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Trends in the immunotherapy for glioblastoma: A two-decade bibliometric analysis

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ABSTRACT

Glioblastoma is a life-threatening primary malignant brain tumor with an unfavorable prognosis. Contributing factors to its poor outcome include tumor heterogeneity, low mutational burden, and immunosuppression within the tumor microenvironment. Recognizing these challenges, immunotherapeutic strategies have emerged as a promising avenue for glioblastoma treatment. Although several dynamic research and scientific trend have increasingly taken pace in the immunotherapeutic approaches to glioblastoma, systematic bibliometric studies on such trends are few. On this note, this study explores a bibliometric analysis of the research hotspots and trends in glioblastoma immunotherapy. We conducted a search in the Web of Science Core Collection database for articles on glioblastoma immunotherapy published between 2004 and 2024. Using VOSviewer and CiteSpace software, we analyzed collected articles to explore aspects such as country of origin, journal of publication, affiliated institute, authorship, keywords, and citation patterns. As of May 1, 2024, we retrieved 3,729 papers on Glioblastoma Immunotherapy. In the field of glioblastoma immunotherapy, the United States stands out as the leading contributor, with 1,708 publications and a substantial 90,590 citations. Following closely, China has made significant contributions through 926 publications, earning 17,533 citations, while Germany adds to the body of knowledge with 349 publications and 16,355 citations. Furthermore, Authoritative journals in this field include Clinical Cancer Research and Neuro-Oncology. The top five keywords during this period were temozolomide, radiotherapy, dendritic cell, cytotoxic T lymphocyte, and vaccination. Moreover, Hotspots in the field include immune checkpoint inhibitors and chimeric antigen receptor T cell therapy.

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Introduction

Glioblastoma, classified as a WHO grade IV tumor, is an extremely aggressive malignant brain tumor associated with an unfavorable prognosis. Its global incidence rate is below 0.01%. Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor in adults, accounting for approximately 14.2% of all central nervous system (CNS) tumors and 50.9% of all malignant CNS tumors.[1] Glioblastoma is more prevalent among males, predominantly affecting those aged 65 and older.[2] The standard treatment involves surgical resection, combined with radiotherapy and temozolomide (TMZ) chemotherapy, resulting in incremental improvements in survival outcomes.[3] However, the 5-year survival rate remains merely 7.2%, with a median survival of around 8 months post-diagnosis. Notably, almost all glioblastoma tumors eventually recur.[2] This highlights the urgent requirement for innovative treatments.

Immunotherapy, which triggers a tumor-specific immune response and targeted elimination of malignant cells, has been proven effective in numerous solid tumors.[4] However, glioblastoma has been presented as an immunologically "cold" tumor, characterized by multiple mechanisms that suppress the immune response.[5–8] The low mutational burden in glioblastoma suggests limited presence of neoantigens available for immune stimulation.[9] To evade T cell anti-tumor effects, glioblastoma releases paracrine immunosuppressive mediators.[6,7] Resected tumor specimens revealed a scarcity of tumor-infiltrating lymphocytes, underscoring challenges in glioblastoma immunotherapy.[5] Current investigations have explored diverse immunotherapeutic approaches, including oncolytic viruses (OVs),[10–12] immune checkpoint inhibitors, adoptive cell therapies, cancer vaccines[13] and combination therapies.[14–16] Immunotherapy for glioblastoma is gaining traction given the shortcomings of traditional treatments. Nevertheless, a comprehensive analysis of developmental dynamics, current challenges, emerging topics, and perspective trends in this field is needed.[17–19]

Bibliometrics, a statistical methodology, acts as a robust tool for evaluating the status, evolution, and scholarly impact of academic journals. By quantitatively analyzing and visually representing scientific publications and citation data, it provides a systematic and transparent approach to exploring research trends.[20,21] While it is widely adopted across diverse

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fields,[22,23] its reproducible nature enables comprehensive examination of field dynamics. Facilitated by the Web of Science Core Collection (WoSCC), bibliometric analyses aid in understanding scholarly interplay and citation patterns,[24] essential for examining glioblastoma immunotherapy research. This involves condensing and categorizing papers across various countries, regions, journals, institutions, authors, categories, keywords, and citations. A bibliometric study offers valuable insights into glioblastoma immunotherapy research, and serve as a significant reference for future studies. Additionally, it contributes to informing policies and clinical guidelines for diverse diseases, highlighting the growing importance of bibliometric approaches in contemporary research.[25,26] Despite increasing research on glioblastoma immunotherapy, systematic bibliometric analyses exploring trends and research hotspots in this area are scarce. Such analyses are critical for understanding the evolving landscape of immunotherapeutic strategies for glioblastoma.

Previous bibliometric studies have highlighted significant trends in glioblastoma immunotherapy research.[27–29] For example, Zhang et al. focused on 2000–2023 and reported that chimeric antigen receptor T-cell (CAR-T) therapy, programmed death-1 (PD-1), and nivolumab are prominent research topics, with the United States being the dominant contributor in terms of publication output.[29] Similarly, Yuan et al. (focusing on 1990–2023) identified immune checkpoint inhibitors as a major hotspot, with the Journal of Neuro-oncology leading in publications.[30] Additional insights for the immunotherapy in glioma can be drawn from Zhou et al (focusing on 2003–2022), who indicated "Microglia" and "polarization" as hotspots for future research, with Duke University as the leading institution and Clinical Cancer Research as the leading journal in the field.[31] However, these studies have examined the prominence of CAR-T and immune checkpoint inhibitors but lack a comprehensive focus on systematic trends and research hotspots in glioblastoma immunotherapy, emphasizing the need for further analysis. This study aims to address this gap.

Over the past two decades, the world has undergone significant social, economic, and political transformations that have profoundly influenced research priorities and funding allocations, presenting unprecedented opportunities for the study of GBM. The awakening of societal awareness, strengthened economic power, and evolving policy environments have collectively enhanced the focus on GBM research. Heightened public health consciousness and an increasing demand for effective medical solutions have led to substantial increases in funding from both governmental and private sectors toward neuro-oncology. Concurrently, supportive policies enacted by governments worldwide have not only fostered robust domestic research activities but also promoted cross-border academic exchanges and technical collaborations. Moreover, rapid advancements in biotechnology and information technology have provided powerful tools that enable researchers to delve deeper into the molecular mechanisms of GBM and develop more precise and efficacious therapeutic strategies. Collectively, these factors have greatly propelled advancements in the field of GBM research; however, this highly aggressive brain tumor remains one of the most formidable challenges in modern medicine. Research conducted within this timeframe captures the impact of these changes on scientific inquiry, making it particularly relevant to current issues. By analyzing the volume and trends of publications over the past two decades, we can gain a deeper understanding of the growth, evolution, and development of knowledge within the field, offering valuable insights to address contemporary challenges.

In this study, we conducted a comprehensive bibliometric analysis employing advanced tools such as VOSviewer and CiteSpace software. Our objective was to scrutinize the global landscape of glioblastoma immunotherapy research from 2004 to 2024. The analysis is conducted with goals not only to elucidate existing patterns and the current state of research but also to discern perspective trends within the field. Our findings provide valuable insights into the trajectory of glioblastoma immunotherapy research, offering a glimpse into potential future hotspots in the scientific landscape. As an increasing number of researchers are involved in this field. Our study can help them make decisions in the following parts: research direction, collaborating scientific institutions, and journals for submission.

Materials and methods

Data collection

The exploration of relevant literature centered around the theme "Immunotherapy* AND Glioblastoma." The search was meticulously executed using the WoSCC Expanded database (Thomson Reuters, New York, USA). Our search spanned from May 1st, 2004, to May 1st, 2024. The article types were filtered to include "articles" and "reviews," while articles in non-English languages were excluded. Figure 1 illustrates the article search process. The investigation was independently carried out by researchers Z.L. and B.L.

