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Research article

# Unveiling research trends in the prognosis of osteosarcoma: A bibliometric analysis from 2000 to 2022

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ABSTRACT

*Background:* Osteosarcoma (OSA) is the most prevalent form of malignant bone tumor in children and adolescents, producing osteoid and immature bone. Numerous high quality studies have been published in the OSA field, however, no bibliometric study related to this area has been reported thus far. Therefore, the present study retrieved the published data from 2000 to 2022 to reveal the dynamics, development trends, hotspots and future directions of the OSA.

*Methods:* Publications regard to osteogenic sarcoma and prognosis were searched in the core collection on Web of Science database. The retrieved publications were analyzed by publication years, journals, categories, countries, citations, institutions, authors, keywords and clusters using the two widely available bibliometric visualization tools, VOS viewer (Version 1.6.16), Citespace (Version 6.2. R1).

*Results:* A total of 6260 publications related to the current topic were retrieved and analyzed, revealing exponential increase in the number of publications with an improvement in the citations on the OSA over time, in which China and the USA are the most productive nations. Shanghai Jiao Tong University, University of Texas System and Harvard University are prolific institutions, having highest collaboration network. Oncology Letters and Journal of Clinical Oncology are the most productive and the most cited journals respectively. The Wang Y is a prominent author and articles published by Bacci G had the highest number of citations indicating their significant impact in the field. According to keywords analysis, osteosarcoma, expression

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and metastasis were the most apparent keywords whereas the current research hotspots are biomarker, tumor microenvironment, immunotherapy and DNA methylation.
*Conclusion:* Our findings offer valuable information for researchers to understand the current research status and the necessity of future research to mitigate the mortality of the OS patients.

## 1. Introduction

Osteosarcoma (OSA) is the most prevalent form of malignant bone tumor, with a worldwide annual incidence ranging from one to three cases per million individuals. The overall global incidence of OSA is 4.4 cases per million per year [1]. This malignancy primarily affects individuals during their youthful growth spurt and exhibits a smaller peak in older age groups [2]. During puberty, rapid bone growth is associated with the progression of OSA. Osteosarcomas are tumors composed of malignant osteoblasts that generate immature bone or osteoid tissue. These tumors can be categorized into various histological forms, including conventional, low-grade central, periosteal, parosteal, telangiectatic, chondroblastic, and small cell types. Each of these forms exhibits distinct molecular and biological characteristics [3]. The development of OSA is influenced by various factors, including epidemiological factors, genetic abnormalities, and environmental factors. Known risk factors associated with the progression of OSA include Paget's disease, hereditary retinoblastoma, other chromosomal abnormalities, exposure to ionizing radiation, and the use of alkylating agents [4]. Mainly, genomic alterations in TP53, particularly TP53 inactivation, as well as RB inactivation, are present in the majority of OSA cases [5].

As per the World Health Organization (WHO), the histological classification of the OSA is classified into two categories, including central (medullary) and superficial (peripheral) tumors, each harboring various subtypes. The central forms comprise conventional, telangiectatic, low-grade, and small-cell variations. Similarly, the superficial include parosteal, periosteal, and high-grade surface variants [6]. The etiology of OSA includes epidemiological and environmental aspects, as well as genetic factors. Notably, ionizing radiation stands out as a thoroughly established causative element. Furthermore, instances of OSA have been linked to the intravenous application of radium and Thorotrast. The potential influence of exposure to alkylating agents on its development also warrants consideration, appearing to operate distinctly from the administration of radiotherapy [7].

The diagnosis of OSA, which is a complex type of primary bone malignancy, is best achieved through a comprehensive multidisciplinary approach. This approach may involve techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, as well as positron emission tomography (PET) imaging [8]. In addition, serum biomarkers, such as alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) are used to aid in the diagnosis of OSA [9]. However, the final step in the diagnostic process for OSA is typically an incisional or core needle biopsy [6]. The standard treatment for OSA, which involves a combination of surgery and chemotherapy, was established in the 1980s and has resulted in long-term survival rates of over 60% for patients with localized disease [10]. Current therapies typically include surgical resection and combination chemotherapy, often using doxorubicin and cisplatin, with or without methotrexate, and this approach achieves a cure rate of approximately 70%. In patients with localized disease, the response to preoperative combination chemotherapy is a significant predictor of overall survival [11].

The four chemotherapy agents that are used in nearly all treatment regimens include methotrexate with leucovorin rescue, doxorubicin, cisplatin, and ifosfamide. However, the international standard perioperative regimen for patients under 40 years of age is accepted to be high-dose methotrexate, doxorubicin and cisplatin (MAP) [12]. After conducting numerous clinical studies, it becomes evident how significant chemotherapy is in terms of its clinical applications. It has elevated the probability of disease-free survival from 10% to 20% when using surgery alone, to an impressive rate of over 60% in a curative context. The degree of histological response observed after preoperative chemotherapy serves as a valuable predictor for survival outcomes, as indicated by previous studies [13]. The extent of tumor necrosis following neoadjuvant chemotherapy holds significant importance as a prognostic indicator for both local recurrence and overall survival in OSA. Numerous studies have reinforced this notion, consistently demonstrating that achieving a tumor necrosis rate of 90% or higher is indicative of a positive response, while a rate below 90% signifies a less favorable outcome [14].

Significant progress has been made in OSA research in recent years, resulting in a vast body of scientific literature. These studies have provided valuable insights into the intricate mechanisms underlying the development and progression of the disease, unravelling the genetic and molecular factors involved. Furthermore, there have been remarkable advancements in diagnostic techniques, including advanced imaging methods and molecular profiling, allowing for earlier and more precise detection of the disease. Additionally, novel therapeutic approaches such as targeted therapies and immunotherapies have been explored and have shown promising results in both preclinical and clinical studies. The rapid expansion of scientific knowledge in the field of OSA has paved the way for an improved understanding and enhanced management strategies for this challenging disease [15]. Our aim was to offer a thorough overview of the evolutionary aspects of OSA, with the goal of providing guidance for future research endeavors in this field.

Bibliometric analysis has gained significant recognition and widespread use in research evaluation, encompassing both basic and clinical medicine. This scientific approach provides quantitative and statistical analyses of publications in specific areas, effectively identifying the most influential and representative studies [16–19]. In addition, the application of knowledge maps enables researchers to examine the advancements within a specific discipline by presenting rich data, thus facilitating a comprehensive understanding of emerging trends at the forefront of research [18]. Although numerous prognostic studies have been published in the field of OSA, conducting a bibliometric analysis to evaluate the existing literature is not only feasible but also necessary, as it can provide valuable insights to guide future research efforts. However, to date, such analyses in this particular area have been limited and scarce. To

analyze OSA studies from 2000 to 2022, this study utilizes two prominent bibliometrics software packages, CiteSpace [20] and VOSviewer [21]. This study focuses on several aspects, including quantifying individual impacts, collaborations, and publications, identifying highly cited articles to assess the knowledge base, exploring knowledge structures and hotspots through keyword and co-cited reference analyses, and determining the research content and future directions by analyzing journals, countries, and keywords of the articles. By conducting these analyses, the study aims to evaluate the key factors contributing to the successful citation of OSA related research, thereby enhancing our understanding of its development and expansion. Furthermore, the findings from this study can offer valuable insights and perspectives for researchers to guide future studies in OSA research.

## 2. Methods

### 2.1. Search strategy and data collection

We selected the Science Citation Index Expanded (SCI-EXPANDED) from the Web of Science Core Collection (WoSCC) as our primary database for data retrieval. WoSCC is a renowned online database that offers standardized and up-to-date scientific research data. Among the databases in WoSCC, SCI-EXPANDED is considered the most suitable for bibliometric analysis. The search topic for our study focused on the terms "osteosarcoma" or "osteogenic sarcoma" in conjunction with keywords related to prognosis, such as "prognosis," "prognostic," or "survival," or "survive" or "Kaplan-Meier". The articles were collected from January 2020 to December 2022. Initially, 6712 publications were found, with 6260 of them being incorporated into the bibliometric analysis after excluding inappropriate and non-English articles. The work has been reported in line with the guidance of the PRISMA statement [22] and conforms to AMSTAR-2 guidelines [23].

