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Review

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# A scientometric and visualization analysis of 3D printing scaffolds for vascularized bone tissue engineering over the last decade



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# A R T I C L E I N F O

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#### ABSTRACT

The introduction of three-dimensional (3D) printing scaffolds has emerged as an effective approach to achieving satisfactory revascularization for bone tissue engineering (BTE). However, there is a notable absence of analytical and descriptive investigations concerning the trajectory, essential research directions, current research scenario, pivotal investigative focuses, and forthcoming perspectives. Hence, the objective of this research is to offer a thorough overview of the advancements achieved in 3D printing structures for vascularized BTE within the last 10 years. Information extracted from the Web of Science repository spans from January 1, 2014, to April 1, 2024. Utilizing advanced analytical instruments, we conducted comprehensive scientometric and visual analyses. The findings underscore the predominant influence of China, representing 59.62 % of the overall publications and playing a pivotal role in shaping research within this field. Notable productivity was evident at various institutions, including Shanghai Jiao Tong University, Chinese Academy of Sciences, and Sichuan University. Wang Jinwu and Wu Chengtie stand out as the most prolific contributors in this domain. The highest number of publications in this area was contributed by the journal Advanced Healthcare Materials. In this study, osteogenesis imperfecta, osteosarcoma, fractures, osteonecrosis, and cartilage diseases were identified as the most significant disorders investigated in this research area. By providing a comprehensive scientometric assessment, this study benefits both experienced researchers and newcomers alike, offering prompt access to essential information and fostering the extraction of innovative concepts within this specific field.

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# 1. Introduction

Bones, as load-bearing tissues with varying mechanical properties, exhibit diverse geometry and mechanical characteristics along different axes. The human body contains 206 bones, and the mechanical properties of each bone vary based on its location and age [1,2]. Bone tissue possesses inherent regenerative abilities, facilitating self-repair following fractures under normal circumstances [3]. However, complex large segmental bone defects-exceeding 2 cm in length or 2 to 2.5 times the long bone diameter-may arise from severe trauma, infection, or tumor resection, leading to delayed healing and permanent shape and size alterations [4,5]. With failure rates reaching up to 50 %, bone repair failures pose significant societal and familial burdens [6,7]. Inadequate bone healing may result in tissue ischemia, osteonecrosis, and nonunion, necessitating stent implantation. The introduction of scaffold transplantation techniques has revolutionized bone defect treatment through advancements in bone tissue engineering (BTE). These scaffolds, made from various materials like autologous or allogeneic bones, metals, and synthetics, address limitations of conventional repair materials such as donor scarcity, singular structure, and limited functionality. For example, autologous bones may have limited availability, whereas synthetic materials may lack biological activity. Moreover, due to its high vascularity, bone regeneration requires a well-established vascular network for proper development and repair post-injury, highlighting the critical role of blood vessel formation and maturation [8-11].

In recent years, three-dimensional (3D) printing technology has rapidly advanced as an appealing alternative approach, extensively used to produce functional tissue structures with intricate geometries [12–14]. In the field of vascularized BTE, 3D printing technology presents novel research prospects compared to traditional methods and offers several advantageous characteristics: (1) the capability to manufacture intricate 3D shapes with spatially organized multiple materials; (2) a comprehensive fabrication platform addressing most essential requirements outlined by bone-healing mechanisms; (3) streamlined processing simplifying elaborate procedures involving numerous experimental steps; (4) consistent reproducibility across all production batches; (5) automation and cost-effectiveness for large-scale manufacturing; and (6) heightened flexibility and adaptability to tailor each fabrication process to specific patient needs [15–22]. These attributes align closely with the requirements of vascularized osteogenesis, reducing complications from inadequate blood supply [23,24], thus positioning 3D printing scaffolds for vascularized BTE as a significant research area [25]. Scholars from developmental biology, tissue engineering, regenerative medicine, and materials science are increasingly contributing to advancements in this field.

While many reviews have explored the application of 3D printing scaffolds for vascularized BTE from various perspectives [22,26–33], they frequently lack empirical support with objective visualized data, relying heavily on researchers' subjective interpretations. Consequently, these evaluations display variability and subjectivity, impeding comprehensive analysis and the establishment of the current research landscape. To address these limitations, this study utilizes scientometric analysis to visually depict various aspects of publications, nations/regions, authors, organizations, keywords, references, fields, and journals over the past decade. The objectives of this comprehensive analysis include analyzing the current distribution of research output, recognizing major contributors, identifying hotspots, assessing the current status, and exploring frontiers, all of which facilitate a deeper understanding of 3D printing scaffolds for vascularized BTE. Establishing such a systematic and comprehensive knowledge base not only assists researchers from diverse fields in navigating the breadth of the domain but also serves as a valuable reference for newcomers, guiding them toward promising research trajectories. To the best of our knowledge, no prior scientometric investigations have been conducted on this specific subject.

#### 2. Materials & methods

#### 2.1. Data source & retrieval strategy

The Web of Science Core Collection (WoSCC) was chosen as the primary source for scientometric statistics for several key reasons. First, BTE is a multidisciplinary field that includes materials science, medicine, chemistry, pharmacy, and biology. Therefore, it is essential to use integrated databases to ensure comprehensive analysis. Second, the WoSCC dataset includes cited references, which are invaluable for knowledge mapping [34]. This helps deepen our understanding of the connections within the BTE field. Third, WoSCC offers citation reports as a validation tool to ensure the accuracy and credibility of scientometric analysis results.

Fourth, WoSCC, as a key platform, offers scientometric tools for general statistics and provides higher accuracy in classifying document types compared to other databases [35,36]. This prevents issues like data corruption or missing fields, ensuring the integrity of the analysis. Fifth, the WoSCC database includes the Science Citation Index Expanded, enabling tracking of scientific frontier evolution and facilitating comprehensive analysis of publication trends [35,37–39]. This ensures stringent quality control for journals and publications. Finally, the journal selection in WoSCC follows Bradford's and Garfield's Laws [34]. This ensures that scientometric analyses capture core publications and minimize potential omissions. Thus, WoSCC is the most frequently used database in scientometric studies.

For this study, an extensive online search was conducted using WoSCC to explore original research and reviews on the application of 3D printing scaffolds for vascularized BTE. The search included articles published between January 1, 2014, and April 1, 2024, using a combination of Medical Subject Heading terms and free words for data collection. The retrieval methodology underwent multiple revisions, guided by a team of three researchers, with the goal of improving sensitivity and precision, as extensively described in the Supplementary Materials.

#### 2.2. Inclusion & exclusion standards

Special attention was given to studies and reviews published in English, focusing on the application of 3D printing scaffolds for vascularized BTE. Exclusions comprised dissertations, letters, comments, editorials, conference abstracts, and duplicate research published under identical titles across multiple journals. In-depth discussions regarding the inclusion and exclusion criteria were conducted among team members and peer groups.

