A bibliometric analysis of immunotherapy in glioblastoma

· Authors' names:

Wei Li [1,2,#], Ruimin Guo[1,2,#] , Rongrong Zhang [3,#], Guojia Wu[2], Runzhe Chen[2], Dong Wang [1,*]

· Authors' affiliations:

[1]Department of Neurosurgery, Tianjin Medical University General Hospital; Tianjin Key Laboratory of Injuries, Variations, and Regeneration of Nervous System; Tianjin Neurological Institute; No.154 Anshan Road, Tianjin, China;

[2]Graduate School, Tianjin Medical University, Tianjin Medical University, Tianjin 300070, China.

[3] Department of Stomatology, The First Affiliated Hospital of Nanchang University, Nanchang, China

[4]Medical College, Nanchang University, Nanchang, China

# These authors are first author

· Corresponding author:

Dong Wang, Department of Neurosurgery, Tianjin Medical University, General Hospital; Tianjin Key Laboratory of Injuries, Variations, and Regeneration of Nervous System; Tianjin Neurological Institute; No.154 Anshan Road, Tianjin, China; E-mail address: zdongwang@tmu.edu.cn;

Keyword: Glioblastoma, Bibliometric analysis, Immunotherapy

Abstract

Background The glioblastoma (GBM) is a type of cancer of the nervous system that has a high mortality rate. The tumor microenvironment (TME) is complicated and flexible, and immunotherapy is often used to alter the microenvironment. Researchers are exploring ways to boost survival through immunotherapy. There is, however, a lack of comprehensive trend analysis. An analysis of bibliometrics can provide insight into this problem by visualizing research patterns. A study was conducted to map these trends between 2005 and 2024 in GBM immunotherapy.

MethodsWithin the Web of Science Core Collection, spanning 2005 to 2024, an immunotherapy search was conducted on GBM. This search provides an insight into the current state of research in this field, despite its narrow focus. The following software programs were used for the bibliometric analysis: VOS viewer, Cite space, Scimago Graphica, and R-software.

Results A total of 2064 publications have been published in this field between 2005 and 2024, most of them coming from China and the United States. According to co-citation counts, Roger Stupp is the most valuable contributing author. Frontiers in Oncology holds the top publication volume spot. The clinical community has a keen interest in researching nivolumab and chemotherapy, as seen by keyword burst analysis, which suggests that neoadjuvant immunotherapy represents a promising therapeutic avenue in the future.

Conclusions This study summarized current trends in immunotherapy aspects of GBM and the research frontiers. As a useful reference and source of new insight into this area of research, this summary can be very valuable.

1 Background

In adults, glioblastoma (GBM) is most commonly a neurogenic tumor originating from normal glial cells[1]. Patients generally survive between 12 and 14 months, with a 5-year survival rate of less than 5%[2]. To increase survival rates, many therapeutic approaches have been explored and refined. GBM is currently treated with surgery, which aims to remove the primary tumor while preserving function[3].Despite this, it remains challenging to accurately define the margins of excision for given lesions. Excessive excision can adversely affect a patient's quality of life following surgery. Hence, radiotherapy and temozolomide are often used in conjunction with this approach, despite radiotherapy having some limitations and damaging normal brain tissue in the surrounding areas[4, 5]. There are a number of adverse effects associated with temozolomide, including physical discomfort, profound psychological effects and resistance[6, 7].

The advancement of research indicates that neoadjuvant immunotherapy may be a more effective treatment[8, 9].For patients who cannot undergo radical surgery or radiotherapy, immunotherapy has been proposed[10].A number of studies have demonstrated that immune checkpoints (e.g. PD-1, CTLA-4) can be used to treat tumors[11]. Approaches can be developed by combining immune checkpoint blockade therapies[12]. In light of this, finding new therapeutic targets for GBM that are both high-specificity and high-sensitivity is a very important research direction.

An imbalance in the immune system can also cause cancer due to mutations in cancer cells. There has been a preference for focusing on cancer cells over immune cells, with a common approach of targeting cancer cells directly rather than addressing the cause or preventing recurrences[13].A more effective immunotherapy would benefit from enhancing its effects within the tumor microenvironment (TME), which contains immune cells, microglia, and the extracellular matrix[14]. In spite of the fact that the relationship between immune checkpoints and glioma is not fully understood and some patients do not respond well to immune-checkpoint blockade (ICB) therapy, it is vital to discover new targets and understand their mechanisms within the TME in order to provide a more targeted treatment[15].

The literature summaries that have explored the immune link to GBM are often poorly organized, lacking a coherent understanding of immunotherapy's role and benefits. Although neoadjuvant immunotherapy has been evaluated in numerous clinical trials, it is still not preferred. This may be due to several factors: immunotherapy is poorly understood, it isn't a major focus of research, or it has not yet demonstrated comparable effectiveness to traditional treatment[15]. It is therefore difficult to find comprehensive articles in this area and robust data about research hotspots and trends. The use of bibliometrics, a useful method for analysis and

induction, can aid in uncovering the academic development network and hotspots quickly.

The use of CiteSpace, VOSviewer, and other relevant tools is used to categorize extensive datasets, which include institutional affiliations, authorship, introductions, geographical origins, journals, and other relevant factors. Using this method, contributions can be evaluated objectively as well as emerging research trends within the field can be predicted. An analysis of bibliometrics is conducted on GBM and immunotherapy research from 2005 to 2024 for this study. Using this approach, the study distribution can be mapped, hotspots can be identified, future trends can be predicted, and the research platform can be developed[16, 17].

2.Methods:

2.1 Data collection

Web of Science Core Collection is a citation-type database, containing citation information in addition to literature abstracts, unlike PubMed, which is typically an abstract-type database. It is true that Scopus and WOS cover mainly natural sciences, engineering, and biomedical research, but Scopus is superior to WOS when it comes to covering aspects of the social sciences and humanities. It is, however, WOS that is most commonly used for statistical analysis[18-20]. There is a possibility that WOS does not include all relevant publications, leading to bibliometric studies being omitted[21]. In addition to its ability to identify reviews or articles that meet specific criteria, it also contains a vast body of scientific literature across a broad range of subject areas[22]. The restrictions are as follows: Topic = (“glioblastoma” OR “GBM”) and (“immunotherapy” OR “immune checkpoint” OR “Chimeric Antigen Receptor-T cell” OR “PD-1/PD-L1”). The search spanned from 2005 to 2024. A total of 2077 results were found, containing articles and reviews. A total of 2064 English-language articles were exported after screening. This figure illustrates how to screen the resulting table and export the data (Fig. 1 and Table 1).

2.2 Data analysis and visualization

A variety of tools were employed for data analysis and visualization of the results, including VOSviewer(1.6.20.0), CiteSpace(6.3.1.0), Scimago Graphica(1.0.42.0) and Microsoft Excel 2021. Using VOSviewer, one can examine the characteristics of a scientific field from a variety of perspectives, including publications, countries, authors, journals, references, and so forth[23]. It is possible to generate three kinds of graphs by importing paper data: network visualization graphs, overlay graphs, and density visualization graphs[24]. The most detailed analysis is the network visualization graph, where all the data is clustered using an algorithm and colored differently. Clusters consist of distinct nodes corresponding to parameters such as country/region, institution, journal, author, or keyword. It is possible to measure the strength of associations between different parameters by measuring the size of nodes, while the thickness of lines indicates the strength of citations between parameters[25]. Using CiteSpace, another Java-based visualization tool, occurrence citations can be

visualized and web maps can be displayed[26]. The keyword outbreak map, in particular, facilitates rapid recognition of sudden increases in scientific activity as well as trend analysis by highlighting temporal and quantitative distributions of keyword trends[27]. Using Scimago Graphica, we visualized the number of publications and collaborations between countries across different countries[28]. Collectively, each tool contributed to this study in a specific way. Using Lockhart's theorem, we can investigate the research forces and representative scholars in this field through an analysis of the authors of the literature. (I= N_{max} is the number of papers written by the most productive author/documents/citation in the field, N is the total number of authors,m is the minimum number of papers published by the core author)

$$\sum_{m+1}^{I} n(x) = \sqrt{N}$$

Results:

3.1 World publication trends

The WOS database contains 2064 documents on immunotherapy studies of GBM between 2005 and 2024, including 1252 articles and 812 reviews. In order to illustrate the number of publications over time, a time-series graph was showed (Fig. 2). During the period 2005-2009, more than 20 documents were filed. From 2010 to 2016, the number fluctuated between upper and lower 60 each year. It is estimated that over 100 publications were published after 2017, with a notable increase of over 70 publications in 2021. Based on the fitted regression line formula, it appears this trend is well-fitted. There is a cyclical fluctuation every 5–6 years, with an overall upward trend. This field's publication numbers fluctuate significantly every five to six years and grow steadily within a certain range based on a superficial analysis of the data. The majority of these 2064 articles were published within the past 4 years, with 53.8%.

