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Emerging Research on Complement Activation in Bone Oncology: A Bibliometric Analysis

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Abstract

This study aims to analyze and compare the literature published on the relationship between complement proteins and bone-specific tumors from 1965 to 2026. This bibliometric analysis gathered data from the Web of Science Core Collection using keywords such as complement, bone, tumor, metastasis, and inflammation. The retrieved data were visualized using VOSviewer and the Web of Science Core Collection, with a primary focus on publication counts, countries, keywords, and organizations across 879 documents. The analysis indicates that complement-related bone cancer research has expanded substantially in recent years, reflecting growing interest in the immunological functions of complement proteins and their potential therapeutic applications. The United States, the People's Republic of China, and Germany were the most prominent contributors, producing the majority of publications and shaping the global research landscape. These patterns suggest that complement biology in bone tumors remains an emerging field with significant room for development. Overall, this analysis highlights the evolving intersection between complement immunology and oncology and underscores how future mechanistic and translational advances may contribute to new clinical strategies in cancer treatment.

Categories: Oncology, Orthopedics, Allergy/Immunology
Keywords: bibliometric analysis, cancer, complement, immunology, inflammation, metastasis, oncology, tumors

Introduction And Background

Cancer incidence and mortality rates continue to rise globally, emphasizing the extensive damage caused by cancer despite major advances in detection and treatment [1]. Standard treatment options, such as chemotherapy, radiotherapy, and surgery, remain critical to cancer therapy. However, each has limitations related to toxicity and collateral damage to surrounding tissues. Chemotherapy, for example, is widely regarded as a "double-edged sword," capable of inducing malignant cell death while simultaneously killing other rapidly dividing cells and inducing immunosuppression [2]. Although radiation therapy has recently made significant strides in treatment targeting [3], it continues to cause damage to surrounding tissue cells and increase toxicity [4]. Many surgical complications can occur during oncological treatment, particularly those involving the gastrointestinal region [4]. These limitations have driven interest in alternative approaches, including immune-modulating and precision-based methods [5].

The complement system is an integral component of both tumor microenvironments and cancer biology [6]. A key question remains: does complement activation benefit patients with cancer by boosting antitumor immunity, or does it harm them by supporting tumor growth [7]? Evidence suggests that both possibilities are likely. Persistent complement activation has been observed in malignant tumors, with cancer often attracting these proteins to promote a tumor-supportive environment. This has been observed in the interaction between complement and breast cancer [8]. The complement system is a key component of the innate immune system, using activation pathways (classical, lectin, and alternative) to induce opsonization and phagocytosis and attract immune cells, such as macrophages and neutrophils, to attack pathogenic or malignant cells [9]. Macrophages and neutrophils often induce inflammatory reactions around targeted sites, potentially allowing malignant cells to gain more resources and accelerate cellular division [10]. Complement proteins, specifically anaphylatoxins such as C5a, are generated during complement activation, which can amplify inflammation. IgG-containing immune complexes can initiate the classical complement pathway [11]. Together, these interactions position the complement system as a multifaceted regulator of tumor immunity.

The complement system also plays a key role in modulating responses to treatment within the tumor microenvironment. Chemotherapy has been reported to induce complement signaling (C3, C3b, etc.), influencing antitumor immunity and B-cell function [12]. Complement activation and downstream anaphylatoxins (such as C5a) modulate leukocyte recruitment and inflammatory signaling within tumor microenvironments [9-11]. Beyond classical immune cell recruitment, complement interactions have been theoretically linked to broader metabolic and cellular stress axes, including lipid mediator dynamics, damage-associated molecular patterns (such as extracellular HMGB1), and metabolic markers (such as lactate and lactate dehydrogenase), which may influence tumor survival and treatment sensitivity [12-15].

However, the exact mechanistic crosstalk between these pathways and complement activation within specialized bone tumor microenvironments remains an emerging area of investigation. These mechanisms demonstrate the complement system's role as a dynamic modulator of tumor immunological interactions and therapeutic responses.

Bone cancers, such as osteosarcoma and Ewing sarcoma, are rare and aggressive malignancies with high rates of metastasis. Osteosarcoma originates from primitive bone-forming mesenchymal cells that produce malignant osteoid [16]. The different types of osteosarcoma include osteoblastic, chondroblastic, and fibroblastic subtypes, each of which differs in aggressiveness and prognosis but shares the ability to produce disorganized, malignant bone [16]. Bone tumor cells are often genetically unstable, exhibiting widespread chromosomal abnormalities, disrupted cell-cycle regulation, and suppressed pathways such as WNT/β-catenin [16]. A key aspect of bone tumors is that malignant cells are influenced by a complex microenvironment that includes tumor-associated macrophages, tumor-infiltrating lymphocytes, and prognostic biomarkers [16].

Bibliometric analysis highlights the importance of complement research in bone tumors and identifies complement-related mechanisms in bone metastasis as a significant research gap. This study focuses on geographical and institutional patterns, thematic clusters, temporal gaps, and research areas related to complement proteins in bone cancer, providing insight into this rapidly evolving field of oncology.

Review

Methods

Dataset Selection and Classification

Bibliometric analysis was used to examine publication patterns, research themes, and collaborative structures within complement-related bone cancer literature. The analysis focused on publication counts by year, country, and institution, as well as keyword patterns in both the complement-cancer dataset and the bone-specific subset. The search was conducted on June 18, 2026, and publications indexed up to that date were included. Web of Science and VOSviewer served as the primary tools for data collection and analysis. Web of Science provided citation metrics, document-type distributions, research topics, publication counts, and additional data used to identify trends in the dataset. Visualizations and network mapping were performed using VOSviewer (version 1.6.18), utilizing the full counting method and association strength normalization.

