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Ewing sarcoma: what trends in recent works? A holistic analysis with global productivity

A cross-sectional study

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Abstract

Advances in the biology of Ewing sarcoma, which continues to be an important cause of mortality, have caused an increase in information in the literature related to the underlying molecular base of the disease and discussions of new treatment approaches. In this study, we aimed to comprehensively analyze the published scientific articles on Ewing sarcoma. The Web of Science database was used to obtain and statistically analysis articles on Ewing sarcoma that were published between 1980 and 2021. Maps of network visualization were used to reveal trending topics, global collaborations, and the most effective studies. Correlation analysis was performed using Spearman's correlation coefficient. A total of 3236 articles were analyzed. The first 3 countries that contributed the most to the literature and cooperated most intensively were USA (1194, 36.8%), Germany (293, 9%), Italy (254, 7.8%). Pediatric Blood & Cancer (n = 122), Cancer (87), Journal of Pediatric Hematology Oncology (71) were among the top 3 journals with the most articles. The most active author was Piero Picci (n = 94). High-income countries have a great effect on the literature on this subject. The most studied trend topics in recent years were pediatric oncology, EWS RNA Binding Protein 1 (EWSR1), EWSR1-FL1, epigenetics, bioinformatics, microRNA, gene expression, metastasis, migration, biomarker, immunotherapy, survival, outcomes, surveillance epidemiology and end results (SEER), nomogram, temozolomide, irinotecan, and drug resistance. Genetic studies, metastasis, immunotherapy, life analyses/nomogram based on new data obtained from SEER, and chemotherapy with irinotecan and temozolomide combination, were seen to be the topics researched in recent years.

Abbreviations: ES = Ewing sarcoma, EWSR1 = EWS RNA Binding Protein 1, GDP = gross domestic product, GDP per capita = gross domestic product per capita, HDI = human development index, NC = number of co-citation, SCI-Expanded = Science Citation Index Expanded, SEER = surveillance epidemiology and end results.

Keywords: bibliometric analysis, Ewing Sarcoma, Ewing's Sarcoma, trends

1. Introduction

Ewing sarcoma (ES), which was first described in 1921 by James Ewing, is a small, round, blue cell mesenchymal malignancy, which is seen most often in children and young adults.[1,2] The Ewing sarcoma family of tumors includes peripheral primitive, neuroectodermal Ewing sarcoma (ES) tumor, and extraosseous ES.[3] ES is pathologically associated with small round cells and t (11;22) (q24;q12) translocation, with FLI1 of the EWS gene or hybrid transcripts of the ERG gene.[4–7] Most cases of ES include chromosomal translocations resulting in t (11;22) (q24;q12) between chromosome 11 and 22. This exchange encodes EWS/FLI fusion protein. The EWS/FLI formation seems to be a critical oncogenic event in the development of ES.[1,2]

Prognostic factors at the time of diagnosis are metastasis, primary localization, and age. Early diagnosis before metastasis is of critical importance for the better survival of ES patients.[8] The most common regions of metastasis are the lungs and pleural cavity, the skeletal system, and bone marrow, or a combination of these.[7] The most important prognostic factor in ES is metastasis, and while the 5-year survival rate is approximately 70% when there is no metastasis, this rate falls to around 30% when metastasis is present. Despite recorded advances in multi-modal strategies including optimal combination chemotherapy, and the 5-year survival rate of 70% in non-metastatic ES patients, the 5-year survival rate remains <30% for patients with recurrence and/or metastasis.[6,9]

As a treatment strategy for ES, 4 types of standard treatment are used; surgery, radiation therapy, chemotherapy, and high-dose chemotherapy with stem cell salvage. New treatment types have been tested in clinical studies, such as target-directed treatment (monoclonal antibody therapy, kinase inhibitor therapy, NEDD8-activating enzyme inhibitor therapy)

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This article does not contain any studies with human participants or animals performed by any of the authors.

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and immunotherapy.[10] For successful treatment, extremely intense chemotherapy is required together with surgery and/or radiation.[1] In the first study between groups of non-metastatic ES, as better results were obtained with the inclusion of doxorubicin, almost all chemotherapy protocols are based on 4 drugs: doxorubicin, cyclophosphamide, vincristine, and dactinomycin.[11]

At the start of the 1980s, following the standard treatment for ES, ifosfamide treatment with or without etoposide, produced noteworthy responses in patients with recurrence.[12] The addition of ifosfamide and etoposide to a standard regimen does not affect the result in patients with metastatic disease, but significantly improves the result in patient with non-metastatic ES, primitive neuroectodermal bone tumor, or primitive bone tumor.[13] The development of cytotoxic chemotherapy since the 1970s has provided improvements in the prognoses of patients with ES in particular. However, despite the establishment of several new targeted drugs and immunotherapies since the 2000s, the desired increase in the prognosis of patients with bone sarcoma has not been seen.

There are various histological types of bone sarcoma and genomic mutations show significant differences according to the histological types. This has created a limitation in the development of new molecular-targetted drugs. Another limitation is in the evaluation of treatment efficacy because of the high rates of pediatric and young adult patients and the difficulty in conducting large-scale randomized clinical trials.[6]

Bone sarcomas constitute only approximately 0.2% of all solid malignancies; ES followed by osteosarcoma are the most frequently seen primary malignant bone cancers.[2,7] In a study of the incidence using the surveillance, epidemiology, and end results (SEER) database, Esiashvili et al (2008) reported the general age-adjusted ES incidence (per 1 million) for patients aged 1 to 19 years for the years 1973 to 1982, 1983 to 1992, and 1993 to 2004 to be 2.92, 3.07, and 2.72, respectively, and the 5-year survival rates to be 36.4%, 52.7%, and 60.2%.[14]

Advances in the biology of ES, which continues to severely affect the quality of life of patients, and to be a significant cause of mortality, have caused an increase in information in the literature related to the underlying molecular base of the disease and discussions of new treatment approaches. However, despite the rise in the number of publications worldwide about ES, there has been no bibliometric research on this subject. Bibliometry is the analysis of scientific publications using statistical methods.[15–17] Using the statistical analysis results of many articles in literature, bibliometric studies provide a holistic summary of the subject to researchers interested in the subject by presenting the most active institutions, authors, and journals, international collaborations, and trend topics studied in recent years.[15–17] In this study, we used statistical and bibliometric techniques to conduct a comprehensive analysis of the scientific papers on Ewing sarcoma that were published between 1980 and 2021.

