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Bibliometric evaluation of research trends and hotspots concerning the interaction between immune checkpoint inhibitors and glioma

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Abstract

Introduction Immune checkpoint inhibitors have revolutionized oncology, but their efficacy in glioma remains a major focus of research. This study employs bibliometric methods to analyze the current research status and emerging trends in the field of Immune Checkpoint Inhibitors and Glioma, providing a reference for subsequent research in this domain.

Methods This study retrieve articles related to Immune Checkpoint Inhibitors and Glioma from the WOS Core Database, covering the period from the database's inception to April 9, 2025. Following rigorous selection criteria, employ VOSviewer and CiteSpace to conduct analyses on quantity, collaboration networks, clustering, and citation bursts.

Results The number of publications concerning Immune Checkpoint Inhibitors and Glioma has been increasing annually, with a significant surge post-2017. China leads in publication volume, while the United States has the highest citation count. Harvard Medical School stands out as both the institution with the highest number of publications and citations. Among the top ten journals with the most publications, seven are classified in the Q1 category of the JCR. The most cited article is "Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial" by Reardon DA et al., published in 2020 in JAMA ONCOLOGY. The ten most frequently occurring keywords include glioma, immunotherapy, glioblastoma, expression, cancer, central nervous system, prognosis, blockade, survival, and T-cells. The keyword cluster "cuproptosis" has emerged as a novel area of focus in recent years, whereas oncolytic virotherapy remains a current research hotspot.

Conclusion This study employs bibliometric analysis to elucidate publication trends in the domain of Immune Checkpoint Inhibitors and Glioma, examining the collaborative networks among countries, institutions, and authors. It further identifies recent research hotspots, thereby providing an objective data-driven reference for scientific inquiry into Immune Checkpoint Inhibitors and Glioma.

Keywords Bibliometric analysis, Immune checkpoint inhibitors, Glioma, Publication, Oncolytic virotherapy

1 Introduction

Gliomas, as the most aggressive primary intracranial tumors of the central nervous system, pose a significant threat to human health due to their malignant biological behavior [1]. According to the World Health Organization's grading criteria, these tumors are classified into four malignancy grades [2, 3]. Despite multimodal therapeutic approaches, the prognosis for patients with high-grade gliomas, particularly GBM, remains poor [4, 5].

Current research focuses on two critical immune checkpoints: the CTLA-4 and PD-1/PD-L1 pathways [6]. CTLA-4 acts as an immune regulatory hub, primarily modulating the activation of CD4 + helper T cells and promoting the proliferation of regulatory T cells (Tregs). Although the representative inhibitor ipilimumab theoretically holds therapeutic potential, clinical data indicate significant limitations and drug resistance in glioma treatment [7]. PD-1 pathway inhibitors, such as pembrolizumab, have not yet demonstrated significant survival benefits in clinical trials for GBM monotherapy [8]. To overcome the limitations of single therapies, researchers are actively exploring combination treatment strategies, including radiosensitization, chemotherapy adjuncts, molecular targeting, and oncolytic virotherapy. Notably, the combined application of CTLA-4 and PD-1 inhibitors has entered clinical validation stages, with potential mechanisms involving multi-target intervention of tumor cells and synergistic activation of immune functions [9].

Despite the growing body of research in this field, bibliometric studies systematically organizing the knowledge structure remain scarce, hindering a comprehensive understanding of the discipline's developmental trajectory. This study employs bibliometric methods to systematically analyze academic output from the Web of Science core database, aiming to construct a knowledge map of the field, revealing the evolutionary patterns, interdisciplinary characteristics, and frontier directions of immune checkpoint inhibitors in glioma research, thereby providing a multidimensional theoretical reference for subsequent studies.

2 Methods

2.1 Literature search and screening strategy

2.1.1 Search strategy

The Web of Science Core Collection (WoSCC) database was utilized for literature retrieval based on its established utility in bibliometric studies and extensive disciplinary coverage of high-impact journals. As a leading database for bibliometric analysis, WoS provides robust citation data and standardized metadata, which are crucial for the accuracy of co-citation and collaboration network analyses performed by tools like VOSviewer and CiteSpace. The search period extended from the database's inception to April 9, 2025. The search strategy was informed by the methodologies of Huo X and Zhang H et al. [10, 11], incorporating terms from the Medical Subject Headings (MeSH) database to ensure exhaustive retrieval of relevant keywords. The search terms included: TS = ((Glioma) OR (Gliomas) OR (Glial Cell Tumors) OR (Glial Cell Tumor) OR

(Mixed Glioma) OR (Mixed Gliomas) OR (Malignant Glioma) OR (Malignant Gliomas) OR (Glioblastoma) OR (Glioblastomas) OR (GBM) OR (Glioblastoma Multiforme)) AND TS = ((Immune Checkpoint Inhibitors) OR (Immune Checkpoint Blockers) OR (Immune Checkpoint Inhibitor) OR (CTLA-4 Inhibitors) OR (CTLA 4 Inhibitors) OR (Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitors) OR (Cytotoxic T Lymphocyte Associated Protein 4 Inhibitors) OR (Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitor) OR (Cytotoxic T Lymphocyte Associated Protein 4 Inhibitor) OR (CTLA-4 Inhibitor) OR (CTLA 4 Inhibitor) OR (PD-1 Inhibitors) OR (PD 1 Inhibitors) OR (Programmed Cell Death Protein 1 Inhibitor) OR (Programmed Cell Death Protein 1 Inhibitors) OR (PD-1 Inhibitor) OR (PD 1 Inhibitor) OR (Immune Checkpoint Blockade) OR (Immune Checkpoint Inhibition) OR (PD-L1 Inhibitors) OR (PD L1 Inhibitors) OR (Programmed Death-Ligand 1 Inhibitors) OR (Programmed Death Ligand 1 Inhibitors) OR (PD-L1 Inhibitor) OR (PD L1 Inhibitor) OR (PD-1-PD-L1 Blockade) OR (PD 1 PD L1 Blockade)).

2.1.2 Inclusion/exclusion criteria

Inclusion criteria encompassed studies related to Immune Checkpoint Inhibitors and Glioma; the document type was restricted to "Article (specifically including original research articles)" and "Review"; and the language was restricted to English by selecting "English" from the language menu.

2.1.3 Screening process

Post-screening, the "Export Records to Plain Text File" option was selected to export the literature for subsequent bibliometric analysis. "Remove Duplicates" function in CiteSpace was used to ensure that all included references were free of duplication. Two authors (DX and LH) independently conducted the literature screening and data extraction. Potentially eligible papers underwent full-text review. Disagreements were resolved by consensus or adjudication by a third author (ZY) (Fig. 1).

