Research Article (Araştırma Makalesi)

Mesenchymal Stem-Cell Derived Treatment In Osteosarcoma Between 1993-2023: A Bibliometric Study

1993-2023 Yılları Arasında Osteosarkomda Mezenkimal Kök-Hücre Kaynaklı Tedavi: Bibliyometrik Çalışma

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Özet

Amaç: Osteosarkom, ergenlik ve çocukluk çağında görülme sıklığı yüksek olan kötü huylu bir kemik tümörüdür. Osteosarkom tedavisi kemoterapi, radyoterapi ve ortopedik cerrahiyi içeren uzun ve zorlu bir süreçtir. Kök hücre kaynaklı tedavi de osteosarkomda son zamanlarda çalışılmaktadır. Bu bibliyometrik çalışmada, osteosarkom ve kök hücre kaynaklı tedavi arasındaki araştırma eğilimini aydınlatmayı amaçladık.

Materiyal ve metod: Osteosarkom ile ilgili yayınlar Web of Science Core Collection'dan alınmıştır. Veri analizi için R studio yazılımı ve VOS viewer analiz programı kullanılmıştır.

Bulgular: Yapılan analizde 853 yayın olduğu ve her yılla ortalama 7,7 yayın düşmekteydi. En üretken ülkeler ilk sırayı ABD ve ikinci sırayı Çin olmıştır. WoS'ta tanımlanan kategorik sınıflandırmaya göre, onkoloji (%41,7) ve hücre biyolojisi (%18,1) tanı ve tedavi açısından ilk iki alan olurken, patoloji (%3,7) ve ortopedi (%2,2) daha düşük çalışma seviyelerine sahipti. Ancak, en çok atıf alan yazar Gibbs idi. (USA; University of Florida University of Alberta UF Orthopedic & Sports Med Inst). "cancer stem cell", "bone cancer" ve "mesenchymal stem cell" anahtar kelimelerinin osteosarkomla güçlü bağlantıları olduğu belirlenmiştir. Bunun yanında, Cancer Res. en çok atıf alan dergi olduğu belirlenmiştir.

Sonuç: Sonuç olarak, hücre kaynaklı tedavi ile osteosarkom arasında güçlü bir ilişki ortaya koyan ilişki araştırmasıyla olan bağlantıların son yıllarda artış gösterdiği tespit edildi.

Anahtar Kelimeler: Kök hücre, Osteosarkom, Bibliyometri

Abstract

Objective: Objective: Osteosarcoma is a malignant bone tumor with a high incidence in adolescence and childhood. Treatment is long and difficult, including chemotherapy, radiotherapy, and orthopedic surgery. Stem cell-derived treatment has also recently been studied in osteosarcoma. In this bibliometric study, we aimed to illuminate the trend of research between osteosarcoma and stem cell-derived treatment.

Materials and methods: Publications on osteosarcoma were retrieved from the Web of Science Core Collection. R studio software and the VOS viewer analysis program were used for data analysis.

Results: There were 853 publications with an average of 7.7 publications per year. The most productive countries were the USA and China respectively. According to the categorical classification described in the WoS, oncology (41.7%), and cell biology (18.1%) were the first two fields in terms of diagnosis and treatment, while pathology (3.7%) and orthopedics (2.2%) had lower levels of work. However, the most cited author locally was Gibbs from the University of Florida University of Alberta UF Orthopedic & Sports Med Inst. in the USA. The keywords "cancer stem cell", "bone cancer", and "mesenchymal stem cell" had been determined to have strong links to osteosarcoma. Cancer Res was the most cited journal.

Conclusion: As a result, it has been found that research presenting strong links to the relationship between cell-derived therapy and osteosarcoma has shown an increase in recent years.

