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Visual analysis of bone malignancies immunotherapy

A bibliometric analysis from 2010 to 2023

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Abstract

Background: Bone malignancies (BM), including osteosarcoma, Ewing's sarcoma, chondrosarcoma, and chordoma, are characterized by high rates of recurrence and mortality, despite the availability of diverse treatment approaches. Immunotherapy has gained increasing importance in cancer treatment. However, there is a lack of comprehensive studies that utilize bibliometric analysis to explore immunotherapy for BM.

Methods: A literature search of English studies on BM and immunotherapy from 2010 to 2023 was conducted in the Web of Science Core Collection database. Bibliometric analysis tools such as VOSviewer, CiteSpace, and R Studio were utilized to examine global trends and research hotspots in this field.

Results: A total of 719 eligible articles, including 528 original research articles and 191 reviews, were analyzed. The number of publications has shown an increasing trend over the past 14 years, particularly in the last 5 years. The majority of the published articles on this topic originated from China (284 articles), followed by the United States and Japan. The institution with the highest number of publications and citations was the University of Texas MD Anderson Cancer Center (30 articles; 1638 citations). Dean A. Lee (12 articles) and Richard Gorlick (576 citations) were the authors with the highest contribution in terms of article count and citation count, respectively. Among these journals, Frontiers in Oncology had the highest number of articles (39 articles), while the Journal of Clinical Oncology had the highest number of citations (1878 citations). Additionally, there has been a shift in the keywords from "antitumor activity" and "NK cells" to popular topics such as "PD-L1," "open label," and "single arm."

Conclusion: A better understanding of the current status and prospects of immunotherapy for BM is crucial for the rationale selection of appropriate BM patients for immunotherapy. This study is expected to help clinical physicians and researchers gain comprehensive insights into the developmental trends of BM immunotherapy, providing practical guidance for the application of immunotherapy in BM patients.

Abbreviations: BM = bone malignancies, IF = impact factor, HER2 = human epidermal growth factor receptor 2, NK cells = natural killer cells, PD-1 = programmed cell death protein 1, PD-L1 = programmed cell death 1 ligand 1, WoSCC = Web of Science Core Collection.

Keywords: bibliometric study, bone malignancies, clinical trials, immunotherapy, VOSviewer

1. Introduction

Bone malignancies (BM) include osteosarcoma, Ewing's sarcoma, chondrosarcoma, and chordoma, among others. BM typically arises from genetic mutations and epigenetic changes, including DNA methylation and histone modifications that are correlated with an unfavorable prognosis in the condition.[1,2] BM can induce a range of symptoms, including bone pain and fractures, leading to a substantial impact on the patients' quality of life. Moreover, the elevated mortality rate associated with BM can result in emotional distress, depression, and even suicidal tendencies among patients.[3] Common treatment modalities for BM encompass surgical intervention, neoadjuvant chemotherapy, and adjuvant chemotherapy.[4,5] The advancement of molecular biomarker research has paved the way for the gradual integration of targeted therapy in BM treatment. Multifaceted antiangiogenic targeted drugs comprising small molecules, including sorafenib, apatinib, and others, such as tyrosine kinase inhibitors, have demonstrably

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The datasets generated during and/or analyzed during the current study are publicly available.

The data in this article were obtained from public databases. The authors confirmed that no ethical approval is required.

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enhanced patient survival rates. Nevertheless, treatments for patients with metastatic or recurrent BM continue to stagnate,[6] and the prognosis has not experienced substantial improvement.

Over the past decade, immunotherapy, including the interaction between immune checkpoints, has demonstrated promising therapeutic effects in treating various malignant tumors.[7] This approach holds significant potential for cancer treatment. Tumor immunotherapy reactivates and sustains the body's immune system by reinstating the "tumor-immune cycle" and eliminating tumor cells.[8] However, in inoperable BM, the overall survival rate is currently low, possibly due to resistance and early hematogenous metastasis. Additionally, chemotherapy resistance and tumor immune evasion are common challenges in current treatment methods. These limitations are further compounded by cancer stem cells and the microenvironment.[9] Immunotherapy encompasses the use of cytokines, tumor vaccines, immune checkpoint inhibitors, and immune regulators.[10] Notably, Zheng et al discovered a close association between the expression of programmed cell death protein 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) in osteosarcoma and patient prognosis. Their in vitro and animal experiments revealed that PD-1/PD-L1 inhibitors partially alleviate the malignant progression of osteosarcoma.[11] Moreover, Ghisoli et al[12] reported a significant improvement in the survival rate of Ewing's Sarcoma patients following treatment with the FANG (Vigil) vaccine. Furthermore, the PD-1 inhibitor nivolumab was found to alleviate the progression of Chondrosarcoma and Chordoma.[13,14] Currently, ongoing clinical trials are being conducted on immunotherapy for BM, cementing its place as an integral component of future treatment strategies. However, the existing literature on immunotherapy for BM lacks systematic organization, resulting in confusion regarding relevant knowledge gaps and inhibiting researchers from effectively comprehending the development trends in this field.

Bibliometrics is a mathematical and statistical approach that integrates keywords, journals, authors, and their affiliations to describe, evaluate, and predict the current status and future trends of scientific and technological development. Its wide application in solving medical issues is well-documented.[15–17] The publication of research studies on immunotherapy for BM is increasing. Nevertheless, there is currently no specific bibliometric research focusing on BM immunotherapy. This study seeked to evaluate the literature on BM immunotherapy from 2010 to 2023, aiming to utilize immunotherapy more effectively to enhance the prognosis of BM patients in future clinical practice. The insights gained from this study have the potential to introduce new perspectives to the treatment strategies for BM in the clinical setting.

2. Materials and methods

2.1. Data collection

Utilized the following search formula to query the Web of Science Core Collection (WoSCC) on July 15, 2023, for articles related to BM immunotherapy from 2010 to July 14, 2023: TS=("Bone Sarcoma" OR "Osteosarcoma" OR "Ewing Sarcoma" OR "Chondrosarcoma" OR "Chordoma") AND TS=("Immunotherapy" OR "Immunotherapies" OR "Immunotherapeutic"). The inclusion criteria for the literature were as follows: Manuscripts needed to relate to BM immunotherapy; only original articles and reviews were considered; the language of the literature had to be English; the WoS index type used was Science Citation Index-Expanded; nonoriginal literature such as conference abstracts, book chapters, editorial material, online publications, conference proceedings papers, and letters were excluded. The following information was extracted after identifying each article: title, keywords, author's country, institution, abstract, and references. Items from Taiwan were classified as belonging to China in the country analysis, whereas items from England, Scotland, Northern Ireland, and Wales were classified as belonging to the United Kingdom. Download the text in TXT file format. Data collection was independently performed by 2 authors (SKY and KSY), who subsequently resolved any disagreements through negotiation.

2.2. Bibliometric analysis

The main software tools utilized in this study were R (version 4.1.0) with the "bibliometrix" package, VOSviewer (version 1.6.19),[18] Citespace (version 6.2.R4),[19] the Literature Econometrics Online Analysis Platform (http://bibliometric.com/), and Microsoft Excel 2019. Among them, R (version 4.1.0) with the "bibliometrix" package, Microsoft Excel 2019, and VOSviewer (version 1.6.19) were used for data extraction, analysis, and visualization of country, institution, and coauthor information. These tools facilitated the generation of analysis graphs, journal co-citation analysis, and keyword co-occurrence analysis. Citespace (version 6.2.R4) was specifically selected to create keyword and reference co-occurrence detection maps. The following parameters were set for the CiteSpace (version 6.2.R4) software: The time period was set to run from January 2010 to July 2023, with 1 year per slice. Keywords, categories, cited authors, and references were the node types. The top 50 results for each slice were the selection criteria. Pathfinder, sliced networks pruning, and merged network pruning were among the pruning options used. The default settings applied to the remaining parameters. Pruning techniques for sliced networks and merged networks were used. The default settings applied to the remaining parameters. For the VOSviewer (version 1.6.19) software, the following parameter settings were used: the normalization method was set to strength of association; 5 was the minimum threshold for the number of publications from the institution, author, and country/region; 100 was the minimum threshold for the number of journal citations; and 20 was the minimum threshold for the frequency of keyword occurrence. Additionally, the Bibliometrics Online Analysis Platform was employed to determine the number of literature publications per year.

