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Research Paper

How has the field of metastatic breast cancer in bones evolved over the past 22 years?

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HIGHLIGHTS

- This is the first report showing a relatively objective, comprehensive, and quantitative analysis of changes in research hotspots in the field of metastatic breast cancer in bones in the past 22 years.
- We found that using different indicators and diverse analyses of the same indicators can widely determine the main clinical practice, clinically related trials, and directions of metastatic breast cancer in bones, the changes in the past 22 years, and the current challenges in the field of breast cancer bone metastasis. For example, we hope that what is currently relatively weak research on metastatic breast cancer in bones should be developed, including finding more valuable potential targets, refining molecular mechanisms, and accelerating the process of clinical application of basic research results.
- In view of the relatively weak basic research in the field of breast cancer bone metastasis and the lack of cure plans, we put forward some preliminary suggestions.

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ABSTRACT

Background: Although knowledge on metastatic breast cancer in bones (MBCB) has increased rapidly over the past 22 years, a comprehensive and objective bibliometric analysis is still lacking.
Materials and methods: We used R, VOSviewer, and Citespace software to conduct a bibliometric analysis of 5,497 papers on MBCB from the Web of Science Core Collection (WOSCC) using author, institution, country/region, citation, and keyword indicators.
Results: A general strong sense of scholarly collaboration was noted in the MBCB field at the author, research institution, and country/region levels. We discovered some outstanding authors and highly productive institutions, but with less collaboration with other academic groups. Unbalanced and uncoordinated developments were observed among countries/regions in the field of MBCB research. We also found that by using various indicators and applying different analysis methods to them, we were able to broadly identify primary clinical practices, relevant clinical experiments, and directions for bioinformatics regarding MBCB, changes over the past 22 years, and current challenges in the field. The development of knowledge on MBCB is progressing greatly; however, MBCB is still incurable.
Conclusion: This study is the first to use bibliometrics to provide an overall analysis of the scientific output of MBCB studies. Palliative therapies for MBCB are mostly in a mature state. However, research on the molecular mechanisms and immune response to tumors related to the development of treatments to cure MBCB remains relatively immature. Therefore, further research should be undertaken in this area.

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1. Background

Breast cancer (BC) is the most common malignancy found in women. Each year, approximately two million women develop BC and more than 600,000 women die from it—and the incidence rate is increasing [1,2]. BC not only dramatically decreases a woman's quality of life but also seriously affects her appearance [3–5]. Because of continuous progress in diagnosing and treating BC in recent years—including a precision medical plan proposal—the mortality rate has decreased considerably, especially for those who detected the cancer early [2,6,7]. However, the lack of a standard presentation in the early stages of BC makes early diagnosis difficult [8,9]. When a patient's disease progresses to an advanced stage, existing conventional treatment options are limited, and the patient often has a poor prognosis [10].

Studies have reported that distant metastatic lesions in patients with advanced BC are mostly found in the bones, simultaneously the most common primary site of bone metastasis is also breast [11–13]. Once bone metastasis occurs, patients often present with bone or joint pain, pathological fractures, or neuropathic pain [14,15]. Patients with metastatic breast cancer in bones (MBCB) are usually not able to be cured by available treatment options, and they often die from multiorgan failure within five years [13]. Therefore, this disease should be further studied to improve the above situation. MBCB has received attention from a large number of scholars during the last 22 years, and scientific development in this field has expanded greatly. However, the current concern is that the research data are scattered, especially the knowledge on the mechanisms of MBCB seem to be chaotic when people need to read many different literatures, which is not conducive to the efficient work for relevant researchers to grasp the chief findings of the previous studies and to refine the hot spots of the future prospective research for MBCB[16].

Many traditional reviews and *meta*-analyses have been conducted on MBCB. However, they are limited to certain perspectives on or indicators of MBCB research, they involve relatively small research samples, and they present relatively limited analyses and discussions. All of these are not conducive to a systematic and intuitive presentation of the entirety of the research, nor do they allow readers to grasp the overall dynamics of the research and development in the field [14,17–19]. Moreover, traditional reviews are influenced by authors' biases, making conclusions less accurate [20].

By the integration of mathematics, bibliographies, and statistics, bibliometrics focuses on quantifying an integrated body of knowledge; thus, it can, to some extent, solve the above-mentioned problems [21,22]. Bibliometric analyses have already been applied to various fields of medical research and have assisted to resolve medical issues [16,20]. Unfortunately, few researchers have used this method to estimate the scientific output regarding MBCB comprehensively and quantitatively. Therefore, to fill this gap, we used bibliometric methods to comprehensively and objectively analyze the authors, citations, keywords, and other indicators in the papers related to MBCB. We hope that this study will not only help researchers who are interested in this subject to understand the relevant development directions quickly and accurately, but also provide new insights into researching, diagnosing, and treating MBCB.

2. Materials and methods

2.1. Data collection

All data for this study were collected from the Web of Science Core Collection (WOSCC), a commonly used comprehensive journal citation index database. The following search terms were used: TS = ((“osseous metastas*”) OR (“metastatic tumor of bone*”) OR (“bone metastas*”) OR (“osteolytic metastas*”) OR (“osteoblastic metastas*”) OR (“skeletal metastas*”) OR (“bone marrow metastas*”) OR (“metastatic carcinoma of bone marrow”)) AND ((“breast cancer”) OR (“breast carcinoma”) OR (“breast tumor”) OR (“mammary cancer”) OR (“mammary carcinoma”) OR (“mammary tumor”)). Only articles, reviews, and early access papers written in English that were published between January 1, 2000, and December 27, 2022 were included. The content of all data records in this study is “Full Record and Cited Reference.” Papers were downloaded in BibTeX format from WOSCC on December 27, 2022.

Two authors (Chen Y and Guo ZN) independently conducted the data collection. Any disagreement over data inclusion was resolved through discussion among all authors. The detailed data collection process is shown in Fig. 1.

2.2. Bibliometric analysis

The main software used in this study was R (4.2.2), VOSviewer (1.6.18), and Citespace (6.1.R2 Basic). R was used for data manipulation, statistical visualization, and complete bibliometric analysis to construct keyword cloud maps, topic trend maps, and keyword time heat maps. VOSviewer was used for country/region co-authorship analysis maps, keyword clustering maps, literature coupling maps, etc. Citespace was selected to efficiently mine hotspots to create a keyword burst detection map.

3. Results

3.1. Primary information

We collected data from 5,497 papers authored by 21,703 researchers. One hundred and ninety papers were written by single authors. Of the rest, 22.99% were internationally co-authored. A total of 131,029 references were cited, averaging about 41 references per paper. The papers generated 8,042 Keywords Plus and 7,131 Author's Keywords (see Table 1).

3.2. Analysis of scientific output at the distinguished author level

We found 101 researchers who co-authored at least 11 papers on MBCB. Fig. 2a and 2b show that most of these authors were in several large collaborative groups, revealing the collective efforts to expand the development of the MBCB field. Some of the highly productive authors had less collaboration with other scholars.

As shown in Fig. 2b, almost no new prolific academic groups or collaborations emerged after 2018. The number of citations an author receives can reflect their influence in the field to some extent. As seen in Fig. 2c, fewer new distinguished authors have emerged in recent years. Moreover, the majority of distinguished authors have been long-time practitioners in the field.

3.3. Analysis of scientific output from the perspective of High-Producing institutions

Of the 5,182 research institutions identified, 68 produced more than 26 publications (see Fig. 3). Overall, there were relatively close collaborations between research institutions in Europe and the USA. For example, the University of Texas MD Anderson Cancer Center, the University of Sheffield, and Amgen Inc. have high volumes of publications, citations, and total link strength. These institutions were at the center of the collaborative network, as shown in Fig. 3.

Other national research institutions had relatively weak collaborative relationships. As shown in Fig. 3b, new participation in MBCB research has been low, and new interinstitutional collaborations have been few in recent years. However, Fig. 3b also reflects that research institutions in China, such as China Medical University, Shanghai Jiao Tong University, and Harbin Medical University, have become more influential in the field of MBCB.

