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# A Quantitative Bibliometric and Growth-Modelling Analysis of Sonodynamic Therapy for Cancer from 2001 to 2025

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**Background:** Sonodynamic therapy (SDT) is an emerging noninvasive cancer treatment strategy that involves the activation of sonosensitizers with ultrasound. Driven by advances in nanotechnology and multimodal combination therapies, research in this field has grown exponentially. However, quantitative analyses of its macrolevel trends and evolutionary patterns are lacking. To address this gap, bibliometric analysis of cancer SDT research published between 2001 and 2025 was performed, and a piecewise growth model was constructed to quantify the developmental stages, growth characteristics, and underlying driving mechanisms.

**Methods:** Relevant literature published from January 1, 2001, to December 31, 2025, was retrieved from the Web of Science Core Collection (WoSCC). CiteSpace and VOSviewer were used to analyze collaboration networks, co-occurrence, co-citation, and burst detection. Developmental stages were identified on the basis of temporal characteristics, and a segmented exponential growth model was established. Log-linear regression was applied to estimate the growth rate parameter ($\beta$), goodness-of-fit ($R^2$), and growth characteristics for each stage.

**Results:** A total of 1,053 publications were included in the analysis. Bibliometric analysis revealed that China held a leading position in both publication volume and research impact; nanoscience emerged as the predominant research field, whereas breast cancer and hepatocellular carcinoma were the most frequently studied tumor types. Growth model analysis revealed three distinct developmental stages: (1) the exploratory stage (2001–2014), characterized by an annual growth rate of 17.0% and a low goodness-of-fit ($R^2 = 0.56$); (2) the technology-driven stage (2015–2019), with an annual growth rate of 19.4% and a markedly improved goodness-of-fit ($R^2 = 0.85$); and (3) the

explosive growth stage (2020 – 2025), characterized by a surge in the annual growth rate to 30.4% while maintaining an excellent goodness-of-fit ($R^2$ = 0.87) despite a high publication baseline. The average annual publication output in Stage III (147.7 articles) represented a 2,635% increase over that in Stage I (5.4 articles).

**Conclusion:** Through bibliometric and piecewise growth model analyses, this study systematically delineates a three-stage evolutionary trajectory of cancer SDT research (the exploratory stage, technology-driven stage, and explosive growth stage). China holds a central position in terms of publication output, research influence, and international collaboration networks. Research hotspots exhibit a clear evolutionary progression from fundamental mechanisms to nanotechnology and subsequently to multimechanism synergy, with the knowledge structure centered on sonosensitizers and extended by synergistic strategies involving multiple mechanisms. The field is currently in a phase of rapid innovation diffusion and is anticipated to gradually transition toward clinical translation-oriented development. Clinical translation, mechanistic elucidation, and material innovation represent key directions for the long-term advancement of the field.

## Keywords

Cancer, Sonodynamic therapy, Bibliometric, Nanoparticle, Ultrasound, Knowledge map

## Introduction

Sonodynamic therapy (SDT) is a novel noninvasive cancer treatment modality developed from photodynamic therapy (PDT)[1]. Its mechanism leverages the favorable tissue-penetrating properties of ultrasound to activate sonosensitizers within the target region, generating cytotoxic reactive oxygen species (ROS)[2][3], which in turn induce tumor cell death[3]. Compared with conventional therapies, SDT offers advantages such as noninvasiveness, minimal side effects, and the potential for multimodal combination[4][5].

The antitumor mechanism of SDT relies primarily on the synergistic effect of ultrasonic cavitation and sonosensitizers. As ultrasound propagates through tissues, it generates localized high temperatures, high pressures, and microjets via cavitation while simultaneously activating sonosensitizers to produce reactive oxygen species (ROS), including singlet oxygen ($^1O_2$), superoxide anion ($O_2^-$), and hydroxyl radical (·OH) [2][3]. These ROS can directly induce various forms of tumor cell death, such as apoptosis, necrosis, pyroptosis, and ferroptosis[6][7].

Since the early 2000s, research on SDT in the field of cancer therapy has gradually emerged [4][8]. In particular, the

introduction of nanotechnology has led to the development of a series of novel nanosonosensitizers (metal–organic frameworks, nanosheets, and nanozymes) [5][9], which have significantly improved the efficacy and specificity of SDT. Concurrently, combination strategies that integrate SDT with immunotherapy, chemodynamic therapy, and ferroptosis have continuously expanded the therapeutic options [10][12]. Over the past decade, research output in this field has exhibited exponential growth, forming a substantial body of knowledge [13].

However, the exponential growth in the literature also presents a challenge for researchers, particularly in synthesizing the overall landscape and identifying emerging trends in the field.

Although several reviews on SDT have been published, most have focused on mechanistic or technical details, and quantitative analyses of macrolevel developmental trends in the field are lacking[14][15]. Bibliometrics, as an interdisciplinary method that integrates statistics and library science, enables the elucidation of disciplinary development patterns, the evolution of knowledge structures, and research frontiers through the quantitative analysis of large-scale literature data[16].

This study aims to systematically analyze the literature on cancer SDT published between 2001 and 2025, with the following objectives: (I) to delineate the knowledge structure by identifying core researchers, institutions, and countries; (II) to quantify the developmental stages and growth characteristics through a segmented growth model; and (III) to elucidate the evolutionary trajectory of research hotspots and predict future directions. This study represents the first application of a piecewise exponential growth model to trend analysis in the SDT field, providing a data-driven macrolevel perspective for navigating this rapidly advancing area.

## Methods

### Data Sources and Search Strategy

To ensure data comprehensiveness and representativeness, the Science Citation Index Expanded (SCI-Expanded) within the Web of Science Core Collection (WoSCC) was selected as the primary data source. This database was selected because it covers multiple disciplinary fields, includes core subdatabases such as SCI and SCIE, and offers robust citation analysis capabilities[17], making it well suited for bibliometric analyses. The appropriateness of this choice has been extensively validated in previous studies[18][19]. A systematic literature search was performed on January 16, 2026, for publications from 2001--2025. The search strategy was formulated as follows:

(TI=(sonodynamic* OR sonosensitizer) OR AK=(sonodynamic OR sonosensitizer)) AND (TI=(cancer OR tumor* OR tumour* OR neoplasm* OR malignan) OR AK=(cancer OR tumor* OR tumour* OR neoplasm* OR malignan)). The document types were restricted to “Article” and “Review”. In this search, TI represents title, AK represents author keywords, and “*” denotes a wildcard character. This search strategy was designed to comprehensively capture cancer SDT-related research. Following the screening process, a total of 1,053 publications met the inclusion criteria and were included in the final analysis dataset, comprising 922 original research articles and 131 reviews (Fig.1).

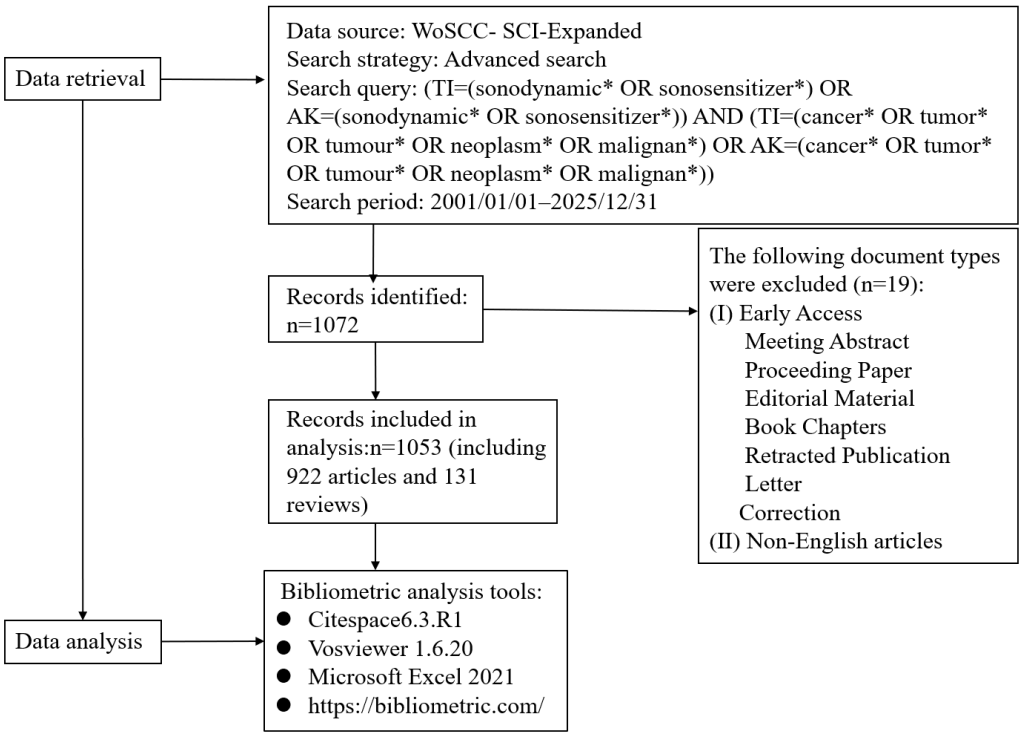



Figure 1. Literature screening process. WoSCC: Web of Science Core Collection; SCI-Expanded: Science Citation Index Expanded; TI: Title; AK: Author Keywords; *: Wildcard character.