3.2 International contributions by countries and institutions analyses

There were documents from 54 countries and 1297 institutions. In terms of the number of documents with thirty or more, China and America dominated the top ten, followed by Europe. United States led with 462 publications, China followed by the (n = 264), Germany (n = 69), Italy (n =53), and Iran (n = 34). United States publications are of higher quality as they have published more articles and are cited more frequently (average citation = 66.37). The average number of citations per article was much lower for China than for Occidental countries in the second position, with 7,531 and 3,712 citations, respectively. Occidental countries, such as Switzerland (average citation = 78.66), Canada (average citation = 66.92), the United Kingdom (average citation = 60.37), and Australia (average citation = 54.90), have a higher

average number of citations per article (Fig. 3a). There is evidence that the quality of articles published in Asia may need improvement, whereas European countries produce more sophisticated and influential studies in this field, providing scholars with a wealth of knowledge. This phenomenon may be caused by state funding constraints and the absence of universal screenings for glioblastoma. In order to illustrate the intersections between these countries, we have presented a linking circle diagram (Fig. 3b). A visual map shows that the United States of America is centered, significantly interconnected with China, indicating that both countries have made substantial contributions to the development of this field. Meanwhile, the United States of America has the most extensive collaborative efforts, particularly with China, Canada, Germany, and Switzerland (Fig. 3c). The most research studies in this field were conducted at Capital Medical University, while Duke University received the most citations (Fig. 3d).

3.3 Author and co-cited author analyses

There were 5,755 authors who contributed to the 1274 immunity studies on glioblastoma, with 27 core authors who published ≥ 7 documents (Fig. 4a). Michael Lim (n=29), John H Sampson (n=28) and Amy B Heimberger (n=20) were the most prolific authors. According to the citation statistics, Michael Lim has 29 publications and 3097 citations, with an average of 42 citations per article. It indicates significant impact and influence in the field that Behnam Badie has the highest average number of citations per article, with 2265 citations from only seven papers (Fig. 4a). A VOS viewer was used to visualize the relationships between authors with ≥ 7 publications, revealing 6 clusters and 52 links. The network is centered on John H Sampson and David A Reardon, with both working closely together. (Fig. 4b). The research they conducted is, however, limited to 2015-2018, and it is not considered new (Fig. 4c). The field has 27,628 co-cited authors, filtered to include those with at least 40 publications. Roger Stupp (n = 786) and David A Reardon (n = 629) were the authors with the most co-citations (Fig. 4d).

3.4 Journal and co-cited journal analysis

A total of 2064 publications were published on immunotherapy for GBM. Frontiers in Oncology (n = 59), Cancers (n = 49), and Frontiers in Immunology (n = 40) were the top three journals. In terms of impact factor, Frontiers in Immunology (IF = 7.3) was the best journal, followed by Oncology (IF = 2.5) (Fig. 5a). The correlation visualizations for 63 journals with ≥4 publications revealed that Frontiers in Oncology has the strongest relationship with Journal of Neuro-oncology and Cancers (Fig. 5b). Based on the time-series graph, it appears that the most recent studies have been published in Journal for immunotherapy of cancer (Fig. 5b). As shown in Fig. 5c, among the 3,929 co-cited journals, two were cited more than 4000 times: Neuro-oncology (4,464 times) and Clinical cancer research (4,443 times).

Among the top 10 co-cited journals, Nature (IF = 64.8) and Cell (IF = 64.5) have the highest impact factors. Three clusters are visible in co-citation network graphs based on 33 journals with a minimum citation count of 300. Co-citations between Frontiers in immunology and Journal of neuro-oncology, Cancers, neuro-oncology are positive. (Fig. 5d).

3.5 Analysis of commonly cited references

Over the last 20 years, there have been 40,617 co-cited references on GBM immunotherapy studies. The most frequently cited article is “Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma” by Roger Stupp, with 329 citations. Published in NEJM: The New England Journal of Medicine, with an impact factor of 96.3, it leads the list [29]. Additionally, two other references comprising ≥ 200 citations include “A single dose of peripherally infused EGFR VIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma” (n = 241) by Donald M O'Rourke and “Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy”(n = 237) by Christine E Brown, published in Science Translational Medicine and the New England Journal of Medicine , respectively [30, 31]. Furthermore, the graph shows that most of the highly cited studies were published between 2011 and 2016 (Fig. 6a). References with ≥ 90 citations were visualized for correlation using VOSviewer. The visualization shows that “Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma” by Roger Stupp exhibited a positive co-citation relationship with“Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy”(n = 237) by Christine E Brown (Fig. 6b).

3.6 Keyword analysis

The keywords in a paper convey the essence of the paper, and their co-occurrence can pinpoint research hotspots[32]. Using VOSviewer, 1124 documents were analyzed to generate a network view of keyword co-occurrences. The results show that 3,604 keywords were identified, with 44 (⩾ 40 occurrences) selected for visualization (Fig. 7a). Keywords such as "immunotherapy," "glioblastoma," and "glioma" are frequently used in research. Red, green, and blue clusters represent distinct directions of research on the map. The red cluster addresses the treatment method of glioblastoma, including terms such as temozolomide, radiotherapy, nivolumab, immunosuppression, and nivolumab. This blue cluster emphasizes "T-cells," incorporating keywords such as "growth factor receptor," "dendritic cell," "stem cell," and "chimeric antigen receptor," highlighting research on T-cell function in glioblastoma. A green cluster, on the other hand, focuses on "tumor," with keywords like "brain tumor", "high-grade glioma," highlighting the type of brain tumor. Recent years have seen increased research focus on improving T-cells as well as immune checkpoint inhibitors. During a specific time period, a keyword outbreak

indicates an increase in citations for that term. In the analysis, it is revealed that there has been a shift towards immunotherapies like nivolumab. The following research hotspots are likely to continue to be important in GBM immunotherapy after 2017 (Fig. 7b).

4 Discussion

This research gathered 2064 publications focused on immune research in glioblastoma from the Web of Science (WOS), spanning from 2005 to 2024. Regarding temporal patterns, the number of publications in this field has greatly increased since 2016. Four primary types of immunotherapies are used for treating gliomas: immune checkpoint inhibitors (ICIs), Chimeric Antigen Receptor T (CAR-T) cell therapies, vaccines, and oncolytic virotherapy (OV)[33]. ICI therapy effectively blocks immune checkpoints like PD-1/PD-L1, thereby preventing immune suppression[34]. Peptide-based and dendritic vaccines target tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs)[35]. CAR-T cell therapies have been explored in GBM treatment, targeting molecules on tumor surfaces such as EGFR variant III (EGFRvIII), IL13Rα2, and HER2[36]. Oncolytic virotherapy, a novel treatment for GBM, has gained significant attention in recent years, with G47Δ being conditionally approved as a treatment in Japan, paving the way for further progress in immunotherapy development[37].

Oncological immunotherapy is progressively being combined with surgery, chemotherapy, radiotherapy, and targeted treatments to offer patients innovative therapeutic options. In the past five years, the resistance and lack of response to PD-1/PD-L1 blockade therapy have generated growing interest in exploring new immune checkpoints (such as CTLA-4, TIM-3, and LAG-3) and other targets aimed at restoring T-cell function and preventing tumor immune escape through combination approaches[38]. However, no successful phase III clinical trials or marketing approvals for immune checkpoint blockade (ICB) therapies have been achieved in the treatment of GBM globally[39]. To summarize, immunotherapy for GBM is still in its early developmental stages.

Over the last 20 years, an analysis of academic contributions shows that the United States has made the largest impact in this field, with the top ten institutions being based there. This trend may be related to the high incidence of glioblastoma in the United States, where glioblastoma is also common[40]. China follows as the second-largest contributor. Sichuan University leads in China, ranking 11th worldwide. European nations, including Germany and the United Kingdom, have also made notable contributions. Strengthened international cooperation between countries and research institutions could further improve the five-year survival rate of GBM.

Among the top ten journals, Frontiers in Immunology published over 50 papers,

followed by Cancers with more than 40, while the other journals published over 20 each. Prominent journals commonly cited in this field include Frontiers in Oncology, Neuro-Oncology, and The Journal of Neuro-Oncology. These specialized journals, which focus on cancer, feature prominently both in the top publishing and co-cited journal lists, highlighting their importance in this research area. This distribution highlights the broad interest and substantial progress in the field, especially in both foundational research and clinical applications.

From the perspective of keywords, nivolumab, chemotherapy, recurrence, and T cells are central to immunity research in glioblastoma. When considering the leading researchers, Michael Lim, John H. Sampson, and Amy B. Heimberger have higher average citations per paper, indicating the high impact of their work. Their research primarily targets the PD-1/PD-L1 axis and aims to rejuvenate the immune function of exhausted T-cells to eradicate tumors. In clinical settings, immunotherapies designed to improve the tumor microenvironment (TME) have become a significant research focus in recent years[41]. Nivolumab is used either alone or in combination with chemotherapy. Additionally, these researchers have investigated emerging CAR-T therapies, which, although still in early stages for GBM, have made significant advances in hematological cancers and some solid tumors[42]. The emergence of innovative immunotherapies has led to a wider range of treatment options for GBM, with these therapies becoming more integrated into the management of glioblastoma.

This study has a few limitations. First, the data were sourced from a single database (WOS), which may have missed relevant publications from other databases. Second, it is important to note that the analysis focused only on English-language papers, which could introduce bias in the selection of materials. To ensure the dataset's objectivity and completeness, publications from 2025 that were incomplete were excluded. However, this may limit our ability to capture emerging trends, evaluate citation impacts, and understand patterns of collaboration. Therefore, we plan to update the dataset in the next phase by including all publications from 2025. Lastly, the quality assessment of the studies included in this research was based only on the attention given to the authors, which limits the analysis. Using a standardized quality scoring tool in future studies could provide a more comprehensive evaluation of GBM immunotherapy research.