3. Results

A total of 785 articles were initially identified in the WoSCC database. After applying the exclusion criteria, 27 articles were excluded as they were not published between 2010 and 2023. Furthermore, 7 conference abstracts, 10 book chapters, 9 editorial materials, 8 online publications, 2 conference proceedings papers, 1 letter, and 1 meeting were also excluded. Additionally, 1 article written in Polish was excluded. Ultimately, 719 articles that fulfilled the inclusion criteria were included in this study, comprising of 528 treatises and 191 reviews (Fig. 1).

3.1. Country distribution

All articles included in this study originated from 51 different countries. The analysis of annual publications from 2010 to 2022 revealed a general upward trend (Fig. 2A), indicating a growing focus on immunotherapy for BM research. However, there was a decrease in the number of publications in 2023, possibly due to the timing of the statistics. Table 1 presents the top 10 countries in terms of publications during the 2010 to 2023 period. According to the statistical analysis, China ranked first in terms of publications (n = 284, 39.50%), followed by the United States (n = 251, 34.91%), Japan (n = 54,

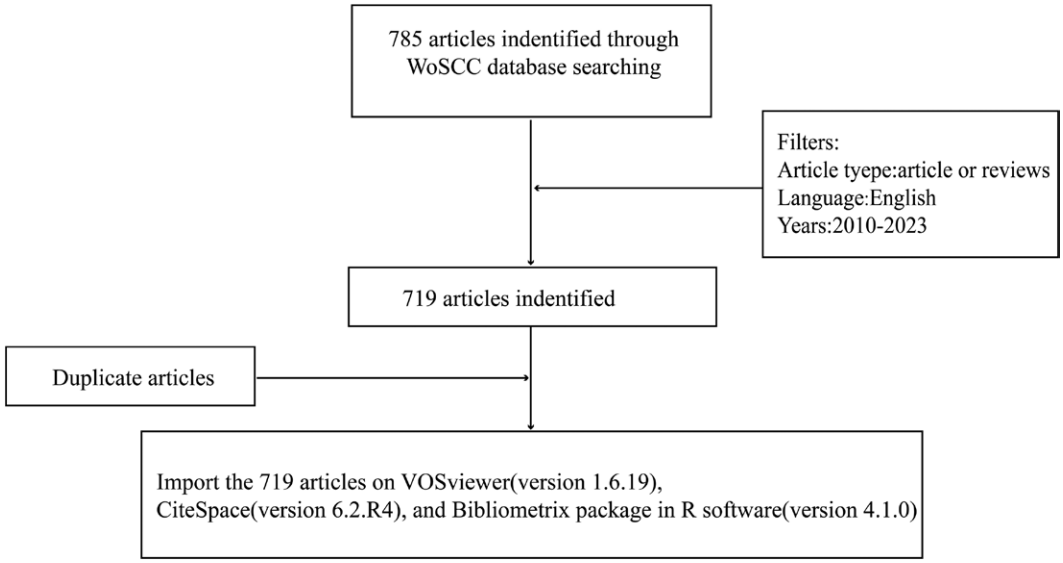

Figure 1. Flow chart of literature inclusion and exclusion.

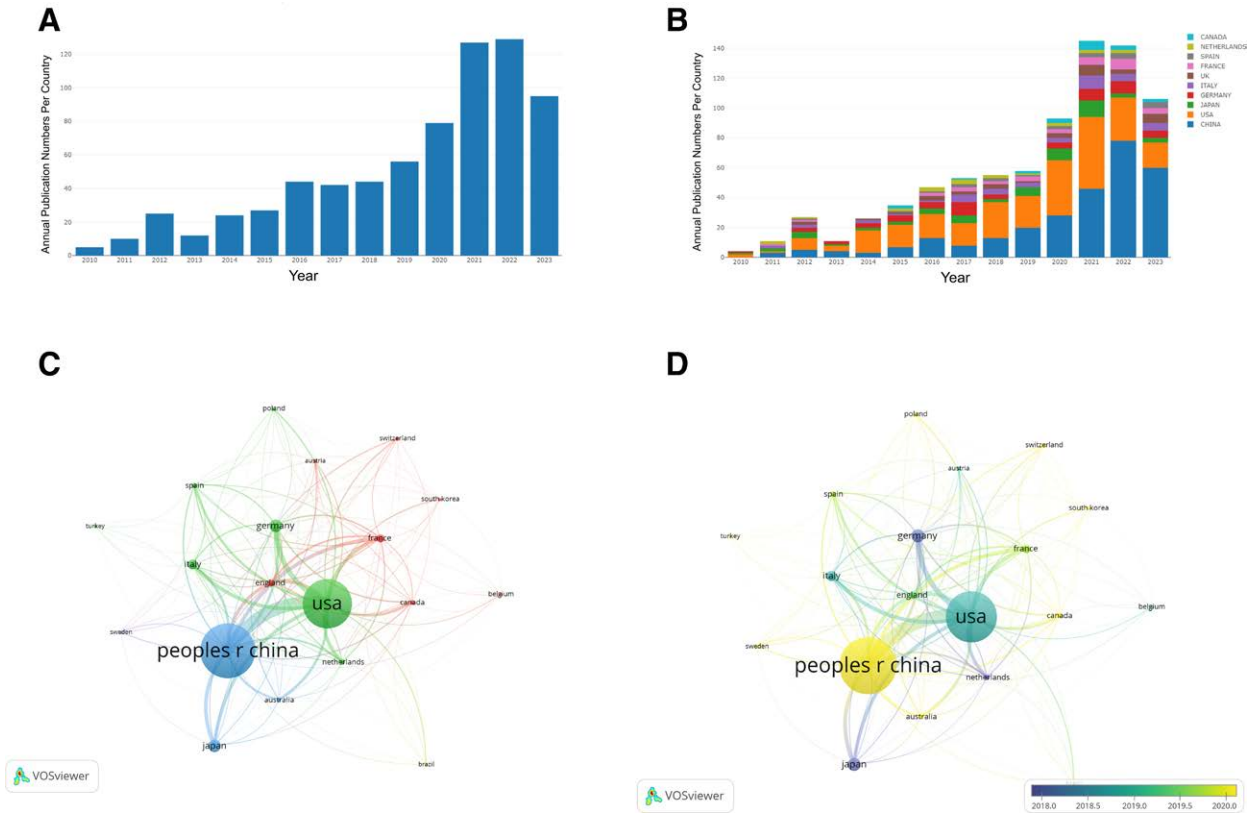

Figure 2. Country analyses of the BM immunotherapy study. (A) The annual number of publications on BM immunotherapy from 2010 to 2023. (B) The number of publications in the top 10 countries for BM immunotherapy from 2010 to 2023. (C) Analysis of the cooperation network among countries in the field of BM immunotherapy. (D) Analysis of major research countries over the period from 2010 to 2023. The circle size represents the number of papers. The breadth of the curves represents the connection strength.