## Bibliometric and Visualization Analysis

A multi-tool collaborative strategy was adopted to systematically process and visualize the literature data retrieved from the Web of Science Core Collection (WoSCC). A variety of tools, including Microsoft Excel 2021, CiteSpace, VOSviewer, and an online bibliometric analysis platform, were employed to perform multilevel, multidimensional data mining and map construction.

Specifically, VOSviewer (version 1.6.20) was used to generate network maps, density maps, and overlay visualizations and to calculate total link strength to quantify associations between nodes. This software was primarily

used to analyze country/regional collaboration networks, author co-occurrence relationships, and keyword co-occurrence patterns [20]. In the generated maps, nodes represent entities (countries, authors, keywords), with node size proportional to the frequency of occurrence[21][22], line thickness reflecting the strength of associations, and colors indicating different clusters or temporal evolution[23].

CiteSpace (version 6.2. R3) was utilized for keyword burst detection, timeline view construction, reference co-citation analysis, and identification of publications with the strongest citation bursts [24]. Microsoft Excel 2021 was used to compile annual publication counts and visualize trends, with curve fitting and calculation of the coefficient of determination ($R^2$) to reveal overall growth patterns.

In addition, an online bibliometric platform was used to assist in constructing international collaboration networks.

To characterize the developmental stages of the field quantitatively, a piecewise exponential growth model was further constructed[25][26]. This model is based on the exponential growth pattern commonly observed in scientific research output[27][28], and its basic form is expressed as

$$P(t) = \alpha e^{\beta t}$$

where $P(t)$ represents the number of publications in year t, $\alpha$ is a scaling parameter, and $\beta$ is the growth rate parameter. After logarithmic transformation, the model becomes

$$ln(P_t) = ln(\alpha) + \beta t$$

The division of stages was determined on the basis of multiple lines of evidence, including inflection points in the annual publication trend, burst onset times of keywords and references [25][29], thematic evolution in keyword timeline maps [30], and key technological breakthroughs in the field. Once the stages were defined, least-squares linear regression was performed on the data for each stage [31], yielding fitting equations of the form

$$ln(P_t) = \beta t + C$$

where $C = ln(\alpha)$, The primary parameters reported include the growth rate $\beta$, the intercept $C$, and the coefficient of determination $R^2$. The compound annual growth rate ($CAGR$) was further calculated as

$$CAGR = e^{\beta} - 1$$

By comparing $\beta$, $R^2$, and $CAGR$ across different stages, this study aims to systematically characterize and elucidate the dynamic evolutionary patterns of growth in this field.

## Results

### Literature Search and Inclusion Overview

A total of 1,072 publications were initially retrieved via the search strategy. After screening, 1,053 studies met the inclusion criteria and were ultimately included, comprising 922 original research articles and 131 reviews. The literature screening process is shown in Figure 1.

## General Characteristics of the Bibliometric Analysis

### Annual Publication Trends

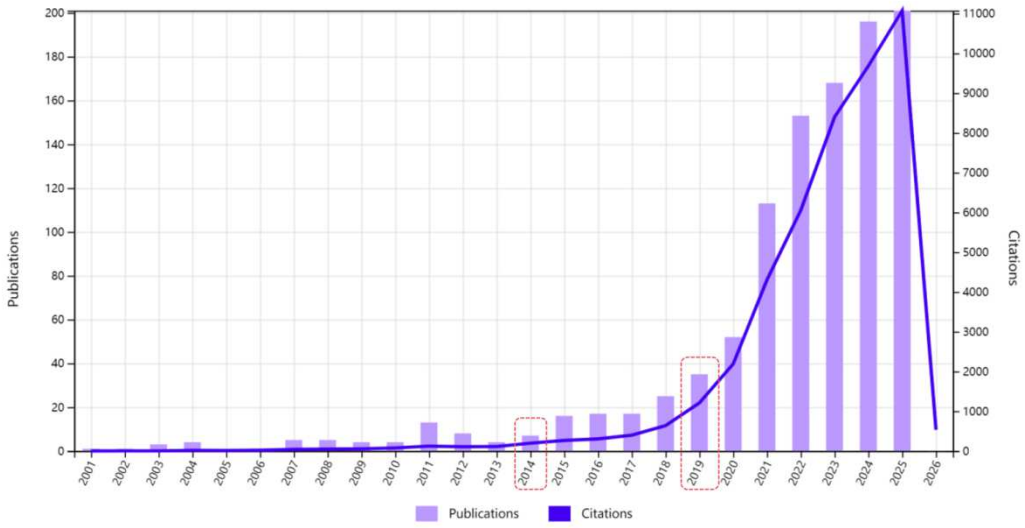



Figure 2. Annual Publication and Citation Trends in Cancer Sonodynamic Therapy (SDT) Research, 2001 – 2025. The blue line represents annual publication output, the purple bars represent annual citation counts, and the dashed boxes indicate inflection points for stage division (2014 and 2019).

As illustrated in Figure 2, the annual publication output of cancer SDT research from 2001--2025 clearly shows a three-stage pattern. The initial stage (2001 – 2014) is characterized by slow and fluctuating growth, with an average annual publication count of 5.4. This is followed by a period of stable growth (2015 – 2019), during which the average annual output increased to 21.4. The subsequent stage (2020 – 2025) experienced an explosive surge, with the average annual number of publications reaching 147.6 and the highest output recorded in 2025 (232 publications).

### Country/Regional Contributions

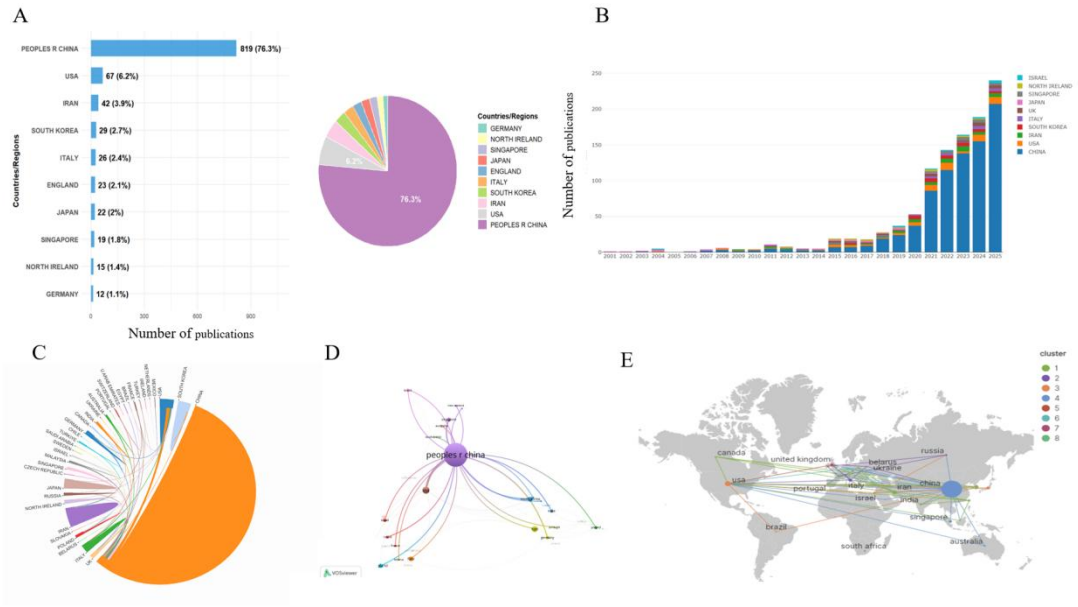



Figure 3. Analysis of country/regional contributions. (A) Distribution of the top 10 countries/regions by publication volume; (B) Trends in annual publication volume for the top 10 countries/regions; (C)International collaboration network of countries/regions (node size represents publication volume, line thickness represents collaboration intensity); (D) VOSviewer country collaboration map; (E) Scimago geographic visualization collaboration map.

Researchers from 43 countries/regions contributed to the relevant publications. Figure 3A presents the top 10 countries/regions by publication volume. China maintains a dominant position, contributing 819 publications (76.3% of the total), substantially exceeding all other countries. No other country exceeded 100 publications. The United States ranks second with 67 publications (6.2%), followed by countries such as Iran, South Korea, and Italy, which published between 12 and 42 papers, showing a relatively dispersed distribution. China has exhibited the most pronounced growth trend in publication volume, particularly with a rapid increase in recent years. In contrast, other countries demonstrate relatively moderate growth, collectively reflecting a temporal evolution characterized by China's increasingly dominant position (Fig. 3B).