During the analysis, we observed that the majority of the studies focused on clinical research exploring the effectiveness of neoadjuvant immunotherapy, either alone or in combination with other treatments. However, there is a lack of detailed research into the specific role of immunity in GBM and its underlying target mechanisms.

Moreover, there is a noticeable absence of pioneering and authoritative discoveries in this area. Many researchers have concentrated on inhibiting disease

progression, reducing recurrence, or alleviating drug resistance. However, the knowledge gap regarding prevention strategies remains. Improving the prognosis of GBM is crucial, and addressing this issue largely depends on early detection, diagnosis, and treatment. Therefore, it is essential to study the pathogenesis and immunotherapy of GBM from both preventive and therapeutic perspectives to overcome clinical challenges. In conclusion, GBM immunotherapy research shows a promising development trajectory in both basic research and clinical applications.

5 Conclusions

Recent advancements in science and technology, coupled with a better understanding of immunotherapy, have brought neoadjuvant immunotherapy, particularly nivolumab and CAR-T therapy, into the forefront. Their significant benefits have been proven both as standalone treatments and in combination with other therapies. The bibliometric analysis conducted in this study highlights the importance of glioblastoma (GBM) as a critical disease that demands further attention. Tackling the significant challenges in cancer treatment requires prioritizing research into neoadjuvant immunotherapy. Looking ahead, it will be crucial to investigate more effective combination therapies involving neoadjuvant immunotherapy. Furthermore, a meta-analysis of immune checkpoint inhibitors in GBM should be conducted to assess their efficacy, safety, tolerability, and the factors influencing their effectiveness. Despite these advancements, substantial progress remains necessary to fully harness the therapeutic potential of these treatments and propel this promising field forward.

Acknowledgements: Not applicable.

Author contributions: Wei Li worte the main manuscipt text, Ruimin Guo prepared Formal analysis and Data curation, Rongrong Zhang is responsible for Project administration and Investigation and Guojia Wu and Runzhe Cheng is responsible for fomal analysis. Dong Wang is responsible for Methodology, Investigation and Funding acquisition. All authors reviewed the manuscript.

Funding This work was sponsored by National Natural Science Foundation of China (Grant No. 82171359).

Data availability All data generated or analysed during this study are included in this published article.

Declarations Ethics approval and consent to participate Review and/or approval by an ethics committee as well as informed consent was not required for this study because this article only used existing data from published studies and did not involve any direct experimentation/studies on living beings.

Reference

1. Stupp, R., et al., Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. Jama, 2017. 318(23): p. 2306-2316.
2. Sun, X., et al., BRD8 maintains glioblastoma by epigenetic reprogramming of the p53 network. Nature, 2023. 613(7942): p. 195-202.
3. Stupp, R., et al., Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol, 2009. 10(5): p. 459-66.
4. Brennan, C.W., et al., The somatic genomic landscape of glioblastoma. Cell, 2013. 155(2): p. 462-77.
5. César-Razquin, A., et al., A Call for Systematic Research on Solute Carriers. Cell, 2015. 162(3): p. 478-87.
6. Herrlinger, U., et al., Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet, 2019. 393(10172): p. 678-688.
7. Tomar, M.S., et al., Elucidating the mechanisms of Temozolomide resistance in gliomas and the strategies to overcome the resistance. Biochim Biophys Acta Rev Cancer, 2021. 1876(2): p. 188616.
8. Berghoff, A.S. and M. Preusser, Does neoadjuvant anti-PD1 therapy improve glioblastoma outcome? Nat Rev Neurol, 2019. 15(6): p. 314-315.
9. Cloughesy, T.F., et al., Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med, 2019. 25(3): p. 477-486.
10. Nguyen, N.P., et al., Immunotherapy and Radiotherapy for Older Patients with Locally Advanced Non-Metastatic Non-Small-Cell Lung Cancer Who Are Not Candidates for or Decline Surgery and Chemotherapy: A Practical Proposal by the International Geriatric Radiotherapy Group. Cancers (Basel), 2024. 16(17).
11. Chan, H.Y., et al., Combination immunotherapy strategies for glioblastoma. J Neurooncol, 2021. 151(3): p. 375-391.
12. Arrieta, V.A., et al., Immune checkpoint blockade in glioblastoma: from tumor heterogeneity to personalized treatment. J Clin Invest, 2023. 133(2).
13. Chen, Y. and Z. Tian, HBV-Induced Immune Imbalance in the Development of HCC. Front Immunol, 2019. 10: p. 2048.
14. Espinoza, F.I., et al., Targeting HIF-2α in glioblastoma reshapes the immune infiltrate and enhances response to immune checkpoint blockade. Cell Mol Life Sci, 2025. 82(1): p. 119.
15. Pan, Z., et al., EWSR1-induced circNEIL3 promotes glioma progression and exosome-mediated macrophage immunosuppressive polarization via stabilizing IGF2BP3. Mol Cancer, 2022. 21(1): p. 16.
16. Zeng, L., et al., Bibliometric analysis of rheumatic immune related adverse events associated with immune checkpoint inhibitors. Front Immunol, 2023.

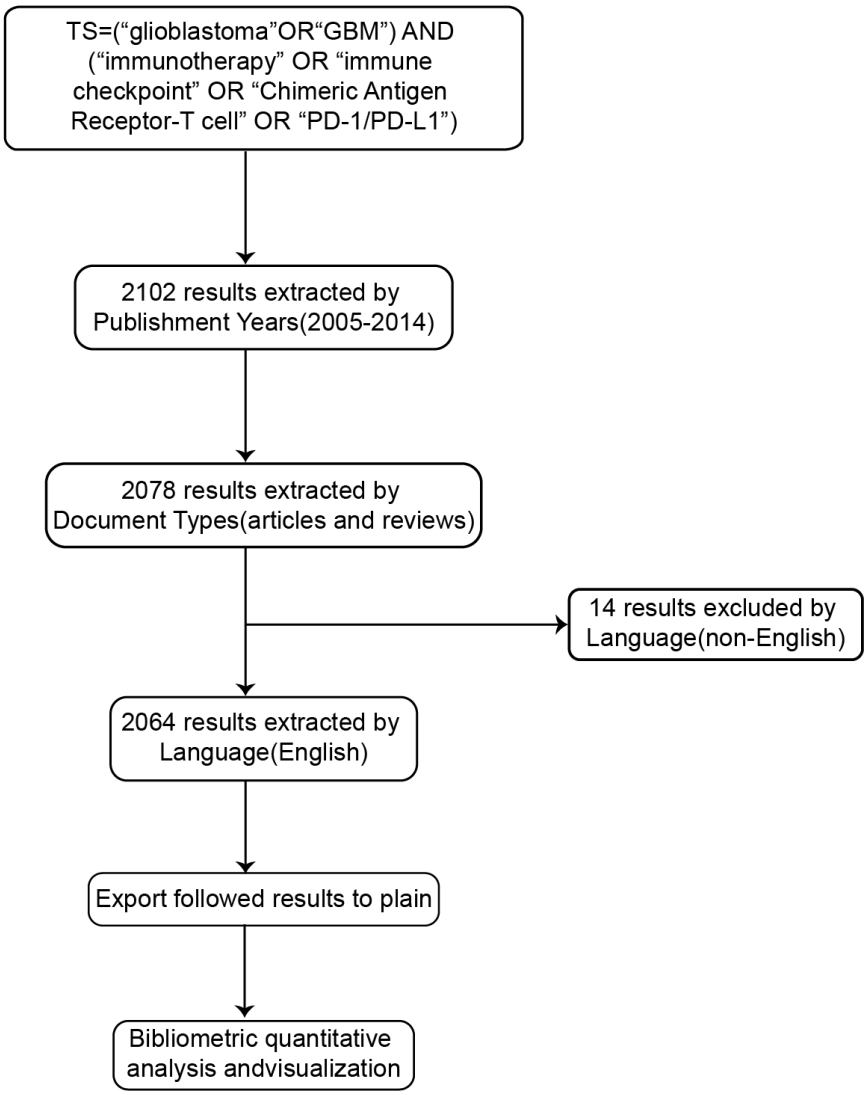
14: p. 1242336.
17. Wang, J., Z. Gong, and M. Yu, Bibliometric study on the knowledge graph of immunotherapy for head and neck cancer. Front Oncol, 2023. 13: p. 942777.
18. Chen, H., et al., Career Adaptability Research: A Literature Review with Scientific Knowledge Mapping in Web of Science. Int J Environ Res Public Health, 2020. 17(16).
19. Kallio, H., et al., Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. J Adv Nurs, 2016. 72(12): p. 2954-2965.
20. O'Brien, B.C., et al., Standards for reporting qualitative research: a synthesis of recommendations. Acad Med, 2014. 89(9): p. 1245-51.
21. The seamless web of science: a skeptical view. Nat Neurosci, 2001. 4(6): p. 551.
22. Guo, L., G. Lu, and J. Tian, A Bibliometric Analysis of Cirrhosis Nursing Research on Web of Science. Gastroenterol Nurs, 2020. 43(3): p. 232-240.
23. Arruda, H., et al., VOSviewer and Bibliometrix. J Med Libr Assoc, 2022. 110(3): p. 392-395.
24. Fu, R., et al., A VOSviewer-Based Bibliometric Analysis of Prescription Refills. Front Med (Lausanne), 2022. 9: p. 856420.
25. van Eck, N.J. and L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics, 2010. 84(2): p. 523-538.
26. Liu, S., et al., Knowledge domain and emerging trends in Alzheimer's disease: a scientometric review based on CiteSpace analysis. Neural Regen Res, 2019. 14(9): p. 1643-1650.
27. Liu, X., et al., Frontier and hot topics in electrochemiluminescence sensing technology based on CiteSpace bibliometric analysis. Biosens Bioelectron, 2022. 201: p. 113932.
28. Huang, Y., et al., A bibliometric insight into neoadjuvant chemotherapy in bladder cancer: trends, collaborations, and future avenues. Front Immunol, 2024. 15: p. 1297542.
29. Stupp, R., et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 2005. 352(10): p. 987-96.
30. Brown, C.E., et al., Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy. N Engl J Med, 2016. 375(26): p. 2561-9.
31. O'Rourke, D.M., et al., A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med, 2017. 9(399).
32. Akmal, M., et al., Glioblastome Multiforme: A Bibliometric Analysis. World Neurosurg, 2020. 136: p. 270-282.
33. Wang, S.J., S.K. Dougan, and M. Dougan, Immune mechanisms of toxicity from checkpoint inhibitors. Trends Cancer, 2023. 9(7): p. 543-553.
34. Tang, Q., et al., The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. Front Immunol, 2022. 13: p. 964442.
35. Saxena, M., et al., Therapeutic cancer vaccines. Nat Rev Cancer, 2021. 21(6):

