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Review article

# Thematic trend mapping and hotspot analysis in bone marrow aspirate concentrate therapy: A scientometric literature analysis and advances in osteoarthritis

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ABSTRACT

Bone marrow aspirate concentrate (BMAC) therapy has been spotlighted as a promising regenerative tool with its abundant source of mesenchymal stromal cells (MSCs) and growth factors. The spectrum of the utility of BMAC therapy has been expanding day by day to harness the potential for varied therapeutic purposes. In the due course of its evolution, it is often essential to have a comprehensive summary of progress to have a greater understanding and refine our future directives. With technological developments such as data mining, graphic drawing and information analytics combined with computational statistics, visualization of scientific metrology has become a reality. With this newer perspective, we intend to use scientometric tools including text mining, cocitation analysis, keyword analysis and cluster network analysis to perform thematic trend mapping and hotspot analysis of the literature on BMAC therapy and evaluate its progress in the management of osteoarthritis.



## Introduction

Bone marrow aspirate concentrate (BMAC) therapy has been spotlighted as a promising regenerative tool with its abundant source of mesenchymal stromal cells (MSCs) and growth factors [1,2]. The spectrum of the utility of BMAC therapy has been expanding day by day to harness the potential for varied therapeutic purposes ranging from small cartilage defects to erosive arthritic diseases [3]. This therapy has been recently approved by the U.S. Food and Drug Administration (FDA) for procedures of standalone homologous use by following minimally manipulative methods on its harvest, processing and delivery [4]. With continued global research analyzing the efficacy and safety of BMAC therapy for clinical utility, it is often essential to have a comprehensive summary of progress to have a greater understanding and refine our future directives. Apart from osteoarthritis, MSCs derived from the BMAC have also been tried for various regenerative modalities of use in plastic surgeries, aesthetic medicine, cardiovascular diseases, endocrine and nervous system diseases, cell transplantation, and the repair of damaged musculoskeletal tissues [5].

Osteoarthritis (OA) is a degenerative joint disease with destruction of cartilage, alteration in the microarchitecture of the subchondral bone, and osteophyte formation resulting in significant morbidity [6]. Articular cartilage has limited healing potential owing to the lack of vascularity and limited stem cells in its vicinity to aid in the regenerative process [7,8]. With the focus on cartilage conservation, various surgical strategies from microfracture to autologous osteochondral transplantation are being tried in the management of OA [9–11]. Of all the methods being tried, BMAC therapy has been considered as relatively promising, with its abundant regenerative potential. To streamline our research in BMAC therapy for OA and target the key attributes to harness its full potential, a comprehensive

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summary of its research progress is mandatory. With technological developments such as data mining and information analytics combined with computational statistics, visualization of scientific metrology has become a reality.

Scientometrics is a quantitative method of analyzing evolutionary processes through various parameters such as citation metrics, keywords and author networks [12]. Scientometrics can visualize this panorama of information through knowledge maps to explore hotspots in research [13]. It has been widely used in other fields such as public health [14,15], artificial intelligence [16] and education research. With this newer perspective, we intend to use scientometric tools including text mining, cocitation analysis, keyword analysis and cluster network analysis to perform thematic trend mapping and hotspot analysis of the literature on BMAC therapy and evaluate its progress in the management of osteoarthritis.

## Methodology

### *Data source*

We used the Web of Science (WoS) as the source for data retrieval. We searched core collection databases included in WoS such as SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, and IC, with a detailed data retrieval strategy as given in Figure 1. We did not use any time limit to the search query. Preliminary data was standardized with deduplication and merge functions in CiteSpace. Two authors performed an independent review of the search results for their relevance to be included in the analysis. The literature search date was May 27, 2021.

### *Data visualization and analysis*

We used CiteSpace (5.7.R5) for scientometric and visualization analysis [17]. CiteSpace was used to visualize the structure, regularity and distribution of research domains in BMAC therapy for OA and analyze the article cocitation data to mine the knowledge clustering and citation space distribution. We also analyzed the co-occurrence between the additional research units such as cooperation among various authors, institutions and countries in the field of BMAC therapy. Consolidating the results of the analysis, we built a comprehensive knowledge map elaborating on the emerging research trend with the potential research domains in BMAC therapy, with a special focus on OA [18].

The scientometric analysis results are depicted as knowledge maps with the key parameters detailed as follows. The research variables such as authors, institutions, country, keywords are depicted as nodes, and the size of the nodes in the knowledge graphs indicates their frequency, while the connection between them indicates that they are related [19]. The scientometric analysis uses certain parameters for evaluation. Burst is a measure of the frequency of citations acquired by an article in a period that indicates the impact and influence of the article on the subject based on the burst value and duration of burst respectively [17].

## Results

### *Field activity analysis*

We recovered 1281 studies from the WoS core collection database following the search strategy given in Fig. 1. The results were independently reviewed by two authors for relevance, to yield a final total of 1064 research works published on BMAC therapy, consisting of 770 articles, 381 meeting abstracts, 58 reviews and 28 proceeding papers. Figure 2 shows the research output published every year on BMAC in the last three decades. There is an overall rising trend in the scientific production involving BMAC therapy. It is also noted that there is a proportionate growing trend noted in all types of research documentation such as original articles, reviews, proceedings papers and meeting abstracts.

### *Global contribution*

The top contribution in BMAC therapy was from China (404 publications) followed by the United States (321 publications), Germany (79 publications), England (56 publications), and Japan (50 publications). The global cocitation network map is shown in Fig. 3. The size of the circles indicates the total cocited publications, and the strength of the lines connecting them shows their degree of collaboration. China and the United States have made a significant contribution in the field, accounting for 68.13% (n = 725) of the global output. Countries such as the United States, Germany, England and Italy with high citation frequency burst were highlighted in pink circles in Figure 3, and they hold the current influence on BMAC therapy in the research front.

### *Institutional contribution*

Among the top 10 institutions with the most publications on BMAC therapy, five were from China, namely Shanghai Jiao Tong University (37 publications), Sun Yat-Sen University (22 publications), Zhejiang University (22 publications), Air Force Military Medical University (19 publications) and Peking University (19 publications). Figure 4 shows the collaborative network among the institutions contributing to the field. Of the Chinese universities, Shanghai Jiao Tong University, Sun Yat-Sen University and Nanjing Med University were the top contributors, with high citation bursts as shown in Figure 4, and considered as pivotal points of research in BMAC therapy.