Dataset Structure

The search produced 879 records, which constitute the full complement-cancer dataset. Within this dataset, bone-specific records were identified by the presence of bone-related terms (osteosarcoma, Ewing sarcoma, bone metastasis, bone tumor, and bone neoplasm) in titles, abstracts, or author keywords. These bone-specific records form a subset of the 879-record dataset. Because this is a bibliometric review rather than a clinical systematic review, subset totals are not expected to sum to 879, and all figures specify whether they represent the full dataset or the bone oncology subset.

Eligibility and Screening

Eligibility criteria included English-language records and document types classified as articles, reviews, or conference papers. Deduplication was performed manually using DOI matching. Records were exported in the “Full record + cited references” format. The unit of analysis was the individual Web of Science record. Synonym handling included complement/complement cascade, osteosarcoma/osteogenic sarcoma, and metastasis/bone metastasis. After inclusion, bone-specific records were identified using keyword filtering (osteosarcoma, Ewing sarcoma, bone metastasis, bone tumor, and bone neoplasm), yielding 55 bone-specific records.

Data Acquisition

The complement-bone tumor dataset (1965 to June 18, 2026) was retrieved from the Web of Science Core Collection (SCI-EXPANDED, SSCI) on June 18, 2026, using the search query: TS=(complement*) AND TS=("bone metast*" OR osteosarcoma OR "ewing sarcoma" OR "bone tumor*" OR "bone neoplasm*"). This unified search perimeter was intentionally broad to capture complement-related literature across both primary bone malignancies and secondary metastatic bone niches, consistent with prior work describing complement activity across diverse tumor microenvironments [6,7].

The PRISMA diagram shows that all 879 records were retained after screening (Figure *1*). Bone-specific records were identified after inclusion using keyword filtering (osteosarcoma, Ewing sarcoma, bone metastasis, bone tumor, and bone neoplasm), resulting in a subset of 55 records.

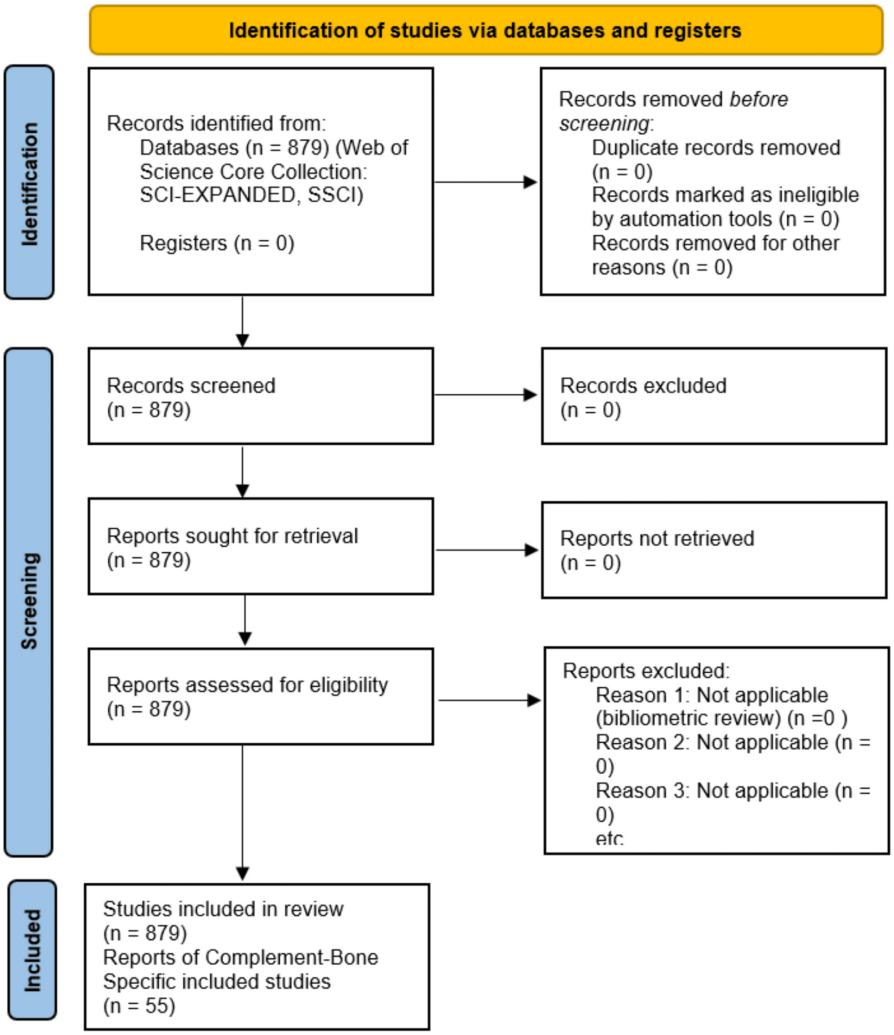


FIGURE 1: PRISMA 2020 study selection flow diagram showing the identification of 879 complement-cancer records and the inclusion of 55 bone-specific records after keyword filtering.

Zero exclusions occurred because bibliometric reviews retain all records meeting the search criteria.

Results

All country, topic, language, and institutional totals represent the full 879-record dataset. Bone-specific analyses represent a keyword-filtered subset of 55 records and are not expected to sum to 879.