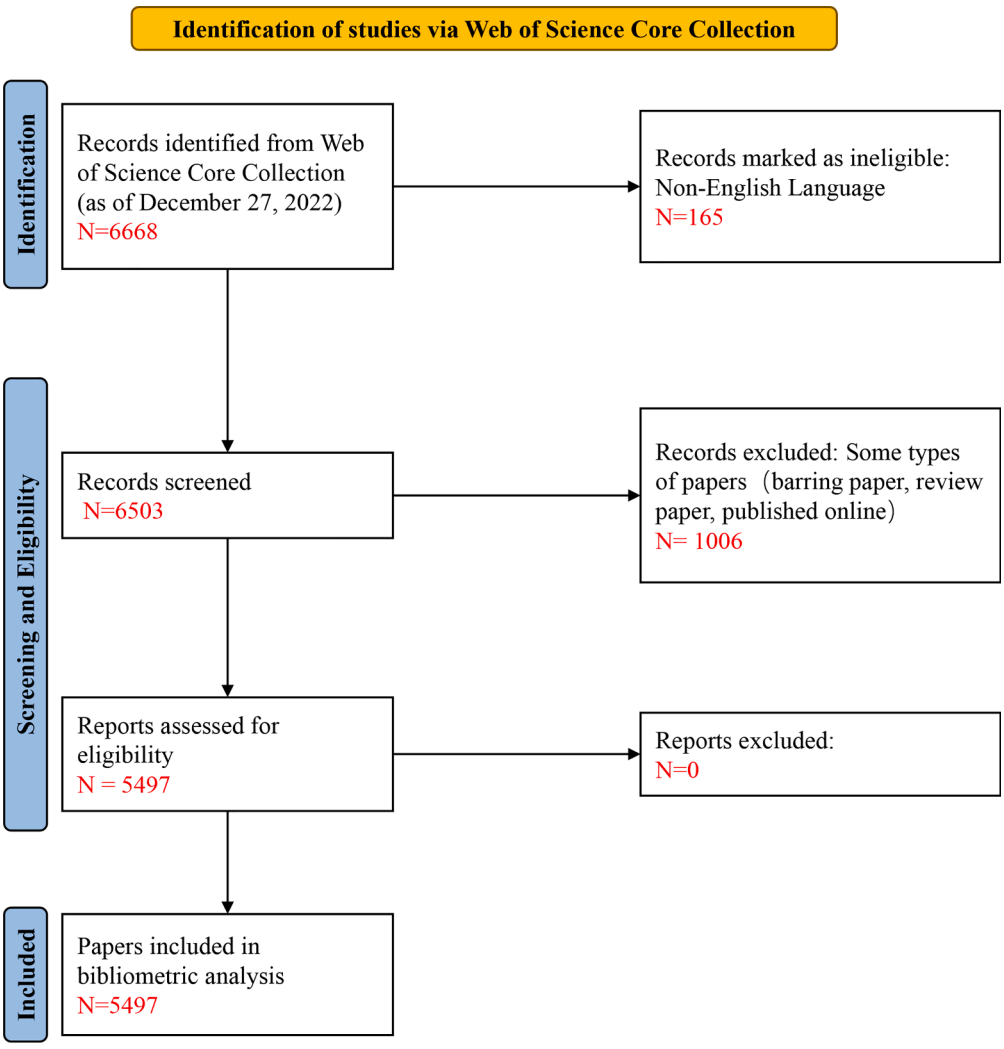


Fig. 1. MBCB paper data collection flow chart.

3.4. Analysis of scientific output at the National/Regional level

About one-third of the papers included in this study were published in the USA (n = 1,847). Other countries in which many papers were published were China (n = 881), the UK (n = 568), and Germany (n = 518).

We also found that the largest contribution to MBCB research mainly came from developed countries, indicating that developed countries have higher levels of research and influence and have contributed more to the development of the MBCB field. As shown in Fig. 4b and S1, there have been strong collaborations between European countries and the USA. Fig. 4c and S1 show that developing countries, such as China, India, and Tunisia, have seen a rapid increase in the number of publications and new collaborations in recent years.

3.5. Analysis of scientific output from the publications and citations of outstanding papers

Since 95 publications and 42 citations in 2000, the overall trend in the number of publications and citations has been increasing each year (see Fig. 5a), despite fluctuations. In the past five years, although the average number of publications has been above 250, the annual volume of publications has not been stable. For example, in 2022, a significant drop could be seen in the number of publications and citations. However, the exponential increase in citation frequency over the last five years reflected the fact that this research field continued to receive attention from relevant scholars.

We used VOSviewer to select the top 80 papers that were cited more than 110 times. As seen in Fig. 5b, we broadly classified them into three categories. Cluster 1 (in red) contained studies on relevant mechanisms, including papers by TA Guise (1996, *J Clin Invest*[23]; 2006, *Clin Cancer Res*[24]) and JJ Yin (1999, *J Clin Invest*[25]). Cluster 2 (in blue and green) contained studies on relevant clinical experiments, including a paper by JR Berenson (1998, *J Clin Oncol*[26]). Finally, Cluster 3 (in yellow) contained studies on clinical diagnosis and treatment, including papers by RE Coleman (1987, *Brit J Cancer*[27]; 2006, *Clin Cancer Res*[28]).

The classification clusters indicate that current MBCB research is mainly focused on related mechanisms, clinical trials, and clinical diagnosis and treatment. The co-citation intensity of these papers was high (Fig. 5b), indicating that the research directions of the papers were somewhat similar.

3.6. Analysis of research focus and development trends from High-Frequency keywords

3.6.1. Analysis of High-Frequency keywords

Tables 2 and 3 and Fig. S2 show the analysis of the research history, dynamics, and future of the MBCB research field, respectively. In addition to phrases corresponding to BC and BM, keywords that appeared

Table 1
Main information of MBCB papers included in this study.

Description	Results
MAIN INFORMATION ABOUT DATA	
Timespan	2000:2022
Sources (Journals, Books, etc.)	1057
Documents	5497
Annual Growth Rate %	4.42
Document Average Age	9.1
Average citations per doc	41.18
References	131,029
DOCUMENT CONTENTS	
Keywords Plus (ID)	8042
Author's Keywords (DE)	7131
AUTHORS	
Authors	21,703
Authors of single-authored docs	190
AUTHORS COLLABORATION	
Single-authored docs	278
Co-Authors per Doc	6.37
International co-authorships %	22.99
DOCUMENT TYPES	
article	4166
article; book chapter	17
article; early access	21
article; proceedings paper	150
article; retracted publication	3
editorial material; early access	1
review	1130
review; book chapter	5
review; early access	4

frequently included prostate cancer, expression, and zoledronic acid.

We used VOSviewer to select 100 high-frequency keywords from the included papers (see Fig. 6a), which were classified into three categories. Cluster 1 (in green) had words relating to clinical diagnosis and treatment, including chemotherapy, positron emission, tomography, and diagnosis. Cluster 2 (in blue) had words relating to relevant clinical experiments, including efficacy, quality of life, and long-term efficacy. Cluster 3 (in red) had words relating to basic experiments, including in vitro, cells, hormone-related protein, and transforming growth factor-β (TGF-β).

From the 100 keywords, we removed phrases with meanings similar to "breast cancer" and "bone metastasis" and created Fig. 6b based on them. As can be seen, the remaining keywords were also divided into three categories. Cluster 1 (in blue) had words relating to clinical diagnosis and treatment, including positron emission tomography (PET), scintigraphy, and chemotherapy. Cluster 2 (in green) had words relating to clinically relevant experiments, including Phase III, efficacy, and quality of life. Cluster 3 (in red) had words relating to basic experiments, including TGF-β, hormone-related protein, and NF-κβ.

From a keyword perspective, we can conclude that the current MBCB research is focused on clinical diagnosis and treatment, clinically relevant experiments, and basic experiments (Fig. S3).

3.6.2. Analysis of keyword evolution

To further understand the past and emerging research directions, we analyzed current research hotspots and future development trends (Figs. 7 and S1). In general, as shown in Figs. 7 and S4–6, fewer new keywords have appeared in the past five years. Moreover, most of the high-frequency keywords were concentrated in studies from the past five years. To a certain extent, this indicated not only a decrease in emerging research directions but also weak emerging research directions.

As shown in Figs. 7, S5, and S6, MBCB papers from 2000 to 2014 contained keywords related to relevant clinical experiments (e.g., therapy oncology group and randomized trial), basic research (e.g., parathyroid hormone-related protein, TGF-β, and hormone-related protein), and clinical diagnosis and treatment (e.g., bone pain, oral clodronate, chemotherapy, and radiotherapy). The word "guidelines" was also common during this period.