### *Journal contribution*

More than the number of articles the journal publishes, the number of literature citations of the published article can reflect better on the importance and influence of a journal in the field. Hence, we used CiteSpace to analyze the list of journals where the retrieved results were published. The journal citation network had 672 nodes and 5674 links among them. The top five journals that published highly referenced articles on BMAC therapy are *Blood, Stem Cell Research & Therapy, Cytotherapy, Circulation*, and *Bone Marrow Transplantation.* The journal *Blood* (impact factor 17.794) published 41 research articles on BMAC therapy; *Stem Cell Research & Therapy* (impact factor 5.554) published 29 articles and *Cytotherapy* (impact factor 4.218) published 25 articles on the subject. Despite publishing maximum articles, the journal citation network shows *Stem Cells, PLOS One, Science, Proceedings of the National Academy of Science USA*, and *Nature* to be the top five journals with high citation bursts on the subject, as shown in Figure 5.

### *Landmark articles and authors*

The author with the highest number of publications on BMAC therapy was Steinhoff Gustav from Rostock University, Germany, with 1557 citations. Also, the most cited work on the subject was from his co-author Christof Stammtenger, who is also from Rostock University, Germany. Their team worked predominantly on the application of BMAC therapy for myocardial regeneration following ischemia. The list of top 10 articles based on their cumulative citation is listed in Table 1.

We further constructed a reference co-citation network of the selected articles as shown in Figure 6A. The research article by Pittenger et al. [20] was the key node in the network analyzed. His work was mainly on the biology of stem cells and their applications. We also made an in-depth analysis of his article with the highest citation rate as shown in Figure 6B. We then made a cluster analysis of the

