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Review article

Global research landscape and hotspots for ferroptosis in glioma: A comprehensive bibliometric and visual analysis

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ABSTRACT

Studying ferroptosis is crucial for understanding the mechanisms underlying the onset and progression of glioblastoma, identifying therapeutic targets, and improving prognosis assessment and diagnostic methods. While recent research has explored the link between ferroptosis and glioblastoma, there is a lack of comprehensive bibliometric analyses specifically addressing this relationship and its connection to glioblastoma. To address this gap, we conducted a thorough analysis of 225 relevant articles on glioma and ferroptosis obtained from the Web of Science database covering the period from 2012 to 2023, employing rigorous exclusion criteria. Visual and statistical analyses were performed using CiteSpace, VOSviewer, R Studio Plotting, and Scimago Graphica Beta. Our findings revealed a significant exponential growth in the number of studies during the last decade. China, the United States, and Germany made the most substantial contributions to research in this field, collectively accounting for 76.2 % of the total research output. Notably, Central South University, Shandong University, and Zhejiang University emerged as leaders in both literature production and research collaboration. *Frontiers in Oncology* stood out as the most prolific journal, encompassing a wide array of topics from molecular mechanisms to potential therapeutic strategies. Visual keyword analysis highlighted "tumor biology" "cell death mechanisms" and "gene expression and metabolic processes" as central themes in the research network. This study offers a comprehensive visual perspective on the global publication landscape of ferroptosis in glioma, providing valuable insights for researchers seeking to understand the current state of the field and identify potential directions for future studies.

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1. Introduction

Glioblastoma (GBM) is one of the most common malignant primary intracranial brain tumor in adults, characterized by its strong invasiveness and extremely poor prognosis. In 2021, the World Health Organization (WHO) classified it as a Grade IV glioma in the central nervous system (CNS) tumor classification [1]. An epidemiological study spanning from 2009 to 2015 indicated a survival rate of less than 10 % for GBM patients [2]. Despite advancements in standard treatment strategies such as surgical resection, radiotherapy, and chemotherapy, GBM patients exhibit strong resistance to conventional treatment methods due to the tumor's highly-invasive nature, leading to frequent recurrence and worsening of the tumor after treatment failure [3,4].

Ferroptosis has been confirmed to play an important role in the occurrence, development, and therapeutic application of GBM [5]. Evidence suggested that targeting ferroptosis can induce lipid peroxidation in tumor cells, which may subsequently regulate immune cells in the tumor microenvironment [6]. Other studies have indicated that ferroptosis-related gene sets closely associated with clinical manifestations of GBM patients can serve as independent biomarkers for disease prediction [7]. For example, plumbagin can effectively mediate ferroptosis by targeting NQO1/GPX4, thereby inhibiting the *in vitro* and *in vivo* growth of GBM cells [8]. Furthermore, the activation of ferroptosis on $CD8^+$ T cells and its potential enhancement of anti-PD-1/PD-L1 immunotherapy effectiveness indicate a new direction in combining ferroptosis with immunotherapy strategies for GBM treatment [9,10]. Therefore, study of ferroptosis is of great significance for understanding the occurrence and development mechanisms of GBM, identifying therapeutic targets, and improving prognosis evaluation and diagnostic methods.

Bibliometrics employs statistical and mathematical methods to quantitatively analyze literature, offering unique value in revealing trends and directions within specific research fields. Currently, despite a plethora of studies and reviews focusing on the role of ferroptosis in GBM, there is a lack of bibliometric analysis specifically related to ferroptosis within the context of glioma. In this study, we utilized the Web of Science system and manually screened studies from January 1, 2012, to December 31, 2023, pertaining to "ferroptosis" AND "glioma". Subsequently, we employed the Bibliometric Online Analysis Platform (http://biblimetric.com) [11], (https://biit.cs.ut.ee/gprofiler/gost), along with the VOSviewer software [12] and CiteSpace software [13], to analyze the collected data. This involved visualizing annual publications, countries/regions, institutions, journals, and authors; evaluating global collaboration patterns among authors, institutions, and countries; and determining and predicting trends and hotspots in the field through visual analysis of keyword clustering, citation, and co-citation of references. Through bibliometric analysis, we aim to provide new insights for subsequent studies on the complex mechanisms of ferroptosis in GBM and the development of attractive therapeutic strategies.

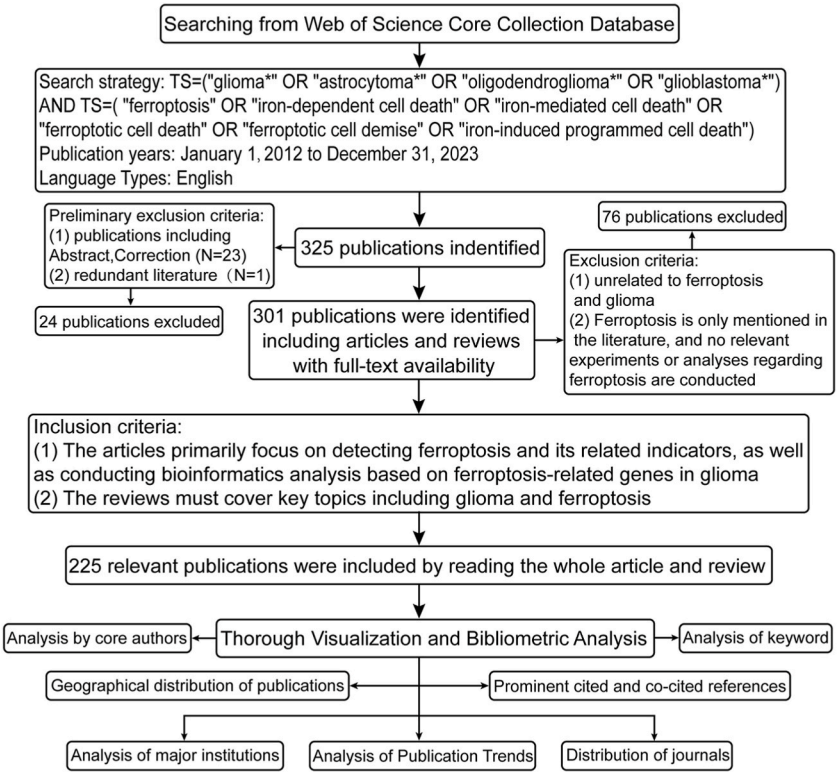

Fig. 1. Flowchart of Literature Search Strategy. Description of the steps of bibliometric analysis for identifying and screening papers from the WoSCC database in this field. The search scope is from 2012 to 2023 and includes only papers and reviews published in English. Detailed exclusion criteria were applied to ensure high relevance and quality, followed by manual exclusion to refine the dataset, specifically targeting studies directly related to ferroptosis and glioma with substantial experimental or analytical content.

2. Material and methods

2.1. Data collection and search strategies

In this study, we selected the Expanded Science Citation Index from Clarivate Analytics' Web of Science Core Collection (WOSCC) as the primary data source. Considering the authority and coverage of this database in academic research, literature retrieval was conducted on December 31, 2023, aiming to obtain literature related to the mechanisms of ferroptosis and gliomas between 2012 and 2023. A comprehensive search was conducted using the following key words combination: TS=("glioma*" OR "astrocytoma*" OR "oligodendroglioma*" OR "glioblastoma*") AND TS=("ferroptosis" OR "iron-dependent cell death" OR "iron-mediated cell death" OR "ferroptotic cell death" OR "ferroptotic cell demise" OR "iron-induced programmed cell death"), with the query strings and filtering strategies were detailed in the flowchart (Fig. 1). Utilizing truncation search method to improve the precision of retrieval, and considering only articles and reviews, the time range was set from January 1, 2012, to December 31, 2023, with language limited to English. A total of 325 relevant articles were retrieved. Following a manual screening process, preliminary exclusion criteria included publications classified as abstracts, corrections, or redundant literature, reducing the count by 24. After reviewing 301 remaining full-text articles and reviews, 76 were further excluded for being unrelated to ferroptosis and glioma or merely mentioning ferroptosis without relevant experiments or analyses. The final inclusion criteria required articles to focus on detecting ferroptosis and related indicators or conducting bioinformatics analysis on ferroptosis-related genes in glioma, and reviews to cover key topics on both glioma and ferroptosis. Ultimately, 225 articles meeting these criteria were selected for detailed analysis (see Supplementary Table S1), with the search and filtering process detailed in the flowchart (Fig. 1).