The international collaboration network (Fig. 3C) shows China at the core, with dense collaborative ties to Western countries such as the United States, Singapore, and Germany, forming a closely connected subnetwork. In the VOSviewer collaboration map (Fig. 3D), China features the largest node and the most connections, highlighting its central hub role in international collaboration. Node size is positively correlated with publication volume, whereas the lines between nodes represent collaborative relationships, collectively illustrating a multilateral collaboration pattern centered on China. Cluster analysis (Fig. 3E) grouped countries/regions into eight collaborative clusters,

indicating that international scientific collaboration presents distinct clustering characteristics. Notably, China and the United States have the strongest collaboration. This clustering structure may reflect geographic proximity, linguistic or cultural ties, or collaboration preferences in specific research fields.

Table 1 presents the top 10 countries/regions by publication volume. China ranks first with 819 publications, accounting for 76.3% of the total, and leads in total citation count (36,281), with an average of 44.30 citations per publication. China also records the highest total link strength (54), reinforcing its central position in the international collaboration network. The United States ranks second with 67 publications, with an average of 69.31 citations per publication, demonstrating notable research influence. South Korea has the highest average number of citations per publication (88.03), followed by Northern Ireland (80.60), reflecting the high impact of their research. Countries such as Iran, Italy, and Germany have relatively lower publication volumes and weaker international collaboration intensity.

Table 1 Top 10 countries/regions by publication volume.

| Rank | Country | Documents(n) | Citations | Average Citations | TLS |
|---|---|---|---|---|---|
| 1 | China | 819 | 36281 | 44.30 | 54 |
| 2 | USA | 67 | 4644 | 69.31 | 47 |
| 3 | Iran | 42 | 1029 | 24.50 | 6 |
| 4 | South Korea | 29 | 2553 | 88.03 | 7 |
| 5 | Italy | 26 | 979 | 37.65 | 9 |
| 6 | United Kingdom | 23 | 1232 | 53.57 | 22 |
| 7 | Japan | 22 | 1178 | 53.55 | 2 |
| 8 | Singapore | 19 | 1166 | 61.37 | 11 |
| 9 | Northern Ireland | 15 | 1209 | 80.60 | 14 |
| 10 | Germany | 12 | 173 | 14.42 | 10 |

TLS: Total Link Strength, which reflects the closeness of international collaboration networks.

## Analysis of Research Institutions

Researchers from 826 institutions contributed to the relevant publications. The top 10 institutions in terms of publication volume were all from China.

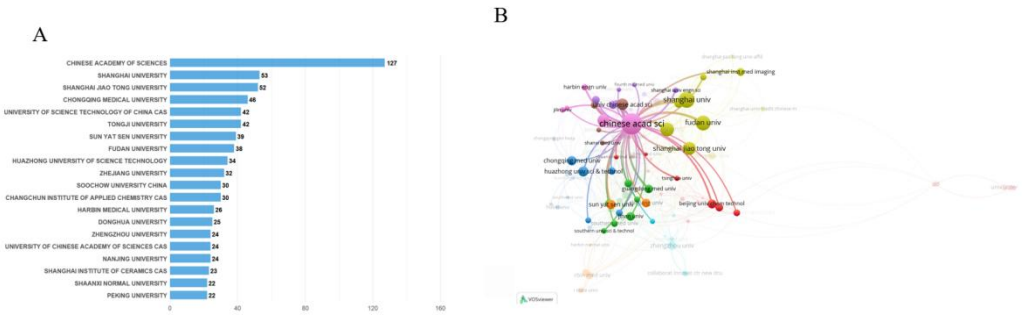



Figure 4. Institutional publication volume and co-authorship network. (A) Distribution of the top 20 institutions by publication volume; (B) VOSviewer institutional collaboration network map (node size represents publication volume, line thickness represents collaboration strength, and colors indicate different clusters).

Table 2 Top 10 institutions by publication volume.

| Rank | Institution | Country | Documents(n) | Citations | Average Citations | TLS |
|---|---|---|---|---|---|---|
| 1 | Chinese Academy of Sciences | China | 104 | 10691 | 102.80 | 67 |
| 2 | Shanghai University | China | 53 | 2371 | 44.74 | 46 |
| 3 | Chongqing Medical University | China | 45 | 1764 | 39.20 | 6 |
| 4 | Shanghai Jiao Tong University | China | 44 | 2186 | 49.68 | 34 |
| 5 | Tongji University | China | 42 | 2730 | 65.00 | 35 |
| 6 | University of Science and Technology of China | China | 41 | 2967 | 72.37 | 27 |
| 7 | Fudan University | China | 37 | 1697 | 45.86 | 50 |
| 8 | Sun Yat-sen University | China | 37 | 1229 | 33.22 | 7 |
| 9 | Huazhong University of Science and Technology | China | 33 | 2309 | 69.97 | 7 |
| 10 | Zhejiang University | China | 32 | 1323 | 41.34 | 9 |

TLS: Total Link Strength, which reflects the closeness of collaboration among institutions.

The Chinese Academy of Sciences ranks first with 104 publications, leading significantly in total citation count (10,691) and average citations per publication (102.80), and has the highest total link strength (67), underscoring its central role in the field. Universities such as Shanghai University, Shanghai Jiao Tong University, and Chongqing Medical University follow closely in publication volume; among them, Shanghai University contributed 53 publications with a total link strength of 46, indicating close collaboration with the Chinese Academy of Sciences.

Although Fudan University ranks seventh in publication volume, it has a notably high total link strength of 50, reflecting its active engagement in collaboration networks. Figure 4 presents the institutional collaboration network map, showing the Chinese Academy of Sciences at the core of the network, with thick lines connecting it to universities in Shanghai, indicating frequent collaboration.

## Author Contributions

A total of 5,267 authors were involved in the relevant studies.

Table 3 Top 10 authors by publication volume.

| Rank | Author | Institution | Documents(n) | Citations | Average Citations |
|---|---|---|---|---|---|
| 1 | Chen, Yu | Shanghai University | 40 | 4881 | 122.03 |
| 2 | Cheng, Liang | Soochow University | 29 | 3745 | 129.14 |
| 3 | Geng, Bijiang | Shanghai University | 23 | 1012 | 44.00 |
| 4 | Wang, Zhigang | Chongqing Medical University | 21 | 1258 | 59.90 |
| 5 | Lin, Jun | Chinese Academy of Sciences | 20 | 2970 | 148.50 |
| 6 | Wang, Xiaobing | Shaanxi Normal University | 20 | 926 | 46.30 |
| 7 | Liu, Quanhong | Shaanxi Normal University | 20 | 836 | 41.80 |
| 8 | Wang, Pan | Shaanxi Normal University | 19 | 884 | 46.53 |
| 9 | Liu, Zhuang | Soochow University | 19 | 3083 | 162.26 |
| 10 | Ma, Ping'an | Chinese Academy of Sciences | 18 | 2340 | 130.00 |

TLS: Total Link Strength, which reflects the closeness of collaboration among authors.

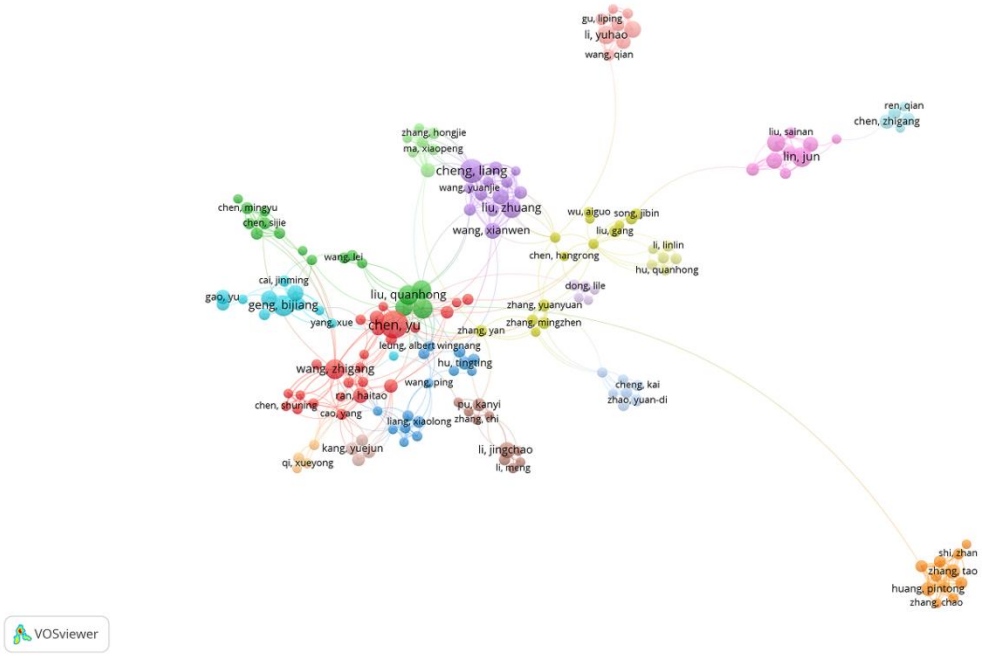



Figure 5. VOSviewer author collaboration network map. Node size represents author publication volume, line thickness represents collaboration strength, and different colors represent different collaboration clusters (17 clusters in total).