Data analysis

For visual analysis and the generation of maps and clusters, we utilized CiteSpace (version 5.8.R1) and VOSviewer (Leiden University, Leiden, The Netherlands). Specifically, CiteSpace was employed for keyword analysis and identification of co-citation bursts. The analytical settings included time slicing from 2004 to 2024, one year per slice, selection criteria based on the g-index (k = 25), and no pruning. Cluster labels within the co-citation literature graph were assigned using index terms and the log-likelihood ratio (LLR).[32]

VOSviewer, a powerful bibliometric tool, was used to create knowledge maps based on web data and to visualize and explore these maps.[33] In the network visualization produced by VOSviewer, consistent colors indicate the same clusters, while node size reflects the frequency of co-occurrence. Total Link Strength (TLS) represents the cumulative weight of connections between nodes, visually depicted by the width of links, highlighting collaboration strength. This study leveraged VOSviewer for clustering analyses of countries, institutions, journals, authors, citations, and keywords due to its intuitive and clear performance in clustering tasks.[32]

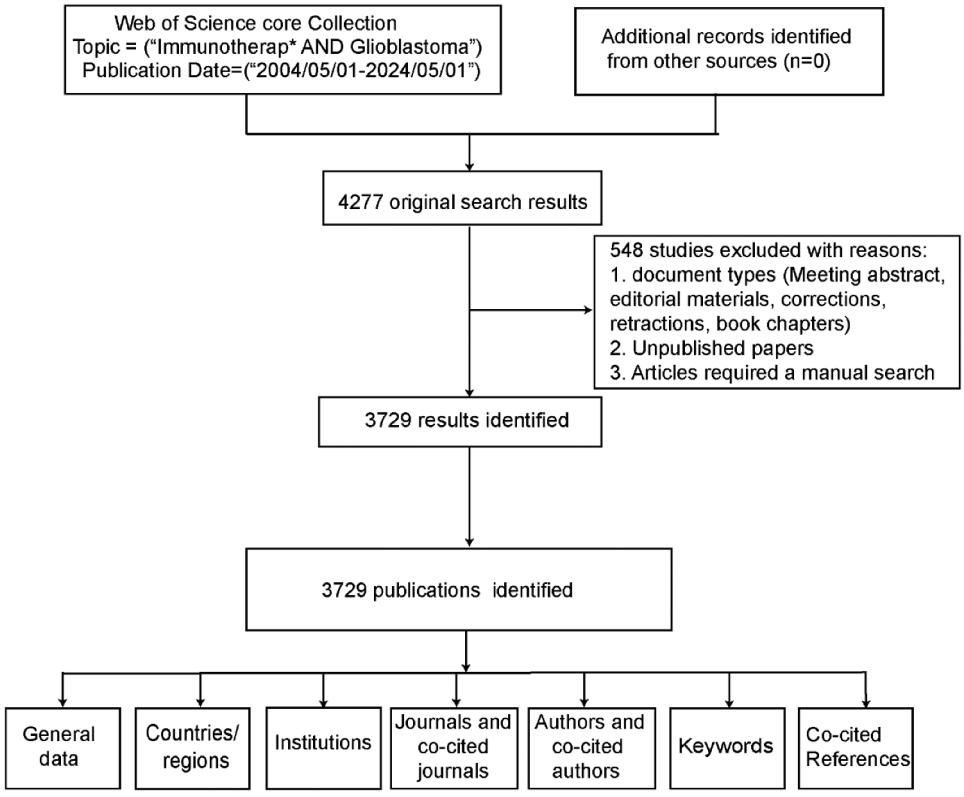

Figure 1. Data collection and bibliometric analysis process.

In this study, we employed Price's Law, Bradford's nucleus, and Lotka's Law to analyze the distribution of author productivity in scientific literature, while also using the Hirsch index (h-index) to evaluate highly cited papers. Specifically, Price's Law describes the phenomenon where a small number of highly productive authors contribute the majority of papers; through analysis of annual publication trends using Microsoft Excel 2021, we identified exponential growth patterns and calculated the coefficient of determination (R^2) to assess model fit. Utilizing the concept of Bradford's nucleus, which refers to the most central portion of journals within a specific field containing the majority of important literature, we identified core journals in our research area, laying the foundation for subsequent analyses. Additionally, based on Lotka's Law, which reveals the inverse power-law distribution of the number of papers published by authors, we analyzed the distribution of prolific authors, further understanding the unevenness in author productivity. To evaluate the impact of the literature, we applied the Hirsch index (h-index), an indicator of researchers' academic output and influence, particularly suitable for identifying highly cited papers. Through the comprehensive application of these theoretical tools, we gained a deeper understanding of bibliometric characteristics and provided valuable references for future research.[32]

Result

Global publication volume and trend analysis

After excluding papers written in languages other than English and restricting the selection to original research and review articles, a final corpus of 3,729 papers was selected for further analysis (Figure 1). Subsequently, a meticulous examination of bibliometric data from these studies, published between May 1, 2004, and May 1, 2024, revealed a substantial citation corpus totaling 86,845 citations. Moreover, the dataset primarily consisted of original research articles (66%), complemented by review articles (34%). Additionally, an analysis of publication trends over time revealed a distinct upward trajectory in annual publications.

The application of Price's Law, which posits exponential growth in scientific literature, demonstrated a robust exponential relationship between the year and the number of publications, with an R^2 value of 0.964, indicating a very strong fit (Figure 2). This finding underscores the rapid expansion of research activities in the field of glioma immunotherapy over the past two decades.

Country contributions to global publications

Among the 79 countries contributing to the field of glioblastoma immunotherapy, the United States leads with 1,708 publications and 90,590 citations. Following closely, China contributes 926 publications and 17,533 citations, while Germany ranks third with 349 publications and 16,355 citations (Table 1). Furthermore, the network map highlights the collaborative landscape, with the United States, China, Germany, and Italy emerging as prominent nodes. Notably, the United States demonstrates the most extensive cooperative network, with a Total Link Strength (TLS) of 25,035. Additionally, strong collaborative networks are also evident between the United States and China (TLS = 5,696) and between the United States and Germany (TLS

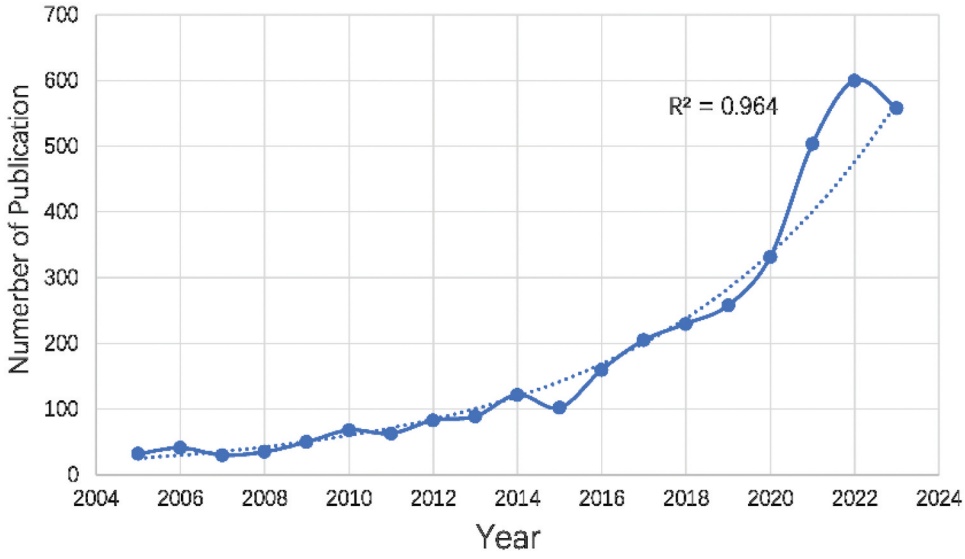

Figure 2. Publications distribution by year.