2.2. Data visualization and analysis tools

We exported the network graphs generated by tools such as VOSviewer (Version 1.6.16) and CiteSpace (Version 6.2.2) in high-resolution PNG or PDF formats. Tables were organized in Microsoft Excel, and both extracted and generated data were archived. VOSviewer is utilized for constructing visual maps of network relationships among entities within the research domain, such as countries, institutions, journals, and researchers. CiteSpace is a free Java based application that is employed in this article to generate visualizations of scientific literature trends and patterns. R Studio Plotting (Version R 4.2.0) is used for visual analysis of trends in authorship over time and affiliation relationships, as well as the evolution of keywords. Scimago Graphica Beta (Version 1.0.34) is an online tool where we created specific regional distribution maps. The gprofiler (https://biit.cs.ut.ee/gprofiler/gost) is a functional enrichment tool used in this study to identify biological pathways, specifically analyzing KEGG and WikiPathways.

3. Results

3.1. Analysis of publication trends

From 2012 to 2023, research on ferroptosis in gliomas accumulated a total of 325 articles in the Web of Science Core Collection (WoSCC). Through analysis of the selected 225 articles, no article was published between 2012 and 2014. However, from 2015 to 2023, there was a significant exponential growth in the number of studies. The orange bar plot illustrates the cumulative number of publications per year, providing a visual representation of the continuous growth in this research field over time. The blue line represents the annual addition of new publications, revealing the yearly publishing dynamics (Fig. 2). Meanwhile, orange dots indicate

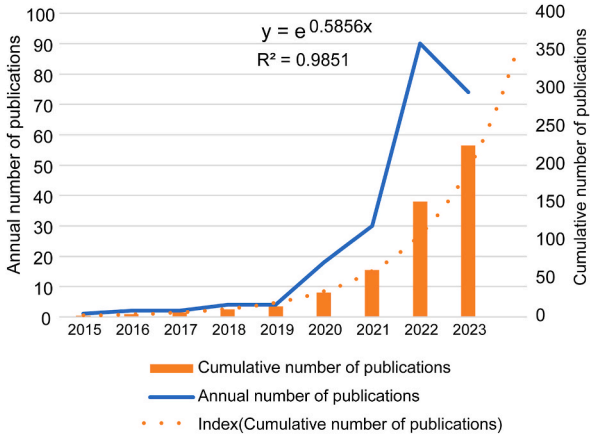

Fig. 2. Annual Publication Status and Time Distribution (2015–2023). The orange bars represent the cumulative number of publications each year, the blue line graph represents the number of publications each year, and the orange dots indicate the logarithmic growth rate of cumulative publication count.

the exponential growth rate of publications each year, demonstrating an exponential increase in the number of publications. These trends reflect an active and rapidly evolving field of research on ferroptosis and gliomas, with increasing research momentum and impact.

3.2. Geographical distribution of publications

In this study, we analyzed 225 publications from 28 countries. Significant contributions from China, the United States and Germany were observed, collectively accounting for 76.2 % of all publications. China leads with 170 publications, representing 64.4 %, while the United States exhibits significant citation frequency and influence (see Supplementary Table S2). Specifically, the Scimago

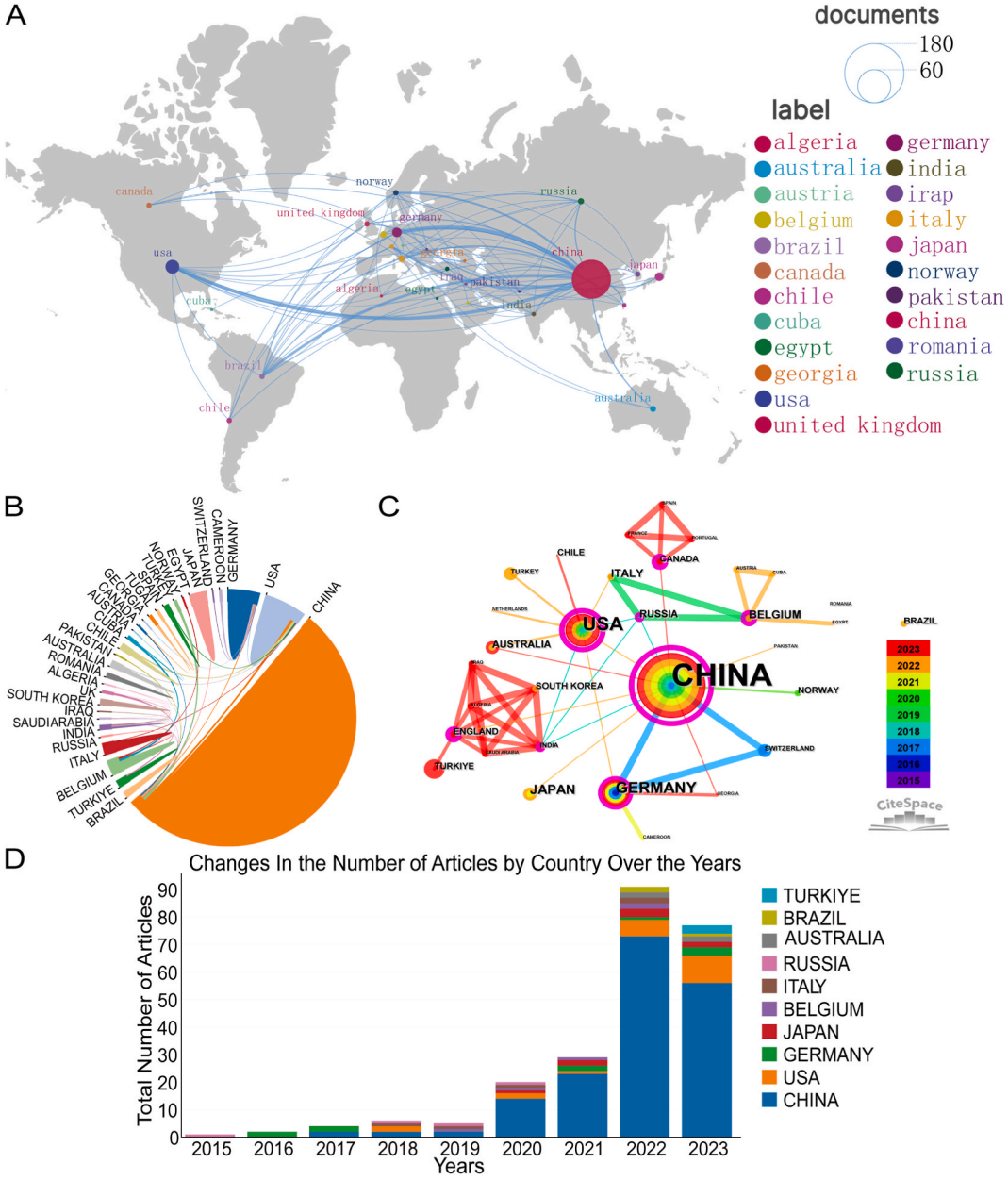

Fig. 3. Global Overview and International Collaboration of Publications. (A) Global distribution map of publications created by Scimago Graphica Beta, where the size of the circles is proportional to the number of publications in each country, and the thickness of the blue connecting lines represents the strength of collaboration between countries. (B) Chord diagram analysis of international collaboration among different countries/regions created by bibliometric analysis. (C) Visualization of collaboration networks among countries using CiteSpace. (D) Stacked bar chart created by bibliometric analysis, where different colors represent different countries.