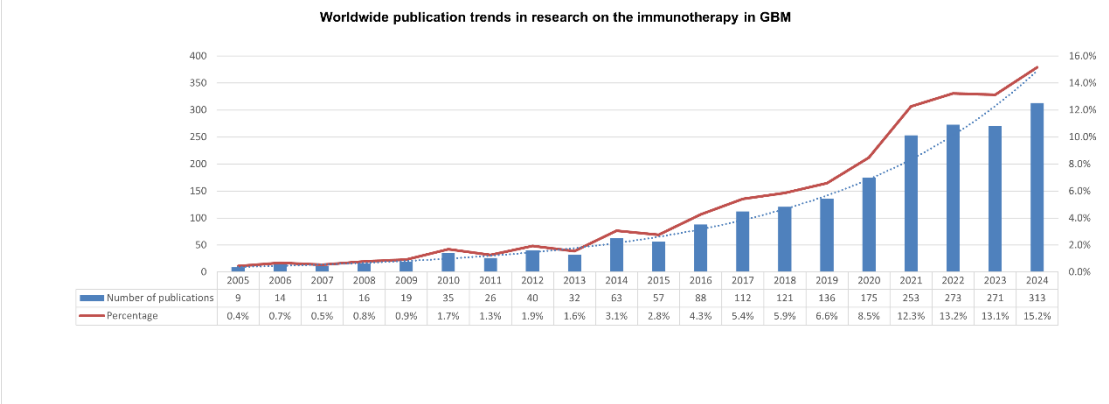
p. 360-378.
36. Lin, Y.J., L.A. Mashouf, and M. Lim, CAR T Cell Therapy in Primary Brain Tumors: Current Investigations and the Future. Front Immunol, 2022. 13: p. 817296.
37. Todo, T., et al., Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial. Nat Med, 2022. 28(8): p. 1630-1639.
38. De Waele, J., et al., Poly(I:C) primes primary human glioblastoma cells for an immune response invigorated by PD-L1 blockade. Oncoimmunology, 2018. 7(3): p. e1407899.
39. Ye, Z., et al., Targeting Microglial Metabolic Rewiring Synergizes with Immune-Checkpoint Blockade Therapy for Glioblastoma. Cancer Discov, 2023. 13(4): p. 974-1001.
40. Ostrom, Q.T., et al., CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016-2020. Neuro Oncol, 2023. 25(12 Suppl 2): p. iv1-iv99.
41. Bikfalvi, A., et al., Challenges in glioblastoma research: focus on the tumor microenvironment. Trends Cancer, 2023. 9(1): p. 9-27.
42. Bernstock, J.D., et al., Next-generation CAR T cell therapies for glioblastoma. Sci Transl Med, 2024. 16(762): p. eadp2660.

Table1: Selection criteria for the study

Category	Specific standard requirements
Research database	Web of Science core collection
Citation index	All
Searching period	2005–2024
Language	“English”
Searching topic	(“glioblastoma” OR “GBM”) and (“immunotherapy” OR “immune checkpoint” OR “Chimeric Antigen Receptor-T cell” OR “PD-1/PD-L1”).
Document types	“Article” OR “Review Article”
Subject categories	All

Fig.1 The procedure of acquiring data

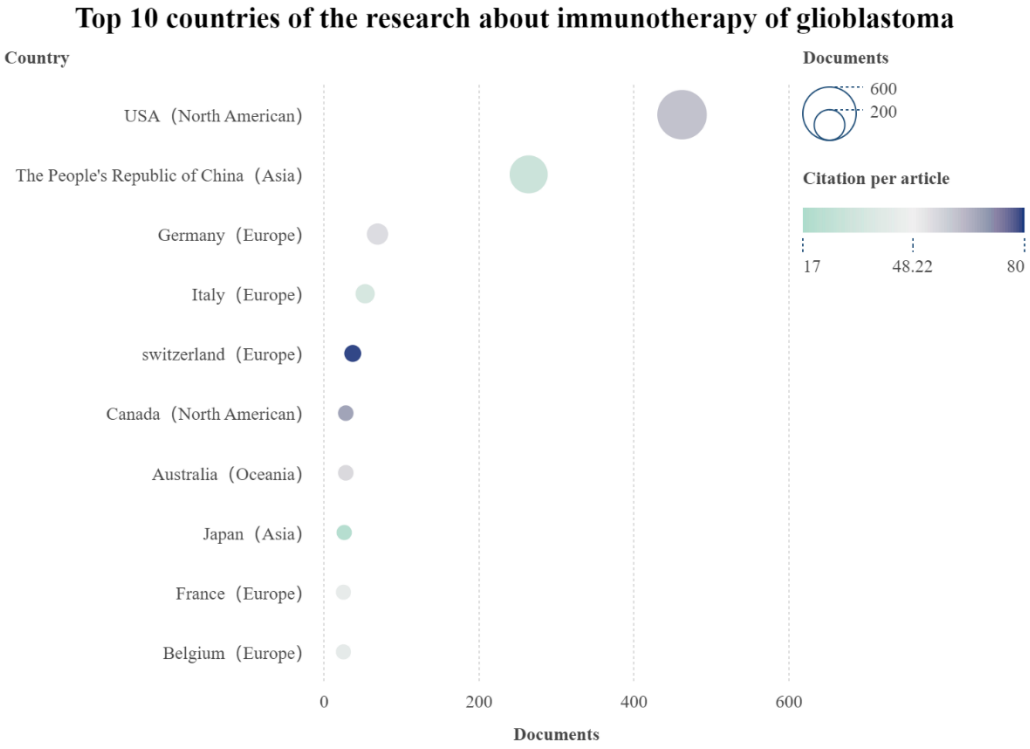




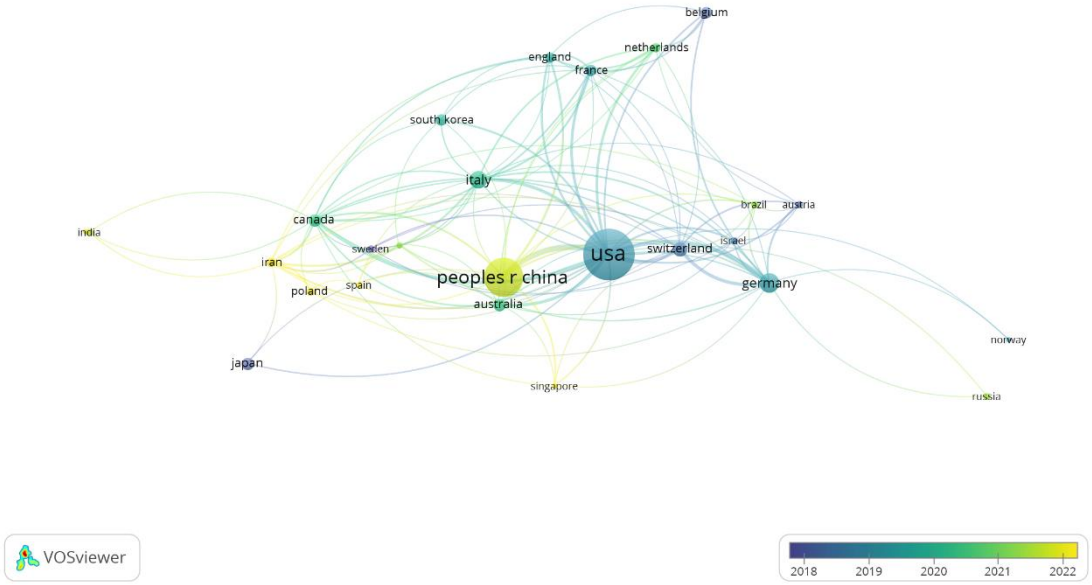
Data extraction	Export with full records and cited references in plain text format
Search results	2064