Table 1. The top ten countries according to total publications during 2004–2024.

Rank	Country	Number of publications	Proportion(%)	Total citations	Total link strength
1	The USA	1708	45.80%	90590	25035
2	China	926	24.83%	17533	10640
3	Germany	349	9.35%	16355	8243
4	Italy	215	5.76%	7256	4731
5	Japan	145	3.88%	5508	2541
6	France	130	3.48%	6196	2922
7	Switzerland	127	3.40%	8294	4339
8	England	110	2.94%	4983	3041
9	Canada	92	2.46%	5696	3189
10	Belgium	87	2.33%	4225	2296

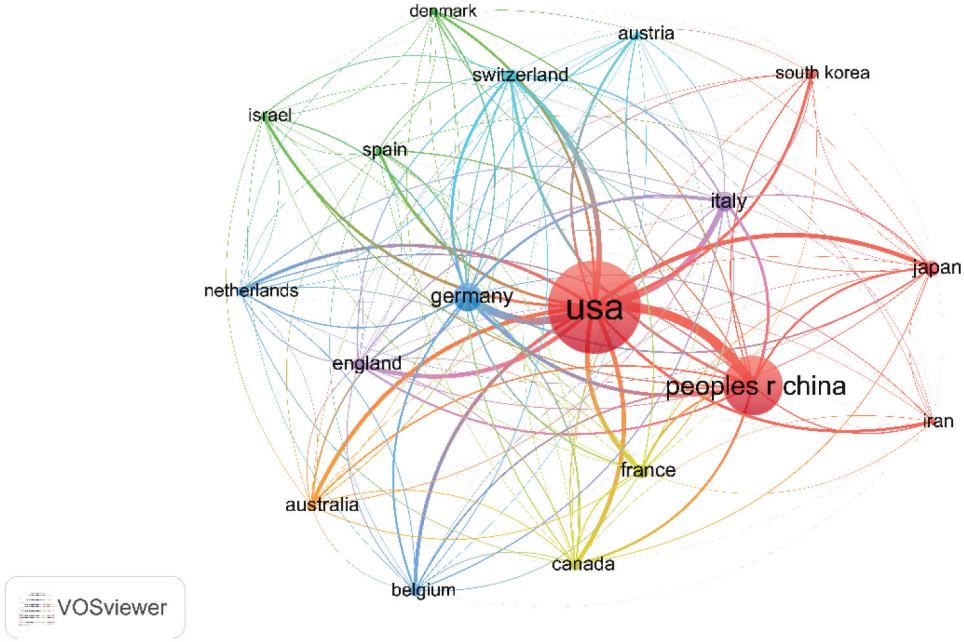

Figure 3. Cooperationmaps of country by VOSviewer. Node size indicates the number of publications. Link size refers to the intensity of collaboration.

= 3,818) (Figure 3). These connections underscore the closely intertwined research endeavors between these countries.

Analysis of institutions publishing on glioblastoma immunotherapy

Among the top ten institutions with the highest number of publications, Duke University (USA) leads with 150 contributions, closely followed by Harvard Medical School (USA) with 141 publications and the University of California, Los Angeles (USA) with 109 publications. Notably, eight of these top ten institutions are based in the United States. Furthermore, in terms of scholarly impact, Duke University (USA) stands out as the most cited institution, accumulating a significant total of 11,205 citations (Table 2). This underscores its leading role in the field. Additionally, Figure 4 illustrates the collaboration network among the top 19 institutions, highlighting the strongest collaborative ties between Duke University and Harvard Medical School, with a Total Link Strength (TLS) of 337. This emphasizes the pivotal role these institutions play in fostering collaborative research within the field.

Analysis of top journals and co-cited journals

Figure 5 visualizes the collaboration network among the 18 core journals, with the highest level of collaboration observed between Frontiers in Immunology and Cancers, exhibiting a Total Link Strength (TLS) of 269. According to Table 3, Frontiers in Immunology leads with 201 publications (Impact Factor = 7.3, 2022), followed by Cancers with 141 publications (IF = 5.2, 2022), and Frontiers in Oncology with 128 publications (IF = 4.7, 2022). Moreover, these journals demonstrate exceptional effectiveness in both publication volume and co-citation frequency.

Regarding co-cited journals, Neuro-Oncology has the highest number of co-citations at 11,852, followed by Clinical Cancer Research with 11,550 co-citations, and Cancer Research with 9,991 co-citations. Additionally, these three journals clearly exert significant authoritative influence within the field.

Analysis of main authors and co-cited authors

Over the past two decades, a cohort of 13,292 authors has actively contributed to the Journal of Glioblastoma for Immunotherapy. Table 4 showcases the 11 most productive authors, highlighting their potential as key collaborators and influential figures in the field. Notably, Sampson from the United States leads with 76 publications, closely followed by Lin (59 publications) and Mitchell (49 publications), both also based in the United States.

Furthermore, the frequency of co-citations serves as a substantial metric for evaluating scholarly impact. Bump, Reardon, and Sampson emerge as the top three most frequently co-cited authors, underscoring their significant influence within the field. Figure 6a visualizes the collaboration network, revealing the strongest collaboration intensity between Lowenstein and Castro, with a Total Link Strength (TLS) of 363. Moreover, among more than 200 co-citations, Stupp emerges as the most prominent author, as illustrated in Figure 6b.

Analysis of high-frequency keywords

We extracted 7,356 keywords from 3,729 papers and subsequently identified 50 high-frequency keywords that occurred more than 81 times. The co-occurrence network (Figure 7a) categorizes these keywords into three distinct clusters: Firstly, Cluster 1 (Red) centers around basic science and includes keywords such as regulatory T-cells, dendritic cells, T-cells, stem cells, and vaccination. Secondly, Cluster 2 (Green), corresponding to clinical science, this cluster encompasses terms like immunotherapy, glioblastoma, expression, survival, and prognosis. Lastly, Cluster 3 (Blue), pertaining to chemotherapy and radiotherapy, this cluster features keywords such as temozolomide, radiotherapy, chemotherapy, bevacizumab, and newly-diagnosed glioblastoma.

Furthermore, using CiteSpace for analyzing outbreak terminologies and emerging research patterns (Figure 7b), we identified 25 keywords with substantial citation bursts. Noteworthy terms with heightened burst intensity include dendritic cell, cytotoxic T lymphocytes, vaccination, and activated killer cell. These emerging trends highlight key areas of active research and innovation within the field.

The top cited and co-cited references analysis

As illustrated in Figure 8a, the most cited paper is authored by Andrew et al., published in 2007, titled "Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma." ($n = 1083$).[34] Co-cited reference refers to works that are referenced together in the bibliographies of other publications.[35] Among the 2563 publications, we identified 121,872 co-cited references. Furthermore, the article titled "Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy,"[36] published in the New England Journal of Medicine in 2016 by Brown et al. ($n = 471$) was the most frequently co-cited article. Additionally, closely following this work is the study by O'Rourke et al. in Science Translational Medicine in 2017 ($n = 428$), titled "A Single Dose of Peripherally Infused EGFRvIII-directed CAR T Cells Mediates Antigen Loss and Induces Adaptive Resistance in Patients with Recurrent Glioblastoma."[37] Moreover, in the third position is the publication by Cloughesy et al. in Nature Medicine in 2019 ($n = 394$), titled "Neoadjuvant anti-PD-1 Immunotherapy Promotes a Survival Benefit with Intratumoral and Systemic Immune Responses in Recurrent Glioblastoma" (Table 5).[38]

Additionally, a co-citation network graph was constructed using over 133 co-citations (Figure 8a). Citation bursts, indicative of references that researchers frequently cite within a specific timeframe, were analyzed using CiteSpace. Consequently, Figure 8b displays the top 25 references with the strongest citation bursts, ranging from 30.73 to 69.51 burst intensity values. Notably, "Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The

Table 2. The top ten most productive institutions between 2004 and 2024.