Keywords: Stem cells, Osteosarcoma, Bibliometrics

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INTRODUCTION

Osteosarcoma is the most common primary malignant bone tumor of the bone (1). The historical evolution of its treatment includes the amputation of the diseased extremity which was reported not the best but the only option in primitive papers. However, the survival rate was only 15-17 % (2). After the invention of chemotherapeutics, the treatment paradigm changes eventually (3). The shrinkage effect of the systemic treatment facilitates the resection of the tumor with a negative margin which is the cornerstone of the treatment. The replacement of limb-sparing surgery with amputation has appeared to be an innovative approach, and an increase in survival rates was gained. The desired overall survival rates had not been reached yet (4). The biggest step to obtaining successful results is the invention of systemic treatment (chemotherapy), so the main objective of the scientists in terms of treatment advances (5). Two main problems stand still in front of the conventional chemotherapeutic method. One is the devastating side effects of chemotherapy, and the second is the potential resistance that arises during the treatment. Besides, the genetics and the biology of the disease were not elucidated completely because of its heterogeneous genomic features. Target therapy merged to be a prospective treatment option for the patients. Theoretically, both copy number-driven and mutation-driven cancer approaching derivatives were put forward in terms of the design of target-based treatments (6).

Cancer stem cells (CSC) have already been described as having a potential role in certain cancer types. Treatment shifted to the based-on stem cell target. CSC was also described as having a potential role in treatment resistance, metastasis, and tumor recurrence. Research on CSC appeared to have an increase in the trend to direct systemic treatment apart from conventional methods (7). So, this study aimed to show recent trends and their evolution during the time in the studies that illuminate the relationship between osteosarcoma and CSC.

MATERIALS AND METHODS

The bibliometric technique was applied for the words "stem cell" and "osteosarcoma". For the prevention of data deflection due to the ongoing data stream, the endpoint for the study was determined as 16. 2023 December for Web of Science Core Collection (WoSCC). All research articles and books in all languages were included in the research. Search results related to the words were saved as "Plain Text Files" or "BibTex". Bibliometric analysis was performed on four categories general perspective, countries/regions, authors/affiliations, sources, and trends. Data were visualized by WoS, Biblioshiny (R version 4.3.3; Vienna, Austria; www.r-project.org), and VOS Viewer (1.6.20; Leiden, Netherlands) programs (8,9).

This study presents an enhanced graphical analysis of bibliographic data utilizing VOSviewer software. VOSviewer is adept at analyzing and visualizing bibliometric network data, including citation relationships among publications, collaborative relationships between researchers, and co-occurrence relationships among scientific terms.

RESULTS

There were 853 online publications determined between November 1993 and December 2023 according to WoS related to the keywords "stem cell and osteosarcoma". The distribution of the data set was composed of 693 research articles, 13 book chapters, 36 memorandum articles, and 104 review articles. There were 1860 Keywords Plus (ID) and 1482 Author's Keywords (DE).

Annual Publication Analysis

There was only one publication relating to "stem-cell" and "osteosarcoma" in 1993 when the first paper was published. Till now the mean number of papers relevant to the topic was 7.77 per year. Assessment of the dataset showed an increase in the number in the following years and reached two-digit numbers in the 2000's **(Figure 1/A)**. The highest number of papers was reached in 2021 with 56 research articles (76 publications total) and slightly diminished in the last two years. According to WoS categories, the top 3 contenders of these publications are Oncology, Cell Biology and Biochemistry Molecular Biology, while Orthopedics is ranked 22th **(Table 1)**. This steady increase and continuous growth reveal that there is an important trend

in which diagnostic and therapeutic researchers, as well as molecular medicine and engineering research, are shifting to this field.

Research hotspots: Keywords network analysis

The co-occurrence network diagram was analyzed by Vos Viewer divided the groups into 4 as red, yellow, blue, and green, and the size of each node reflects the frequency of the relevant keyword in the literature. In addition, the thicker the connection between two keywords, the more frequently the two keywords occur together. It manifests itself as osteosarcoma (red) as the largest node. It has also been determined that osteosarcoma has a strong connection with cancer stem cells, bone cancer, and mesenchymal stem cells **(Figure 1/B)**.