#### 2.3. Scientometric visualization & data analysis

Data from the WoSCC database were collected and imported into Microsoft Excel (Office 365, Microsoft). Subsequently, analysis was conducted using VOSviewer 1.6.18 (Leiden University, Netherlands), Citespace version 6.3. R1 (Chaomei Chen, China), Pajek version 5.16 (University of Ljubljana, Slovenia), Scimago Graphica version 1.0.35 (https://www.graphica.app/, USA), and the chorddiag R package (R Studio, version 4.2.0).

We employed the chorddiag R package in combination with VOSviewer to create visual representations depicting collaboration at national or regional levels and graphs analyzing published works. Co-occurrence analyses encompassing countries/regions, institutions, authors, journals, research fields, and keywords were performed utilizing VOSviewer, Scimago Graphica, and Pajek. Data on countries/regions, institutions, authors, journals, co-citations, and keywords were visually represented and analyzed using Citespace. Additionally, the evolving popularity of keywords over time was examined via Scimago Graphica.

Data on illnesses was gathered from the Citexs Data Analysis Platform (https://www.citexs.com). This platform streamlines the process of creating informative visualizations, facilitating comprehensive analysis of the present status, main areas of interest, and forthcoming trends within this particular research domain.

#### 3. Results & discussion

# 3.1. Scientific output

The process of retrieving and collecting data is depicted in Fig. 1A. The progress of research can be gauged by the number of scientific reports it generates over a specified timeframe [40,41].

Between 2014 and 2024, a total of 426 relevant scientific reports on "3D printing scaffolds for vascularized BTE" were compiled. This compilation consisted of 370 original articles and 56 reviews, leading to an average yearly publishing rate of 42.6. This highlights the substantial attention and interest directed towards this field. In 2021. the annual number of pertinent publications surpassed 50, hitting its peak at 98 by 2023. The diagram depicts a remarkable increase of over 49-fold since 2014, indicating a substantial surge in research endeavors in this field and emphasizing its significant research importance. The exponential equation  $(y = 4.8683x^2 -$ 13.574x + 12.321) effectively represents the yearly trend, with x denoting the year and y denoting the number of publications, achieving a high R<sup>2</sup> value of 0.9915. This illustrates the precision and thoroughness applied in data analysis, resulting in a well-fitted curve (Fig. 1B). The graph indicates an anticipated increase in annual research activities, indicative of an expanding interest in utilizing 3D printing scaffolds for vascularized BTE. Consequently, substantial advancements are anticipated in this field in the coming years.

These findings highlight the importance and relevance of researchers' work in the field. The growing number of publications signifies an expanding pool of knowledge and insights available for researchers to progress their studies. The precision and thoroughness displayed in data analysis, as indicated by the well-fitted curve of the exponential equation, inspire confidence in the accuracy and reliability of the identified research trends. For industry practitioners, the increasing interest in employing 3D printing scaffolds for vascularized BTE suggests promising prospects for innovation and commercialization. The expected increase in research activities implies a rising market demand for technologies and products associated with vascularized BTE. With significant progress anticipated in the field in the near future, industry practitioners can take advantage of emerging trends and developments, potentially resulting in the development of innovative therapeutic approaches and medical devices for tissue regeneration and repair. Overall, these findings emphasize the transformative potential of 3D printing scaffolds for vascularized BTE and underscore the collaborative efforts of researchers and industry stakeholders in advancing regenerative medicine.

# 3.2. Countries/regions

Globally, research on utilizing 3D printing scaffolds for vascularized BTE involves 39 countries/regions. Fig. 2A and B depict national collaboration networks, providing tangible representations of the importance of each country or region in the field, with a minimum publication count of one from each. This offers valuable insights for strategic collaborations and knowledge exchange. Particularly noteworthy is China's leadership with 254 publications, constituting 59.62 % of the total research output, underscoring its crucial role in advancing knowledge in the utilization of 3D printing scaffolds for vascularized BTE. Subsequently, the USA and Germany make significant contributions, representing 19.95 % (85 publications) and 6.57 % (28 publications) of global research on the utilization of 3D printing scaffolds for vascularized BTE. The peripheral curve segments in the chord diagram visually represent countries and regions. The length of each segment corresponds to the publication volume of the respective country or region. The levels of collaboration among nations are reflected in their connectivity levels. In terms of global cooperation, China demonstrates the highest frequency, mainly participating in collaborations with the USA (link strength = 17) and Germany (link strength = 9) (Fig. 2B). This information is of immense value to researchers seeking potential collaborators and industry practitioners aiming to



B



**Fig. 1.** (A) Schematic representation outlining the methodology used for literature search and selection. (B) Temporal trend analysis depicting the evolution of research focused on the application of 3D printing scaffolds for vascularized bone tissue engineering from 2014 to 2024.





# Top 10 Countries with the Strongest Citation Bursts

| Countries   | Year St | rength | Begin | End  | 2014 - 2024 |
|-------------|---------|--------|-------|------|-------------|
| USA         | 2014    | 5.1    | 2014  | 2016 |             |
| AUSTRIA     | 2019    | 1.42   | 2019  | 2020 |             |
| BRAZIL      | 2018    | 1.36   | 2018  | 2019 |             |
| SOUTH KOREA | 2015    | 1.23   | 2015  | 2016 | _           |
| SPAIN       | 2017    | 1.13   | 2020  | 2021 |             |
| INDIA       | 2017    | 0.97   | 2020  | 2022 |             |
| FRANCE      | 2015    | 0.81   | 2015  | 2017 | _           |
| CANADA      | 2019    | 0.72   | 2019  | 2020 |             |
| SWITZERLAND | 2017    | 0.59   | 2017  | 2018 |             |
| ITALY       | 2017    | 0.59   | 2019  | 2020 |             |

**Fig. 2.** (A) Global distribution of research on the application of 3D printing scaffolds for vascularized bone tissue engineering (BTE). Each sphere represents a country, with the thickness of connecting lines indicating the level of collaboration between nations. The size of each sphere corresponds to the number of publications from that country. (B) Chord diagrams illustrating international collaborations, where each outer curve represents a country, and the thickness of the lines denotes the strength of collaboration between countries. (C) Research output on the application of 3D printing scaffolds for vascularized BTE from the top 10 countries (highlighted in red, indicating increased document production).

stay informed about international collaborations that may impact clinical practices [42].