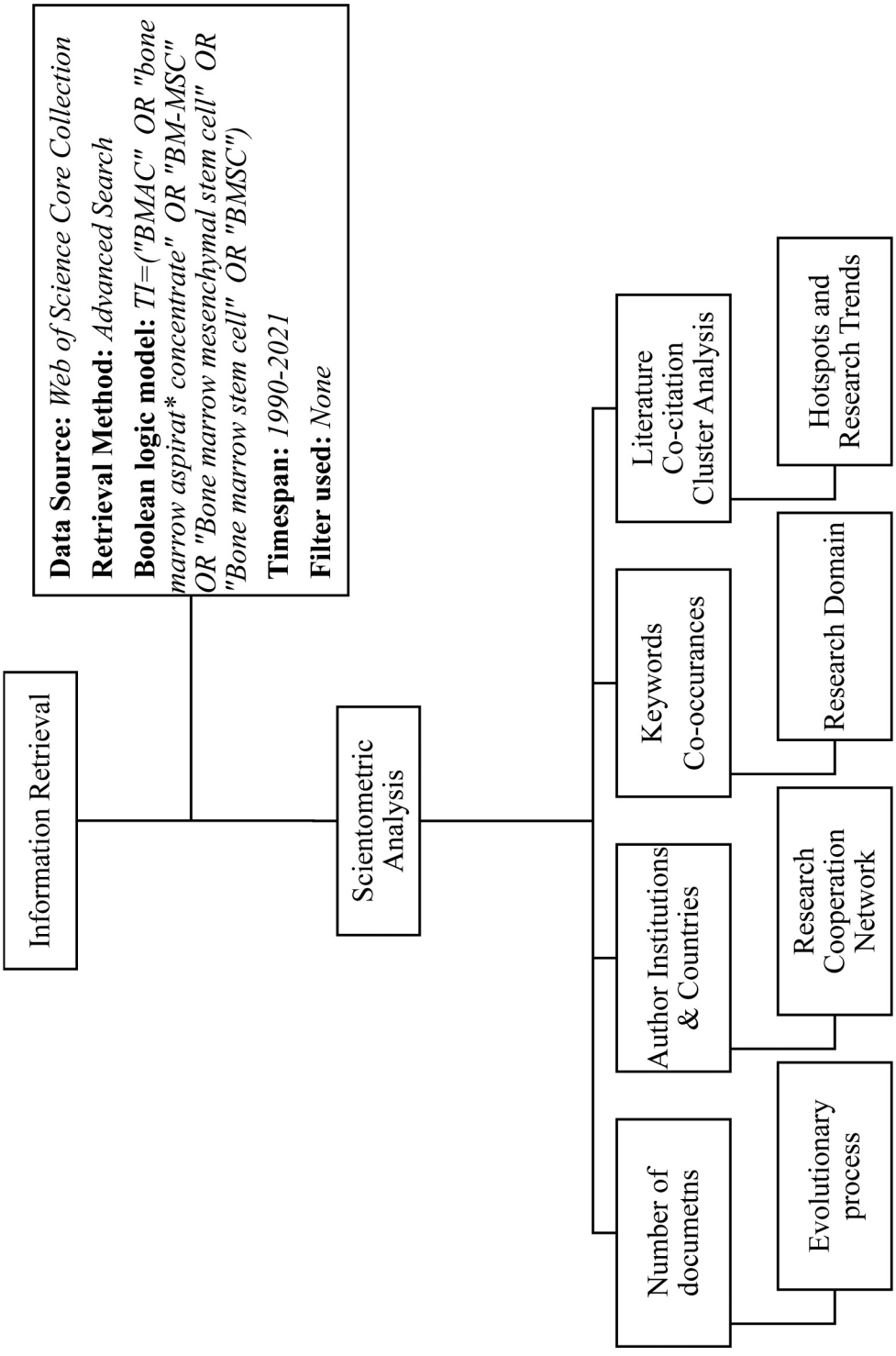


**Figure 1**. Scientometric analysis framework.

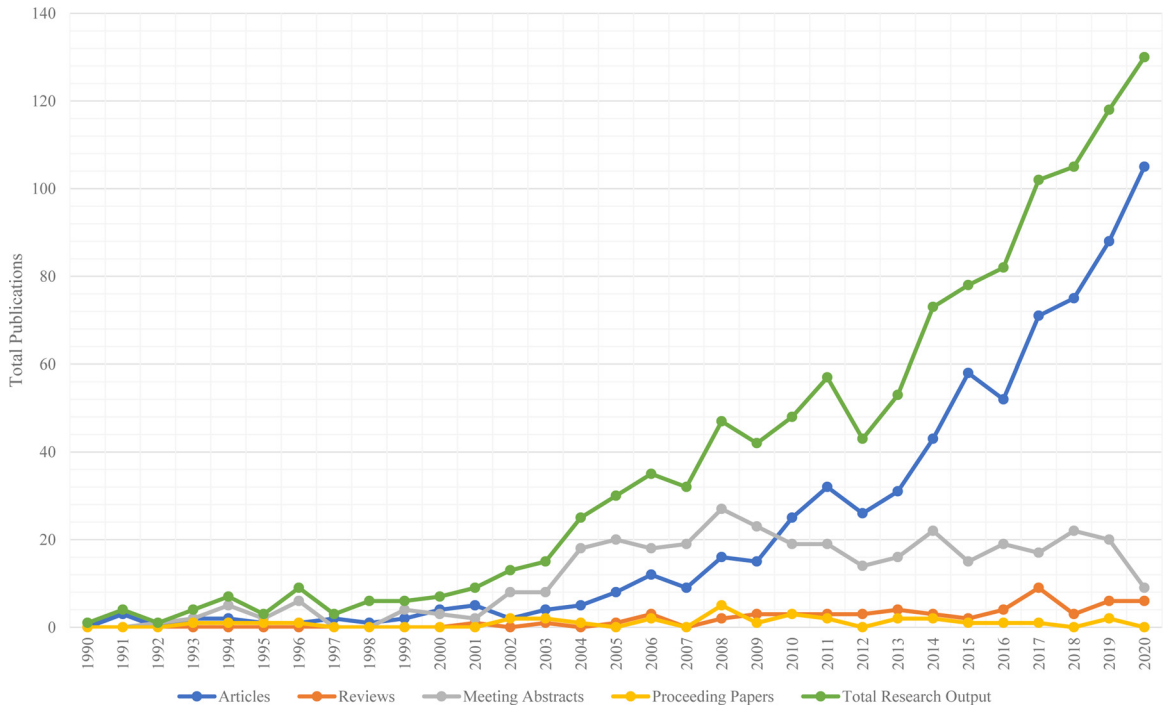


**Figure 2.** Scientific research output on BMAC therapy from 1990 to 2020.

cocitation network and categorized the nodes into 10 distinctive clusters. They are labeled by extricating terms from the titles of the cited publications as shown in Figure 6C. On analyzing the evolutionary trend of the article clusters, it is noted that the initial research on BMAC therapy was mainly on its utility for myocardial infarction, stroke, and their scaffolds, whereas the current research in BMAC therapy is focused on clinical research, osteoarthritis knee and exosomes.

We also used the burst detection function of CiteSpace to obtain the research frontiers. We presented the top 25 citation burst noted in the referencing pattern in BMAC therapy as shown in Figure 6D and found a gradual change in the citation trend of the articles

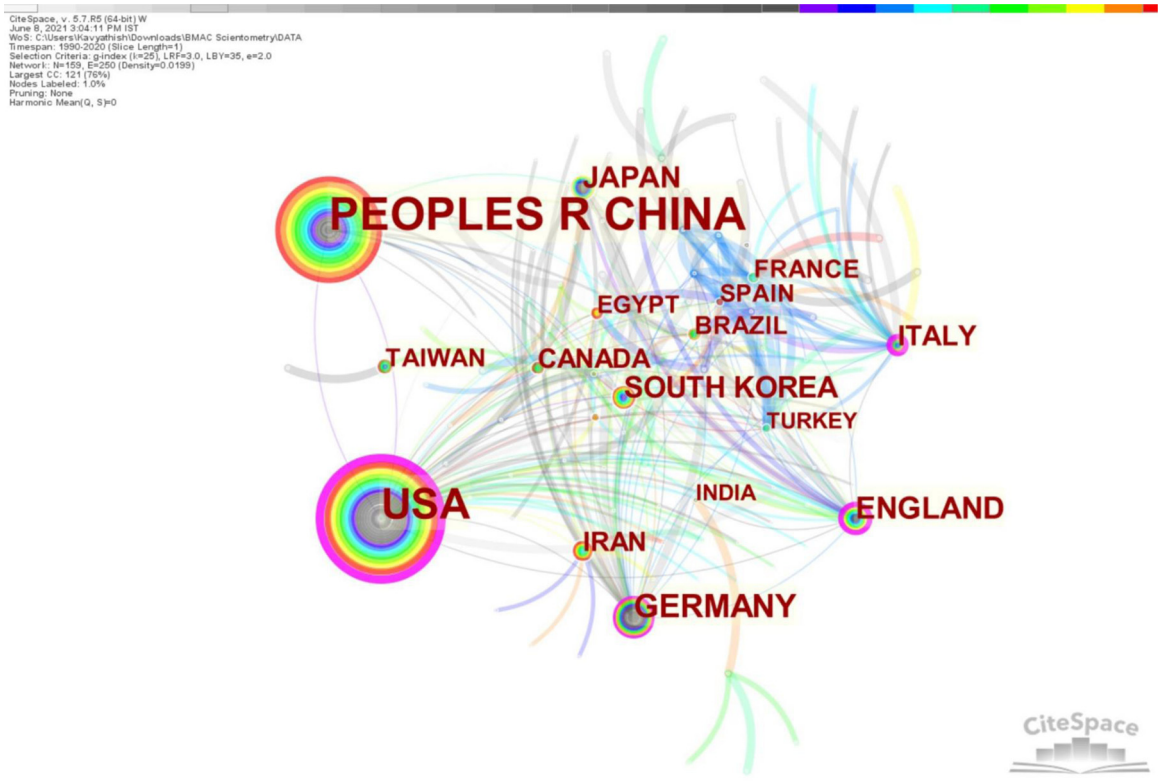


**Figure 3.** Global cocitation network on the contribution of individual countries on BMAC therapy.


**Figure 4.** Global cocitation network on the contribution of institutions on BMAC therapy.

included in the analysis. It is observed that the frontiers of current research in BMAC therapy revolve around its clinical applications such as osteoarthritis and osteonecrosis of the femoral head, and its advanced method of delivery, such as bone marrow mesenchymal stem cell–derived exosomes.

*Keyword co-occurrence analysis*

Keywords represent the theme of the research article, and analyzing their co-occurrence helps us to systematically understand the relationship among the research themes on the subject under study.