Graphica Beta provides a global overview of all publications (Fig. 3A). The chord diagram illustrates international collaboration analysis among different countries (Fig. 3B). Notably, China not only leads in research output but also demonstrates close collaboration with other countries, as evidenced by the country collaboration network generated by CiteSpace (Fig. 3C). China has the highest total link strength, indicating its core role in advancing international cooperation in this research field. However, China's average citation rate is relatively low. In contrast, the United States dominates with significantly higher average citation rates than China (see Supplementary Table S2). It is noteworthy that from 2020 to 2023, China's publication quantity almost equals the total of all other countries, particularly since 2019, making China the most active country in this research field (Fig. 3D).

3.3. Analysis of major institutions

Through comprehensive radar chart visualization (Fig. 4A) and network analysis using VOSviewer (Fig. 4B), we have gained a comprehensive understanding of the academic institutional activities in the field of ferroptosis and glioma research. Among the 225 publications, a total of 325 institutions participated in the research. Among the top ten most productive institutions, Central South University and Shandong University lead with 15 and 14 publications, respectively (see Supplementary Table S3). It is noteworthy that although Zhejiang University only published 9 papers, its centrality score of 0.12 indicates the institution's core position in the academic network. Furthermore, CiteSpace software deepened our understanding of the positions and connections of various institutions

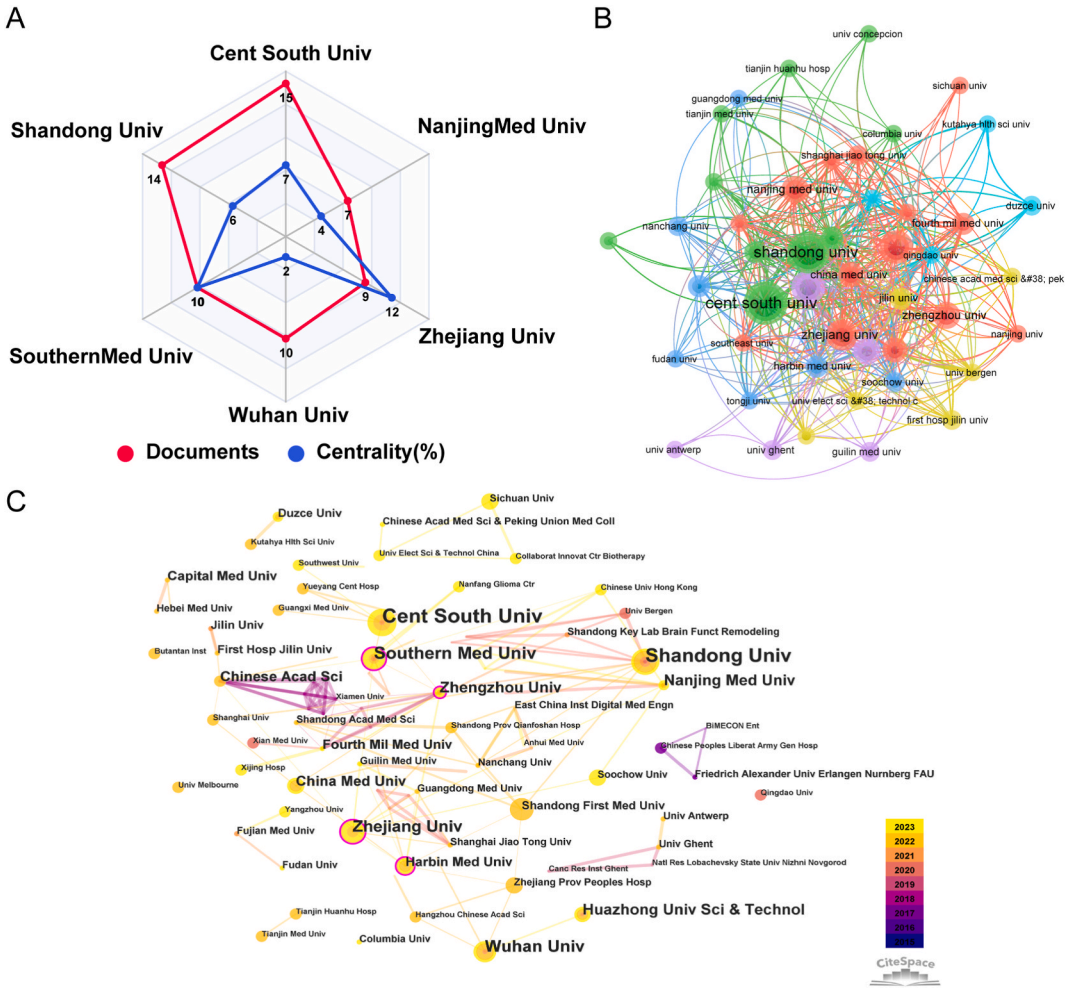

Fig. 4. Visualization Analysis of Institutions. (A) Radar chart created by R Studio, where the red line represents the number of publications, and the blue line represents the size of centrality (Centrality is derived from the Citespace and values represent its influence). (B) VOS visualization network displays 46 institutions, where the size of the circles represents the number of papers (a total of 325 institutions were involved, with a minimum threshold of 5 for clustering). The lines between the circles represent collaborations, and institutions within the same color cluster exhibit stronger collaborative relationships. (C) CiteSpace generated a visualization network map of institutions. Each node represents an institution, and its size is proportional to its publication output. The lines between the nodes represent collaborations, with thicker lines indicating closer collaborations. Different colors represent the publication year of the papers. The colors of the nodes and lines indicate different time intervals, with lighter colors representing more recent years. Nodes with high centrality (>0.1) are marked with a purple ring.