Research on "3D printing scaffolds for vascularized BTE" has expanded rapidly, with China emerging as the leading contributor. China's dominance can be attributed to several factors: 1. Research Infrastructure and Funding: China's 59.62 % contribution to global research output in 3D printing scaffolds for vascularized BTE is largely due to its strong research infrastructure and significant government funding for science and technology. The Chinese government's heavy investment in biomedical engineering, regenerative medicine, and advanced manufacturing, including 3D printing, has positioned China as a global leader in this field. 2. National Science and Technology Policies: Initiatives like "Made in China 2025" and "Healthy China 2030" focus on technological innovation and healthcare advancement, aligning with 3D printing scaffold research in tissue engineering. These initiatives promote crossdisciplinary collaboration, foster innovation, and provide incentives to researchers and institutions, driving China's dominance in this field. 3. Focus on Regenerative Medicine: Regenerative

medicine and tissue engineering have been strategic priorities in China's broader healthcare reforms. Chinese research institutions have heavily invested in 3D printing to develop cutting-edge solutions for healthcare challenges, particularly in tissue regeneration and bone repair. This focus on a rapidly growing field further explains China's significant research output. 4. International Collaboration and Talent Recruitment: China has developed strong international collaborations with leading countries like the USA and Germany. Its research exchange programs and talent recruitment initiatives (e.g., the "Thousand Talents Plan") have attracted global experts in biomedical engineering, further enhancing China's contributions to the field. These collaborations also enhance the global impact of Chinese research. 5. Reflecting Global Trends: While China's dominance may seem disproportionate, it reflects the country's substantial investment in infrastructure and human resources, resulting in a significant research output. However, the USA and Germany, which also make significant contributions, remain influential in advancing cutting-edge technologies. Therefore, China's contribution aligns with global trends while

# A



**Fig. 3.** (A) Clustering networks of pertinent research institutions are illustrated, with distinct colors denoting different clusters identified through the literature co-citation network among these institutions. Institutions with robust co-citation relationships are clustered, generating a hierarchical diagram to depict these associations. The thickness of lines between circles indicates the strength of cooperation among institutions, while the size of each circle positively correlates with the number of documents issued by the institution. (B) Diagram depicting the intensity of institutional cooperation, where the thickness of connecting lines between circles represents the level of cooperation between institutions. Additionally, the size of each circle is proportional to the number of documents issued by the respective institution. (C) Citation bursts at the top 10 institutions are represented by red bars, indicating periods of increased citation activity for each institution.

showcasing its emerging leadership. 6. Role of Key Institutions: China's research output is heavily influenced by key institutions such as Shanghai Jiao Tong University and the Chinese Academy of Sciences, which lead research in this field. Their large-scale projects, well-funded labs, and access to advanced technology foster innovation in 3D printing scaffolds. The concentration of research in these institutions explains China's substantial share of publications. While China's large share of research output reflects its leadership in the field, global trends in 3D printing scaffolds for vascularized BTE are shaped by contributions from multiple countries. China's dominance is significant, but it must be considered alongside contributions from the USA, Germany, and other nations to gain a balanced understanding of global advancements in this field. Some regions, particularly in Europe and developing countries, may be underrepresented due to limitations in resources or research infrastructure. Future studies incorporating more diverse geographical contributions may offer a more comprehensive view of global trends, highlighting the impact of smaller or emerging research hubs.

2021

1.57 2022 2024

1.56 2022 2024

**Oueensland Univ Technol 2022** 

Chongqing Med Univ

Identifying publications that have experienced substantial increases in citations over a designated time frame is crucial, and this is achieved through the recognition of citation bursts. Fig. 2C

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A



Å VOSviewer

B

# Top 10 Authors with the Strongest Citation Bursts

| Authors         | Year | Strength | Begin | End  | 2014 - 2024 |
|-----------------|------|----------|-------|------|-------------|
| Zhang, Xingdong | 2022 | 3.63     | 2022  | 2024 |             |
| Fan, Yujiang    | 2022 | 2.62     | 2022  | 2024 |             |
| Zhang, Jing     | 2018 | 2.29     | 2018  | 2019 |             |
| Wang, Chong     | 2021 | 2.17     | 2021  | 2022 |             |
| Shie, Ming-You  | 2018 | 2.05     | 2018  | 2019 | _           |
| Jiang, Xinquan  | 2017 | 2.01     | 2017  | 2019 |             |
| Tu, Xiaolin     | 2022 | 1.96     | 2022  | 2024 |             |
| Zhou, Xiaojun   | 2021 | 1.95     | 2021  | 2024 |             |
| Zhang, Yu       | 2020 | 1.94     | 2020  | 2021 |             |
| Ma, Limin       | 2020 | 1.94     | 2020  | 2021 | _           |

Fig. 4. (A) Co-occurrence map of authors, where circles and text labels form nodes, and distinct clusters are indicated by different colors. (B) Top 10 authors exhibiting the most significant citation bursts in publications concerning the application of 3D printing scaffolds for vascularized bone tissue engineering.



E



**Fig. 5.** (A) A density visualization map illustrating journal citations. The color intensity directly corresponds to publication volume. (B) Distribution of journals based on average publication year (blue: earlier, yellow: later). Each circle and its label form a node, where circle size correlates with keyword frequency. The color gradient of each circle in the lower right corner indicates average publication year. (C) Top 20 journals with the most significant citation bursts. (D) A dual-map overlay depicting journals relevant to 3D printing scaffolds for vascularized bone tissue engineering. Each point represents a journal, with curves linking the left and right sides of the graph indicating citation connections. These

demonstrates the citation spikes for the top 10 countries/regions with the most significant citation bursts, illustrated by the intensity of each spike shown by the red line. Notably, there was a substantial increase in publication citations observed in the USA (strength = 5.1) from 2014 to 2016, closely followed by Austria (strength = 1.42) and Brazil (strength = 1.36). Among the top 10 countries, the USA first appeared in citation bursts in 2014, indicating its early attention to this field and its high academic influence in the early stages of research, whereas the time periods of citation bursts for most of the top 10 countries were between 2017 and 2019.

Several factors may explain the citation burst: 1. Technological Advancements: The 2014~2016 citation burst, especially in the USA, is likely tied to major advancements in 3D printing technology during this time. Refinements in biocompatible materials and advanced printing techniques likely spurred interest in applying 3D printing to scaffold fabrication, resulting in a surge of publications and citations as the technology became more viable for medical applications. 2. Early Adoption and Funding: The USA's early involvement, reflected by a 2014 citation burst, suggests early government and private-sector funding initiatives. Strong funding support for biomedical research in the USA likely accelerated earlystage research. Pioneers in the field likely published groundbreaking work, attracting significant attention and contributing to the citation burst. 3. Academic Collaborations: Global collaboration likely contributed to citation bursts. The USA's academic influence and international partnerships likely facilitated knowledge exchange, leading to concentrated publication output. Subsequently, countries like Austria and Brazil followed from 2017 to 2019. reflecting the global spread of 3D printing scaffold research as international collaborations expanded. 4. Clinical Applications and Interest: The rapid progress in regenerative medicine and the potential for 3D printing to create vascularized bone tissue scaffolds likely fueled the citation surge. As the field advanced toward clinical practice, researchers and industry professionals focused on the practical applications of scaffolds in improving patient outcomes, driving increased citation activity in both academic and industry sectors. 5. Increased Global Awareness: The delay between the USA's citation burst and those of other countries, notably from 2017 to 2019, may reflect growing global awareness and interest in 3D printing scaffolds for BTE. As the field matured, researchers worldwide began recognizing the potential of 3D printing scaffolds, resulting in global adoption and a surge in citations. This surge may also be linked to new research directions and integration with other biomedical advances.

For both researchers and industry practitioners, understanding global cooperation patterns and emerging research trends is crucial for staying informed about international collaborations that may impact clinical practices. The identification of citation bursts and the associated temporal trends provide insights into evolving research areas and potential areas for application in clinical settings. By leveraging these insights, industry practitioners can anticipate and adapt to changing trends in the utilization of 3D printing scaffolds for vascularized BTE, ultimately enhancing patient care and treatment outcomes.