Rank	The name of institution	Publications	Citations	Location
1	Duke Univ	150	11205	The USA
2	Harvard Med Sch	141	8320	The USA
3	Univ Calif Los Angeles	109	7901	The USA
4	Univ Calif San Francisco	107	9753	The USA
5	Univ Texas Md Anderson Canc Ctr	100	8136	The USA
6	Johns Hopkins Univ	98	4245	The USA
7	Capital Med Univ	94	6099	China
8	Northwestern univ	93	4376	The USA
9	German Canc Res Ctr	83	9391	German
10	Dana Farber Canc Inst	82	1744	The USA

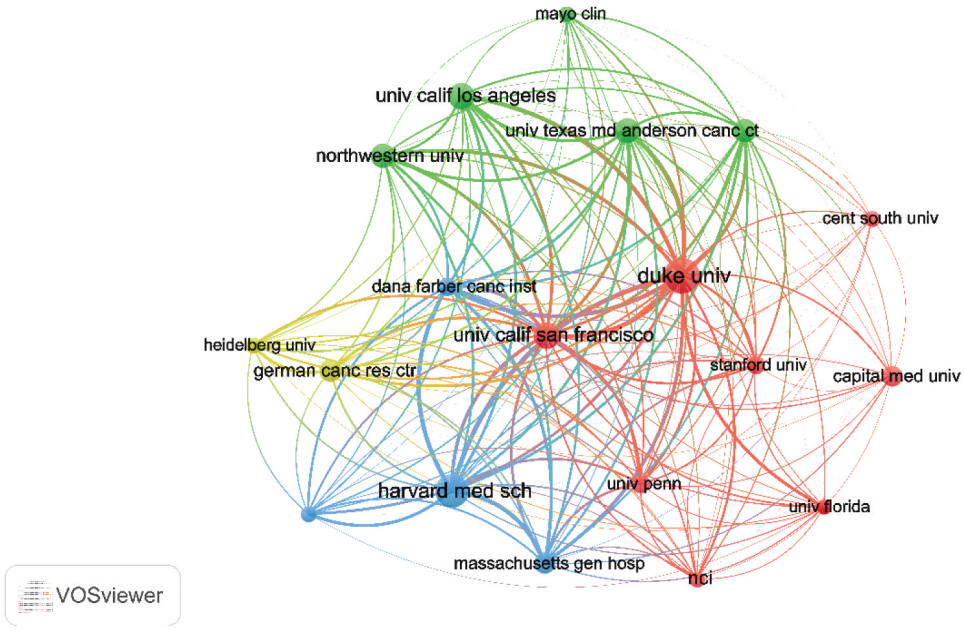

Figure 4. Map of institutional collaboration based on VOSviewer. Node size indicates the number of publications. Link size refers to the intensity of collaboration.

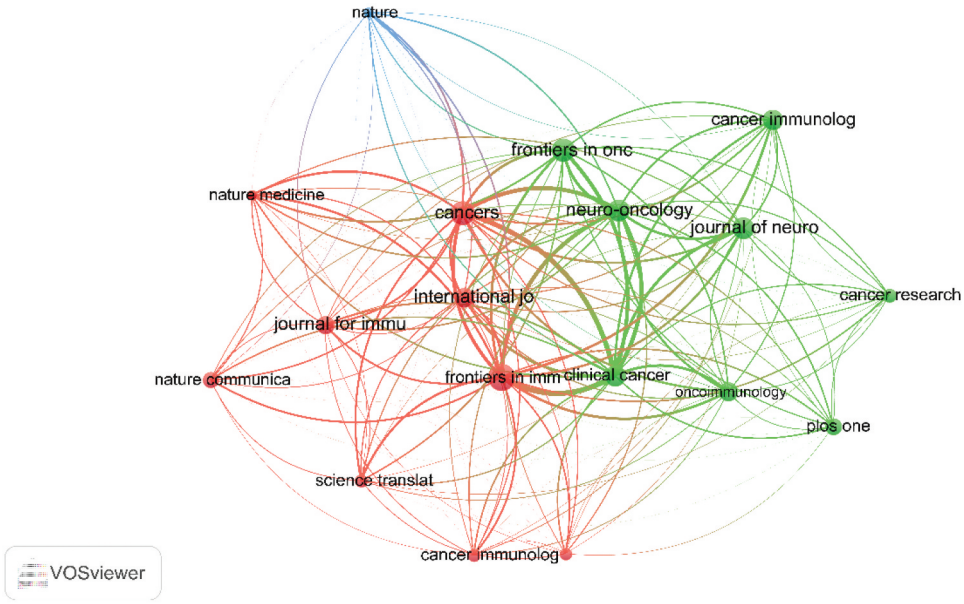

Figure 5. Cooperationmaps of journal by VOSviewer. Node size indicates the number of publications. Link size refers to the intensity of collaboration.

Table 3. Top ten prolific journals and co-cited journals on Glioblastoma immunotherapy research from 2004 to 2024.

Rank	Journal	Publications	Citations	IF*	Co-cited journal	Co-citations	IF*
1	Frontiers in Immunology	201	4477	7.30	Neuro-Oncology	11852	15.90
2	Cancers	141	2198	5.20	Clin Cancer Res	11550	11.50
3	Frontiers in Oncology	128	2326	4.70	Cancer Res	9991	11.20
4	Journal of Neuro-oncology	110	3414	3.90	New Engl J Med	7197	167.082
5	Neuro-Oncology	103	6977	15.90	J Clin Oncol	7175	45.3
6	Clinical Cancer Research	98	10000	11.50	Nature	6168	64.8
7	Cancer Immunology Immunotherapy	84	3281	5.80	J Neuro-oncol	5684	4.506
8	International Journal of Molecular Sciences	78	1253	5.60	P Natl Acad Sci Usa	4979	9.41
9	Oncoimmunology	65	2549	7.20	J Immunol	4815	5.42
10	Journal for Immumotherapy of Cancer	57	1736	10.90	Nat Med	4479	82.9

Abbreviation: IF*, impact factor.

Table 4. Top 11 prolific authors and co-cited authors on Glioblastoma immunotherapy research from 2004 to 2024.

Rank	Author	Publications	Citations	Country	Co-cited author	Co-citations	Country
1	Sampson, JH	76	6647	USA	Stupp, R	2352	USA
2	Lim, M	59	5461	USA	Reardon, DA	1399	USA
3	Mitchell, DA	49	3214	USA	Sampson, JH	1166	USA
4	Heimberger, AB	49	3976	USA	Brown, CE	1053	USA
5	Reardon, DA	47	3984	USA	Weller, M	948	Switzerland
6	Weller,M	44	3867	Switzerland	Louis, DN	837	USA
7	Okada, H	43	3149	USA	Ostrom, QT	758	USA
8	Castro, MG	41	1773	USA	Liau, LM	672	USA
9	Lowenstein, PR	38	1696	USA	Heimberger, AB	643	USA
10	Bigner, DD	31	2898	USA	Wen, PY	633	USA
11	Wick, WG	31	1485	USA	Fecci, PE	581	USA