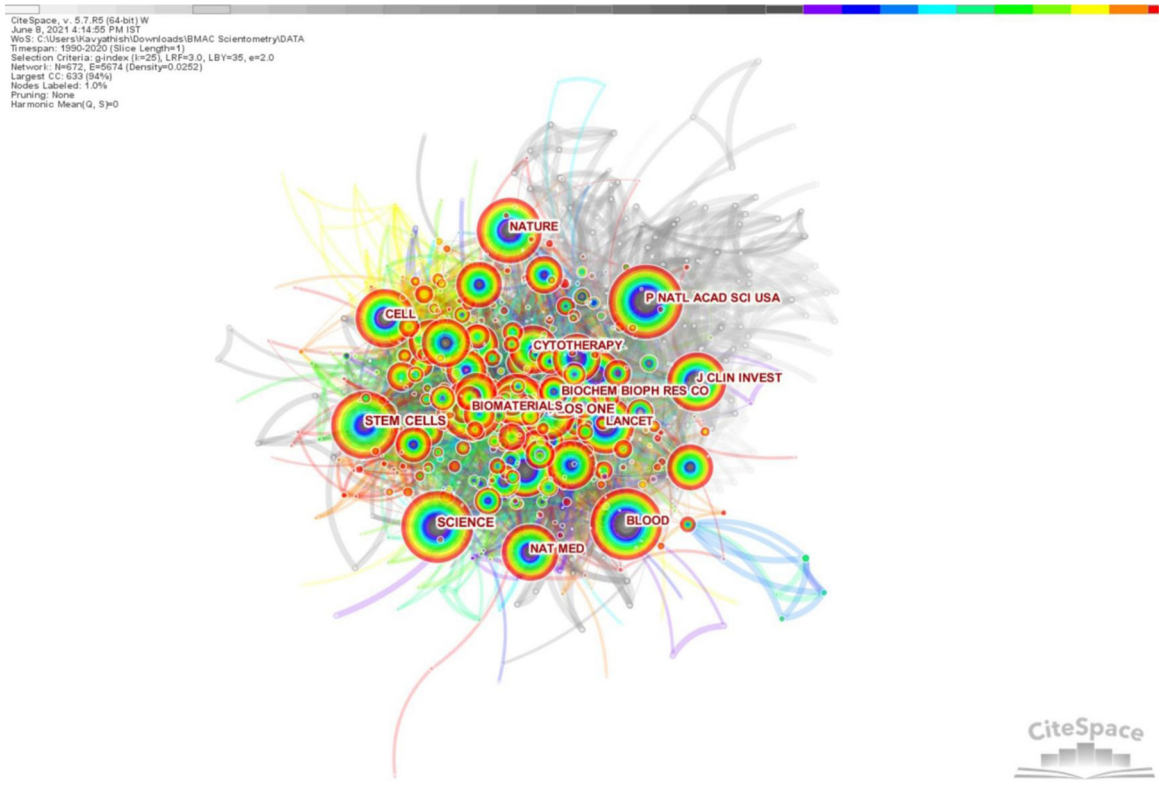


**Figure 5.** Journal cocitation network of research articles on BMAC therapy.

**Table 1**
Top 10 highly cited articles on BMAC therapy.

| Rank | Author | Year | Title | Journal | Total citations |
|---|---|---|---|---|---|
| 1 | Stamm, C | 2003 | Autologous bone-marrow stem-cell transplantation for myocardial regeneration | *Lancet* | 1124 |
| 2 | Chen, SL | 2004 | Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction | *American Journal of Cardiology* | 986 |
| 3 | Zhu, YX | 2008 | Adipose-derived stem cell: A better stem cell than BMSC | *Cell Biochemistry and Function* | 469 |
| 4 | Ehninger, A | 2011 | The bone marrow stem cell niche grows up: Mesenchymal stem cells and macrophages move in | *Journal of Experimental Medicine* | 386 |
| 5 | Hu, H | 2012 | Antibacterial activity and increased bone marrow stem cell functions of Zn-incorporated $TiO_2$ coatings on titanium | *Acta Biomaterialia* | 318 |
| 6 | Powles, R | 2000 | Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: A randomised trial | *Lancet* | 293 |
| 7 | Haider, HK | 2008 | IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1 alpha/CXCR4 signaling to promote myocardial repair | *Circulation Research* | 277 |
| 8 | Peng, L | 2011 | Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: Short-term and long-term outcomes | *Hepatology* | 256 |
| 9 | Yamout, B | 2010 | Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: A pilot study | *Journal of Neuroimmunology* | 220 |
| 10 | Mohamadnejad, M | 2007 | Phase 1 trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis | *Archives of Iranian Medicine* | 251 |

We used the Keywords Plus feature of the WoS, which gives the author keywords along with the keywords generated from the titles of the cited articles. We extracted a total of 663 keywords from the included studies. On co-occurrence analysis, the top five keywords were “mesenchymal stem cell” (n = 215), “differentiation” (n = 146), “stromal cell” (n = 140), “transplantation” (n = 120), and “expression” (n = 113) as shown in Figure 7A. We clustered the keywords to identify their relationship based on the research theme under which they are used, as shown in Figure 7B.

We used the CiteSpace burst detection functionality to ascertain the transition of keywords with high citation bursts from 1990 to 2020 as shown in Fig. 7C. None of the keywords had a sudden change in the number of citations in recent years. The basic science keywords such as “colony-stimulating factor”, “progenitor cell”, “bone marrow stromal cell” had high citation burst in 1990-2000. While in the last two decades, extensive research is directed towards the applied aspects of the therapy such as “myocardial infarction”, “transplantation”, “spinal cord injury”, “nerve regeneration”, “osteogenesis”, “knee”, “femoral head”, etc., The current research hotspot in BMAC therapy revolves around its role in osteogenesis and chondrogenesis as a regenerative remedy for osteonecrosis of the femoral head and osteoarthritis knee respectively. This transition in the research trend is better depicted by the timeline analysis of the research keywords as shown in Figure 7D.