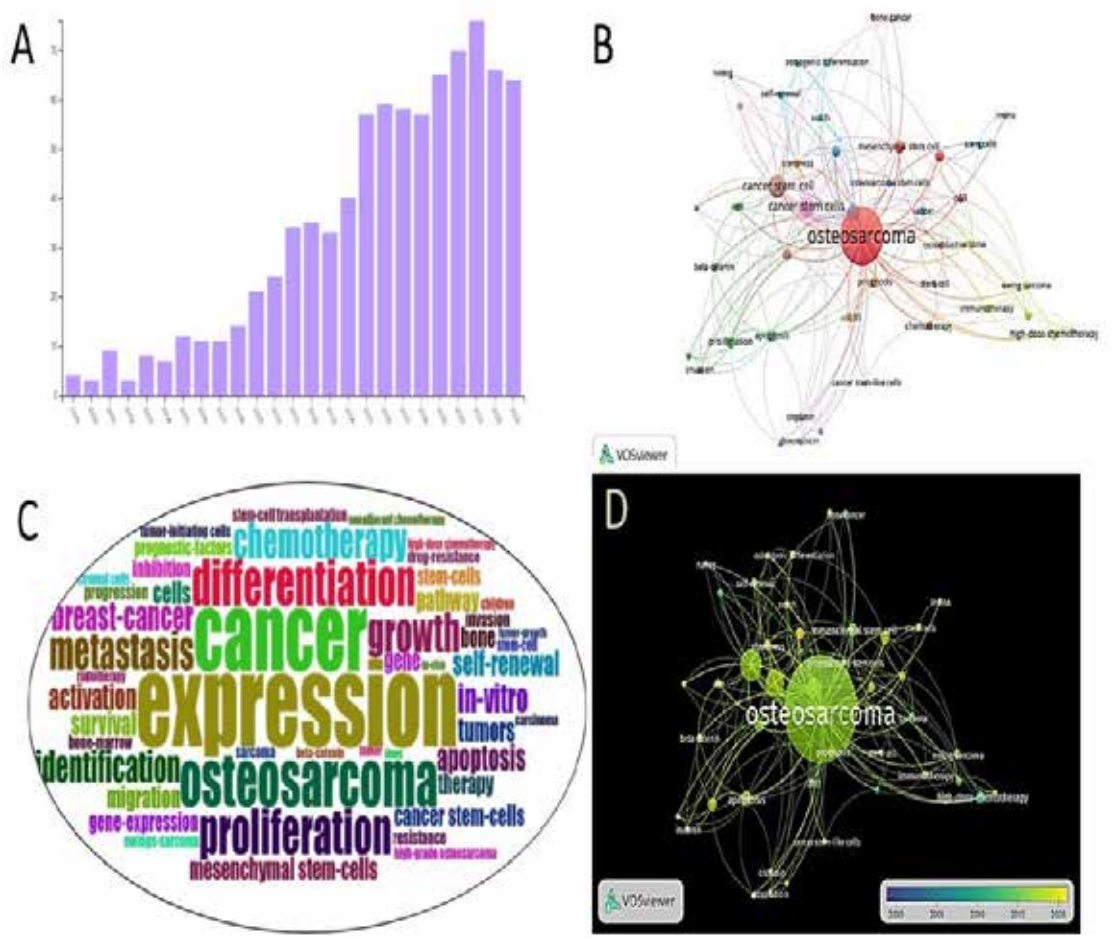

Figure 1. A: The increase in papers over the past years **B:** The relationship between keywords. Osteosarcoma is strongly connected to cancer stem cells, bone cancer, and mesenchymal stem cells **C:** keywords selected for stem-cell-derived therapies showed the most common keywords used between 1993-2023 **D:** The distribution of keywords during the timeline

Figure 1/C represents the 50 most frequently used author keywords using a word cloud where the size of each keyword represents its frequency. In parallel with the results of the Vos viewer analysis, it was determined in the Biblioshiny program analysis that the terms "expression" and cancer were used most frequently in research from 1993 to 2023. At that time, most researchers preferred the genetic-level learning approach for cancer and osteosarcoma research. The third most used word after "cancer" and "expression" was "osteosarcoma" **(Figure 1/C)**. In addition, it was observed that terms such as "stem cell transplantation" and "chemotherapy" were not used very frequently in the word cloud.