## 3.3. Institutions

Over the last ten years, 621 academic organizations have collaborated on studies regarding the application of 3D printing frameworks for vascularized BTE. This underscores the significant interest and effort directed towards advancing this area of study. The identification of Shanghai Jiao Tong University (n = 57, 13.38%) as the most prolific institution highlights its leadership role in driving research output in this field. It is closely followed by other prominent institutions such as the Chinese Academy of Sciences (n = 35, 8.22 %) and Sichuan University (n = 28, 6.57 %). This information is crucial for researchers and industry practitioners as it helps them identify key collaborators and potential research partners. By setting a minimum publication threshold of 3 and 5 documents per institution, we created maps illustrating cooperation relationships and clustering patterns among research institutions (Fig. 3A and B). Each color-coded region in the maps indicates a unique clustering pattern. The strength of collaboration between institutions is reflected in the thickness of the lines connecting them, while the size of each circle corresponds to the number of documents published by that institution. Among the various institutions, Shanghai Jiao Tong University stood out as a key player in collaboration, showing a strong interest in partnering with other organizations. This is evident from the significant connections between Shanghai Jiao Tong University and numerous highly regarded scholarly institutions. Interestingly, most of these institutions prefer domestic collaborations over international ones.

Organizations displaying significant citation spikes were distinguished using CiteSpace (Fig. 3C). This pertains to the leading 10 establishments experiencing notable surges in citations within a specific timeframe, highlighted by the red regions representing the periods of heightened citation activity for each institution. From the figure, it can be observed that during this period. Southern Medical University experienced a surge from 2020 to 2022, with a burst intensity of 3.64. The University of Maryland had the longest duration of burst, indicating that the research published by this institution has had academic influence in the field for a longer period of time. Over the last couple of years, Wenzhou Medical University, Queensland University of Technology, and Chongqing Medical University have seen a significant increase in citations, suggesting that their published works have garnered more interest within the field recently. The majority of the top ten institutions with the most significant citation surges witnessed these bursts between 2018 and 2024, illustrating a focused research period that attracted increased attention within the past decade.

Several factors may explain the causes of the citation burst: 1. Institutional Leadership: Southern Medical University's citation burst from 2020 to 2022, with a burst intensity of 3.64, suggests its leadership in advancing 3D printing scaffolds for vascularized BTE during this period. This may result from high-impact research, breakthrough discoveries, or innovative methodologies that gained global attention and citations. 2. Long-term Academic Influence: The University of Maryland's extended citation burst indicates sustained academic influence over time. The institution likely contributed foundational research, methods, or reviews that became key references for later studies. The burst's longevity suggests consistent production of impactful research that remains essential to the field. 3. Recent Focus and Innovation: Wenzhou Medical University, Queensland University of Technology, and Chongqing Medical University have recently shown notable citation bursts. These institutions likely produced cutting-edge research or introduced innovative 3D printing scaffold applications in vascularized BTE, drawing attention for novel techniques or clinical potential, thus increasing citations. 4. Geographical Shifts in Research: The top ten institutions experiencing citation surges are

paths provide insights into interdisciplinary relationships and illustrate citation inception and progression. (E) Analysis of research subject areas, with colored spheres representing distinct converging fields.





B

# **Top 20 References with the Strongest Citation Bursts**

| References  | Year Stre | ength Begin      | End 2014 - 2024 |
|---|-----------|------------------|-----------------|
| Bose S, 2013, MATER TODAY, V16, P496, DOI 10.1016/j.mattod.2013.11.017, DOI                             | 2013      | 6.41 2016        | 2018            |
| Murphy SV, 2014, NAT BIOTECHNOL, V32, P773, DOI 10.1038/nbt.2958, DOI                                   | 2014      | <b>5.58</b> 2016 | 2019            |
| Jakus AE, 2016, SCI TRANSL MED, V8, P0, DOI 10.1126/scitranslmed.aaf7704, DOI                           | 2016      | <b>4.97</b> 2019 | 2021            |
| Mercado-Pagán AE, 2015, ANN BIOMED ENG, V43, P718, DOI 10.1007/s10439-015-1253-3,<br>DOI                | 2015      | <b>4.76</b> 2015 | 2020            |
| Temple JP, 2014, J BIOMED MATER RES A, V102, P4317, DOI 10.1002/jbm.a.35107, DOI                        | 2014      | <b>3.98</b> 2017 | 2019            |
| Yang BW, 2018, ADV MATER, V30, P0, DOI 10.1002/adma.201705611, <u>DOI</u>                               | 2018      | <b>3.85</b> 2020 | 2021            |
| Roseti L, 2017, MAT SCI ENG C-MATER, V78, P1246, DOI 10.1016/j.msec.2017.05.017, DOI                    | 2017      | <b>3.6</b> 2021  | 2022            |
| Kang HW, 2016, NAT BIOTECHNOL, V34, P312, DOI 10.1038/nbt.3413, <u>DOI</u>                              | 2016      | <b>3.57</b> 2019 | 2021            |
| Cox SC, 2015, MAT SCI ENG C-MATER, V47, P237, DOI 10.1016/j.msec.2014.11.024, DOI                       | 2015      | <b>3.48</b> 2017 | 2019            |
| Chia HN, 2015, J BIOL ENG, V9, P0, DOI 10.1186/s13036-015-0001-4, DOI                                   | 2015      | <b>3.42</b> 2018 | 2019            |
| Mandrycky C, 2016, BIOTECHNOL ADV, V34, P422, DOI 10.1016/j.biotechadv.2015.12.011,<br>DOI              | 2016      | <b>3.37</b> 2020 | 2021            |
| Wang WH, 2017, BIOACT MATER, V2, P224, DOI 10.1016/j.bioactmat.2017.05.007, DOI                         | 2017      | <b>3.34</b> 2019 | 2022            |
| Byambaa B, 2017, ADV HEALTHC MATER, V6, P0, DOI 10.1002/adhm.201700015, DOI                             | 2017      | <b>3.29</b> 2019 | 2021            |
| Adepu S, 2017, CURR OPIN BIOMED ENG, V2, P22, DOI 10.1016/j.cobme.2017.03.005, DOI                      | 2017      | <b>3.26</b> 2019 | 2020            |
| Bertassoni LE, 2014, LAB CHIP, V14, P2202, DOI 10.1039/c4lc00030g, DOI                                  | 2014      | <b>3.1</b> 2015  | 2018            |
| Yan YF, 2019, BIOMATERIALS, V190, P97, DOI 10.1016/j.biomaterials.2018.10.033, DOI                      | 2019      | <b>3.02</b> 2021 | 2022            |
| Gao GF, 2015, BIOTECHNOL LETT, V37, P2349, DOI 10.1007/s10529-015-1921-2, DOI                           | 2015      | <b>2.89</b> 2017 | 2020            |
| Schemitsch EH, 2017, J ORTHOP TRAUMA, V31, PS20, DOI 10.1097/BOT.00000000000978, DOI                    | 2017      | <b>2.88</b> 2021 | 2022            |
| Pati F, 2014, NAT COMMUN, V5, P0, DOI 10.1038/ncomms4935, DOI   | 2014      | <b>2.85</b> 2018 | 2019            |
| Gómez-Lizárraga KK, 2017, MAT SCI ENG C-MATER, V79, P326, DOI<br>10.1016/j.msec.2017.05.003, <u>DOI</u> | 2017      | <b>2.85</b> 2018 | 2019            |

