

# Research trends of glioma-related epilepsy: A bibliometric analysis from 2004 to 2023

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## ABSTRACT

Glioma-related epilepsy (GRE) is a hotspot in recent years and there remains many urgent unsolved issues. This study aimed to conduct bibliometric analysis on GRE research over the past 2 decades. We collected scientific outputs relating to GRE on Web of Science Core Collection (WoSCC) from 2004 to 2023 and conducted visual analysis using VOSviewer and Microsoft Excel. A total of 2697 publications were retrieved with an increasing trend over the past 20 years. The USA ranked first in publication number, total citation and H-index. Institut National de la Sante et de la Recherche Medicale (Inserm) was the institution with the most publications. In the field of GRE, core journals were Journal of Neurosurgery, Epilepsia and Neurology. Duffau, Hugues was the author with the most papers and total citations, and the highest H-index. Co-occurrence analysis revealed that the latest research focus of GRE were awake craniotomy, immunotherapy, cognitive impairment, and basic research on pathogenesis, with particular emphasis on the IDH1 mutation. This study intended to gain a deeper understanding of the current global GRE research and identify hotspots, as well as to provide theoretical reference for further studies.

**KEYWORDS:** Glioma-related epilepsy, bibliometric analysis, VOSviewer, visual analysis

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## Introduction

Glioma remains a common malignant brain tumor in adults, accounting for approximately 70% of all malignant primary brain tumors.<sup>1,2</sup> According to the 2021 World Health Organization (WHO) classification of gliomas, adult diffuse gliomas are categorized into 3 types: glioblastomas, oligodendrogliomas, and IDH-mutant astrocytomas.<sup>3</sup> Traditionally, grades 1 and 2 are classified as low-grade gliomas (LGG), while grades 3 and 4 are classified as high-grade gliomas (HGG). With the continuous development of surgical treatment techniques and widespread promotion of concurrent chemoradiotherapy, immunotherapy and other comprehensive treatments, survival rate of glioma has been improved in recent decades. However, a deeper understanding of related areas, such as glioma-related epilepsy (GRE), is required. Epilepsy is a prevalent neurological disorder characterized by recurrent seizures.<sup>4,5</sup> GRE specifically refers to symptomatic epileptic seizures that occur secondary to gliomas.<sup>6</sup> Around 30% of GRE patients remain insensitive to antiepileptic drugs after surgery,<sup>7</sup> severely impacting their quality of life. Currently, although the mechanism of GRE is not fully understood, there is no doubt that the formation process is influenced by multiple factors including glioma location, peritumoral edema, alterations in intrinsic genes of the tumor, and alterations in the tumor microenvironment.<sup>8-12</sup> In recent years, with the growing attention paid to the quality of life among glioma patients, GRE has gradually become a research hotspot for scholars. Therefore, scientific systematic analysis of the literature in the GRE research area is of vital importance.

Based on publications, bibliometrics performs structured analysis on number of publications and citations, institutional and author contributions, in order to investigate current research status, trends and hotspots.<sup>13,14</sup> Researchers have conducted bibliometric analysis on several diseases such as liver fibrosis, cerebral cavernous malformations, chronic urticaria, hypertension, and cancer,<sup>15-21</sup> but no known bibliometric analysis has focused on GRE. Thus, this study aimed to carry out statistical analyses on GRE-related publications over the past 2 decades, so as to understand the current global GRE research and identify hotspots, and to provide theoretical reference for further studies as well.

## Materials and Methods

### *Bibliometric Search Strategy*

We used Web of Science Core Collection (WoSCC) as our data source and followed the search strategy below: TS = (glioma OR astrocytoma OR oligodendroglioma OR oligoastrocytoma OR glioblastoma) AND TS = (seizure OR epilepsy). We restricted the search to article or review article in English. The search was conducted on July 9, 2024, and the time frame chosen was from 2004 to 2023.

### *Data Collection*

Data were extracted in terms of total publications (TP), year, annual publication number, total citations (TC), countries/



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regions, institutions, journals, authors, references, H-index, and impact factor (IF) in 2023.