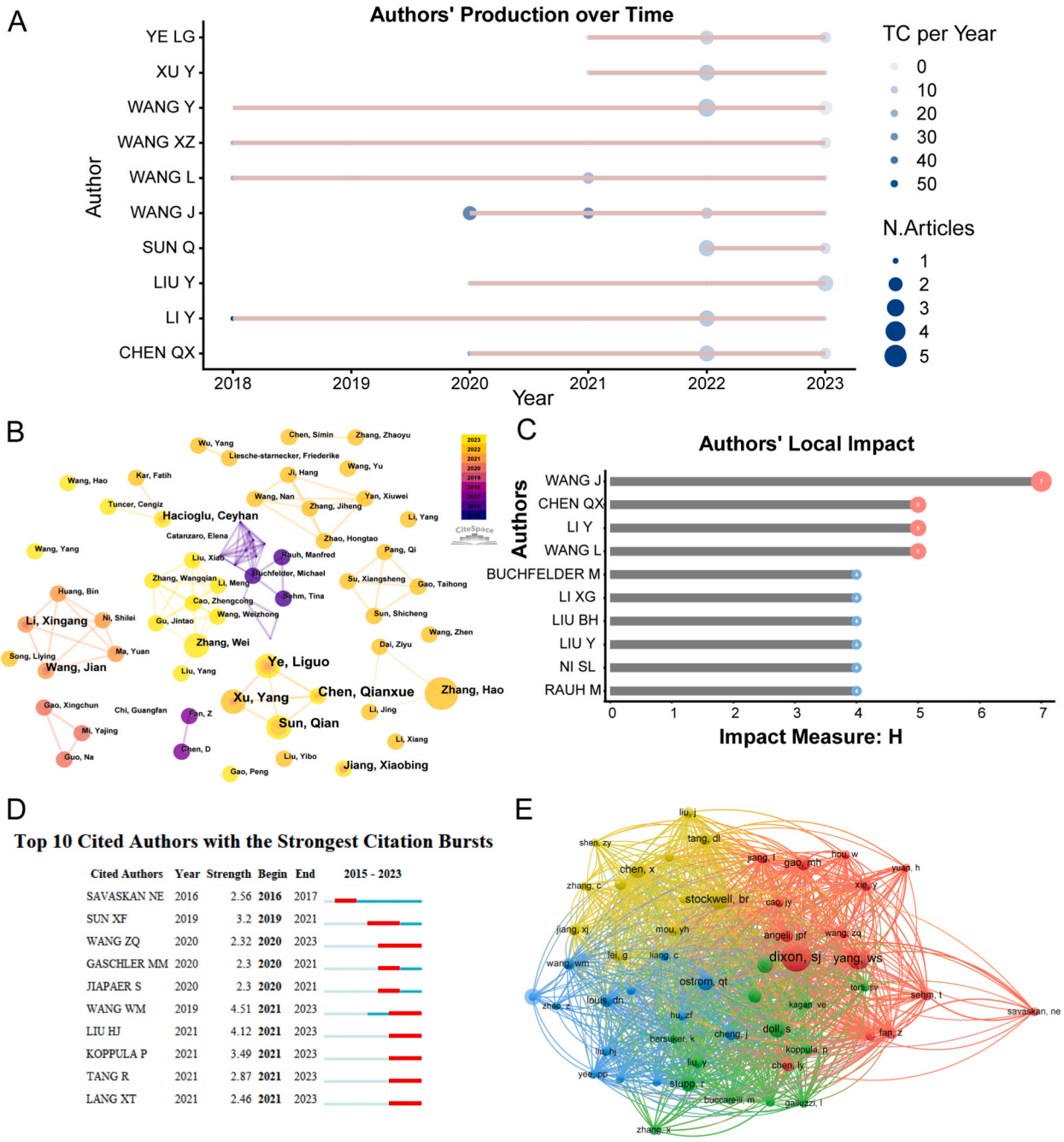

Fig. 5. Visualization of Author Productivity and Collaborations. (A) Visualization created by R Studio, where circles of different sizes represent the number of articles, and the color intensity of the circles represents the citation count. (B) CiteSpace software analysis generated a collaboration network among authors, with differently sized nodes representing their publication output, and the thickness of the lines indicating the level of collaboration between them, with color intensity representing transitions over time. (C) Visualization of author impact created by R Studio, measuring impact based on H-index. (D) CiteSpace software visualized the top 10 most highly cited authors based on citation burst intensity. "Begin" and "end" represent the start and end times of the mutation, respectively. "Strength" indicates the intensity of the keyword mutation, with higher intensity signifying greater impact. The blue line represents the time interval, while the red line indicates the time interval during which the keyword emergence occurs. (E) VOS software tool analyzed the co-citation network of authors, with different colors representing different clusters. The link density between two nodes indicates the co-citation relationship between authors.

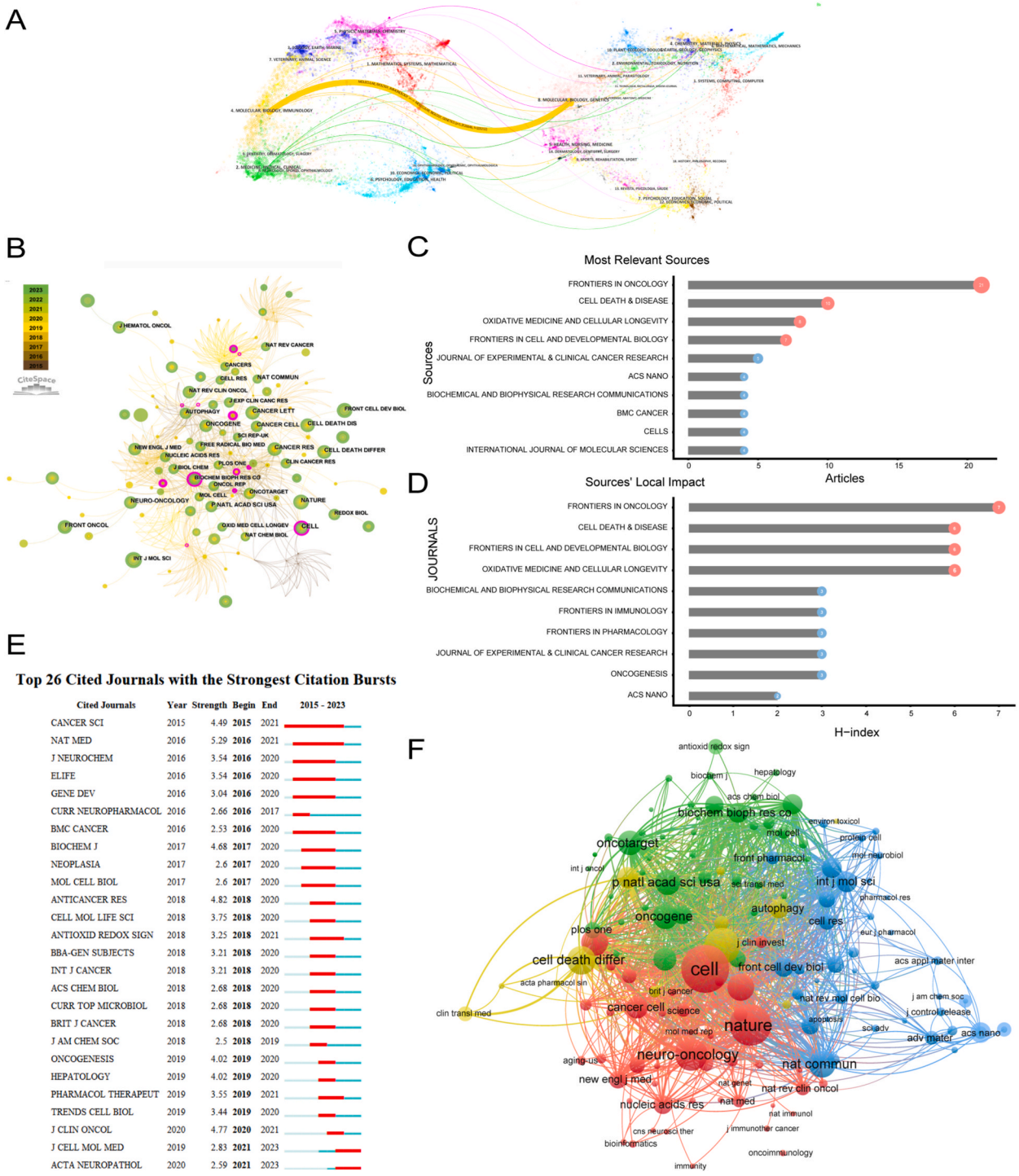

Fig. 6. Visualization of Journal Productivity and Collaborations. (A) Overlay map generated by CiteSpace, with the right side showing cited literature and the left side showing citing literature, connected by citation lines. The more papers a journal publishes, the more lines it has. Different colors represent different citation trajectories, with the thickness of trajectories proportional to citation frequency. (B) Collaboration network among journals generated by CiteSpace software, with differently sized nodes representing the publication output of journals, and the thickness of the lines indicating the level of collaboration between them, with color intensity representing transitions over time. (C) Visualization of journal productivity created by R Studio. (D) Visualization of journal impact created by R Studio, measured using the H-index as a standard. (E) CiteSpace software visualized the top 26 journals with the highest citation burst intensity. (F) VOS software tool analyzed the co-citation network of journals, with different colors representing different clusters. The link density between two nodes indicates the co-citation relationship between journals.