Dataset Composition and Subset Structure

As shown in Table *1*, the full complement-cancer dataset (n = 879) displays broad geographic, linguistic, and topical diversity, whereas the bone-specific subset (n = 55) reflects a more concentrated distribution. The United States and the People's Republic of China (PRC) dominate both datasets, but representation in the bone subset is proportionally smaller because of keyword-based filtering rather than independent indexing. Topic distributions also differ: oncology, radiology/nuclear medicine, and molecular biology remain the most represented fields in both datasets, but the bone-subset values reflect the narrower scope of complement-related bone oncology literature. Because bibliometric subsets are filtered rather than independently indexed, bone-subset totals are not expected to sum to 879.

Category	Full dataset (n = 879)	Bone subset (n = 55)
Countries	USA 243; PRC 156; Germany 77; France 72; Italy 61; Japan 27; England 25; Spain 24; Canada 24; Netherlands 24	USA 20; PRC 12; Germany 6; France 4; Italy 3; Japan 3; England 2; Spain 2; Canada 2; Netherlands 1
Languages	English 823; French 22; German 16; Italian 2; Polish 1	English 53; French 1; German 1
Topics	Oncology 240; Radiology/Nuclear 153; Biochemistry/Molecular 82; Cell Biology 57; Surgery 41; Pathology 30; Pharmacology 25; Endocrinology/Metabolism 20; Orthopedics 15	Oncology 25; Radiology/Nuclear 10; Biochemistry/Molecular 8; Cell Biology 5; Surgery 3; Pathology 2; Pharmacology 1; Endocrinology/Metabolism 1; Orthopedics 1

TABLE 1: Relationship between the full dataset (n = 879) and the bone-specific subset (n = 55).

Bone-subset values were derived through keyword filtering and represent a subset of the 879 records. Because bibliometric subsets are filtered rather than independently indexed, bone-specific totals do not sum to 879.

Publication Volume and Temporal Trends

As illustrated in Figure 2, annual publication volume in complement-related bone cancer research has expanded over recent decades, reaching a peak annual output of 57 documents in 2025. Because data extraction concluded in June 2026, the 2026 data point represents a partial calendar year (January-June 2026) and is excluded from direct comparisons with complete 12-month annual outputs. Rather than demonstrating a lack of scientific attention, lower absolute document counts are inherently linked to the rare epidemiological incidence of primary bone malignancies within global cancer metrics [1] and their distinct developmental features [16]. Far from lacking global coverage, research in musculoskeletal oncology is actively driven by international multi-institutional task forces and dedicated scientific societies, including the Musculoskeletal Tumor Society (MSTS), the International Society of Limb Salvage (ISOLS), the European Musculo-Skeletal Oncology Society (EMSOS), the Asia-Pacific Musculoskeletal Tumor Society (APMSTS), and the Sociedad Latinoamericana de Tumores Musculoesqueléticos (SLATME), which lead multi-institutional efforts in molecular characterization [16], bibliometric advances [17], and specialized clinical management [18]. While these international groups have advanced primary surgical and therapeutic management [4,5], a significant knowledge gap remains regarding the precise mechanistic crosstalk between complement activation cascades [6,7] and the specialized bone microenvironment [16], offering substantial room for future translational investigation.

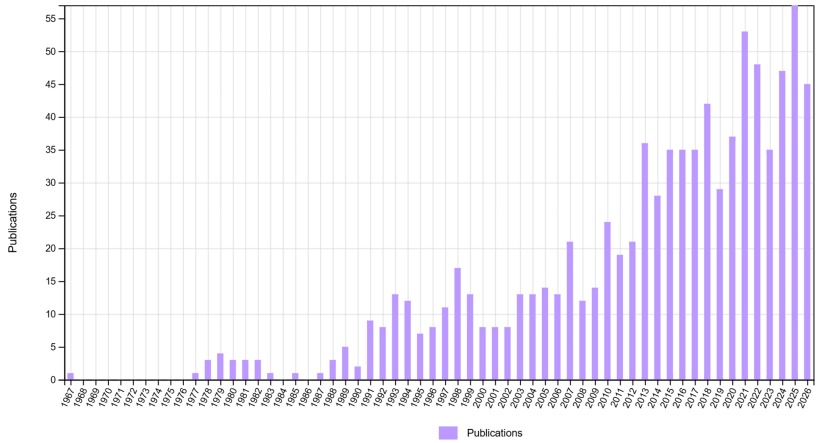


FIGURE 2: Publication data for research on the relationship between complement proteins and cancer overall from 1967 to 2026 (January-June, partial year) (n = 879).

Geographic and Language Distribution

Figures 3-6 show the country distribution, language distribution, and organizational affiliations for the full 879-record dataset. Figure 1 illustrates the identification and screening of all records, followed by keyword filtering that produced a bone-specific subset of 55 records. Figures 3, 4 depict the distribution of research

on the relationship between complement proteins and cancer across three major countries known for their scientific research: the United States (243 documents), the PRC (156 documents), and Germany (77 documents). Figure 5 focuses on specific organizations, most of which are from North America, such as Harvard University (51 documents), the University of Texas System (25 documents), and the University of London (24 documents). Most publications are from well-established universities and medical schools, while others are from hospital groups, including UNICANCER (24 documents). Figure 6 presents language data for publications on the relationship between complement proteins and cancer. As illustrated in Figure 6, English was the primary language, accounting for 823 documents, while other languages, such as French (22 documents) and German (16 documents), were less represented.