### 2.2. Data extraction and preprocessing

In our analysis, certain materials such as editorial pieces, letters, revisions, books, biographies, news articles, patents, and unspecified document types were excluded. Our screening process prioritized articles and reviews for selection. The selection outcomes were presented in descending order based on the total number of citations received by each publication. Language was restricted to publications in English. We downloaded and exported the retrieved data for further analysis using CiteSpace software. The downloaded files were labelled as "download *.txt". The retrieval results, which included the content of the articles and the references they cited, were recorded in the "Full Record and Cited References" format. To ensure clarity and organization, these files were saved in a "Plain Text" file format and subsequently renamed. A PRISMA flow diagram to provide detailed pictorial representation of the literature search, screening, methods, metrics and analysis of the study (Fig. 1).

### 2.3. Analysis methods

Visualization plays a crucial role in bibliometric analysis as it allows for intuitive observation of collaborative networks, research hotspots, and trends in a new field through visual maps. CiteSpace software (CiteSpace 6.2. R1), developed by Professor Chen Chaomei of Drexel University, is a citation visualization analysis tool based on scientometrics and data visualization.

For this study, we performed data analysis using Microsoft Office Excel and CiteSpace. Microsoft Office Excel was utilized to manage the database and analyze the annual publication output and trends in OSA publications. Subsequently, the data were input into CiteSpace software to generate visualized maps for analyzing annual output counts, countries, top-cited references, keywords, and burst detection. Keywords of high occurrence was estimated with Zipf's Law. According to Price's law, the core authors refer to the authors with more than, of which, Nmax represents the number of articles of the highest-ranking authors, and in this paper, the highest number of articles Nmax = 99, which can be obtained and rounded up to the nearest 7, and the number of the first authors with more than 7 articles can be included in the core authors, but the actual number of the first authors with more than 7 articles has reached 522, and there are more juxtapositions among the lower-ranking authors. However, the actual number of first authors with more than 7 articles reaches 919, and there are many cases of juxtaposition of authors at the back of the ranking. Furthermore, cooperative relationships between identified publications were examined through visualizations of co-citations and co-references. The analysis methods employed included co-occurrence, clustering, and burst analysis. Various types of visualization diagrams, such as histograms, cluster views, time lines, and collinearity plots, were used. All clusters were labelled with keywords, and the log-likelihood rate (LLR) was used as the clustering algorithm. Synonyms were combined in the analysis map based on the actual situation.

We also utilized VOSviewer as a powerful tool for constructing visualization and investigation maps using online information. Specifically, we employed VOSviewer 1.6.16 to identify prolific periodicals, co-cited periodicals, authors, co-cited authors, and knowledge graphs based on bibliographic data. By analyzing the cleaned data, we generated co-occurrence and cluster maps that incorporated text information. Additionally, we set the maximum author count at 25 and employed fractional counting, which calculates link strengths by considering the weights of articles. We determined that fractional counting was more suitable for our research objectives.

## 3. Results

### 3.1. The annual evolution of publication and citation outputs

During the study period, a remarkable 6260 articles have been published, highlighting the extensive research conducted in the field (Fig. 1). As depicted in Fig. 2, the publication trend exhibits an exponential increase from 2000 to 2022 ($R^2 = 0.977$). This significant upward trajectory demonstrates the continuous development and growing interest in the OSA subject. From the year 2000–2011, the trend of publication intensity remained relatively stable, indicating a consistent level of scholarly activity in the field. However, starting from the year 2012, a notable shift occurred, with a significant increase in the number of published articles. This upward surge continued until 2022, with slight fluctuations observed in the years 2013 and 2018. In parallel to the rise in publication numbers, the field has witnessed a significant increase in the number of citations over the past two decades ($R^2 = 0.9782$). Beginning in 2000, the annual citations consistently exceeded 2292 by 2021, exemplifying the growing prominence and heightened interest in this area of research (Fig. 3).

### 3.2. Regional distribution and cooperation analysis

Table 1 presents the top 10 countries contributing to research on OSA in terms of publications. Among these countries, China (N = 2756, 44.02%) and the USA (1438, 22.97%) accounted for more than 60% of the publications in OSA research. Notably, Japan (412, 6.58%) and Italy (388, 6.19%) also made significant contributions to the field, as depicted in Fig. 4. The analysis of country co-authorship networks revealed that China and the USA are often recognized for their significant contributions in producing groundbreaking research, which can serve as a bridge in advancing the field. This co-authorship analysis reported that the USA is the central country, which makes the proper cooperation with other countries such as the links density China, France and Germany (Fig. 5).

### 3.3. Institutional distribution and cooperation network analysis

Similar to the geographical distribution, institutional contributions play a significant role in OSA research. A comprehensive