It was surprising that, for 15 years from 2006 to 2021, the keyword "bone remodeling" had appeared with high frequency (and still appears frequently). From 2015 to 2022, the high-frequency keywords used in basic MBCB research included CDK4, signaling pathway, epithelial-mesenchymal transition (EMT), and tumor microenvironment. The highest-frequency keyword found in clinical trials was open-label. Popular keywords related to the diagnostic and therapeutic fields included denosumab, immunotherapy, stereotactic body radiotherapy, and fulvestrant. Finally, keywords related to recent advances in bioinformatics included the Surveillance, Epidemiology, and End Results (SEER) database, *meta*-analysis, and statistics.

3.7. Analysis of the state of the main research directions in the MBCB field

Fig. 8 was presented to validate the results of the above analysis and to achieve a better understanding of the development status of each direction in the MBCB research field. The first quadrant shows motor themes (e.g., radiotherapy, denosumab, and zoledronic acid), indicating that the direction of therapeutic and clinical experiments related to these keywords is important and well developed. The second quadrant shows niche themes, including imaging and computed tomography (CT), reflecting that although the clinical diagnostic direction related to these keywords has been initially developed, the current influence on the field is low and should be further strengthened. The third quadrant's emerging or declining themes have phrases related to clinical practice directions, such as chemotherapy, which indicates that the clinical practice directions related to these keywords might be experiencing a rise or decline. Finally, quadrant 4 comprises basic themes with keywords related to other tumors and mechanisms, such as lung cancer and osteoclast, indicating that MBCB not only has features common with other tumors but also that osteoclast-related mechanism research has some influence but has not been well developed and should continue to be strengthened in the future. Also, there were keywords related to MBCB mechanisms, such as in vitro, mechanisms, and hormone-related protein, at the junction of the first and second quadrants, indicating that the influence of these mechanism-related studies might be gradually expanding.

Directions related to the keywords appearing at the junction between the first and fourth quadrants might suggest that the relevant contents begin to gain better development and gradually expand in influence. Also, phrases/words such as "positron emission tomography" and "scintigraphy" were distributed in different themes (Fig. 8A and 8B), which suggests that the direction associated with these keywords might be somewhere between the two states of the first and fourth quadrants. However, the facts may be biased toward the results of the analysis of phrases originating from Keywords Plus. This is because the number of phrases sourced from keywords and those included in this study was much higher than the number of phrases sourced from the Author's Keywords. Furthermore, some papers might not have Author's Keywords, which might lead to more accurate results for the analysis of phrases originating from Keywords Plus.

4. Discussion

We performed bibliometric analyses using indicators of authors, institutions, countries/regions, citations, and keywords from the data of 5,497 papers from WOSCC. We found a generally strong sense of scholarly collaboration at the author, research institution, and country/region levels, which is consistent with the status of single-authored documents and international co-authorships (see Table 1). However, there were some problems with collaboration in the MBCB field. This might be because the research has encountered difficulties that have not been well addressed by research institutions with high previous scientific output, which might also explain the inconsistent scientific output

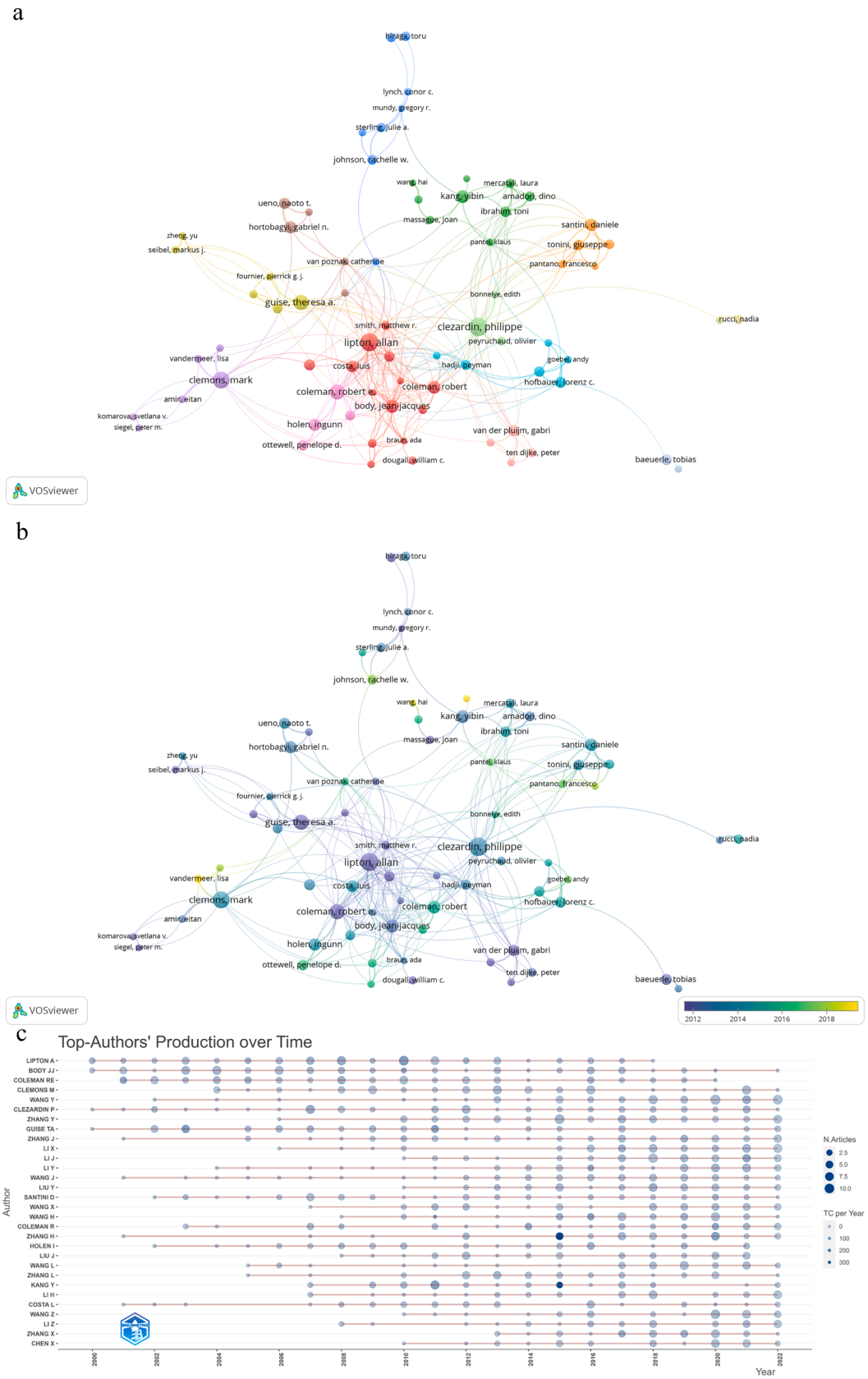


Fig. 2. Author-level analysis. a. Co-author network visualization map*; b. Co-author overlay visualization map*; c. Top 30 authors over time. * Small circles represent co-authors; areas inside the small circles represent the number of papers; lines represent cooperation between authors.