7.51%), Germany (n = 53, 7.37%), and Italy (n = 41, 5.70%). The trend of national publications over time is illustrated in Figure 2B, with a significant increase observed in China in 2022. Notably, the United States had the highest total number of citations (8013), while Canada had the highest average citations (41.11). In order to explore inter-country collaboration, VOSviewer (version 1.6.19) software was employed, revealing that China and the United States had the closest collaboration (Fig. 2C). Furthermore, Figure 2D presents a temporal overlay of the national/regional cooperation networks, wherein the color of the yellow nodes indicates later average publication timings, while the purple nodes indicate earlier average publication times. The findings indicate that while China, Australia, and Canada began their BM research later, nations like Germany, Japan, and the Netherlands began their research sooner.

3.2. Institution distribution

A total of 1055 institutions participated in the study on immunotherapy for BM, with 67 of them publishing at least 5 papers (Fig. 3A). These 67 institutions were categorized into 5 groups. The red cluster consisted of Chinese institutions, including Zhejiang University, Shanghai Jiao Tong University, Zhengzhou University, and Sichuan University. The blue cluster included Memorial Sloan Kettering Cancer Center, University of Washington Seattle, and Technical University of Munich. The yellow cluster consisted of the University of Texas MD Anderson Cancer Center, Central South University, and the University of Pittsburgh. The green cluster included Nationwide Children's Hospital, the University of California Davis, and the University of Minnesota System. Finally, the purple cluster consisted of the National Cancer Institute and Harvard Medical School. There was a close collaboration between institutions in China and the U.S., with the University of Texas MD Anderson Cancer Center being the core institution in the field of BM immunotherapy research and having close links with research centers in many other countries. Additionally, the top 3 institutions in terms of literature publication were the University of Texas MD Anderson Cancer Center (n = 30), Zhejiang University (n = 28), and Memorial Sloan Kettering Cancer Center (n = 24) (Table 2). Chinese and U.S. institutions made major contributions in this area. Among the top 3 institutions in terms of total citations in the literature, the University of Texas MD Anderson Cancer Center ranked first, followed by the National Cancer Institute and Baylor College of Medicine (with 1638, 1015, and 973 citations, respectively) (Table 2). It is evident that most of the high-quality papers come from U.S. institutions. Overlay visualization analysis revealed that during the early years (around 2016), major institutions studying immunotherapy for BM were Memorial Sloan Kettering Cancer Center, Leiden University, and Harvard University. However, in recent years (around 2022), Shanghai Jiao Tong University and Sichuan University have emerged as significant forces (Fig. 3B).

3.3. Analysis of authors and cited authors

All papers sampled on immunotherapy for BM were authored by a total of 4432 individuals. We visualized the collaborations among 73 authors who have published more than 5 studies in this field. The top 5 most prolific authors were Dean A. Lee (n = 12), Zhaoming Ye (n = 11), Binghao Li (n = 10), Toshihiko Torigoe (n = 10), and Tomohide Tsukahara (n = 10) (Table 3). Additionally, the top 5 most cited authors were Richard Gorlick, Nai-Kong V. Cheung, Eugenie S. Kleinerman, Yi Huang, and Wei Guo, with a total of 576, 401, 399, 352, and 349 citations respectively. These authors primarily hail from the United States, China, and Japan. Moreover, as illustrated in Figure 4A, the author group centered around Zhaoming Ye from China and Dean A. Lee from the US exhibited close collaborations with other author groups. Figure 4B depicts the graph of author impact over time. Based on the number of publications and citation, Wei Guo may be regarded as an influential researcher in the field of immunotherapy for BM after 2020. Subsequently, we employed Bibliometrix in R software (v4.1.0) to generate the "author output over time" graph (Fig. 4C), which revealed that Zhaoming Ye, Yong Zhou, Toshihiko Torigoe, and Tomohide Tsukahara have been conducting research in this field for the

Table 1

Top 10 countries contributing to publications of immunotherapy for bone malignancies.

Rank	Country	Articles	Percentage (N/719)	Total citations	Average citations
1	China	284	39.50	3855	13.57
2	United States of America	251	34.91	8013	31.92
3	Japan	54	7.51	1258	23.30
4	Germany	53	7.37	1907	35.98
5	Italy	41	5.70	1014	24.73
6	France	31	4.31	890	28.70
7	England	27	3.76	888	32.89
8	Netherlands	20	2.78	884	36.83
9	Spain	20	2.78	522	26.10
10	Canada	18	2.50	740	41.11

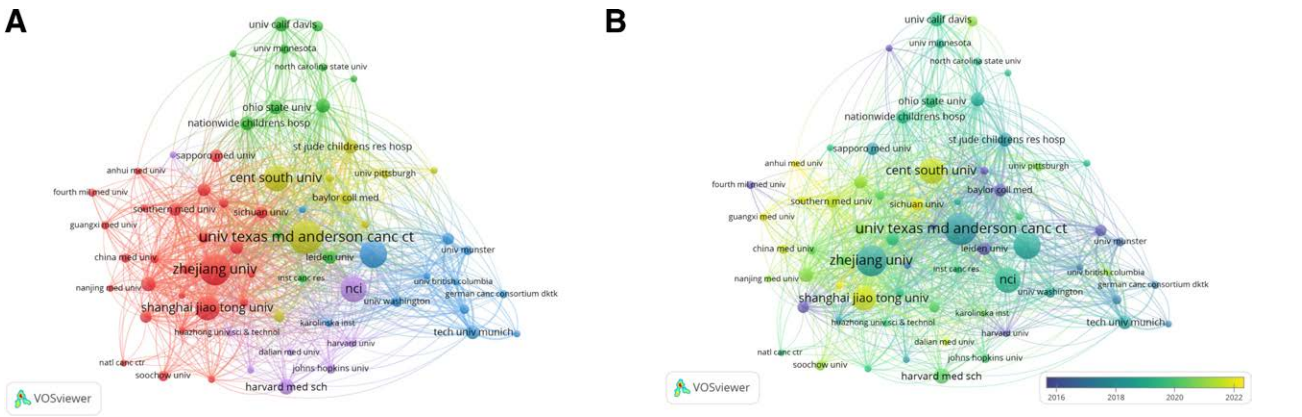

Figure 3. Network visualization maps of organizations. (A) Analysis of the cooperation network among institutions in the field of BM immunotherapy. (B) Analysis of major research institutions over the period from 2010 to 2023. The circle size represents the number of papers. The breadth of the curves represents the connection strength.

Table 2

Top 10 contributed institutions in the field of immunotherapy for bone malignancies.

Rank	Organization	Articles	Country	Rank	Organization	Citations	Country
1	University of Texas MD Anderson Cancer Center	30	United States of America	1	University of Texas MD Anderson Cancer Center	1638	United States of America
2	Zhejiang University	28	China	2	National Cancer Institute	1015	United States of America
3	Memorial Sloan Kettering Cancer Center	24	United States of America	3	Baylor College of Medicine	973	United States of America
4	National Cancer Institute	23	United States of America	4	Texas Children's Cancer Center	959	United States of America
5	Central South University	23	China	5	Texas Children's Cancer Center	879	United States of America
6	Shanghai Jiao Tong University	21	China	6	Zhejiang University	689	China
7	Harvard Medical School	13	United States of America	7	University of Pennsylvania	631	United States of America
8	University of California Davis	12	United States of America	8	St Jude Children's Research Hospital	520	United States of America
9	Peking University	12	China	9	Leiden University	495	Netherlands
10	University of Pennsylvania	11	United States of America	10	Nationwide Children's Hospital	465	United States of America

Table 3

Top 10 most productive and cited authors in the field of bone malignancies immunotherapy.