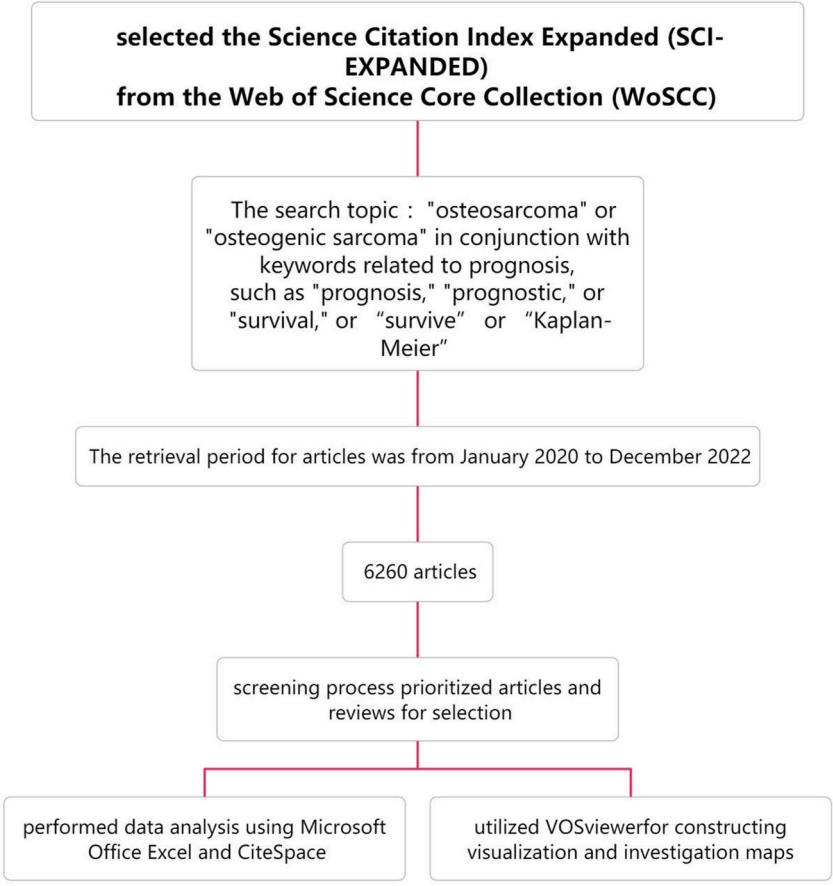


**Fig. 1.** PRISMA flowchart.

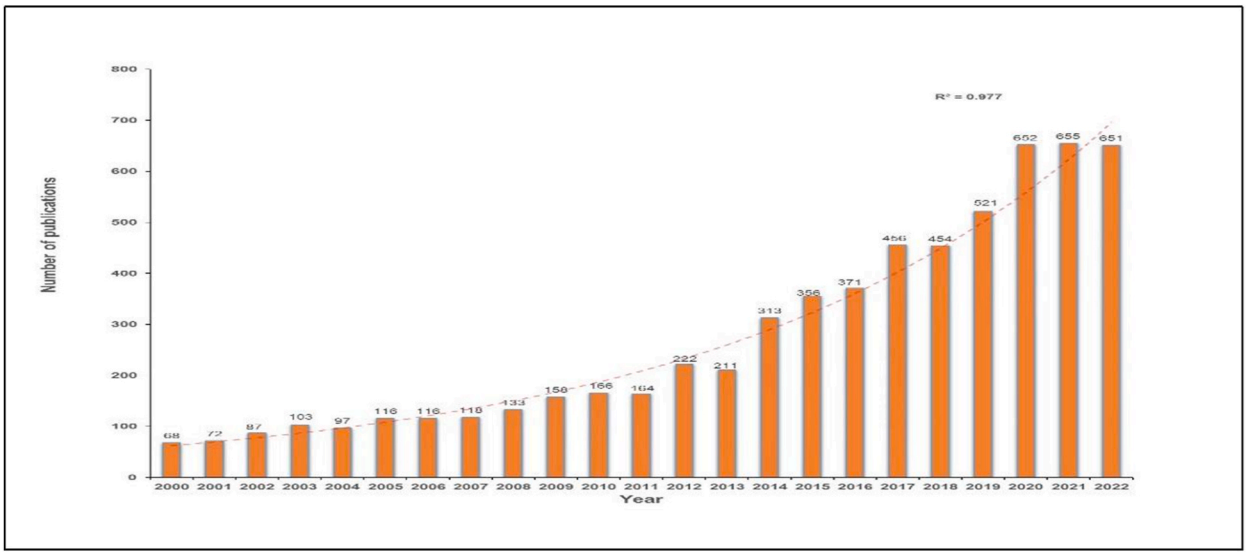


**Fig. 2.** Annual publications from 2000 to 2022 on Osteosarcoma and prognosis -related research.

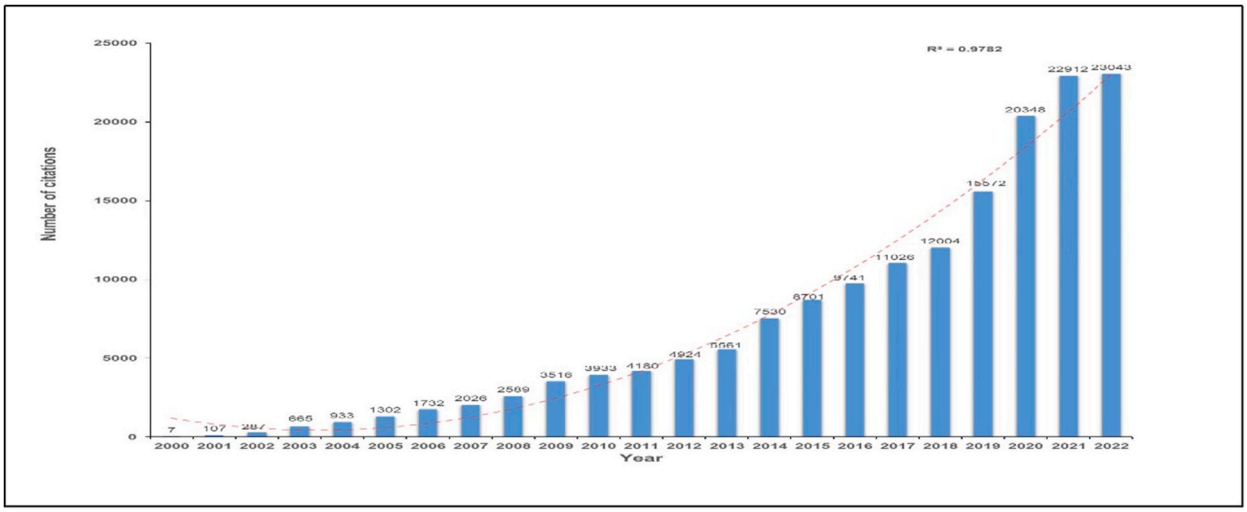


**Fig. 3.** Annual citation trend graph in the Web of Science about Osteosarcoma and prognosis -related research.

analysis reveals that over 4000 institutions have actively participated in the publication of OS-related articles. Table 1 highlights the top 10 institutions that have made substantial contributions to OSA research. Notably, leading the pack are institutions such as Shanghai Jiao Tong University (241, 3.851%), University of Texas System (199, 3.179%), and Harvard University (175, 2.796%), which occupy the first, second, and third positions, respectively. Fig. 6 provides a network visualization depicting all the institutions involved in OSA and prognosis-related research. The Figure reveals that institutions lacking collaborations are dispersed on the periphery, resembling a dial outside the circles. On the other hand, Fig. 7 showed the top productive institutions and their collaborative relationships. Notably, institutions such as Shanghai Jiao Tong University, Harvard University, and UTMD Anderson Cancer Center have established connections with several other institutions and universities. This observation suggests that collaboration among these institutions plays a vital role in driving significant advancements in the field.

### *3.4. Journal and co cited journal network analysis*

We have observed that all 6260 articles were published within 1066 journals. Table 2 demonstrates the distribution of publications among various journals. Oncology Letters reported the highest number with 134 publications (2.141%), followed by Pediatric Blood Cancer with 107 publications (1.70%), and Oncotarget with 105 publications (1.677%). Regarding the top 10 published articles on OSA, Cancer had the highest impact factor of 6.921 (Q1), followed by Cancers and Frontiers in Oncology with impact factors of 6.575

**Table 1**
Distributions of publications in top 10 nations and institutions of OS research.

| No | Country | Count (%) | Institution | Count (%) | Institution/Country (%) |
|---|---|---|---|---|---|
| 1 | PEOPLES R CHINA | 2756 (44.026) | SHANGHAI JIAO TONG UNIVERSITY | 241 (3.851) | 8.745 |
| 2 | USA | 1438 (22.971) | UNIVERSITY OF TEXAS SYSTEM | 199 (3.179) | 13.839 |
| 3 | JAPAN | 412 (6.581) | HARVARD UNIVERSITY | 175 (2.796) | 42.476 |
| 4 | ITALY | 388 (6.198) | UTMD ANDERSON CANCER CENTER | 173 (2.764) | 44.588 |
| 5 | ENGLAND | 268 (4.281) | IRCCS ISTITUTO ORTOPEDICO RIZZOLI | 149 (2.388) | 55.597 |
| 6 | GERMANY | 250 (3.994) | CENTRAL SOUTH UNIVERSITY | 146 (2.332) | 58.400 |
| 7 | FRANCE | 220 (3.514) | UNIVERSITY OF CALIFORNIA SYSTEM | 145 (2.316) | 65.909 |
| 8 | CANADA | 180 (2.875) | SUN YAT SEN UNIVERSITY | 134 (2.141) | 74.444 |
| 9 | SOUTH KOREA | 170 (2.716) | UDICE FRENCH RESEARCH UNIVERSITIES | 124 (1.981) | 72.941 |
| 10 | NETHERLANDS | 149 (2.389) | INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM | 116 (1.853) | 77.852 |

It is a multi-authored contribution publications.

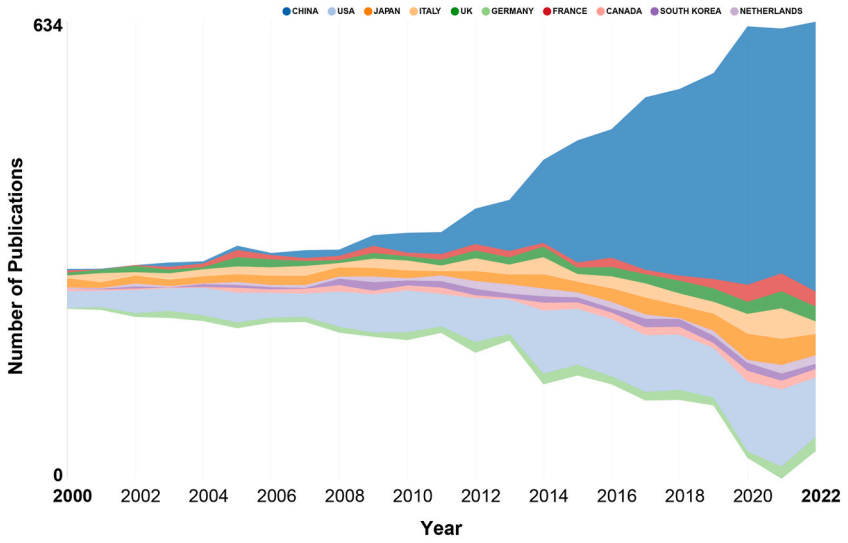


**Fig. 4.** Temporal distribution map of publications and citations of article from 2000 to 2022.

(Q1) and 5.738 (Q2) respectively. Analyzing the distribution of published article sources is valuable in identifying core and journals. These metrics reveal that articles are published not only in high-impact factor journals but also in numerous articles on OSA with depression. This makes these journals attractive to researchers in this field.