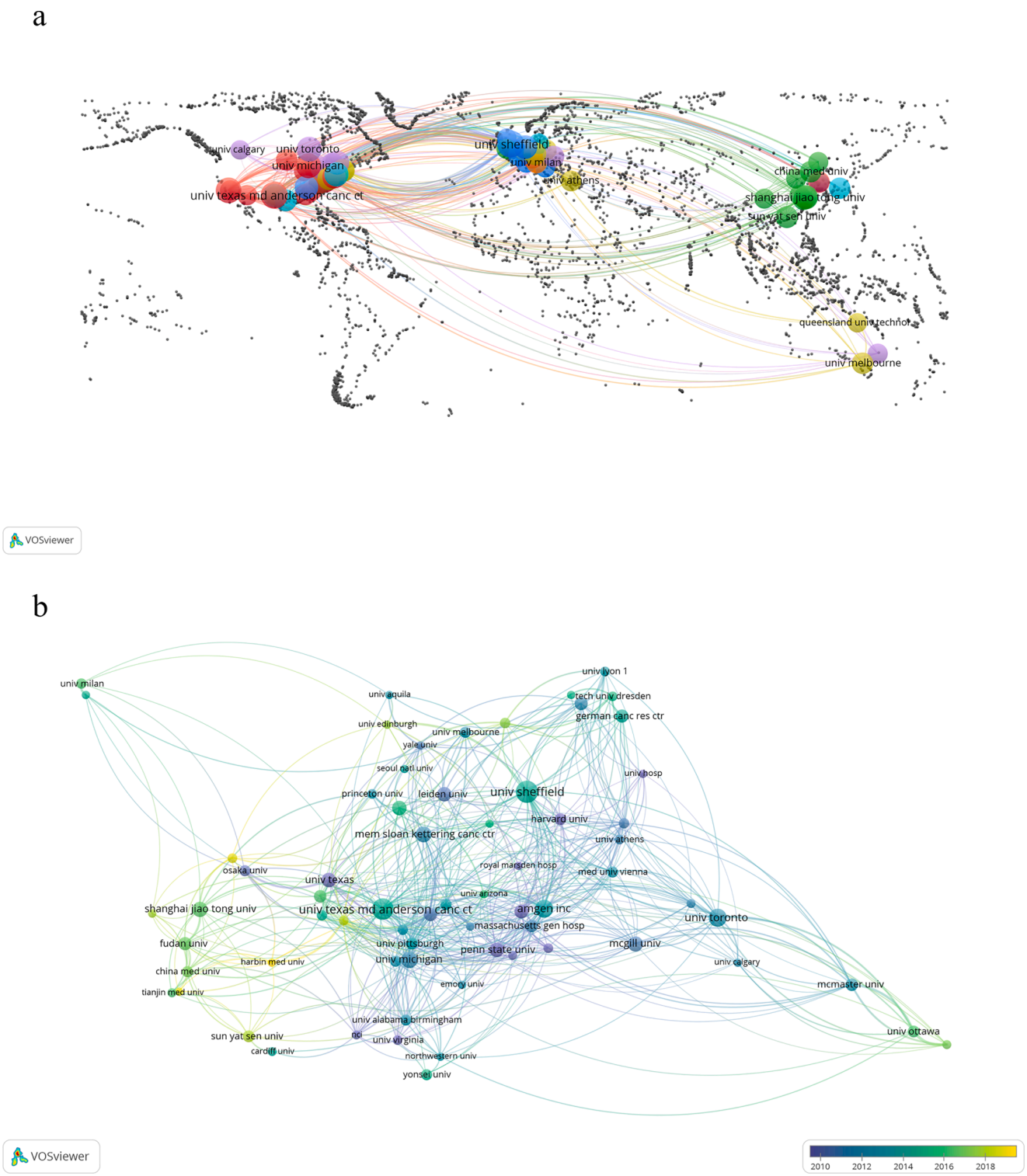
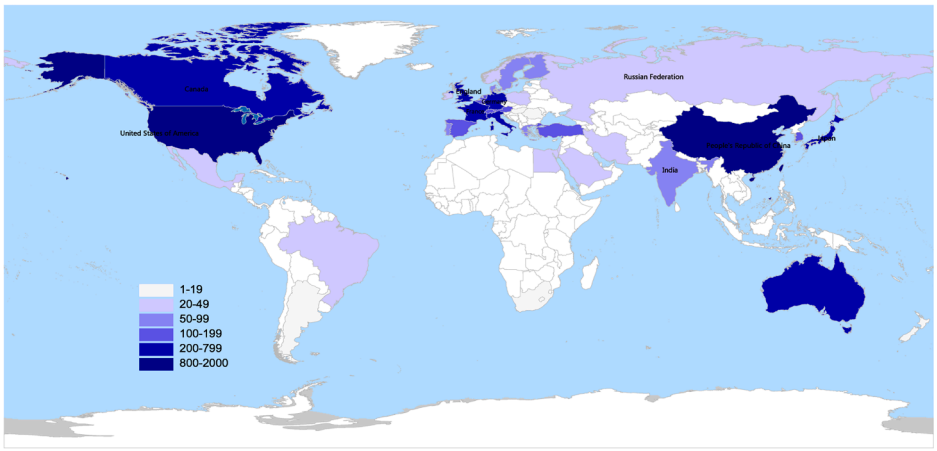


Fig. 3. Institution-level analysis. a. Network visualization map of cooperative institutions*; b. Overlay visualization map of cooperative institutions*. * Small circles represent cooperative institutions; areas inside the small circles represent the number of papers; lines represent cooperative relationships between institutions.

in recent years. Therefore, in the future, distinguished authors and highly productive institutions should strengthen their collaborations with scholars and research institutions outside academic groups.

In the country/region level analysis, we found uneven, uncoordinated development among countries/regions. Although the fact that the situation in BC is relatively optimistic (lower morbidity and mortality), developed countries have made enormous contributions to the development of the MBCB field [1,2]. In contrast, the situation has been the opposite in developing countries [1,2,29,30]. If MBCB relevant research in developing countries can be assisted and supported by the research groups from developed countries, the research progress in this field of MBCB will be greatly promoted. The patients of MBCB in developing countries will gain more medical attention, as well as better diagnosis and treatment resources. Hence, more international cooperation groups are encouraged. It was inspiring to note that, in recent years, some developing countries have been expanding their influence in the MBCB

a



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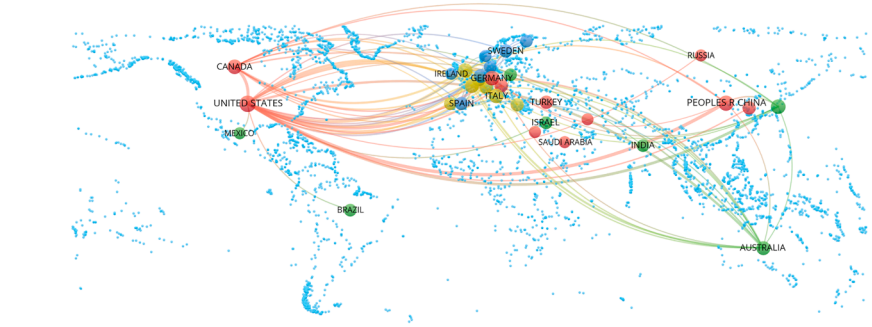

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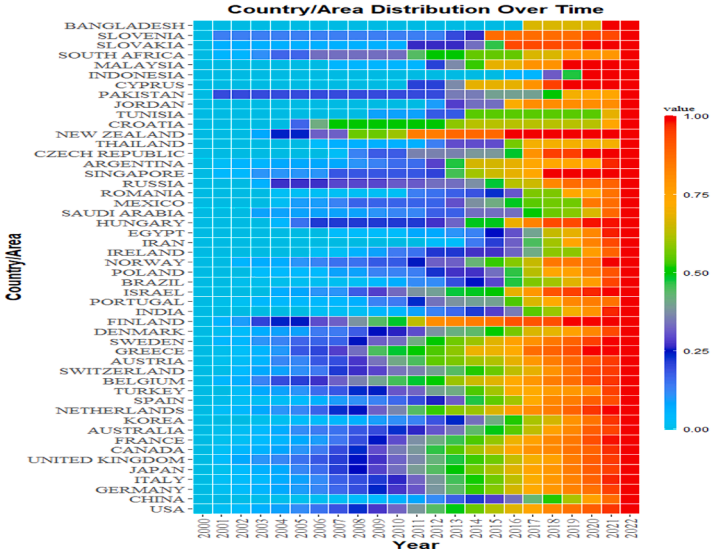

Fig. 4. Country/regional-level analysis. a. Published paper distribution map; b. Network visualization map of cooperative countries/regions in papers*; c. Thermal diagram of the time distribution of national/regional papers**. * Small circles represent co-authors' countries/regions of origin; areas inside the small circles represent the number of papers; lines represent cooperative relationships between countries/regions. ** Values represent the ratio of the total number of papers published from 2000 to a certain year in a country to the total number of papers published in the country.