Rank	Author	Articles	Country	Rank	Author	Citations	Country
1	Dean A. Lee	12	United States of America	1	Richard Gorlick	576	United States of America
2	Zhaoming Ye	11	China	2	Nai-Kong V. Cheung	401	United States of America
3	Binghao Li	10	China	3	Eugenie S. Kleinerman	399	United States of America
4	Toshihiko Torigoe	10	Japan	4	Yi Huang	352	China
5	Tomohide Tsukahara	10	Japan	5	Wei Guo	349	China
6	Wei Guo	10	China	6	Zhenfeng Duan	347	China
7	Hiroyuki Tsuchiya	9	Japan	7	Marco W. Schilham	337	Netherlands
8	Robert J canter	9	United States of America	8	Dean A. Lee	320	United States of America
9	Eugenie S Kleinerman	8	United States of America	9	Zhaoming Ye	318	China
10	William J Murphy	8	United States of America	10	Pancras C W Hogendoorn	306	Netherlands

longest period of 13 years and have continued to publish new works this year.

3.4. Analysis of journals and co-cited journals

We conducted a co-cited journal analysis using the Bibliometrix package of R software (v4.1.0) and VOSviewer (v1.6.19) with a minimum citation threshold of ≥100. The study included a total of 3254 journals, 91 of which were co-cited at least 100 times. The top 10 journals for studies related to immunotherapy for BM are listed in Table 4. The top 5 journals with the highest number of publications were Frontiers in Oncology (n = 39, impact factor [IF] = 4.7), Frontiers in Immunology (n = 33, IF = 7.3), Cancers (n = 32, IF = 5.2), Journal for the ImmunoTherapy of Cancer (n = 21, IF = 10.9), and OncoImmunology (n = 19, IF = 7.2), with Clinical Cancer Research having the highest IF. Additionally, the top 5 journals with the most co-citations were Journal of Clinical Oncology (IF = 45.3), Clinical Cancer Research (IF = 11.5), Cancer Research (IF = 11.2), New England Journal of Medicine (IF = 158.5), and Lancet Oncology (IF = 51.1). These journals had total citations of 1878, 1808, 1363, 776, and 767, respectively (Table 5), with the New England Journal of Medicine having the highest IF. Figure 5A depicts the connection between the journals Journal of Clinical Oncology, Clinical Cancer Research, and Cancer Research, suggesting they may be core journals in the field of immunotherapy for BM. Additionally, we utilized a bimap overlay of journals to analyze the connections between journals that cite each other across different research areas (Fig. 5B). The sample waves from left to right represented the citation paths. Orange paths indicated that studies published in molecular, biology, and immunology journals often cite studies in molecular/biology/genetics journals, while green paths showed that the majority of citations for studies published in medicine/medical/clinical journals originate from health/nursing/medicine journals.

3.5. Analysis of references and co-cited references

The present study conducted a comprehensive literature analysis, and the findings are summarized in Table 6. This table highlighted the top 5 most frequently cited publications out of the 719 articles included in the analysis. Notably, the article titled "Human epidermal growth factor receptor 2 (HER2)-specific chimeric antigen receptor-modified T cells for the immunotherapy of HER2-positive sarcoma" received the highest number of citations, with a total of 706. The publication titled "CAR T cells targeting B7-H3, a pan-cancer antigen, demonstrate potent preclinical activity against pediatric solid tumors and brain tumors" ranked second, with 282 citations. Furthermore, "Future directions in the treatment of osteosarcoma" was the third-ranked publication, garnering 223 citations. These studies focusing on immune therapy had made significant contributions to enhancing the prognosis of BM patients.

Subsequently, we employed VOSviewer software (version 1.6.19) for co-citation analysis of the 719 articles. From a pool of 29,545 citations, we identified 47 articles that exceeded 30 citations (Fig. 6A). Furthermore, to present a more comprehensive overview, we utilized CiteSpace software (version 6.2.R4) to visualize the top 25 co-cited articles across different time periods (Fig. 6B). Interestingly, 4 specific articles, namely, "Cytotoxicity of activated natural killer cells against pediatric solid tumors," "Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1," "Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of

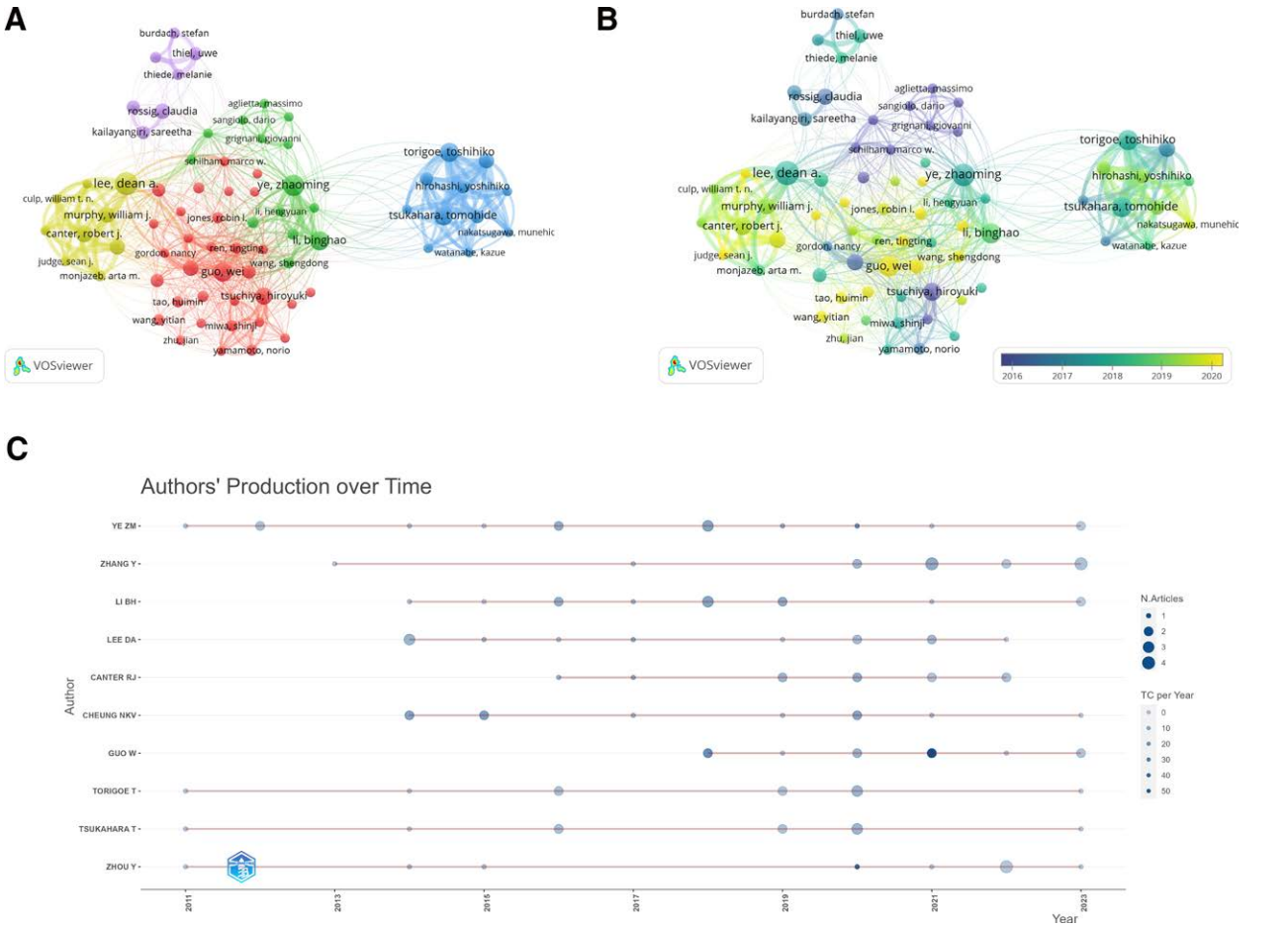

Figure 4. Author network analysis. (A) Analysis of the cooperation network among authors in the field of BM immunotherapy. (B) Analysis of major research authors over the period from 2010 to 2023. The size of the circle is indicative of the number of papers. The width of the curves corresponds to the strength of the connections. (C) Top 10 authors over time.