Fig2:Worldwide publication trends in research on the immunotherapy in GBM

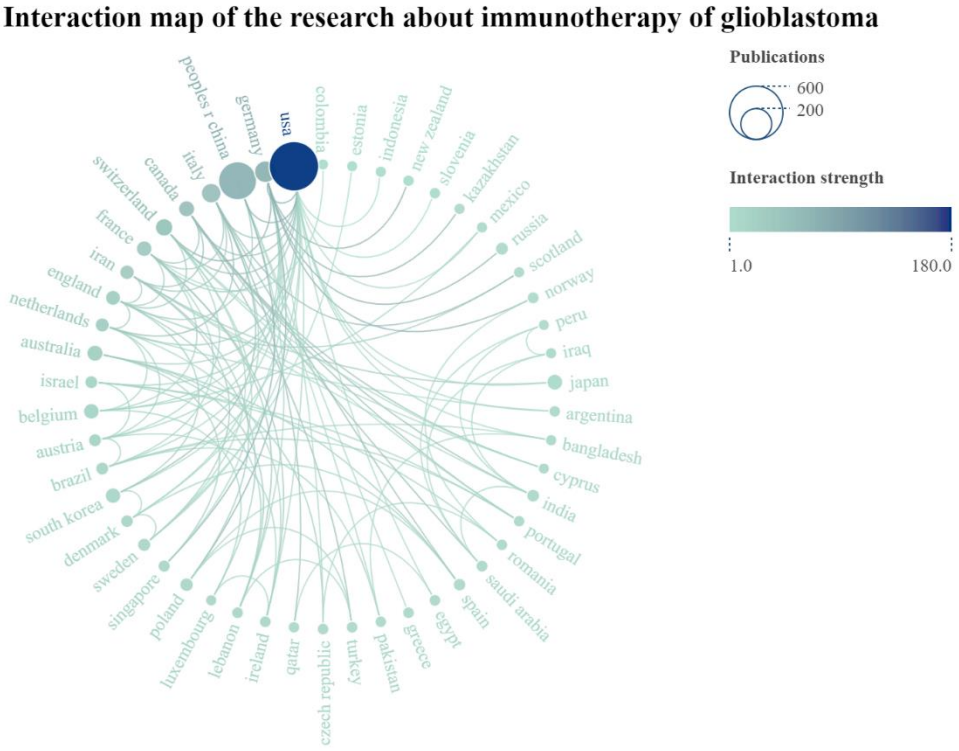
A.



B.


belgium
netherlands
england
france
south korea
italy
brazil
austria
canada
india
israel
sweden
iran
usa
switzerland
peoples r china
poland
spain
germany
australia
norway
japan
singapore
russia
VOSviewer
2018
2019
2020
2021
2022

C.


Interaction map of the research about immunotherapy of glioblastoma
Publications
600
200
Interaction strength
1.0
180.0
usa
peoples r china
germany
italy
canada
switzerland
france
iran
england
netherlands
australia
israel
belgium
austria
brazil
south korea
denmark
sweden
singapore
poland
luxembourg
lebanon
ireland
qatar
czech republic
turkey
pakistan
greece
egypt
spain
saudi arabia
romania
portugal
india
cyprus
bangladesh
argentina
japan
iraq
peru
norway
scotland
russia
mexico
kazakhstan
slovenia
new zealand
indonesia
estonia
colombia

D.

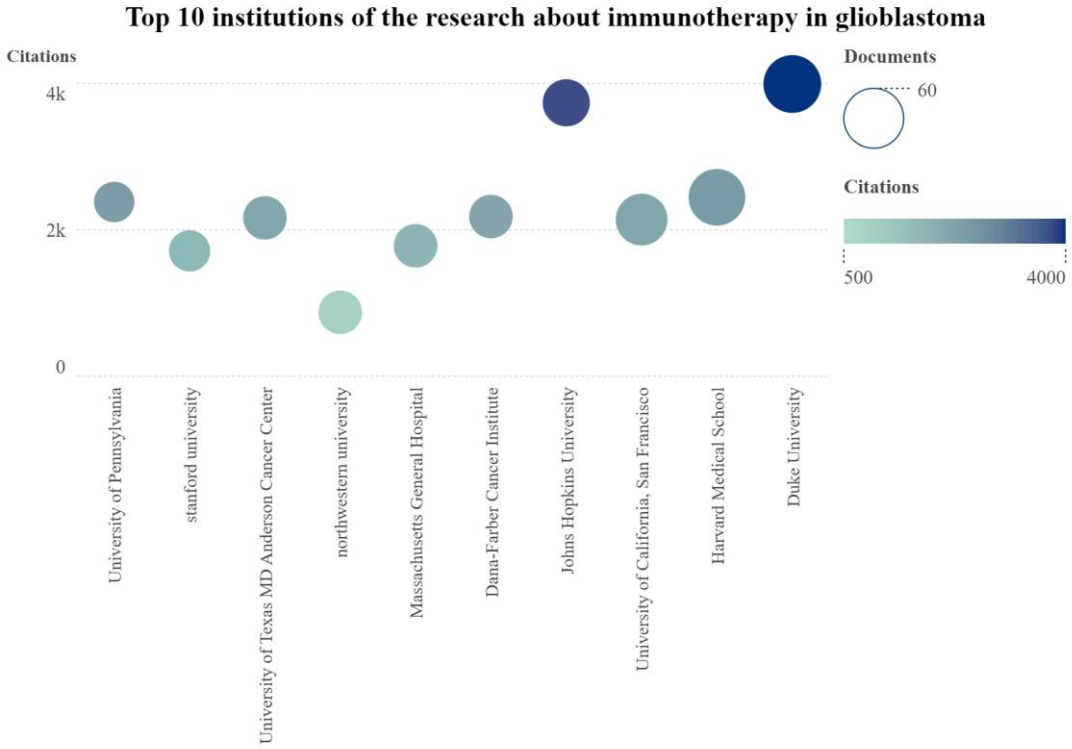
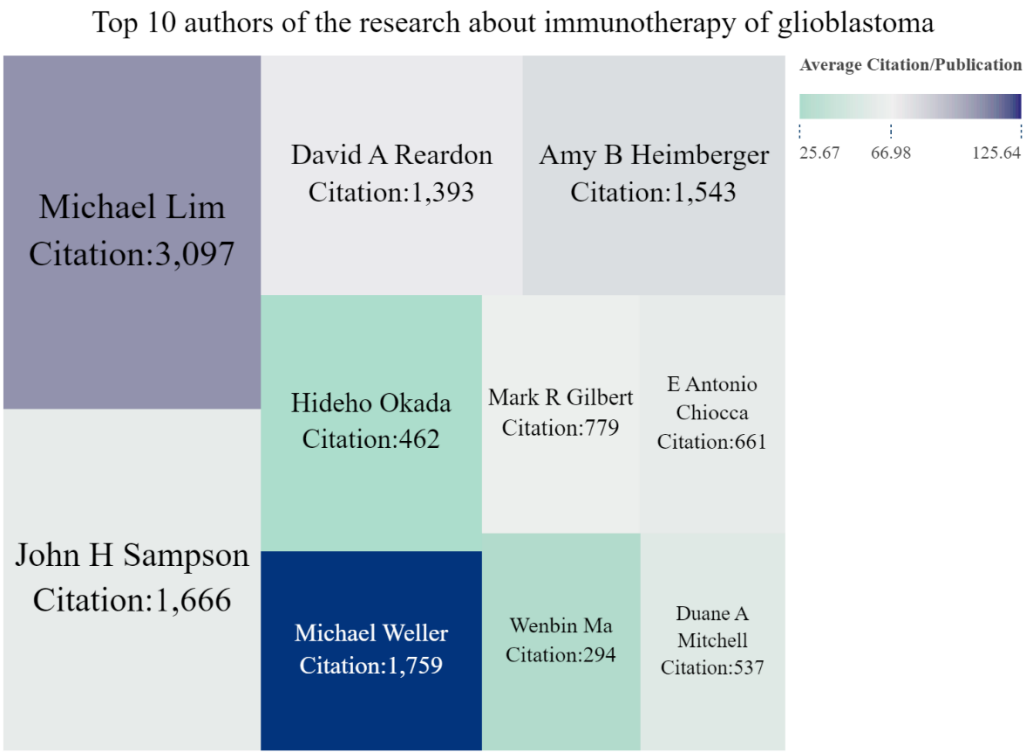
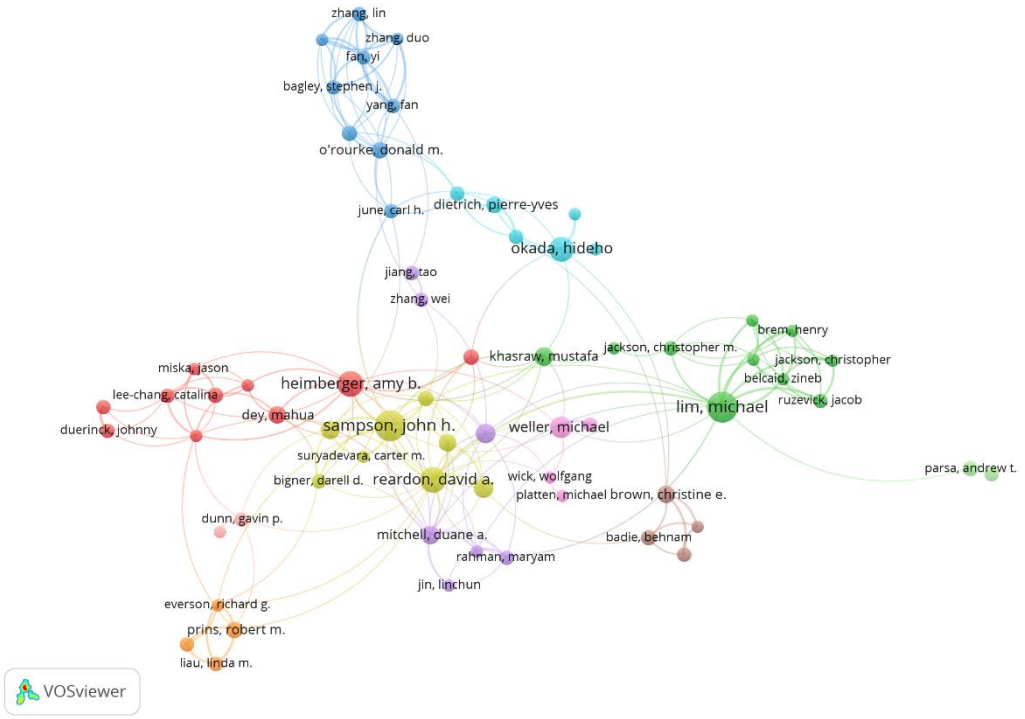


