Asian Journal of Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Review Article

A scientometric analysis of immunotherapies for gliomas: Focus on GBM

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ARTICLE INFO

Article history:
Received 20 September 2023
Received in revised form
5 February 2024
Accepted 23 February 2024
Available online xxx

Keywords:
Scientometrics
Immunotherapy
GBM
Vaccine
Oncolytic virus

ABSTRACT

Gliomas are the most prevalent primary malignant brain tumors worldwide, with glioblastoma (GBM) being the most common and aggressive type. The standard therapy for GBM has remained unchanged for nearly two decades, with no significant improvement in survival outcomes. Despite several barriers such as the tumor microenvironment (TME) and blood–brain barrier, immunotherapies bring new hope for the treatment of GBM. To better understand the development and progress of immunotherapies in GBM, we made this scientometric analysis of this field. A total of 3753 documents were obtained from the Web of Science Core Collection, with publication years ranging from 1999 to 2022. The Web of Science platform, CiteSpace, and VOS viewer were used to conduct the scientometric analysis. The results of scientometric analysis showed that this field has recently become a popular topic of interest. The United States had the most publications among 89 countries or regions. Keyword analysis indicated significant areas in the field of immunotherapies for GBM, especially TME, immune checkpoint blockades (ICBs), chimeric antigen receptor T (CAR-T) cells, vaccines, and oncolytic viruses (OVs). Overall, we hope that this scientometric analysis can provide insights for researchers and promote the development of this field.

1. Introduction

Gliomas are the most prevalent primary malignant brain tumors worldwide. They are typically divided into four grades (I, II, III, and IV) according to the *World Health Organization* grading system.[1] Glioblastoma (GBM), a grade IV astrocytoma, is the most common and aggressive malignancy among gliomas, accounting for 50% of all cases.[2] Moreover, patients diagnosed with GBM usually have a median overall survival (mOS) of less than 2 years, with a 5-year survival rate of 10%.[3–5]

The current standard treatment for GBM is the Stupp regimen, which includes maximal surgical resection of the tumor and then a combination of radiotherapy and chemotherapy.[6] However, almost all patients with GBM show recurrence after receiving standard treatment because of its high invasiveness, thus necessitating the exploration of other treatments for GBM. In recent years, immunotherapeutic strategies have revolutionized the treatment of various cancers, such as melanoma and lung cancer, and have brought new hope for the treatment of GBM.[7–9]

Currently, more than 88 clinical trials on immunotherapies for GBM are being conducted worldwide.[10] Moreover, the efficacy of several immunotherapeutic treatments, including the dendritic cell (DC) vaccine DCVax-L[11,12] and oncolytic virus (OV) G47Δ,[13] has been demonstrated in phase II and III clinical trials. However, several barriers including the blood–brain barrier (BBB), tumor microenvironment (TME), and substantial heterogeneity largely weaken and limit the efficacy of immunotherapies for GBM. Therefore, novel effective therapeutic approaches are constantly being studied.

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https://doi.org/10.1016/j.asjsur.2024.02.138

Please cite this article as: Y. Xing, F. Yasinjan, H. Geng *et al.*, A scientometric analysis of immunotherapies for gliomas: Focus on GBM, Asian Journal of Surgery, https://doi.org/10.1016/j.asjsur.2024.02.138

Abbreviation

GBM	glioblastoma
TME	tumor microenvironment
WoSCC	Web of Science Core Collection
ICB	immune checkpoint blockade
CAR-T	chimeric antigen receptor-T cell
OV	oncolytic virus
BBB	blood–brain barrier
CTLA-4	cytotoxic t lymphocytes-associated antigen 4
DC	dendritic cell
EGFR	epidermal growth factor receptor: newly diagnosed glioblastoma
rGBM	recurrent glioblastoma
HER2	human epidermal growth factor receptor 2
HSV	herpes simplex virus
PD-1	Programmed Death 1
PD-L1	programmed cell death ligand 1
ORR	overall response rate

Scientometrics is an emerging field that efficiently detects research advances, hotspots, and trends by analyzing literatures in a certain field.[14–18] Based on the limitations of current treatments and rapid development of immunotherapies for GBM, it is vital to identify the research advances, hotspots, and trends in this field to provide insights for researchers and promote the development of this field.

2. Materials and methods

2.1. Data sources and search strategy

The data source for scientometric analysis was the Science Citation Index Expanded in the Web of Science Core Collection (WoSCC), which ensures comprehensive and accurate data retrieval. The Web of Science (WoS) is a reputable digital literature database with comprehensive, up-to-date resources; therefore, it is widely considered an appropriate database for scientometric analysis.[14–19] The retrieval strategy for this scientometric analysis was based on the Medical Subject Headings database: topic subject (TS) = (glioma OR glioblastoma OR GBM) AND TS = (immunotherapy). The publication years were set from 1999 to 2022, the document types included original research and review articles, and the language was set as English. The database was searched on January 11, 2023, and 3753 documents were included in this study. A flowchart of the scientometric analysis was created (Fig. 1).

2.2. Data analysis and methodology

CiteSpace 6.1.R6 Advanced software was used to analyze the literature included in this study. The 3753 records were exported from the WoSCC as plain text files. Then, CiteSpace was adjusted as follows: 1) the time slices were from January 1999 to December 2022, and each slice corresponded to 1 year; 2) the top 50 most cited or appearing items from each slice were set as the selection criteria; and 3) the pathfinder, pruning sliced networks, and pruning the merged network were chosen as the pruning functions. Other default functions were retained. CiteSpace was used to analyze the research countries and institutions, references, clustering, timeline view, time-zone view, and burst analysis of keywords.