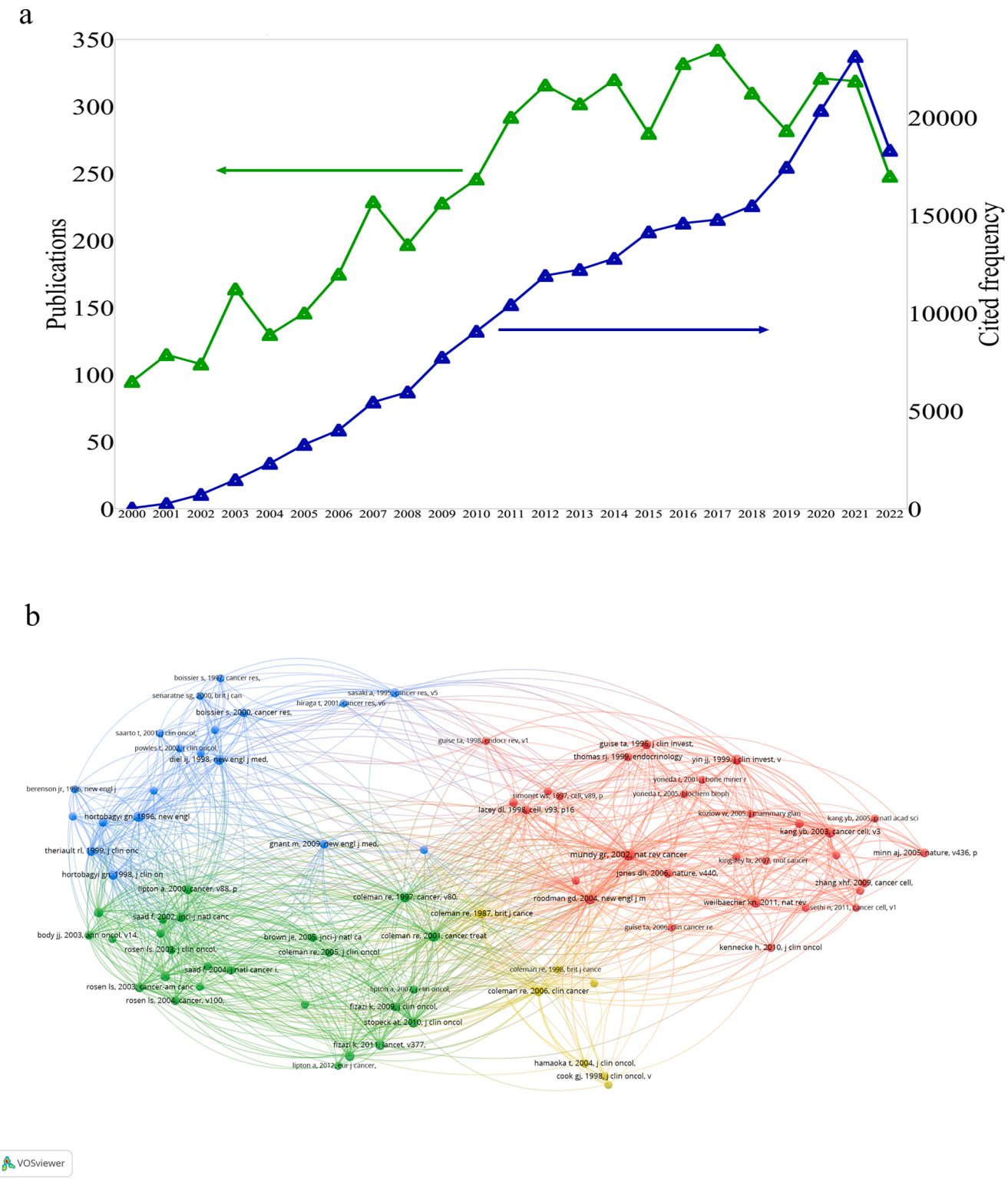

Fig. 5. Published paper volume and citation analysis chart. a. Annual publications and citations of papers from 2000 to 2022; b. Co-citation analysis network map of high-frequency references*. *Small circles represent high-frequency references; areas inside the small circles represent the number of citations; lines represent the co-citation relationships between citations.

field and have been actively integrating into the academic cooperative community. This has not only helped alleviate the problem of uneven, uncoordinated development among countries/regions but also promoted the reduction of BC morbidity and mortality in developing countries. It has also helped address difficulties encountered in the MBCB field, as reflected by indicators such as high-yielding institutions, publications, citations, and keywords.

The instability of the annual volume of knowledge on MBCB indicates that the field may have encountered some difficulties or that relevant research has not yet matured, and further research is needed to improve it. This is similar to the results of the analysis of scientific output from highly productive institutions.

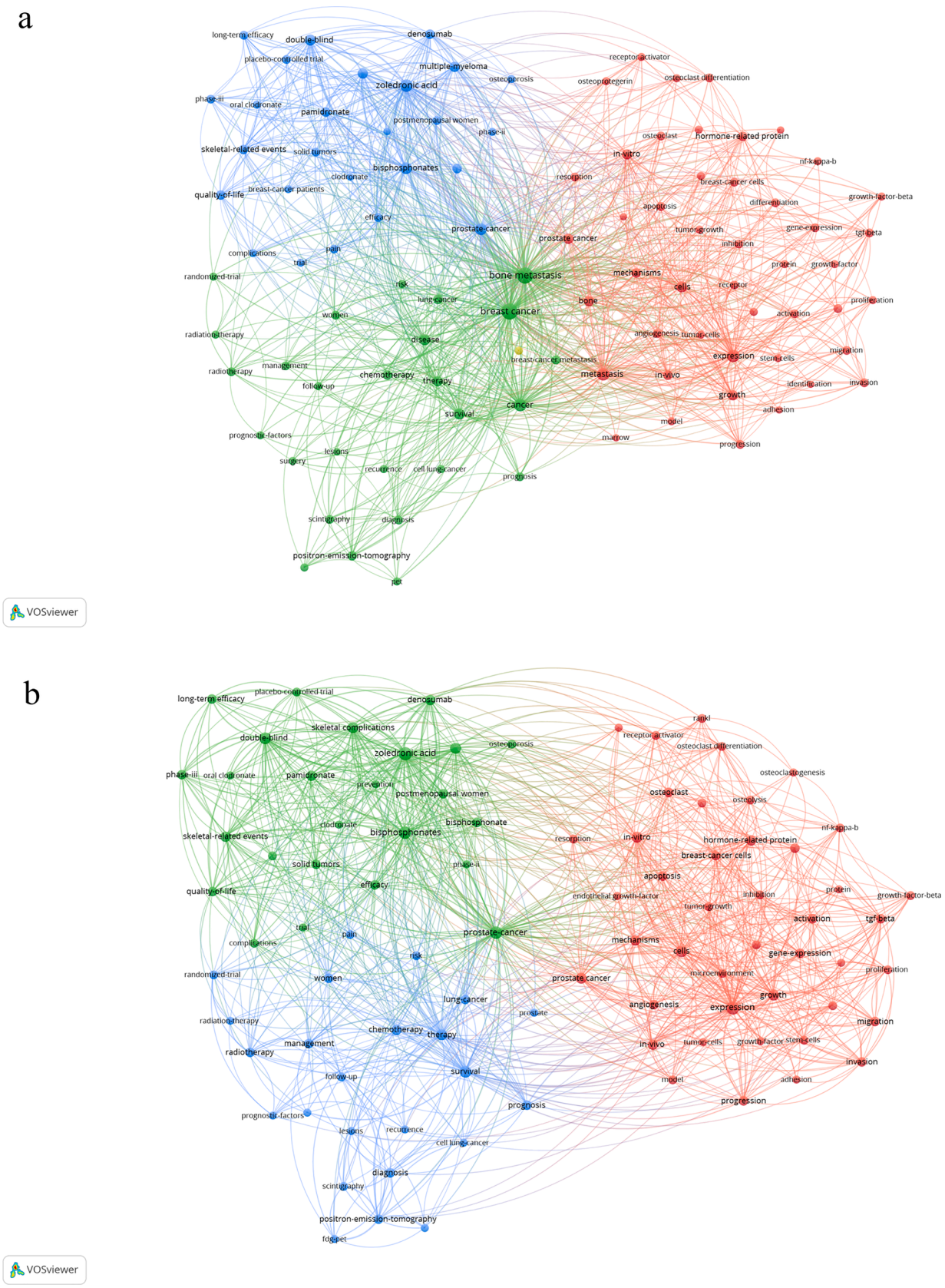

Fig. 6. Keyword co-occurrence analysis map (all keywords)*. *Small circles in a and b represent keywords; areas inside the small circles reflect keyword frequency; different colors represent categories; lines connecting circles represent keywords that appear in the same paper. Note: Some phrases meaning the same as "breast cancer" and "bone metastasis" have been removed in b.