Additionally, the figure shows the annual change of the top 50 keywords from purple to yellow. The purple color represents the keywords that were widely used before the 2000s, and the yellow color represents the keywords that were widely used from 2015 to the present. While the keywords "chemotherapy" and "cancer" were mainly used until the beginning of 2010, it was determined that "bone" and osteosarcoma were widely used after 2010, and "cancer stem cell" was used after 2015. In addition, the keywords "chemoresistance" and "WNT", "tumor microenvironment" and "stemness" have recently started to be used **(Figure 1/D)**. Additionally, the relationships and evolution of keywords were examined using Biblioshiny in the analysis slice. Accordingly, the change in the use of the keyword 'cancer' in previous years (1993-2017) has dramatically shifted to the words "stem cell" and differentiation between 2018 and 2023. The keywords "MicroRNAs" (1993-2017) evolved into the terms "cancer", "osteogenetic differentiation" and "osteosarcoma", and mesenchymal stem cell (1993-2017) evolved into Ewing sarcoma and exosome **(Figure 2/A)**. Osteosarcoma was the most frequently used term and has shown a steady increase since 1997 **(Figure 2/B)**.

Author Analysis

Analysis of citation data is known as an important factor in bibliometrics. Examining the impact and importance of scientific research and research outputs is an important indicator.

Table 1. The top 25 categories of research according to WOS

Categories	Record Count	% of 853
Oncology	356	41.7
Cell Biology	154	18.1
Biochemistry Molecular Biology	97	11.4
Medicine Research Experimental	82	9.6
Hematology	65	7.6
Pharmacology Pharmacy	54	6.3
Pediatrics	42	4.9
Genetics Heredity	37	4.3
Cell Tissue Engineering	36	4.2
Chemistry Multidisciplinary	36	4.2
Multidisciplinary Sciences	34	4.0
Pathology	32	3.8
Biotechnology Applied Microbiology	31	3.6
Biophysics	30	3.5
Immunology	30	3.5
Nanoscience Nanotechnology	25	2.9
Transplantation	23	2.7
Materials Science Multidisciplinary	22	2.6
Materials Science Biomaterials	20	2.3
Medicine General Internal	20	2.
Orthopedics	19	2.2
Physiology	19	2.2
Surgery	18	2.1
Endocrinology Metabolism	17	2.0
Engineering Biomedical	16	1.9

It can be used to investigate the impact of a particular author and work by looking at how often a work is cited, how many times it is cited, by whom it is cited, and for what purpose. In addition, it is important to show that the subject in the most cited source is within the scope of the journal or journal group.

According to the total citation frequency, the most relevant author is Wang Y (USA) in the first place, LI Y (China) in the second place, and Wang J China) in the third place. The number of authors working on the keywords "osteosarcoma and stem cell" was 3031, the number of studies with a single author was 15, and the number of studies with more than one author was 3016. Locally the most cited authors are Gibbs CP (University of Florida University of Alberta UF Orthopedics & Sports Med Inst), Ghivizzani SC (USA) ranked second, and Ignatova TN (USA) ranked third. The findings in terms of author show two different steps of analysis, first the most relevant authors **(Figure 2/C)**, and second, the most cited locally **(Figure 2/D)**.

Most country's production and Cited Sources Analysis

When we look at the geographical distribution of publications based on the data analysis of our keywords, it has been determined that the studies have an international scale, although they have different degrees of productivity. When it comes to the scientific production of countries and the geographical distribution of research outputs, most scientific outputs are led by the USA in the Americas, China in the Asian continent, and Italy in the European continent **(Figure 3/A)**. According to WOS, the most range of productive country is the United States, accounting for 32.7% of total publications. Türkiye is in 16th place with 1.87%. This study is also important in terms of publishing the results related to the countries of the relevant authors and explaining their active participation in osteosarcoma stem cell research. In the analysis, when the publications on this subject are compared at the country level; In the case where only corresponding authors