Fig3： International contributions by countries and institutions analyses A, the graph of publications and citations is presented. A darker board color indicates a higher average citation rate. B, Illustrates the interaction strength among all 53 countries through SCImago Graphica. The degree of international collaboration is shown by the size of the circles (reflecting the number of publications) and the connecting lines (indicating cooperation). C, The overlap map in shows the timeline of each country using VOSviewer. The size of the nodes stands for the number of publications, the lines between nodes signify collaborations, and the color shades represent the years when the country carried out relevant research publications. D, The trend chart in depicts the top ten institutions globally that are engaged in research on GBM immunotherapy. The size of the circles in this chart represents the number of documents.

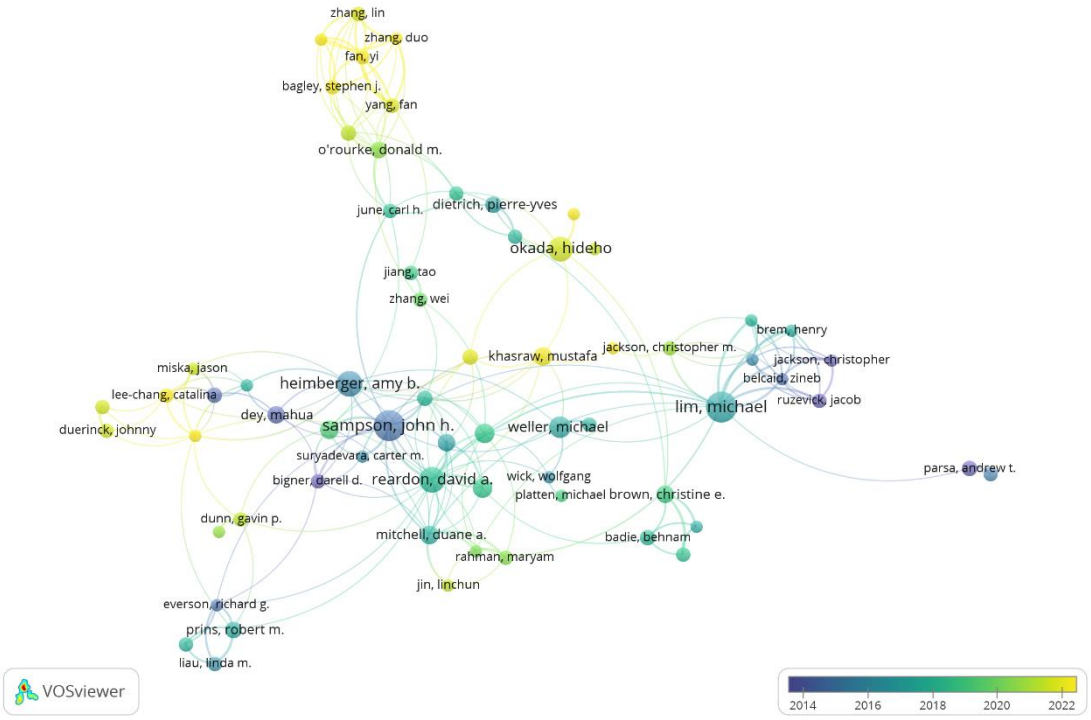
A.


Top 10 authors of the research about immunotherapy of glioblastoma
Average Citation/Publication
25.67
66.98
125.64
Michael Lim
Citation:3,097
David A Reardon
Citation:1,393
Amy B Heimberger
Citation:1,543
Hideho Okada
Citation:462
Mark R Gilbert
Citation:779
E Antonio Chiocca
Citation:661
John H Sampson
Citation:1,666
Michael Weller
Citation:1,759
Wenbin Ma
Citation:294
Duane A Mitchell
Citation:537

B.


zhang, lin
zhang, duo
fan, yi
bagley, stephen j.
yang, fan
o'rourke, donald m.
june, carl h.
dietrich, pierre-yves
okada, hideho
jiang, tao
zhang, wei
khasraw, mustafa
jackson, christopher m.
brem, henry
jackson, christopher
belcaid, zineb
ruzevick, jacob
lim, michael
miska, jason
heimberger, amy b.
lee-chang, catalina
dey, mahua
sampson, john h.
weller, michael
duerinck, johnny
suryadevara, carter m.
bigner, darell d.
reardon, david a.
wick, wolfgang
platten, michael
brown, christine e.
parsa, andrew t.
dunn, gavin p.
mitchell, duane a.
badie, behnam
rahman, maryam
jin, linchun
everson, richard g.
prins, robert m.
liau, linda m.
VOSviewer

C.



D.

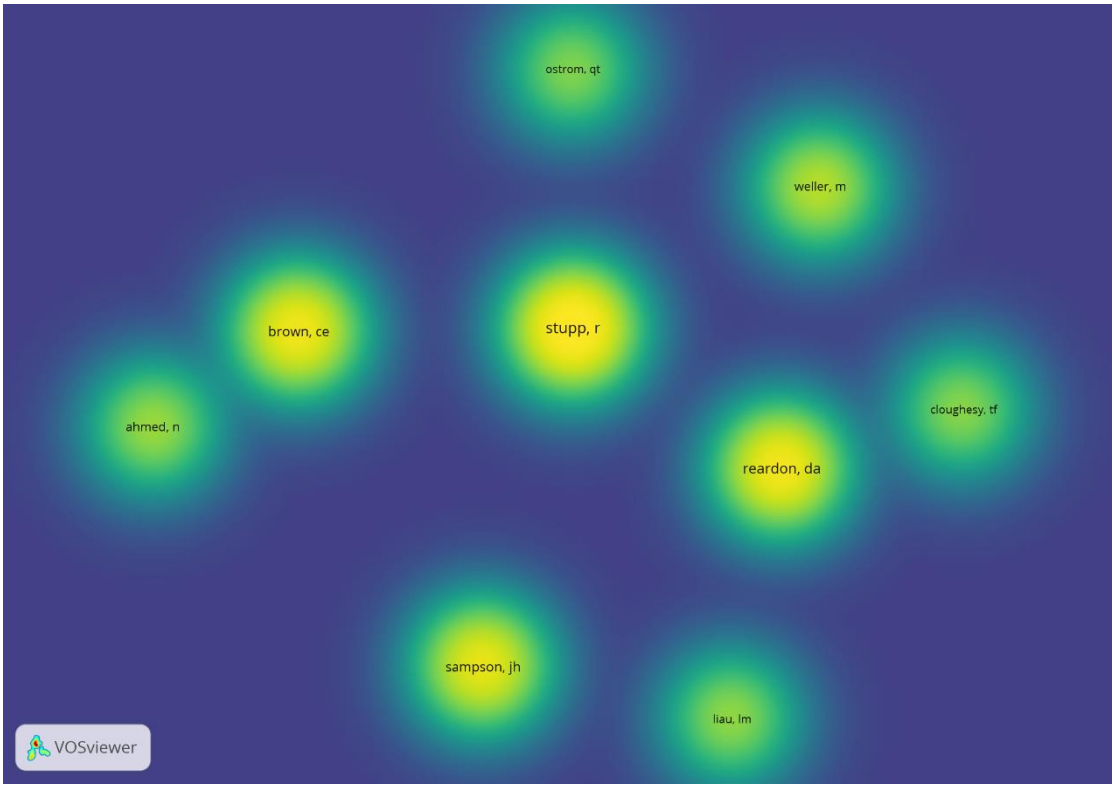
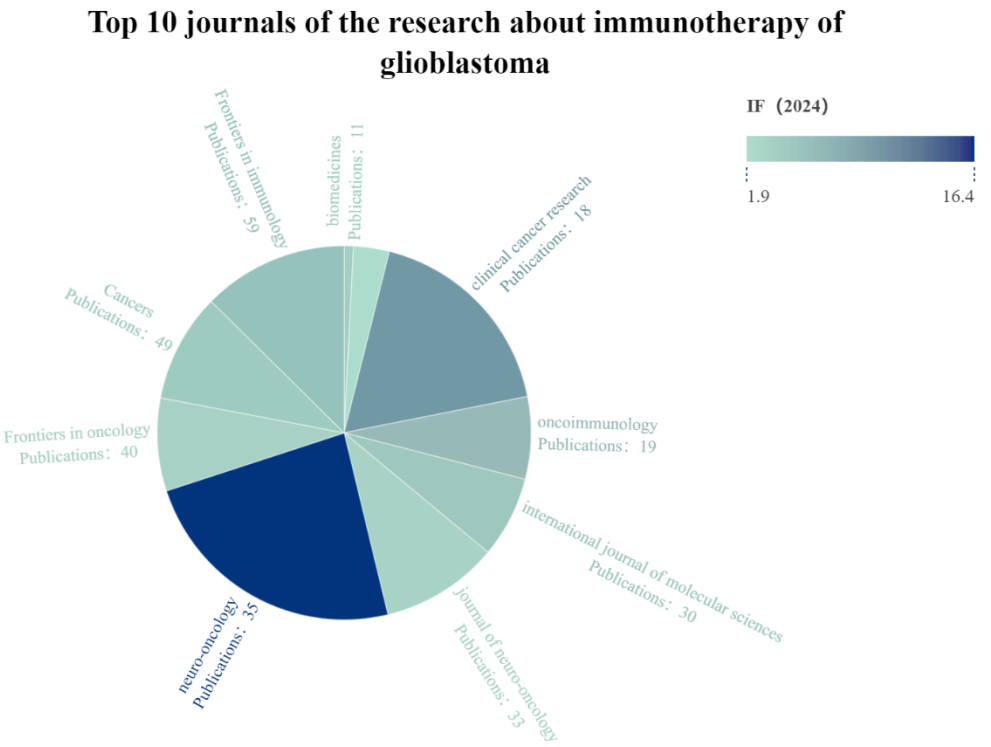