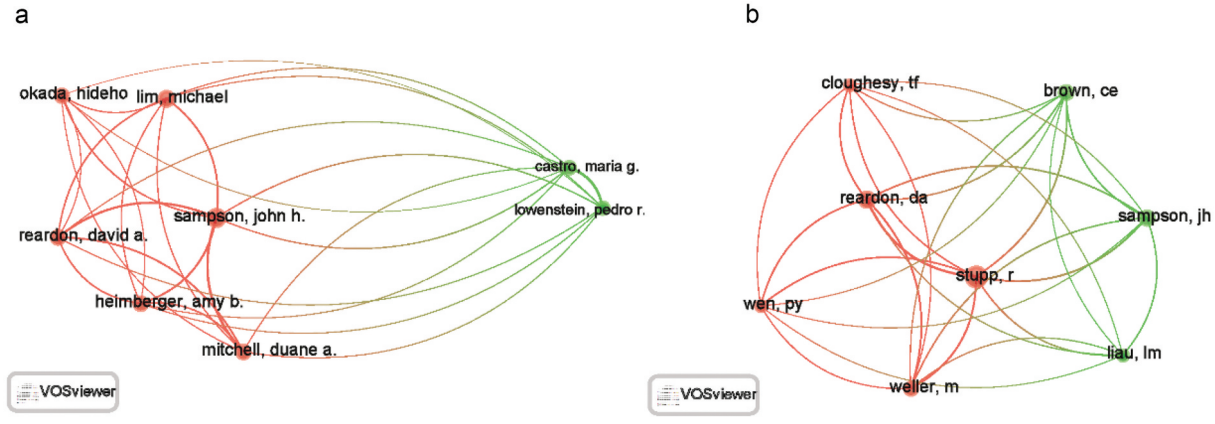

Figure 6. Cooperationmaps of author (a) and coauthor (b) by VOSviewer. Node size indicates the number of publications. Link size refers to the intensity of collaboration.

CheckMate 143 Phase 3 Randomized Clinical Trial"[39] exhibited the highest burst intensity (69.51), underscoring the influential and instructive nature of this article in the realm of glioblastoma treatment.

Discussion

When choosing a research direction, the researchers primarily consider whether the research area is a current hotspot and aligns with ongoing trends. To address this issue, we conducted a bibliometric analysis of publications on glioblastoma immunotherapy published globally from 2004 to 2024. Our analysis revealed a steady annual increase in publications on glioblastoma immunotherapy, with a substantial surge observed in the past five years (2020–-2023). There is an increasing trend that researchers are interested in this field.

The United States takes the lead in disseminating publications on glioblastoma immunotherapy, underscoring its prominent position in medical research. Moreover, the United States exhibits robust collaborative networks with other countries, particularly with China and Germany, which promotes interdisciplinary and international research partnerships.

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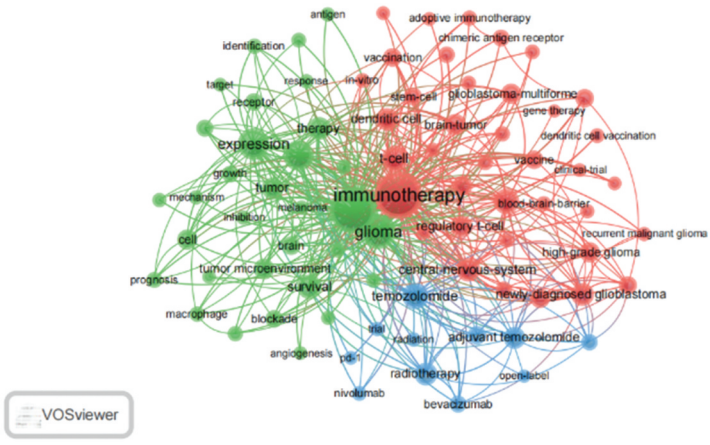

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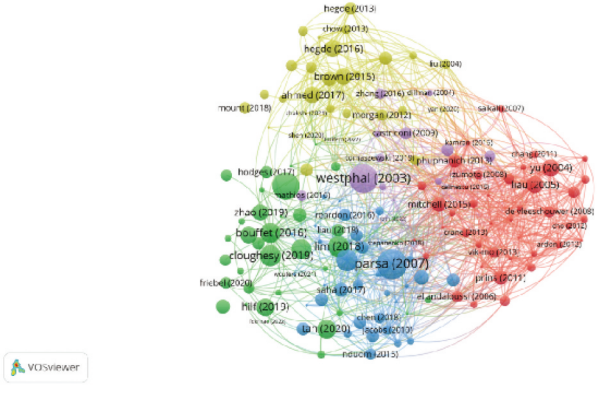
Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2004 - 2024
glioblastoma multiforme	2004	55.93	2004	2014	
malignant glioma	2004	45.62	2004	2015	
brain tumor	2004	36.46	2004	2013	
dendritic cell	2004	26.2	2004	2014	
vaccination	2004	21.67	2004	2016	
monoclonal antibody	2004	13.27	2004	2015	
in vivo	2004	12.65	2004	2015	
phase ii trial	2004	10.11	2004	2014	
colony stimulating factor	2004	9.21	2004	2017	
cytotoxic t lymphocyte	2004	14.11	2005	2016	
immune response	2004	13.83	2006	2014	
growth factor receptor	2004	13.48	2006	2017	
antitumor immunity	2004	12.73	2006	2017	
apoptosis	2004	9.67	2006	2011	
regulatory t cell	2004	16.29	2007	2018	
recurrent glioma	2004	11.37	2007	2016	
dendritic cell vaccination	2004	12.09	2008	2017	
egfrviii	2004	10.64	2008	2017	
pulsed dendritic cell	2004	9.5	2008	2015	
activated killer cell	2004	11.22	2009	2014	
metastatic melanoma	2004	9.63	2009	2017	
nivolumab	2004	13.94	2017	2019	
mismatch repair	2004	9.71	2017	2020	
tumor microenvironment	2004	11.83	2021	2024	
landscape	2004	9.39	2021	2022	

Figure 7. Author keyword analysis. (a) Visualization of author keyword co-occurrence networks using VOSviewer. Large nodes represent keywords with relatively high occurrences; the same color indicates relatively close relationships; (b) the top 25 most frequently cited keywords. Red bars indicate burst duration. Burst intensity refers to the importance of the keyword to the field of study.

a



b

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2004 - 2024
Stupp R, 2005, NEW ENGL J MED, V352, P987, DOI 10.1056/NEJMoa043330, DOI	2005	47.04	2006	2010	
Liau LM, 2005, CLIN CANCER RES, V11, P5515, DOI 10.1158/1078-0432.CCR-05-0464, DOI	2005	35.76	2006	2010	
De Vleeschouwer S, 2008, CLIN CANCER RES, V14, P3098, DOI 10.1158/1078-0432.CCR-07-4875, DOI	2008	35.83	2009	2013	
Wheeler CJ, 2008, CANCER RES, V68, P5955, DOI 10.1158/0008-5472.CAN-07-5973, DOI	2008	33.4	2009	2013	
Stupp R, 2009, LANCET ONCOL, V10, P459, DOI 10.1016/S1470-2045(09)70025-7, DOI	2009	44.26	2010	2014	
Sampson JH, 2010, J CLIN ONCOL, V28, P4722, DOI 10.1200/JCO.2010.28.6963, DOI	2010	51.4	2011	2015	
Prins RM, 2011, CLIN CANCER RES, V17, P1603, DOI 10.1158/1078-0432.CCR-10-2563, DOI	2011	42.61	2011	2016	
Okada H, 2011, J CLIN ONCOL, V29, P330, DOI 10.1200/JCO.2010.30.7744, DOI	2011	40.42	2011	2016	
Hodi FS, 2010, NEW ENGL J MED, V363, P711, DOI 10.1056/NEJMoa1003466, DOI	2010	34.42	2011	2015	
Plaphanich S, 2013, CANCER IMMUNOL IMMUN, V62, P125, DOI 10.1007/s00262-012-1310-0, DOI	2013	42.25	2013	2018	
Topalian SL, 2012, NEW ENGL J MED, V366, P2443, DOI 10.1056/NEJMoa1200690, DOI	2012	33.94	2013	2017	
Gilbert MR, 2014, NEW ENGL J MED, V370, P699, DOI 10.1056/NEJMoa1308573, DOI	2014	40.92	2014	2019	
Chinot OL, 2014, NEW ENGL J MED, V370, P709, DOI 10.1056/NEJMoa1308345, DOI	2014	39.71	2014	2019	
Zeng J, 2013, INT J RADIAT ONCOL, V86, P343, DOI 10.1016/j.ijrobp.2012.12.025, DOI	2013	37.01	2014	2018	
Bergholt AS, 2015, NEURO-ONCOLOGY, V17, P1064, DOI 10.1093/neuonc/nou307, DOI	2015	44.51	2015	2020	
Wainwright DA, 2014, CLIN CANCER RES, V20, P5290, DOI 10.1158/1078-0432.CCR-14-0514, DOI	2014	41.51	2015	2019	
Mitchell DA, 2015, NATURE, V519, P366, DOI 10.1038/nature14320, DOI	2015	33.23	2015	2020	
Schuster J, 2015, NEURO-ONCOLOGY, V17, P854, DOI 10.1093/neuonc/nou348, DOI	2015	30.73	2015	2019	
Louveau A, 2015, NATURE, V523, P337, DOI 10.1038/nature14432, DOI	2015	33.02	2016	2020	
Brown CE, 2015, CLIN CANCER RES, V21, P4062, DOI 10.1158/1078-0432.CCR-15-0428, DOI	2015	31.28	2016	2020	
Brown CE, 2016, NEW ENGL J MED, V375, P2561, DOI 10.1056/NEJMoa1610497, DOI	2016	55.64	2018	2021	
Louis DN, 2016, ACTA NEUROPATHOL, V131, P803, DOI 10.1007/s00401-016-1545-1, DOI	2016	47.21	2018	2021	
Reardon DA, 2017, NEURO-ONCOLOGY, V19, P21, DOI 10.1093/neuonc/nox036.071, DOI	2017	31.2	2018	2020	
Rearden DA, 2020, JAMA ONCOL, V6, P1003, DOI 10.1001/jamaoncol.2020.1024, DOI	2020	69.51	2021	2024	
Tan AC, 2020, CA-CANCER J CLIN, V70, P299, DOI 10.3322/caac.21613, DOI	2020	34.02	2022	2024	