Journal co-citations occur when two or one or more articles cite more articles simultaneously. These co-citations are utilized to evaluate the connection between articles and assess the impact of a journal. Co-citation analysis is a method that utilizes the co-citation frequency as a metric to standard the influence and significance of the journal within a particular research domain. Out of all the co-cited journals, 165 journals have been co-cited more than 300 times (Fig. 8). Journal of Clinical Oncology, Cancer research and cancer are most frequently co-cited journals among which Journal of Clinical Oncology cited with 9994 times **(Table 2)**. According to the journal citation report, it has been observed that nearly all top co-cited journals hold a reputable Q1 status. Notably, Journal of Clinical Oncology, Cancer Research, Cancer, Clinical Cancer Research, and Clinical Orthopaedics and Related Research are identified as centrally located journals with numerous connections. This signifies their importance as reference journals for acupuncture research in the field of OSA. The dual-map overlay of journals visualizes the distribution of relationships between journals, with citing journals on the left and cited journals on the right. Colored lines between right and left are generally considered as paths. In Fig. 9, it is depicted that two yellow citation paths indicate the inclusion of molecular/biology/immunology journals in both molecular biology/genetics

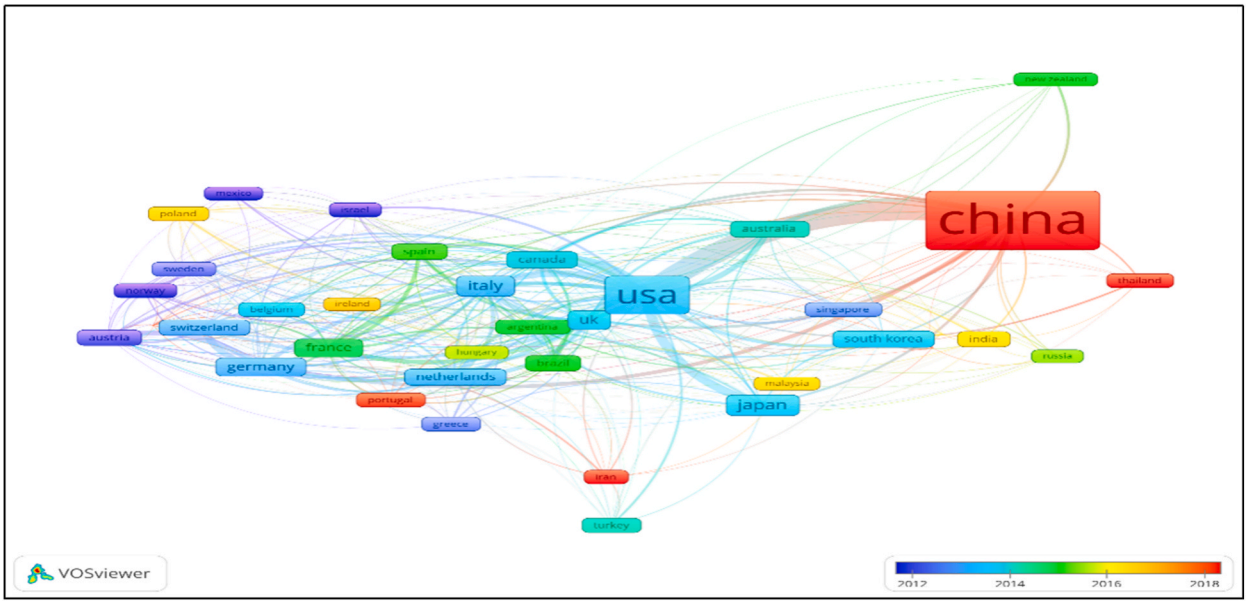


**Fig. 5.** Country co-authorship network map of the OSA research.


**Fig. 6.** Network visualization map of the institutions involved in OSA research (Created by Citespace).

and health/nursing/medicine fields. Additionally, two spring green paths demonstrate the presence of medicine/medical/clinical journals within the cited health/nursing/medicine journals. This highlights the transformation of OSA prognosis into medicine and clinical progression.

### *3.5. Author and Co-cited author network analysis*

In various journals, a remarkable number of more than 20,000 authors were recognized as actively contributing participants who published articles concerning the prognosis of OSA. The authors such as Wang Y (99, 1.581%), Zhang Y (83, 1.326), Gorlick R (80, 1.278), Ferrari S (77, 1.230), Wang J (73, 1.166%) who published articles over 60 articles (data not shown). Nevertheless, a significant portion of the identified authors has published a relatively low number of articles, indicating a need for further enhancement in osteosarcoma research. Moreover, our investigation delved into the co-citation information of the authors. Notably, we discovered that certain authors, namely Bacci G (n = 2280), Bielack SS (n = 1221), Meyers PA (n = 1207), Mirabello L (n = 982), and Ferrari S (n = 857) have made remarkable contributions in this field. Furthermore, we conducted an author co-authorship analysis network visualization map, considering authors who had contributed to more than 15 articles. In this analysis, we identified 88 authors and

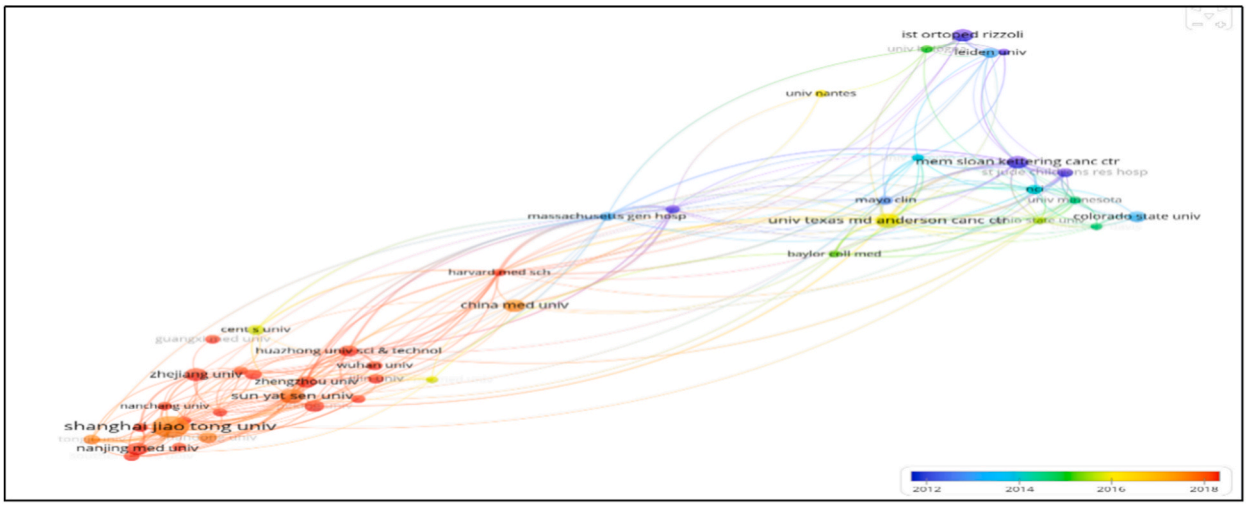


**Fig. 7.** The co-authorship network of affiliations involved in published papers for OS and prognosis-related research.