**Fig. 6.** (A) Co-citation analysis chart illustrating the application of 3D printing scaffolds for vascularized bone tissue engineering. Circle sizes, akin to those on annual rings, represent citation counts. Purple denotes earlier citations, while yellow denotes later ones. Overlapping colors signify citations in the same years. Lines connecting circles depict co-citation patterns, with magenta nodes highlighting critical nodes possessing a centrality exceeding 0.1. (B) Top 20 references with the highest citation bursts.

distributed across regions like China, Australia, and the USA, reflecting the globalization of research in this field. This geographic diversity indicates growing international collaboration and interest in 3D printing scaffolds from institutions beyond traditional

biomedical powerhouses, contributing to broader academic engagement and citation activity. 5. Focused Research Period: The concentration of citation bursts between 2018 and 2024 marks an active phase in the field, likely driven by technological



CiteSpace

**Fig. 7.** (A) Visualization of keyword intensity over time, where each circle and its label constitute a node. The size of the circle correlates positively with the frequency of keyword occurrence. The color gradient in the lower right corner indicates the average year of occurrence, with blue representing relatively early keywords and yellow indicating recently emerged keywords that may lead to new research directions. (B) Top 10 keywords with the strongest citation bursts identified by CiteSpace. (C) Clustering analysis of keyword frequencies. The size of the overlaid circles, which corresponds to the size of the circles on the annual ring lines, is proportional to the number of co-citations. Purple indicates earlier citation times, while yellow represents later citation times. The overlay of colors indicates that the keyword was cited in corresponding years. Connecting lines between circles represent the co-citation of keywords, and nodes marked in magenta are critical nodes with centrality greater than 0.1. (D) Temporal trends in keyword co-occurrence are depicted.

advancements in 3D printing and biomedical engineering. As the technology matured, research became more application-driven, increasing its relevance to clinical practice, which likely attracted greater interest from academia and industry, amplifying citation activity. 6. Research Synergy: Citation bursts from multiple institutions may reflect synergistic advances, where research from different universities builds on each other, collectively increasing citation activity. Collaboration between institutions, either directly or through cited work, may have created a feedback loop of recognition and citation, as different groups advanced the research together.

Professionals in the field can leverage these findings to identify potential research partners or institutions that demonstrate significant bursts in research activity. When assessing partnerships, it is important to consider not only the volume of publications but also the lasting impact and adaptability of research initiatives over time. Recognizing top institutions and their collaborative strategies provides opportunities for knowledge exchange, joint research projects, and the development of innovative ideas by combining expertise from diverse organizations. Overall, understanding the performance, collaboration dynamics, and trends among leading research institutions in the application of 3D printing scaffolds for vascularized BTE provides valuable insights for both researchers and industry experts. These findings inform strategic collaboration decisions, highlight influential institutions, and emphasize the importance of continuous innovation and flexibility to maintain sustained research impact.

#### 3.4. Authors

By identifying leading experts and analyzing their collaborative networks, the study facilitates knowledge exchange and fosters collaborative research endeavors. Experts with exceptional citation rates and consistent publication records provide valuable insights that shape the direction of future research. Through a comprehensive analysis of authorship in the field of utilizing 3D printing scaffolds for vascularized BTE, a total of 2,629 scholars were identified as significant contributors, highlighting the breadth and depth of expertise within the field. Among them, six researchers stood out for their prolific work, each authoring at least ten papers. These scholars possess significant expertise and abilities, making their contributions crucial for researchers in the field. To further investigate collaboration patterns, VOSviewer software was utilized to generate visual diagrams, enabling researchers and practitioners to identify potential collaborators and explore interdisciplinary research opportunities. These diagrams were created with the requirement of four publications per author. The visual representations depict the sizes of nodes, representing the publication count for each author, with various colors indicating different author categories. The strength of the connections between nodes reflects the level of collaborative interactions. Remarkably, 73 authors surpassed the publication threshold. Notably, Wang Jinwu and Li Tao exhibited the strongest collaborative relationships, as illustrated in Fig. 4A. Additionally, Wang Jinwu and Wu Chengtie have the highest number of publications, each with 13 papers (3.05 %); followed by Zhang Xingdong and Zhou Xiaojun, tied for second with 12 papers (2.82 %), highlighting their significant contributions to this scientific field.

Studying citation bursts is a significant metric that reveals how frequently authors receive citations within a specific field of study during a designated timeframe [43,44]. In Fig. 4B, the top ten authors with the highest number of citations in the field of utilizing 3D printing scaffolds for vascularized BTE are ranked. From the figure, it is evident that Zhang Xingdong experienced a citation burst from 2022 to 2024, with the highest burst strength value of 3.63. Citation bursts for the top 10 authors mostly occurred after 2020, indicating a heightened research interest in this field since that year. Authors who experienced a surge in citations in the past two years include Zhang Xingdong, Fan Yujiang, Tu Xiaolin, and Zhou Xiaojun, suggesting that their research achievements have garnered significant attention in this field during the same period. This information can inform strategic decision-making in research collaboration and funding allocation, ultimately advancing the field of 3D printing scaffolds for vascularized BTE.

# 3.5. Journals & related fields

By employing a visualization of journal publication data, insights into the scholarly communication landscape are provided through 149 journals featuring articles on the utilization of 3D printing scaffolds for vascularized BTE. A heatmap graph was generated, indicating that each journal must have a minimum of two papers to display how documents are distributed among different journals. The color depth on the graph represents the number of papers published in each journal (Fig. 5A), assisting researchers in selecting appropriate journals for their publications. Leading the rankings with the highest quantity of published documents is Advanced Healthcare Materials (n = 18), followed by Frontiers in Bioengineering and Biotechnology (n = 16), and Bio*fabrication* (n = 15). The identification of top journals and their citation rates offers valuable information for researchers assessing the impact of their work and selecting potential outlets for publication.

In Fig. 5B, journals of varying emergence years are depicted with different colors. Circular nodes represent each journal, with the size of the circle positively correlated with the number of articles published by the journal. The color of each circle indicates the average publication year, with blue representing earlier publications and yellow representing the most recent ones. From the figure, it can be observed that among the top ten journals with the highest number of publications, Biomaterials had an earlier average publication year, in 2019, indicating that this journal has focused on research in this field earlier. Among the journals with an average publication year after 2022, Frontiers in Bioengineering and Biotechnology and International Journal of Bioprinting have published a larger number of articles in the utilization of 3D printing scaffolds for vascularized BTE, suggesting that research in this field has been a recent hotspot and focus for these journals over the past two years.