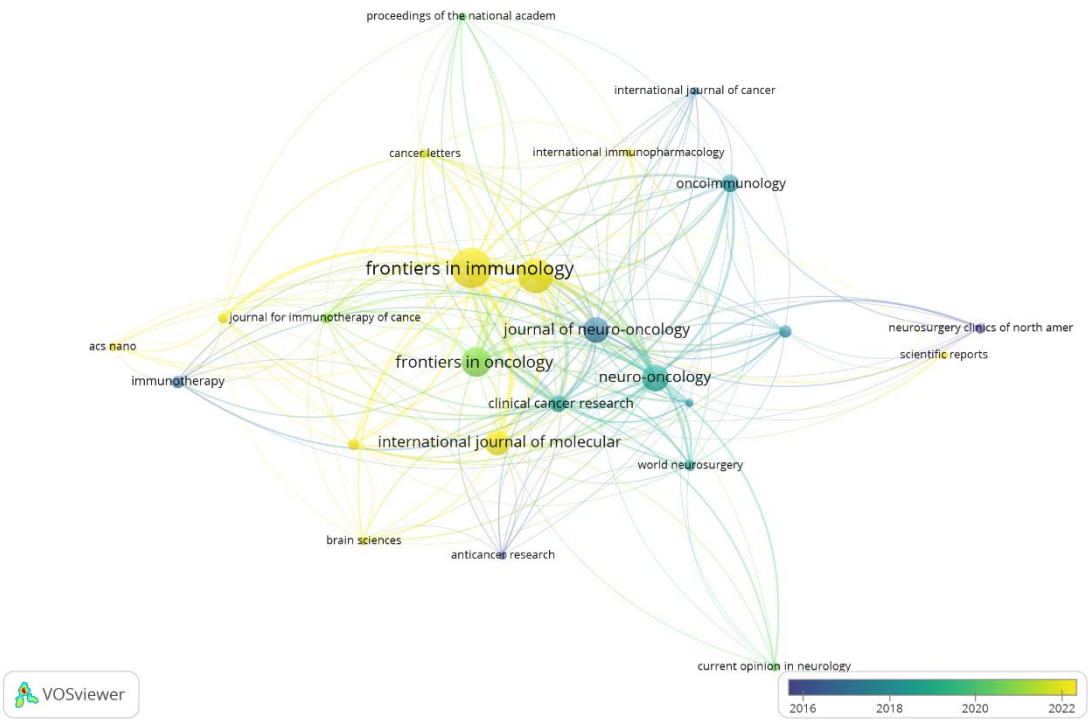
Fig. 4 presents analyses of authors and co-cited authors in the realm of GBM immunotherapy. A, the number of documents and citations of authors are depicted.The network map in part B and the overlay map in part C display the

interactions among authors. The size of the nodes corresponds to the number of publications an author has. The lines connecting the nodes denote mutual collaboration, while the color shades represent the time when the authors published their relevant research. D, the density map illustrates the interactions of co-cited authors. Darker colors signify a greater number of citations. Additionally, the size and distribution of the circles indicate the extent of collaboration between authors.

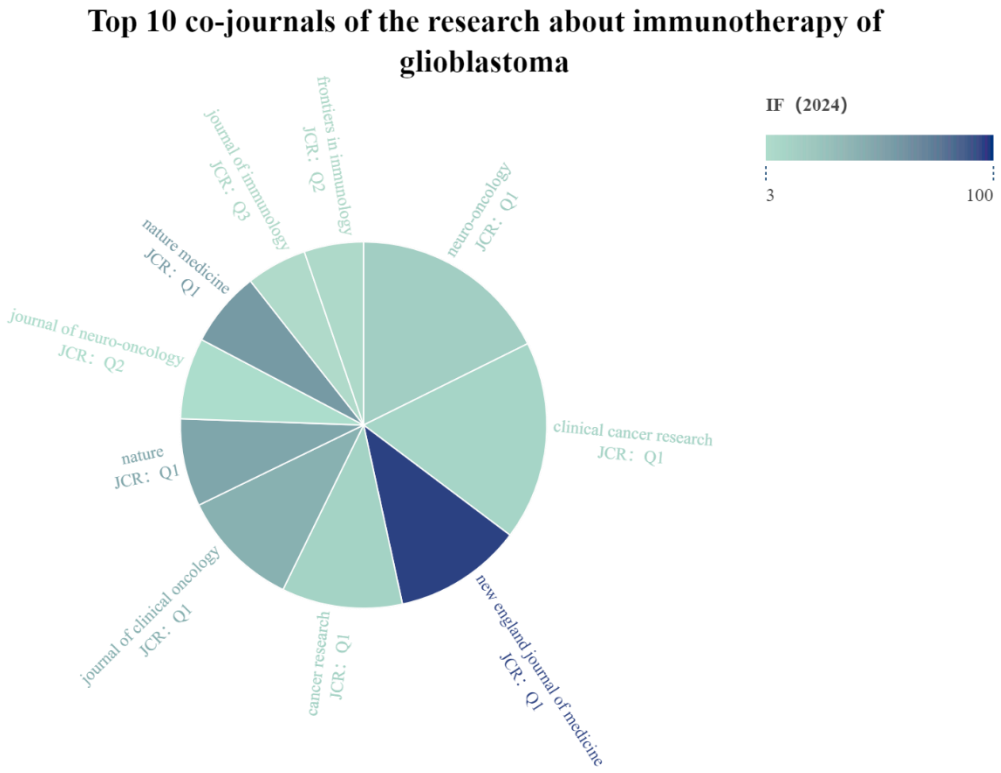
A.



B.



C.



D.