VOS Viewer 1.6.18 was also used in this study. The 3753 records were exported from the WoSCC as tab-delimited files. Moreover, a VOS viewer was used to identify related authors in this field.

3. Results

3.1. Annual distribution of publications and citations

Publication and citation data were obtained from the WoS platform. There were 3753 documents in this field, with a total citation frequency of 12,035 and an average citation frequency of 32.06. The H-index in this field was 148, indicating that at least 148 articles were cited more than 148 times. To better understand the change in the number of publications in this field over time, a regression model $y = 21.039e^{0.124x}$ ($R^2 = 0.8953$) was used for fitting. The annual publication number steadily increased from 1999 to 2019 (Fig. 2), with a more pronounced increase from 2019 to 2022 and is likely to continue to grow rapidly in the future. A similar trend was observed in the citation number, which increased rapidly from 2016 to 2022, especially from 2019 to 2021.

3.2. Countries (or regions) and institutions

CiteSpace was used to analyze and collect data concerning the distribution of related publications based on different countries, regions, and institutions. Country- or region-specific data were transferred to a global geographical distribution map (Fig. 3). A total of 3753 articles related to immunotherapy for gliomas were published in 89 countries or regions. Moreover, 20 or more articles have been published in 25 countries or regions. The United States had the most publications (n = 1649), accounting for 33.92% of the total.

In CiteSpace, the betweenness centrality is an important index for evaluating the importance of a node in a network.[20] The United States obtained the highest betweenness centrality value (0.82), indicating its strong influence in this field. Furthermore, China had the second-highest number of publications (n = 980, 20.16%) with a betweenness centrality value of 0.75, which was the second-highest among all countries. Except for China (with the first publication in 2004) and England (with the first publication in 2001), the top 10 countries with the most publications published their first article in 1999.

A network map of the institutional publications (Fig. 4A) was obtained directly from CiteSpace. In the cooperative network of institutions, 57 institutions had at least 1 publication on the topic of immunotherapy for gliomas. The nodes represent the research institutions in the network; the larger the node, the greater the publication volume. Regarding the most productive organizations, four of the top five were in the United States, and one was located in China. Institutions with high betweenness centrality ($\geq$0.10) include the University of California, Los Angeles (0.18); University of Pittsburgh (0.16); University of California, San Francisco (0.14); and University of Michigan (0.12), indicating their predominance in this field.

3.3. Related authors

To understand the leading scholars in this field and their collaborations, VOS Viewer was used to detect the publications, citations, and co-citations of related authors. According to the results, 19 authors had more than 20 publications, among whom Sampson JH, the most cited author in this field (n = 4467), ranked first with 65 publications. The top 300 authors, who were co-cited more than 20 times, were included in the author cooperation network diagram (Fig. 4B). Co-citation means that two publications (or authors) are cited simultaneously by another publication (or author).[21] Moreover, with high co-citation numbers, closer relationships

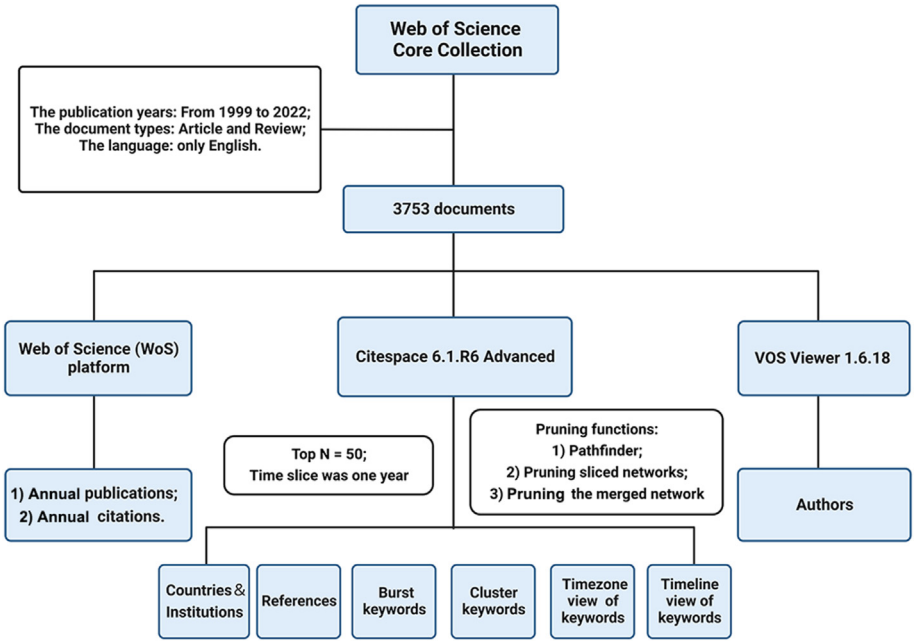

Fig. 1. The flowchart of the bibliometric analysis.

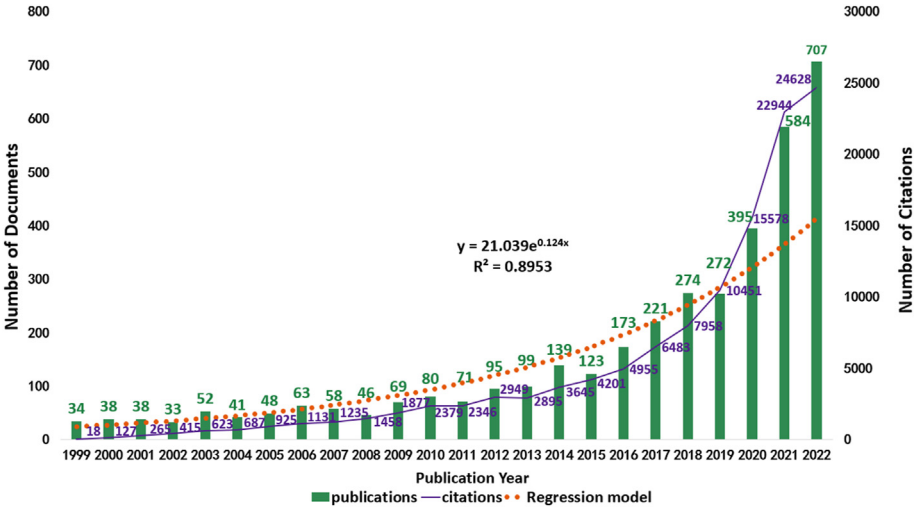

Fig. 2. The annual distribution of publications and citations. The regression formula is $y = 21.39e^{0.124x}$, $R^2 = 0.8953$.