**Table 2**
Top journals and co cited journals related to the OS research.

| NO | Journal | Count (%) | IF (2022) | JCR | Co-cited Journal | Citations | IF (2022) | JCR |
|---|---|---|---|---|---|---|---|---|
| 1 | ONCOLOGY LETTERS | 134 (2.141) | 3.111 | Q2 | JOURNAL OF CLINICAL ONCOLOGY | 9994 | 50.739 | Q1 |
| 2 | PEDIATRIC BLOOD CANCER | 107 (1.709) | 3.838 | Q1/ Q2 | CANCER RESEARCH | 6642 | 13.312 | Q1 |
| 3 | ONCOTARGET | 105 (1.677) | 0.966 | | CANCER | 5581 | 6.921 | Q1 |
| 4 | CLINICAL ORTHOPAEDICS AND RELATED RESEARCH | 102 (1.629) | 4.837 | Q1 | CLINICAL CANCER RESEARCH | 4265 | 13.801 | Q1 |
| 5 | CANCER | 99 (1.581) | 6.921 | Q1 | CLINICAL ORTHOPAEDICS AND RELATED RESEARCH | 3972 | 4.837 | Q1 |
| 6 | FRONTIERS IN ONCOLOGY | 96 (1.534) | 5.738 | Q2 | ONCOTARGET | 3443 | 0.966 | |
| 7 | ONCOLOGY REPORTS | 88 (1.406) | 4.136 | Q1/ Q2 | ONCOGENE | 3314 | 8.756 | Q1 |
| 8 | PLOS ONE | 85 (1.358) | 3.752 | | PLOS ONE | 3229 | 3.752 | Q1 |
| 9 | BMC CANCER | 81 (1.294) | 4.638 | Q1/ Q2 | EUROPEAN JOURNAL OF CANCER | 2849 | 10.002 | Q1 |
| 10 | CANCERS | 78 (1.246) | 6.575 | Q1 | JOURNAL OF BIOLOGICAL CHEMISTRY | 2830 | 5.485 | Q1 |

observed the formation of 13 distinct clusters. As illustrated in Fig. 10, each node in the graph represents an author, with the size of the node corresponding to the number of articles published by that author. Notably, the node associated with Bacci G represents a significantly larger number of published articles attributed to this particular author. Meanwhile the lines and thicker lines between or among authors denoting the strong cooperation represented the closer cooperation between authors. Authors such as Bacci G, Bielack SS, Meyers PA, Mirabello L, and Ferrari S have noticeably thicker connection links, indicating their significant importance in collaborating with other authors in OSA research.

### *3.6. Keyword co-occurrence and clustering analysis*

Keywords are crucial for describing research topics and content. They indicate current trends and cutting-edge subjects in academic publications, offering valuable insights into research areas. These concise terms serve as a resource for researchers and readers, enabling navigation and exploration of scholarly knowledge. Therefore, we performed the key word density visualization as it helps identify central themes, emerging trends, and key areas of focus in a specific field, facilitating efficient navigation and valuable insights. In Fig. 11, keywords such as osteosarcoma, expression, metastasis, cancer, prognosis, apoptosis, and proliferation are associated and grouped together with high density. This indicates the significant occurrence and relevance of these keywords in osteosarcoma research. The clustering of these keywords highlights their importance in understanding the disease and its various aspects, such as prognosis and metastasis.

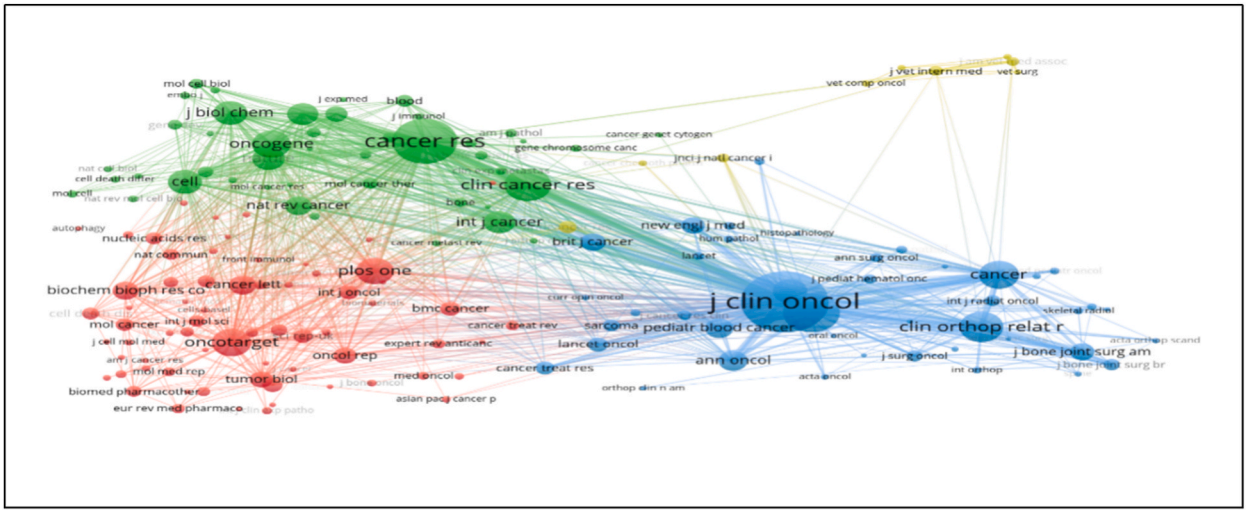


**Fig. 8.** Network visualization map of co-cited journals related to acupuncture for OS research from 2000 to 2022.

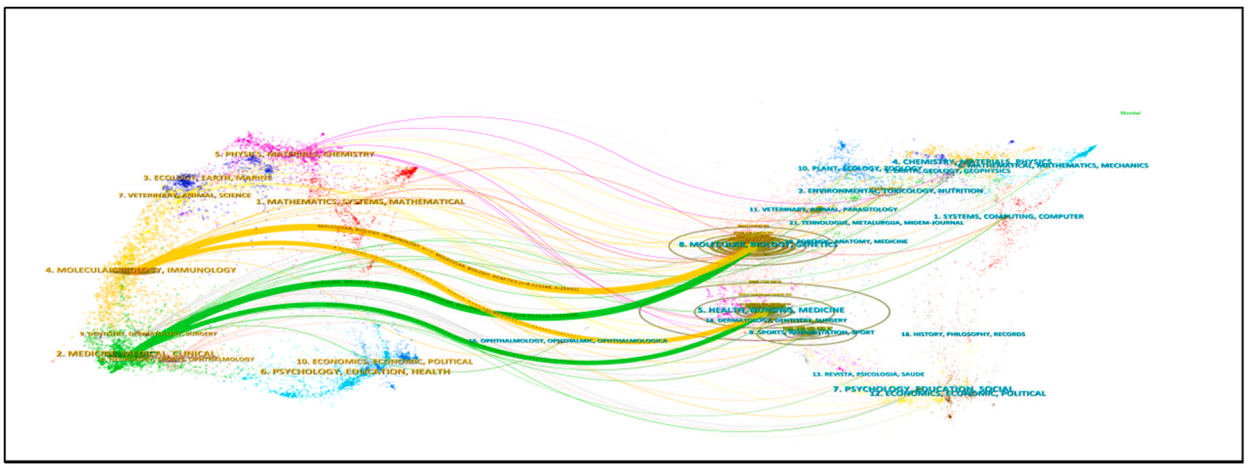


**Fig. 9.** The dual-map overlay visually represents the association of periodicals with Osteosarcoma studies. Labels indicate the disciplines covered by the journals, and colored paths indicate citation associations among different nations/regions and organizations.

In our study, we performed a clustering analysis of keyword occurrences across various papers, as depicted in Fig. 12. The analysis resulted in the formation of distinct clusters, which are represented by different colors in the figure. The primary cluster, denoted by the green color, contains key search terms like osteosarcoma, cancer, and metastasis, indicating its dominance and significance in the research. Two additional clusters, represented by blue and yellow colors, emerged with key search terms such as proliferation, migration, invasion, overall survival, chemotherapy, radiotherapy, and surgery. These clusters shed light on important aspects related to the disease, highlighting the interconnection of these keywords within the research literature. The timeline view captures keyword relationships, aiding the exploration of a field's evolution. As it visually represents keyword progression over time, revealing turning points, dynamics, and trends, we used the CiteSpace and performed the keyword timeline visualization. Our CiteSpace study has gathered data starting from 1995, revealing that between 1995 and 2020, there was a dearth of research carried out in the field of OS. The predominant areas of research during this period centered on novel adjuvant treatment, molecular pathology, and local reoccurrence. From 2001 to 2015, the research trend is elevated towards the OSA research, which includes main key words such as current concept, non-coding RNA, localized osteosarcoma, potential targets and canine appendicular Osteosarcoma. In recent years, there has been a significant increase in research efforts dedicated to understanding Osteosarcoma and researchers have directed their attention towards exploring various aspects, such as the tumor microenvironment, single-arm open-label phase studies, circular RNA, and extracellular vesicles (Fig. 13).