The overlay of dual-maps in journals offers a valuable method to showcase the changing locations of scientific research centers and the distribution of journals across various fields [45]. The research areas covered in all papers are shown by the labels on the map. Journal citations are visible to the right of the citation map, while citations from other sources are located on the left. Colorful lines starting from the citation map and ending visually illustrate the citation pathways. The intensity of these connections is determined by the frequency of citations, assessed via a *z*-score scale [35]. This visualization facilitates the identification of emerging trends and shifts in scientific focus, guiding researchers in directing their

The sizes of the circles overlaid on the annual rings are proportional to the frequency of keywords. Lines between keywords represent co-occurrence. Purple indicates relatively early appearance times of keywords, while yellow represents later appearances, with overlapping colors denoting keywords appearing in corresponding years. Magenta nodes, positioned centrally, denote nodes with relatively strong centrality, acting as hubs. Keywords within the same cluster are aligned on a horizontal line. The top of the view shows the first appearance time of keywords, progressing towards the right.

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|                        | femur head necrosis           | jaw neoplasms   |
|------------------------|-------------------------------|---|
|                        | chondro                       | sarcoma osteoid osteoma   |
|                        | pinal injuries                | calcinosis  |
|                        | osteosarc                     | coma osteogenesis imperfecta illa syndrome                                |
| auriculo-condylar sync | rome haterotonic ossification | osteonecrosis   |
|                        | neer or oper opping of the    | femoral fractures<br>calvarial hyperostosis                               |
|                        | joint dise.                   | ases naitux vaigus<br>osteomyelitis                                       |
| craniosynost           | ses<br>arthritis              | osteolysis  |
|                        | craniofacial abn              | congenital limb deformities ankle injuries congenital lower extremity def |
| tibial meniscus inj    | ries                          | fractures   |
|                        |                               | absence of tibia<br>spinal diseases pseudarthrosis                        |
|                        | cartila <mark>ge di</mark>    | iseases   |
| bone cysts             | osteochondritis               | femoral neoplasma<br>Ubial neuropathy                                     |
|                        | median-ulnar n                | interverteoria dos organetas  |
|                        |                               | bone resorption   |
|                        | maxillofacial abnormalities   |   |
| A VOSviewer            |                               |   |

B

Å VOSviewer



Fig. 8. (A) Density visualization map of associated diseases, where the intensity of color is directly proportional to the frequency of occurrence of the represented disease. (B) Disease clustering analysis chart, where nodes of different colors form distinct clusters, with each color representing a specific disease cluster indicative of particular biological or medical fields or groups of diseases.

efforts effectively. Fig. 5D shows that studies related to the utilization of 3D printing scaffolds for vascularized BTE are mainly focused on five major areas: physics, materials science, chemistry, molecular biology, and genetics.

Utilizing the VOSviewer software, the domain categories of 426 articles were visually analyzed, resulting in the categorization of these papers into five primary fields. This classification allows for a deeper understanding of research domains and their interrelations, providing valuable insights for both researchers and industry professionals seeking to navigate the evolving landscape of the utilization of 3D printing scaffolds for vascularized BTE. The clustering is visualized in Fig. 5E, with spheres of various colors representing different domains. The findings indicate that a noteworthy percentage of relevant studies center around the field of "Chemistry and Physics", with a large number of papers falling into categories such as "Materials Science", "Biomaterials", "Multidisciplinary", and "Nanoscience & Nanotechnology".

The findings contribute to advancing knowledge in the field, informing research directions, and guiding decision-making for both academia and industry, ultimately driving innovation and progress in the utilization of 3D printing scaffolds for vascularized BTE.

## 3.6. Co-cited references

It is crucial for researchers to recognize the significance of identifying the most frequently referenced and impactful publications to enhance their understanding and contribute to the progression of their respective fields. The network diagram in Fig. 6A illustrates the connections among scholarly articles focusing on the application of 3D printing scaffolds for vascularized BTE from January 1, 2014, to April 1, 2024, as analyzed using CiteSpace. The circles' sizes combined across each year indicate their co-citation occurrences, with the color scale representing the chronological age of citations, ranging from purple for older citations to yellow for more recent ones. When colors merge on circles, it signifies consistent citations throughout the designated years. The connections represented by circles symbolize the co-citation relationships among different publications. Nodes highlighted in a pink hue signify crucial points within the network, determined by a centrality exceeding 0.1. One of the highly cited works is the original research titled 'Vascularized 3D printed scaffolds for promoting bone regeneration', authored by Yufei Yan et al. and published in *Biomaterials* in 2019, with the highest co-citation count (n = 40)[46]. Fig. 6A depicts a network diagram of co-citations, illustrating connections within research literature and highlighting key publications and their influence over time. Researchers can leverage this information to explore emerging trends and prioritize areas for further investigation.

CiteSpace was employed to analyze and identify citation bursts in the application of 3D printing scaffolds for vascularized BTE research within the time frame of January 1, 2014, to April 1, 2024. Fig. 6B illustrates the impact of the top 20 references, demonstrating significant scholarly attention. The majority of papers among the top 20 references experienced notable increases in citation counts from 2016 to 2022, indicating heightened interest in the research field during this period. Susmita Bose et al.'s paper had the highest citation burst intensity, reaching 6.41, during the period of 2016~2018, signifying its significant impact on the field [47]. Angel E. Mercado-Pagán et al.'s paper had the longest citation burst duration, spanning 5 years from 2015 to 2020, indicating its sustained impact on the field [48]. Researchers can use this information to stay informed about the evolving landscape of 3D printing scaffolds for vascularized BTE research, identify collaboration opportunities, and guide future research directions. Industry

practitioners can leverage these insights to inform decision-making processes, such as investment strategies and product development initiatives, aligning their efforts with emerging research trends and priorities in the field.

# 3.7. Keywords

The VOSviewer software was utilized for clustering analysis based on keyword co-occurrence to identify thematic clusters, with a minimum threshold of three instances. This enables researchers to discern prevalent research themes and track how they have evolved over time. The visualization included only keywords meeting this requirement from a pool of 945 unique keywords (excluding duplicates). A selection of 80 keywords was curated for network representation in Fig. 7A. The graph in the figure depicts temporal trends in word frequency, with each node represented by a circle and label. In the visual representation, the frequency of a keyword is reflected in the size of a circle. Additionally, the intensity of connections between circles reflects the level of their co-occurrence relationships. The color of each circle located in the lower right corner serves to indicate the average year of occurrence. Keywords appearing in earlier years are denoted by blue, while those appearing in later years are denoted by yellow. Analysis of the data presented in Fig. 7A shows that 'stem cells' were subjects of earlier research, while 'magnesium' and 'Wnt signaling' have become recent focal points of study and exploration. By identifying prevalent keywords and their temporal patterns, researchers can better understand the shifting landscape of research interests and prioritize areas for further investigation.

Fig. 7B exhibits the detection of keyword bursts, especially those experiencing significant citation surges. This highlights the topics that have attracted considerable academic interest. Analyzing the temporal patterns of keyword bursts can inform researchers, funding agencies, and industry stakeholders regarding investment and collaboration opportunities, facilitating alignment with prevailing research trends and fostering strategic partnerships. Fig. 7B displays the keyword with the strongest citation burst intensity as "stem cells", with a burst intensity value of 1.8, occurring during the period of 2019~2020. Among the top 10 keywords, "bone scaffolds" and "vascularized bone" experienced early citation bursts, indicating early attention to these research hotspots in the field. Keywords appearing in citation bursts after 2022, as identified in the analysis, include "macrophage polarization", indicating that in recent years, this has emerged as a key focus area in the field.