and similar content were observed between any two publications (or authors). In Fig. 4B, the size of the circles indicates the co-citation number of authors, the lines between authors represent the cooperation relationship, and the same-colored circles (called a cluster) indicates a high frequency of co-citations for authors in the same cluster. Among the top 10 authors with the highest co-citations, Stupp R had the most co-citations (1587 times) and strongest total correlation strength, indicating its great influence on this field. Stupp R was followed by Sampson JH (1,002) and Reardon DA (977). As shown in Fig. 4B, some close co-citation relationships can be observed, such as those between Reardon DA and Stupp R, Sampson JH and Fecci PE, and Louis DN and Ostrom QT. These highly co-cited authors and their close relationships have significantly contributed to the development of this field.

3.4. References

We used CiteSpace to conduct a co-citation analysis of related references and explore the co-citation status of references in the previous two decades. Fig. 4C is the co-citation network map from 1999 to 2022. It shows that the most highly co-cited references have been centered in recent years, indicating the increasing popularity of the topic. Correspondingly, Table 1 provides detailed information on the top 10 co-cited references published within the last 7 years. Seven clinical trials were associated with the treatment of GBM, including one related to vaccine therapy, three related to chimeric antigen receptor T (CAR-T) cell therapy, and three related to immune checkpoint blockades (ICBs), indicating the rapid development and active and quick implementation of strategies such as CAR-T and ICBs in clinical practice. Lim et al[22] conducted a comprehensive review of immunotherapies used for GBM

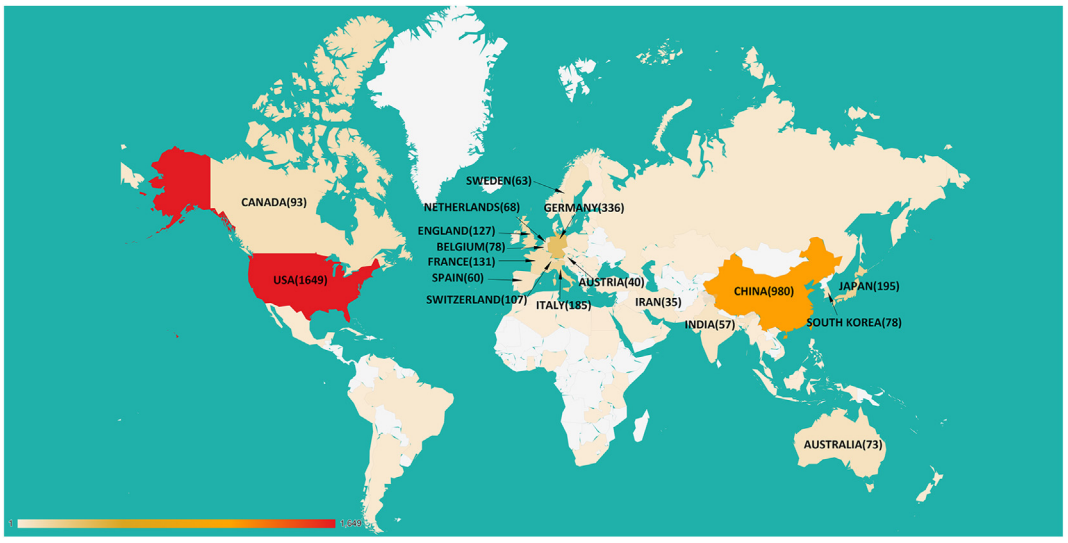

Fig. 3. The geographical visualization of publications related to immunotherapies in gliomas.