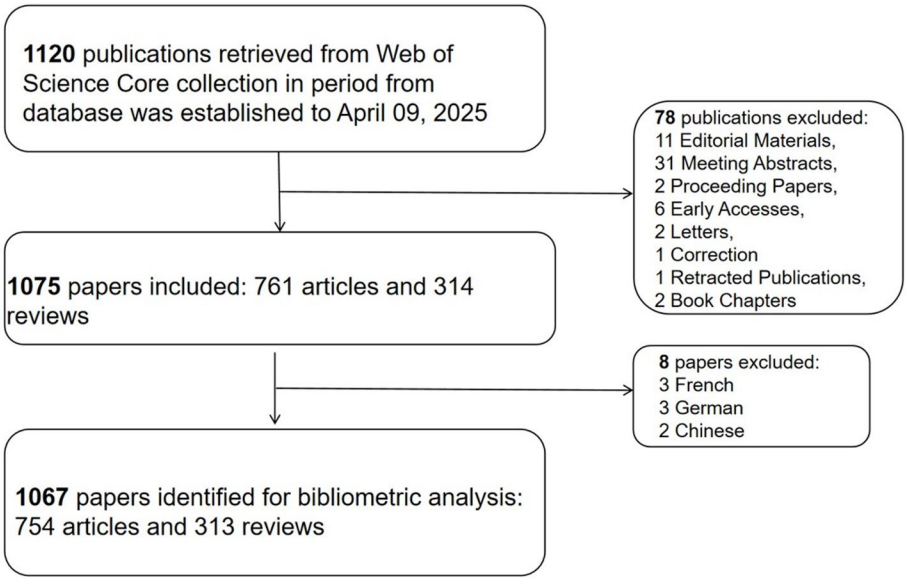

Fig. 1 Schematic representation of the systematic literature search and screening methodology

2.2 Bibliometric analysis

VOSviewer and CiteSpace software were employed for bibliometric and visualization analysis of the rigorously screened literature. These tools utilize co-occurrence, co-citation, and collaboration data to map the intellectual structure of a research field.

VOSviewer was primarily used for constructing and visualizing networks of co-authorship (among countries, institutions, and authors), bibliographic coupling (among journals), and keyword co-occurrence. A key strength of VOSviewer is its ability to calculate and visualize the strength of relationships within a network. The Total Link Strength (TLS) metric, for instance, is a quantitative measure of the total strength of the co-occurrence or collaboration links of a given item with all other items in the network. A higher TLS indicates a more central and intensely collaborative or frequently co-occurring entity within the research landscape..

CiteSpace was utilized for its robust capabilities in detecting emerging trends and abrupt changes in the literature through citation burst analysis and timeline visualization of clustered networks. It helps identify pivotal points and frontier areas by detecting articles or keywords that experience a sudden surge in citation frequency over a specific period.

While powerful, both tools have inherent limitations. The analyses are constrained by the quality and granularity of the metadata provided by the data source (WoSCC). VOSviewer's clustering algorithm prioritizes association strength, which may sometimes group conceptually similar but terminologically distant terms separately. CiteSpace's burst detection can be sensitive to parameter settings (e.g., the burst duration), and its results require careful interpretation within the specific scientific context to avoid overstating the significance of short-term fluctuations. All network maps were interpreted with these considerations in mind.

3 Results

3.1 Assessment of annual academic outputs

As of April 9, 2025, a total of 1,075 articles meeting our selection criteria have been published in the Web of Science database, comprising 761 articles and 314 reviews. The first publication related to Immune Checkpoint Inhibitors and Glioma appeared in 2000. As illustrated in Fig. 2, prior to 2016, the annual number of publications remained below 50. However, post-2017, there was a rapid increase, with the number of publications rising to 139 in 2021 and further to 195 in 2022. From 2021 to 2024, despite minor fluctuations, the annual publication volume consistently exceeded 100.

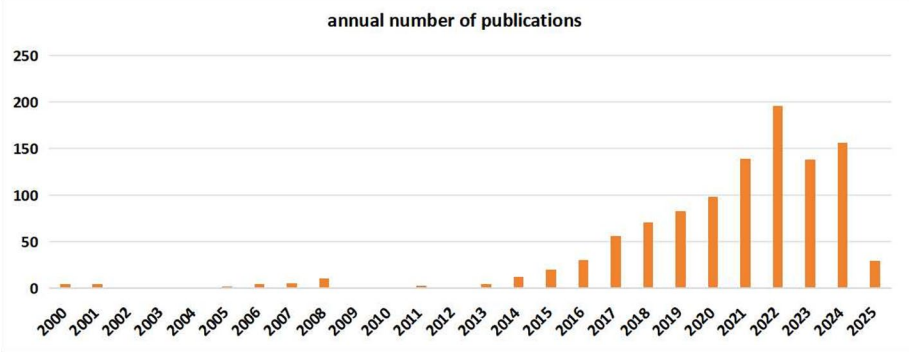

Fig. 2 Annual publication volume analysis

3.2 Analysis of country

A total of 58 countries have contributed to the field of Immune Checkpoint Inhibitors and Glioma. The publication and citation volumes for each country are depicted through density visualization maps (Figs. 3A-B), where increased brightness indicates higher values. Among the top ten countries in terms of publication volume, China leads with 446 publications, followed by the United States ($n = 406$) and Germany ($n = 79$). Regarding total citation counts, the leading countries are the United States ($n = 25{,}967$), China ($n = 9914$), and Germany ($n = 5986$) (Fig. 4A). A co-authorship analysis of these countries reveals that the United States exhibits the highest level of international collaboration (Total link strength, TLS = 290), followed by Germany (TLS = 149) and China (TLS = 91). Notably, the collaboration between China and the United States is the most robust (Link strength = 48) (Fig. 4B). Additionally, the United States also maintains significant collaborative ties with Germany and the United Kingdom. This disparity between China's high output volume and the United States' superior citation impact and central collaborative