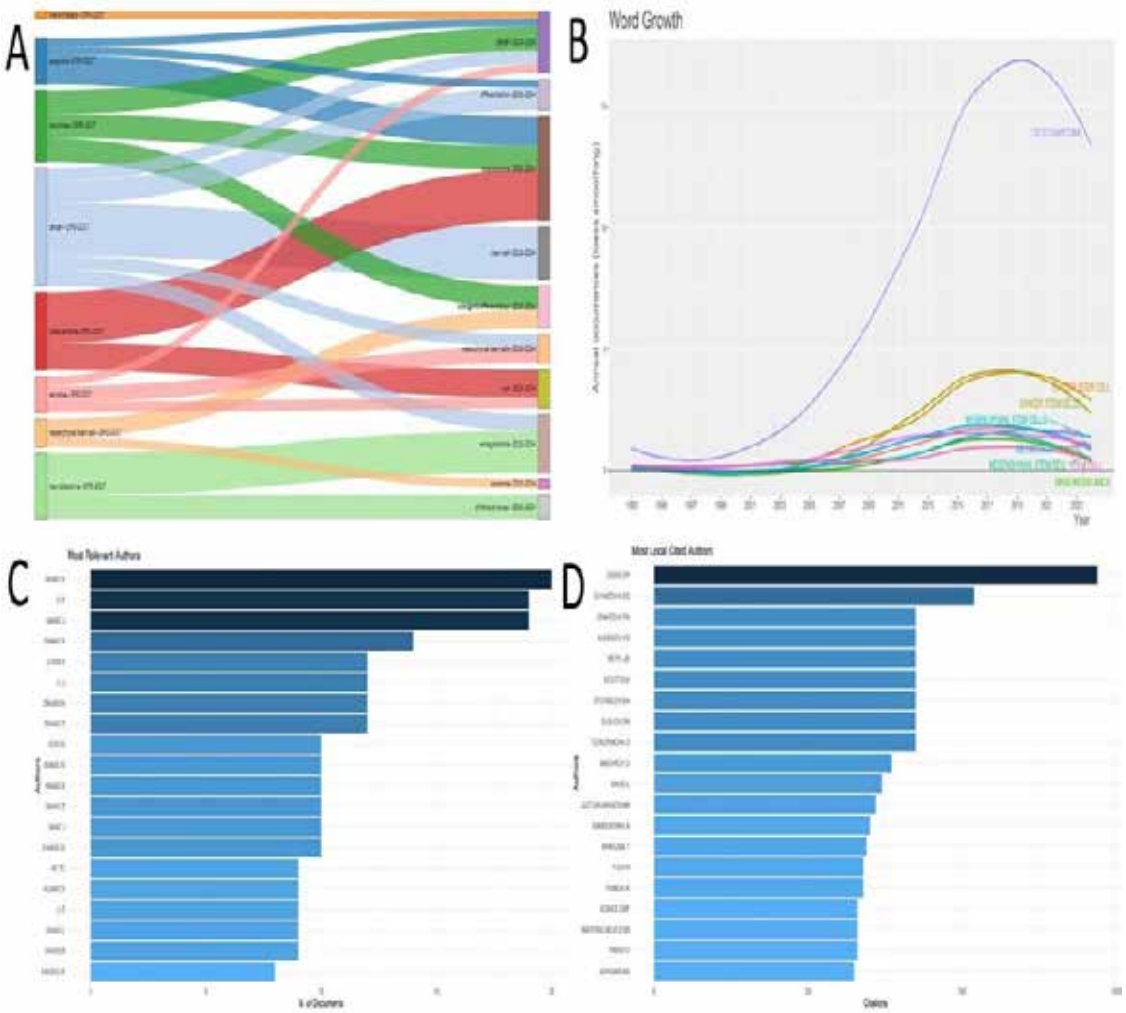

Figure 2. A. Keyword shifting between the time interval 1993-2017 and 2018-2024 **B.** In addition, the usage change of frequently used keywords over the years is shown. **C, D.** Most relevant authors and most local cited authors, respectively

were included, a total of 56 countries contributed to the relevant publications. China, the USA, and Japan lead the list of countries where the corresponding authors are included. In addition, when evaluated in terms of Multiple Country publication (MCP), the USA, Italy, and the UK are in the first place **(Figure 3/B)**.

In addition, the most cited sources are CANCER RES. In second place is J CLIN ONCOL, and in third place is PLOS ONE. When we look at the change in sources over the years, although the International Journal of Malevolent Sciences has gained great momentum in recent years, there is a decline in oncology letters and oncotarget journals **(Figure 3/C)**.