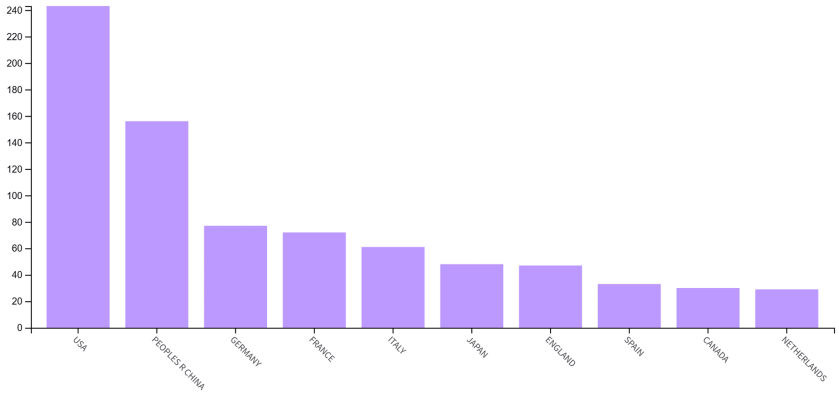


FIGURE 3: Publication data by country for research on the relationship between complement proteins and cancer overall from 1965 to 2026 (January-June, partial year) (n = 879).

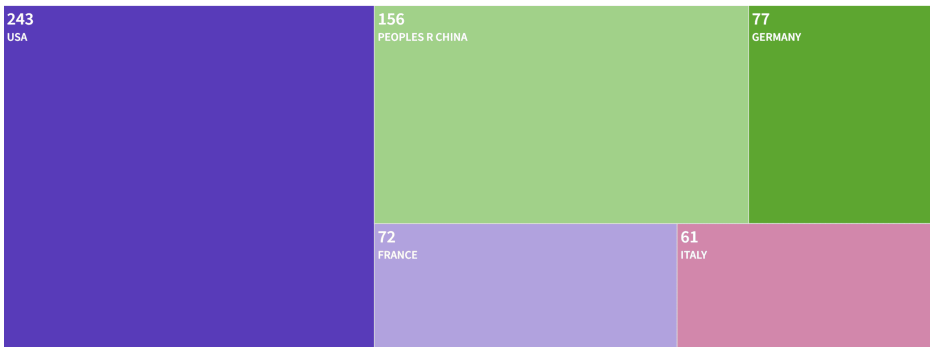


FIGURE 4: Publication data by the top five countries for research on the relationship between complement proteins and cancer overall from 1965 to 2026 (January-June, partial year).

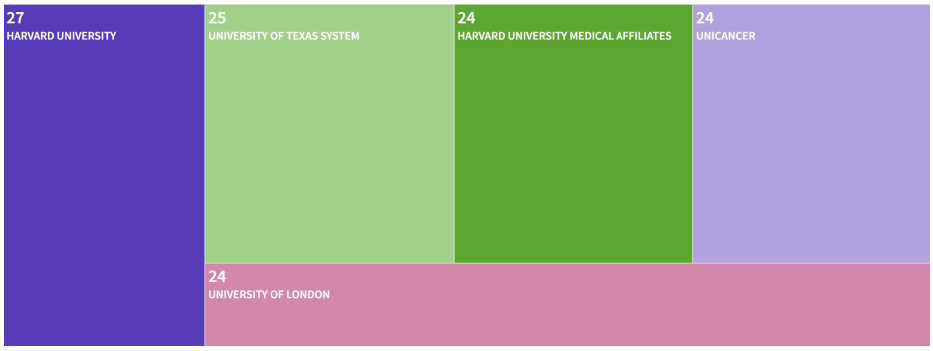


FIGURE 5: Publication data by the top five affiliations and organizations for research on the relationship between complement proteins and cancer overall from 1965 to 2026 (January-June, partial year).

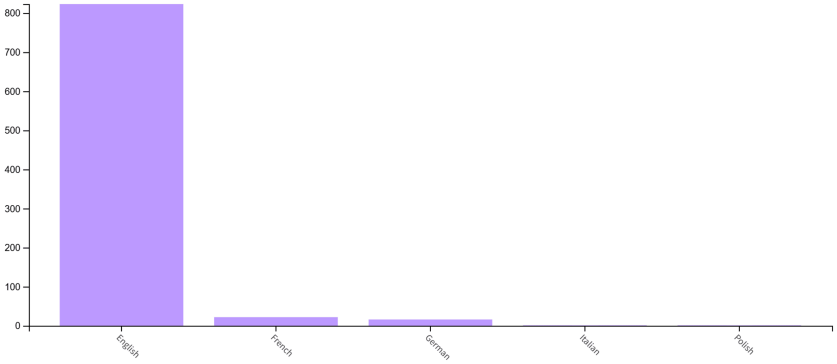


FIGURE 6: Publication data by language for research on the relationship between complement proteins and cancer overall from 1965 to 2026 (January-June, partial year) (n = 879).

Coauthorship and Research Topics

Figures *7*, *8* show the distribution of research topics and coauthorship patterns. Figure *7* shows that most research on this topic is concentrated in three fields: oncology, radiology and nuclear medicine, and biochemistry and molecular biology. Oncology has the highest publication yield, followed by radiology and nuclear medicine and biochemistry and molecular biology. The oncology category contains 240 documents, followed by radiology and nuclear medicine with 153, biochemistry and molecular biology with 82, cell biology with 57, and surgery with 41. Additional contributions originate from pathology, pharmacology, and endocrinology/metabolism.