The top 10 authors by publication volume are presented in Table 3. All 10 authors are from China, highlighting the central role of Chinese researchers in this field. Chen Yu ranks first with 40 publications, with a total citation count of 4,881 and an average of 122.03 citations per publication, establishing him as one of the most influential authors in the field. Cheng Liang published 29 articles, with an average of 129.14 citations per publication, reflecting the high impact of his research. Although Liu Zhuang ranks ninth in publication volume, it has the highest average number of citations per publication (162.26), indicating exceptional impact per article. In terms of institutional distribution, institutions such as Shanghai University, Soochow University, Shaanxi Normal University, and the Chinese Academy of Sciences contributed the most prolific authors. Figure 5 illustrates the author collaboration network, which comprises 17 major research clusters characterized by a multicenter parallel structure with close intracluster collaboration but relatively weak intercluster connections.

## Distribution of Journals and Publishers

Figure 6A presents the top 15 academic journals by publication volume in this research field. As shown, the Chemical Engineering Journal ranks first with 51 publications, establishing it as the most productive journal in the

field. It is closely followed by ACS Applied Materials & Interfaces with 49 publications, and Advanced Functional Materials ranks third with 33 publications. Overall, journals in this field exhibit a multidisciplinary character, with materials science and nanotechnology journals playing a dominant role, as exemplified by Advanced Functional Materials, ACS Applied Materials & Interfaces, and ACS Nano. These are followed by biomedical and chemical engineering journals such as Chemical Engineering Journal and Biomaterials. As shown in Figure 6B, regarding the distribution of journal publishers, Elsevier leads significantly with 352 publications, establishing itself as the dominant publisher and occupying a dominant position in the field, followed by Wiley (211 publications) and ACS (125 publications).

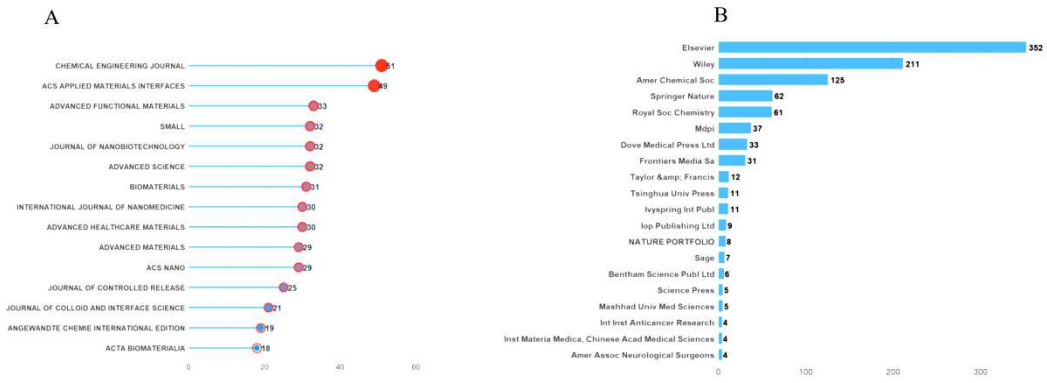



Figure 6. Distribution of journals and publishers. (A) Top 15 journals by publication volume; (B) top 15 publishers by publication volume.

## Distribution of Research Areas

Figure 7A presents the top 20 research directions in this field by publication volume. Materials Science (Matter, 484 publications) and Engineering (408 publications) rank first and second, respectively, followed closely by Chemistry (405 publications). Together, these three constitute the core research foundation of the field. At the application level, pharmacology (148 publications) and pharmacy (105 publications) demonstrated notable prominence, reflecting the close connection between this research field and drug development. In addition, life science-related directions such as biotechnology (151 publications), bioengineering (69 publications), and biochemistry (52 publications) also occupy important positions.

The radar chart in Figure 7B illustrates the top 10 scientific categories by publication volume, with Materials Science ranking first with 329 publications, further confirming its central role in the research. Chemistry and engineering are

also among the top 10, corroborating the findings presented in Figure 7A. Notably, although oncology is ranked 10th, as an important research direction within the biomedical field, it is closely associated with core areas such as nanomedicine, drug delivery, and biomaterials, fully reflecting the close connection between basic research and clinical translation.

In summary, Figure 7 demonstrates that this research field has an interdisciplinary character grounded in the physical sciences and oriented toward the life sciences and medicine, reflecting a research landscape that emphasizes both basic research and translational applications.

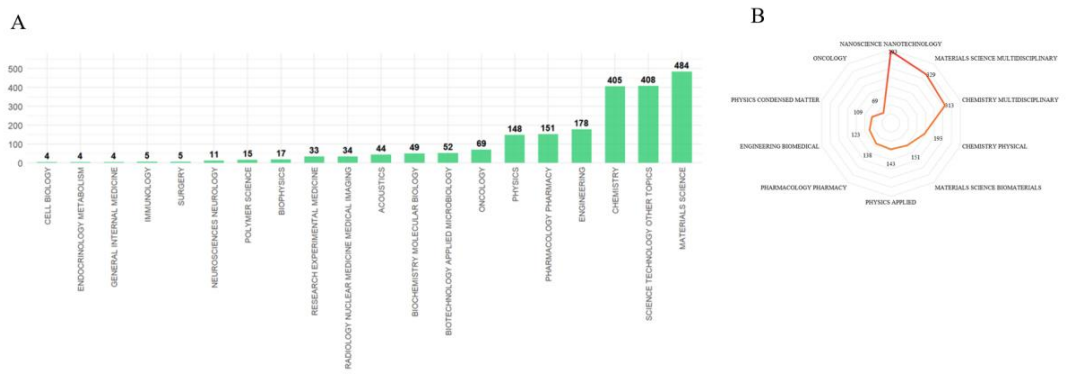



Figure 7. Distribution of research areas and scientific categories. (A) Top 20 research directions by publication volume. (B) Radar chart of the top 10 scientific categories by publication volume.

## Evolution of the Knowledge Structure

### Keyword Co-occurrence Analysis

To explore the research hotspots and thematic structure of the field, this study performed a co-occurrence analysis of author keywords via VOSviewer software. A minimum frequency threshold was set to identify high-frequency keywords, and a keyword co-occurrence network map was constructed. In the generated map, the node size represents the keyword occurrence frequency, the line thickness reflects the co-occurrence strength, and different colors indicate distinct clusters. A total of 301 keywords with an occurrence frequency of ≥5 were included.

The keyword density visualization map in Figure 8A displays a gradient color scheme ranging from blue to yellow, with yellow areas representing research hotspots characterized by high frequency and strong co-occurrence. The density distribution reveals several high-density core regions. The most prominent yellow area is centered around “sonodynamic therapy” and “ultrasound”, indicating that sonodynamic therapy constitutes the most central and

mature research theme in the field. A secondary high-density region is distributed around keywords such as “nanoparticles”, “drug delivery”, and “combination therapy”, reflecting that nanomaterials and combination therapy strategies represent important research branches. Another yellow cluster is concentrated around keywords such as “immunotherapy”, “cancer immunotherapy”, and “immune checkpoint blockade”, indicating that tumor immunotherapy has emerged as a rapidly developing hotspot in recent years. In addition, keywords such as “photodynamic therapy”, “photosensitizers”, “focused ultrasound”, and “ferroptosis” also exhibit high density, highlighting the important roles of photodynamic therapy, focused ultrasound technology, and novel cell death mechanisms in the field.