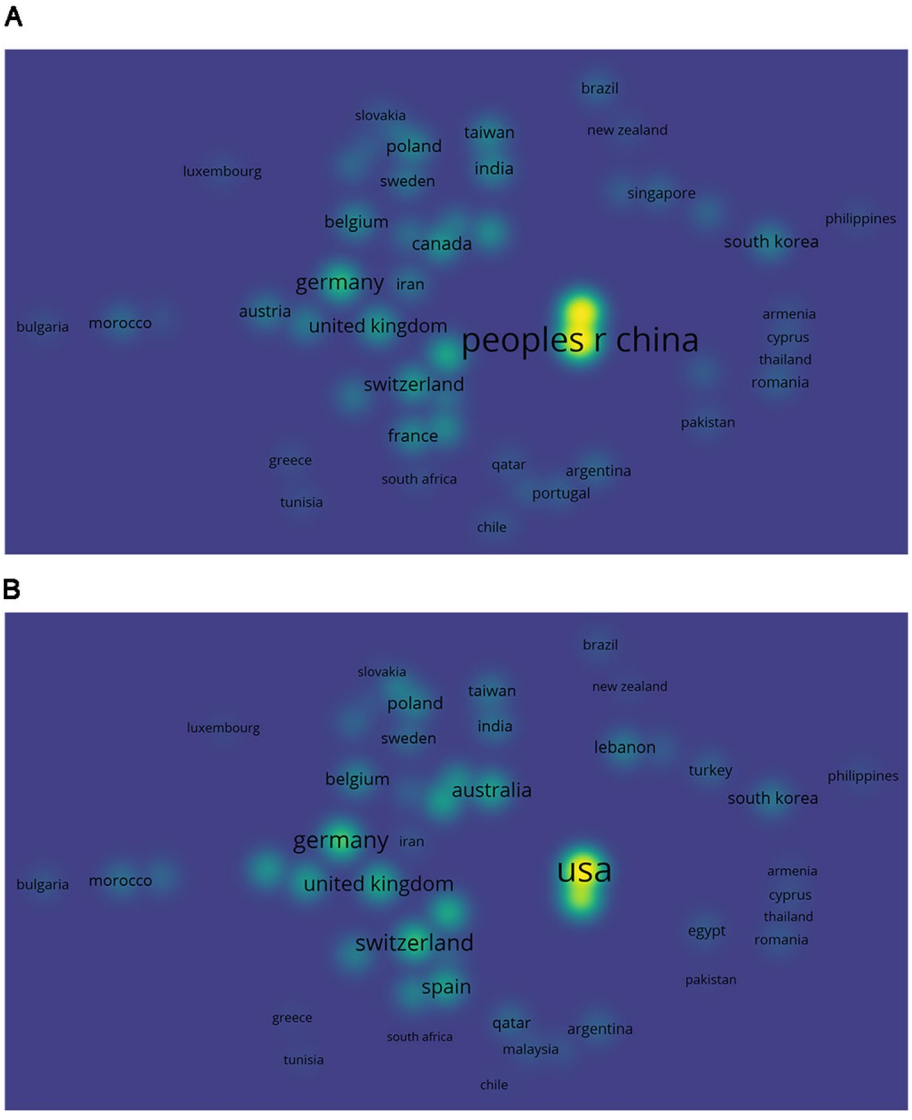

Fig. 3 Density visualization maps of national publication volume (**A**) and citation volume (**B**)

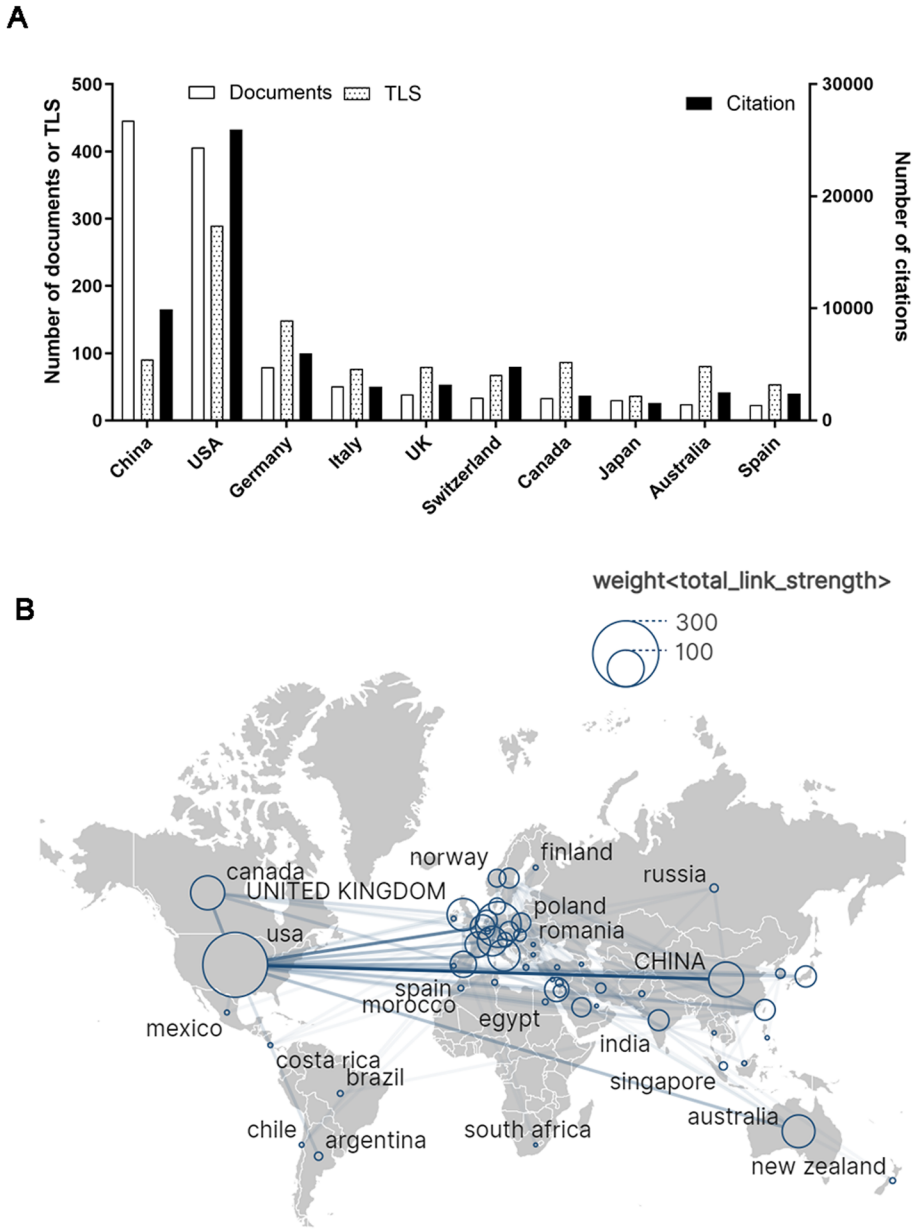

Fig. 4 Analysis of top 10 countries and international collaboration. **A** Annual publication volume of the top 10 countries by research output. **B** Geographical map illustrating international collaboration

position suggests a potential qualitative difference in the nature of their research contributions..

3.3 Analysis of organization

A total of 1578 institutions have published articles on Immune Checkpoint Inhibitors and Glioma, with the top 10 institutions in terms of publication volume illustrated in Fig. 5A. Harvard Medical School leads with 51 publications, followed by Capital Medical University ($n = 46$) and Central South University ($n = 34$). The institutions with the highest citation counts are Harvard Medical School with 3,464 citations, University of Texas MD Anderson Cancer Center with 3,155 citations, and University of California, San Francisco with 3,084 citations. The top three institutions in terms of