Table 4

Top 10 journals with the most published articles.

Rank	Journals	Articles	IF (2022)	JCR (2022)
1	Frontiers in Oncology	39	4.7	Q2
2	Frontiers in Immunology	33	7.3	Q1
3	Cancers	32	5.2	Q2
4	Journal for ImmunoTherapy of Cancer	21	10.9	Q1
5	OncoImmunology	19	7.2	Q1
6	Clinical Cancer Research	16	11.5	Q1
7	International Journal of Molecular Sciences	14	5.6	Q1
8	Oncotarget	12	–	–
9	Cancer Immunology Immunotherapy	11	5.8	Q1
10	Oncology Letters	10	2.9	Q4

soft tissue sarcomas," and "Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, 2-cohort, single-arm, open-label, phase 2 trial," exhibited citation strengths >10. This suggested a surge in citations for these articles shortly after their publication, indicating the necessity for further in-depth investigations.

To gain deeper insights into the research trends within the field of BM immunotherapy, we conducted cluster analysis on the keywords present in the co-cited references (Fig. 6C). Additionally, we integrated clustering with time slice techniques to ascertain the evolving patterns of research hotspots (Fig. 6D). Notably, the clustering parameter Modularity (Q) = 0.8181 (Q > 0.3) and Weighted mean Silhouette (S) = 0.9295 (S > 0.5) validated the significance and reliability of our clustering approach. The findings of this study strongly indicated that keywords such as "soft tissue sarcoma," "Ewing sarcoma," "tumor microenvironment," "PD-L1," "Natural Killer cells (NK cells)," and "cancer immunotherapy" are likely to be prominent topics among the co-cited references. Specifically, during the period from 2010 to 2015, research attention primarily focused on "soft tissue sarcoma," "Ewing sarcoma," "GD2," "cancer immunotherapy," and "NK cells." Subsequently, from 2015 to 2020, the research hotspots shifted towards "PD-L1," "tumor microenvironment," and "immune suppression." Notably, the research hotspot from 2020 to 2022 continues to be the "tumor microenvironment."

Table 5

Top 10 journals with the most cited journals.

Rank	Co-cited Journals	Total citations	IF (2022)	JCR (2022)
1	Journal of Clinical Oncology	1878	45.3	Q1
2	Clinical Cancer Research	1808	11.5	Q1
3	Cancer Research	1363	11.2	Q1
4	New England Journal of Medicine	776	158.5	Q1
5	Lancet Oncology	767	51.1	Q1
6	PLoS One	712	3.7	Q2
7	Cancer	683	6.2	Q1
8	Blood	674	20.3	Q1
9	Oncotarget	653	–	–
10	Journal of Immunology	644	4.4	Q2

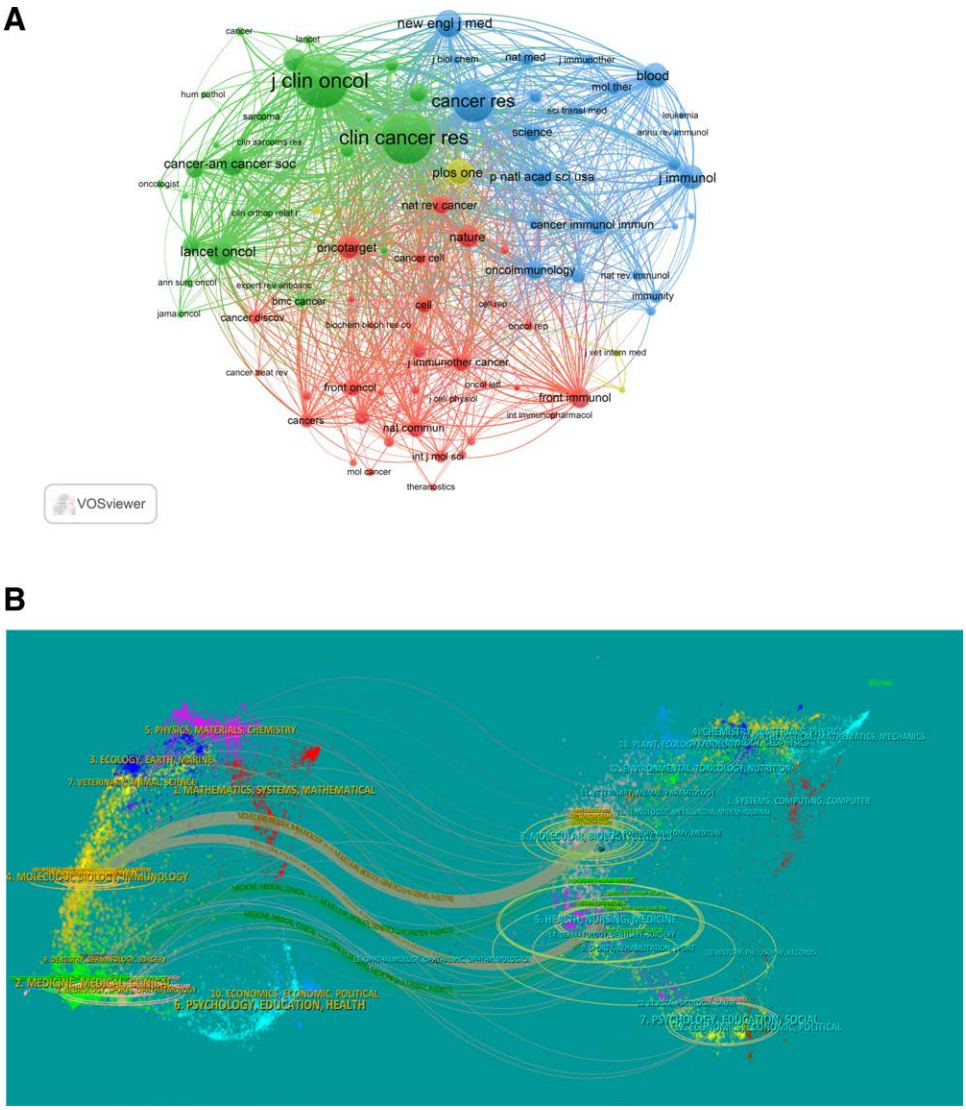

Figure 5. Journal analysis of BM immunotherapy. (A) A network map depicting academic journals that publish research on immunotherapy associated with BM. (B) A dual-map overlay depicting journals associated with research on immunotherapy in BM.

3.6. Analysis of keywords

Visual maps of keywords were generated using VOSviewer software (version 1.6.19). In total, 2971 keywords were included, and 62 terms with at least 20 occurrences were identified. Research keywords in popular research areas change over time. For instance, during 2017 to 2020, the transition occurred from "antitumor-activity" and "NK cells" to "osteosarcoma," "immunotherapy," "PD-L1," "open label," "single arm," etc (Fig. 7A). The keywords were also clustered into 4 groups in the network diagram (Fig. 7B). The red group included "immunotherapy," "T cell," "ewing sarcoma," and "soft tissue sarcoma." The green group consisted of "osteosarcoma," "tumor microenvironment," "metastasis," and "expression." The yellow group contained "PD-1," "PD-L1," "nivolumab," and "blockade." Lastly, the blue group primarily features terms related to tumors

Table 6

Top 5 highly cited articles in the field of immunotherapy for bone malignancies.