The keyword timeline map in Figure 8B illustrates the temporal evolution of research hotspots in the field, with keywords distributed along the time axis according to their year of first appearance and colors ranging from dark blue to yellow indicating earlier to later time points. The early stage (dark blue region) focused on fundamental concepts and classic technologies such as “ultrasound”, “sonodynamic therapy”, “photodynamic therapy”, and “photosensitizers”, which formed the foundational research directions of the field. The middle stage (green region) featured a shift toward nanomaterial development and combination therapy strategies, as reflected by keywords such as “nanoparticles”, “drug delivery”, “combination therapy”, and “chemotherapy”, indicating that nanotechnology and combination therapy have emerged as research hotspots. The recent stage (yellow region) is characterized by emerging research directions concentrated on immunotherapy, cell death mechanisms, and precision therapy, as exemplified by keywords such as “immunotherapy”, “immune checkpoint blockade”, “ferroptosis”, “cuproptosis”, “starvation therapy”, and “tumor microenvironment”, which have significantly increased in frequency in recent years, representing the research frontiers of the field. This temporal view demonstrates that the field has undergone an evolutionary trajectory from basic sonodynamic mechanisms to nanomaterial-mediated approaches and further to immunomodulation and precision therapy, reflecting a progressive shift from fundamental exploration toward clinical translation. As shown in Figure 8C, seven clusters were formed, representing the main research directions in the field. The node size is proportional to the keyword occurrence frequency, and the line thickness reflects the co-occurrence strength.

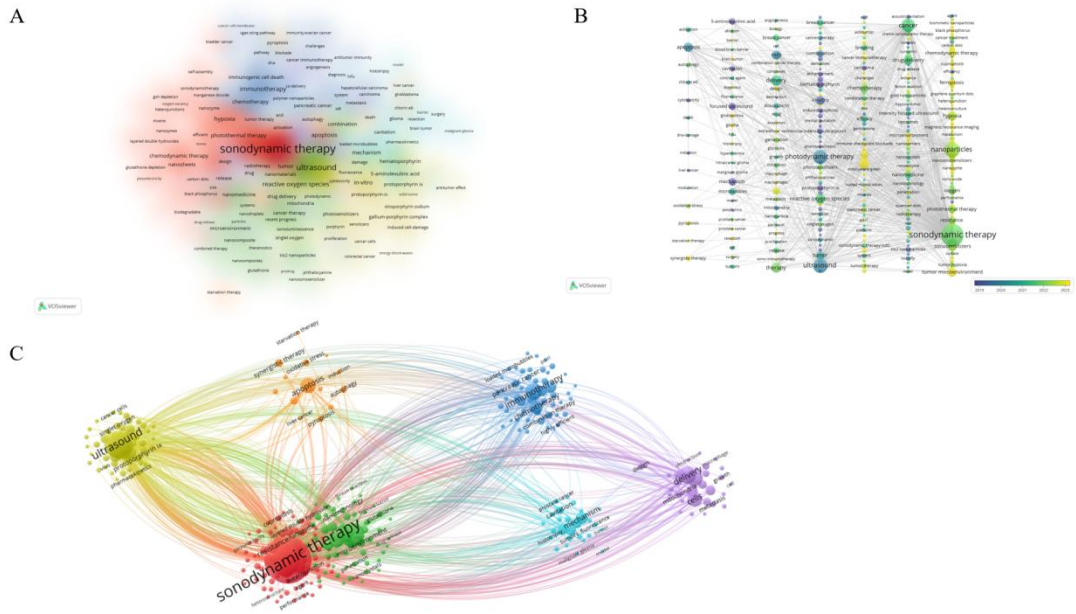



Figure 8. VOSviewer keyword co-occurrence and cluster analysis. (A) VOSviewer keyword density visualization map (warm colors indicate high-density research hotspots); (B) VOSviewer keyword timeline map (colors ranging from dark blue to yellow represent time from early to late); (C) Keyword cluster map (seven clusters were formed, with different colors representing different research themes).

Cluster 1 (red) focuses on the application of inorganic nanomaterials in sonodynamic therapy and represents the largest cluster (70 keywords). The core keywords include “metal-organic framework”, “black phosphorus”, “MXene”, “bismuth”, and “manganese dioxide”, indicating that researchers are extensively exploring various types of inorganic nanomaterials as sonosensitizers or nanocarriers. In addition, the presence of mechanism-related terms such as “glutathione depletion”, “ferroptosis”, “cuproptosis”, and “gas therapy” reflects the field’s interest in multiple cell death pathways induced by nanomaterials. This cluster also encompasses application directions such as “cancer treatment”, “bladder cancer”, and “colon cancer”, highlighting the close integration of fundamental materials research with oncological therapeutic applications.

Cluster 2 (green) focuses on combination strategies and nanodrug delivery systems in sonodynamic therapy (59 keywords). Keywords such as “chemo-sonodynamic”, “combined therapy”, and “combination therapy” reflect the research trend toward synergy between sonodynamic therapy and other treatment modalities. Terms such as “drug delivery”, “liposomes”, “nanocarriers”, “nanocomposites”, and “nanobubbles” reflect the diversity of nanodelivery systems. Keywords such as “microenvironment”, “hypoxic tumor”, and “glutathione” indicate that researchers are investigating the regulatory effects of the tumor microenvironment on therapeutic outcomes. This cluster reflects the evolutionary trend of sonodynamic therapy progressing from monotherapy to multimodal combination therapy.

Cluster 3 (blue) focuses on immune responses induced by sonodynamic therapy and tumor immunotherapy (51 keywords). The core keywords included “cancer immunotherapy”, “antitumor immunity”, “immune checkpoint blockade”, “cgas-sting pathway”, and “immunogenic cell death”, indicating that sonodynamic therapy can activate antitumor immune responses by inducing immunogenic cell death. This cluster also encompasses immune combination strategies such as “dendritic cells”, “codelivery”, and “chemotherapy”, highlighting the broad application prospects of sonodynamic therapy in the field of tumor immunotherapy. Cluster 4 (yellow) focuses on photodynamic therapy and its intersection with sonodynamic therapy (50 keywords). Keywords include “photodynamic therapy”, “photosensitizers”, “hematoporphyrin”, “phthalocyanine”, and “porphyrin”, highlighting the foundational role of photosensitizers in the field. Tumor types such as “breast cancer”, “colorectal cancer”, and “melanoma” represent the main application directions of this therapeutic approach. In addition, mechanism-related terms such as “reactive oxygen species”, “cell damage”, and “induced apoptosis”, along with research methodology keywords such as “pharmacokinetics” and “invitro”, collectively constitute the research content of this cluster. Cluster 5 (purple) focuses on tumor biology mechanisms and nanodrug mechanisms of action (30 keywords). Keywords cover core tumor biology processes such as “angiogenesis”, “glycolysis”, “metastasis”, “proliferation”, “apoptosis”, and “autophagy”, as well as regulatory targets at the cellular and subcellular levels, including “macrophage”, “exosomes”, and “mitochondria”. This cluster also includes chemotherapeutic agents such as “doxorubicin” and “paclitaxel”, along with combination strategies such as “sono-immunotherapy”, reflecting the close connection between fundamental mechanistic research and drug development. Cluster 6 (cyan) focuses on high-intensity focused ultrasound and neuro-oncology therapy (27 keywords). The core keywords included ultrasound technology-related terms such as “focused ultrasound”, “hifu”, “histotripsy”, “microbubbles”, and “cavitation”, as well as core neuro-oncology terms such as “glioblastoma”, “glioma”, “brain tumor”, and “blood–brain barrier”. This cluster reflects the application potential of focused ultrasound technology in the treatment of central nervous system tumors, particularly for drug delivery via microbubble-mediated opening of the blood–brain barrier. Cluster 7 (orange) focuses on cell death mechanisms and synergistic therapy strategies (14 keywords). Keywords encompass multiple cell death and stress response mechanisms, such as “apoptosis”, “autophagy”, “ferroptosis”, “pyroptosis”, “DNA damage”, and “oxidative stress”, reflecting the multiple pathways through which sonodynamic therapy induces tumor cell death; “Chlorin e6”, a representative sonosensitizer/photosensitizer; “starvation therapy”, a synergistic treatment strategy; and “synergistic therapy”, a core concept collectively constitute the main research thread of this cluster. This clustering structure reflects the multidisciplinary nature of the field, with sonodynamic therapy at its core, nanomaterials as the foundation,

combination therapy and immunomodulation as extensions, and precision oncology as the application orientation.

## Burst Detection Analysis

Keywords burst refers to research hotspots that exhibit a significant increase in frequency during a specific period, reflecting shifts in research frontiers within the field. The burst keywords can be divided into three stages on the basis of the burst onset time. The early stage (2001–2008) focused on fundamental research and classic technologies, with “hematoporphyrin” exhibiting the highest burst strength (15.78) and lasting for 17 years, reflecting its foundational role as a photosensitizer/sonosensitizer. Burst keywords such as “focused ultrasound” (4.66), “gallium porphyrin complex” (4.83), “enhancement” (6.77), and “mechanism” (6.33) indicate that focused ultrasound technology, metalloporphyrin complexes, and therapeutic mechanisms were core research themes during this early period.