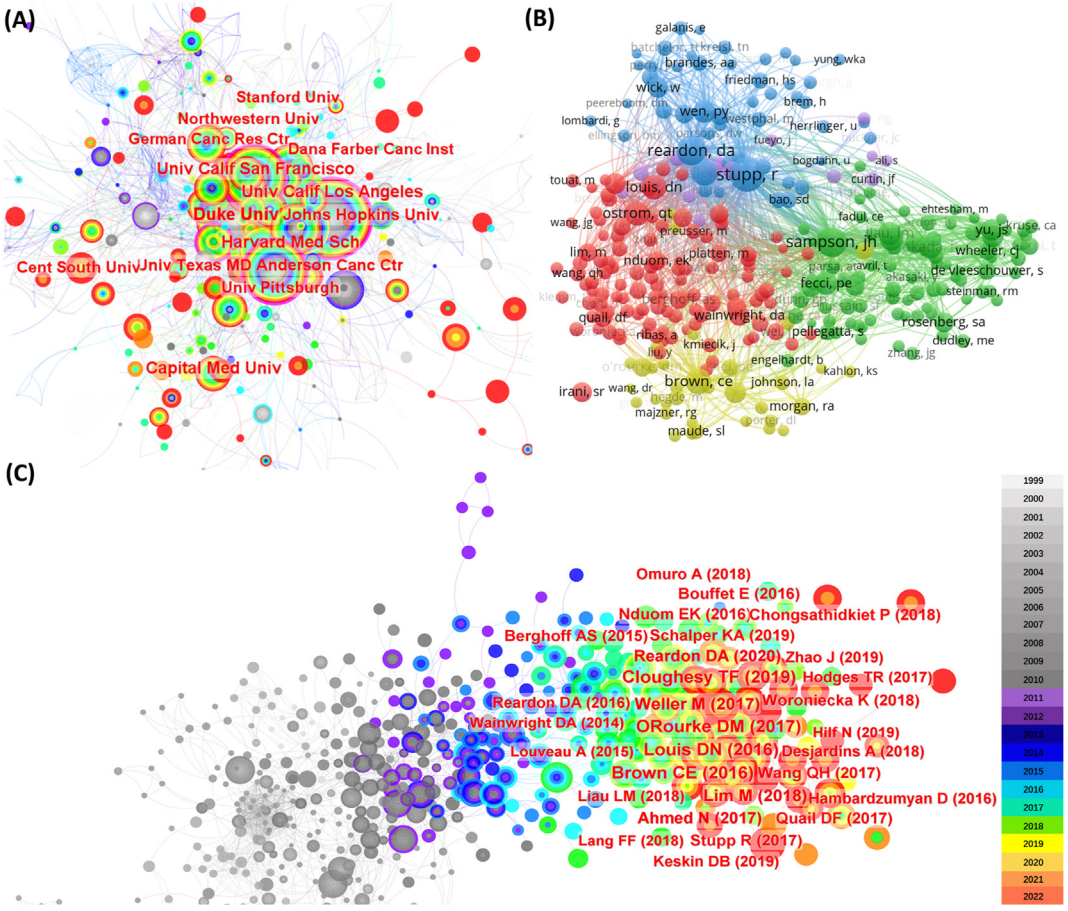

Fig. 4. Scientometric analyses of research institutions, authors, and references. **(A)** The co-occurrence map of research institutions. **(B)** The network map of research authors. **(C)** The co-citation map of references of this field. The different colors represent different publication years of papers, as displayed on the right. The development of this field by years is basically from left to right. In addition, the circle size indicates the occurrence (frequency)/citation/co-citation number of items (such as institutions, authors, and references), the lines between the items represent the cooperation relationship, and the same-colored circles (called a cluster) indicates a high frequency of citation/co-citations for items in the same cluster. These explanations are also made for Figs. 6 and 7.

treatment in 2018, which provided a good reference for future research in this field. Wang et al[23] conducted transcriptome profiling to explore the characteristics of the microenvironment in various GBM gene expression subtypes, both before and after

Table 1
Top 10 co-cited references.

Year	Title	Type	First author	Journal	Focus and main idea	IF (2021)	JCR	Co-citation
2017	A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma	Clinical Trial	O'Rourke, DM[43]	SCI TRANSL MED	A first-in-human study of intravenous delivery of a single dose of autologous CAR-T cells targeting EGFRvIII in patients with recurrent GBM was reported.	19.343	Q1	292
2016	The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary	Review	Louis, DN[24]	ACTA NEUROPATHOL	An updated classification of tumors of the central nervous system in 2016 was released.	15.887	Q1	276
2019	Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma	Clinical Trial	Cloughesy, TF[29]	NAT MED	The enhanced antitumor effect of neoadjuvant pembrolizumab in patients with recurrent and resectable GBM was observed.	87.244	Q1	265
2016	Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy	Clinical Trial	Brown, CE[44]	NEW ENGL J MED	A clinical trial identified the regression of GBM after CAR-T treatment.	176.082	Q1	264
2018	Current state of immunotherapy for glioblastoma	Review	Lim, M[22]	NAT REV CLIN ONCOL	A review on the current state of immunotherapy in patients with GBM was made.	65.011	Q1	240
2017	Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial	Clinical Trial	Weller, M[39]	LANCET ONCOL	A phase III trial studied the efficacy of rindopepimut combined with temozolomide in patients with newly diagnosed EGFRvIII^{+} GBM.	54.433	Q1	234
2020	Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma The CheckMate 143 Phase 3 Randomized Clinical Trial	Clinical Trial	Reardon, DA[30]	JAMA ONCOL	A phase III trial studied the efficacy of Nivolumab versus Bevacizumab in patients with recurrent GBM.	33.012	Q1	194
2017	HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma A Phase 1 Dose-Escalation Trial	Clinical Trial	Ahmed, N[45]	JAMA ONCOL	A phase I trial studied the safety and antitumor activity of HER2-specific CAR-modified VST in patients with progressive GBM.	33.012	Q1	186
2019	Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma	Clinical Trial	Schalper, KA[31]	NAT MED	A phase II trial of neoadjuvant nivolumab in patients with resectable GBM.	87.244	Q1	153
2017	Tumor Evolution of Glioma-Intrinsic Gene Expression Subtypes Associates with Immunological Changes in the Microenvironment	Article	Wang, QH[23]	CANCER CELL	Three tumor-intrinsic transcriptional subtypes of glioma were defined using gene expression profiles.	38.585	Q1	151

treatment.

Thereafter, 25 references that represented the highest citation burst strength (Fig. S1, Table S1) were obtained, which included 12 clinical trials, 9 original articles, and 4 reviews. A review of the classification of central nervous system tumors in 2016 showed the highest burst intensity.[24] In addition, two clinical trials reported the use of CAR-T for GBM treatment, and another reported pembrolizumab for recurrent GBM (rGBM). Lim et al[22] reviewed the current status of immunotherapy for GBM and also had a strong citation burst. It can also be seen from the burst analysis of references that most references with high citation bursts were centered in the past 10 years, especially in the past 5 years.