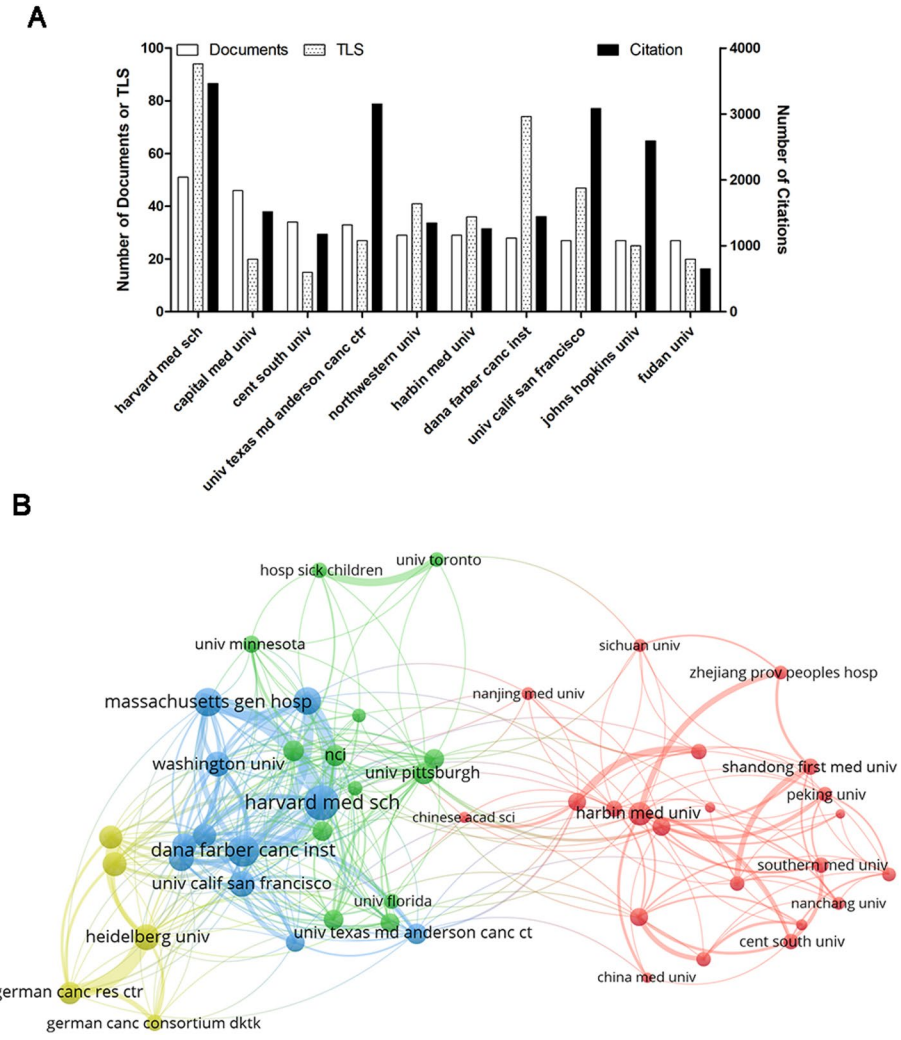

Fig. 5 Institutional analysis. **A** The leading 10 countries ranked by publication volume, accompanied by their citation metrics and TLS. **B** Collaborative network visualization for institutions with a publication count exceeding 10 articles

collaboration strength are Harvard Medical School (TLS = 94), Dana-Farber Cancer Institute (TLS = 74), and University of California, San Francisco (TLS = 47) (Fig. 5A). Additionally, 51 institutions have published more than 10 articles, and a network visualization of institutional collaborations reveals that clusters formed by Harvard Medical School, Massachusetts General Hospital, Washington University, University of California, San Francisco, and University of Texas MD Anderson Cancer Center exhibit the highest collaboration strength (TLS = 94), with particularly strong collaboration between Harvard Medical School and Massachusetts General Hospital (Link strength = 16) (Fig. 5B).

3.4 Analysis of authors

A total of 6,969 authors have contributed articles on Immune Checkpoint Inhibitors and Glioma. Among them, 10 authors have published more than 10 articles each, with their output, citation counts, and collaboration levels illustrated in Fig. 6A. Notably, Lim Michael from Stanford University has the highest publication and citation counts.

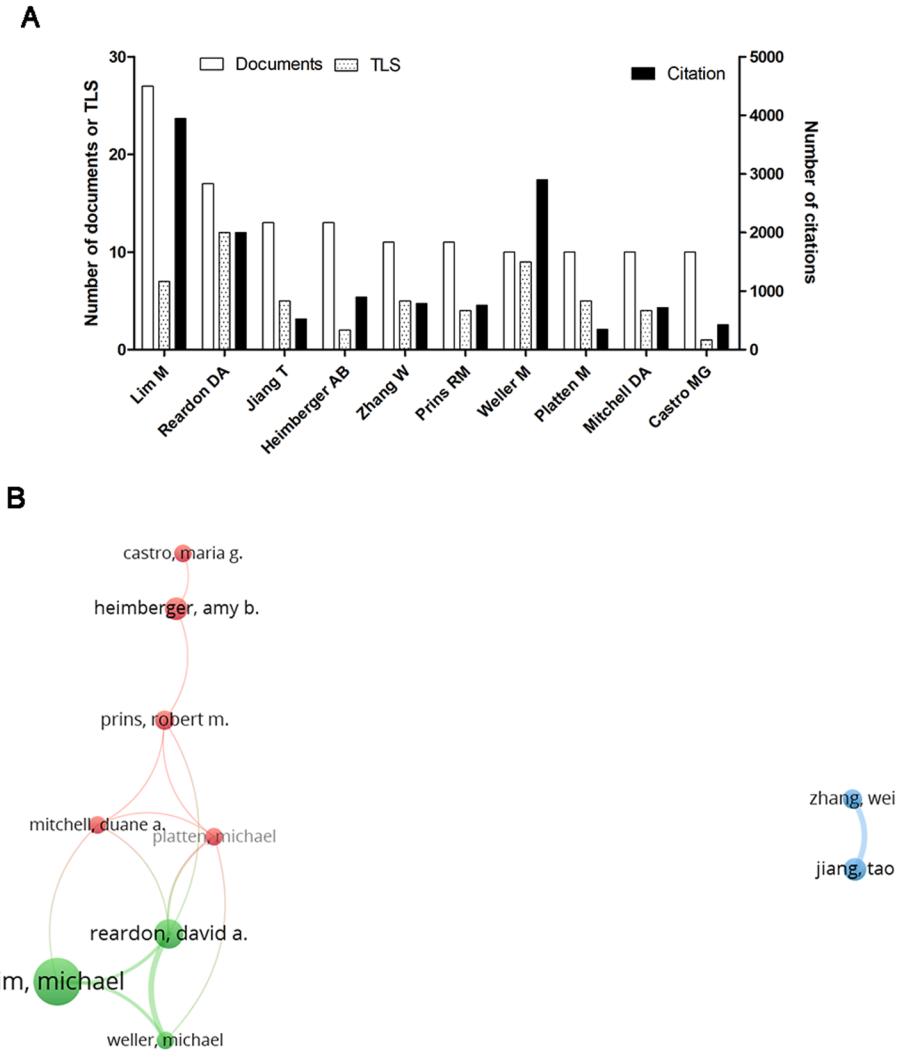

Fig. 6 Analysis of authors. **A** The leading 10 authors ranked by publication volume, accompanied by their citation metrics and TLS. **B** Collaborative network among authors with a publication output surpassing 10 articles

Figure 6B depicts the collaborative relationships among these prolific authors, with the cluster formed by Lim M, Reardon DA, and Weller M exhibiting the highest degree of collaboration (Fig. 6A-B).

3.5 Analysis of journals

A total of 359 journals have contributed articles on Immune Checkpoint Inhibitors and Glioma, with 47 journals publishing more than five articles in this domain. "Frontiers in Immunology" has the highest number of publications ($n = 69$), followed by "Frontiers in Oncology" ($n = 44$) and "Cancers" ($n = 33$). The citation counts for these three journals are 1,488, 847, and 741, respectively. The top 10 journals by publication volume are listed in Table 1, with three journals having an impact factor greater than 10, and seven journals classified in the Q1 JCR category, while three are in Q2. A bibliographic coupling network analysis using VOSviewer on the 56 journals with more than five publications revealed that "Discover Oncology," "Pharmaceutics," and "Heliyon" have recently shown a significant increase in publication volume (Fig. 7).

