the publishing patterns and emerging themes surrounding BMSCs within the discipline of tissue engineering. The study centered on evaluating the dimensions of country, institution, journal, author, keywords, and references to generate comprehensive insights into academic trends and publication characteristics. Overall,

there has been a steady increase in publications in this field; however, the growth rate has decreased in the last three years, possibly due to the global COVID-19 pandemic [37–39]. In this research, we analyzed 2845 articles and 122 reviews on BMSCs in tissue engineering, utilizing the WoSCC database. The data revealed that this topic was studied by 14,859 researchers from 2454 institutions across 65 countries, with findings published in 605 journals. The study further demonstrated that the foremost nations in BMSC research within tissue engineering are situated in three main geographical zones: East Asia (including China, Japan, South Korea, and Iran), North America (the USA), and Western Europe (Germany, the United Kingdom, Italy, and the Netherlands). Among these, China leads in the number of published articles, exerting a significant impact in the field and playing a pivotal role in stimulating research beyond its borders. The USA ranks second in terms of article output but exhibits superior centrality, indicating higher research quality across US academia. In terms of institutional contributions, **Table 2** highlights the leading organizations in BMSC research, with Shanghai Jiao Tong University (SJTU), Sichuan University, and the Chinese Academy of Sciences emerging as top contributors. Notably, SJTU demonstrates the highest level of academic institution cooperation. These studies are often published in reputable journals, with Biomaterials identified as the central journal in the field, underscoring its role in disseminating pivotal research findings.

We incorporated these findings into the Discussion, emphasizing the significant influence of global collaboration on research impact. The leading roles of China and the USA reflect the critical importance of transnational research cooperation in advancing innovations in BMSC-related tissue engineering. This collaboration fosters technological innovation, with key institutions playing a central role in shaping global research efforts. The connection between leading journals and the dissemination of critical research highlights their role in defining scientific directions and advancing clinical applications in regenerative medicine. Furthermore, the contributions of prolific researchers and collaborative teams are vital in advancing knowledge in this area, as their collective efforts are instrumental in driving both innovation and global research output. The dominance of Chinese authors is particularly noteworthy, reflecting China's growing influence in BMSC research and its impact on global innovation and knowledge production in this field. Finally, it is essential to closely consider the contributions of individual authors who publish research in this area, as they may provide valuable insights into the latest developments and help guide future research directions in the field of BMSC-based tissue engineering.

4.2. Research status and development trend

The keyword clustering and research frontier analysis presented in this study reveal critical insights into evolving research trends in BMSCs and tissue engineering. The seven main clusters identified using VOSviewer reflect diverse research themes, with "scaffolds" and "3D printing" emerging as key focuses. This shift toward scaffold-based innovations highlights a paradigm change from traditional cell culture systems to more complex, biomimetic environments that mimic the extracellular matrix. The increasing relevance of 3D printing and cell sheets aligns with recent advances in precision tissue engineering, where custom-designed biomaterials support

cell growth and differentiation. The identification of "exosomes" and "hydrogels" as late-appearing keywords further emphasizes the move toward dynamic biomaterials with enhanced bioactivity, which can improve therapeutic outcomes. The analysis also uncovers a decline in the general keyword frequency trend from 2019 to 2023, suggesting a possible saturation in traditional scaffold research while newer technologies like extracellular vesicles gain momentum. However, the sustained increase in "stent" frequency indicates a burgeoning interest in bioactive scaffolds for stem cell delivery, a direction that may shape future clinical applications. The robustness of these trends is supported by their statistical recurrence across diverse bibliometric analyses, confirming their significance within the scientific discourse. In the co-citation analysis, highly cited articles (e.g., Pittenger et al., 1999, and Langer and Vacanti, 1993) form foundational knowledge in stem cell research and tissue scaffolding. The strong citation bursts observed for references such as Bose et al. in Trends in Biotechnology reflect contemporary interest in using nanofibrous scaffolds to enhance osteogenesis. The clustering of citations into thematic groups over different periods illustrate the evolution of research priorities, from early investigations into MSC biology to recent emphasis on composite hydrogels and cartilage regeneration. This progression marks a significant transition from foundational cell studies to the development of multifunctional biomaterials. Statistical significance and citation bursts serve as indicators of a reference's influence and relevance during specific periods. For instance, Roseti et al. in Materials Science and Engineering C demonstrated a burst intensity of 9.33 over five years, reflecting ongoing innovation in cartilage tissue engineering using hydrogel composites. These metrics not only highlight seminal contributions but also pinpoint emerging fields with substantial growth potential, such as nanoparticle-based delivery systems and bioactive scaffolds. By integrating these findings, this study underscores both historical milestones and future research avenues. The strategic use of short-term keyword bursts and citation analyses enables researchers to align with dynamic frontiers in BMSCs-based tissue engineering, supporting the development of tailored therapeutic strategies and advanced scaffold systems for regenerative medicine.