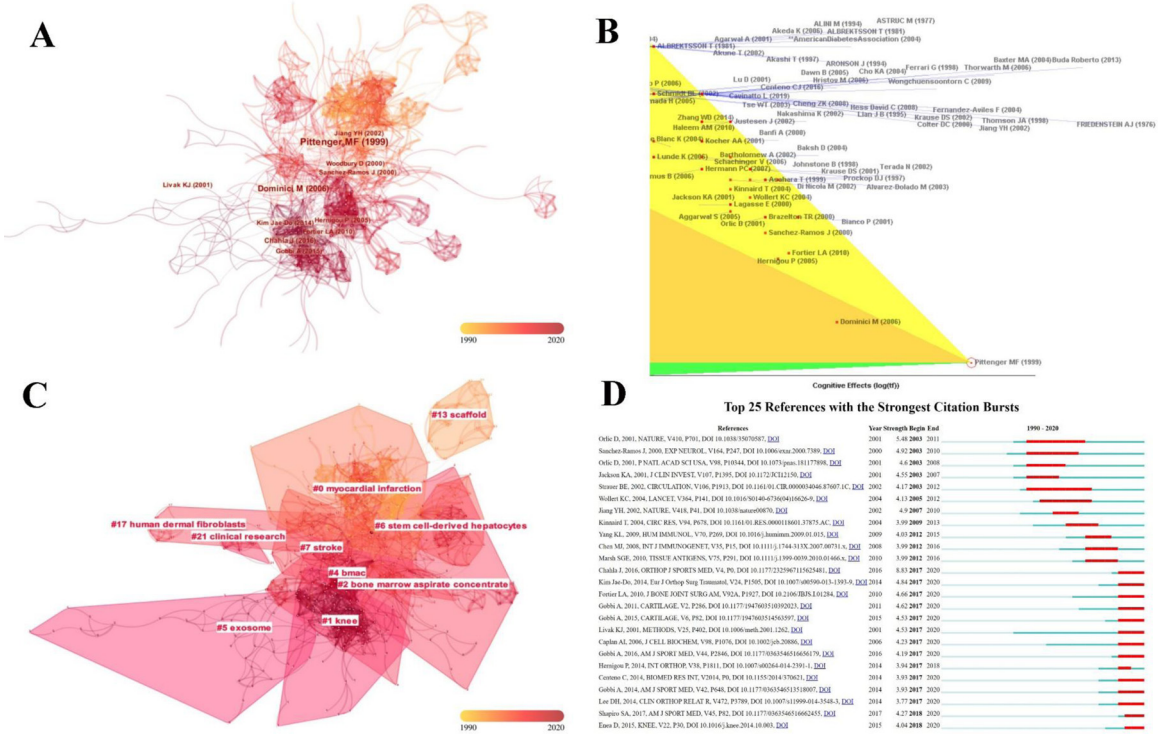


**Figure 6.** Reference mapping of studies on BMAC therapy. (A) Cocitation network of references on BMAC therapy. (B) The article with highest citation was processed for in-depth analysis. (C) Cluster analysis of the cocitation network of references on BMAC therapy. (D) List of top 25 references with the strongest citation bursts using CiteSpace burst detection functionality along with the time period of their burstness.

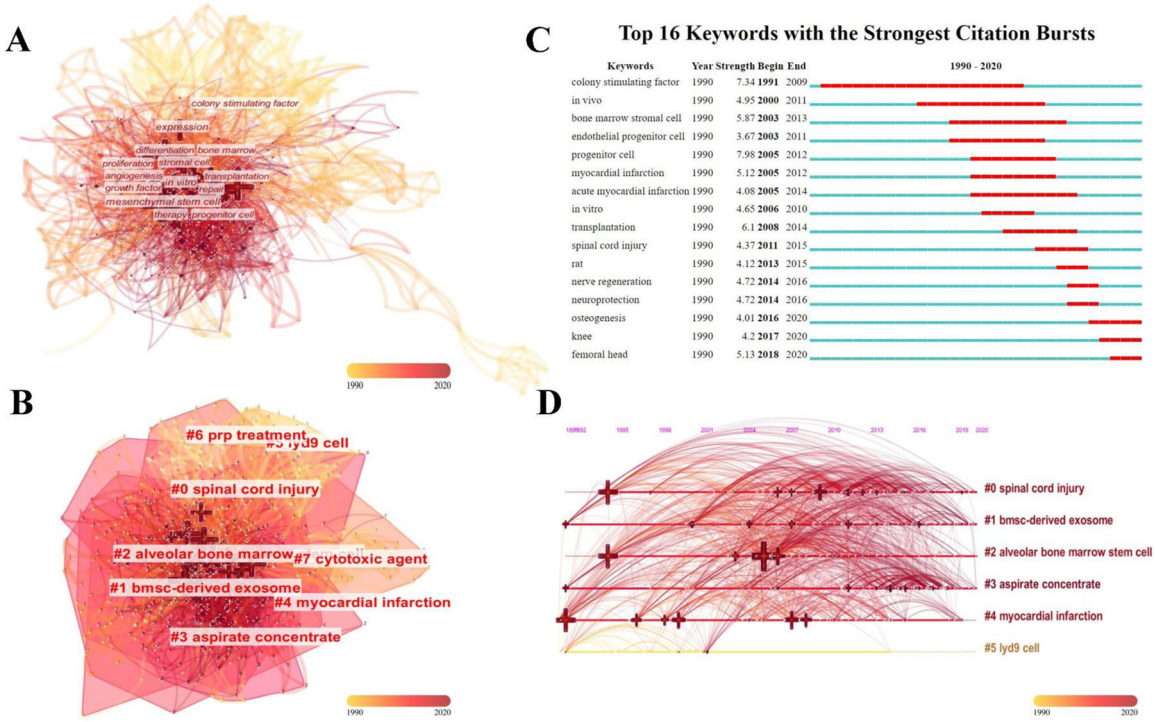


**Figure 7.** Keyword mapping of studies on BMAC therapy. (A) Cocitation network of keywords on BMAC therapy. (B) Cluster analysis of the cocitation network of keywords on BMAC therapy. (C) Top 16 keywords with the strongest citation bursts using CiteSpace burst detection functionality along with the time period of their burstness. (D) Timeline view of the research trend transition from *in vitro* studies using cell lines during 1990–2000 to clinical studies for practical application in spinal cord injury and myocardial infarction in the late 2010–2020.