The opinions of research institutions have a strong influence. Following global data analysis, the institutions that produce the most publications are the University of Minnesota Twin Cities School of Medicine, second is Shanghai Medical University, and third is University of Chicago Division of The Biological Sciences **(Figure 3/D)**.

DISCUSSION

Bibliometric studies have an important place in terms of developments in the scientific field, journal efficiency, and the impact of publication. It is known in the literature that the bibliometric method is used in many fields of medical sciences. Although there are bibliometric studies on osteosarcoma, studies on osteosarcoma and stem cells are scarce. Osteosarcoma is an aggressive primary bone tumor seen mainly in young people and children of almost all ages and has a poor prognosis. Standard treatment methods are not always optimistic and alternative treatment methods and the search for new therapeutic targets are discussed in the literature. According to country distribution, they are America, Asia, and Europe on a continental basis. After the USA, China, Italy, and Japan were determined to be the most productive countries. As reported in previous studies on osteosarcoma (10), the USA and China show that they may be potential areas for research on this subject. According to the data obtained from individual publications, Wang Y. (China), Na DL (South

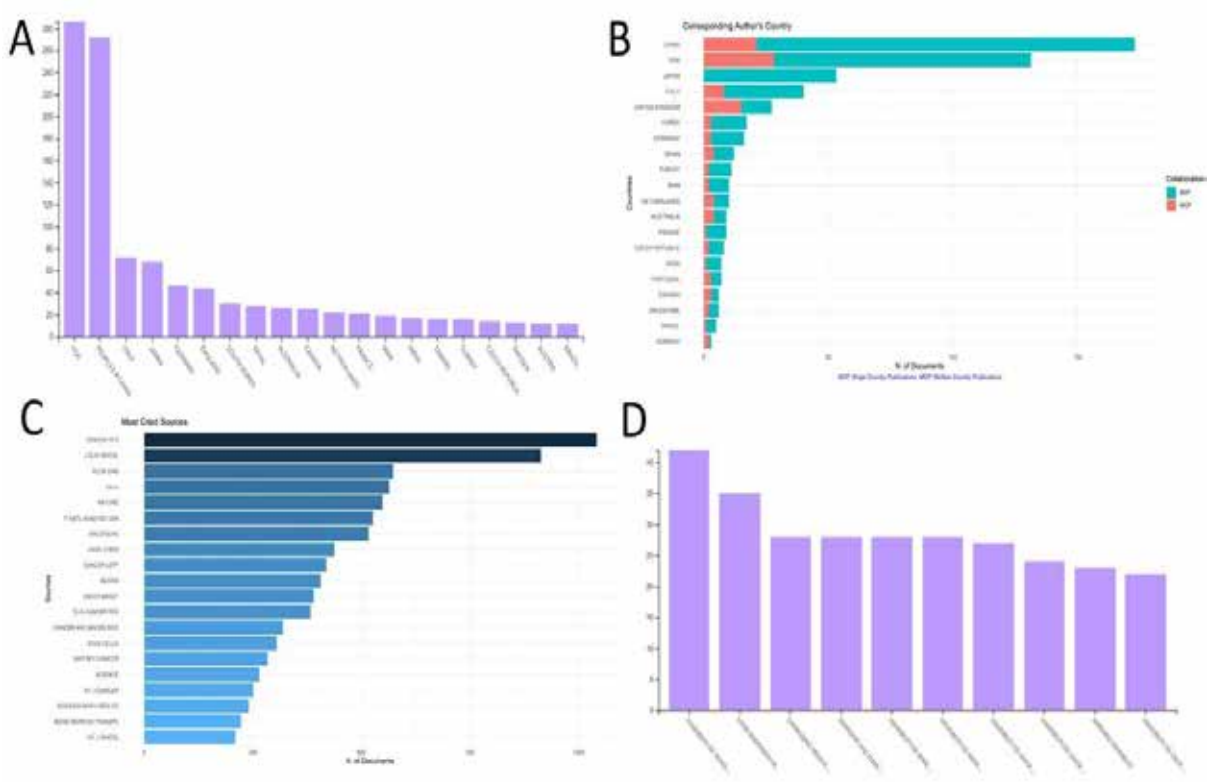

Figure 3. A. Scientific productions of the countries **B.** The nationality of corresponding authors **C.** The distribution of affiliations in terms of publications. **D.** The most common sited journals

Korea), Zhang Y. (China), Kim HJ (South Korea), and Zhao J. (China) were determined to be the countries with the most individual publications.