3.5. Burst analysis of keywords

To better detect the research trends and hotspots in this field, a burst analysis of keywords was performed using CiteSpace (Fig. 5). Burst analysis helps obtain keywords that have rapidly gained popularity in a short period of time and can facilitate the analysis of emerging trends in a particular field. In Fig. 5, the burst period of a keyword is indicated by the red line segment.[25] Among the 25 most representative keywords, TME was the keyword with the strongest outbreak intensity (42.84). Furthermore, TME first appeared in 2012 and showed the strongest bursts from 2020 to 2022, indicating that this keyword has gained particular attention recently. Second, the keyword cytotoxic T lymphocytes (28.95) appeared early and had the longest burst duration from 1999 to 2012. The keyword nivolumab (25.48) had the third-strongest burst strength from 2017 to 2020. In addition, immune checkpoint and checkpoint blockade was also identified as burst keywords in recent years. Several keywords including DC, cancer vaccination, vaccination, dendritic cell vaccination, colony-stimulating factor, and interleukin 2 showed burst in a more recent period, which may indicate the popularity of vaccination. In addition, two other common therapies, the CAR-T therapy and OV therapy, were revealed in this burst analysis. The bursting period of keyword phase II was from 2016 to 2019, although it first appeared in 2000, indicating that clinical trials on immunotherapies for gliomas have continued to develop over the past two decades and have become especially popular recently. This could also be indicated by 7 clinical trials of the 10 references from the co-citation analysis of references. Cancer stem cell was also a burst keyword with a long-lasting period from 2013 to 2020. The burst keywords in the last 5 years included nivolumab (2017), bevacizumab (2017), immune checkpoint (2017), suppressor cell (2018), checkpoint blockade (2018), BBB (2018), resistance (2019), OV (2020), TME (2020), and tumor-associated macrophage (2020). These newly developed keywords show new trends in recent years, namely ICBs, OVs, and TME.

3.6. Clustering analysis of keywords

CiteSpace was used to conduct co-occurrence and clustering analyses of keywords to identify the primary content and research hotspots in this field. Through the co-occurrence analysis, 10 keywords with the highest frequency were obtained as follows: immunotherapy (n = 787), expression (n = 777), cancer (n = 656), glioblastoma (n = 499), malignant glioma (n = 466), T cell (n = 463), dendritic cell (n = 430), central nervous system (n = 422), brain tumor (n = 407), and glioblastoma multiforme (n = 356).

We then conducted a clustering analysis of the keywords based on a co-occurrence analysis (Fig. 6). There are 16 clusters shown in Fig. 6, including #0 cancer immunotherapy, #1 immune checkpoint, #2 dendritic cells, #3 glioblastoma multiforme, #4 activation, #7 newly diagnosed glioblastoma, #10 gene therapy, #12 TME, #13 T cells, #14 antitumor immunity, and #15 tumor antigen. Most of the cluster keywords are further clarified in the Discussion section. A landscape view of each cluster was obtained (Fig. S2). Intuitively, clusters including #0 cancer immunotherapy, #1 immune checkpoint, #6 tumor, #9 expression, #10 gene therapy, and

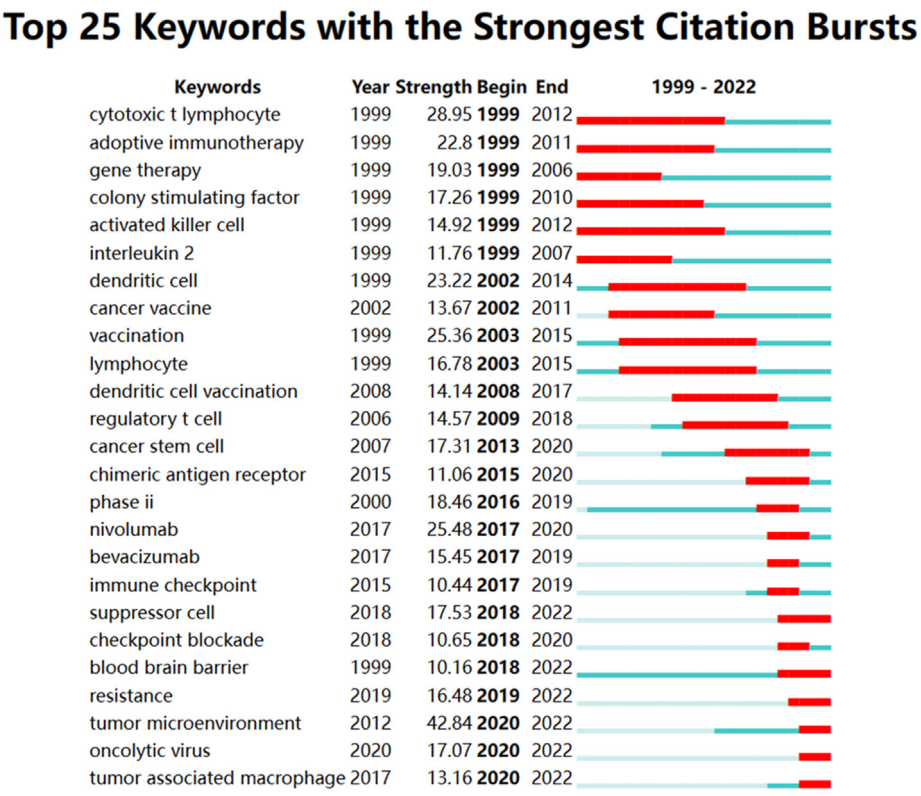

Fig. 5. The top 25 keywords with the strongest citation bursts.