Figure 8. Co-cited References analysis. (a) Visualization of co-cited references networks using VOSviewer. Large nodes represent reference with relatively high occurrences; the same color indicates relatively close relationships. (b) The top 25 references with the strongest citation bursts. Red bars indicate burst duration. Burst intensity refers to the importance of the reference to the field of study.

The dominance of the United States in glioblastoma immunotherapy is further emphasized by the inclusion of eight institutions within the top 10, when it comes to publication count, while Germany and China each contribute one institution to this ranking. This is consistent with previous results showing the dominance of the United States since the 1990s in glioblastoma research.[29,30] Therefore, it is recommended that Chinese institutions and researchers strengthen collaborations with leading figures in the field and allocate more resources to advance research on immunotherapy for glioblastoma. In terms of overall citations, Duke University holds the top position, and it is followed by Univ Calif Los Angeles and Harvard Med School, exemplifying the esteemed status of these institutions in the field.

Table 5. Top ten co-cited reference according to total publications on Glioblastoma immunotherapy research during 2002 to 2024.

Rank	Co-cited reference	Co-citations
1	brown ce, 2016, new engl j med, v375, p2561	471
2	o'rourke dm, 2017, sci transl med, v9	428
3	cloughesy tf, 2019, nat med, v25, p477	394
4	sampson jh, 2010, j clin oncol, v28, p4722	236
5	weller m, 2017, lancet oncol, v18, p1373	221
6	liau lm, 2005, clin cancer res, v11, p5515	210
7	lim m, 2018, nat rev clin oncol, v15, p422	205
8	hegi me, 2005, new engl j med, v352, p997	201
9	hodi fs, 2010, new engl j med, v363, p711	188
10	reardon da, 2020, jama oncol, v6, p1003	187

Regarding journal rankings, as shown by the data, Frontiers in Immunology exhibits the most comprehensive collection of publications and maintains a dominant place in publications since the 2000s[30], followed by Cancers and Frontiers in Oncology. On the other hand, in terms of paper co-citations, Neuro-Oncology papers amass the most citations, trailed by Clin Cancer Research and Cancer Research. Although Frontiers in Immunology has published a considerable number of papers on immunotherapy for glioblastoma, the impact of the research findings remains limited. Conversely, Neuro-Oncology is the most influential journal in this field of research. Researchers should be familiar with these highly productive journals as they provide valuable guidance in choosing appropriate platforms for their scholarly work. Furthermore, publications originated from the leading journals, based on co-citations, can be considered representations of the field. Therefore, researchers aiming for high visibility and impact might prioritize these journals for their submissions.

Renowned figures such as Sampson JH, Lim M, and Mitchell DA, who are affiliated with institutions in the United States, have made pivotal contributions to glioblastoma immunotherapy. Sampson, JH's research centers on exploring the immunotherapeutic effects of vaccination for glioblastoma.[40–42] In contrast, Lim M, explores the potential of combining anti-PD-1 antibodies with other immunotherapies for glioblastoma.[43–45] Meanwhile, Mitchell DA is dedicated to the development of cytomegalovirus-targeted immunotherapy for glioblastoma.[43,46,47] Notably, Stupp R is distinguished as the most cited author, highlighting his profound impact on the field.

The keywords of included researches can be categorized into three principal domains: "basic science," "clinical research," and "radiotherapy and chemotherapy." These keywords effectively encapsulate prevalent subjects, research trends, and potential future directions within the field. Currently, there is a burgeoning interest among researchers in immunotherapy for glioblastoma, positioning it as a key focus of research. Ongoing investigations center on immune checkpoint inhibitors and CAR-T cell therapies, recognized for their efficacy in aggressive cancers, with active exploration of their potential in glioblastoma.[48–51] CAR-T has increasingly become a hotspot since the 2000s.[29]

The thematic cluster designated as "basic science" highlights pivotal keywords such as regulatory T-cells, dendritic cells, T-cells, stem cells, and vaccination. The intricate microenvironment orchestrated by glioblastoma encompasses a dynamic interplay between glioma cells and non-tumor components, predominantly including resident and invasive immune cells, such as macrophages, T cells, and dendritic cells (DCs). Notably, glioma cells feature immunosuppressive molecules, including programmed cell death 1 (PD-1) and its ligand (PD-L1). Glioma-associated macrophages promote regulatory T (Treg) cell activity through the production of indolamine 2,3-dioxygenase (IDO), concurrently inhibiting T cell function by depleting tryptophan from the microenvironment.[52] These infiltrative tumor-associated macrophages and Tregs serve as a primary source of immunosuppressive cytokines, including transforming growth factor β (TGF-β) and interleukin 10 (IL-10), effectively suppressing inflammatory cytokine production and impeding relevant immune cell responses.[53]

The forefront of glioblastoma immunotherapy research includes the exploration of CAR-T Cell Therapy, a notable modality utilizing synthetic receptors, CARs, to guide T cells in recognizing and eliminating cells expressing the target antigen.[54] To investigate the potential of CAR-T cell therapy for glioblastoma, Brown et al. targeted the tumor-specific antigen IL13Rα2[36], resulting in a remarkable improvement in clinical symptoms and radiological findings after a 7.5-month treatment duration. O'Rourke et al. conducted a study assessing the efficacy of CAR-T cell therapy targeting EGFRvIII in ten patients with recurrent glioblastoma.[37] Though CAR-T cells showed good expansion and an acceptable safety profile, the study did not demonstrate a significant improvement in overall survival. Given the inherent heterogeneity of glioblastoma, researchers are devising CAR-T cell therapy strategies to target more clonal populations.[55] Currently many phase I trials of CAR-T therapy in malignant glioma are ongoing, including T×103 [NCT06482905], SNC-109 [NCT05868083], Tris-CAR-T cell [NCT05577091], CARv3-TEAM-E T Cells [NCT05660369], and etc. [NCT06355908, NCT06186401, NCT05768880, NCT05474378, NCT05353530, NCT05298995]. Most of these trials investigate the CAR-T mono-therapy that is first applied in human patients. The CARs cover a range of neoantigens, for example, IL13Ra2A, NKG2D, GD2, EGFR806, HER-2 and B7-H3. Furthermore, investigations are underway to engineer CAR-T cells capable of recognizing multiple antigens.