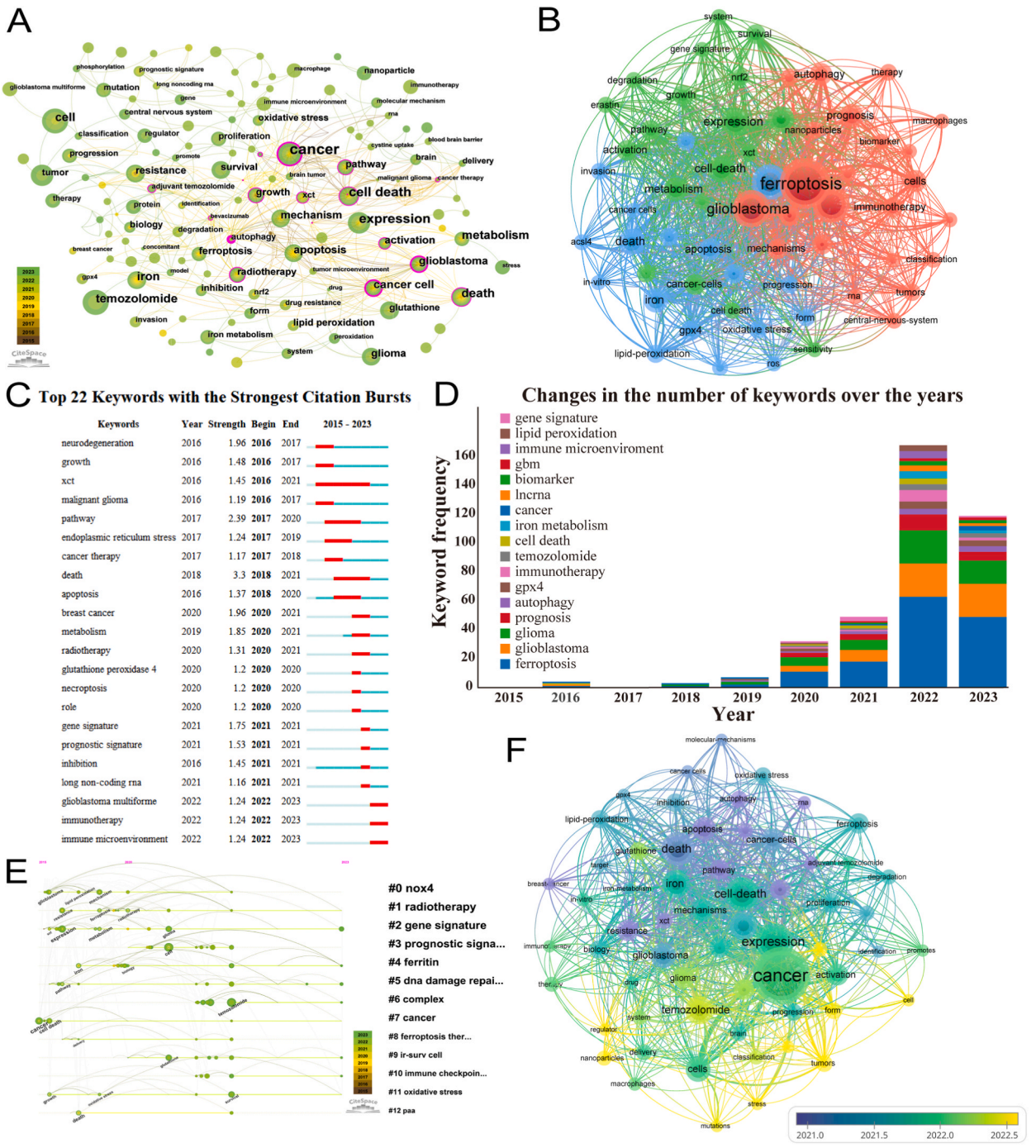

Fig. 7. Visualization Analysis of Bibliometrics for Keywords. (A) CiteSpace thematic network map illustrating keyword trends in research in this field from January 1, 2012, to December 31, 2023. Nodes with high centrality (>0.1) are marked with a purple ring. (B) VOS generated a visualization network map of keyword themes, categorizing different research fields by color. (C) CiteSpace software visualized the burst keywords with the strongest burst intensity among the top 22. (D) Time trend stacked bar chart visualizing the emergence of keywords at different times, with different colors representing different keywords. (E) In the CiteSpace timeline, we can observe the distribution of different keywords over time. Using software to cluster the included keywords by publication time with one year as a time zone, a timeline of keywords related to ferroptosis research in gliomas was generated. The same level indicates the same cluster, with the time getting closer as you move to the right. with cluster sizes arranged in descending order of labels, with the largest cluster at the top of the view. (F) VOS software visualizes different keywords in different time zones and domains, with lighter colors representing more recent times and darker colors representing past time domains.

in the research network (Fig. 4C). Southern Medical University, Zhejiang University, and Zhengzhou University occupy important positions in the collaborative network.

3.4. Analysis of core authors

Through visualizations generated using R studio, the number of articles published by the top ten authors from 2018 to 2023 and the total citation count per year reflect the intensity of academic activities and the importance of research outcomes in this field (Fig. 5A). It shows that Ye Li-Guo, Xu Yang, Chen Qian-Xue, and Sun Qian have the highest output, each with 6 articles, with a significant amount of output in 2022 (see Supplementary Table S4). The research output of Wang Jian and Ni Shi-Lei received the most citations in 2020, with their collaborative research published in Biomaterials introducing a novel biocompatible nanoformulation aimed at disrupting the redox balance of GBM cells, promoting concurrent apoptosis and ferroptosis. From the author collaboration network, it can be observed that the degree of collaboration among authors from different institutions is limited (Fig. 5B). Using the H-index as a benchmark, the breadth and depth of citations of these authors were quantified (Fig. 5C).

By using CiteSpace to explore the top 10 authors with the strongest burst strength in citations, we found that the burst strength of author Wang Zong-Qi reached 2.32, with the longest duration spanning from 2020 to 2023 (Fig. 5D). In his paper titled "Pseudolaric acid B triggers ferroptosis in glioma cells via activation of Nox4 and inhibition of xCT" published in Cancer Letters in 2018, he discussed how pseudolaric acid B (PAB) induces ferroptosis in glioma cells by activating Nox4 and inhibiting xCT, and the impact of this mechanism on the survival of glioma cells. This work not only deepens our understanding of the role of ferroptosis in glioma cell death but also provides potential molecular targets for the development of new therapies targeting gliomas. Additionally, in the analysis of the co-citation author relationship network, which encompasses 6691 co-cited authors, the research scope was further refined to 53 authors who have published at least 20 articles for in-depth analysis of academic contributions (Fig. 5E). In this cluster, Scott J. Dixon stands out with his 188 cited articles and a central linkage strength of up to 2031. His review article entitled "Ferroptosis: an iron-dependent form of nonapoptotic cell death" has been cited as many as 4983 times, emphasizing his pioneering contribution.

3.5. Distribution of journals

CiteSpace is used to analyze and display the distribution of papers, citation trajectories, and centroid drifts. We identified significant citation paths extending from "Molecular Biology, Immunology" to "Molecular Biology, Genetics" (Fig. 6A). With a Z-score of 5.352, this path is statistically significant and occupies a central position in scientific discourse. Then, we analyzed the scientific collaboration network of relevant research. We examined the patterns of collaboration and distribution of influence within this interdisciplinary research field (Fig. 6B), indicating that several high-impact journals such as *Nature*, *Cell* and *Journal of Hematology and Oncology* hold central positions in ferroptosis-related research. On the other hand, we identified several core journals by analyzing the publication sources, identifying the top 10 journals by publication numbers (see Supplementary Table S5). *Frontiers in Oncology* (IF 4.42) topped the productivity list with 21 related articles, followed by *Cell Death and Disease* (IF 9.0) with 10 related articles (Fig. 6C, Supplementary Fig. S1). The impact factors and SJR scores of these journals confirmed their authority and research quality in the academic community (see Supplementary Table S5). The citation counts of *ACS Nano* is as high as 406, followed by *Cell Death and Disease* cited 264 times and *Frontiers in Oncology* cited 228 times (see Supplementary Table S5). Through Citespace bibliometric analysis, *Frontiers in Oncology* stands again the first contributor to this filed. (Fig. 6D). Citation bursts typically refer to a sudden surge in the number of citations a journal receives within a specific period. Using CiteSpace software, we identified the top 26 journals ranked by citation burst (Fig. 6E). *Cancer Science* had the longest span from 2015 to 2021, with a burst intensity of 4.49. *Nature Medicine* had the highest burst intensity from 2016 to 2021 at 5.29.