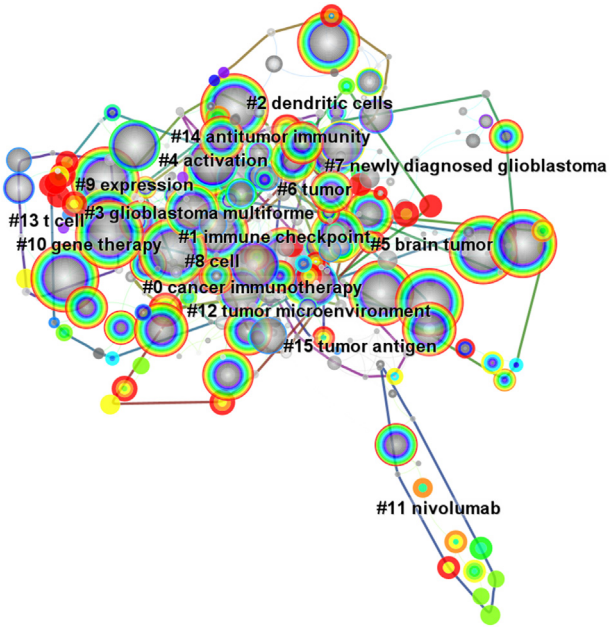

Fig. 6. The clustering analysis of keywords. A total of 16 clusters were obtained.

#12 TME showed continuous development from 1999 to 2022.

3.7. Timeline view and time-zone view of keywords

The timeline view of keywords in clusters can be regarded as a more specific version of the landscape view. In the timeline view of the clusters (Fig. 7), the continuous clusters remained the same as those in the landscape view. From the timeline view of treatment-related clusters, research on DCs was mainly concentrated before 2015, whereas research on immune checkpoints, T cells, nivolumab, and gene therapy has continued to thrive in recent years. In addition, we can see many novel keywords arising in the last 3 years, indicating their relevance and high popularity in this field.

A time-zone view analysis of keywords was performed to understand the development of immunotherapy for gliomas (Fig. S3). Many nodes, especially larger ones, were centered in the early years because keywords often appeared early. Frequent links can be observed between early and newly appearing nodes. Except for the first 3 years, the numbers of newly appearing keywords in 2003, 2006, 2017, and 2022 were higher than those in other years, which might represent the appearance of new trends during those periods.

4. Discussion

The results of scientometric analysis indicated recent situations, research trends, and hotspots in the field of immunotherapy for gliomas/GBM. From 1999 to 2022, the number of published articles in this field and their citations maintained a steady growth, with a sharp increase over the past 3 years. In addition, most references with high citation bursts were published in the last 10 years, especially in the last 5 years, indicating that the field has developed rapidly and received continuous attention. In the analysis of countries (or regions), the United States and China occupied important leading positions. Stupp R, Sampson JH, and other highly co-cited authors, with their close cooperation, have greatly contributed to the development of this field. The analysis of references and keywords revealed the significance of ICBs, CAR-T cell therapies, and vaccine therapies in GBM treatment. The importance of OV therapies, acting as up-to-date bursting keywords, has also

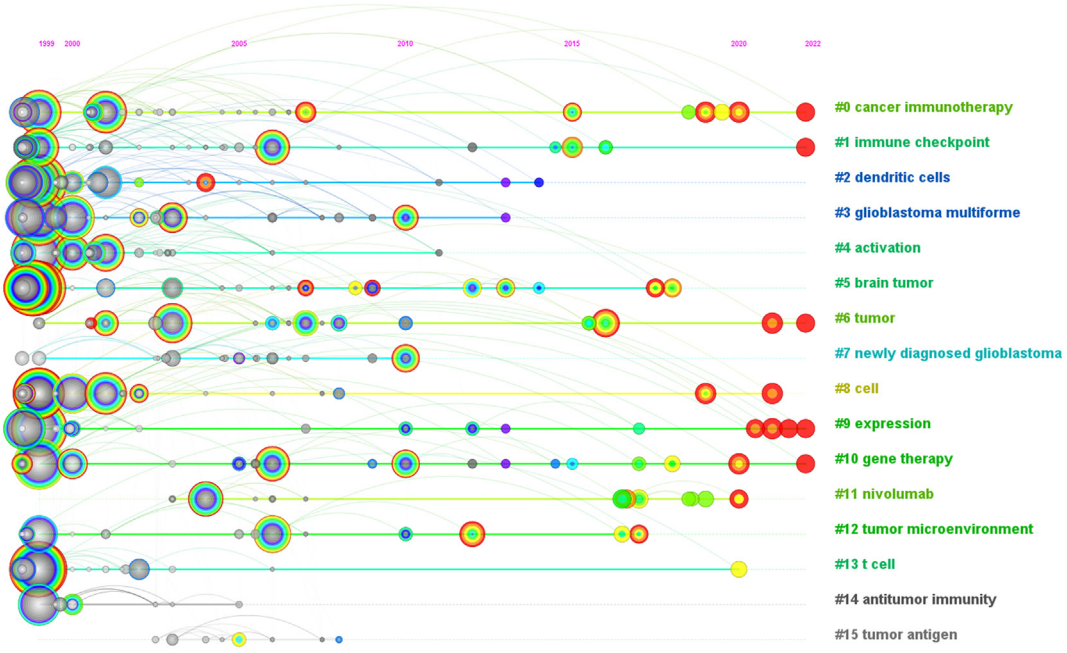

Fig. 7. The timeline view of 16 clusters based on the cluster analysis. The development of this field by years is from left to right.

been identified in burst analyses. Moreover, the importance of the TME was stressed in the clustering and burst analyses of keywords. Other emerging keywords with the strongest citation bursts included cancer stem cell (2013–2020), BBB (2018–2022), and tumor-associated macrophages (2020–2022). It was found that GBM (both newly diagnosed GBM [nGBM] and rGBM) is the most studied type of glioma in this field. Hence, GBM is our main focus in the discussion. Besides, gene therapy, which has multiple connections to immunotherapy, appeared as a cluster and burst keyword. According to the scientometric analysis, we identified four main types of immunotherapies used for the treatment of gliomas: ICBs, CAR-T cell therapies, vaccine therapies, and OV therapies.