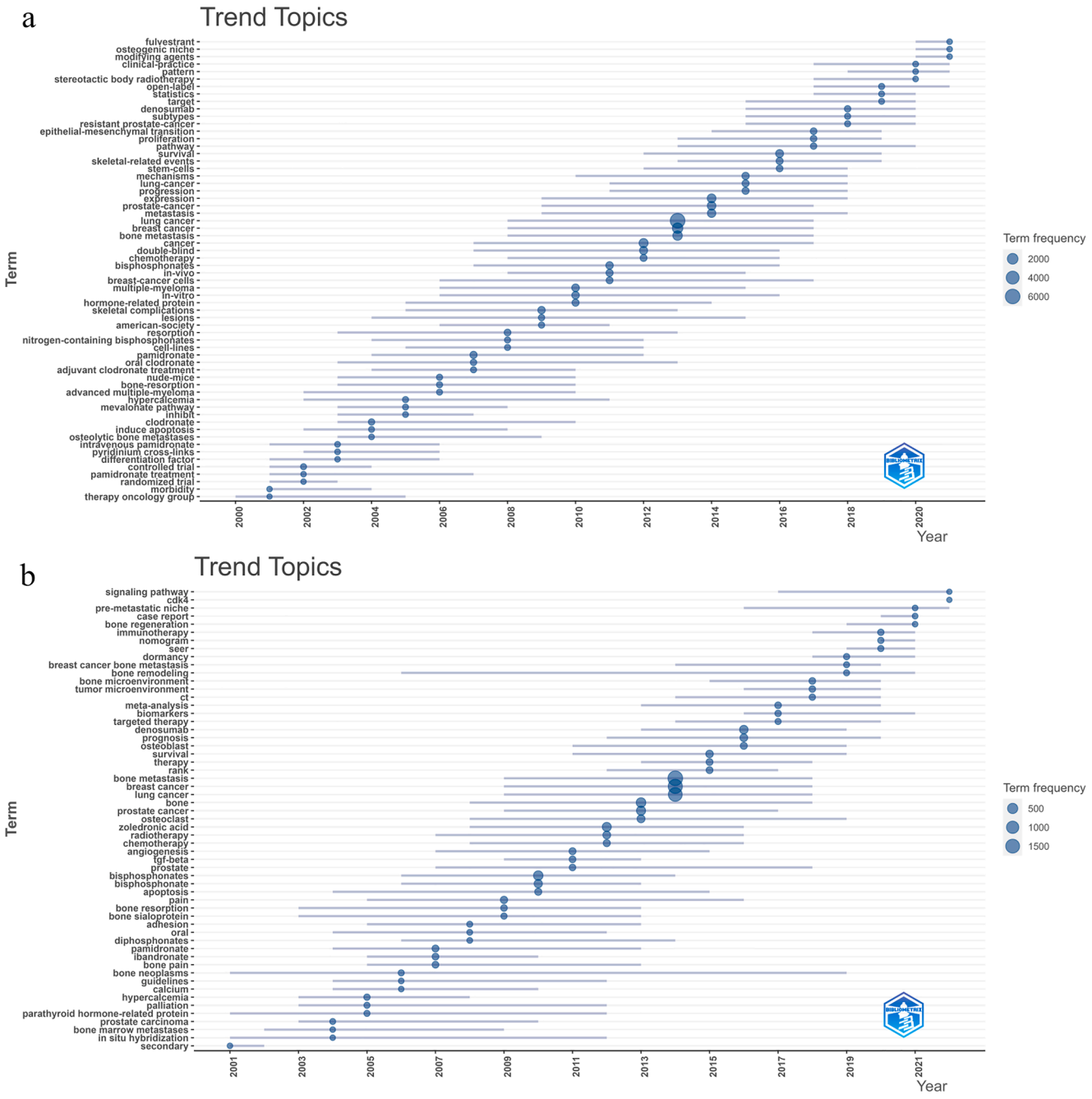

Fig. 7. Graph of trending topics. a. Keywords Plus; b. Author's Keywords.

We also identified the main clinical practices, relevant clinical experiments, and bioinformatics directions, their changes over the past 22 years, and the current challenges in the MBCB field. Our main analysis process is detailed in Fig. 9. Based on the results presented in the previous section, we will discuss the analysis item by item.

4.1. Clinical practice and related experimental directions

Clinical practice and related experimental directions were divided into two main categories, including the diagnostic and therapeutic ones. The diagnostic aspects of the MBCB field were becoming increasingly popular in terms of nuclear medicine and molecular imaging. Molecular imaging can be used to diagnose, stage, and evaluate other clinical indicators of BC by reflecting changes in certain molecules and elucidating their biological behavior in the living state using imaging methods [31]. In earlier years, the application of Tc-99 m-related drugs as imaging agents yielded excellent consequences in the diagnosis of breast and lung cancer metastases in bones [32]. However, almost no studies on Tc-99 m have been reported in recent years. This might be related to the fact that 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) is significantly better than Tc-99 m in diagnosing MBCB [33]. In recent years, FDG-PET/CT has become more widely used and has achieved encouraging results in terms of diagnosing certain conditions, clinical staging, and detecting recurrence [31,34,35]. However, it is worth noting that FDG-PET/CT is currently not applicable to the clinical staging of early and operable advanced BC [31]. Some novel radiotracers have potential clinical applications but are still far from widespread clinical practice [31,36–38]. CT has important applications in studying the molecular mechanisms of MBCB and in exploring new treatments and more effective therapeutic drugs [39,40].

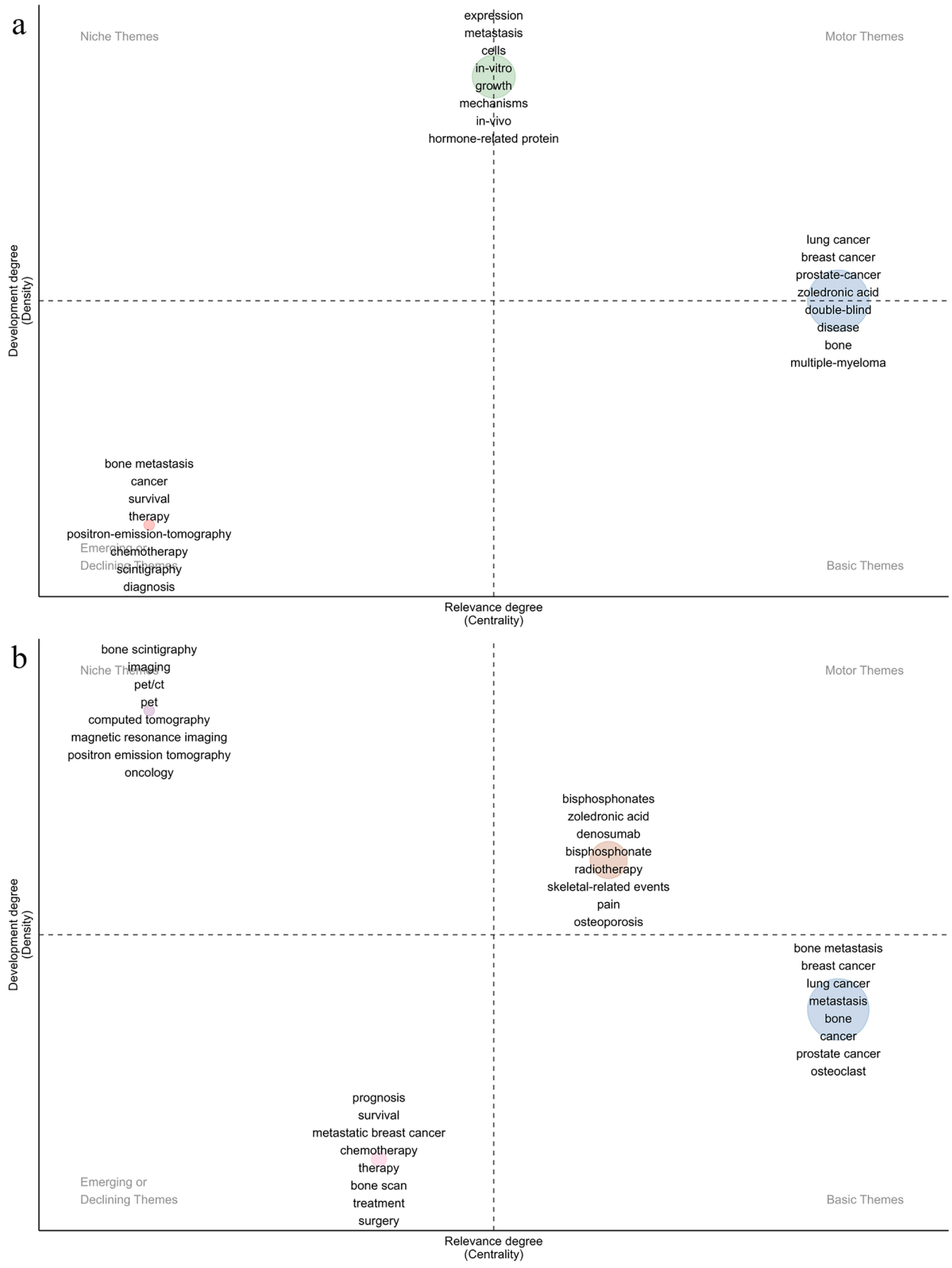

Fig. 8. Strategic coordinate map of themes. a. Keywords Plus; b. Author's Keywords.