2. Material and methods

2.1. Search strategy

Web of Science Core Collection (WoS by Clarivate Analytics: https://www.webofknowledge.com) database was used for literature search. Keywords (search in article title) to access all published articles about Ewing Sarcoma were *Ewing* sarcoma** (Includes all articles with the words "Ewing" and "sarcoma" in the title, such as *Ewing sarcoma, Ewing's sarcoma, Ewings sarcoma, Ewing-like sarcoma, Ewing sarcomas, Ewing's sarcomas*). The years evaluated are 1980 to 2021 (Due to different access dates, search results may differ slightly, accessed April 20, 2022). The search was carried out in all research areas. VOSviewer (Version 1.6.18, Leiden University's Center for Science and Technology Studies) software was used for trend keyword analysis, cluster analysis, bibliometric network visualizations and citation analysis.[18]

This article was not ethical approval is not necessary because it is a bibliometric analysis of published articles. Because the current study which did not involve any clinical trials and patient consent.

2.2. Statistical analysis

The Statistical Package for the Social Sciences (Version 22.0, SPSS Inc., Chicago, IL, License: Hitit University) software was used to conduct statistical analyses. A world map displaying the global article productivity of nations on Ewing sarcoma was generated using the website (https://app.datawrapper.de). The Exponential Smoothing estimator, which incorporates seasonal smoothing, was used in Microsoft Office Excel to calculate the potential number of articles that could be published over the next 5 years based on past article trends. Before the correlation analysis, the data were tested for normal distribution using the Kolmogorov–Smirnov test. Since the data were not normally distributed, the effect of some economic development indicators (gross domestic product [GDP], gross domestic product per capita [GDP per capita], human development index [HDI]) on the productivity of the article on Ewing sarcoma was examined using the Spearman correlation coefficient (data sourced from the World Bank)[19]). P value < .05 was accepted for a statistically significant correlation.

3. Results

As a result of the literature scan of all the research areas published on the subject of ES between 1980 and 2021 in the WoS database, a total of 5883 publications were identified. Of these publications, 55% (n = 3236) were Articles, 30.7% (n = 1805) Meeting Abstracts, 5.3% (n = 311) Review Articles, 3.4% (n = 199) Letters, 1.5% (n = 89) were Proceedings Papers and the rest were in other publication types (Editorial Materials, Notes, Books, Book Chapters, Early Access, News Items, Corrections, Additions, Discussions, Retracted Publications). The bibliometric analyses of these were limited to 3236 articles published under the category of "Article," with all other publication types being disregarded. Of these articles, 90% (n: 2906) were scanned in Science Citation Index Expanded (SCI-Expanded) and 9% (n = 290) in the Emerging Sources Citation Index, and the remaining small number in the Book Citation Index—Science, Index Chemicus and Social Sciences Citation Index. The language of publication of the articles was English in 95.4% (n: 3086) and other languages (French [n = 60], German [51], Spanish [19], Russian [11], Japanese [2], Turkish [2], Chinese [1], Croatian [1], Italian [1], Polish [1], Portuguese [1]) in the others. In the 3236 articles, the h-index was 115, the average number of citations per article was 24.71, and there were 79,965 total citations (without self-citations: 54,798).

3.1. Research areas with the most published articles on Ewing sarcoma

The 16 most active research areas with 50 or more articles published on Ewing sarcoma were Oncology (n = 1531, 47.3%), Pediatrics (403, 12.4%), Surgery (347, 10.7%), Pathology (332, 10.2%), Radiology Nuclear Medicine Medical Imaging (246, 7.6%), Hematology (245, 7.5%), Cell Biology (244, 7.5%), Orthopedics (212, 6.5%), Medicine General Internal (184, 5.6%), Biochemistry Molecular Biology (165, 5%), Genetics Heredity (144, 4.4%), Clinical Neurology (118, 3.6%), Medicine Research Experimental (103, 3.1%), Multidisciplinary Sciences (81, 2.5%), Otorhinolaryngology (54, 1.6%), and Pharmacology Pharmacy (51, 1.5%), respectively.

3.2. The development of articles according to years

Figure 1 shows a bar graph showing the number of articles published each year. The statistically estimated results and the Exponential Smoothing estimation model used to estimate the number of articles to be published in the next 5 years are shown in Figure 1. According to the exponential model determined as the most successful estimation model when seasonal correction was taken into consideration, it was estimated that 196 (95% confidence interval: 171–221) articles on the subject of ES would be published in 2022, and 240 (95% CI: 194–286) in 2026 (Fig. 1).

3.3. Active countries

The distribution of the number of articles according to country is shown on a world map, and the top 15 countries contributing most to literature are presented as a bar graph in Figure 2. The top 15 countries with the most articles were USA (1194, 36.8%), Germany (293, 9%), Italy (254, 7.8%), France (215, 6.6%), Japan (215, 6.6%), China (192, 5.9%), India (182, 5.6%), Spain (181, 5.5%), United Kingdom (173, 5.3%), Austria (108, 3.3%), Canada (107, 3.3%), Netherlands (106, 3.2%), Turkey (106, 3.2%), Switzerland (83, 2.5%), and South Korea (53, 1.6%), respectively (Fig. 2). International collaboration analysis and cluster analysis was applied to the 54 countries found to have international collaboration among writers and the 80 countries that produced at least 2 articles on the subject of ES (The top 10 countries with the greatest ratings in terms of global cooperation [total link strength], which represents the capacity for cooperation among 54 countries: USA [454], Germany [338], Italy [228], France [213], Spain [210], Austria [191], England in United Kingdom [181], Netherlands [181], Switzerland [141], Canada [113]). The density map according to the strength of collaboration is shown in Figure 3a and the cluster analysis results are shown in Figure 3b. According to the cluster analysis results, 12 different clusters were formed related to international collaboration (Cluster 1: Argentina, Brazil, Finland, Nepal, Norway, Philippines, Portugal, South Korea, Sweden, Uruguay. Cluster 2: Egypt, India, Indonesia, Israel, Japan, Pakistan, Saudi Arabia. Cluster 3: Austria, Czech Republic, Denmark, Netherlands, Scotland, Switzerland. Cluster 4: Bulgaria, Chile, Colombia, Cuba, Germany, Italy. Cluster 5: Lebanon, New Zealand, Qatar, USA. Cluster 6: Australia, Hungary, Jordan. Cluster 7: England, Serbia, Slovakia. Cluster 8: France, Luxembourg, Thailand. Cluster 9: Canada, China, Singapore. Cluster 10: Mexico, Poland, Russia. Cluster 11: North Ireland, Spain, Turkey. Cluster 12: Belgium, Greece, Ireland).