Like CAR-T therapy, driven by advances in genetic engineering, oncolytic adenoviruses therapy gets the success of combination therapies, promising clinical trials, and the potential for personalized cancer treatment. A phase I study investigating DNX-2401 (Delta-24-RGD) in the treatment of recurrent malignant glioma was conducted in 37 patients.[56] In the 25-patient group, tumor reductions were observed in 72% of patients. The DNX-2401 showed radiographic signs of inflammation, which was confirmed by replicates and spreads within the post-treatment surgical specimens.

Vaccines represent a distinct category of tumor therapeutic agents that encompass tumor antigens. The primary goal of vaccine-based therapies is to instigate antitumor responses by exposing T cells to immunogenic tumor-specific antigens, exclusive to tumor cells or characterized by an overexpression of tumor-associated antigens.[9,57] Presently, glioblastoma-based vaccines include peptide vaccines, DNA vaccines, RNA vaccines, and cellular vaccines. The mechanism of peptide vaccines, DNA vaccines and mRNA vaccines are similar. Through injection, they introduce tumor-associated antigens (TAAs), and activate cytotoxic response and immune memory after taken up by antigen-presenting cells (APCs). Peptide vaccines are conventional vaccination methods.[58] DNA vaccines utilize plasmid DNA-encoding TAAs. The advantage of peptide and DNA vaccines is their rapid and cost-effective generation, but there are safety concerns in DNA vaccines due to potential integration into the host genome. RNA vaccines, including mRNA and non-coding RNAs like siRNA and circRNA, avoid these risks and are gaining interest. Currently, more and more trials are focused on long-peptide neoantigen vaccines and circRNA vaccines. Neoantigens are mutated TAAs exempt from central tolerance, which are highly specific to tumors. Though glioblastomas usually have a relatively low mutation load, after a multi-epitope personalized neoantigen vaccination, neoantigen-specific T cells from the peripheral blood infiltrated into tumor tissue.[59] As circRNA are good in stability, long life, low immunogenicity, and translatability, compared to other RNA vaccines, represent an emerging area,[60] though trials in glioblastoma are lacking. Targeting proteins encoded by circular genes, like SHPRH, could be a future research focus.[61]

Neoantigen vaccines targeting IDH, H3K27M and EGFPVIII hold great promise. Most IDH mutations, especially the substitution of arginine 132 with histidine (IDH1R132H), create an immunogenic neoepitope that is presented on MHC-II molecules within glioma tissue. This triggers spontaneous CD4+ T cell responses and can be effectively targeted with peptide vaccines in MHC-humanized preclinical models.[62] NOA-16 trial showed 93.3% vaccine-induced immune response in IDHmt astrocytoma patients. 64% progression-free survival and 84% overall survival at 3 years were achieved and no significant adverse events observed.[63] An ongoing 3-arm trial, AMPLIFY-NEOVAC, explores combined IDH vaccine and PD-1 inhibitors.[64] H3.3K27M mutation has been shown as a shared neoantigen in HLA-A *02.01+, H3.3K27M+ diffuse midline gliomas (DMGs).[65] A previous trial on DMGs involved 29 newly diagnosed patients with HLA-A *02.01+ and H3.3K27M+ mutation. The regime includes an H3.3K27M-targeted peptide vaccine in combination with polyinosinic-polycytidylic acid-poly-I-lysine carboxymethylcellulose (poly-ICLC). Immunological responses were assessed using mass cytometry, which showed a median OS of 16.1 months for patients who had an expansion of H3.3K27M-reactive CD8+ T cells compared with 9.8 months for their counterparts ($p = .05$).[66] For adult diffuse midline glioma, H3K27M-targeted long peptide vaccine (H3K27M-vac) showed safety and mild-to-strong mutation-specific immune responses in five patients.[67] Several phase 1 trials on H3K27M-vac are currently ongoing (NCT06305910, NCT04943848, NCT04749641).

Cellular vaccines, also known as DC vaccines, utilize peripheral blood mononuclear cells (PBMCs). DC vaccines utilize pulsed DCs that have been "loaded" or "pulsed" with specific antigens like tumor-associated antigens (TAAs). While this methodology is under continual development, only PPV 97–99, peptides, and DCvax have been advanced to phase III clinical trials. Single peptides, neoantigens, or dendritic cell vaccines in glioblastoma have not yielded substantial advancements and widespread implementation. Despite demonstrated tolerability and feasibility in numerous studies, DC vaccine approaches did not exhibit a survival advantage in meta-analyses.[68] Considering the substantial variability in dosing schedules employed in previous DC vaccine studies, optimizing vaccination timing and patient selection based on HLA profiles may enhance outcomes. Hybrid neoantigen-pulsed DC vaccines, which contain a class II-affinity neoantigen peptide with a class I-restricted neoantigen epitope, can activate both class I-restricted CTL and class II-restricted helper T cells for a long term. In the hybrid neoantigen-pulsed DC vaccine trial, researchers induced strong T-cell reactions in four patients.[69] Such hybrid/combination with DC vaccines could be a future direction.

The development of nanoparticles has entered a new era. Nanoparticles can be engineered to deliver immunomodulatory agents or directly target immune-suppressive cells within the TME, thereby remodeling the TME to enhance the efficacy of PD-1 treatment.[70,71] Tumor vaccine such as peptide vaccines or RNA vaccines can be transported inside these particles, which offer better BBB penetration than traditional carriers. Various types of nanoparticles have been used extensively to improve cancer immunotherapy by remodeling TME. The nanoplatform can be loaded with different functional components to achieve combination therapy easily. For example, The tunable small size of gold nanoparticles makes them ideal candidates as carriers for delivering therapeutic and diagnostic agents across the BBB and targeting brain tumors. Specifically, TAT peptide-targeted multifunctional Au NPs have demonstrated the ability to efficiently cross the BBB in an intracranial GBM mouse model, effectively delivering the anticancer drug doxorubicin and gadolinium-based contrast agents to brain tumor tissues.[72]

Safety analyses of the combination of anti-PD-1 antibodies and radiotherapy, with or without temozolomide, have shown favorable tolerability. Phase III clinical trials, including Checkmate 498 (NCT02617589) and Checkmate 548 (NCT02667587), are currently investigating these combinations. CheckMate 498 specifically assessed the efficacy of anti-PD-1 antibodies combined with TMZ and radiotherapy in

newly-diagnosed O-6-methylguanine-DNA methyltransferase (MGMT)-unmethylated glioblastoma patients. Results from recent trial indicate a failure to achieve the primary objective of enhancing overall survival (OS). The combination of radiotherapy and immunotherapy in glioblastoma patients, despite the presence of immune cell isolation in the bone marrow associated with glioblastoma, has not witnessed significant advancements. Both patients and preclinical models exhibit T-cell isolation in the bone marrow, which is associated with glioblastoma.[6] Treatments like radiotherapy, TMZ, and steroids can exacerbate existing immune dysfunction. High-grade radiation has been shown to induce severe systemic immunosuppression. Current studies are evaluating the viability of low-grade radiation therapy for glioblastoma.[73] Moreover, TMZ has been found to adversely affect immunotherapy, inducing immunosuppression and hindering the development of efficacious memory T cells in a mouse model of glioblastoma.[74] Thus, immunotherapy may face challenges in efficacy compared to TMZ, which may inhibit its effects through immunosuppression. In the future of glioma research, the focus of anti-PD-1 combination therapies may include multi-immune checkpoint inhibitors, neoadjuvant chemo-immunotherapy, small molecule degraders, and tumor microenvironment therapies based on nanoparticles.