*BMAC therapy for osteoarthritis*

Concerning the utility of BMAC therapy for OA, we made a subset analysis of the articles that dealt with the application of the therapy toward cartilage regeneration in the management of OA. We obtained 50 articles among the 1064 that dealt with the use of BMAC therapy in OA. The list of top 10 articles based on their cumulative citation is listed in Table 2. The placebo-controlled, single-blinded clinical trial by Shapiro et al. [21] that established the safety of the therapy was the top-cited research work on the field. On analyzing the cocitation network of references of the included studies, it was noted that the systematic review of outcomes on the use of BMAC therapy for chondral injuries and osteoarthritis of knee by Chahla et al. [3] was the most cocited research work, as shown in Figure 8A. Using the bust detection functionality of CiteSpace, we probed into the key articles that had citation burst across the timeline, as shown in Figure 8B, and noted that the key articles on trophic mediators involved in the immunomodulation of inflammation in osteoarthritis [22], and preliminary pilot studies to establish the efficacy and safety of BMAC therapy for OA knee [23,24], had high citation frequency bursts in recent years.

We further categorized the network of the cocited articles into seven distinctive clusters as shown in Figure 8C and analyzed the transition in the trend of research on the subject. It is noted from Figure 8D that the trend of research on BMAC therapy for OA transitioned from analyzing the biology of the mesenchymal stem cells and

**Table 2**
Top 10 highly cited articles on BMAC therapy for osteoarthritis.

| Rank | Author | Year | Title | Journal | Total Citations |
|---|---|---|---|---|---|
| 1 | Shapiro, SA | 2017 | A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis | *American Journal of Sports Medicine* | 101 |
| 2 | Lei, M | 2008 | Resveratrol protects bone marrow mesenchymal stem cell derived chondrocytes cultured on chitosan-gelatin scaffolds from the inhibitory effect of interleukin-1 beta | *Acta Pharmacologica Sinica* | 37 |
| 3 | Oladeji, LO | 2017 | Effects of autogenous bone marrow aspirate concentrate on radiographic integration of femoral condylar osteochondral allografts | *American Journal of Sports Medicine* | 36 |
| 4 | Chahla, J | 2017 | Bone marrow aspirate concentrate harvesting and processing technique | *Arthroscopy Techniques* | 34 |
| 5 | Madry, H | 2017 | Bone marrow aspirate concentrate-enhanced marrow stimulation of chondral defects | *Stem Cells International* | 26 |
| 6 | Sun, Y | 2019 | 3D-bioprinting a genetically inspired cartilage scaffold with GDF5-conjugated BMSC-laden hydrogel and polymer for cartilage repair | *Theranostics* | 25 |
| 7 | Mahboudi, H | 2018 | Enhanced chondrogenesis of human bone marrow mesenchymal stem cell (BMSC) on nanofiber-based polyethersulfone (PES) scaffold | *Gene* | 24 |
| 8 | Gobbi, A | 2019 | Long-term clinical outcomes of one-stage cartilage repair in the knee with hyaluronic acid-based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate | *American Journal of Sports Medicine* | 21 |
| 9 | Kraeutler, MJ | 2017 | Biologic options for articular cartilage wear (platelet-rich plasma, stem cells, bone marrow aspirate concentrate) | *Clinics in Sports Medicine* | 20 |
| 10 | Mautner, K | 2019 | Functional outcomes following microfragmented adipose tissue versus bone marrow aspirate concentrate injections for symptomatic knee osteoarthritis | *Stem Cells Translational Medicine* | 18 |

**Table 3**
List of completed clinical trials using BMAC therapy in osteoarthritis.

| Sl. No | NCT Number | Title | Conditions | Interventions | Phases | Locations |
|---|---|---|---|---|---|---|
| 1 | NCT02123368 | Treatment of knee osteoarthritis by intra-articular injection of bone marrow mesenchymal stem cells | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 1, 2 | Spain |
| 2 | NCT01485198 | Autologous stem cells in osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 1 | Mexico |
| 3 | NCT01183728 | Treatment of knee osteoarthritis with autologous mesenchymal stem cells | osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 1, 2 | Spain |
| 4 | NCT01895413 | Autologous bone marrow mesenchymal stem cells transplantation for articular cartilage defects repair | Osteoarthritis | Bone marrow mesenchymal stem cells, autologous | 1, 2 | Brazil |
| 5 | NCT00850187 | Autologous transplantation of mesenchymal stem cells (MSCs) and scaffold in full-thickness articular cartilage | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 1 | Iran |
| 6 | NCT01038596 | Mesenchymal stromal cells and osteoarthritis | Osteoarthritis | Bone marrow concentrate injection | NA | Germany |
| 7 | NCT01931007 | Use of autologous bone marrow aspirate concentrate in painful knee osteoarthritis | Osteoarthritis, knee | Bone marrow concentrate injection | 1 | USA |
| 8 | NCT01499056 | Mesenchymal stem cell transplantation in osteoarthritis of hip joint | Osteoarthritis, hip | Bone marrow concentrate injection | 1 | Iran |
| 9 | NCT01586312 | Treatment of knee osteoarthritis with allogenic mesenchymal stem cells | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, allogeneic | 1, 2 | Spain |
| 10 | NCT01601951 | Outcomes data of bone marrow stem cells to treat hip and knee osteoarthritis | Osteoarthritis, hip and knee | Bone marrow mesenchymal stem cells, autologous | NA | USA |
| 11 | NCT01873625 | Transplantation of bone marrow derived mesenchymal stem cells in affected knee osteoarthritis by rheumatoid arthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 2, 3 | Iran |
| 12 | NCT02958267 | Investigation of mesenchymal stem cell therapy for the treatment of osteoarthritis of the knee | Osteoarthritis, knee | Bone marrow concentrate injection, PRP injection | 2 | USA |
| 13 | NCT02118519 | Mesenchymal stem cells in knee cartilage injuries | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 2 | Jordan |
| 14 | NCT01504464 | The effects of intra-articular injection of mesenchymal stem cells in knee joint osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 2 | Iran |
| 15 | NCT01879046 | Regenerative medicine of articular cartilage: Characterization and comparison of chondrogenic potential and immunomodulatory adult mesenchymal stem cells | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | NA | France |
| 16 | NCT03289416 | Bone marrow aspirate compared to platelet rich plasma for treating knee osteoarthritis | Osteoarthritis, knee | Bone marrow concentrate injection, PRP injection | 4 | USA |
| 17 | NCT01436058 | Side effects of autologous mesenchymal stem cell transplantation in ankle joint osteoarthritis | Osteoarthritis, ankle | Bone marrow mesenchymal stem cells, autologous | 1 | Iran |
| 18 | NCT01227694 | Adult stem cell therapy for repairing articular cartilage in gonarthrosis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 1, 2 | Spain |
| 19 | NCT03130335 | Intra-articular autologous bone marrow aspirate injection for knee osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | NA | USA |
| 20 | NCT02351011 | Human autologous MSCs for the treatment of mid to late stage knee OA | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | 1, 2 | Canada |
| 21 | NCT04326985 | RCT mesenchymal stem cells versus hyaluronic acid in Oa knee | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | Early 1 | Hong Kong |
| 22 | NCT02034032 | Regenexx SD versus exercise therapy for treatment of knee osteoarthritis with historical comparison to TKA | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, autologous | NA | USA |