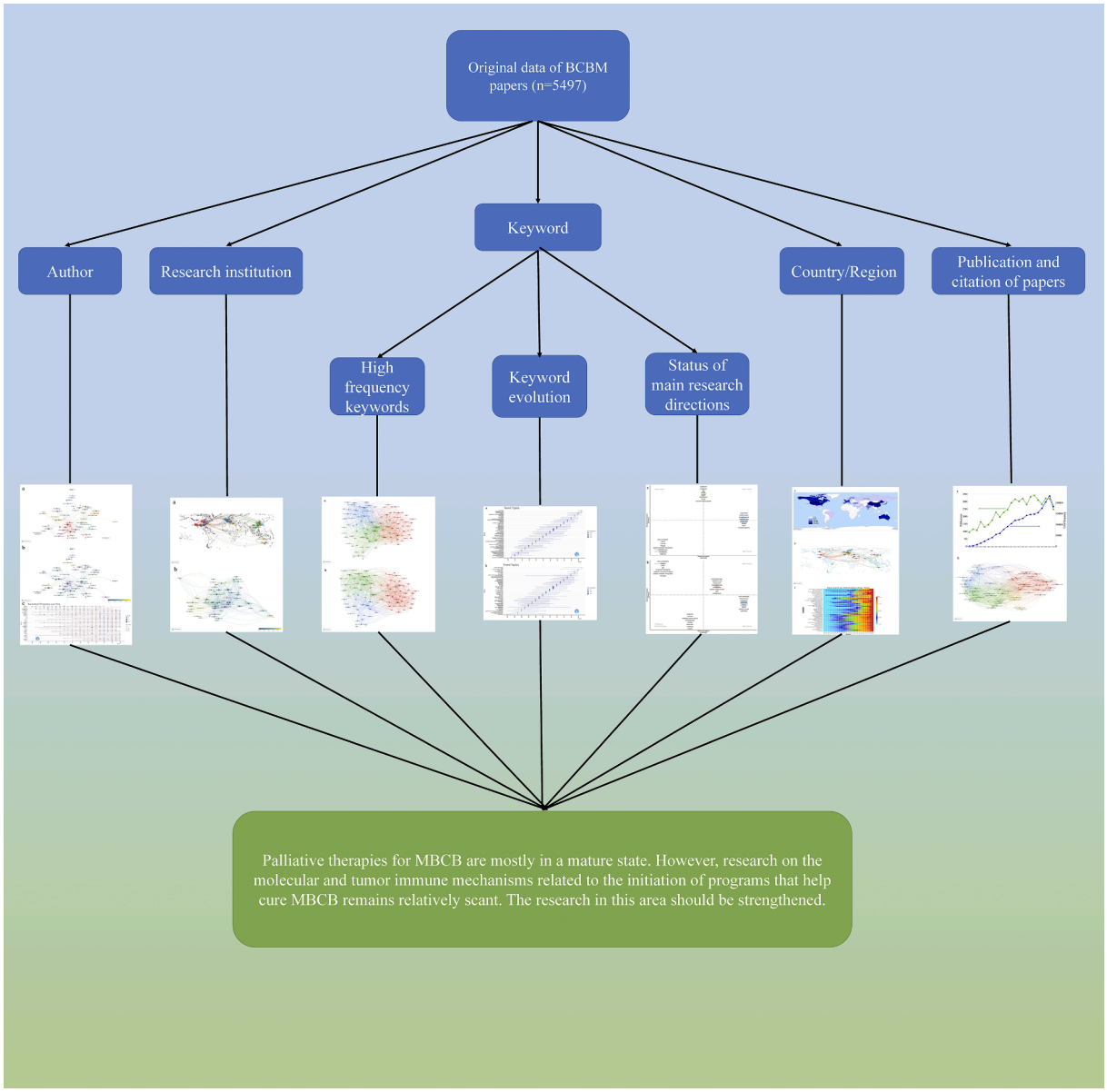

Fig. 9. Brief flowchart of the study.

Therapeutic aspects can be divided into radiotherapy, chemotherapy, targeted therapy, immunotherapy, and multidisciplinary management. Radiotherapy has become more popular because it can effectively reduce the damage caused by the disease and prolong the lives of patients to some extent [41,42]. In the early years, radiotherapy was mainly focused on palliative and localized treatment. Although this could improve patients' quality of life to some extent, such treatment options have certain side effects and have limited value for MBCB patients [15,43–45]. However, in recent years, with the emergence of new radiotherapy techniques (e.g., stereotactic body radiotherapy and multidisciplinary oncology management), combining radiotherapy with new systemic combination therapy regimens (e.g., targeted therapy and immunotherapy) can improve patients' quality of life to a greater extent than earlier techniques, thus helping alleviate patients' diseases, prolonging survival significantly, and causing less toxicity from treatment [15,46]. However, it is worth noting that most of these new research results are still in the clinical trial stage.

Despite the high number of scientific outputs related to chemotherapy, it remains a marginal topic in the field of MBCB. This may be related to the resistance and toxicity associated with chemotherapy, making it less effective in patients with MBCB [47]. Although recent studies have reported that highly anticancer-selective, platinum-loaded, selenium-doped hydroxyapatite nanoparticles address the shortcomings of conventional chemotherapy, they are only in the basic research stage [48]. Adjuvant chemotherapy, surgery, and targeted therapy with phosphonates also achieve better therapeutic results [49–53]. However, there are also serious side effects that affect the quality of life of patients, such as osteonecrosis of the jaw and heart damage[54–56].

In recent years, the influence of targeted therapies has gradually expanded due to the more thorough interpretation of relevant mechanisms. Denosumab is a classic drug that targets the receptor activator of the NF-κβ ligand (RANKL) [57]. A retrospective study of 84 patients with MBCB found that most patients treated with denosumab benefited from fracture arrest, improved quality of life, and prolonged survival [58]. Others have mentioned that the use of denosumab is effective in reducing the probability of skeletal-related events, including disability and bone pain [52,53]. However, as with the use of phosphonates, adverse outcomes, such as atypical femur fractures, hypocalcemia, and osteonecrosis of the jaw, should be kept in mind in clinical practice [55,56]. Fulvestrant, pyrotinib, lapatinib, and trastuzumab all target

estrogen receptors (ERs), which can provide significant relief in patients with certain types of MBCB [59,60]. Also, most current molecule-targeting therapies are ineffective against triple-negative breast cancer (TNBC) [61].

Immunotherapy may be effectual for patients who are inoperable or resistant to chemotherapy and other conventional treatments [62,63]. Immunotherapy is likely to be widely used for MBCB patients, mainly including immune checkpoint inhibitors (ICI) targeting CTLA-4 and PD-1, activating T cells and chemokines, etc. [63–66]. However, in general, the development of immunotherapy for MBCB is immature. Most studies are in the animal experiment stage or, at best, clinical trials. A recent review stated that there have been no evaluations of the effect of ICIs in the treatment of MBCB patients lately [62]. There is also a possibility that MBCB patients could develop resistance to ICIs [67]. Therefore, the field of MBCB is relatively limited in its use of immunotherapy in clinical practice. The above information is consistent with the fact that no effective immune drugs for BM have been proven by the current bibliometric investigation. There have been few reports on the clinical effect of immunotherapy in BM. For example, a case report showed that the combination of nivolumab and ipilimumab in metastatic renal cell carcinoma (mRCC) with adjuvant surgery resulted in a complete remission of BM[68]. Another retrospective study demonstrated that ICIs can effectively inhibit the progression of BM from advanced lung cancer and significantly prolong the survival of patients[69]. In particular, pembrolizumab combined with denosumab has the best therapeutic effect on BM from lung cancer[69]. In addition, there is a phase II clinical study showing that the combination of bone-targeted drugs (BTA) and immunotherapy has a favorable effect on reducing the incidence of SRE in RCC patients who have already developed BM[70]. Due to the lack of clinical studies with large size of samples, although these immune drugs show a certain advantage in the treatment of MBCB, their development is still immature and still in its initial stage.