The middle stage (2007–2016) involved a shift toward mechanistic deepening and combination applications, with “protoporphyrin ix” emerging as the most prominent keyword, with a burst strength of 10.72. Burst keywords such as “cavitation” (4.1), “in vitro” (6.39), “damage” (3.76), “apoptosis” (5.28), and “5-aminolevulinic acid” (5.52) indicate that cavitation effects, apoptosis, and in vitro studies have become research hotspots.

Further analysis of burst time windows revealed that nanomaterial-related keywords such as “delivery”, “tio2 nanoparticles”, “microbubbles”, and “release” exhibited bursts concentrated from 2016–2018. This time window falls precisely within the middle to late period of Model Stage II (2015–2019), reflecting the rapid diffusion of nanotechnology during Stage II. In contrast, novel mechanism-related keywords such as “breaking”, “singlet oxygen”, and “oxidative stress” presented bursts concentrated from 2019–2022, which align closely with the onset of Model Stage III (2020–2025), indicating that multi-mechanism synergy served as the core driving force for the explosive growth observed in Stage III.

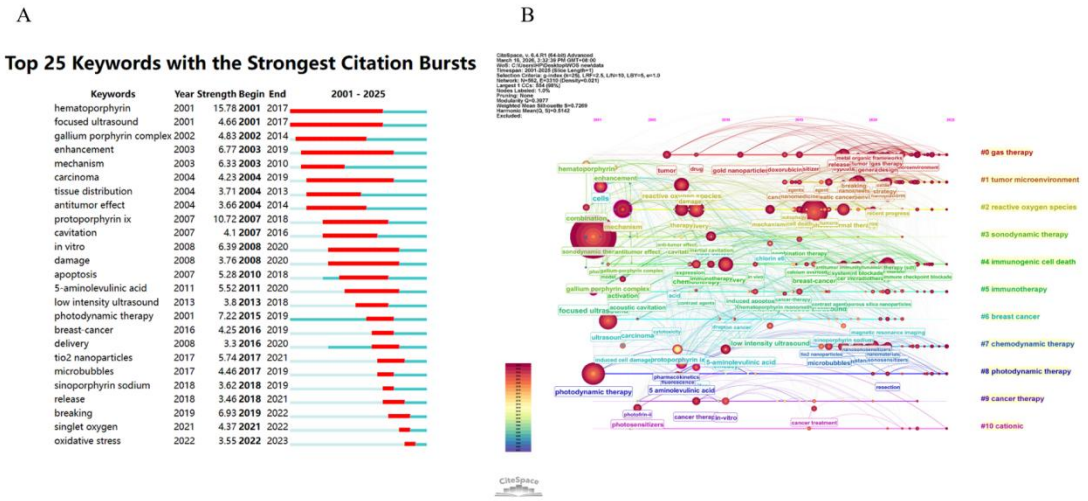



Figure 9. CiteSpace keyword burst detection analysis. (A) Top 25 keywords with the strongest citation bursts (red bars indicate burst durations); (B) CiteSpace keyword timeline map (research theme clusters are labeled on the right).

Combining the research theme clusters automatically labeled by CiteSpace with the temporal distribution of keyword bursts, the research hotspots in this field clearly exhibit a pattern of stage-based evolution. The foundational stage (2001–2008), centered on “hematoporphyrin” and “focused ultrasound”, focused on sonosensitizer development and focused ultrasound technology, laying the groundwork for research in this field. The deepening stage (2007–2016), represented by “protoporphyrin ix”, “cavitation”, and “apoptosis”, shifted focus toward the mechanisms of sonodynamic therapy, cavitation effects, and cell death pathways. Moreover, the burst of “5-aminolevulinic acid” reflected the continued advancements in sonosensitizer research. The expansion stage (2015–2023), represented by “tio2 nanoparticles”, “immunotherapy”, and “oxidative stress”, has led to research hotspots extending toward nanomaterial-mediated precision therapy, immunomodulation, and reactive oxygen species mechanisms. The emergence of themes such as “tumor microenvironment”, “immunogenic cell death”, and “chemodynamic therapy” in cluster analysis further corroborates the field’s trajectory toward multimodal combination therapy and immunomodulation.

## Cocitation Analysis

On the basis of cluster analysis of cocited references via CiteSpace, nine major research theme clusters were identified, reflecting the knowledge base structure and mechanistic research directions in the field. Among them,

Cluster #4, “sonosensitizers”, focuses on the core elements of sonodynamic therapy, encompassing research on the development, screening, and optimization of sonosensitizers. Cluster #3, “oxygen evolution reaction”, addresses the physicochemical mechanisms of reactive oxygen species generation in sonodynamic therapy. Clusters #7, “cuproptosis”, and #8, “immunogenic cell death”, focus on novel cell death mechanisms, reflecting the field’s deep expansion from traditional apoptosis mechanisms to multi-mechanism synergy involving ferroptosis, cuproptosis, and pyroptosis. Clusters #1, “immunotherapy”, and #0, “photothermal therapy”, represent combination strategies that integrate sonodynamic therapy with immunotherapy and photothermal therapy. Cluster #2, “trastuzumab”, reflects the cross-integration of targeted therapy. Clusters #5, “antitumor effect”, and #6, “5-aminolevulinic acid”, focused on efficacy evaluation and continued research on classic sonosensitizers, respectively.

The above clustering structure indicates that the knowledge base of the field centers on sonosensitizer development and forms a multidimensional research framework encompassing reactive oxygen species generation mechanisms, cell death pathways (e.g., ferroptosis, cuproptosis, and immunogenic cell death), and combination therapy strategies (e.g., immunotherapy and photothermal therapy). This reflects a developmental trajectory extending from basic mechanistic exploration toward multimodal combination therapy.

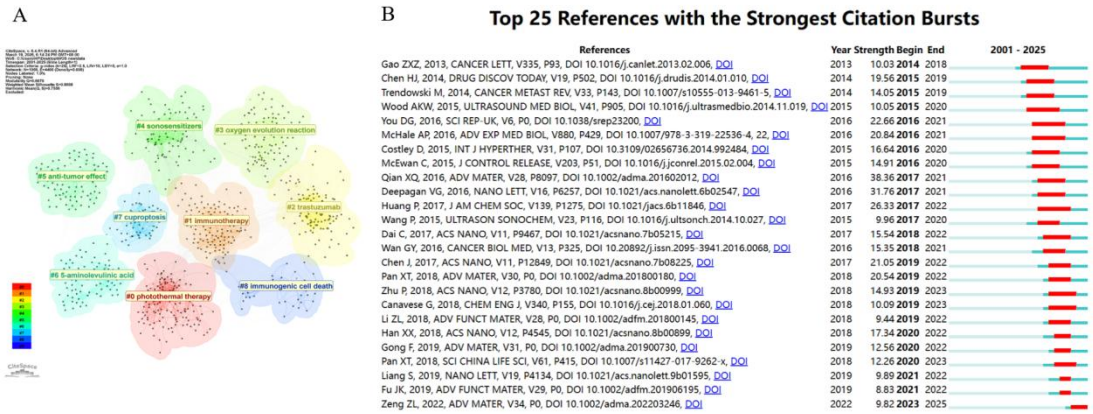



Figure 10. Cluster and burst detection analysis of cocited references. (A) Cluster map of cocited references (9 clusters in total). (B) Top 25 references with the strongest citation bursts (red bars indicate burst durations).

Reference burst analysis reveals the evolutionary trajectory of research frontiers in this field. In terms of burst strength, the paper by Qian et al.[32] The material published in Advanced Materials in 2016 presented the highest burst strength (38.36), followed by the paper by Deepagan et al. [33] published in Nano Letters in 2016 (31.76), indicating that the application of nanomaterials in sonodynamic therapy represented the most influential research frontier during this period. From the perspective of temporal evolution, burst references can be divided into three

stages. The first stage (2014–2015) featured studies by Gao et al.[34], Chen et al.[35], and Wood et al.[36], which focused on the basic mechanisms of sonodynamic therapy and ultrasound-mediated treatment strategies. The second stage (2016–2017) featured a marked increase in burst strength, with a concentration of papers by Qian et al.[32], Deepagan et al.[33], and Huang et al.[37] indicating that the design of nanomaterials and sonosensitizers has emerged as research hotspots. The third stage (2018–2023) saw a continued increase in burst references, with studies by Pan et al.[38], Zhu et al. [39], Gong et al. [40], and Zeng et al. [41] focusing on multifunctional nanoplatforms, combination therapy, and the development of novel sonosensitizers. Notably, the burst of Zeng et al. [41] persisted until 2025, indicating that the field remains in a phase of rapid development. In summary, the reference burst analysis demonstrated that the research frontiers in this field have undergone an evolutionary trajectory from the exploration of sonodynamic mechanisms to nanomaterial-mediated approaches and subsequently to multifunctional synergistic therapy.