CiteSpace examines metrics like Modularity (*Q*) and Mean Silhouette (*S*) to evaluate network structures and clustering quality. Nodes with a *Q* value greater than 0.3 display significant clustering, whereas those with an *S* value over 0.5 show clear and effective clustering. Upon evaluation, we obtained a Modularity (*Q*) value of 0.8603 and a Mean Silhouette (*S*) value of 0.9876, validating the existence of strong and united clustering patterns in the network. The examination revealed 10 unique clusters, labeled as #1 bone tissue engineering, #2 3D printing, #3 additive manufacturing, #4 3D printed scaffold, #5 bone defect, #6 gelatin methacrylate, #7 mechanical properties, #8 angiogenesis and osteogenesis, #9 osteogenic differentiation, #11 calcium phosphates, as illustrated in Fig. 7C. This clustering approach facilitates knowledge organization and enhances the understanding of research trends and priorities.

Examining the evolving patterns and key research areas in the application of 3D printing scaffolds for vascularized BTE is essential for informing decisions regarding funding, collaborations, and alignment with current research priorities. Fig. 7D presents a timeline illustrating clustering of keyword frequencies in

significant areas of study. The diagram displays circles of varying sizes, with each circle's size corresponding to the frequency of the keywords in each year. Connections between keywords represent their co-occurrence. Nodes highlighted in rose color emphasize important keywords with central relevance, highlighting their pivotal position as focal points within the network. Keywords in each cluster are organized in a horizontal alignment, with the placement starting from the first occurrence on the left and progressing chronologically to the right. This graphical representation assists in understanding the distribution of keywords within clusters, with larger sizes indicating higher group significance. Furthermore, it illustrates the temporal distribution of keywords within each cluster. The keywords have been classified into 11 separate clusters: #0 tissue regeneration, #1 bone tissue engineering, #2 3D printing, #3 additive manufacturing, #4 3D printed scaffold, #5 bone defect, #6 gelatin methacrylate, #7 mechanical properties, #8 angiogenesis and osteogenesis, #9 osteogenic differentiation, #10 calcium phosphates.

By providing clear visualizations of clustering patterns and the temporal distribution of keywords within clusters, this research facilitates collaboration and funding decisions. Stakeholders can identify key research areas, prioritize funding allocations, and foster strategic partnerships to advance vascularized BTE. Overall, the comprehensive analysis presented in this research enhances our understanding of the current state of the field and provides actionable insights for driving future research directions, facilitating collaboration, and maximizing the impact of research efforts in vascularized BTE.

#### 3.8. Related diseases

By gaining insight into the illnesses most closely associated with the utilization of 3D printing scaffolds in vascularized BTE studies, scientists can concentrate their efforts on specific health conditions. This focused strategy holds the promise of hastening the progress of medications and therapies tailored to combat these illnesses, ultimately enhancing the chances of more effective treatments. The Citexs Data Platform detected 308 illnesses from 426 documents, necessitating a minimum of two documents mentioning each illness for consideration. These illnesses that met the criteria were displayed in a heatmap produced with VOSviewer, demonstrating the frequency and connections of illnesses linked to the utilization of 3D printing scaffolds in vascularized BTE studies (Fig. 8A). The most frequently mentioned top five diseases are osteogenesis imperfecta, osteosarcoma, fractures, osteonecrosis, and cartilage diseases. Furthermore, a cluster analysis based on cooccurrence was conducted, with each disease requiring at least two instances, using VOSviewer (Fig. 8B). In this representation, the size of the circles and labels representing nodes is determined by disease occurrence. The thickness of the connections between diseases can be seen through the lines connecting the circles. Unique clusters related to specific disease groupings are identified by different colors.

The research trends of the above-mentioned diseases may be attributed to the following reasons: 1. Clinical Demand and Disease Prevalence: Osteogenesis imperfecta and osteosarcoma are key areas in bone pathology. Osteogenesis imperfecta is a genetic disorder weakening bone strength, while osteosarcoma is a severe bone cancer primarily affecting adolescents. The high mortality and morbidity of these diseases drive research toward effective treatments. Fractures, osteonecrosis, and cartilage diseases are common in orthopaedics. Fractures are widespread, osteonecrosis causes severe pain and disability, and cartilage diseases like osteoarthritis affect millions globally, emphasizing the need for innovative treatments. 2. Technological Advancements: Advances in 3D printing, especially in fabricating complex tissue scaffolds with precise control over shape and architecture, are crucial. These technologies enable custom scaffolds tailored to the complex anatomy of bone and cartilage. The development of novel biomaterials that promote bone and cartilage regeneration, while being biocompatible, biodegradable, and mechanically robust, has driven significant research interest. 3. Research Funding and Investment: Despite their rarity, conditions like osteosarcoma and osteogenesis imperfecta often receive research funding due to their severity and the young age of affected patients, attracting both public and private interest. Common conditions like fractures and osteoarthritis impose a significant economic burden, driving substantial funding for innovative solutions to reduce long-term healthcare costs. 4. Academic and Industrial Collaborations: The field benefits from interdisciplinary research among biologists, material scientists, and engineers. Collaborations between academia and industry are vital for translating research into practical applications and clinical trials. The growing interest from the biomedical device industry in 3D printing technologies fuels research into diseases where these innovations can be effectively applied.

The findings presented in the paragraph have significant implications for both researchers and industry practitioners in the field of the application of 3D printing scaffolds for vascularized BTE. Through the identification of the illnesses that are most commonly linked with the application of 3D printing scaffolds for vascularized BTE studies, scientists can strategically focus their attention on comprehending and tackling particular health issues. This specific strategy holds promise in accelerating the progress of creating medications and treatments customized to effectively manage these medical conditions. For industry practitioners, understanding the landscape of the application of 3D printing scaffolds for vascularized BTE research diseases can inform decision-making processes related to drug development, treatment strategies, and resource allocation. The visualization of disease frequency and relationships through tools like VOSviewer provides valuable insights into the prevalence and interconnections of diseases within the application of 3D printing scaffolds for vascularized BTE domain, aiding both researchers and industry practitioners in navigating this complex field and fostering collaborations to advance medical interventions.

#### 3.9. Challenges & future vistas

Recognized as a critical milestone in BTE, achieving rapid vascularization holds paramount importance. Bone vascularization, unlike direct vascular tissue regeneration, poses unique challenges. Scaffolds must not only meet the requirements for osteogenesis but also possess sufficient mechanical properties. Utilizing 3D printing scaffolds allows for the fabrication of customized structures meeting these criteria, thereby accelerating the establishment of a vascular network. Despite significant advancements in BTE facilitated by the application of 3D printing scaffolds [25,26], there are still numerous challenges that need to be addressed.