To enhance our analysis, we conducted a keyword burst analysis utilizing the top 30 keywords. Burst strength and burst period are crucial factors that serve as primary indicators for detecting bursts in the data using the CiteSpace (Fig. 14). Observations revealed that the red line typically signifies the temporal span during which a burst occurs, indicating both its starting and ending time. The green

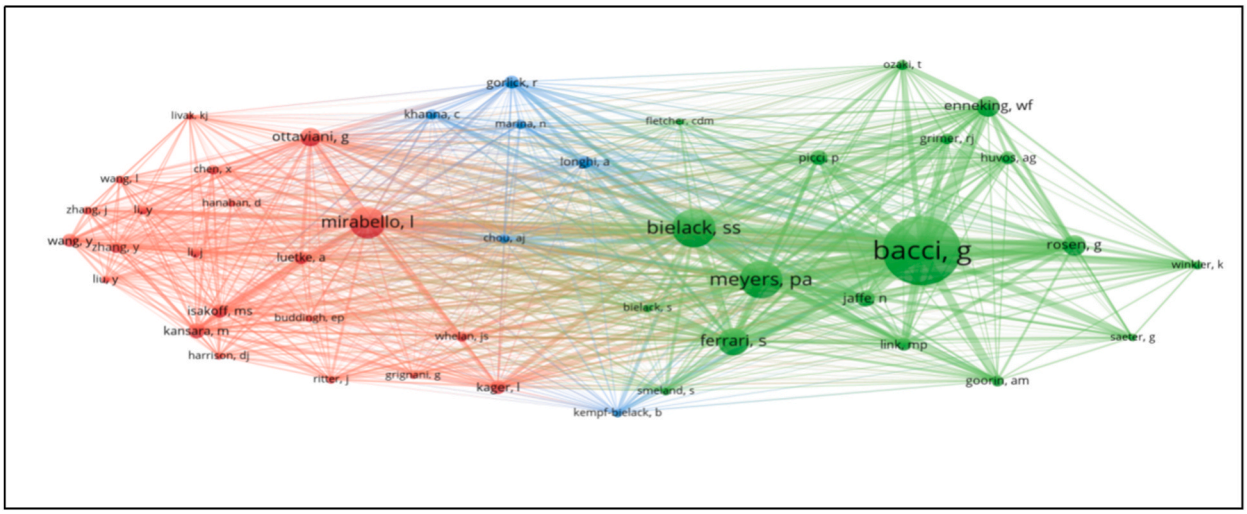


**Fig. 10.** Author co-citation analysis-Network Visualization Map in the field of prognosis of Osteosarcoma.

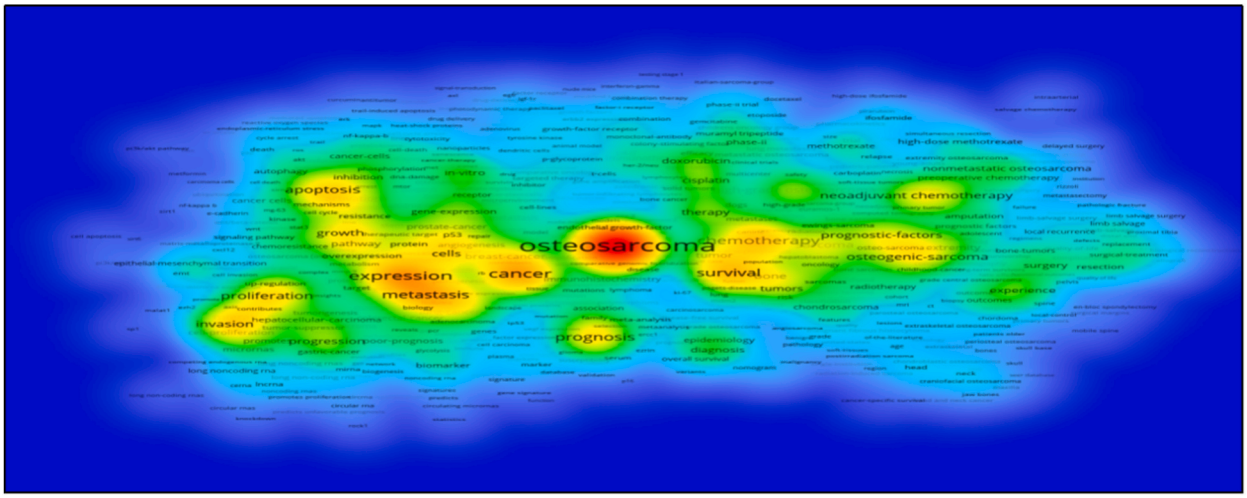


**Fig. 11.** Grouping of keywords Density Visualization Map for OSA.

line represents the entire time span covered by the analysis for a particular keyword, encompassing both the pre- and post-burst periods. The keywords such as osteogenic sarcoma, adjuvant chemotherapy, neo adjuvant chemotherapy, prognostic factor and high dose methotrexate had the highest strength including 88.53 (200–2012), 36.6 (2000–2012), 29.55 (2000–2011), 27.49 (2005–2011) and 27.17 (2000–2013) respectively. The top recent burst words are Biomarker, tumor microenvironment (2000–2022), immunotherapy (2000–2022), migration (2000–2022) and DNA methylation (2000–2022).

## 4. Discussion

As research continues to expand rapidly in every field, it has become increasingly important for researchers to gain the understanding of the current advancements in their respective study areas, particularly in light of the widespread acceptance of big data era. Rather than relying solely on meta-analysis and systematic review methodologies, bibliometric analysis offers a simpler visualization approach to validate and analyze existing literature. OSA was identified long ago [24], and extensive research has been conducted on this topic since then. Upon retrieving OSA and its related articles, we observed a relatively stable publication trend with slow growth from 2000 to 2013 (Fig. 2). However, starting from 2014 to 2019, there has been a steady increase in publication, indicating a growing focus on the role of OSA in the field of cancer [2,10]. Over the past three years, the publication rate has experienced a rapid increase, underscoring the significance of OSA research in real clinical practice [15]. The annual citation rate of published journals has rapidly increased alongside the rise in publications. Research on OSA is growing in quantity and gaining recognition from the scientific community, as seen in the increasing number of citations.