Rank	Title	DOI	Journal	IF (2022)	Publication year	Total citations
1	Human epidermal growth factor receptor 2 (HER2)-specific chimeric antigen receptor-modified T cells for the immunotherapy of HER2-positive sarcoma	10.1200/JCO.2014.58.0225	Journal of Clinical Oncology	45.3	2015	706
2	CAR-T cells targeting B7-H3, a pan-cancer antigen, demonstrate potent preclinical activity against pediatric solid tumors and brain tumors	10.1158/1078-0432.CCR-18-0432	Clinical Cancer Research	11.5	2019	282
3	Future directions in the treatment of osteosarcoma	10.1097/MOP.0000000000000298	Current Opinion in Pediatrics	3.6	2016	223
4	Immune infiltration and PD-L1 expression in the tumor microenvironment are prognostic in osteosarcoma	10.1038/srep30093	Scientific Reports	4.6	2016	200
5	Novel insights and therapeutic interventions for pediatric osteosarcoma	10.2217/fon-2016-0261	Future Oncology	3.4	2017	174

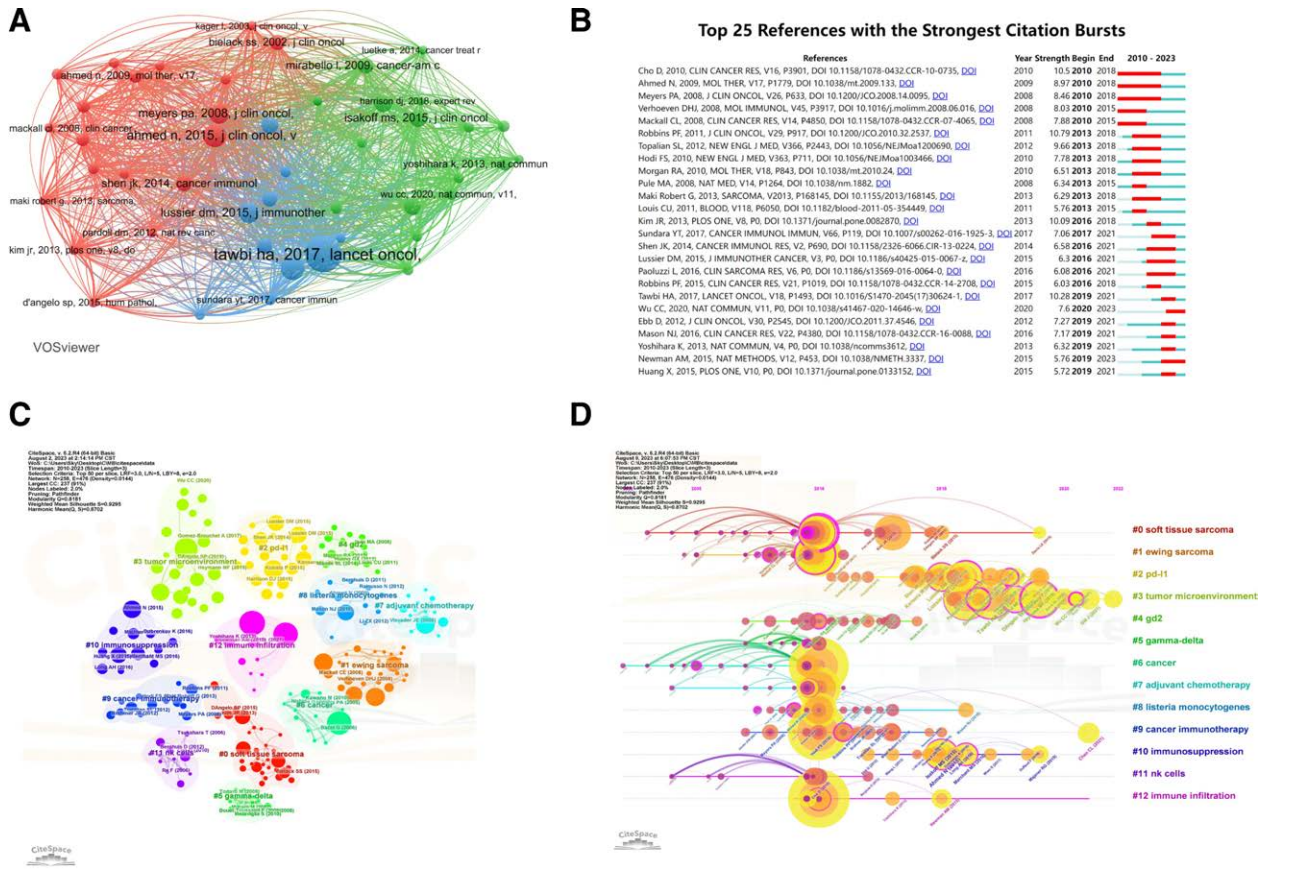

Figure 6. Co-cited references involved in BM immunotherapy. (A) Interaction network graphs for co-cited references. (B) Top 25 references with the strongest citation bursts on BM immunotherapy. (C) Keyword cluster analysis of co-cited references. (D) Timeline view of co-cited references related to immunotherapy for BM. The horizontal position of each node indicates the reference's initial appearance. The size of a node corresponds to the number of co-citations for that reference. The lines connecting the nodes depict co-cited relationships. The color shading intensifies towards yellow, indicating a closer temporal proximity to 2023.

and chemotherapy. Figure 7C indicates that "osteosarcoma" and "immunotherapy" serve as the core terms in the keyword network. For analyzing the emerging terms in the field of immunotherapy for BM during specific time periods, we employed CiteSpace software (version 6.2.R4). Figure 7D displays the top 25 exploding keywords. The results demonstrated that the research frontrunners from 2010 to 2018 are "in vitro," "receptor," and "NK cells," indicating a focus on basic experiments. This period spans 9 years and suggested that research in the field of immunotherapy for BM during this time was still in the preliminary stage of in vitro experiments and theory. The research frontrunners for 2019 to 2023 were "phase II trial," "single arm," "open label," and "tumor microenvironment." This suggested that the field of immunotherapy for BM would likely witness an increase in clinical trials related to immunotherapy for BM and more complex basic research focusing on the "tumor microenvironment" in the coming years.

4. Discussion

4.1. General information

BM is most commonly found in the form of osteosarcoma, followed by chondrosarcoma and Ewing sarcoma. The progress of research in bone sarcoma treatment has been relatively slow, with the primary treatment method being surgical resection. Despite extended survival in some patients through adjuvant and neoadjuvant chemotherapy and radiation therapy, over half of the