4.2.1. Cell derivatives

(1) Bioactive substances. After transplantation into the body, BMSCs could selectively be home to the vicinity of damaged tissues. They also secrete pro-growth factors and anti-inflammatory factors, promoting the regeneration of damaged tissues [40,41]. The repair function of BMSCs is attributed to their ability to secrete bioactive substances, such as cytokines and growth factors [41]. These factors help to balance the internal homeostasis of the organism and provide a suitable environment for stem cell immunomodulation and anti-apoptosis [42]. The bioactive substances secreted by BMSCs are mainly involved in immunomodulation and anti-apoptosis [43]. However, there is increasing evidence that stem cell-secreted factors are also functionally important for tissue regeneration, organ repair, and their protective effects [44]. The paracrine effects of stem cells influence several aspects of angiogenesis, including vascular cell proliferation, migration, adhesion, and extracellular matrix formation [45].

(2) Exosomes. Exosomes are nanoscale vesicles (30–150 nm in diameter) with a double-layer lipid membrane structure that are secreted by the inner membrane of cells [46,47]. They contain abundant proteins, nucleic acids, and endogenous factors and act as paracrine products [48]. BMSCs exosomes, which are paracrine products of BMSCs, have functions similar to those of stem cells [49]. Research has found that BMSC exosomes can promote tissue repair and inhibit scar formation by attenuating inflammatory responses, promoting cell proliferation and migration, promoting angiogenesis, and regulating extracellular matrix remodeling [50]. Compared to the direct application of BMSCs, BMSC exosomes offer several advantages. Exosomes can directly fuse with target cells, resulting in a more significant regulatory effect [51,52]. The vesicles of exosomes can protect the signal molecules secreted by BMSCs from destruction. Exosomes are also better controlled in terms of usage, dosage, administration method, and administration time [53,54]. They help avoid tumor formation and are more convenient to store and transport after extraction. Therefore, exosomes from BMSCs have great potential in promoting tissue repair.

(3) Extracellular vesicles (EVs). EVs are organelles enclosed by lipid bilayers that contain various bioactive molecules and cytokines. They play a crucial role in the complex intercellular communication system [55,56]. Cells can actively release EVs into the surrounding space through paracrine action. This process inhibits inflammatory responses, regulates immune function, and counteracts tissue fibrosis [57]. Research has demonstrated that the regenerative function of EVs derived from BMSCs (BMSCs-EVs) is dependent on the proteins, lipids, DNA, RNA, and microRNAs (miRNAs) that they transport. Through their paracrine function, miRNAs delivered by BMSCs-EVs can modify gene expression in recipient cells and facilitate tissue regeneration. Furthermore, due to their drug-delivery capability, BMSCs-EVs have become a promising tool for delivering therapeutic miRNAs [58].

4.2.2. Biological scaffold

(1) Hydrogel. Hydrogel is a biomaterial that can encapsulate BMSCs with superior biocompatibility and biodegradability, excellent mechanical properties, and low cytotoxicity [59]. This solves the problem of maintaining cell survival and viability after transplantation and improves the microenvironment by forming a localized cellular niche to transport cells to the site of injury and allow stem cells to avoid immune cell attack [60,61]. Furthermore, the hydrogel's porous structure facilitates signaling and the transportation of growth factors and nutrients [62]. Additionally, its primary advantage is that the degradation products are less likely to cause cytotoxic or inflammatory reactions and can participate in tissue metabolic processes. This allows for easy elimination from the body, thereby reducing damage to the organism [63,64]. However, most current studies have focused on the starvation properties, biocompatibility, and the ability of hydrogels to protect stem cells. There are fewer studies on the biodegradability of hydrogels and the controlled release of BMSCs, which is a key area for further research.

(2) Nano. In recent years, the regulation of directed stem cell differentiation through the use of physical properties of nanomaterials has been a significant research focus in the fields of tissue engineering and regenerative medicine [65]. Nanostructures play a crucial role in determining the morphology and function of cells

and tissues, and their interactions with tissues and cells in the human body have a significant impact on the fate of stem cells. It has been demonstrated that nanomaterials can promote the differentiation of BMSCs into osteoblasts [66,67]. Additionally, the use of nanostructures to grow different cells at distinct locations on the same material achieves the localization and directed differentiation of stem cells on the same material [68]. This has significant theoretical value and application prospects in the design and application of multi-cellular constructs and implanted materials for cell engineering in the same material system.

In the realm of nanotechnology, nanoscale materials have been engineered to direct stem cell fate through surface topography and mechanical cues. Recent developments highlight the role of nanofibers, nanotubes, and nanopatterned surfaces in enhancing the differentiation efficiency of mesenchymal stem cells into specific lineages, including osteogenic and chondrogenic pathways [69,70]. Furthermore, nanocarriers have been refined for targeted delivery of bioactive molecules, offering improved control over drug release profiles and minimizing systemic side effects [71]. Research is increasingly focused on bioactive nanoscaffolds that combine structural support with dynamic biochemical signaling to promote tissue regeneration. The development of stimuli-responsive nanomaterials that release therapeutic agents in response to environmental triggers—such as pH or temperature changes—holds promise for enhancing localized treatment efficacy [72]. Additionally, nanotechnology-driven immunomodulation strategies are emerging as pivotal for reducing inflammatory responses in regenerative therapies [73].