The European Society for Medical Oncology's (ESMO) 2014 clinical practice guidelines mentioned that individualized treatment for MBCB patients was still in the clinical evaluation stage [71]. In the personalized treatment section of ESMO's 2020 guidelines, it was mentioned that some types of BC patients can already receive treatment to reduce the probability of BM [72]. Unfortunately, for a long period of time, drugs with many side effects, such as bisphosphonates and denosumab, were the only options for the majority of MBCB patients and BC patients who wanted to prevent BM [71,72]. The American Society of Clinical Oncology (ASCO) also wrote that there is currently a lack of effective personalized treatment options for MBCB patients, mentioning that bisphosphonates and denosumab are still the main applications in current clinical practice [73,74]. Indeed, ASCO currently recommends patients' continuous use of bisphosphonates and denosumab [74]. Therefore, it is necessary for scientists to develop personalized therapy with few side effects for MBCB patients.

4.2. Basic research directions

It is worth noting that there have been fewer established research directions and substantial breakthroughs in basic research. Early on, a study of the OPG/RANK/RANKL pathway revealed that when RANKL is upregulated relative to OPG, the inhibition of OPG's role in the bindings of RANKL and RANK is diminished, which dysregulates the number of osteoclasts and osteoblasts in the bone microenvironment, resulting in a greater breakdown and destruction of bone and the accelerated progression of bone metastasis [75–77]. Understanding this pathway facilitated the creation and use of denosumab in clinical practice [75].

One study reported that zoledronic acid induced apoptosis in BC cells and prevented the development of BM by inhibiting the mevalonate pathway [78]. These basic research findings have been translated into a clinical setting with the application of the phosphonic acid drugs. Thus, basic research leads to clinical development. Also, during this period, some scholars discovered through conducting in vitro and animal experiments that TGF-β can significantly promote the upregulation of the expression of the Hedgehog signaling molecule Gli2, which increases the production of osteolytic genes in metastasized BC cells in bones, leading to the expression of parathyroid hormone-related proteins (PTHrPs) and other osteolytic factors that cause malignancy-associated hypercalcemia and the vicious cycle associated with MBCB [79–81]. PTHrPs are still a popular subject in MBCB therapeutic research [82].

Advances in MBCB basic research are important in understanding the mechanisms of metastasis and advancing diagnosis and targeted therapy. Recently, scholars have found that when runt-related transcription factor 2 expression is upregulated, BC cells release extracellular vesicles (EVs) into bones. Messenger proteins in EVs interact with osteoblasts, causing them to recognize BC-derived EVs and integrin α5, which contributes to preosteogenic metastatic ecotone formation in preparation for subsequent BC cell transfer to the bones [83]. Other researchers have designed arsenic nanoparticles to prevent BM by hindering the colonization of BC cells in the bone microenvironment [84].

Reprogramming processes, such as EMT, also play an important role. For example, Chen et al. found that after interacting with integrins, intercellular adhesion molecule 1 caused tumor cells to undergo EMT via TGF-β/SMAD signaling, after which the cells' mesenchymal properties facilitated tumor cell metastasis through blood circulation [85]. Furthermore, because BC cells' exosomes disrupt bone remodeling in the BM process, they may effectively serve as drug carriers for treating MBCB [86,87]. Therefore, it is not surprising that "bone remodeling" continues to be a keyword in the field of MBCB.

4.3. The direction of bioinformatics analysis

In the era of big data, many in silico studies have been undertaken in the field of MBCB. Bioinformatics analyses, mostly through public databases, have been widely used to study diseases and other biological problems using epigenomics, metabolomics, and microbiomics, achieving impressive results in studies of molecular diagnosis and therapy, tumor typing, disease prognosis, and disease mechanisms [88–90]. For example, Wang et al. screened predictors using univariate and multivariate Cox analyses and built a prognostic line chart for young female patients with MBCB to perform preliminary validation [91]. Their research may help doctors accurately predict the prognoses of patients and develop precise medical treatment plans, further improving prognoses. Studies applying statistical analysis methods to BC found that men with different molecular subtypes with MBCB had very different onset patterns and prognoses [92]. This information facilitates the development of precise treatment plans for patients of all molecular subtypes. Other scholars analyzed TNBC case data using epigenomic and transcriptomic approaches and found that when the expression of essential amino acid metabolism-related genes increased, bone metastasis was more likely to occur [93]. This finding increases the scope of the understanding of the TNBC mechanisms, and allows us to expect new possible targets for the treatment of TNBC.

Bioinformatics effectively studies the molecular mechanism, diagnosis, and treatment of MBCB in the context of big data. However, most of these bioinformatics studies' theories must be validated in further studies.

4.4. Prospects for future research

The current study revealed that existing MBCB treatment options cannot cure patients. Cures for metastatic melanomas using immunotherapy have been reported [94], so for patients with MBCB, emerging immunotherapies may offer them some hope.

Topics that have been neglected should be developed, including unveiling novel potential targets, refining the molecular mechanisms, and accelerating the process of clinical application, all of which are crucial in the development of therapies for MBCB. In the era of big data, new technology and public databases play significant roles in promoting

the development of the MBCB research field. We hope that this study will provide assistance to researchers, especially those who have recently become interested in MBCB, to advance the development of MBCB research.

4.5. Limitations and future work

Because our results were mostly obtained by analyzing common bibliometric indicators, we may have missed important indicators, thereby omitting valuable information. In the future, we will build on this study and analyze a wider range of indicators. Second, we used only one method (bibliometrics) to analyze and evaluate past scientific results, which may be somewhat biased. In the future, we will use multiple methods to validate and complement our findings. Third, the papers included in this study were derived only from WOSCC. In the future, we will include more databases for validation and supplementation. Fourth, because the MBCB field is evolving rapidly, the newest publications were not included in our study. In the future, we will include these in our analysis. Fifth, due to the limitations of our analysis tools, we included only papers written in English; thus, papers written in other languages were ignored. In the future, we will use new analytical tools to improve our study. Sixth, due to the large sample, the results we obtained represent the overall situation of the MBCB field. We have likely overlooked some directions that may be very valuable at some point. In the future, we will refine our analysis based on this study and produce more detailed results.

5. Conclusion

This study is the first to use bibliometrics to provide an overall analysis of the scientific output of the MBCB field. We discovered prolific authors and highly productive institutions as well as developed countries that should engage in more international collaboration. Furthermore, we found that the MBCB field is primarily divided into themes of clinical practice, relevant clinical experiments, basic research, and bioinformatics. We discussed how these areas have changed over the past 22 years and examined the current dilemmas in the MBCB field. We hope that this study will help scholars understand the entire situation of MBCB research and promote its progress. Finally, we wish to provide suggestions for the future progress of the MBCB field. Researching molecular and tumor immune mechanisms may lead to the development of a cure. Therefore, we must strengthen our basic research in this area.

Statements and Declarations

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Ethics approval

This study did not involve any animals or experiments; hence, ethical, and moral consent was not required.

Consent to participate

This paper was a research and analysis of the previously published papers, and did not involve any human subjects. Therefore, no informed consent was required.

Availability of data and materials

All the data used in this study can be obtained through the public network platform.

Consent to publish

All the authors of this paper finally reviewed it and agreed to publish it.

CRediT authorship contribution statement

Yi Chen: Data curation, Investigation, Writing – original draft, Software, Formal analysis, Visualization. **Zhen-Ning Guo:** Data curation, Investigation, Software, Formal analysis, Writing – original draft. **Rong-Quan He:** Writing – review & editing, Supervision. **Zhi-Guang Huang:** Writing – review & editing, Supervision. **Jia-Yuan Luo:** Writing – review & editing, Supervision. **Wei Tang:** Writing – review & editing, Supervision. **Su-Ning Huang:** Writing – review & editing, Supervision. **Gang Chen:** Writing – review & editing, Supervision, Project administration, Methodology, conceptualization. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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

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