Table 1 The 10 leading journals with the highest publication output

Journals	Documents	Citations	Total link strength	Impact factor (2023)	JCR
Frontiers in Immunology	69	1488	36,222	5.7	Q1
Frontiers in Oncology	44	847	24,299	3.5	Q2
Cancers	33	741	25,761	4.5	Q1
Neuro-oncology	31	2635	17,145	16.4	Q1
Oncoimmunology	27	1342	14,577	6.5	Q1
International Journal of Molecular Sciences	26	805	19,813	4.9	Q1
Journal of Neuro-oncology	23	758	8752	3.2	Q2
Clinical Cancer Research	20	2173	9281	10.4	Q1
Journal for Immunotherapy of Cancer	17	1212	6362	10.3	Q1
Frontiers in Genetics	16	112	7151	2.8	Q2

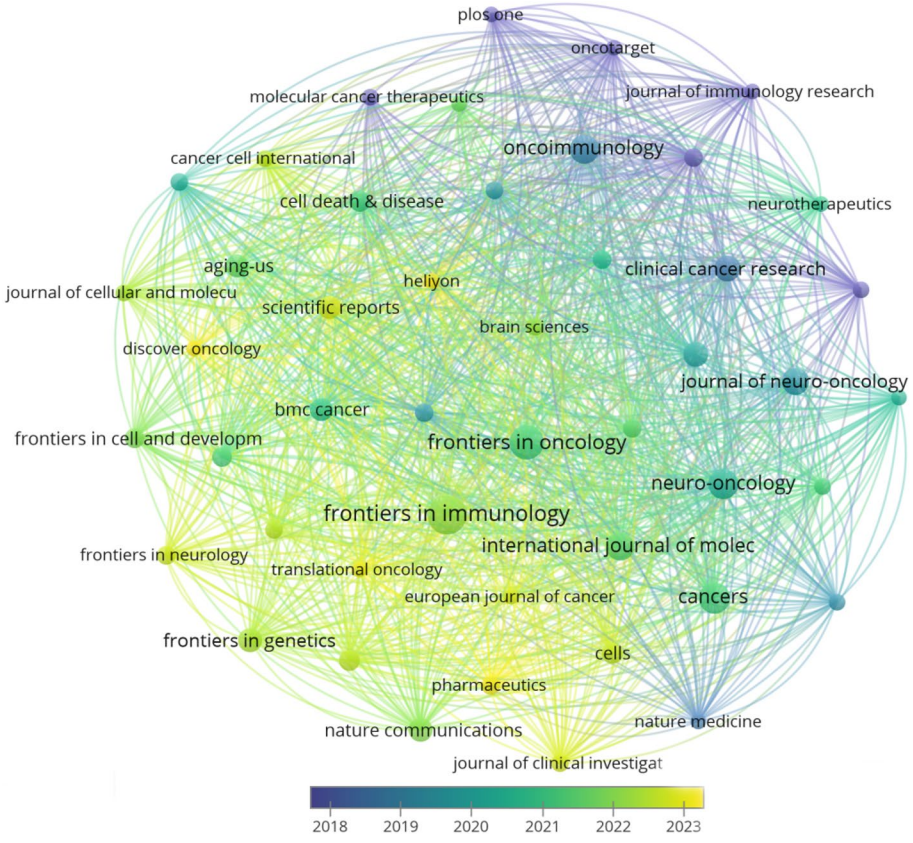

Fig. 7 Overlay visualization map illustrating bibliographic coupling analysis of scholarly journals

3.6 Analysis of references

In the domain of research on immune checkpoint inhibitors and glioma, the most frequently cited article is authored by Reardon DA et al., titled "Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial," published in JAMA ONCOL in 2020 [12], with a total of 159 citations and a citation half-life of 2.5 years. Following this, the article by Cloughesy TF et al., published in NAT MED in 2019, "Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma," [13] has been cited 155 times, also with a citation half-life of 2.5 years. Subsequently, the paper by Louis DN et al., published in NEURO-ONCOLOGY in

Table 2 The 10 most frequently referenced publications

Article	Citation frequency	Half-life
Reardon DA, Brandes AA, Omuro A, et al. Effect of Nivolumab vs. Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2020;6(7):1003–1010.	159	2.5
Cloughesy TF, Mochizuki AY, Orpilla JR, 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):477–486.	155	2.5
Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231–1251.	105	1.5
Nduom EK, Wei J, Yaghi NK, et al. PD-L1 expression and prognostic impact in glioblastoma. *Neuro Oncol*. 2016;18(2):195–205.	97	2.5
Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, et al. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. *Nat Med*. 2019;25(3):470–476.	91	2.5
Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131(6):803 – 20.	88	3.5
Zhao J, Chen AX, Gartrell RD, et al. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. *Nat Med*. 2019;25(3):462–469.	87	2.5
Reardon DA, Gokhale PC, Klein SR, et al. Glioblastoma Eradication Following Immune Checkpoint Blockade in an Orthotopic, Immunocompetent Model. *Cancer Immunol Res*. 2016;4(2):124 – 35.	83	2.5
Lim M, Xia Y, Bettegowda C, et al. Current state of immunotherapy for glioblastoma. *Nat Rev Clin Oncol*. 2018;15(7):422–442.	81	3.5
Berghoff AS, Kiesel B, Widhalm G, et al. Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. *Neuro Oncol*. 2015;17(8):1064-75.	75	2.5

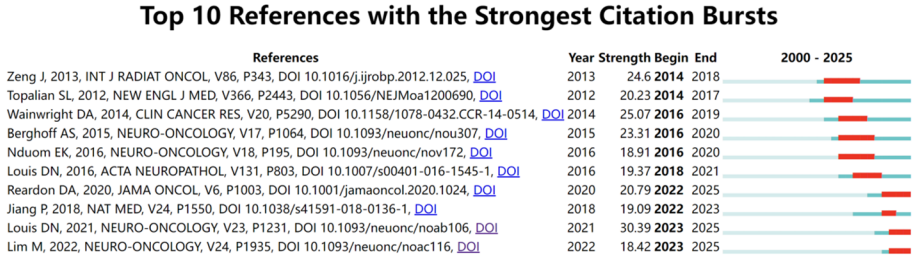

Fig. 8 Analysis of references. **A** Co-citation analysis of references with more than 20 citations (node size represents citation frequency). **B** Analysis of citation bursts in references

2021, "The 2021 WHO Classification of Tumors of the Central Nervous System: a summary," [14] has received 105 citations, with a citation half-life of 1.5 years (Table 2). Utilizing CiteSpace for citation bursts analysis of references, the top 10 articles with the strongest citation bursts were analyzed. The findings indicate that the article "The 2021 WHO Classification of Tumors of the Central Nervous System: a summary" by Louis DN et al., published in NEURO-ONCOLOGY in 2021 [14], exhibits the most significant citation burst (Strength = 30.39) and remains in a period of citation surge (2023–2025). Additionally, the study "Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter" by Lim M et al., published in NEURO-ONCOLOGY in 2022 [15], is also currently experiencing a citation burst (2023–2025) (Fig. 8).