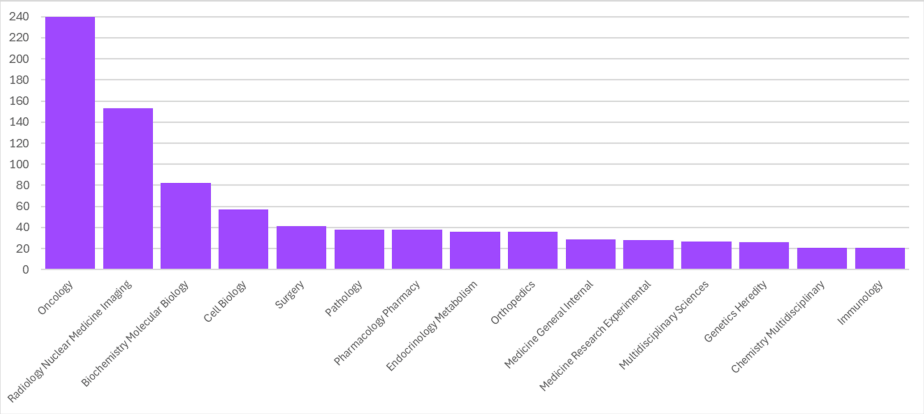


FIGURE 7: Publication data by research topic on the relationship between complement proteins and cancer overall from 1965 to 2026 (January-June, partial year) (n = 879).

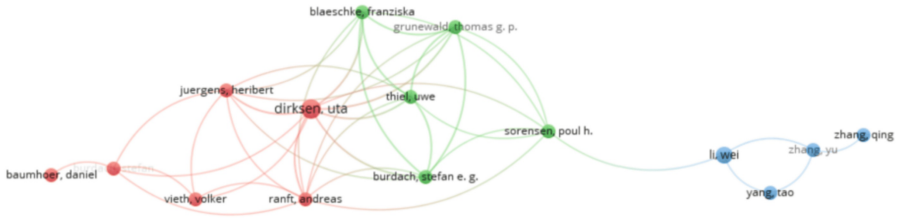


FIGURE 8: Coauthorship data by author on the relationship between complement proteins and bone cancer from 1965 to 2026 (January-June, partial year).

Figure *8* highlights coauthorship patterns across the complement-bone subset, showing several small groups of authors collaborating within a single interconnected network. For example, the red cluster contains the authors Braumhaer, Vieth, Ranft, Jügens, and Burdach. This cluster shows strong internal collaboration and connections with the green cluster. The blue group consists of four authors: Li, Wang, Zhong, and Zhang. Figure *8* shows that the author groups are interconnected; however, they share only a single connection with the blue group: Sorens. The total number of authors is very small, with approximately 14 individuals.

Keyword Co-Occurrence Network

Keyword co-occurrence analysis was performed using keyword frequency and co-appearance patterns extracted from Web of Science titles. Four major thematic clusters emerged: complement activation, bone tumor biology, imaging/detection, and experimental models.

Table *2* shows the keyword co-occurrence structure of the complement-cancer and complement-bone oncology literature, showing how keywords cluster across studies and which terms most frequently co-occur. These clusters and their frequencies, drawn from Tables *3*-*6*, provide the same interpretive information normally conveyed by a VOSviewer network map.

Dataset	Cluster	Main keywords/topics	Interpretation
Full dataset	Complement and immune activation	Complement, immune, inflammation, macrophages	Dominant research theme focusing on complement-mediated immune responses and inflammation in cancer
	Cancer progression	Tumor, cancer, metastasis, apoptosis	Studies examining tumor development, metastatic spread, and mechanisms of cancer cell death
	Molecular regulation	HMGB1, MIR155, sialic acid, lactate, LDH, base excision repair	Research on molecular signaling, metabolic regulation, and DNA repair pathways associated with complement-cancer interactions
Bone subset (n = 55)	Complement activation	Complement-related pathways and components	Investigates complement activation mechanisms in bone malignancies
	Bone tumor biology	Bone cancer, tumor microenvironment, progression	Focuses on biological processes underlying bone tumor development and progression
	Imaging and detection	Imaging technologies, diagnostic biomarkers	Research on detection, visualization, and diagnosis of bone tumors
	Experimental models	Animal models, in vitro studies, mechanistic investigation	Studies utilizing experimental systems to examine complement-related effects in bone cancer

TABLE 2: Keyword co-occurrence network summary for complement-cancer literature (full dataset and bone subset).

Cluster	Keywords	Description
1	complement, C5, C1q, ClQ, complement fixation, complement-dependent cytotoxicity, immune infiltrates	Complement activation and immune signaling terms frequently co-occur
2	osteosarcoma, bone morphogenetic proteins, prognosis, bone sarcoma	Bone tumor biology and osteosarcoma-specific terms cluster together
3	FDG PET, nuclear medicine imaging, metastasis, monoclonal antibodies	Imaging and detection-related terms form a distinct cluster
4	xenograft, murine sarcoma, engraftment	Experimental model terms cluster together

TABLE 3: Keyword clusters (bone subset, n = 55).

Cluster	Keywords	Interpretation
1. Complement-immune activation	complement, immune, inflammation, macrophages	Complement + inflammatory signaling
2. Cancer progression	tumor, cancer, metastasis, apoptosis	Tumor biology + metastasis
3. Molecular regulation	HMGB1, MIR155, sialic acid, lactate, LDH, base excision repair	Molecular/metabolic regulators

TABLE 4: Full dataset: keyword clusters (n = 879).

Keyword	Total frequency	Frequency per paper	Meaning of number
complement	9	0.1636	Appears in 9 titles (16.36% of papers)
sarcoma	7	0.1272	Appears in 7 titles
osteosarcoma	4	0.0727	Appears in 4 titles
metastasis	3	0.0545	Appears in 3 titles
C1q / CIQ	2	0.0363	Appears in 2 titles
complement fixation	2	0.0363	Appears in 2 titles
C5	1	0.0181	Appears in 1 title
complement-dependent cytotoxicity	1	0.0181	Appears in 1 title
bone morphogenetic proteins	1	0.0181	Appears in 1 title
immune infiltrates	1	0.0181	Appears in 1 title
FDG PET	1	0.0181	Appears in 1 title
nuclear medicine imaging	1	0.0181	Appears in 1 title
monoclonal antibodies	1	0.0181	Appears in 1 title
xenograft	1	0.0181	Appears in 1 title
murine sarcoma	1	0.0181	Appears in 1 title
prognosis	1	0.0181	Appears in 1 title

TABLE 5: Bone subset: keyword frequencies.