Citation theme analysis revealed that at the micro level, research has focused on specific directions, such as magnetic nanoparticles, nanocarriers, photodynamic therapy, porphyrins, and cell death mechanisms (autophagy, apoptosis, and DNA damage). At the macro level, the field encompasses multidisciplinary areas, including nanotechnology, molecular and cellular biology, immunology, and inorganic chemistry. Overall, this study presents a research landscape centered on nanomaterials, with equal emphasis on fundamental mechanisms and translational applications.

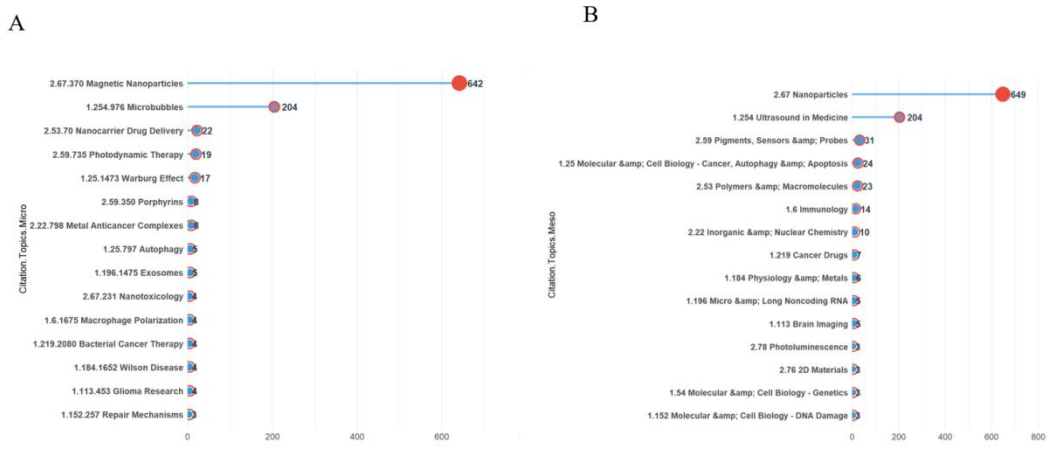



Figure 11. Distribution of citation themes. (A) Research themes at the micro level; (B) Disciplinary areas at the macro level.

## Piecewise Growth Model Analysis

### Basis for Stage Division

The period from 2001--2025 was divided into three stages on the basis of the following evidence: inflection points in annual publication volume (2014 and 2019); the emergence of burst keywords (nanomaterial-related keywords such as “delivery”, “tio2 nanoparticles”, “microbubbles”, and “release” first exhibited bursts concentrated in 2016--2018, falling within the middle--to-late period of Stage II; novel mechanism-related keywords such as “breaking”, “singlet oxygen”, and “oxidative stress” first exhibited bursts concentrated in 2019--2022, aligning closely with the onset of Stage III); key technological breakthroughs (key papers on nanotechnology-enhanced SDT were concentrated in 2015--2017, while key papers on combination therapy strategies emerged after 2020); and the three knowledge layers revealed by the keyword timeline map. Notably, the onset of Stage II (2015) preceded the first bursts of nanomaterial-related keywords (2016–2018), indicating that the model division captured the initial signal period of technology introduction rather than the peak burst period. In contrast, the onset of Stage III (2020) was nearly synchronous with the first bursts of novel mechanism-related keywords (2019–2022), reflecting the feature that multi-mechanism synergy drove accelerated growth.

## Key Findings

The annual growth rate of cancer sonodynamic therapy research increased from 17.0% in Stage I to 30.4% in Stage III. The goodness-of-fit $(R^2)$ improved from 0.56 to above 0.87. The average annual publication volume increased from 5.4 articles in Stage I to 147.7 articles in Stage III, representing a cumulative increase of 2,635%. Moreover, Stage III maintained an excellent goodness-of-fit of 0.87 despite a high growth rate of 30.4%, demonstrating a nonlinear accelerated growth pattern transitioning from random fluctuations to systematic exponential explosion.

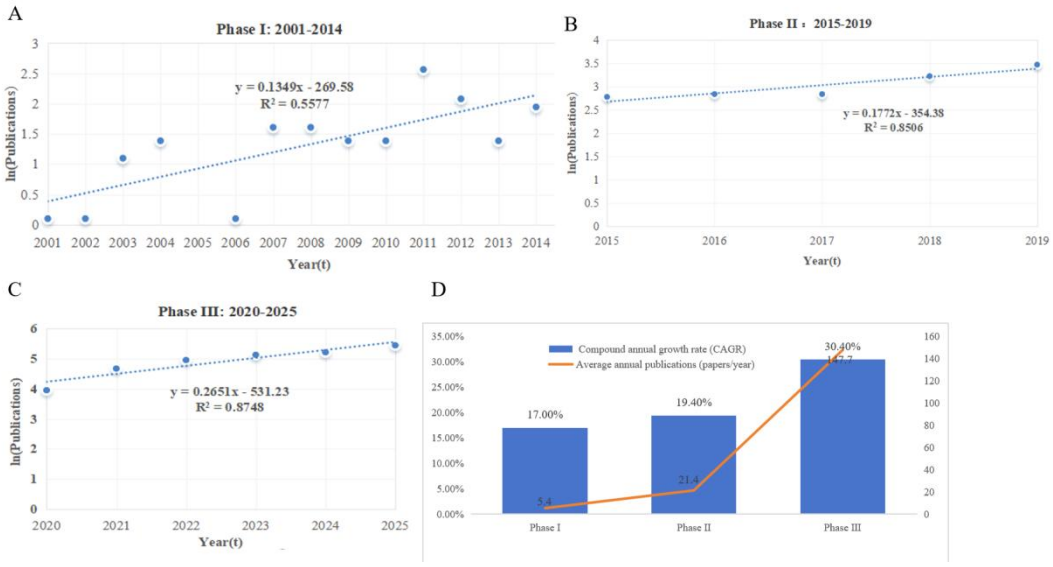



Figure 12. Three-stage piecewise exponential growth model fitting for cancer SDT research. (A) 2001–2014 (Stage I): $ln(P_t) = 0.135t - 269.58$, $R^2 = 0.56$; (B) 2015–2019 (Stage II): $ln(P_t) = 0.177t - 354.38$, $R^2 = 0.85$; (C) 2020–2025 (Stage III): $ln(P_t) = 0.265t - 531.23$, $R^2 = 0.87$ (dashed lines indicate log-linear regression fit lines); (D) Compound annual growth rate and annual publication volume, where t represents the actual year. The annual growth rate was calculated as $(e\beta - 1) \times 100\%$.

## Correlation Analysis of the Driving Factors

According to the growth model analysis, the stage characteristics were highly coupled with major advancements in the field. The inflection point in 2015 marked the onset of Stage II (2015–2019) and closely aligned with the first burst years of nanomaterial-related keywords (“delivery”, “tio2 nanoparticles”, “microbubbles”, “release”) from 2016 to 2018, reflecting a paradigm shift from the introduction to rapid diffusion of nanotechnology, which drove the improvement of the goodness-of-fit from 0.56 to 0.85 in Stage II. The inflection point in 2020 corresponded to the onset of Stage III (2020–2025) and was nearly synchronous with the first burst years of novel mechanism-related keywords (“breaking”, “singlet oxygen”, “oxidative stress”) from 2019--2022, marking the emergence of multi-mechanism synergy (“immunotherapy combination”, “ferroptosis”). This shift expanded the research depth from single-technology approaches to multi-mechanism synergy, resulting in an increase in the growth rate to 30.4% in Stage III (compared with 19.4% in the previous stage).

## Discussion

## Summary of Key Findings

To our knowledge, this study is the first to systematically reveal the macrolevel developmental trends of cancer SDT research over the past 25 years by integrating bibliometric analysis with a piecewise growth model. This analysis delineates a three-stage evolutionary trajectory, reveals an accelerating exponential growth pattern, and demonstrates the evolution of the knowledge structure from basic mechanisms to nanotechnology and, subsequently, to multi-mechanism synergy. China demonstrates comprehensive leadership in both publication output and research influence, and interdisciplinary characteristics are reflected in the deep integration of materials science, chemistry, and oncology.

## Driving Mechanisms of Growth

Behind the stage evolution lies the synergistic effect of multiple driving factors.

## Technological Breakthroughs as Drivers

The introduction of nanotechnology (the onset of Stage II) addressed the bottlenecks of traditional sonosensitizers in terms of targeting, stability, and biocompatibility [4][8]. Novel materials such as metal–organic frameworks and nanosheets not only serve as sonosensitizer carriers but also exhibit unique sonodynamic properties[9][37].