the functional outcome upon their use in the early decades of its evolution to the development of newer joint-preserving techniques for optimization of the functional capabilities of the therapy and exploring a better understanding of the pathogenesis of the disease.

## Discussion

In this study, we made a systematic bibliometric analysis of literature on BMAC therapy through 2020. The bibliometric analysis could help fresh researchers to understand the evolution of the therapy and its recent trends in the topic intuitively and comprehensively. With advanced scientometric techniques, it is possible to analyze the milestones achieved and identify the current research hotspots.

With the advancements in the field of regenerative therapy, the treatment spectrum of modalities such as BMAC therapy is expanding day by day. Based on the research output analyzed, a rising trend is noted year by year in the published literature on BMAC therapy, as shown in Figure 2. We also noted a proportionate increase in the number of proceedings papers and meeting abstracts, which shows that there is an increase in the number of international academic activities on BMAC therapy. Moreover, the top journals publishing the research on BMAC therapy have high impact factors, which show that the topic has widespread attention, and further research will also be published in the future on its application prospects.

Regarding the contribution of various countries toward the total number of publications on BMAC therapy and the citations acquired, China made a significant contribution to the field and ranked first. Regarding the cocitation network, the United States also had a predominant influence on the subject. China has made a paramount contribution in this field, with around six of the top 10 high research output institutions located there, producing four of the top 10 highly cited research works on the subject, as shown in Table 1. From a

timeline perspective, there is a progressive increase in the research output from the contributing countries without any drastic change in the citation pattern over the years across the various keywords and references analyzed, as shown in Figures 6 and 7. This shows that the research on the subject is mostly a completion or supplementation of previous breakthroughs rather than being original creative discoveries and techniques on the subject. With the expansion of this therapy to varied clinical scenarios, there is an impeding innovative breakthrough on the subject to cater to the challenges ahead.

On considering the authors' contributions, Gustav Steinhoff (Rostock University, Germany) is the most productive author, with 17 publications and a cumulative 1557 citations, accounting for a

**Table 4**
List of ongoing clinical trials using BMAC therapy in osteoarthritis.

| Sl. No | NCT Number | Title | Conditions | Interventions | Phases | Locations |
|---|---|---|---|---|---|---|
| 1 | NCT04351932 | Bone marrow versus adipose autologous mesenchymal stem cells for the treatment of knee osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, adipose mesenchymal stem cells | 3 | Ecuador |
| 2 | NCT04453111 | Efficacy of bone-marrow-derived and placenta-derived multipotent mesenchymal stem / stromal cells for osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, placenta derived mesenchymal stem cells | 1, 2 | Ukraine |
| 3 | NCT03014037 | Comparing mesenchymal stem cell counts in unilateral vs. bilateral posterior superior iliac spine bone marrow aspiration | Osteoarthritis | Bone marrow mesenchymal stem cells | NA | USA |
| 4 | NCT03579407 | Open ended trocar vs. fenestrated blunt trocar in bone marrow aspirate for osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | NA | USA |
| 5 | NCT03818737 | Multicenter Trial of Stem Cell Therapy for Osteoarthritis (MILES) | Osteoarthritis | Bone marrow concentrate injection, adipose-derived stromal vascular fraction, umbilical cord tissue | 3 | USA |
| 6 | NCT03067870 | Transplantation of autologous bone marrow derived stem cells in patients with rheumatoid arthritis | Osteoarthritis, knee, hip; rheumatoid arthritis | Bone marrow mesenchymal stem cells | 1 | Jordan |
| 7 | NCT04815902 | Use of senolytic and anti-fibrotic agents to improve the beneficial effect of bone marrow stem cells for osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, fisetin, losartan | 1, 2 | USA |
| 8 | NCT03984461 | The combined use of PRP with lipoaspirate and/or bone marrow aspirate in osteoarthritis | Osteoarthritis | Bone marrow mesenchymal stem cells, adipose mesenchymal stem cells, platelet-rich plasma | 2 | Canada |
| 9 | NCT04240873 | Clinical study of intra articular injection of Catholic MASTER Cell (bone marrow derived mesenchymal stem cell) in knee osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | 1, 2 | Republic of Korea |
| 10 | NCT03969680 | Mesenchymal stem cell transplantation for osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, platelet-rich plasma | NA | China |
| 11 | NCT03477942 | Impact of mesenchymal stem cells in knee osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | 1 | USA |
| 12 | NCT04205656 | Prospective evaluation of PRP and BMC treatment to accelerate healing after ACL reconstruction | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, platelet-rich plasma | 1, 2 | USA |
| 13 | NCT04595890 | Knee injections for the clinical management of knee osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | 2 | USA |
| 14 | NCT04716803 | Bone marrow aspirate concentrate (BMAC) treatment for knee osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells, platelet-rich plasma | NA | USA |
| 15 | NCT02582489 | Autologous bone marrow aspirate concentrate in patients undergoing meniscectomy | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | NA | USA |
| 16 | NCT04310852 | Knee osteoarthritis treatment with percutaneous injections of autologous bone marrow concentrate | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | 2 | Italy |
| 17 | NCT04826224 | CAM procedure with BMAC for shoulder OA | Osteoarthritis, shoulder | Bone marrow mesenchymal stem cells | 1 | USA |
| 18 | NCT03790189 | Subchondral and intra-articular application of bone marrow concentrate for knee unicompartmental OA | osteoarthritis, knee | Bone marrow mesenchymal stem cells | NA | Italy |
| 19 | NCT03410355 | Bone marrow aspirate concentrate use in hip osteoarthritis | Osteoarthritis, hip | Bone marrow mesenchymal stem cells, platelet-rich plasma | NA | Canada |
| 20 | NCT04308213 | Study on shoulder arthritis treatment with intra-articular injections of autologous bone marrow aspirate | osteoarthritis, shoulder | Bone marrow mesenchymal stem cells | NA | Italy |
| 21 | NCT03909139 | Use of BMAC with hip arthroscopy treatment of FAI and labral tear | Femoroacetabular impingement | Bone marrow mesenchymal stem cells | 2 | USA |
| 22 | NCT04222140 | Early regenerative intervention for post-traumatic osteoarthritis | Osteoarthritis, knee | Bone marrow mesenchymal stem cells | NA | USA |