3.7 Analysis of keywords

Co-occurrence analysis plays a pivotal role in monitoring scientific development by exploring popular research directions and fields through the analysis of relationships between keywords. Utilizing VOSviewer, a co-occurrence analysis was conducted on keywords appearing at least 20 times, resulting in the identification of 113 keywords (Fig. 9A). The top 10 keywords with the highest occurrences are as follows: glioma (Occurrences = 401, TLS = 2267), immunotherapy (Occurrences = 391, TLS = 2341), glioblastoma (Occurrences = 355, TLS = 2257), expression (Occurrences = 252, TLS = 1381), cancer (Occurrences = 224, TLS = 1218), central-nervous-system (Occurrences = 119, TLS = 815), prognosis (Occurrences = 117, TLS = 659), blockade (Occurrences = 114,

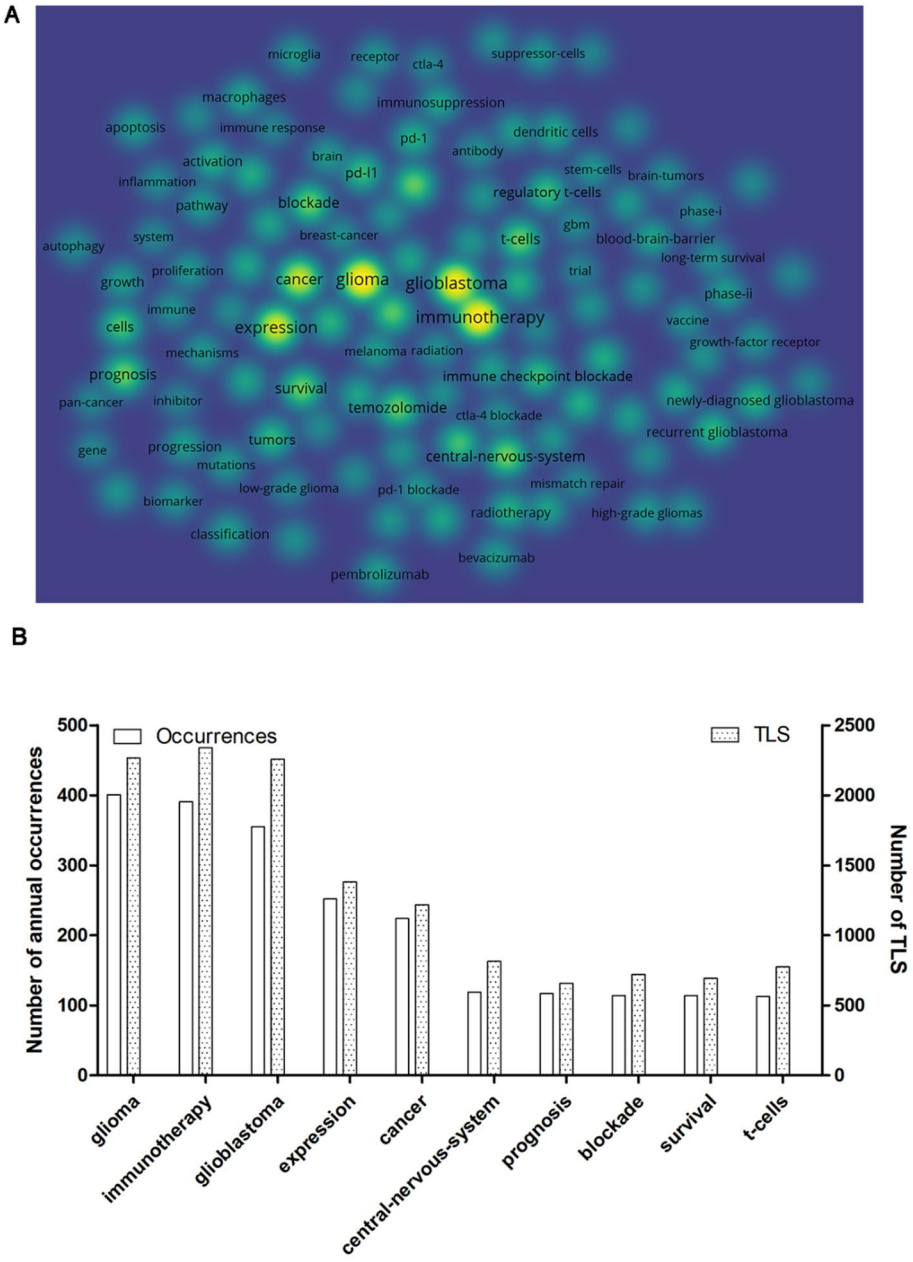

Fig. 9 Keyword frequency analysis. **A** Density visualization maps of keywords appearing at least 20 times. **B** The top 10 most frequently occurring keywords

TLS = 720), survival (Occurrences = 114, TLS = 694), and t-cells (Occurrences = 113, TLS = 775) (Figs. 9A-B). Furthermore, keyword co-occurrence clustering calculated via CiteSpace reveals that keywords can be categorized into 10 clusters: pd-1, prognosis, immune infiltration, growth, malignant glioma cells, immunosuppressant, DNA repair, cuproptosis, TGF-beta, and endothelin (Fig. 10A). The timeline view indicates that cuproptosis is a recently emerging cluster. Keyword citation burst analysis identified 13 keywords with citation bursts post-2020, including system, mechanisms, immune infiltration, immune microenvironment, oncolytic virus, tumor microenvironment, phase I, tumor-associated macrophages, promotes, cell death, inflammation, pathway, and oncolytic virotherapy (Fig. 10B). Notably, two keywords with citation bursts are related to oncolytic virotherapy (namely oncolytic virus and oncolytic virotherapy), and oncolytic virotherapy is currently experiencing a citation burst period (2023–2025).

3.8 Analysis of keywords associated with immunotherapeutic agents

Subsequently, 13 high-frequency keywords related to immunotherapy agents—namely blockade, temozolomide, chemotherapy, immune checkpoint, radiotherapy, PD-L1, immune checkpoint blockade, blood-brain barrier, Nivolumab, immune checkpoint inhibitors, PD-1, pembrolizumab, and resistance—were selected from the top 50 most