In the visualization analysis generated by VOSviewer software of co-cited journals, there were a total of 1453 co-cited journals in this study, with 135 nodes included in the visualization analysis after setting a minimum citation count of 20 times. The map contains 135 nodes, 8748 links, and 4 clusters (Fig. 6F). Cluster 1, represented by the journal *Cell* is one of the top journals in the field of biology, typically publishing advanced research on cellular mechanisms, molecular biology, and disease-related studies. Cluster 2, represented by the journal *Oncogene* focuses on cancer research, possibly including studies on tumor cell proliferation, cancer genetics, and mutations and signaling pathways in GBM. Cluster 3, represented by the journal *Nature Communications* is an interdisciplinary journal covering a wide range of fields from basic science to clinical applications. Cluster 4, represented by the journal *Cell Death and Disease* focuses on how cell death pathways influence disease states and treatments, especially in cancer.

3.6. Analysis of keyword

We conducted in-depth visualization analysis using the CiteSpace and VOSviewer tools in the analysis of co-occurrence and emergence of keywords. Through CiteSpace analysis, we obtained a network graph displaying the co-occurrence of keywords (Fig. 7A). "cancer", "expression", "cell death", "metabolism", "cancer cell", "temozolomide" and "mechanism" are located at the core, forming a research network centered around tumor biology, cell death mechanisms, gene expression, and metabolic processes (see Supplementary Table S6, Supplementary Fig. S2). Further network analysis using VOSviewer refines these research themes by differentiating them with different-colored clusters (Fig. 7B). The red cluster focuses on the interaction between ferroptosis and glioma, highlighting in-depth exploration of autophagy, biomarkers, and the immune microenvironment. The green cluster focuses on tumor treatment and cell biology, particularly the application of chemotherapy drugs such as temozolomide. The blue cluster concentrates on the specific biological mechanisms of ferroptosis, including studies related to treatment resistance, lipid peroxidation, and oxidative stress.

Keyword emergence analysis is a useful method for discovering keywords that have received special attention within a specified period. The 22 keyword emergences revealed by CiteSpace's burst detection include "death", "xct" and "pathway" indicating the increased citation frequency of keywords related to cell death mechanisms, especially the metabolic regulation and signaling pathways involved in ferroptosis (Fig. 7C). Among these keywords, "death" has the highest burst intensity (reaching 3.3) and has received high citation frequencies from 2018 to 2021. The sustained burst of the keyword "xct" and its longest duration of citation from 2016 to 2021 further highlights the importance of studying the metabolic regulation and signaling pathways of the system xc-transporter in the process of ferroptosis. Newly emerging keywords starting in 2022 include "glioblastoma multiforme", "immunotherapy" and "immune microenvironment" indicating that pleomorphic GBM, immunotherapy, and the immune microenvironment will become research focuses in this field. The time trend stacked bar plot displays the increasing frequency trends of keywords such as "ferroptosis", "lncRNA", "biomarker", "gbm", "gene signature" and "lipid peroxidation" since 2015 (Fig. 7D). In Fig. 7E and F, we observed that keywords "cell death", "ferroptosis", "glioblastoma", "iron" and "temozolomide" occupy central positions in the network and exhibit temporal shifts.

To validate these visualizations, we manually screened and selected 198 original research articles, excluding reviews and pure bioinformatics studies, and identified 195 experimentally validated genes, 3 glioma subtypes, and 77 drugs (see Supplementary Table S5). Using the gprofiler tool (https://biit.cs.ut.ee//gost) for pathway analysis, we assessed these genes within the Kyoto Encyclopedia of Genes and Genomes (KEGG) and WikiPathways (WP) databases. Key genes (with frequency $\geq$3), including GPX4, SLC7A11, NFE2L2, ACSL4, FTH1, HMOX1, TP53, BECN1, KEAP1, NCOA4, PTGS2, ATF4, HSPB1, ALDH1A3, CD44, FTL, MAP1LC3B, and MTOR, were identified (see Supplementary Table S6). Additionally, Key drugs (with frequency $\geq$4), including Erastin, Ferrostatin-1, Temozolomide, RSL3, Liproxstatin-1, Sulfasalazine, Dihydroartemisinin, and Sorafenib, were selected (see Supplementary Table S6). The top five KEGG pathways involved were Ferroptosis, Lipid and atherosclerosis, HIF-1 signaling pathway, Shigellosis, and PD-L1/PD-1 checkpoint pathway in cancer, while the top WikiPathways were Ferroptosis, Oxidative stress response, Autophagy in pancreatic ductal adenocarcinoma, Urotensin II mediated signaling pathway etc. (see Supplementary Table S7). These pathways capture key aspects of ferroptosis and glioma, mirroring the research themes identified in the CiteSpace and VOSviewer visualizations. They highlight crucial genes like GPX4, SLC7A11, and NFE2L2, with pathways such as Ferroptosis, Lipid and atherosclerosis, and HIF-1 signaling reflecting essential areas of cell death, metabolic dysregulation, and immune response.

3.7. Prominent cited and co-cited references

Highly cited articles typically represent high-quality, innovative research with substantial impact. Fig. 8A shows 15 clusters of cited references, with 376 nodes and 720 connections between them (Fig. 8A). Labels reveal the main research directions, covering a wide range of topics from molecular mechanisms to potential therapeutic strategies. According to VOS visualization analysis, the 225 selected articles were divided into 7 clusters (Fig. 8B). The work of Shen(2018) published in *ACS NANO* was cited 393 times, followed by Fan(2017) for 367 times, Chen(2017) for 234 times and Ye(2020) for 221 times. Emergent literature analysis refers to node literature where citation suddenly changes, which typically represents the emergence or transformation of a research field. Through CiteSpace, we found that the article "Erastin sensitizes GBM cells to temozolomide by restraining xCT and cystathionine-γ-lyase function" by Chen(2015) had the longest citation span from 2016 to 2020, and the article "Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease" by Stockwell(2017) had the highest citation intensity from 2020 to 2021, reaching 6.31 (Fig. 8C). Co-citation analysis refers to articles appearing together in the reference list of a third citing article, forming a co-citation relationship between these articles (Fig. 8D). Among 8284 cited articles, with a minimum citation frequency set at 20, they can be divided into 38 clusters. We found that the most frequently co-cited reference is the article by Dixon SJ in 2012, co-cited 127 times, with a total link strength of 749. In the CiteSpace timeline graph, we can observe the distribution of literature with different research field labels over time (Fig. 8E). The continued and expanded research on "ferroptosis therapy" indicates the increasing understanding and emphasis of the scientific community on the role of ferroptosis in treating GBM.

4. Discussion

The normal function of the central nervous system is closely related to the balance of trace elements such as iron, selenium, copper, and zinc. These trace elements play important roles in antioxidant defense mechanisms, enzyme activity regulation, and neurotransmission. For example, selenium, by regulating redox homeostasis and enhancing selenoprotein expression, exhibits antioxidant and anticancer properties in gliomas [14,15]. Copper synergistically enhances cytotoxicity with disulfiram in temozolomide-resistant GBM [16,17]. Excessive accumulation of iron elements within cells can lead to iron-dependent lipid peroxidation, thereby promoting ferroptosis [18]. In recent years, numerous studies have focused on the role of ferroptosis in the occurrence, development, and treatment of gliomas. Representative studies have shown that the primary activated programmed cell death (PCD) during glioma progression, ferroptosis is associated with malignant characteristics of tumors, poor prognosis, and an immunosuppressive microenvironment. Inhibiting ferroptosis can improve the efficacy of immune checkpoint blockade (ICB) therapy by reshaping the immunosuppressive microenvironment [19]. These findings highlight the urgent need for bibliometric analysis to reveal research trends and assess research impact, thereby improving academic research efficiency.