3.4. Correlation analysis

It was found that there was a strong positive correlation between a nation's GDP, GDP per capita, and HDI scores and the number of articles it produced about ES ($R = 0.743$, $P < .001$; $R = 0.724$, $P < .001$, $R = 0.700$, $P < .001$, respectively).

3.5. Authors who have published the most articles on Ewing sarcoma

The top 10 most active authors on Ewing sarcoma were Picci P. (n = 94), Dirksen U. (75), Jurgens H. (75), Scotlandi K. (63), Ferrari S. (49), Lessnick SL. (49), Bacci G. (48), Kovar H. (45), Delattre O. (43), and Manara MC. (38), respectively.

3.6. Active institutions that have published the most articles on Ewing sarcoma

League of European Research Universities (n = 197), University of Texas System (170), Unicancer (federation of French comprehensive cancer centers, n = 139), University of Munster (139), National Institutes of Health USA (132), UTMD Anderson Cancer Center (127), Harvard University (124), NIH National Cancer Institute (122), University Of California System (110), Udice French Research Universities (103), Rizzoli Orthopedic Institute (102), Memorial Sloan Kettering Cancer Center (98), Mayo Clinic (84), Institut Curie (83), and PSL Research University Paris (University Paris Sciences & Lettres, n = 81) were the top 15 institutions that produced the most articles on Ewing sarcoma.

3.7. Active journals on Ewing sarcoma

The 3236 papers on ES that have been published have appeared in 914 different journals. In Table 1, the top 60 journals with at

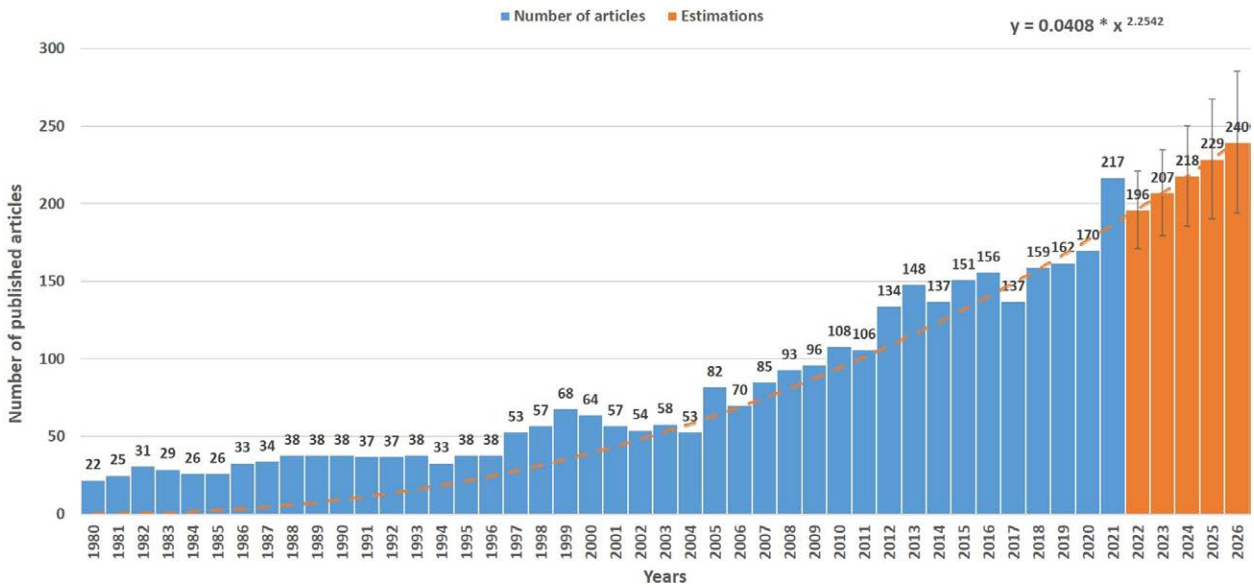

Figure 1. A bar graph illustrating the number of papers published in each year between 1980 and 2021 and the expected number of articles to be published over the following 5 years.