major part of the German contribution to the field. In 2002, Steinhoff started with a phase 1 clinical trial on BMAC therapy for myocardial infarction [25]. In 2003, he documented the results of six patients who underwent this therapy, with five of them showing striking improvement 3 to 9 months after injection of $1.5 \times 10^8$ autologous $AC133^+$ bone marrow cells into the infarct border zone [26]. Later, Steinhoff and his team analyzed the microRNA regulation of endothelial committed $CD133^+$ bone marrow stem cells in collaboration with the German Society for Stem Cell Research & Gene Therapy [27]. In 2010, Steinhoff reported the first case of bone marrow stem cell transplantation along with minimally invasive mitral valve repair [28]. In 2011, his team performed a meta-analysis and proved the effectiveness of this modality compared with controls in chronic ischemic heart disease [29]. They also found that preoperative left ventricle function and time from infarction affected the long-term benefits of this therapy [30]. In 2012, they conducted a phase 3 randomized multicenter trial on this therapy, which was stopped later on due to slow recruitment, with a positive interim analysis that found that the cardiac regeneration from the therapy was linked to circulating $CD133^+$ progenitor cells and thrombocytes with SH2B3 gene expression, which could be identified by a peripheral blood biomarker analysis [31].

As a key node in the cocitation network, Mark F. Pittenger's article [20] not only had the largest number of citations (n = 15,274) but also had the highest impact in the network, as shown in Figure 6B. His research laid the foundation on which all the cellular therapies on mesenchymal stem cells were built. His team worked on the multilineage potential of the mesenchymal stem cell to differentiate into cardiomyocyte phenotype as a potential cardiac therapeutics [32] and into chondrogenic phenotype as a cartilage regenerative therapy [33]. His team also analyzed the role of mitogen-activated protein kinase activation in osteogenic or adipogenic lineage differentiation of adult human mesenchymal stem cells [34]. His team published a recent review on MSC exosomes as a new cell-free therapeutic paradigm that has the potential to be the next generation of regenerative medicine [35].

Keywords reflect the core research content, research theme and main direction of research involved in the article [36]. With text mining and scientometric techniques such as keyword co-occurrence analysis, we can spot trends in research and research hotspots in the field of interest [37]. We have unveiled the emerging trends by analyzing the citation burst of keyword co-occurrences and literature cocitations on BMAC therapy. We found the keywords burst to transcend from initial research domains of this therapy such as "myocardial infarction" and "transplantation" to current hotspots of BMAC therapy research such as "spinal cord injury," "nerve regeneration," "osteogenesis," "knee" and "femoral head." Having explored the potential application of the therapy in the above hotspots with established efficacy and safety analysis studies, the current research involves exploration for enhanced action. For example, the key research article in spinal cord injury cluster evaluates the repair of spinal cord injury with BMAC therapy combined with a neuroprotective anesthetic agent, propofol [38]. In the osteogenesis cluster, the key article analyzed the effects of electromagnetic fields on the differentiation potential of bone marrow–derived MSCs (BM-MSCs) [39]. In the knee cluster, one of the research articles shows that BM-MSC–derived tissues are mechanically superior to meniscus cells, thereby making BMAC therapy a candidate not only for osteoarthritis of the knee but also for meniscal injuries, which is often an overlooked entity [40]. Hence, it is evident from this cluster analysis of the current hotspots that there is scope for improvisation in the current generation of BMAC therapy, with expanded utility and improved outcomes.

### *Future prospects in osteoarthritis*

To explore further the current status of therapy for osteoarthritis, we probed the clinical trial registry database [41] for the list of registered ongoing and completed clinical trials on this therapy. When we look into the applications for which BMAC therapy is being used in the completed trials listed in Table 3, we noted that most were pertinent to osteoarthritis of the knee. It is evident from the results of completed trials that the potential of BM-MSCs could be used not only for osteoarthritis of the knee but also for osteoarthritis of other joints. Hence, we could see in the list of ongoing trials listed in Table 4 that the therapy is being used for osteoarthritis of other joints such as hip (NCT03067870, NCT03410355), shoulder (NCT04826224, NCT04308213) and ankle (NCT01436058). Apart from osteoarthritis, the modality is now being tried for rheumatoid arthritis (NCT03067870) and femoroacetabular impingement of the hip (NCT03909139). With the proven efficacy of this treatment modality in OA, attempts are being taken to standardize the treatment with dose escalation trials (NCT02123368, NCT02351011) to find the optimal volume needed to attain maximum benefits. Of the 22 ongoing trials, 12 were from the United States, highlighting its influence in the field, as noted in our analysis.

Despite its strengths, there are some limitations to this study. From the point of research data used in the article, we used only the WoS core collection database. We did not take the gray literature such as nonpublished conference documents, scientific reports, dissertations, scientific archives, *etc.*, into consideration as a data source. In addition, although keywords better reflect the research theme of the article, the author's preference in using them and limitation in the number of keywords to be used may be a source of bias in using them for trend analysis and hotspot identification.

## Conclusion

We did a comprehensive review of the available literature, analyzed the research trends for the past three decades on BMAC therapy and probed its current status for OA. There is remarkable growth in the number of publications on BMAC therapy. China and the Unites States were the most influential contributors in the field. Use of this therapy for spinal cord injury, nerve regeneration, osteogenesis, osteoarthritis of the knee and osteonecrosis of the femoral head were the research hotspots with great promise in the near future. Despite establishing the clinical efficacy and safety of BMAC therapy in phase 1/2 trials, practical application of BMAC therapy in the above research hotspots needs further research with larger clinical trials.

## Declaration of Competing Interest

The authors declare no conflict of interest.

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