In the bibliometric analysis and network visualization of this study, we comprehensively analyzed 225 studies on ferroptosis in gliomas over the past decade. These studies covered 28 countries, involving 1625 authors and 325 institutions, published in 126 journals, and presented 554 keywords. The number of related studies has undergone significant exponential growth. China, the United States, and Germany have made the most significant contributions to research in this field, accounting for 76.2 % of the total research

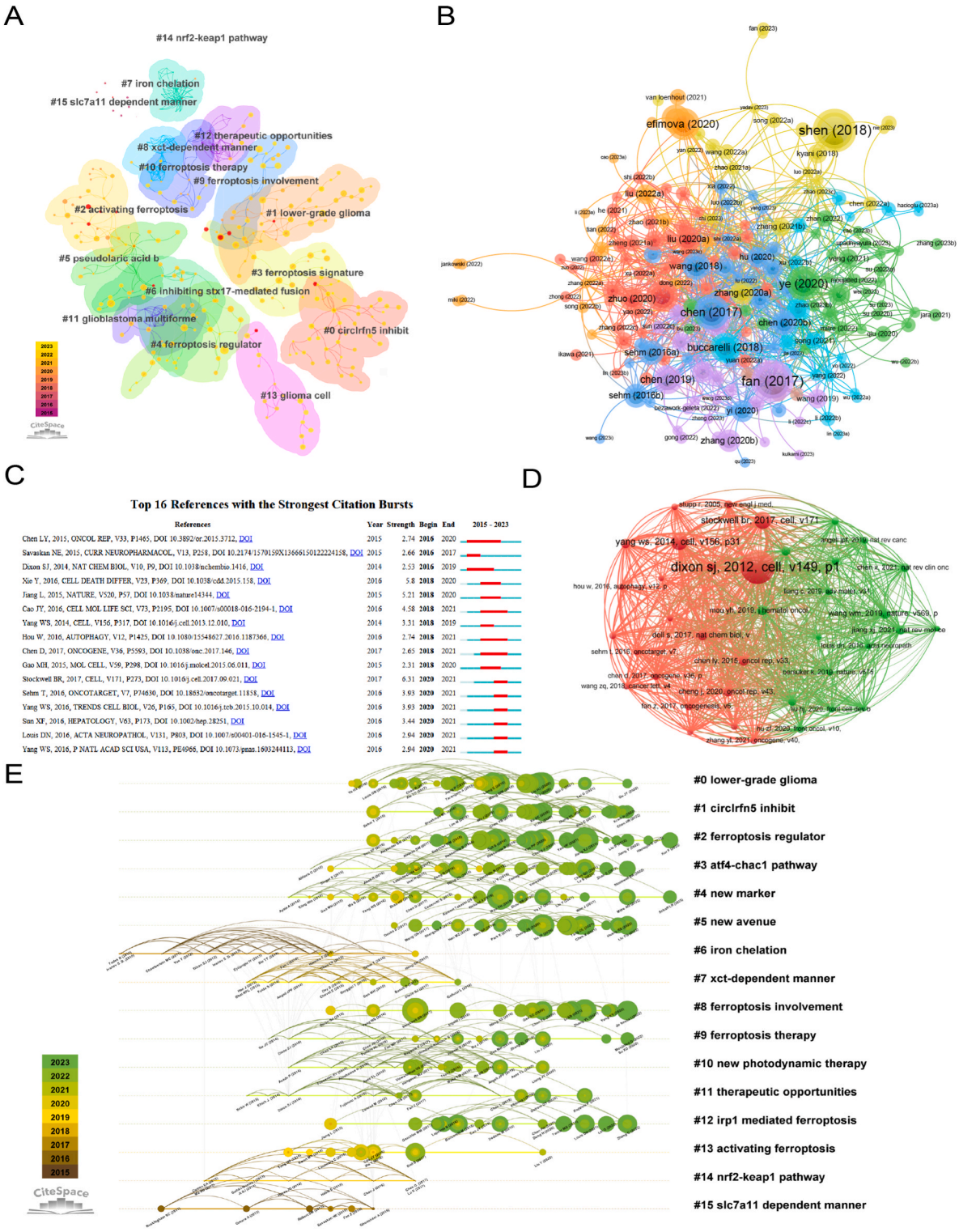

Fig. 8. Visual Analysis of Cited and Co-cited References. (A) Cluster Analysis: CiteSpace analyzes the results of co-cited document clustering. Clustering refers to the interconnected network clusters formed by research topics with similar themes within the field. Clusters are labeled sequentially starting from 0, with smaller numbers indicating clusters containing more documents. This network contains 15 clusters (#0-#14) with 376 nodes (Number of circles) and 720 links between nodes. (B) VOS visualizes literature analysis, where node size represents the frequency of citations and link strength represents citation intensity. (C) The top 25 documents exhibit the most significant co-citation bursts. Co-citation burst strength is a metric quantifying the intensity during a burst period. Higher strength values indicate a more significant increase in citations over a

short period, suggesting greater influence in the field during that time. (D) VOS visualizes co-cited literature analysis, where node size represents the frequency of co-citation and link strength represents citation intensity. (E) CiteSpace timeline visualization. Beneath each timeline are the most cited documents for that year.

volume. Among them, Central South University, Shandong University, and Zhejiang University are leading in literature output and research cooperation. Researchers such as Xu, Yang, Ye Li-Guo, Chen Qian-Xue, and Sun Qian lead in literature output, while the research results of Wang Jian and Ni Shi-Lei in 2020 have been widely cited. In terms of journal publications, *Frontiers in Oncology* has the highest output, covering a wide range of topics from molecular mechanisms to potential therapeutic strategies, focusing on three major research hotspots: prognostic markers, molecular mechanisms, and treatment strategies. Prognostic studies emphasize gene signatures and prognostic signatures. Molecular mechanism studies reveal the core roles of iron metabolism, lipid peroxidation, xCT, autophagy, and the immune microenvironment in gliomas, particularly reflected in the high expression of ferroptosis-regulating factors such as ACSL3, HSPB1, ELAVL1, IL33, and GPX4 in glioma tumor cells, which further confirms their value as prognostic biomarkers. Keyword analysis shows that tumor biology, mechanisms of cell death, gene expression, and metabolic processes are hot topics in current research. Glioblastoma, a highly fatal malignant brain tumor, has attracted significant attention in the oncology field as researchers actively explore new therapeutic methods to improve patient prognosis [20]. Recent studies have confirmed that ferroptosis is a promising cancer therapy, primarily inducing cancer cell death by promoting the Fenton reaction and accelerating the production of reactive oxygen species [21]. In-depth studies of the ferroptosis mechanism have identified several potential therapeutic targets. For example, ACSL4 inhibits the proliferation of glioblastoma cells by activating ferroptosis [22]. Targeting these molecules can effectively induce ferroptosis in glioblastoma cells, thereby inhibiting tumor growth and metastasis. Additionally, fatty acid metabolism during the ferroptosis process plays a crucial role in glioblastoma development. Glioblastoma cells prevent ferroptosis through lipid ROS scavengers such as GPX4 and FSP1 [23]. Our findings support this by identifying key genes (GPX4, SLC7A11, NFE2L2, ACSL4, FTH1, HMOX1, TP53, BECN1, KEAP1, and others) and essential pathways—Ferroptosis, Lipid and atherosclerosis, and HIF-1 signaling—through pathway analysis, which aligns with core cellular functions like cell death, metabolic dysregulation, and immune response. Furthermore, treatment strategies aimed at ferroptosis, including temozolomide, radiotherapy, and immunotherapy, show potential to improve glioma outcomes by targeting these mechanisms to induce ferroptosis in tumor cells, as highlighted by high-frequency drugs such as Erastin, Ferrostatin-1, and RSL3. This multi-faceted approach underscores the promise of ferroptosis-based therapies in glioma treatment strategies.