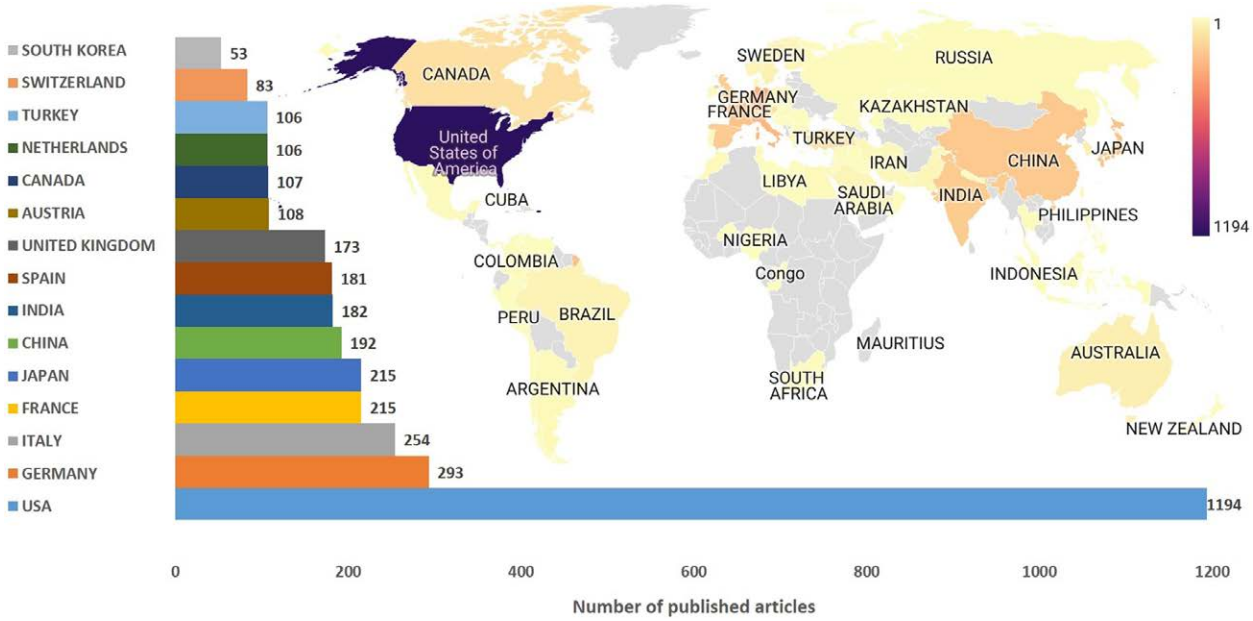

Figure 2. World article density map on Ewing sarcoma and bar chart for the top 15 countries with the most articles.

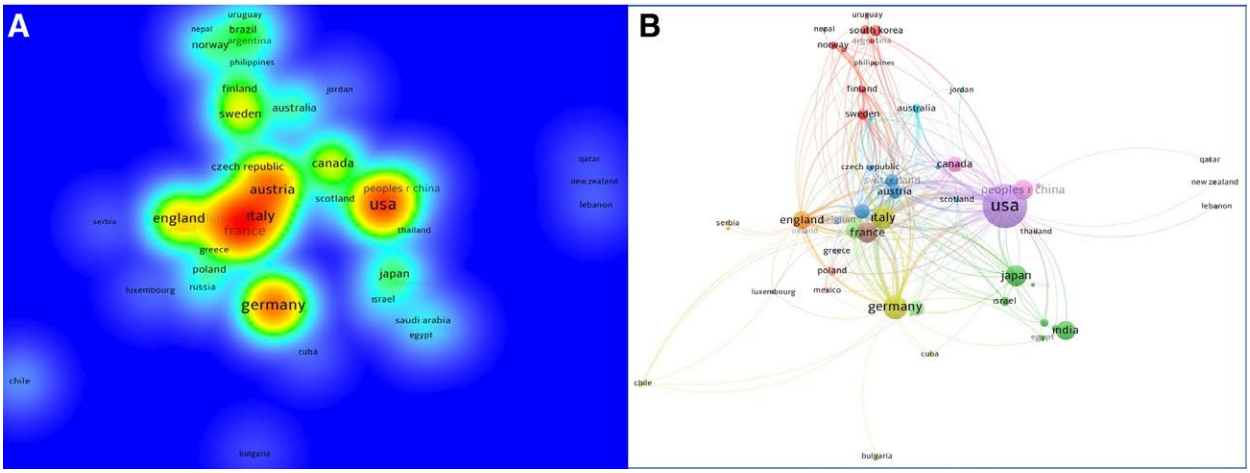

Figure 3. (a) Map of network visualization of cluster analysis results showing international cooperation among countries in Ewing sarcoma. Each color represents a different Cluster. As the number of articles published by the countries increases, the area of the circles representing the countries also increases. The lines show the countries with which they cooperate. (b) Intensity map showing the strength of international cooperation of countries in Ewing sarcoma. The strength of the international cooperation score increases from blue to red (blue-green-yellow-red).

least 10 articles published are listed along with the total number of citations they have received and the average number of citations per article.

3.8. Citation analysis on Ewing sarcoma

The 25 articles that received the most citations according to the total number of citations within the 3236 articles published on the subject of ES are shown in Table 2. The last column of Table 2 displays the articles' annual average number of citations.

3.9. Co-citation analysis on Ewing sarcoma

In the list of references of all the 3236 articles, there were found to be citations in a total of 41,985 studies. The first 6 most influential studies with the most co-citations (>200 citations) among these studies were the studies of Delattre et al (1992) (number of co-citation [NC] = 393), Grier et al (2003) (NC = 354), Cotterill et al (2000) (NC = 341), Delattre et al (1994) (NC = 266), Nesbit et al (1990) (NC = 218), Ewing (1921) (NC = 203), respectively.[4,8,11,13,20,21]

3.10. Trend topics on Ewing sarcoma

In the 3236 articles published on the subject of ES, 4134 different key words were used. Table 3 displays the frequency of 97 different key words appearing in at least 8 different articles. Figure 4 displays the network visualization map displaying the outcomes of the cluster analysis performed on these key words. As a result of the cluster analysis, 11 different clusters were formed on ES topics. Figure 5a displays the trend network visualization map developed to identify trend topics, and Figure 5b displays the citation network visualization map created to identify the topics with the highest citations.

Table 1

The 60 most active journals that have published 10 or more articles on Ewing Sarcoma.