According to their data, the first article on this subject was published in the journal Cancer in 1993 by Kramer et al.'s article titled "Epithelioid Osteosarcoma of Bone - Immunocytochemical Evidence Suggesting Divergent Epithelial and Mesenchymal Difference In A Primary Osseous Neoplasm", which focuses on the possibility of different differentiation of a primitive, multipotent, unregistered stem cell in a primary osseous tumor (11). The number of publications has gained significant momentum in the last 30 years and reached its highest level in 2021.

Citation analysis is the most widely used form of bibliometrics that allows measuring the impact factor of journals (12). It was observed that there were 19,662 citations containing the keywords used. The most cited is Gibs et al. It is an article titled "Stem-like cells in bone sarcomas: Implications for tumorigenesis" and has received 390 citations (13). Kramer et al., building on the publication, reported, using molecular methods, that there is a small subpopulation of anchorage-independent, self-renewing bone sarcoma cells capable of forming suspended spherical, columnar clusters, also called "sarcospheres", in serum-free conditions (14). In addition, Kramer et al. have received around 30 citations so far. In the analysis, the journal with the most citations was Cancer Research. Levings et al.'s publication titled "Expression of an Exogenous Human Oct-4 Promoter Identifies Tumor-Initiating Cells in Osteosarcoma" has received 130 citations (15). In the study, it is seen that the change in the use of the keyword 'cancer' has evolved into the word 'stem cell' and differentiation by 2023.

Recently, the keywords "chemoresistance", "WNT", "tumor microenvironment" and "cancer stem cell" have been frequently used and be the keywords that guide the etiology and treatment of the disease. In our analysis, it is also seen that there is a strong connection between osteosarcoma and cancer stem cells within the word network. Some studies provide solid evidence that mesenchymal stem cells may have the ability to turn into tumor stem cells (16). Studies aiming to isolate tumor stem cells and reveal effective specific surface antigens synthesized by osteosarcoma stem cells, which will eventually generate neutralizing antibodies that will neutralize osteosarcoma or prevent osteosarcoma development, have become trending (17). Among the keyword interactions, the one that stood out was "WNT". Additionally, in our data analysis, the words

expression and cancer osteosarcoma were seen prominently in the word cloud, respectively. Many years of research have revealed that WNT is involved in tumor formation and that the WNT signaling pathway also plays an important role in regulating cancer stem cell function. Studies conducted on humans have reported that the WNT signaling pathway is effective in types of cancer such as colon and sarcoma, as well as playing a role in congenital disorders such as coronary artery disease, tetraamelia, Müllerian duct, and vascular defects. In our analysis, there is evidence that there are weak connections between WNT and osteosarcoma, and the literature review provides evidence that the issue still needs to be clarified (18).

Current treatment approaches for osteosarcoma standard treatment are preoperative chemotherapy, surgical resection, and postoperative chemotherapy, which are effective in localized patients. Stem cells have the potential for self-renewal and differentiation into many cell types, including osteoblasts, myocytes, hepatocytes, and chondrocytes. These cells are known as hematopoietic, non-multipotent cells. Although there is evidence that these cells may be tumor-promoting, there are also strong reports of a role in tumor suppression. This study is very valuable to draw a map to prevent repetitions for future studies by revealing the evolution of current studies of difficult-to-treat diseases such as osteosarcoma over the years. Therefore, it is important to understand the interaction of stem cells and osteosarcoma-related publications to develop new and more effective osteosarcoma treatments and overcome drug resistance.

Ethics Approval: The study complied with the World Medical Association Declaration of Helsinki. Ethics committee approval is not required, as it performs a bibliometric analysis of existing published researches. There is no human or animal research.

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Declaration of Competing Interest: None.

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