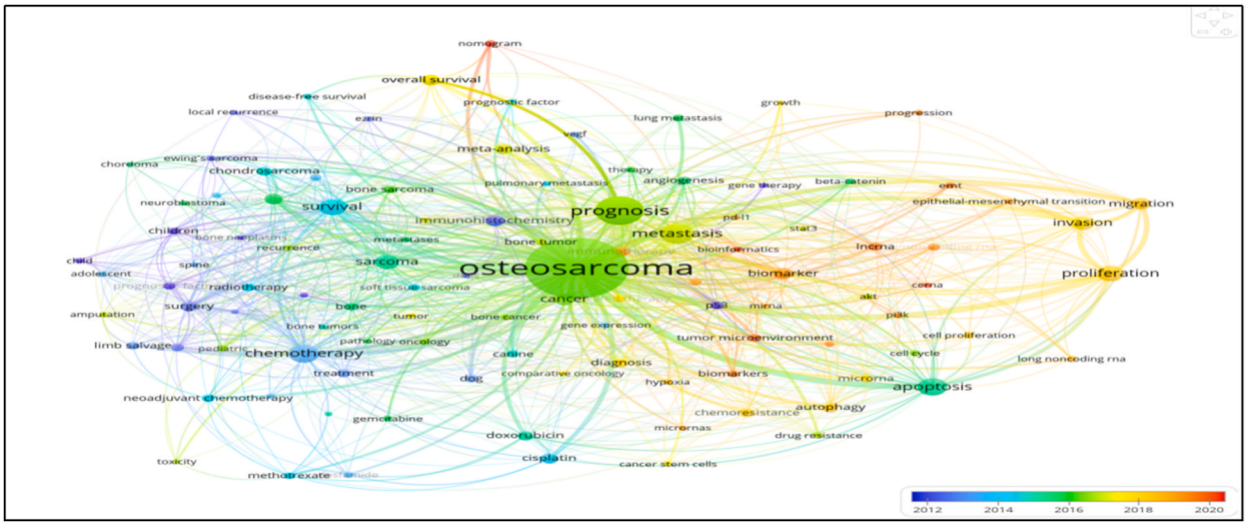


**Fig. 12.** Network visualization map of keywords in the field of OSA.

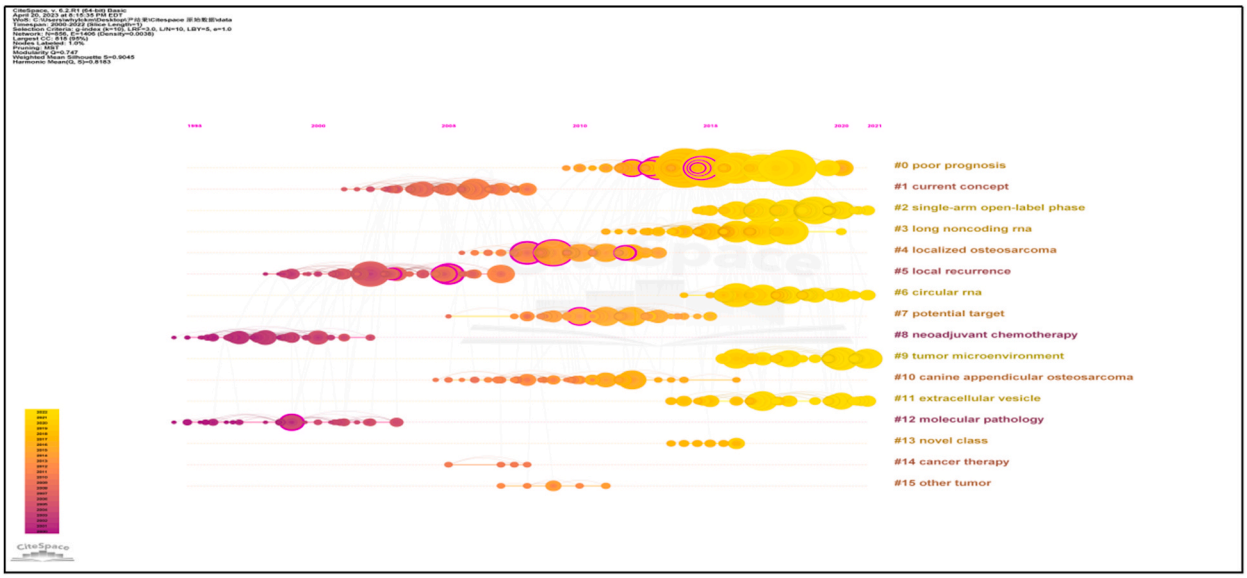


**Fig. 13.** Keyword time zone view of OSA (Keyword timeline visualization).

China and the USA stand out as the leading countries that have made remarkable contributions in the field of OSA research, based on regional distribution (Table 1). When examining the top 10 institutions involved in this area, a majority of them originate from China and the USA. Notably institutions like the University of Texas System, Harvard University, and the Utmd Anderson Cancer Center have played a crucial role in highlighting the significance and relevance of research institutions from the USA in the field of OSA research [25]. In Figs. 5 and 6, it is evident that although the United States has a lower number of publications compared to China, it possesses the highest centrality, serving as a crucial bridge for global collaboration. To bolster its influence further, China should focus on strengthening connections with other nations. Notably, the USA, China, England, and the Netherlands prominently feature in national cooperation networks, indicating a well-established international framework for acupuncture research in OSA. Nonetheless, fostering increased participation from diverse entities is imperative for fostering robust collaboration. According to the data presented in Table 2, analysis of periodicals indicates that Oncology Reports [22], Pediatric Blood & Cancer [23] and Oncotarget [24] have published a significantly higher number of research papers pertaining to the prognosis of OSA. This publication output not only demonstrates their enduring engagement with this community, as reflected by the higher number of citations received. This trend underscores the growing importance and impact of OSA in the research field.

The assessment of national cooperation networks in acupuncture research for OSA reveals extensive networks in the United States, China, England, and the Netherlands, indicating a well-established international cooperation environment. However, to enhance

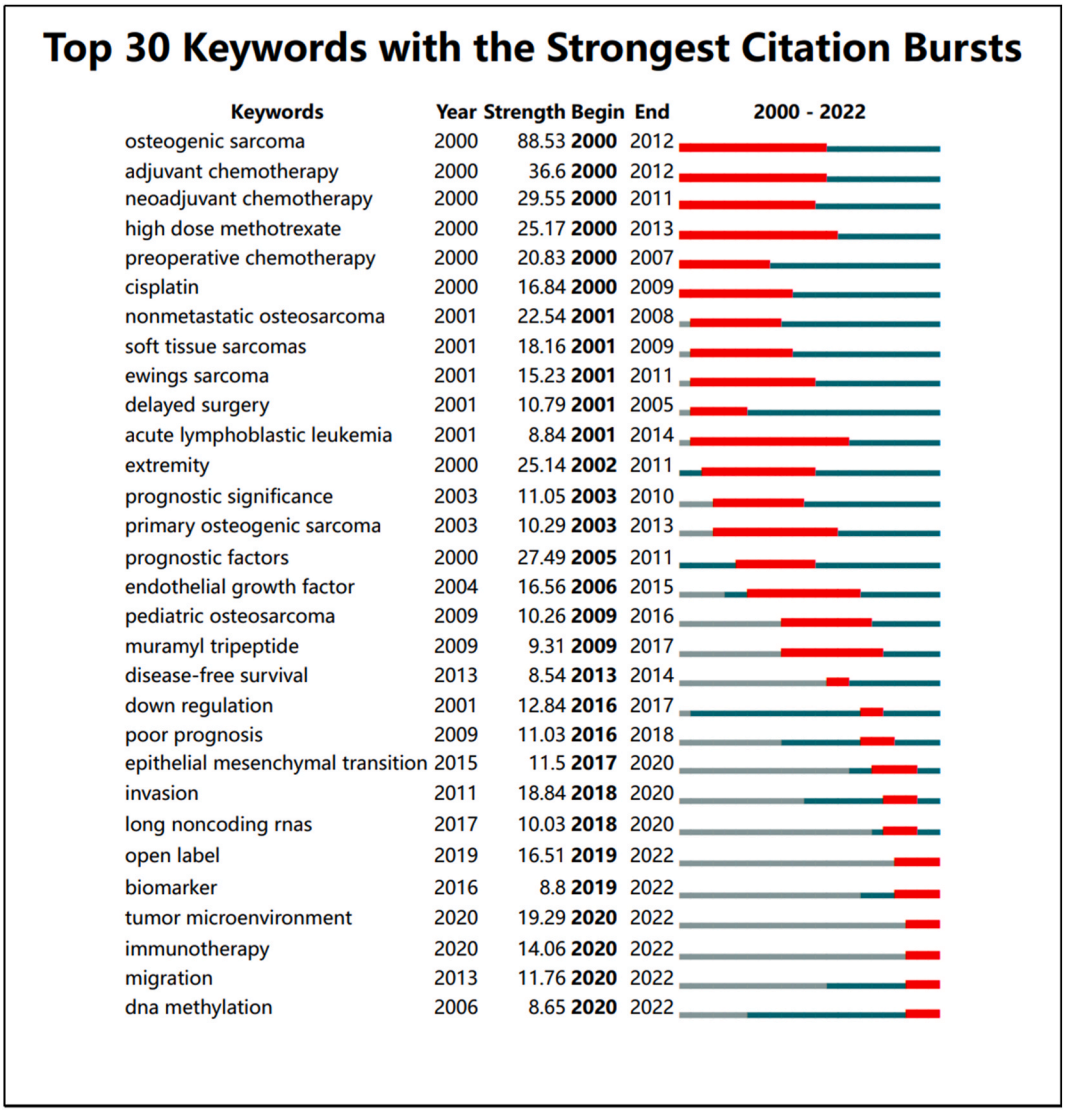


**Fig. 14.** Top 30 keywords with strongest citation bursts.

collaboration, additional participation from diverse entities is crucial. Efforts should be directed towards encouraging more contributors to create a robust international cooperation landscape. As shown in Fig. 9, influential journals such as the Journal of Clinical Oncology and Cancer Research, renowned for their high impact factors, assume a pivotal role in influencing the trajectories of research. The dual-map overlay visually represents the paths of academic journal distribution, elucidating the exploration of OSA from foundational research to its translation into clinical, nursing, and medical studies. Key contributors to OSA research include Wang Y, Zhang Y, Gorlick R, Ferrari S, and Wang J, who form the backbone of OSA studies [26–28]. Notably, researchers from China, affiliated with esteemed institutions like Shanghai Jiao Tong University, have made substantial contributions. Other influential authors from institutions like the University of Texas System and Harvard University have significantly advanced OSA understanding. Authors Bacci G and Bielack SS have over 1500 co-citations, underscoring their importance. In the author co-citation network, Mirabello L, Bacci G, and Bielack SS are prominent, establishing strong connections with other top-cited authors, solidifying their influence in OSA research [26–28].