Journals	RC	C	AC	Journals	RC	C	AC
Pediatric Blood & Cancer	122	2360	19.3	Molecular Cancer Therapeutics	16	340	21.3
Cancer	87	6042	69.4	Pediatric Hematology and Oncology	16	127	7.9
Journal of Pediatric Hematology Oncology	71	1131	15.9	Frontiers in Oncology	15	142	9.5
Cancer Research	61	4776	78.3	Journal of Bone and Joint Surgery-American Volume	15	637	42.5
Journal of Clinical Oncology	59	7828	132.7	Annals of Oncology	14	418	29.9
Oncogene	53	3040	57.4	Molecular Cancer Research	14	410	29.3
Plos One	50	1548	31.0	American Journal of Pathology	13	1170	90.0
Clinical Cancer Research	49	2158	44.0	Japanese Journal of Clinical Oncology	13	173	13.3
Oncotarget	43	976	22.7	Journal of Clinical and Diagnostic Research	13	23	1.8
International Journal of Radiation Oncology Biology Physics	37	1517	41.0	Tumori	13	129	9.9
Medical and Pediatric Oncology	36	817	22.7	Cureus	12	13	1.1
International Journal of Cancer	36	1122	31.2	Journal of Pediatric Surgery	12	177	14.8
Clinical Orthopaedics and Related Research	33	799	24.2	Modern Pathology	12	722	60.2
Skeletal Radiology	33	486	14.7	Virchows Archiv	12	374	31.2
European Journal of Cancer	32	1184	37.0	International Journal of Oncology	12	159	13.3
Cancer Genetics and Cytogenetics	29	1644	56.7	Acta Oncologica	11	264	24.0
Klinische Padiatrie	24	288	12.0	Biochemical and Biophysical Research Communications	11	347	31.5
British Journal of Cancer	23	707	30.7	Medicine	11	13	1.2
Human Pathology	23	903	39.3	International Journal of Surgery Case Reports	11	12	1.1
Journal of Cancer Research and Clinical Oncology	23	532	23.1	International Journal of Surgical Pathology	11	90	8.2
Ewing Sarcoma: Methods and Protocols	22	15	0.7	Acta Orthopaedica Scandinavica	10	70	7.0
Journal of Surgical Oncology	22	289	13.1	American Journal of Clinical Oncology-Cancer Clinical Trials	10	130	13.0
Oncology Reports	22	292	13.3	American Journal of Roentgenology	10	407	40.7
Bone Marrow Transplantation	20	309	15.5	Anticancer Research	10	109	10.9
Cancers	20	46	2.3	Diagnostic Molecular Pathology	10	398	39.8
American Journal of Surgical Pathology	19	1965	103.4	Genes Chromosomes & Cancer	10	651	65.1
BMC Cancer	19	362	19.1	Journal of Laryngology and Otology	10	120	12.0
Oncology Letters	19	81	4.3	Scientific Reports	10	75	7.5
Pathology Research and Practice	18	228	12.7	Spine	10	429	42.9
Journal of Pathology	16	650	40.6	Indian Journal of Medical and Paediatric Oncology	10	7	0.7

AC = average citation per document, C = number of citation, RC = record count.

4. Discussion

When the trends of the articles on the subject of ES were examined according to year, 3 different trend periods were determined. In the first period of 1980 to 1986, mean 33 (range, 22–38) articles per year were published. In the second period of 1997 to 2004, mean 58 (range, 53–68) articles were published, and in the third period of 2005 to 2021, the increasing trend intensified with mean 130 (range, 70–217) articles published each year. According to the results of the model formed with exponential smoothing estimation taking seasonal correction into consideration, the number of studies to be published in the next 5 years showed an exponentially increasing trend in the number of articles on the subject of ES that are expected to be published.

When the article distribution of countries was looked at, 12 of the 15 countries that contributed the most to literature were developed countries (USA, Germany, Italy, France, Japan, Spain, United Kingdom, Austria, Canada, Netherlands, Switzerland, South Korea). The other 3 countries (China, India, Turkey) were developing countries with large economies at GDP level. According to the results of the analysis of correlation, there is a high positive correlation between the production of articles on the topic of ES and the GDP, GDP per capita, and HDI values.

The results of the correlation analysis showed a high level of significant correlation between production of articles on the subject of ES and GDP, GDP per capita, and HDI values. Thus it can be said that the level of development of a country and the size of the economy are factors with an effect on article productivity. In the evaluation of the international collaboration analysis results, the leading countries were determined to be developed countries; the USA, Germany, Italy, France, Spain, Austria, England, the Netherlands, Switzerland, and Canada. When the authorship collaboration was examined, although there was seen to be some regional international collaboration based on geographical proximity, global collaboration was observed to be more common in the production of articles.

Pediatric Blood & Cancer, Cancer, Journal of Pediatric Hematology Oncology, Cancer Research, Journal of Clinical Oncology, Oncogene, Plos One, Clinical Cancer Research and Oncotarget were found to be the journals that published the most articles on Ewing sarcoma, respectively. It can be recommended that authors in the process of research or wishing to publish on the subject of ES should first give consideration to the journals presented in Table 1. According to the average amount of citations per article obtained in the citation analyses of the journals, the New England Journal of Medicine (Average citation per article = 404), Nature Genetics (269), Plos Genetics (229), Nature Reviews Disease Primers (223), Nature Medicine (195), Cancer Discovery (177), Molecular and Cellular Biology (164), Small (158), Human Molecular Genetics (156), Journal of Clinical Oncology (133), Proceedings of the National Academy of Sciences of the United States of America (119), Lancet Oncology (113), Pediatric Clinics of North America (110), Molecular Cell (109), Journal of Clinical Investigation (108), and American Journal of Surgical Pathology (103) were the journals with the greatest influence on Ewing sarcoma. Researchers who wish to see a greater impact of their work which is to be published should consider these journals first.

When the articles under analysis were compared based on the overall number of citations received, the study with the most citations was determined to be the article entitled "Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone" by Grier et al (2003), published in the New England Journal of Medicine.[13] This was followed by the article entitled "Prognostic factors in Ewing's tumor of bone: Analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study group" by Cotterill et al (2000), published in

Table 2

The top 25 most cited articles on Ewing Sarcoma.