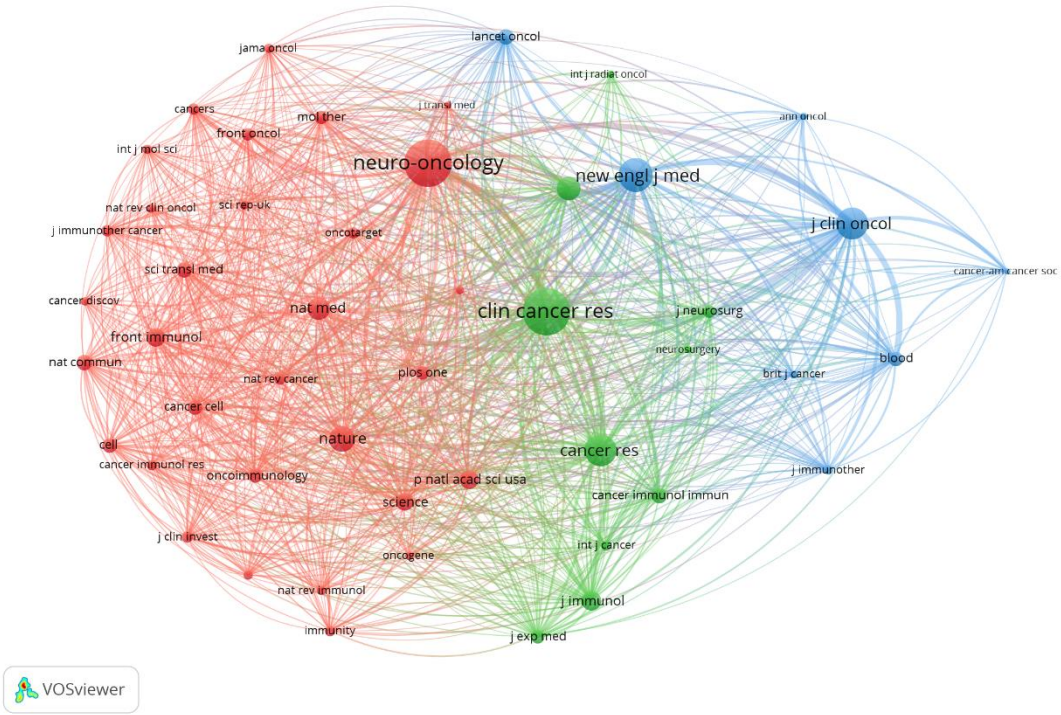
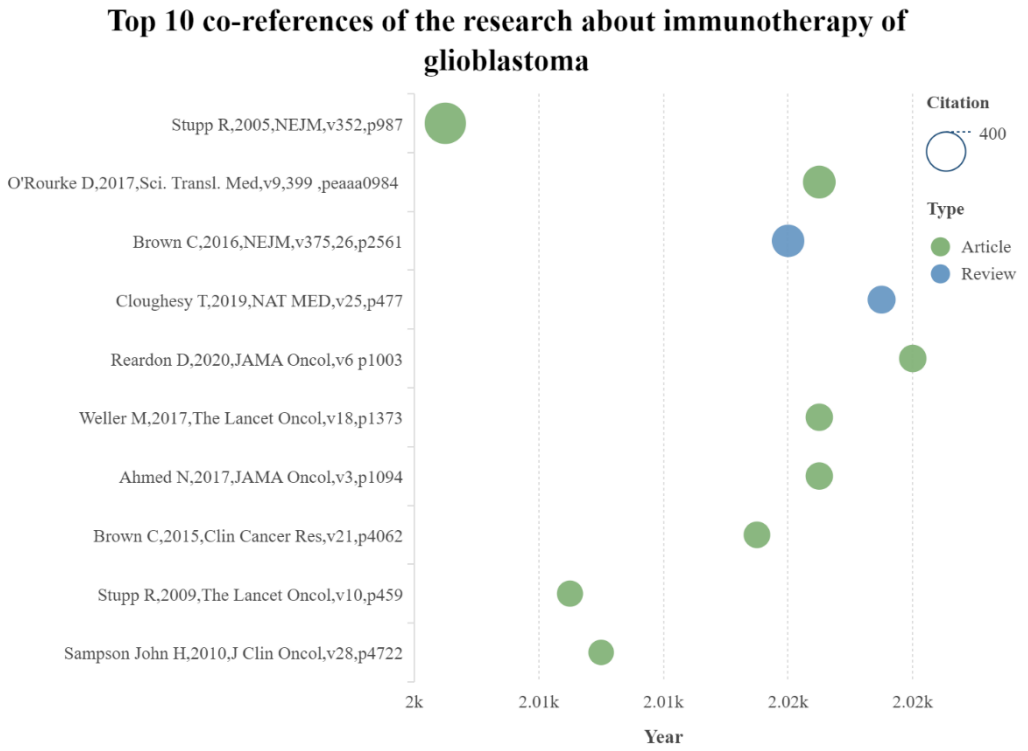


Fig.5 Journal and co-cited journal analysis A,These are the top ten journals. B,The overlay map presents the timely interaction of journals. C,The top ten co - cited

journals. D,The network map depicts the interaction of co-cited journals.

A.



B.

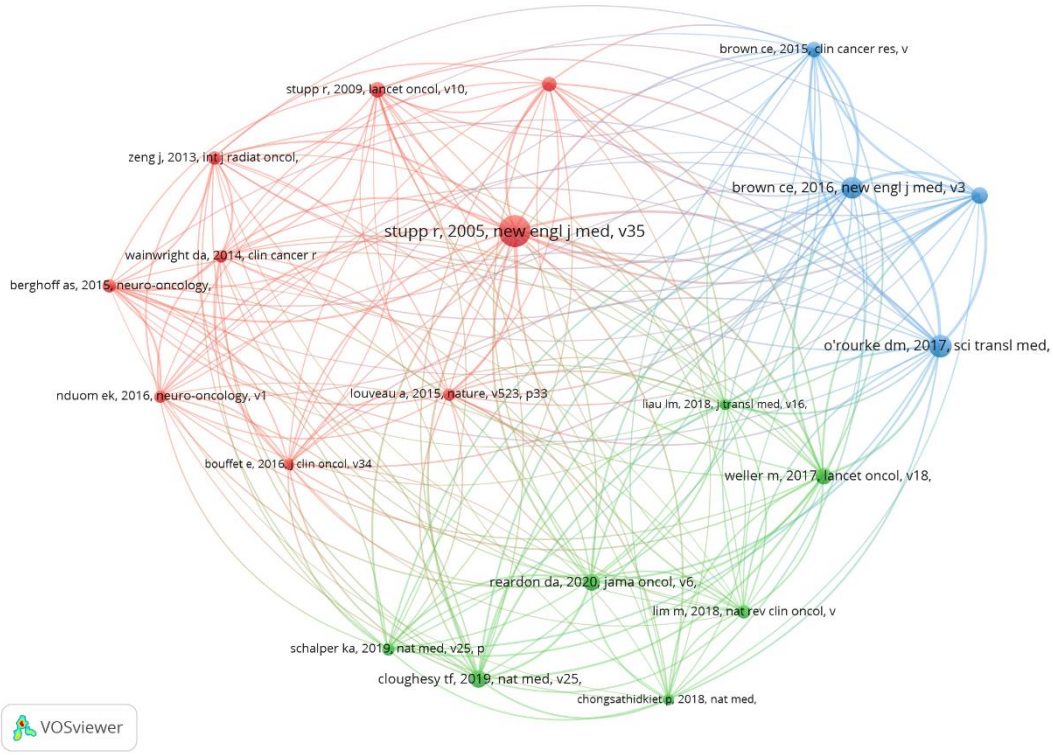
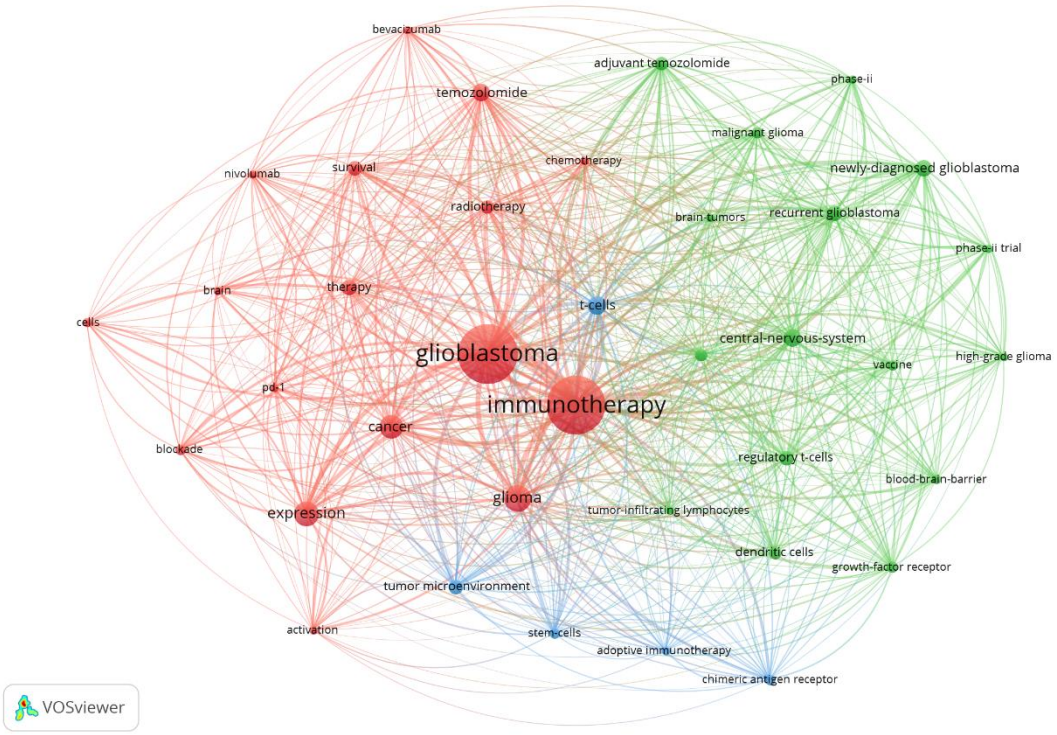


Fig.6 Analysis of commonly cited references A,The top ten co-cited references within the domain of GBM immunotherapy. The magnitude of the circle is proportional to

the citation count, and its placement indicates the year of publication. B, This illustrates the interplay among the co-cited references.

A.



B.

Top 10 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2005 - 2024
malignant glioma	2005	27.86	2005	2016	
vaccination	2005	15.31	2005	2016	
malignant gliomas	2008	10.37	2008	2019	
dendritic cell	2006	11.02	2006	2016	
glioblastoma multiforme	2005	35.72	2005	2014	
dendritic cells	2005	10.71	2005	2014	
brain tumors	2005	15.9	2005	2013	
growth factor receptor	2008	11.34	2008	2015	
activated killer cells	2006	10.46	2006	2013	
nivolumab	2017	9	2017	2020	

Fig.7 Keyword analysis. A, The network map of keywords in the field of GBM immunotherapy. B, The outbreak graph of keywords in the field of GBM immunotherapy. The red color stands for the frequency of word occurrence. Meanwhile, the length of the nodes indicates both the importance and the time persistence.