Keyword burst detection revealed that nanomaterial-related keywords such as “delivery”, “tio2 nanoparticles”, “microbubbles”, and “release” exhibited bursts concentrated from 2016–2018, which fell within the middle to late period of Stage II (2015–2019). This time window coincided closely with the rapid diffusion phase of nanomaterial applications in sonodynamic therapy, directly driving the annual growth rate in Stage II from 17.0% to 19.4% and significantly improving the goodness-of-fit from 0.56 to 0.85, indicating that research has transitioned from random fluctuations to a predictable exponential growth trajectory.

## Mechanism Expansion as a Driver

The discovery and introduction of novel cell death mechanisms, such as ferroptosis and immunogenic cell death (marking the onset of Stage III), have greatly enriched the therapeutic benefits of SDT [7][40] and facilitated its synergy with immunotherapy and other modalities.

Keyword burst detection revealed that novel mechanism-related keywords such as “breaking”, “singlet oxygen”, and “oxidative stress” presented bursts concentrated from 2019–2022, which aligned closely with the onset of Stage III (2020–2025). This time window reflects a deep expansion of research hotspots from nanomaterial applications toward multi-mechanism synergy, driving the annual growth rate in Stage III to further increase to 30.4% and achieving an upgrade in the growth model from “single-technology driven” to “multimechanism synergy driven”.

Taken together, the results of keyword burst detection and piecewise growth model analysis form a clear logical closed loop: burst detection revealed the specific time windows in which research hotspots emerged, whereas the stage division of the model characterized the structural growth changes that occurred following the formation of these hotspots. The concentrated emergence of nanomaterial-related keywords in the middle to late period of Stage II explains the significant improvement in goodness-of-fit during that stage; the synchronous emergence of novel mechanism-related keywords at the onset of Stage III explains the surge in growth rate during that stage. This correspondence validates the rationale for the stage division of the model and provides data-driven support for understanding the dynamic mechanisms underlying growth in this field.

## Current Status and Challenges in Cancer SDT Therapy

From a therapeutic perspective, SDT has demonstrated unique value and potential in cancer treatment. At the basic research level, researchers have developed a variety of novel sonosensitizer systems, including organic sonosensitizers (porphyrin derivatives and phthalocyanines), inorganic nanosonosensitizers ($TiO_2$, Au, and MOFs), and biocompatible polymer sonosensitizers, which have significantly improved reactive oxygen species yield and tumor targeting[4][8][42]. At the mechanistic level, immunogenic cell death (ICD) induced by SDT has emerged as a critical bridge connecting local therapy with systemic immune responses, providing a theoretical foundation for combination immunotherapy[41][43].

Despite these advances, several challenges persist in the clinical translation of SDT. Uniform screening criteria for

ideal sonosensitizers have not yet been established, and the preparation processes and quality control systems for clinical-grade sonosensitizers require further improvement [44]. Standardization of ultrasound treatment parameters (frequency, intensity, duty cycle, and treatment duration) is also lacking, making it difficult to compare results across different studies[Error! Unknown switch argument.]. Furthermore, the timing, sequence, and dosage combinations of SDT-based combination therapies lack evidence-based medical support, necessitating more clinical trials to optimize combination regimens[46]. Moreover, acoustic energy attenuation in deep-seated tumors and the efficiency of sonosensitizer delivery remain key bottlenecks limiting therapeutic efficacy [4].

## Synergistic Mechanisms of Combinations of SDT Strategies

The synergistic application of SDT with multiple treatment modalities has emerged as a core strategy to increase antitumor efficacy. In terms of SDT combined with immunotherapy, SDT-induced ICD promotes dendritic cell maturation and T-cell infiltration, converting “cold tumors” into “hot tumors,” and exhibits synergistic antitumor effects when combined with immune checkpoint inhibitors[41][43][47]. With respect to SDT combined with chemodynamic therapy (CDT), metal ions ($Fe^{2+}$, $Cu^{2+}$) in nanosonosensitizers can mediate Fenton or Fenton-like reactions, generating synergistic oxidative stress with SDT-produced reactive oxygen species (ROS) and enhancing tumor killing effects[11][48]. In the context of SDT combined with ferroptosis/cuproptosis induction, novel sonosensitizer designs have integrated ferroptosis inducers or copper ion carriers to trigger tumor cell death through multipathway synergy[7][12][49]. Research on the synergistic mechanisms underlying these combination strategies forms a solid theoretical foundation for clinical translation.

## Limitations and Future Directions

## Study Limitations

This study has several limitations. First, the data were sourced exclusively from the Web of Science Core Collection, which may have omitted relevant publications from other databases. Second, the literature search was conducted up to December 2025, and some publications from that year may not have been fully indexed at the time of retrieval, introducing a time truncation effect. Third, bibliometric indicators such as citation counts are influenced by factors such as publication date and language preference and thus may not fully and objectively reflect research impact.

Finally, although the piecewise exponential growth model provides a good fit to the historical data, the accuracy of its long-term projections depends on the stability of the current search strategy. If new terminology or research paradigms emerge in the field, the current search query may not comprehensively capture all relevant literature.

## Future Research Directions

Future research can be advanced in multiple directions, with particular emphasis on the frontier areas highlighted by recent keyword burst detection. At the level of clinical translation, although basic research has progressed rapidly, clinical studies are still in their early stages[46][50]. Efforts should focus on facilitating the translation of research findings from the laboratory to clinical practice. At the level of mechanistic exploration, bursts of keywords such as “breaking”, “singlet oxygen”, and “oxidative stress” suggest that cross-investigations of reactive oxygen species-mediated cell death mechanisms with emerging pathways such as ferroptosis and pyroptosis hold significant potential [7][51]. At the level of material innovation, persistent bursts of keywords such as “tio2 nanoparticles”, “microbubbles”, and “delivery” indicate that nanomaterials remain a core research direction. Future efforts should focus on developing intelligent responsive and biodegradable novel sonosensitizers[4][8].

## Conclusions

On the basis of a systematic bibliometric analysis and piecewise growth model analysis of cancer sonodynamic therapy (SDT) research from 2001--2025, this study draws the following conclusions.

**The field has entered a phase of explosive growth:** Cancer SDT research has evolved from a marginal area of exploration into a multidisciplinary frontier hotspot, with a current annual growth rate of 30.4% and an average annual publication volume of 147.7 articles, exhibiting an exponential growth pattern characterized by a “dual acceleration of scale and growth rate.” The piecewise growth model revealed a three-stage evolutionary trajectory: the exploratory stage (2001–2014), which focused on basic mechanisms with slow and fluctuating growth; the technology-driven stage (2015–2019), dominated by nanotechnology with a significant improvement in goodness-of-fit; and the explosive growth stage (2020–2025), characterized by multi-mechanism synergy with the annual growth rate surging to 30.4%.

**China occupies a central position:** China has demonstrated comprehensive leadership in publication volume,

international collaboration networks, and high-impact research, forming a complete innovation chain spanning from basic research to applied exploration. The Chinese Academy of Sciences and universities in Shanghai emerged as core research forces.

**The knowledge structure and research hotspots are continuously evolving:** keyword co-occurrence and burst analyses have revealed a clear trajectory of research themes transitioning from early sonosensitizer development and focused ultrasound technology to mid-stage nanomaterial-mediated combination therapy and subsequently to recent frontier directions such as immunotherapy, ferroptosis, and reactive oxygen species mechanisms, reflecting a progression from basic mechanisms toward multimodal synergy. Cocitation analysis further validated the generational shift in this knowledge structure.

**Future trends and challenges:** On the basis of growth models and frontier analyses, the field is expected to maintain rapid growth over the next 2–3 years, after which it may gradually converge toward a more stable growth range. At the therapeutic level, SDT is evolving from a single local modality toward multimodal combination therapy, and its integration with immunotherapy, targeted therapy, and cell death inducers will drive the development of precision oncology[47][49]. However, clinical translation remains a core bottleneck in the field[45][50]. Clinical translation, mechanistic elucidation, material innovation, and equipment standardization will be key directions for determining the long-term development of the field.

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## Declarations

## Competing interests

The authors declare that they have no competing interests.

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**Author contributions**

WANG Xiaoting: literature search, data curation, investigation, visualization, writing – original draft. YANG Ke: methodology, software analysis, validation, writing, review, and editing. DENG Peitong: literature search, data curation. ZHANG Bo: funding acquisition, writing – review & editing. All the authors have read and approved the final manuscript.

**Data availability**

The bibliometric data supporting this study are available from the Web of Science Core Collection (publicly accessible). This article contains an original dataset, reproducible methods, statistical modeling, and independent results. All data and analyses are presented in the manuscript.

**Code availability**

CiteSpace (version 6.2. R3) and VOSviewer (version 1.6.20) were used for bibliometric analysis. These are publicly available software packages. No custom code was generated during this study.

**Ethics approval**

Not applicable.

**Consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

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