In the domain of clinical research, keywords such as immunotherapy, glioblastoma, expression, and survival dominate the discourse. These terms not only reflect current research hotspots but also outline potential future directions. Immunotherapy, which harnesses the body's immune system to recognize and destroy cancer cells, is emerging as a promising approach against glioblastoma, an aggressive brain tumor where traditional treatments like surgery, radiation, and chemotherapy often fall short. Researchers are exploring various immunotherapeutic strategies, including immune checkpoint inhibitors, CAR-T cell therapy, and vaccines, aiming to enhance or restore immune responses against glioblastoma.

Glioblastoma, characterized by its high heterogeneity and rapid proliferation, poses significant challenges due to difficulties in complete surgical resection and its propensity for recurrence. Consequently, understanding the molecular mechanisms and developing novel targeted therapies, such as those addressing IDH mutations or EGFR amplifications, are critical areas of focus.[75] Changes in gene or protein expression levels serve as crucial indicators for tumorigenesis and progression; in glioblastoma, aberrant expression of molecules like PD-L1 and CD133 can influence immune responses and may act as diagnostic markers or therapeutic targets.[76,77]

Ultimately, the overarching goal of all these endeavors is to improve patient survival rates – measured by overall survival (OS) and progression-free survival (PFS) – and quality of life. Achieving this goal hinges on selecting effective treatment modalities, applying personalized medicine strategies, and optimizing supportive care.

The evolution of glioblastoma therapy has seen a shift from single-agent immunotherapies toward combination approaches that integrate multiple treatment modalities. Pivotal studies such as the 2016 work by Brown et al., titled "Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy,"[36] published in the New England Journal of Medicine, laid foundational evidence for the safety and anti-tumor efficacy of CAR-T cells targeting human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor variant III (EGFRvIII) in patients with malignant brain tumors. This study, marked by its significant citation count, highlighted early successes but also underscored limitations, leading researchers to explore more comprehensive strategies.c

O'Rourke et al.'s 2017 publication in Science Translational Medicine, "A single dose of peripherally infused EGFRvIII-directed CAR-T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma,"[37] revealed reduced antigen levels following peripheral infusion of EGFRvIII-directed CAR-T cells. However, it also exposed challenges within the tumor microenvironment, including increased suppressor molecules and enhanced regulatory T cell infiltration post-administration. These findings suggested that overcoming local adaptive changes and addressing antigen variability would be crucial for improving therapeutic outcomes.

Building on these insights, Cloughesy et al. reported in 2019 on a randomized, multi-institutional clinical trial in Nature Medicine, titled "Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma."[38] Conducted by the Ivy Foundation Early Clinical Trials Consortium, this trial assessed immune responses and survival outcomes in surgically resectable recurrent glioblastoma patients receiving neoadjuvant pembrolizumab. Patients who underwent neoadjuvant therapy followed by continued adjuvant therapy post-surgery showed significantly extended overall survival compared to those receiving only adjuvant therapy followed by post-operative PD-1 blockade. This indicated that combining neoadjuvant PD-1 blockade with subsequent treatments could enhance both local and systemic anti-tumor immune responses.

In 2020, Reardon et al.'s Phase III randomized controlled trial (RCT), "Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase III Randomized Clinical Trial,"[39] provided critical data on the efficacy and safety of the PD-1 inhibitor nivolumab versus bevacizumab. Although nivolumab did not significantly prolong overall survival compared to bevacizumab, its consistent safety profile across different tumor types offered valuable insights for clinical application. The suboptimal response observed in phase III trials evaluating vaccine-based therapies, viral therapies, and immune checkpoint inhibitors underscores the multifaceted challenges in glioblastoma management, including tumor heterogeneity, complex tumor microenvironments, drug delivery limitations, antigen escape, intricate tumor genetics, and the complexity of combination therapies.

To address these challenges, current research is increasingly focusing on integrating diverse immunotherapeutic modalities. For instance, Xing et al. emphasized the potential of combining immune checkpoint inhibitors with oncolytic viruses or nanotechnology-based delivery systems to boost therapeutic efficacy.[28,78] Similarly, Lv et al. highlighted

advancements in personalized immunotherapy approaches, particularly CAR-T cell therapy and neoantigen peptide vaccines, which have emerged as key areas in glioblastoma research.[27] These trends indicate a growing recognition of the need for innovative, multifaceted treatment strategies.

By synthesizing bibliometric findings with experimental research, future efforts aim to accelerate advancements in glioblastoma treatment. The integration of various therapeutic modalities holds promise for overcoming the limitations of single-agent therapies and achieving more effective management of this highly aggressive brain tumor. As research progresses, the hope is to foster breakthroughs that will lead to improved patient outcomes and survival rates.

Strengths and limitations

We offer the initial comprehensive overview of global glioblastoma immunotherapy hotspots and trends. The study draws primarily from the WoSCC, a globally recognized scientometric database; However, the omission of articles not indexed in WoSCC introduces potential bias. Importantly, the utilization of abstracts, rather than full-text analysis, in VOSviewer for co-occurring keyword exploration limits the depth of information available for glioblastoma immunotherapy research.

Conclusions

In summary, our study presents a comprehensive global outlook on trends in glioblastoma immunotherapy research. The exponential rise in publications underscores the escalating attention bestowed upon glioblastoma immunotherapy by researchers worldwide, marking it as a pivotal focus within glioblastoma research. Consequently, the United States emerges as a frontrunner in this domain, showcasing substantial contributions. While China has also made notable strides, there remains a need to enhance the quality and impact of research outcomes. Furthermore, collaborative efforts between authors and institutions across the countries, for instance, two top ranked countries (e.g., USA and China), or one top ranked and one low ranked country (e.g., USA and South Korea, and China and Austria), may help drive further innovation and advancement in this area. Duke University stands out as the foremost institution in this field, attracting researchers seeking to delve deeper into glioblastoma immunotherapy. Moreover, Clinical Cancer Research and Neuro-Oncology stand as premier journals for disseminating research on glioblastoma immunotherapy, providing a conduit for accessing cutting-edge advancements. Among scholars, Sampson, Lim, and Mitchell are prominent figures, frequently spearheading the latest developments in the field. Therefore, researchers would benefit from focusing on their work and establishing collaborations with them in this burgeoning domain.

Glioblastoma immunotherapy has progressed into a phase of personalized and precision treatment investigation. Despite an increasing array of drugs and combination therapies being available, clinical trial outcomes have been underwhelming in terms of efficacy. Delving deeper into the pathogenesis and immune microenvironment of glioblastoma, alongside the identification of novel therapeutic targets, emerges as paramount within immunotherapy research for glioblastoma. The selection of appropriate biomarkers for patient screening and treatment efficacy monitoring are the initial steps toward favorable outcomes. The convergence of immunological and targeted drugs in chemotherapy and adjuvant chemotherapy represents a prospective avenue for future research endeavors. Prominent among current discourse are vaccination strategies, immune checkpoint inhibitors, and CAR-T cell therapy, underscoring their significance as focal points for researchers in the field. While immunotherapy research for glioblastoma is gaining momentum, it warrants heightened attention and investment to catalyze meaningful advancements in patient outcomes.

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Authorship contribution statement

All authors contributed to the manuscript and approved the submitted version. L-Z: write original draft and modify the draft. Y-ZJ: modify the draft. Y-W: reviewed the data. W-HX: reviewed the manuscript.

Data availability statement

In this study, data sharing is not applicable as no new data were generated. The datasets utilized originated from publicly available resources: https://webofscience.clarivate.cn/wos/woscc/summary/.

Ethical approval statement

This study does not involve human participants or animal experiments, and therefore, ethical approval is not required.

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