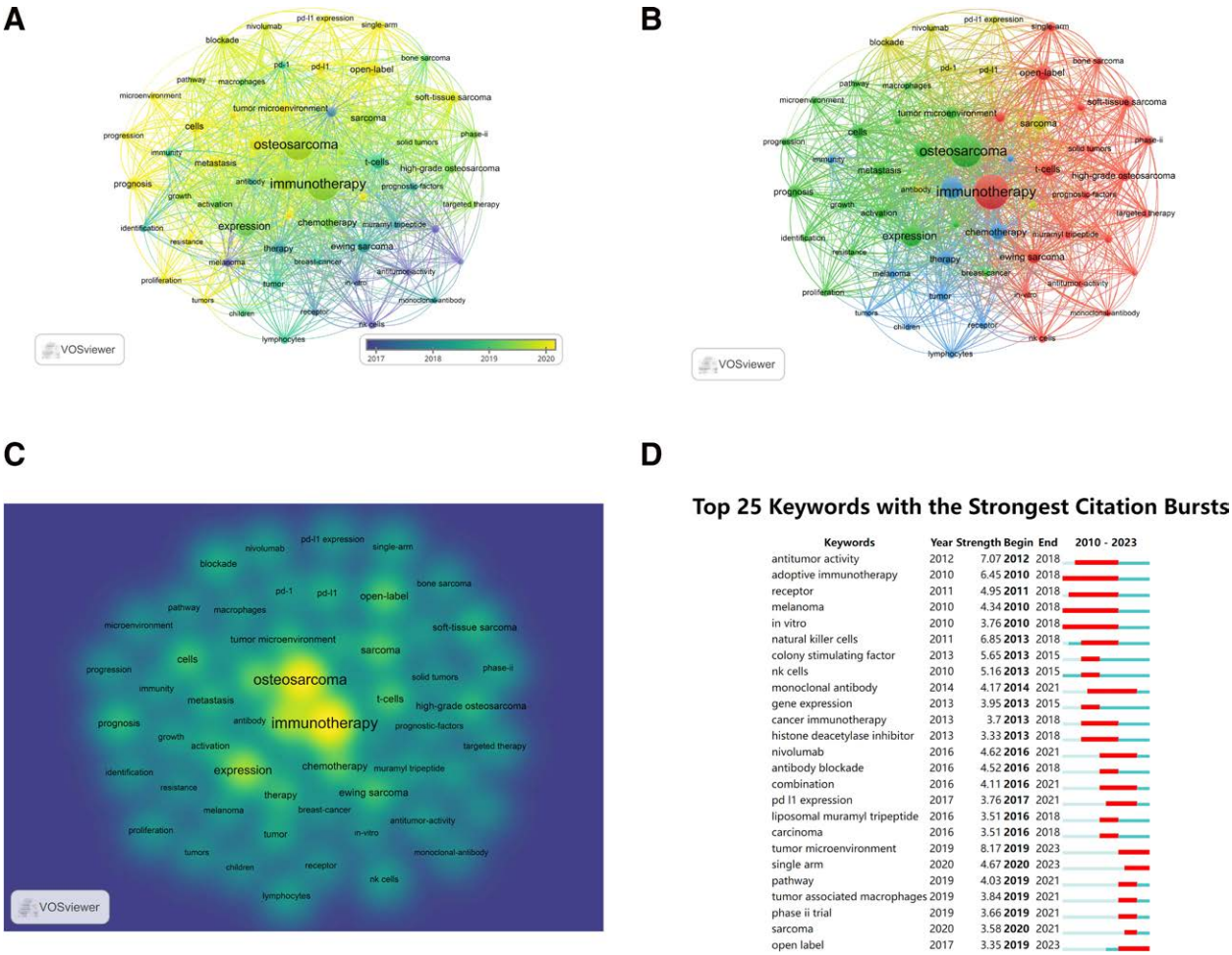

Figure 7. Keyword analysis for BM immunotherapy. (A) A network map of keywords changing over time. (B) Network clustering map of keywords. (C) A keyword density map. (D). The keywords that demonstrate significant spikes in citations in articles pertaining to immunotherapy research in BM.

patients experience recurrence and metastasis, and conventional treatment methods have limited efficacy.[20] Immunotherapy kills tumor cells through the patient's own immune system.[21] In recent years, there has been a gradual increase in the number of publications covering immunotherapy for BM. However, the current research status and trends in this field lack systematic summarization and review. We conducted a bibliometric analysis to assess the research focus and trends of immunotherapy in bone sarcoma. The results demonstrated an increasing trend in publications on immunotherapy in BM research over the past 14 years. This study suggested an increasing interest in immunotherapy in the field of BM research.

4.2. Countries and institutions

In terms of country analysis, China had the highest number of publications (n = 284), while the United States had the highest total citation frequency (8013 citations). China ranked second in terms of total citation frequency, with 3855 citations. Notably, although Canada published fewer papers, it had the highest average number of citations per paper (41.11 citations), suggesting high-quality contributions to BM immunotherapy research. Developed countries initially studied immunotherapy.[22] Furthermore, immunotherapy-related research depends on significant funding and support from advanced scientific and technological resources, providing developed countries with an advantage in this field. Collaborative efforts among institutions in different countries reduce resource wastage and accelerate the pace of immunotherapy research. The collaboration between China and the United States was notably strong, which had led to the significant rise in the number of Chinese publications after 2020. However, the average number of citations per paper from China was the lowest. As a developing country, China still lags behind other developed countries in terms of paper quality, necessitating further measures to enhance the quality of academic publications. Notably, the University of Texas MD Anderson Cancer Center had the highest number of publications and citations, underscoring its central role in the field of immunotherapy for BM. The MD Anderson Cancer Center stands as one of the oldest and most prestigious cancer treatment and research centers in the United States. Moreover, Shanghai Jiao Tong University and Sichuan University in China have made notable contributions to relevant research in recent years.

4.3. Authors and cited authors

The top 10 authors in terms of research contribution mainly originated from the United States, China, and Japan. Dean A. Lee, a scholar from the United States, has the highest number of contributions, with a total of 12 papers published in this field. Notably, despite not having the highest number of publications, Richard Gorlick, another scholar from the United States, had the highest total citation count. In Nature Communications (IF = 16.6), he published an article entitled "Immuno-genomic landscape of osteosarcoma" with the aim of identifying populations that would benefit more from immunotherapy by revealing

the immune expression profile of osteosarcoma.[23] Additionally, the 2022 publication in Clinical Cancer Research (IF = 11.5) titled "Membrane-Anchored and Tumor-Targeted IL12 (attIL12)-PBMC Therapy for Osteosarcoma" demonstrated the potential of Membrane-Anchored and Tumor-Targeted IL12 to activate peripheral blood mononuclear cells, thereby inhibiting the progression of osteosarcoma.[24] Our belief is that the close collaboration among institutions and authors from different countries has significantly contributed to the advancement of research in this field.

4.4. Journals and cited journals

Frontiers in Oncology (n = 37, IF = 4.7), Frontiers in Immunology (n = 33, IF = 7.3), and Cancers (n = 32, IF = 5.2) had all published more than 30 relevant articles in the field. Among highly cited journals, Journal of Clinical Oncology (IF = 45.3), Clinical Cancer Research (IF = 11.5), and Cancer Research (IF = 11.2) have all been cited more than 1000 times. It is worth noting that Clinical Cancer Research appears not only in the top 10 journals with the most publications but also in the top 10 journals with the most citations. It can be concluded that Clinical Cancer Research holds a central position in the journal co-citation network and may be one of the key journals in the field of BM immunotherapy, which is worth the attention of future researchers. The top 10 journals in terms of publication volume are related to clinical medicine, oncology, and immunology, while the top 10 co-cited journals are related to oncology and immunology. The combined analysis of dual-map overlay suggested that BM immunotherapy is transitioning from basic research to clinical research.