Research on prognostic markers for gliomas is one of the core elements in this field of study. Some researchers have pointed out that there is still an urgent need to develop predictive biomarkers for tumor ferroptosis induction, which would be necessary tools for stratified treatment of cancer patients [24]. According to studies, a risk score has been proposed based on 25 ferroptosis-related genes associated with glioma pathological characteristics, which can independently predict the prognosis of glioma patients [7]. Recent research indicates that the identification of ferroptosis biomarkers may help glioma patients achieve better outcomes [25]. Based on survival analysis, a team has identified ACSL3, HSPB1, ELAVL1, IL33, and GPX4 as five ferroptosis regulatory factors to serve as prognostic biomarkers, and their effectiveness has been validated using external datasets [26]. Thus, research on prognostic markers for gliomas has become one of the hot topics in this field.

The molecular mechanisms of ferroptosis in gliomas are another core element of this research area. Studies in the past decade have shown that ferroptosis is a crossroads of metabolism, ROS biology, and iron regulation, serving as a tumor suppression mechanism, but the loss of ferroptosis can also drive tumor occurrence [18]. Consistent with previous literature reports, keyword co-occurrence network analysis revealed that ferroptosis mainly acts through iron metabolism, lipid peroxidation, and the xCT-GPX4 pathway in the occurrence and prognosis of gliomas [27]. Recent studies have found that inhibiting the expression of the COPZ1 or TRIM7 genes *in vitro* and *in vivo* can suppress tumor growth by inducing NCOA4 expression and promoting ferritin autophagy, thereby increasing intracellular labile iron levels and ultimately leading to ferroptosis [28,29]. The latest research indicates that the FHOD1-HSPB1 axis plays a significant regulatory role in ferroptosis in gliomas, where downregulating FHOD1 enhances glioma cell sensitivity to iron apoptosis by upregulating heat shock protein B1 (HSPB1). Overexpression of HSPB1 can significantly reverse FHOD1 knockdown-mediated ferroptosis [30].

Recent studies suggest that combining ferroptosis-based therapies with other treatment modalities may be an effective strategy to improve glioma treatment [31]. Based on bibliometric visualization analysis, traditional Chinese medicine treatment, immunotherapy, and chemotherapy resistance in the treatment of GBM were reported. Natural plant extracts are a promising treatment method widely applicable to various cancers, especially in GBM [25]. For example, artemisinin extracts and its derivative dihydroartemisinin (DHA) counteract GBM through multiple pathways. Studies have found that DHA induces ferroptosis by downregulating glutathione peroxidase 4 (GPX4), leading to lipid ROS accumulation [32]. Additionally, inhibiting endoplasmic reticulum stress or the PERK-ATF4-HSPA5-GPX4 pathway to increase ferroptosis in gliomas enhances DHA's anticancer activity [33]. It is well known that the therapeutic challenges in GBM partly stem from its highly heterogeneous, immunosuppressive, and metabolically stressful tumor microenvironment (TME). Modulating immune cells in the TME through ferroptosis can promote crosstalk between glioma cells and immune cells, opening new avenues for glioma immunotherapy [19,29]. Furthermore, the immunosuppressive microenvironment is a major cause of immunotherapy resistance in GBM. Inhibiting ferroptosis significantly reconstructs the immunosuppressive microenvironment, enhancing the efficacy of immune checkpoint blockade (ICB) [19]. Additionally, resistance to temozolomide (TMZ) is a major reason for poor prognosis in GBM multiforme [34]. The cell death mechanism driven by TMZ is unrelated to ferroptosis, but it can improve TMZ efficacy by inducing ferroptosis [35,36]. The expression level of Xct in gliomas affects the efficacy of TMZ, and when combined with the ferroptosis inducer erastin, the efficacy of TMZ can be further enhanced [37]. Furthermore, cysteine deprivation

and methionine-restricted diets can synergize with the GPX4 inhibitor RSL3 to increase ferroptosis, prolonging the survival of GBM patients, emphasizing the potential of dietary changes to enhance ferroptosis therapy in glioma treatment [38]. Thus, the combination of ferroptosis induction with other treatment modalities shows clinical potential in the field of GBM treatment.

As we have previously highlighted, ferroptosis as a therapeutic target faces several challenges, such as the blood-brain barrier, toxicity, and off-target effects [31]. Addressing these challenges will require the application of advanced research methods or therapeutic strategies. Notably, the key molecules regulating ferroptosis, such as ACSL4, GPX4, and SLC7A11, remain incompletely understood in the context of gliomas, necessitating further investigation into their specific roles in tumor progression. Moreover, gene editing technologies and small molecule inhibitors could be leveraged to develop more precise therapeutic targets. With the increasing need for personalized treatment, research should also aim to identify glioma subtypes that are sensitive to ferroptosis modulators, facilitating tailored therapeutic approaches. Furthermore, while prognostic biomarkers associated with ferroptosis, such as ACSL3, HSPB1, ELAVL1, and IL33, demonstrate considerable promise, their validation in clinical practice is essential to confirm their significance as meaningful biomarkers. Finally, the challenges of drug resistance and the long-term efficacy of ferroptosis-based treatments require deeper exploration to identify resistance mechanisms and devise strategies to overcome them. In summary, addressing these biological and technical challenges will be key to advancing ferroptosis as a viable treatment option for gliomas.

This study provides a comprehensive and multidimensional visual perspective on the publication research of ferroptosis in glioma treatment, summarizing and analyzing the expression, prognosis, mechanisms, and therapeutic applications of ferroptosis-related molecules in gliomas. Although this study provides insights into the development and key trends in this research field using bibliometric analysis, there are some limitations. Firstly, this study only included English publications in the WOSCC core collection, potentially missing publications from other databases and languages. Secondly, due to limitations of software such as CiteSpace and VOSviewer, there may be differences in keyword occurrence and clustering analysis. Despite these limitations, this study emphasizes the important role of the ferroptosis pathway in glioma research, particularly in exploring new treatment strategies and understanding the application potential in tumor biology. The research hotspots and trends revealed by bibliometric analysis provide valuable information for future research directions.

5. Conclusion

This paper comprehensively examines the research progress of ferroptosis mechanisms in the field of glioma treatment through bibliometric analysis methods, providing a comprehensive perspective on the study of ferroptosis in glioma treatment, identifying research hotspots, key trends, and potential therapeutic opportunities. The increasing research on "ferroptosis therapy" indicates a growing recognition and emphasis within the scientific community on the role of ferroptosis in treating gliomas. In summary, the literature included in the analysis has shifted from focusing on prognosis and mechanistic pathways to combining ferroptosis with other treatment strategies. Through innovative interdisciplinary approaches such as nanomedicine, the integration of immunotherapy and overcoming drug resistance, efforts are being made to tackle this challenging tumor.

CRediT authorship contribution statement

Xinyue Zheng: Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Mengyao Diao:** Writing – original draft, Software, Resources, Data curation. **Shan Tong:** Software, Resources, Funding acquisition, Formal analysis, Data curation. **Shuo Yang:** Software, Resources. **Jing Lin:** Visualization, Resources. **Shenghua Zhuo:** Visualization, Validation. **Ting Wang:** Visualization, Formal analysis. **Jian Dai:** Validation, Supervision. **Shenbo Chen:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Kai Wang:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

Data availability statement

Data included in the article is referenced in the article.

Ethical statement

This study does not involve any human or animal subjects, and it is in accordance with research ethical standards.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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Appendix A. Supplementary data

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