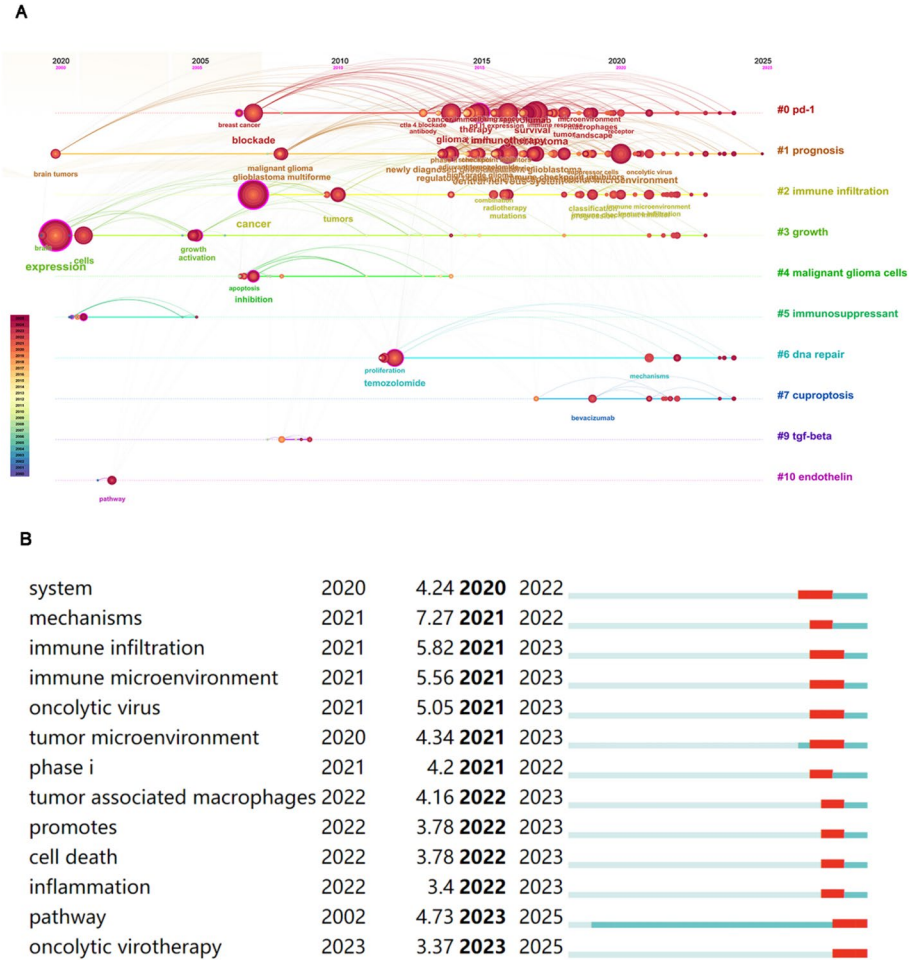

Fig. 10 Analysis of keyword evolution and research frontiers. **A** Timeline view of cluster analysis of keywords. **B** Citation burst analysis of keywords post-2020

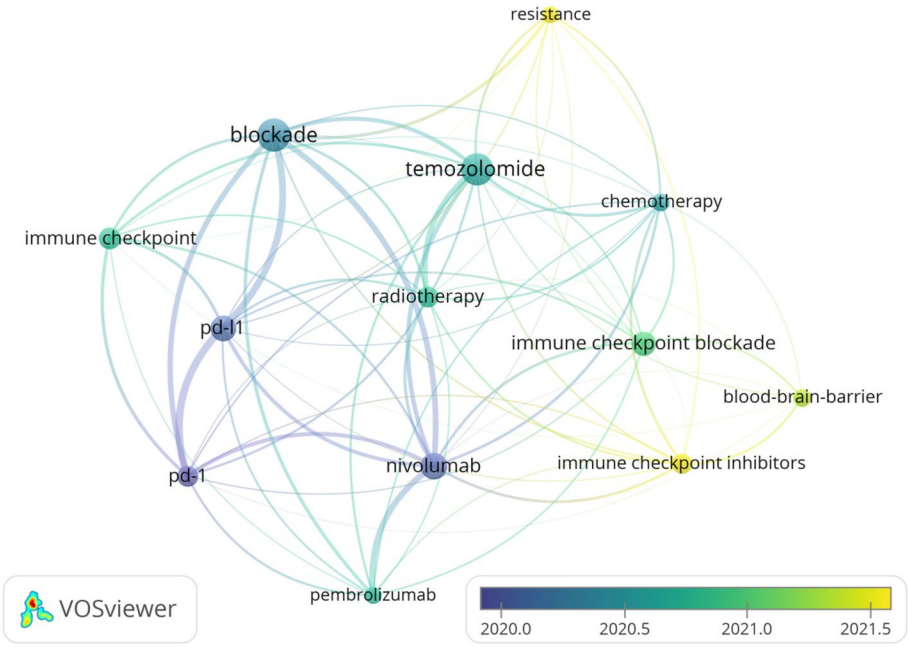

Fig. 11 Analysis of keywords associated with immunotherapeutic agents

frequently occurring terms for co-occurrence analysis. The results revealed that blockade, PD-L1, PD-1, Nivolumab, and pembrolizumab exhibited the strongest co-occurrence strengths with other keywords, indicating that these terms represent the core focus areas in immunotherapy agent research. Notably, resistance emerged as the most recent keyword, highlighting it as an emerging research hotspot. Furthermore, the co-occurrence of Nivolumab and temozolomide with resistance suggests a growing interest in recent years in investigating drug resistance associated with Nivolumab and temozolomide in the treatment of glioma (Fig. 11).

4 Discussion

4.1 Principal findings

Prior to 2016, the number of publications concerning immune checkpoint inhibitors and glioma was relatively low, averaging fewer than 50 articles per year. This scarcity likely reflects two scientific challenges: the constraint of drug delivery imposed by the blood-brain barrier and the limited understanding of the glioma immune microenvironment at that time. The explosive growth observed post-2017 may be closely aligned with three pivotal events: firstly, the successful Phase III clinical trial of the PD-1 inhibitor nivolumab in melanoma in 2015 [16]; secondly, the release of data from the first glioma immunotherapy clinical trial(CheckMate 143) in 2017 [17]; and finally, the breakthrough of CAR-T therapy in hematological malignancies, which spurred a surge of interest in solid tumor research [18]. During this period, the balanced ratio of original research articles (70.8%) to reviews (29.2%) not only reflects the vigor of original innovation but also indicates a rapid restructuring of the knowledge framework in the field.

This study reveals a multipolar yet unbalanced global research landscape in the field of Immune Checkpoint Inhibitors and Glioma. Among the 58 participating countries, China, the United States, and Germany form a “tri-polar system,” yet significant disparities are evident in the quality and impact of their scientific output. Although China leads

with 446 publications (accounting for 41.5%), its average citation per article is markedly lower than that of the United States and Germany. This "quantity-quality paradox" may reflect two underlying issues: firstly, Chinese research may be more focused on technical applications, whereas the United States maintains an advantage in original mechanistic studies; secondly, the United States achieves knowledge dissemination and value addition through high-intensity international collaboration (TLS = 290), while China's relatively insular collaboration network (TLS = 91) may limit international recognition of its achievements. More critically, these collaboration patterns have profound scientific and clinical implications: the extensive U.S.-led international network facilitates access to diverse patient cohorts, accelerates multi-regional clinical trial validation, and promotes the establishment of global consensus guidelines—all enhancing the translatability and impact of research. Notably, the intensity of Sino-American collaboration (Link = 48) far exceeds other bilateral relationships, representing a strategic synergy that combines China's substantial clinical resources and production capacity with U.S. expertise in trial design and mechanistic investigation, potentially accelerating the translation of basic discoveries into clinical applications. This dynamic benefits from the complementarity in clinical trials for brain tumor immunotherapy and may also be driven by the cross-border R&D strategies of Chinese innovative pharmaceutical companies.

In terms of institutional and authorial collaborative contributions, Harvard Medical School and its affiliated institutions, such as Massachusetts General Hospital, have established a research hub through a high-density collaboration network (TLS = 94). Their publication volume (51 articles) and citation advantage (3,464 citations) are closely linked to a core group of authors. Notably, the collaborative clusters led by scholars such as Lim Michael from Stanford University (15 articles, 982 citations) and Reardon DA, Weller M, among others, have leveraged the clinical trial platforms and interdisciplinary resources of these top-tier institutions. This has facilitated breakthroughs in the application of key studies, such as anti-PD-1/CTLA-4 combination therapies, in glioma research [19].