No	Article	Author	Journal	PY	TC	AC
1	Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone	Grier HE. et al	New England Journal of Medicine	2003	804	40.2
2	Prognostic factors in Ewing's tumor of bone: Analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study group	Cotterill SJ. et al	Journal of Clinical Oncology	2000	649	28.22
3	A second Ewings-sarcoma translocation, t (2122), fuses the EWS gene to another ETS-family transcription factor, ERG	Sorensen PHB. et al	Nature Genetics	1994	605	20.86
4	MIC2 is a specific marker for Ewings-sarcoma and peripheral primitive neuroectodermal tumors - evidence for a common histogenesis of Ewings-sarcoma and peripheral primitive neuroectodermal tumors from MIC2 expression and specific chromosome aberration	Ambros IM. et al	Cancer	1991	526	16.44
5	Sequence-specific knockdown of EWS-FLI1 by targeted, nonviral delivery of small interfering RNA inhibits tumor growth in a murine model of metastatic Ewing's sarcoma	Hu-Lieskovan S. et al	Cancer Research	2005	458	25.44
6	Ewing sarcoma 11-22 translocation produces a chimeric transcription factor that requires the DNA-binding domain encoded by FLI1 for transformation	May WA. et al	Proceedings of the National Academy of Sciences of the United States of America	1993	454	15.13
7	The ewings-sarcoma EWS/FLI-1 fusion gene encodes a more potent transcriptional activator and is a more powerful transforming gene than FLI-1	May WA. et al	Molecular and Cellular Biology	1993	426	14.2
8	A variant Ewings-sarcoma translocation (7–22) fuses the EWS gene to the ETS gene ETV1	Jeon IS. et al	Oncogene	1995	421	15.04
9	Chromosomes in ewings-sarcoma.1. An evaluation of 85 cases and remarkable consistency of t (11–22) (q24–q12)	Turccarel C. et al	Cancer Genetics and Cytogenetics	1988	404	11.54
10	Multimodal therapy for the management of primary, nonmetastatic Ewings-sarcoma of bone - a long-term follow-up of the 1st intergroup study	Nesbit ME. et al	Journal of Clinical Oncology	1990	401	12.15
11	Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group	Womer Richard B. et al	Journal of Clinical Oncology	2012	362	32.91
12	Multidisciplinary treatment of primary Ewings-sarcoma of bone - a 6-year experience of a european cooperative trial	Jurgens H. et al	Cancer	1988	356	10.17
13	Primitive neuroectodermal tumor and Ewings-sarcoma	Dehner LP	American Journal of Surgical Pathology	1993	348	11.6
14	EWS-FL11 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma	De Alava E. et al	Journal of Clinical Oncology	1998	333	13.32
15	Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades - Surveillance Epidemiology and End Results data	Esiashvili N. et al	Journal of Pediatric Hematology Oncology	2008	326	21.73
16	DNA-binding and transcriptional activation properties of the EWS-FLI-1 fusion protein resulting from the t (1122) translocation in Ewing sarcoma	Bailly RA. et al	Molecular and Cellular Biology	1994	309	10.66
17	Osteosarcoma, chondrosarcoma, and Ewing's sarcoma	Damron Timothy A. et al	Clinical Orthopaedics and Related Research	2007	305	19.06
18	Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial	Ladenstein R. et al	Journal of Clinical Oncology	2010	288	22.15
19	A small molecule blocking oncogenic protein EWS-FLI1 interaction with RNA helicase A inhibits growth of Ewing's sarcoma	Erkizan Hayriye V. et al	Nature Medicine	2009	283	20.21
20	Localized Ewing tumor of bone: final results of the cooperative Ewing's sarcoma study CESS 86	Paulussen M. et al	Journal of Clinical Oncology	2001	274	12.45
21	Immunohistochemical analysis of Ewings-sarcoma cell-surface antigen P30/32MIC2	Fellinger EJ. et al	American Journal of Pathology	1991	272	8.5
22	Genomic landscape of Ewing sarcoma defines an aggressive subtype with co-association of STAG2 and TP53 mutations	Tirode F. et al	Cancer Discovery	2014	271	30.11
23	Fusion between CIC and DUX4 up-regulates PEA3 family genes in Ewing-like sarcomas with t (4; 19) (q35; q13) translocation	Kawamura-Saito M. et al	Human Molecular Genetics	2006	269	15.82
24	Ewings-sarcoma - ten-year experience with adjuvant chemotherapy	Rosen G. et al	Cancer	1981	266	6.33
25	Multimodal therapy for the management of nonpelvic, localized Ewings-sarcoma of bone - intergroup study IESS-II	Burgert EO. et al	Journal of Clinical Oncology	1990	265	8.03

AC = Average citations per year, PY = Publication year, TC = Total citation.

the Journal of Oncology,[8] then the article entitled "A second Ewings-sarcoma translocation, t(2122), fuses the EWS gene to another ETS-family transcription factor, ERG" by Sorensen et al (1994) published in Nature Genetics.[5] The fourth and fifth most effective articles were by Ambrose et al (1991) and Hu-Lieskovan et al (2005), respectively.[22,23]

When the articles were assessed based on the average annual number of citations, the most effective study was determined to be by Grünewald et al (2018),[24] followed by the above-mentioned study by Grier et al (2003).[13] The third most effective study was the article entitled "Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group" by Womer et al (2012), published in the Journal of Oncology.[25] The fourth and fifth most effective studies were articles by Tirode et al (2014) and Crompton et al (2014), respectively.[26,27]

According to the numbers of co-citations of all the articles, the most effective articles were determined to be those by Delattre et al (1992), Grier et al (2003), Cotterill et al (2000), Delattre

Table 3

The 97 most frequently used keywords in articles on Ewing Sarcoma.

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
Ewing sarcoma (or Ewing's sarcoma)	1578	Rhabdomyosarcoma	21	Skull	11
Chemotherapy	151	Translocation	21	Ewing-like sarcoma	10
Peripheral (primitive) neuroectodermal tumor (s)	114	Pelvis	19	Head and neck	10
Radiotherapy (or radiation therapy)	114	Bone	18	Nomogram	10
Sarcoma	82	Kidney	18	Pregnancy	10
Surgery	82	Pathology	17	Temozolomide	10
Immunohistochemistry	81	Fluorescence in situ hybridization	16	Tumor	10
Metastasis (or metastases)	67	Neuroblastoma	16	Vincristine	10
Extraskeletal Ewing (or Ewing's) sarcoma	66	Oncology	16	Angiogenesis	9
Child (or children, childhood)	63	p53	16	Bone sarcoma	9
Osteosarcoma	60	SEER	16	Case report	9
Prognosis	60	Cancer	15	Epigenetics	9
Apoptosis	54	Fish	15	Gene expression	9
Ewing sarcoma family of tumors (or ESFT)	51	Immunotherapy	15	Irinotecan	9
Survival (or survival analysis)	51	Relapse	14	Metastatic disease	9
Magnetic resonance imaging (or MRI)	48	Cytogenetics	13	Pediatric cancer	9
Prognostic factor (s)	45	Doxorubicin	13	Risk factors	9
Extraosseous Ewing (or Ewing's) sarcoma	43	Bone neoplasms	12	Spinal cord compression	9
EWS-FLI1	41	Childhood cancer	12	Staging	9
PNET	41	Chromosomal translocation	12	Synovial sarcoma	9
Bone tumor (s)	38	EWS	12	Therapy	9
Outcome (s)	38	EWSR1-FLI1	12	Trail	9
Pediatric (s)	36	High-dose chemotherapy	12	Bioinformatics	8
CD99	35	Microrna	12	Drug resistance	8
Adult (s)	32	Migration	12	Etoposide	8
Treatment	32	Neoadjuvant chemotherapy	12	Flow cytometry	8
Computed tomography (or CT)	28	Neoplasms	12	Hand	8
Diagnosis	28	Pediatric oncology	12	Ifosfamide	8
EWSR1	26	Recurrence	12	Neuroectodermal tumors	8
Biomarker (s)	24	Cell cycle	11	Radiology	8
Local control	24	Cytology	11	Soft tissue sarcoma	8
Spine	24	FLI1	11		
RT-PCR	22	Mandible	11		

CD99 = cluster of differentiation 99, EWSR1 = EWS RNA Binding Protein 1, MRI = magnetic resonance imaging, PNET = Primitif Nöroektodermal Tümörler, RT-PCR = A real-time reverse transcription–polymerase chain reaction, SEER = surveillance epidemiology and end results.