Keyword	Total frequency	Frequency per paper	Meaning of number
immune	14	0.0159	Appears in 14 titles (1.59% of papers)
inflammation	12	0.0136	Appears in 12 titles
tumor	11	0.0125	Appears in 11 titles
cancer	10	0.0114	Appears in 10 titles
complement	9	0.0102	Appears in 9 titles
macrophages	7	0.0079	Appears in 7 titles
metastasis	6	0.0068	Appears in 6 titles
apoptosis	5	0.0057	Appears in 5 titles
HMGB1	4	0.0045	Appears in 4 titles
MIR155	3	0.0034	Appears in 3 titles
sialic acid	3	0.0034	Appears in 3 titles
lactate	3	0.0034	Appears in 3 titles
LDH	3	0.0034	Appears in 3 titles
base excision repair	2	0.0023	Appears in 2 titles

TABLE 6: Full dataset: keyword frequencies.

As shown in Table 3, complement activation terms form the largest and most interconnected cluster,

indicating that complement signaling remains the dominant conceptual theme within bone-related complement research. Bone tumor biology terms cluster separately, reflecting osteosarcoma-specific molecular features, while imaging and experimental model terms form distinct clusters, highlighting methodological diversity within the subset.

These patterns are reinforced by the keyword frequency distribution in Table 5, where complement appears in 16.36% of titles, followed by sarcoma (12.72%) and osteosarcoma (7.27%). The "Frequency per paper" values contextualize each keyword's proportional representation within the 55-record subset, demonstrating that complement-focused bone oncology literature is concentrated around a small number of mechanistic and disease-specific terms.

Keyword co-occurrence mapping of the full dataset (n = 879) reveals broader thematic diversity than the bone subset. As shown in Table 4, complement-immune activation terms form the largest cluster, consistent with the central role of complement signaling in cancer immunology. Tumor progression terms cluster together, reflecting shared biological pathways across malignancies, while molecular regulation terms form a third cluster, indicating substantial research focused on metabolic and regulatory mechanisms.

These cluster patterns correspond directly with keyword frequencies in Table 6, where immune-related terms (immune, inflammation, and macrophages) appear most frequently across the dataset. Complement appears in 1.02% of titles, indicating that complement-specific studies represent a focused but distinct subset within the larger cancer immunology landscape.

Citation Analysis

Table 7 shows the citation distribution patterns for both the bone subset and the full complement-cancer dataset. It highlights citation ranges, medians, interquartile ranges, and top-cited thresholds, using data from Tables 8-11. This figure conveys the same insights typically shown in citation histograms or box plots, demonstrating how citation density differs between the smaller bone-focused literature and the broader complement-cancer field.

Citation metric	Full dataset (n = 879)	Bone subset (n = 55)
Median citations	22	6.5
IQR	9-47	1-19
Citation range	3-547	0-114
Top 10% threshold	≥240 citations	≥74 citations
Top 25% threshold	≥150 citations	≥20 citations
Distribution shape	Strong right-skew, driven by several highly cited complement-cancer papers	Right-skewed, with fewer high-impact papers reflecting the smaller and more specialized literature base

TABLE 7: Citation distribution for full dataset (n = 879) and bone subset (n = 55).

Title	Year	Citations	Avg/year	Meaning of number
Sarcoma-specific antigens - complement fixation	1970	114	2.00	114 lifetime citations; ~2 per year
C5 expression and survival in Ewing sarcoma	2011	85	5.31	85 lifetime citations; ~5.31 per year
BMP expression in osteosarcoma	1994	74	2.24	74 lifetime citations; ~2.24 per year
C1Q and immune infiltrates in osteosarcoma	2021	20	3.33	20 lifetime citations; ~3.33 per year
FDG PET imaging of sarcomas	2023	19	3.80	19 lifetime citations; ~3.8 per year
Complement-fixing antigen of human sarcomas	1976	14	0.27	14 lifetime citations; ~0.27 per year
Complement-dependent cytotoxicity	1982	8	0.18	8 lifetime citations; ~0.18 per year
Complement measurement in bone sarcoma	1967	5	0.08	5 lifetime citations; ~0.08 per year
Nuclear medicine imaging in bone tumors	2025	1	0.50	1 lifetime citation; ~0.5 per year
Complement-fixing antibodies to avian antigen	1978	1	0.02	1 lifetime citation; ~0.02 per year
C1qA/B prognosis in osteosarcoma	2023	0	0.00	No citations yet
NSG engraftment of Ewing metastasis	2020	0	0.00	No citations
Pro-tumoral complement activation	2019	0	0.00	No citations
Vaccinia virus antitumor particle	-	0	0.00	No citations
Prognostic kit (ALDH1A3, ANO7)	-	0	0.00	No citations

TABLE 8: Bone subset study list.

Rank	Paper	Total citations (WoS)	Meaning of number
1	B cells and tertiary lymphoid structures	547	Paper has been cited 547 times in total
2	Targeting macrophages in cancer	492	Total lifetime citations
3	Regulation of MIR155 host gene	453	Total lifetime citations
4	Complement signals determine opposite effects	264	Total lifetime citations
5	Resolvins suppress tumor growth	256	Total lifetime citations
6	Migration to apoptotic “Find-me” signals”	244	Total lifetime citations
7	Cancer and the complement cascade	238	Total lifetime citations
8	Immune system and inflammation in breast cancer	219	Total lifetime citations
9	Extracellular HMGB1 blockade	170	Total lifetime citations
10	Base excision repair modulation	159	Total lifetime citations

TABLE 9: Full dataset: top cited papers.