The analysis of journals and referenced papers plays a guiding role in article writing and submission. This study identifies the top 10 most-cited publications in the field, indicating their high authority and widespread recognition among researchers. Notably, seven of these top 10 prolific journals (e.g., *Neuro-Oncology*, *Clinical Cancer Research*) are classified in the JCR Q1 category, reflecting their strong academic influence and consistent publication of high-quality research, while the three Q2 journals (*Frontiers in Oncology*, *Journal of Neuro-Oncology*, *Frontiers in Genetics*) maintain considerable scholarly impact within their respective domains. Authors drafting articles in this domain are advised to thoroughly review these publications, as they provide robust evidence for citation. Furthermore, our bibliographic coupling analysis indicates that journals such as *Discover Oncology*, *Pharmaceutics*, and *Heliyon* have shown a marked increase in publications in this field recently, reflecting a broadening of the publishing landscape for this research topic.

Our bibliometric analysis identified the study by Reardon et al. (2020) as the most cited publication in this field (159 citations), underscoring its pivotal role in shaping research discourse. The CheckMate 143 Phase III clinical trial, published in JAMA Oncology [12], as the first large-scale randomized controlled study on glioblastoma immunotherapy, not only revealed the limitations of PD-1 monotherapy but also serves as a direct

reference point explaining the subsequent research shifts captured by our keyword and citation burst analyses. Specifically, its findings propelled research shifts in three dimensions: firstly, from single ICI to multimodal combinations with anti-angiogenic agents (e.g., bevacizumab) and oncolytic viruses (e.g., DNX-2401) [20]; secondly, from pan-population treatment to patient stratification based on specific molecular alterations, immune expression signatures, and immune infiltration [21]; thirdly, from mere survival assessment to integrated efficacy indicators including neurocognitive function and quality of life [22]. This translational trend refined by our keyword burst analysis. The finding that "oncolytic virotherapy" and its associated terms have shown sustained bursts (2023–2025) strongly suggests that the intense clinical research activity in this area is a primary driver of the current academic dialogue. For instance, clinical studies (such as those registered on ClinicalTrials.gov, e.g., NCT03896568) demonstrating that the oncolytic virus DNX-2401 induces changes in T cell activity are the likely research outputs that contributed to this observed keyword burst, confirming the tight coupling between clinical trial efforts and bibliometric trends [23].

The deepening of the research system is reflected in the synergistic breakthroughs in molecular mechanisms and clinical applications. The revised WHO classification standards by Louis et al. (citation burst intensity 30.39) [14], by integrating molecular features such as IDH1/2 mutations and CDKN2A/B deletions, not only reconstructed the immunogenicity assessment framework for gliomas but also spurred the development of quantitative models of "cold/hot tumor" microenvironments in gliomas [24, 25], directly reflected in the citation burst of keywords like "immune infiltration" (citation burst strength = 5.82) and "tumor-associated macrophages" (citation burst strength = 4.16). It is of significant interest that cuproptosis, as an emergent cluster within the scientific community, presents a pioneering avenue for research in the realm of glioma immunotherapy. The paradoxical role of copper-induced cell death—simultaneously promoting immunogenicity yet facilitating immunosuppressive pathways like PD-L1 upregulation—reveals a complex therapeutic duality. Targeting cuproptosis regulators (e.g., FDX1, SLC31A1) could potentially convert "cold" gliomas into immunoresponsive tumors, but requires careful modulation to avoid exacerbating immune evasion. This represents a critical frontier for developing next-generation metallo-immunotherapies [26–29]. The development of a novel signature based on cuproptosis holds the potential to substantially contribute to the prognostic assessment, elucidation of biological characteristics, and determination of optimal therapeutic strategies for patients afflicted with gliomas [30].

Our focused analysis of immunotherapeutic agent keywords crucially delineates the evolving therapeutic focus in glioma immunotherapy, demonstrating how quantitative literature analysis can help map research priorities and reveal hidden conceptual linkages across disparate studies. The pronounced centrality of PD-1/PD-L1 inhibitors reaffirms their clinical dominance, while the emergent signature of "resistance" exemplifies how temporal keyword tracking can help identify paradigm shifts earlier than traditional review methods. Notably, the convergence of nivolumab, temozolomide, and resistance indicates that co-occurrence metrics may serve as a useful tool for identifying for translational challenges, revealing critical knowledge gaps that demand interdisciplinary solutions. The bibliometric analysis of these convergent resistance pathways offers a potential framework for clinical trial design, which could help accelerate the translation

of mechanistic understanding into practical therapeutic strategies. Collectively, these findings highlight the value of bibliometric methodologies for retrospective evaluation and providing insights for guiding resource distribution and hypothesis development in the evolving landscape of precision immuno-oncology.

4.2 Limitations

Although this study systematically elucidates the research landscape of immune checkpoint inhibitors in the field of glioma, several limitations persist. Firstly, the bibliometric data were retrieved exclusively from the WoSCC database. While this is a common and well-established practice in bibliometric studies due to WoS's comprehensive coverage of high-impact journals and its provision of standardized, high-quality data for analytic software, it may inevitably lead to the omission of some relevant studies indexed in other databases such as PubMed, Scopus, or Embase. This potential omission could introduce bias in assessing the absolute volume of literature, particularly from regions or journals not fully covered by WoS. Secondly, the lack of clinical trial registry data may introduce a "positive results bias." Our analysis, based on published literature, could thus overestimate promising therapeutic strategies by overlooking terminated, negative, or unpublished trials, and may miss early research avenues not yet reflected in high-impact publications. Thirdly, the analysis of international collaboration networks is based solely on co-occurrence strength between institutions, lacking integration with patent data and multi-center participation information from clinical trials, which may underestimate the true scale of academia-industry translational collaborations—for instance, while Chinese institutions lead in total publication volume, the synergistic innovation contributions between industry and academia are not fully reflected. Furthermore, although keyword co-occurrence analysis identifies emerging hotspots such as "cuproptosis," it does not integrate the correlation between preclinical research models and clinical efficacy data, making it challenging to quantify the progression efficiency from fundamental discoveries to translational applications. Lastly, the centralized characteristic of institutional collaboration networks (Harvard Medical School, TLS = 94) may obscure the unique contributions of regional innovation hubs in specific research areas.

5 Conclusions

In summary, this bibliometric analysis delineates the evolving research landscape of immune checkpoint inhibitors (ICIs) in glioma from 2015 to 2024. The global contribution is multipolar yet unbalanced, with China leading in publication volume while the United States demonstrates superior citation impact and functions as the central collaborative hub, highlighting a notable quantity-quality paradox. Keyword and citation burst analyses identify several evolving research frontiers, including a sustained focus on "oncolytic virotherapy" and the emergence of "cuproptosis" as a promising new area, alongside a critical translational focus on overcoming therapy "resistance," particularly in the context of "nivolumab" and "temozolomide" combinations. These findings collectively offer scholars a data-driven overview of the field's structure, key players, and current priorities. Future studies could expand on this work by incorporating data from additional sources, such as clinical trial registries, to further elucidate the trajectory from basic discovery to clinical application.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

Liang He and Zhe Yang designed the study design. Dingwen Xu and Liang He conducted the analysis used VOSviewer. Xu Zhao executed the analysis utilizing Citespace.

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Data availability

All primary data utilized in this research can be accessed upon a justified request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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