- In future investigations, the focus will be on obtaining precise data to produce customized vascularized scaffolds and enhancing the osseointegration capacity of these structures. This will take into account the varied biomechanical characteristics and structural layouts found in different human tissue areas. The complexity of the tissue microenvironment presents challenges to biofabrication printing [49].
- 2) Investigating future directions involves maintaining the sustained release of active molecules while ensuring biosafety and promoting early vascularization for tissue functionalization. The

primary limitation identified is the lack of sustained release behavior throughout the entire tissue repair process. The assessment of the outcomes indicated that the longest sustained release lasted for around four weeks, falling short of the necessary duration for full tissue restoration [50].

- 3) Currently, the focus is on providing functional groups, cells, or bioactive small molecules in creating vascularized 3D printing scaffolds for tissue regeneration. Further research should investigate techniques for preserving the function of bioactive elements altered on or enclosed within scaffold surfaces, guaranteeing continuous delivery [18,51–54].
- 4) The periosteum, a sturdy connective tissue covering the bone surface, plays a critical role in tissue repair by providing blood and nutrients. Furthermore, its rich nerve supply implies that tissue fractures may also result in nerve injury [55,56]. Research on the integration of vascularized additive manufacturing tissue scaffolds with nerve regeneration is anticipated to enhance studies on biomaterials for tissue repair.
- 5) The delicate balance of tissue dynamics includes osteoclasts, which are derived from hematopoietic stem cells and responsible for resorbing dead tissue, along with osteoblasts that originate from mesenchymal stem cell differentiation [57]. Further investigation is necessary to determine a fresh balance between osteoclasts and osteoblasts in the framework of additive fabrication for vascularized bone formation.
- 6) Mineralization of tissues relies on the metabolism of calcium and phosphorus, where calcium ions play a vital role in the coagulation process. In the event of a fracture, these calcium ions are key players in the formation of the initial blood clot and have a substantial impact on the metabolism of both calcium and phosphorus in the aftermath [58–61]. Researching the application of additive manufacturing technology in controlling calcium ions to regulate vascularized osteogenesis represents a promising avenue for further exploration.
- 7) Research has shown the significant involvement of the immune microenvironment in tissue repair. The immune, skeletal, and vascular systems have close associations and exchange numerous cytokines responsible for regulating the immune microenvironment, collectively maintaining tissue microenvironment stability [62–64]. Therefore, combining immune system regulation with vascularized additive manufacturing structures to enhance bone formation could arise as an innovative research avenue moving forward.
- 8) Using 4-dimensional (4D) printing for scaffold preparation shows promise for future applications [25]. 4D printing involves 3D printed objects autonomously and programmatically changing their shapes or functionalities in response to specific external stimuli. These alterations can be pre-planned and "programmable", enabling changes to be executed in a predetermined manner [65]. This advancement allows for the creation of complex structures and makes the resulting constructs dynamic and intelligent. This innovation is of great importance in accelerating the bone repair process and improving bone healing.
- 9) Without a precise design to replicate essential tissue qualities, scaffolds may not fully realize their potential for cell adhesion and tissue regeneration. Various 3D design strategies, including those utilizing scaffold design libraries and artificial intelligence (AI), can be employed to tackle this challenge [66]. Integrating AI into the 3D printing process enables anticipation, adjustment, and autonomous control of parameters, thereby reducing the risk of errors. Furthermore, the incorporation of AI into 3D printing facilitates the customization of patient-specific scaffolds to meet diverse requirements, providing feedback and sufficient data for reproducibility, with potential for future

improvement. These printed scaffolds can serve as an alternative to preclinical animal test models, reducing costs and avoiding immunological interference. Ultimately, continued advancements in 3D printing are expected to propel the field of bone regeneration to unprecedented heights, fueled by ongoing dedication and research efforts.

#### 3.10. Strengths & limitations

In contrast to previous studies heavily relying on narrative reviews, the use of scientometric tools in this study provided a more comprehensive understanding of research focal areas and trends across various aspects. This study is noteworthy as the first to perform scientometric analysis in the past decade, mapping and describing the landscape of knowledge regarding the application of 3D printing scaffolds for vascularized BTE. It acts as an in-depth and impartial guide for forthcoming progress, despite the certain restrictions that are bound to be present.

The limitations encountered in this study were numerous. Firstly, due to CiteSpace's constraints, only publications from WoSCC were gathered, resulting in an unavoidable selection bias [67]. Secondly, relying on citation count as a gauge of a paper's influence is susceptible to numerous interfering variables, which could potentially impact its precision [68]. Thirdly, the extensive number of papers might have compromised the study's credibility by limiting the feasibility of conducting a comprehensive analysis of each paper and its subfields. Fourthly, as demonstrated by previous scientometric studies, scientometric techniques heavily rely on natural language processing, which may introduce bias [69–72]. Fifthly, although restricting the study to English texts may introduce publication bias [73], it does not significantly undermine the global relevance of our conclusions. The global dominance of English-language research ensures that our study captures the main trends and key contributors in the field. Future research incorporating multilingual databases may provide more inclusive insights. We suggest that future research expand its scope by utilizing additional databases that index non-English literature (e.g., China National Knowledge Infrastructure and SinoMed) to evaluate whether regional or language-specific trends differ from those in English-language studies. Lastly, because of incomplete literature collection, recent publications and certain key terms could have been overlooked and omitted from the data analysis in the literature search phase.

# 4. Conclusion

Using scientometric methodologies, this ongoing investigation analyzes trends in the biomedical field concerning the use of 3D printing scaffolds for vascularized BTE over the past decade. The main findings are as follows: 1) Scientometric evaluations have revealed significant advancements in the utilization of 3D printing scaffolds for vascularized BTE, highlighting key contributing countries, institutions, researchers, and core research topics. 2) Exploring co-citations and keywords has highlighted influential studies, emerging patterns, and critical research areas within the domain of 3D printing scaffolds for vascularized BTE, providing guidance for future research directions. 3) Discussions have focused on the significant challenges associated with the use of 3D printing scaffolds for vascularized BTE. Overcoming these challenges enables 3D printing scaffolds to realize their full potential in vascularized BTE. These breakthroughs are crucial for enhancing the scientific community's ability to identify and address existing challenges, as well as for fostering the development of innovative concepts. Comprehensive knowledge of the mechanisms that facilitate bone healing allows for the creation of effective designs and procedures for 3D printing in order to generate functional, clinically relevant vascularized BTE scaffolds. Ultimately, the field of 3D bioprinting, which integrates disciplines such as developmental biology, tissue engineering, regenerative medicine, and materials science, should endeavor to expedite its research development objectives, achieve clinical implementation expeditiously, and deliver greater benefits to individuals in need.

# Credit authorship contribution statement

SYC: Conceptualisation, data analysis, and manuscript writing. YHW: Data curation, investigation, and manuscript writing. YHY and DLW: Methodology, software, reviewing and editing. AX, JY, and HZ: Project administration, supervision, and funding acquisition.

#### Data availability statement

The corresponding authors are available to grant access to the datasets utilized or analyzed in this study upon reasonable request.

# **Ethics** approval

Since the data used in this study were obtained from publicly accessible sources and did not involve any interaction with human subjects, ethical approval or informed consent was considered unnecessary.

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# **Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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# Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2024.10.013.

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