4.5. Reference analysis

This study analyzed the references of 719 articles, identifying and presenting the 5 articles with the highest citation counts, consisting of 3 original articles and 2 reviews. Among these, the journals that published "Human Epidermal Growth Factor Receptor 2 (HER2)-Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma" and "CAR T Cells Targeting B7-H3, a Pan-Cancer Antigen, Demonstrate Potent Preclinical Activity Against Pediatric Solid Tumors and Brain Tumors" have IF >10, with citation counts of 706 and 282, respectively, indicating considerable scholarly interest in these studies. A clinical study conducted by Ahmed et al demonstrated that the infusion of HER2-specific CD28-embedded antigen receptor T cells in patients with HER2-positive bone and soft tissue sarcoma showed good tolerance and inhibited tumor progression. Co-administration of HER2-CAR-T cells and immune checkpoint inhibitors can activate and prolong T cell survival, effectively suppressing invasive growth and proliferation of cancer cells in the tumor microenvironment.[25] B7-H3 upregulation has been reported to mediate immune inhibition in osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma.[26,27] Targeted B7-H3 CAR-T cells, designed by Majzner et al,[28] induced regression of xenografts in osteosarcoma and Ewing's sarcoma, offering a novel treatment strategy for refractory bone and soft tissue sarcoma. The research conducted by Nabil Ahmed and Robbie G. Majzner provides novel strategies for the immunotherapy of bone and soft tissue sarcoma. The key similarity among these highly cited references was the utilization of CAR-T cells in the treatment of bone and soft tissue sarcoma. CAR-T therapy redirects and reprograms T cells using genetic transfer techniques, reintroducing them into the body to enable recognition and attachment to tumor surfaces. This enables selective targeting and killing of tumor cells expressing specific antigens.[29] The clinical implementation of CAR-T cell-based immunotherapy offers a hopeful prospect for patients with refractory bone and soft tissue sarcoma. Frequently cited references are often regarded as significant contributions to research, and they play a crucial role in bibliometric analysis. We analyzed the network graph of co-cited references and identified the top 25 most frequently cited references. Among them, we examined 4 articles that had a citation strength >10. In vitro experiments conducted by Cho et al[30] demonstrated significant cytotoxicity against Ewing's sarcoma and rhabdomyosarcoma cells through co-culturing K562-mb15-41BBL cells and NK cells. Robbins et al[31] discovered that autologous TCR-transduced T cells can alleviate the progression of NY-ESO-1-positive synovial sarcoma by upregulating the NY-ESO-1 cancer/testis antigen. Furthermore, Kim et al[32] identified the potential of PD-1-positive lymphocyte infiltration and PD-L1 expression as prognostic indicators for soft tissue sarcoma and standards for immunotherapy. A clinical trial conducted by Tawbi et al[33] revealed the efficacy of pembrolizumab in treating pleomorphic and liposarcoma, along with observed objective responses in osteosarcoma and chondrosarcoma patients. Subsequently, we conducted cluster analysis on the keywords of the co-cited references. The results indicated that initial research emphasized "Ewing's sarcoma," "soft tissue sarcoma," "GD2," "NK cells," and "cancer immunotherapy." Ewing's sarcoma, a malignant neoplasm primarily affecting the skeletal and soft tissues, predominantly afflicts adolescents. Although it can manifest anywhere in the body, it frequently localizes in the pelvis, femur, sternum, and long bone shafts. Typically diagnosed at an advanced stage with metastasis, it is characterized by an unfavorable prognosis.[34] Previous studies have found that GD2 is a highly expressed tumor-associated immunotherapy antigen in malignant tumors such as osteosarcoma, rhabdomyosarcoma, and liposarcoma. In a mouse model of osteosarcoma, combination therapy with the third-generation GD2-CAR containing 14g2a-scFv and CD28, OX40, and CD3ζsignaling domains, along with all-trans retinoic acid, was shown to inhibit tumor progression.[35] Fisher et al[36] found significant anticancer effects when combining anti-GD2 antibodies with zoledronic acid and IL-2 in Ewing's sarcoma. Moreover, Rossig[37] reported the role of activated NK cells in lysing Ewing's sarcoma cells. The mid-term focus has shifted toward "PD-L1," "tumor microenvironment," and "immune suppression." Previous studies have found upregulation of PD-L1 in osteosarcoma, chondrosarcoma, synovial sarcoma, rhabdomyosarcoma, and Ewing's sarcoma.[38,39] With the development of sequencing technologies, the tumor microenvironment has become a hot topic in the field of cancer research in recent years. Zhou et al revealed the immune-suppressive microenvironment of osteosarcoma through single-cell RNA sequencing, highlighting that T-cell-mediated tumor suppression activity is stronger in the primary tumor site than in metastatic sites. Further research discovered widespread expression of the immune checkpoint TIGIT in T-cell subsets of osteosarcoma, suggesting that the use of TIGIT inhibitors may provide effective treatment for patients. Additionally, significant infiltration of M2 macrophages and CCR7 + dendritic cells was found in osteosarcoma samples, which are closely associated with enhanced metastasis and invasive capabilities of tumors.[40] It is worth noting that "tumor microenvironment" remains a hot topic in the field of BM immunotherapy after 2020. This study believes that in-depth research on the tumor microenvironment in BM can provide a theoretical basis for the development of new immunotherapy strategies and improvement of survival outcomes for patients with BM.

4.6. Keyword analysis

To analyze the research focus of BM immunotherapy, we conducted keyword analysis and emerging trend analysis. The results indicated that early-stage research keywords included "antitumor activity," "in vitro," and "NK cells." These topics mainly revolved around basic research in immunotherapy. NK

cells play a crucial role in tumor immunotherapy as they can directly kill tumor cells without tumor-specific antigen recognition.[41] Kubista et al[42] discovered that high thermal energy enhances the antitumor activity of NK cells against chondrosarcoma and osteosarcoma cells. This mechanism is associated with increased expression of heat shock proteins-72. Guma et al[43] demonstrated that combining IL-2 with NK cell therapy effectively enhances NK cell activity and function, resulting in the inhibition of lung metastasis in osteosarcoma patients. In mid-term research, the core keywords in the keyword network were "osteosarcoma," "immunotherapy," "PD-L1," and "T cell." Additionally, recent keywords included "open label," "single arm," and "tumor immune microenvironment." Somaiah et al[44] conducted clinical trials of Durvalumab plus tremelimumab in different soft tissue sarcomas and osteosarcomas. Bilusic et al[45] found that treatment with HuMax-IL8 (IL-8 monoclonal antibody) effectively suppressed IL-8 in sarcoma patients. Due to its safety and good tolerance, it could potentially be used in combination with other immune therapies. Moreover, the results of the emerging trend analysis align with the aforementioned findings. Recent literature keywords such as "Phase II trial," "single arm," "open label," and "tumor microenvironment" indicate that more clinical trials related to immunotherapy for BM may be conducted in the future. Additionally, more complex basic research will be undertaken in the "tumor microenvironment"

4.7. Limitation

This study conducted a pioneering bibliometric analysis of the literature on BM immunotherapy, offering objective data and insights to enhance our understanding of BM immune therapy research in the future. Nonetheless, several limitations should be acknowledged. Firstly, we solely relied on the WoSCC database as the literature source, which may have resulted in incomplete coverage of relevant studies. Secondly, we exclusively included papers published in English, potentially overlooking notable contributions in other languages. Lastly, due to the time frame of this study in 2023, the most recent publications were not incorporated, thereby limiting its ability to accurately represent the latest research.

5. Conclusions

This study revealed the growing significance of immunotherapy in the realm of BM treatment. By employing bibliometric techniques, we illustrated the noteworthy contributions of countries, institutions, authors, and their research accomplishments within the domain of BM immunotherapy. Consequently, this study offers researchers a comprehensive understanding of the present landscape and future prospects of BM immunotherapy.

Author contributions

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Investigation: Kaiyu Shen.
Methodology: Kaiyu Shen, Liu Yang.
Resources: Liu Yang.
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Supervision: Kaiyu Shen, Liu Yang, Shuaiyi Ke.
Validation: Kaiyu Shen, Shuaiyi Ke.
Writing – original draft: Kaiyu Shen, Wencang Gao.
Writing – review & editing: Kaiyu Shen, Shuaiyi Ke, Wencang Gao.

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