Metric	Value	Meaning of number
Most-cited record	114	Highest citation count
Second-most cited	85	Second-highest
Third-most cited	74	Third-highest
Median citations	6.5	Middle of distribution
IQR	1-19	Middle 50% of papers
Minimum	0	Least-cited papers
Maximum	114	Most-cited
Range	114	Spread
Top 10% threshold	≥74	Top 5-6 papers
Top 25% threshold	≥20	Top quartile

TABLE 10: Bone subset: citation metrics.

Metric	Value	Meaning of number
Most-cited record	547	Highest citation count in dataset
Second-most cited	492	Second-highest citation count
Third-most cited	453	Third-highest citation count
Top 10% threshold	≥240	Papers with ≥240 citations fall in top 10%
Top 25% threshold	≥150	Papers with ≥150 citations fall in top quartile
Minimum	3	Least-cited paper in dataset
Maximum	547	Most-cited paper in dataset
Range	544	Difference between max and min citations

TABLE 11: Full dataset: citation metrics.

A complete list of bone-specific complement studies is provided in Table *8*, including total lifetime citations and average citations per year. Citation density varies widely: foundational complement fixation studies from the 1970s have high lifetime citation counts, while more recent mechanistic or imaging studies have lower citation counts because of their recency. The “Avg/year” metric contextualizes citation performance relative to publication age, allowing comparisons across decades.

Citation distribution statistics for the bone subset are summarized in Table *10*, with counts ranging from 0 to 114 and a median of 6.5 (IQR, 1-19). The top 10% of papers have ⩾74 citations, reflecting the influence of early complement fixation studies and select modern prognostic analyses. These metrics demonstrate that bone-focused complement research is smaller and less cited than the broader complement-cancer field.

The most-cited papers in the full dataset are shown in Table *9*, with citation counts ranging from 159 to 547. These high-impact studies anchor the complement-cancer literature and highlight the prominence of complement signaling, macrophage biology, and tumor microenvironment research within the broader field.

Overall citation metrics for the full dataset are summarized in Table *11*, revealing a wide distribution of counts ranging from 3 to 547. The median citation count is substantially higher than that in the bone subset, reflecting the larger and more mature body of complement-cancer literature. Thresholds for the top 10% (⩾240 citations) and top 25% (⩾150 citations) highlight the presence of several highly influential papers within the dataset.

Discussion

Global Research Distribution

The countries with the largest contributions to research on the relationship between complement proteins and cancer were the United States, the PRC, and Germany, as they had the highest numbers of publications in the complement-bone cancer field. These geographic regions have rapidly evolving biomedical research infrastructures and strong immunology and oncology programs, which likely explain their higher publication output in the complement-bone cancer database in recent years [17]. In Figure *6*, English predominates in the published literature, with other languages represented to a lesser extent. This reflects the global reliance on English-language journals for biomedical research and may contribute to the limited participation of lower-resource or non-English-speaking countries. Geographic and linguistic groupings can slow the development of research areas by limiting the diversity of scientific perspectives and reducing international collaboration [18].

Collaboration Patterns

In Figure *8*, coauthorship patterns in complement-bone cancer research show several small groups of researchers collaborating rather than a single, interconnected global network. Most clusters represent groups of authors who collaborate primarily within their own regional circles, such as those in the PRC or Germany, corresponding to the blue and red nodes, with limited cross-regional interaction. This suggests that complement research, particularly in bone tumors, is conducted by isolated teams rather than through international partnerships. Fields with limited collaboration networks often experience slower conceptual development and reduced methodological standardization [18]. The small size of these groups may contribute to the slower growth of complement-focused bone cancer research. Increasing collaboration across institutions and countries may help accelerate progress, promote shared research frameworks, and expand the scope of future studies.

Research Topic Emphasis

Figure *7* shows the major research themes within complement-related cancer studies overall. Most research on this topic is clustered within oncology, radiology and nuclear medicine, and biochemistry and molecular biology. Oncology leads in publication volume, with radiology and nuclear medicine and biochemistry and molecular biology contributing substantial but smaller shares. Complement activation has been shown to influence immune cell activation, inflammatory signaling, and tumor microenvironment growth, which may explain why immunology-focused studies appear so frequently throughout the dataset [19].

Biological Distinctions in the Bone Microenvironment

While this bibliometric analysis maps literature across the broader bone tumor microenvironment, primary bone sarcomas and secondary bone metastases possess distinct biological profiles [16,20]. Primary bone malignancies, such as osteosarcoma, originate from transformed mesenchymal lineage cells and malignant osteoid [16], whereas secondary bone metastases arise from distant epithelial carcinomas that metastasize to the bone niche [6,8]. Complement activation may contribute to osteolytic remodeling in metastatic bone disease, based on extrapolation from complement-cancer literature [6,7,9]. However, bone-specific mechanistic evidence remains limited.

Structural and Scientific Factors Limiting Progress in Bone Oncology

Although primary bone tumors are rare, rarity alone does not explain the limited complement-specific literature. Musculoskeletal oncology is an active field with substantial international collaboration (MSTS, ISOLS, EMSOS, APMSTS, and SLATME). Instead, the limited number of complement-focused bone oncology publications reflects historical scientific emphasis on genetic, chemotherapeutic, and surgical domains rather than on innate immune pathways such as complement signaling.