(3) 3D bioprinting. 3D bioprinting is an advanced technology that mimics the complexity of natural tissue. Bioprinting can precisely and delicately control the deposition of cells and biomaterials to construct structures that closely resemble the microenvironment of natural tissue [74,75]. 3D bioprinting has the potential to support the regeneration of damaged tissue and halt the progression of disease by replicating the complex structure of the affected site of injury [76,77]. Biomaterials printed using 3D bioprinting can act as carriers for BMSCs, which are then doped into scaffolds to promote tissue repair. Inflammation can be controlled effectively through the local release of anti-inflammatory agents or biologics [78]. One of the most critical aspects of 3D bioprinting is its ability to design treatments based on the specific needs of individual patients. Tailoring biomaterials that support bioprinting to individual characteristics provides a paradigm shift in treatment outcomes [79]. By considering factors such as a patient's physiology, the severity of the condition, and other individual characteristics, 3D bioprinting enables personalized interventions that improve outcomes. Furthermore, 3D bioprinting offers several advantages over traditional therapies by reducing the need for invasive procedures, which are often accompanied by risks and complications, thus providing a safer and less invasive route to recovery [80].

Recent advancements in 3D bioprinting have significantly impacted regenerative medicine and tissue engineering [81]. Innovations in bio-inks, which incorporate living cells, extracellular matrix components, and growth factors, allow for the fabrication of complex tissue-like structures with enhanced precision [61]. Specifically, hydrogels derived from natural biomaterials, such as gelatin methacryloyl and alginate, provide tunable mechanical properties suitable for

mimicking the native extracellular matrix [82]. Current research focuses on developing multi-material bioprinting strategies to replicate heterogeneous tissue architectures. Moreover, the integration of microfluidic systems into bioprinting platforms enables precise control of nutrient delivery and waste removal, enhancing cell viability and functionality in printed constructs [83]. Personalized medicine stands to benefit significantly from patient-specific organ and tissue models, which leverage patient-derived cells to reduce the risk of immune rejection. The use of machine learning algorithms to optimize printing parameters and tissue maturation processes represents another frontier in advancing 3D bioprinting [84]. Additionally, scalable production systems for bioprinted tissues and organs will be crucial for clinical applications, addressing challenges in reproducibility and regulatory compliance.

5. Conclusion

In conclusion, the bibliometric analysis indicates that research on BMSCs in tissue engineering has primarily focused on bioactive substances, such as cytokines and growth factors, as well as biomaterials. We have summarized past and predicted future trends in the field of BMSCs in tissue engineering through relatively comprehensive bibliometric analyses. These findings provide researchers with a comprehensive perspective on the broad prospects of this research field. Bibliometric analyses can aid collaboration by identifying shared clinical practice and research interests, academic affiliations, areas of expertise, and available resources. However, limitations remain. Firstly, despite efforts to obtain comprehensive literature, some articles were not included in the analyses, which may have introduced bias. Secondly, some high-quality studies published in recent years may not have received sufficient citations due to their limited time and, therefore were not highlighted in this analysis. Additionally, this project was conducted using machine algorithms, which may have resulted in a slight lack of evidence.

Author contributions: Conceptualization, XW, CF and SN; methodology, LW and BL; software, XW, HC, MX and TS; validation, XW, HC, MX, LW, BL and YY; formal analysis, TS; investigation, XW, HC, ZH, TS, BL and XJ; resources, ZH; data curation, XW, MX, ZH, TS and DS; writing—original draft preparation, XW, HC, MX, CF and SN; writing—review and editing, XW, CF and SN; visualization, XW, HC and TS; supervision, CF and SN; project administration, CF; funding acquisition, CF and SN. All authors reviewed the results and approved the final version of the manuscript.

Funding: This study is supported by the Beijing Science and Technology Planning Project (Z221100007422061) and the Natural Science Foundation of Shaanxi Province (General Project, 2018SF-159).

Acknowledgments: We would like to thank Home for Researchers and vecteezy for providing some template graphics used in our figures, created with “www.figdraw.com” and “www.vecteezy.com”. These figures have greatly improved the clarity of our graphical abstract.

Availability of data and materials: The data that support the findings of this study are available from the Corresponding Author, SN, upon reasonable request.

Ethical approval: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

BMSCs	Bone marrow mesenchymal stem cells
EVs	Extracellular vesicles
MESH	Medical subject headings
miRNAs	MicroRNAs
SJTU	Shanghai Jiao Tong University
WoSCC	Web of science core collection

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