4.1. ICBs

ICBs mainly refer to blocking immunosuppressive immune checkpoints such as PD-1/PD-L1 and CTLA-4, thus inhibiting their corresponding immunosuppressive and antitumor effects. Burst and clustering analyses of keywords showed the significance of ICBs in the field of immunotherapies for GBM. Among the top 10 co-cited references, three clinical trials were associated with ICBs for GBM treatment. All three studies used anti-PD-1 monoclonal antibodies. However, unlike other cancers such as melanoma and lung cancer, the application of ICBs is unfavorable for the treatment of GBM.[26]

There were two randomized phase III clinical trials (CheckMate 498 and CheckMate 548) that tested the efficacy of nivolumab in patients with nGBM.[27,28] Checkmate 498 compared the efficacy of nivolumab plus radiotherapy with that of temozolomide (TMZ) plus radiotherapy in patients with nGBM with unmethylated MGMT promoters. However, recently published results did not reach the primary endpoint (mOS). The mOSs of the nivolumab plus radiotherapy and TMZ plus radiotherapy groups were 13.4 months and 14.9 months, respectively.[28] CheckMate 548 was a similar phase III study that evaluated the efficacy of nivolumab plus the Stupp regimen (radiotherapy plus TMZ) compared with the Stupp regimen plus placebo in patients with nGBM with a methylated MGMT promoter.[27] However, the results also showed that adding nivolumab to the Stupp regime could not improve the OS and PFS of patients with nGBM with methylated MGMT promoters. In the field of rGBM, a randomized multi-institutional trial involving neoadjuvant pembrolizumab (anti-PD-1) for recurrent, operable GBM, demonstrated promising outcomes.[29] Notably, patients who received pembrolizumab both before and after surgery exhibited markedly better overall survival (OS) and progression-free survival (PFS) compared to those treated post-surgically with pembrolizumab alone (7.5 vs. 13.7 months for OS and 2.4 vs. 3.3 months for PFS, respectively). However, other trials, including CheckMate 143 and NCT02550249, did not yield similarly optimal results.[30,31] Obviously, there is still a long way to the success for ICBs in the management of GBM, possibly through the feasible and effective combined therapies.[10,32]

4.2. Vaccine therapy

Vaccines have a long history of use in cancer treatment,[33,34] as indicated by the burst analysis of keywords. Peptide and DC vaccines are the main strategies of vaccines used for glioma treatment.[35–37] For peptide vaccines, EGFRvIII is one of the most studied TSAs and an ideal vaccine target for GBM.[38] A clinical trial in the top 10 co-cited references 39 used the peptide vaccine rindopepimut. However, this phase III trial of rindopepimut in combination with TMZ in patients newly diagnosed with EGFRvIII-positive GBM did not yield promising results.

DC vaccines are another common type of vaccine for gliomas. Currently, approximately half of phase II and phase III trials involving vaccines are cell-based strategies, especially DC vaccines.[40] Burst and clustering analyses of keywords also revealed the importance of DC vaccines. Recently, a phase III clinical trial of an autologous tumor lysate-loaded DC vaccine (DCVax-L) plus TMZ in patients with nGBM and rGBM showed promising results.[11,12] The primary and secondary endpoints of this study were the mOS of patients with nGBM and rGBM, respectively.[11] In the nGBM group, the mOS in the DCVax-L plus TMZ and TMZ control groups was 19.3 and 16.5 months, respectively ($P = 0.002$). The 2- and 5-year survival rates of patients in the DCVax-L plus TMZ and TMZ control

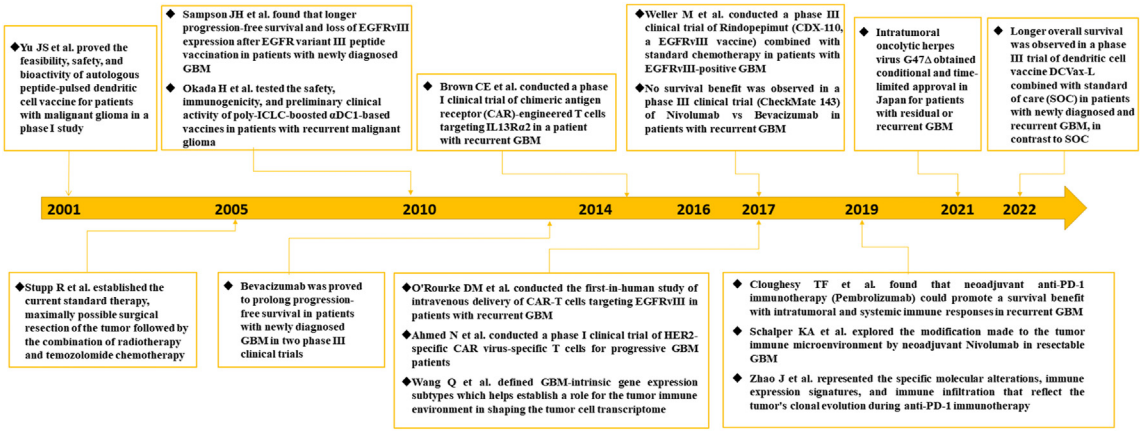

Fig. 8. The landmark achievements of immunotherapies in GBM since 2001.

groups were 15.7% and 9.9% and 13.0% and 5.7%, respectively.[11] In the rGBM group, the mOS in the DCVax-L plus TMZ and TMZ control groups was 13.2 and 7.8 months, respectively ($P < 0.001$), while the two-year and 30-month survival rates in the DCVax-L plus TMZ group and the TMZ control group were 15.7% vs. 9.9% and 13.0% vs. 5.7%, respectively.[11] In addition, DCVax-L-treated patients with nGBM with a methylated MGMT promoter survived longer (21.3 months) than those in the external control group ($P = 0.03$).[11] This phase III trial paved the way for future success in the field of immunotherapy for gliomas, although individual patient-level data from external control populations were not accessible.