Although complement-related cancer research has evolved in recent decades, progress in bone oncology remains comparatively limited because of a combination of structural, scientific, and clinical barriers [20]. A primary constraint is the extreme rarity of bone tumors, which sharply reduces the availability of patient samples, clinical datasets, and opportunities for large-scale mechanistic studies [20]. Primary bone cancers account for fewer than 0.2% of all malignancies and only 2,570 new cases annually in the United States [20]. Similar trends are observed globally, with bone tumors representing less than 1% of diagnosed cancers each year and osteosarcoma occurring at a rate of 3.4 cases per million people [21,22]. In pediatric populations, bone tumors constitute 5-6% of childhood cancers, and even within the broader category of rare cancers, rare bone tumors make up only 5-10% of cases [23-26]. Structural barriers could also restrict further advancement [27]. These include limited sample availability, small patient populations, difficulty obtaining grant funding, and challenges in developing translational research programs. It is "difficult to perform clinical research" on these cancers because of logistical constraints inherent to low-incidence diseases [28]. These epidemiological patterns may limit sample availability but do not inherently restrict immunological

research.

Scientific and clinical complexities also contribute to the slow pace of progress. Bone tumors often present with nonspecific symptoms that mimic common musculoskeletal injuries, leading to delayed diagnosis and low clinical recognition [21]. This reduces the availability of early-stage samples and complicates efforts to study tumor initiation, immune interactions, and complement activity. Furthermore, the bone microenvironment is rigid, mineralized, and biologically specialized, posing technical challenges for imaging, modeling, and mechanistic investigation [29]. These difficulties likely limit the number of laboratories capable of conducting high-fidelity bone tumor research and contribute to fragmented author collaboration.

Together, these structural, scientific, and systemic factors help explain why complement-focused bone tumor research lags behind other cancer fields. The combination of diagnostic challenges, limited funding, small patient populations, and biological complexity creates a research environment in which progress may be inherently slower. These constraints may be reflected in the bibliometric patterns identified in this study, including small collaboration networks, narrow thematic clusters, and lower publication density. Addressing these limitations may require targeted funding initiatives, improved research infrastructure, and stronger interdisciplinary collaboration to accelerate progress in bone oncology.

Applications for Complement Activation in Future Research

This bibliometric analysis highlights several important directions for future research, specifically the clinical potential of complement-based therapies. Although complement activation is well studied in general cancer immunology, its therapeutic applications remain largely theoretical and underdeveloped. There are three major outcomes of complement activation: opsonization, leukocyte recruitment, and membrane attack complex formation, which demonstrate the system's natural ability to identify, tag, and destroy harmful cells. These mechanisms suggest that complement proteins could theoretically be engineered or modified to enhance antitumor immunity, especially in cancers in which immune evasion is a major challenge.

This concept could be expanded by depicting a potential “cancer-fighting complement mechanism,” in which modified complement proteins selectively bind to malignant cells, promote opsonization, and attract macrophages for targeted phagocytosis. This model also shows how healthy cells could be protected through MHC-based recognition, allowing macrophages to remove complement proteins from nonmalignant tissue and potentially limiting the side effects associated with traditional cancer therapies. This model is hypothetical and intended only as a testable conceptual framework; no current evidence supports engineered complement targeting in bone tumors.

Future research could explore how complement-based therapies could be integrated with existing treatments, such as immunotherapy, chemotherapy, or targeted agents. Complement activation could enhance antigen presentation, improve macrophage-mediated tumor clearance, or sensitize tumors to immune checkpoint inhibitors. Additionally, complement modulation may have applications in bone cancers, in which the tumor microenvironment is highly specialized and involves complex interactions between immune cells, osteoclasts, and stromal components. Understanding how complement proteins influence osteolytic activity or metastatic colonization of bone could open new treatment options.

The therapeutic concepts described here are exploratory and theoretical. Although complement activation influences tumor immunity, no current evidence supports engineered complement targeting or MHC-guided complement modulation in bone tumors. The model presented is conceptual and intended only to illustrate potential future directions for complement-based immunological research.

Overall, the combination of natural complement functions and emerging approaches represents a promising frontier for clinical innovation. Expanding mechanistic studies, developing targeted complement-based therapies, and integrating these strategies into multidisciplinary cancer care may significantly advance the field and address current gaps in complement-related bone cancer research.

Limitations

This study focused only on data readily available in the Web of Science Core Collection, which may have excluded other relevant publications. A comprehensive search using other databases would provide a more detailed and accurate depiction of complement proteins in bone-specific and general oncology. It is also important to consider overlap between fields. Many of the search parameters and topics are similar, resulting in the same papers appearing in both datasets. A search method using stricter parameters could provide more accurate results. Another limitation is language bias, as nearly all publications were written in English. This could underrepresent research from non-English-speaking countries and, therefore, skew geographic patterns. Additionally, geographic bias was observed, with most of the data retrieved from the United States, the PRC, and European countries. As a result, cancers considered more prevalent in developed countries may be studied more extensively than those in less-developed regions. Future bibliometric studies can overcome these limitations to produce a more comprehensive view of the literature on the relationship

between complement and cancer.

Conclusions

This bibliometric analysis illustrates that complement-related cancer research has expanded steadily over the past several decades, with the United States, the PRC, and Germany contributing the majority of publications. However, complement-focused bone cancer research remains limited, with fewer publications, narrower research topics, and smaller collaboration networks. These patterns suggest that complement biology in bone tumors is still an emerging field that has not yet reached the level of development seen in broader cancer immunology. Future studies examining complement signaling in bone tumors may reveal new therapeutic targets and deepen our understanding of tumor-immune interactions within the bone microenvironment. As concerns surrounding cancer continue to persist, it is increasingly important to strengthen global participation and advance orthopedic oncology to support the future development of innovative complement-based therapies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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