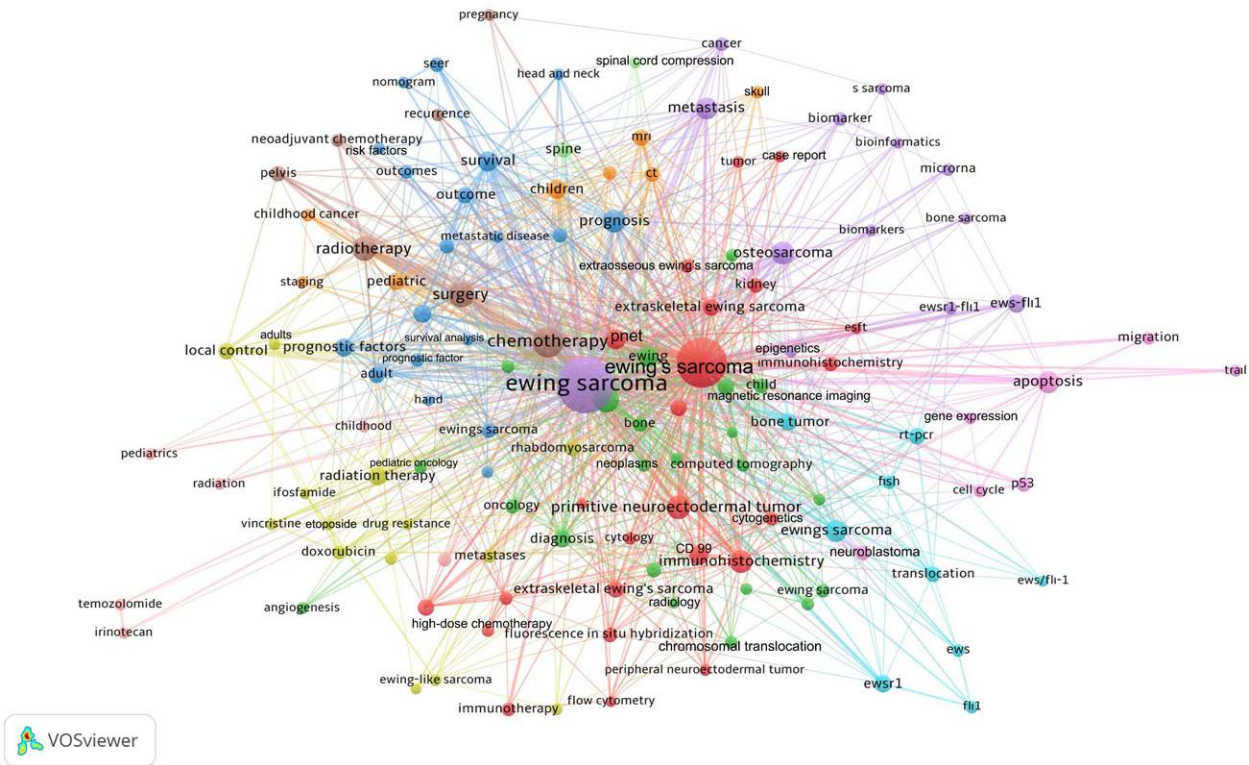

Figure 4. Network visualization map for cluster analysis based on keyword analysis performed to identify clustering of Ewing sarcoma. Each color represents a different cluster. Similar keywords are colored together in a cluster. The greater the number of times the keyword is used in articles, the larger the area of the circle it represents.