4.3. CAR-T cell therapy

CAR-T cell therapy is a typical adoptive T cell therapy.[41] The significance of CAR-T therapy was indicated by the burst analysis of keywords. However, they have not been successfully used to treat gliomas.[42] There were 3 phase I clinical trials associated with CAR-T cell therapy for GBM treatment in the top 10 co-cited references, indicating active attempts in this field. Moreover, several commonly used targeted antigens, including EGFRvIII,[43] IL13Rα2,[44] and HER2,[45] have been identified. CAR-T cell therapy is a step forward for the treatment of both hematologic and solid tumors. However, its use in GBM treatment remains limited because of its role in the BBB, antigen escape, tumor heterogeneity, and TME.[46] Although the three phase I clinical trials indicate strong hope for GBM treatment, more clinical trials with larger samples and more reliable examinations are required.

4.4. OV therapy

OV is an emerging treatment strategy and has been a popular topic in this field,[47] as shown by the keyword burst analysis. Moreover, in 2021, G47Δ was conditionally and time-limitedly approved in Japan by the Japanese Ministry of Health, Labor and Welfare to treat patients with malignant glioma.[13] Gliomas are particularly suitable for OV therapy because tumor growth is primarily confined to the brain and lacks distant metastasis, which allows viruses to require an active cell cycle for replication.[48] Of all OVs, oHSV has shown the greatest progress in clinical practice, including G47Δ, G207, HSV1716, and rQNestin-34.5.[49] UMIN000015995 was a phase II trial of G47Δ in patients with residual or rGBM in Japan.[13] G47Δ is a triple-mutated third-generation oHSV type 1, which is constructed by removing the α47 gene and overlapping the US11 promoter from its parental G207.[50] The primary endpoint, the 1-year survival rate (84.2%), was reached ahead of time. Moreover, the secondary endpoints, OS and PFS after G47Δ initiation, were 20.2 months and 4.7 months, respectively.[13] Based on these results, G47Δ obtained conditional and time-limited approval in Japan for the treatment of malignant gliomas.[13]

4.5. TME in gliomas

As mentioned above, immunotherapies have demonstrated promising outcomes in both preclinical and clinical studies, especially in the successful phase III trial of DCVax-L and conditional approval of G47Δ in Japan. However, there are still many obstacles to its success. The TME is regarded as one of the most important factors in various treatment methods, especially immunotherapies. The immunosuppressive TME of gliomas can result in drug resistance and tumor recurrence. However, an in-depth understanding and making great use of the TME can also promote the progress of immunotherapy for gliomas. Our scientometric analysis also detected the significance of TME in immunotherapies for gliomas. Indeed, TME was the cluster and burst keyword with the strongest burst intensity.

The TME in gliomas is complex and heterogeneous and consists of various components, including astrocytes, pericytes, endothelial cells, glioma stem cells, blood vessels, glioma-associated stromal cells, immune cells, including myeloid-derived suppressor cells, glioma-associated microglia/macrophages, $CD4^+$ T cells, Tregs, and NK cells, and the extracellular matrix.[32,51–53] These components interact to stimulate the growth and invasion of glioma cells. It is widely acknowledged that TME is one of the main reasons for unsatisfactory immunotherapeutic effects on gliomas. Additionally, an increasing number of immunotherapy-related studies have focused on TME in gliomas.[29,31,43]

5. Conclusion

The bibliometric analysis of 3753 publications on immunotherapies for gliomas showed research advances, hotspots, and trends in this field. GBM is the main focus of this field. And based on the bibliometric analysis, recent advances in four main immunotherapies for GBM including ICBs, vaccine therapies, CAR-T cell therapies, and OV therapies were discussed. The important role of TME in GBM was also stressed. In addition, a timeline of the landmark achievements in this field was created (Fig. 8). Overall, immunotherapies are promising in the treatment of GBM; however, more efforts are needed to overcome several challenges including the BBB, immunosuppressive TME, substantial heterogeneity, and glioma stem cells.

6. Limitation

Due to the difficulties and issues of incorporating data from different databases and current drawbacks of the software, the study only adopted the Web of Science Core Collection as the database. And this may lead to the existence of the potential database bias. We sincerely hope that different databases will have similar data forms and the improved software for scientometric analysis.

Author's contributions

BG, LZ, and JZ conceived the study and performed critical revision of the manuscript. YX, FY designed the study, performed statistical analyses, and drafted the manuscript. HG, MH, MY, YG designed the study and wrote the manuscript. YX, FY performed the article retrieval and data interpretation. All authors read and approved the final manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 82273479 to l.Z.) and China-Japan Union Hospital and College of Basic Medical Sciences, Jilin University Union Project (Grant No. KYXZ2022JC05 to l.Z.) and Graduate Innovation Fund of Jilin University (Grant No. 2023CX131 to M.Y.)

Declaration of competing interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2024.02.138.

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