Keywords analysis is a valuable approach that helps uncover fundamental details about a study, including research methods, research subjects, research content and related aspects. Keywords such as “osteosarcoma”, “expression”, “metastasis”, “prognosis”, “proliferation” and “apoptosis” are associated with high density (Fig. 12). The primary cluster contains key search terms like osteosarcoma, cancer, and metastasis, and two additional clusters, represented by blue and yellow colors, emerged with key search terms such as proliferation, migration, invasion, overall survival, chemotherapy, radiotherapy, and surgery [26,27]. Several authors, including Luetke A [29], Isakoff MS [10], and Kempf-Bielack B [30], have published articles in the field of OSA research, garnering significant citations. Similarly, the most co-cited authors have also used the keyword in their research publications, which signifies the

importance of the keyword, osteosarcoma [14]. Apart from the keyword osteosarcoma, other key words such as "expression", "metastasis", "prognosis", "proliferation" and "apoptosis" (Fig. 11) have also been extensively studied in the OSA research [26,31]. Gene microarrays are indispensable tools for profiling gene expressions. The comparison between normal and tumor samples facilitates the identification of dysregulated genes, and most diseases exhibit specific expression profiles. Weighted Gene Co-expression Network Analysis (WGCNA) serves to detect gene modules with similar functions, where genes within a module share expression patterns, and pivotal genes, referred to as hub genes, drive module functionality [32]. Noteworthy genes, including OPG, TGF-β1, PLA2G2A, TREM2, DSP, and ANXA2, significantly impactaffect osteoid remodeling [33]. Concurrently, certain genes like TMSB10, metallothioneins, GSTP1, and CYP4X1 are associated with chemo resistance [34]. The metastatic implications of OSA and patient prognosis are subjects of investigation, though the underlying mechanisms remain unclear. OSA cells exert influence on blood vessel formation, induce endothelial apoptosis, and exhibit a preference for lung targeting. Exosomes play a role in organ prepopulation for metastasis [35], and understanding organotropism provides valuable insights for lung-targeted therapies [36]. Immunotherapy potential is recognized in OSA; however, its applicability is limited for metastatic cases due to unique immune dynamics in OSA patients.

Critical prognostic factors for OSA include tumor size, metastasis at diagnosis, histological grade, response to neoadjuvant chemotherapy, and surgical margin adequacy [37]. However, invasive approaches hinder the practicality and efficacy of some markers. Age at diagnosis, tumor location, and histological subtypes show promise as more accessible prognostic factors, yet debates persist on their definitive impact. Research findings are inconsistent regarding whether outcomes for patients with OSA are more adverse for those aged 40 and above [2]. Despite attempts to address disparities in research efforts, factors such as sample size, study design, and patient attributes continue to impede improvements in overall survival outcomes. In the molecular landscape, genetic factors, particularly TP53 mutations, play a significant role in OSA prognosis, associated with unfavorable outcomes assessments [38,39]. Metastasis at diagnosis is a critical adverse prognostic factor, necessitating multidisciplinary management for worse outcomes, often involving intensified systemic therapies and surgery for metastatic lesions compared to non-metastatic [40]. OSA involves uncontrollable growth of malignant bone cells (osteoblasts), upsetting the balance between cell division and death. Maintaining this balance is vital for effective treatments. TP53 mutations from DNA damage disrupt cell cycle regulation, inhibit apoptosis, and heighten genomic instability, promoting mutation accumulation and OSA development. Activating TGF-β signaling plays diverse roles in cell processes, emphasizing its importance in OSA pathogenesis [41].

An analysis of citation bursts in OSA research has underscored crucial emerging trends. Keywords with high impact, such as osteogenic sarcoma, adjuvant chemotherapy, and prognostic factors, demonstrated substantial prominence. Recent research has delved into key areas including biomarkers, tumor microenvironment, immunotherapy, migration, and DNA methylation. Over the past five years, biomarkers, DNA methylation, tumor microenvironment, and immunotherapy have assumed pivotal roles in OSA research, steering exploration into cutting-edge topics [26,28,42]. Notably, Osteopontin and PODN biomarkers have been identified, emphasizing their importance in OSA prognosis and management [43,44]. Recent research on OSA explores post-transnational modifications and epigenetic changes as prognostic indicators and therapeutic target [45]. Studies investigate miRNA expression and DNA methylation at the 14q32 locus [46]. The utility of methylation profiles in OSA is uncertain and widespread hypomethylation induction in animal models initiates OSA development [47]. In vitro, demethylating agents reactivate silenced tumor suppressor genes, inhibiting OSA cell proliferation [48]. Methylation status of CpG islands (CGIs) holds prognostic value. Therapeutic agents like HDAC4 and its partner MEF2C, target histone modifications [49]. The framework involves replication-dependent core histones from the H1 histone cluster on chromosome 6. H3 histone mutations are prevalent in bone-related tumors and some OSA cases [49]. Evidence supports methylation patterns as OSA prognostic indicators.

Recent research emphasizes understanding the tumor microenvironment (TME) in malignant tumors, exploring its role in initiation, progression, and therapeutic response. The 2013 ESTIMATE algorithm quantifies immune and stromal cells through gene expression data [50]. Subsequent studies, including Zhang C on OSA, reveal potential of TME as a prognostic indicator in various cancers [51]. Tumor-associated macrophages can enhance growth by promoting angiogenesis and suppressing immune responses. While TME and TME-related genes hold prognostic value in different tumors, their specific role in OSA patients remains unclear. Immunotherapy is an advancing OSA treatment with options like Monoclonal antibodies (mAb), cancer vaccines, adoptive cell therapy, immune checkpoint inhibitors, and combinational therapy. mAb binds to tumor antigens, activating NK cells and macrophages, initiating tumor cell destruction through antibody-dependent cellular cytotoxicity. Initial cancer immunotherapy involved tumor vaccines stimulating an antitumor response by presenting tumor antigens [52]. Combining CTLA-4 and PD-L1 blockade in a murine OSA model controlled tumor dissemination in 50% of mice, prompting tumor immunity [53]. The Children Oncology Group is studying this approach for relapsed or refractory solid tumors (NCT02304458).

This study used bibliometric methods and visually depicted research progress, hotspots, and trends, providing insights for future OSA research directions. China and the USA lead contributions, emphasizing the need for strengthened international collaboration. Analyzing authors and co-cited authors information revealed a need for standardized design in OSA research for continued quality. Main keywords, such as osteosarcoma, expression, metastasis, cancer, prognosis, apoptosis, and proliferation, show high association density. Keyword clusters highlight osteosarcoma, prognosis, chemotherapy, and survival as crucial research focal points. Keywords with strong citation burst analysis identified biomarker, tumor microenvironment, and immunotherapy, migration, and DNA methylation as recent key research frontiers. Despite recent advancements, further research is essential to reduce OSA mortality rates by discovering early diagnosis markers and novel therapeutics.

## Limitations

This bibliometric analysis (2000–2022) explores key trends in OSA research and prognosis. Integrating various databases, it

quantifies output, identifies pivotal articles, and uncovers collaborative networks. This informs resource allocation and future research, enhancing OSA patient survival rates. Acknowledging strengths, limitations include exclusion of non-English and grey literature. While statistically insignificant, inclusion of other languages could enhance credibility. Restricted to WoSCC, variations in author names may complicate identification. Citation quantity does not solely indicate article quality, possibly overlooking innovative ideas. Visualization tools like CiteSpace and VOSviewer may offer incomplete representations. Unlike meta-analysis, bibliometric analysis can't assess precise research content, signaling a need for further advancement.

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## Data availability statement

The authors declare that database used in the study is from publicly literature, or are available from the corresponding author on written request.

## CRediT authorship contribution statement

**Chengliang Yin:** Writing – original draft. **Santosh Chokkakula:** Writing – original draft. **Jie Li:** Investigation, Formal analysis. **Wenle Li:** Methodology. **Weiguang Yang:** Software. **Siomui Chong:** Resources. **Wenzheng Zhou:** Project administration. **Haiyang Wu:** Writing – review & editing, Supervision. **Chengbin Wang:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships.

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