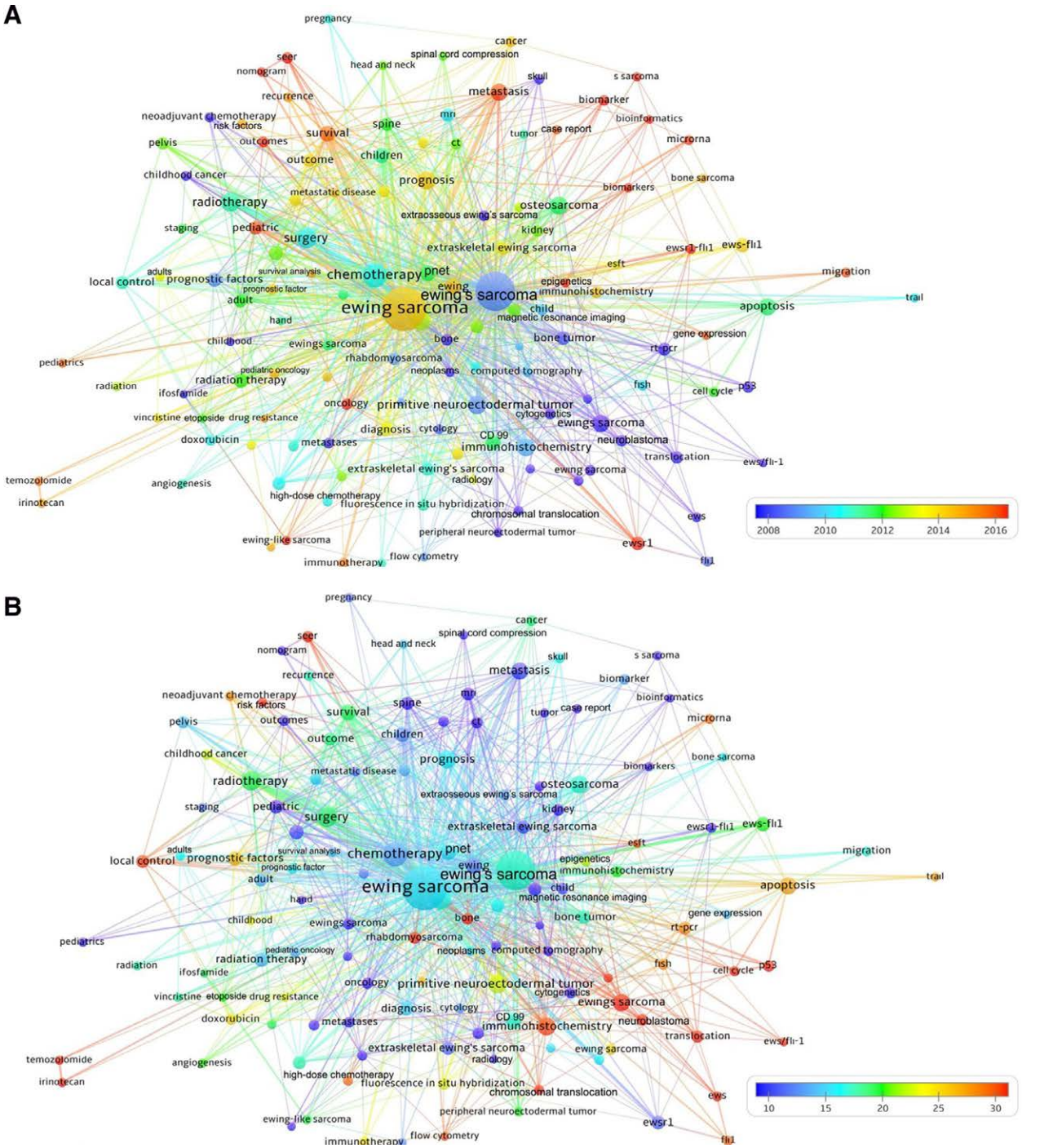

Figure 5. (a) Network visualization map based on keyword analysis to identify past and current trends in Ewing sarcoma. The indicator in the figure's lower right corner changes from blue to red as the text becomes more current (blue-green-yellow-red). The area of the circle that a keyword represents grows as its frequency in articles increases. (b) Network visualization map based on keyword analysis performed to identify the most cited topics in Ewing sarcoma. The amount of citations for the issue increases from blue to red in the indicator in the lower right corner of the figure (blue-green-yellow-red). The area of the circle that a keyword represents grows as its frequency in articles increases.

et al (1994), Nesbit et al (1990), and Ewing (1921).[4,8,11,13,20,21] It can be recommended that orthopedists and other researchers interested in ES read these articles first.

When the results of the keyword analysis were reviewed, the most studied topics on Ewing sarcoma from the past to the present were chemotherapy, radiotherapy, pediatric cancer, surgery, immunohistochemistry, metastasis, extraskeletal Ewing sarcoma, osteosarcoma, prognosis, apoptosis, survival analysis, magnetic resonance imaging, prognostic factors, extraosseous Ewing sarcoma, EWS-FLI1, Primitif Nöroektodermal Tümörler (PNET), cluster of differentiation 99, adults, treatment, computed tomography, diagnosis, EWS RNA Binding Protein 1 (EWSR1), biomarker (s), local control, spine, a real-time reverse transcription–polymerase chain reaction, rhabdomyosarcoma, and translocation. In the evaluation of the cluster analysis results, the subjects were seen to be distributed among 11 different clusters. It was determined that the most cited keywords were immunohistochemistry, local control, translocation, EWS-FLI1, neuroblastoma, rhabdomyosarcoma, SEER, p53, cell cycle, therapy, ESFT, microRNA, risk factors, temozolomide, irinotecan,

high-dose chemotherapy, flow cytometry, chromosomal translocation, neoadjuvant chemotherapy, apoptosis, and a real-time reverse transcription–polymerase chain reaction. The analysis performed to identify trending topics revealed that pediatric oncology, EWSR1, EWSR1-FL1, epigenetics, bioinformatics, microRNA, gene expression, metastasis, migration, biomarker, immunotherapy, survival, outcomes, surveillance epidemiology and end results (SEER), nomogram, temozolomide, irinotecan, and drug resistance were the most studied trend topics in recent years. The subjects researched in recent years were genetic studies, metastasis, immunotherapy, life analyses/nomogram based on new data obtained from SEER, and chemotherapy with irinotecan and temozolomide combination.

In literature, there is no previous bibliometric study on the subject of ES, and therefore, this study is the first comprehensive bibliometric research to have been conducted on this subject. A limitation of the study could be said to be that only the WoS database was used. There are relative advantages of databases over each other. The reason for not selecting the PubMed database was that citation analysis cannot be made with this database. In the Scopus database, in addition to the SCI-Expanded and E-SCI indexes, studies published in some low-impact journals are indexed. In the WoS database, only articles published in journals screened in the SCI-Expanded, E-SCI, and Social Sciences Citation indexes are indexed.[15–17,28,29] The WoS database has been widely used in other recent studies in literature.[15–17,28,29] Moreover, the use of >1 database in bibliometric analyses conducted on high level articles diminishes the reliability of the results. Therefore, the selection of only the WoS database constitutes a response to the limitations.

5. Conclusion

The results of this study demonstrated an increasing trend for article productivity. High-income countries have a great effect on the literature on this subject. The analysis conducted to identify trend topics revealed that pediatric oncology, EWSR1, EWSR1-FL1, epigenetics, bioinformatics, microRNA, gene expression, metastasis, migration, biomarker, immunotherapy, survival, outcomes, surveillance epidemiology and end results (SEER), nomogram, temozolomide, irinotecan, and drug resistance were the most studied trend topics in recent years. Genetic studies, metastasis, immunotherapy, life analyses/nomogram based on new data obtained from SEER, and chemotherapy with irinotecan and temozolomide combination, were seen to be the topics researched in recent years. The statistical analysis results of this study of 3236 articles on the subject of Ewing sarcoma can be a useful resource for orthopedists and other researchers in respect of the past and current trends, and showing global productivity.

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Author contributions

Each author fulfills each of the authorship requirements.
Hassa E: participated in the design of the study and in the acquisition and interpretation of data, performed the statistical analysis, and drafted the final version of the manuscript.
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