### Data Extraction

Microsoft Excel 2019 was used to construct a polynomial regression model. Distribution of countries/regions was displayed

using web tool (<https://www.bioinformatics.com.cn>).<sup>22</sup> Co-countries/regions analysis was performed online at bibliometric platform (<https://bibliometric.com/>). VOSviewer was used to construct and visualize bibliometric networks by co-authorship of countries/regions, institutions and authors, co-occurrence of keywords plus, and co-citation of journals and references. In network graphs developed by VOSviewer,

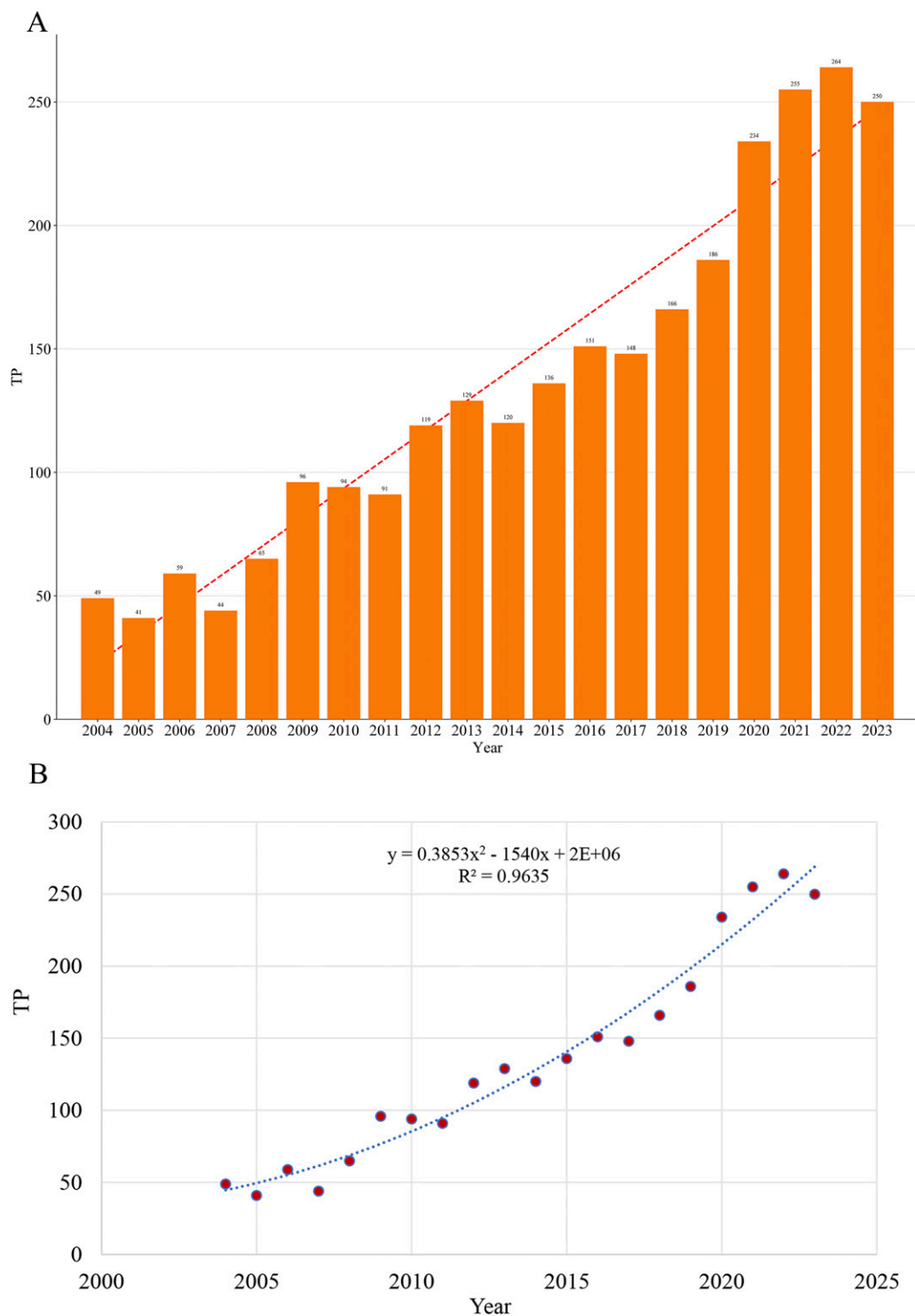


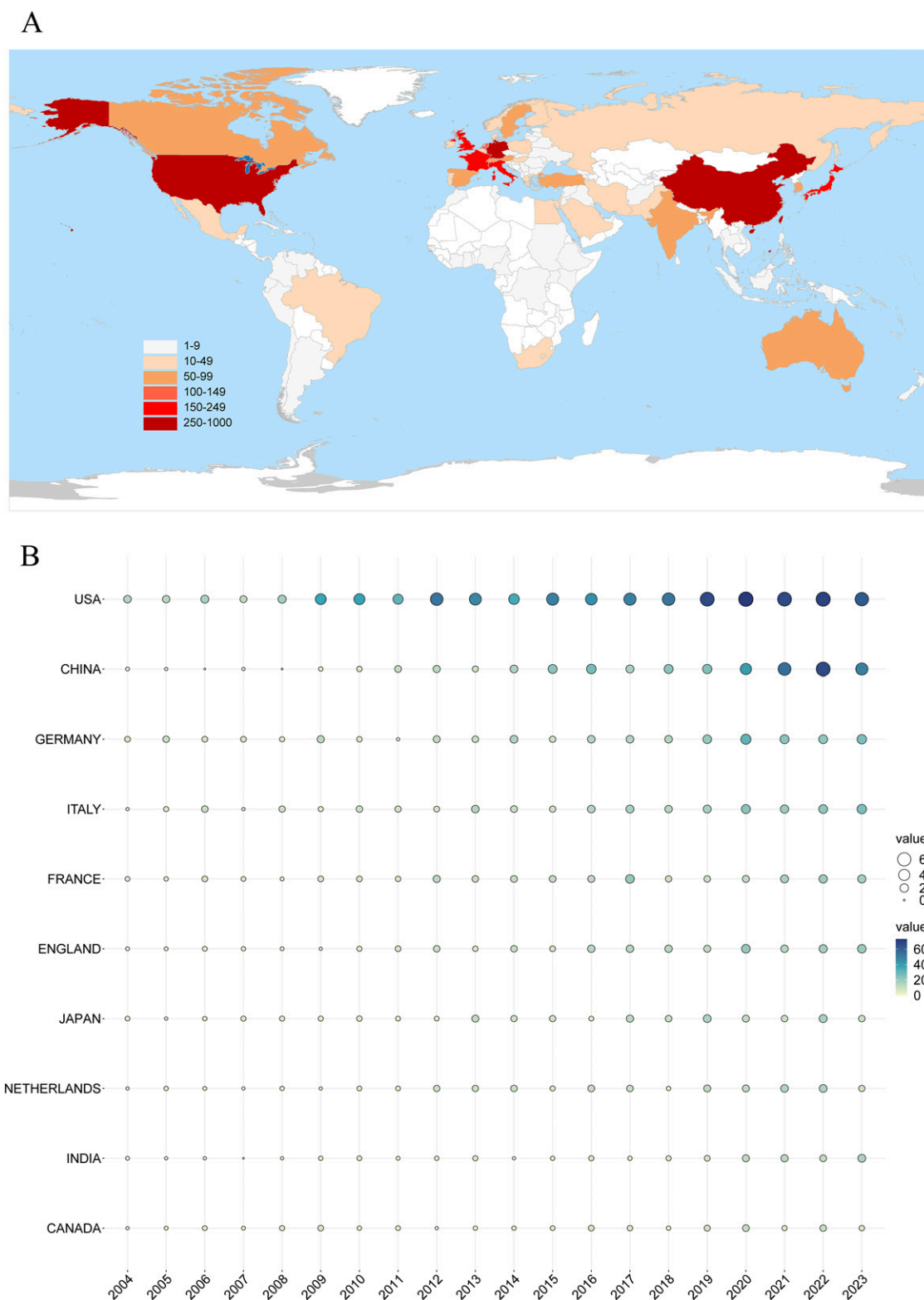
Figure 1. (A) Annual publication number; (B) Polynomial fitting curve of trend in annual publication number.

different nodes represented different parameters such as countries/regions, institutions, authors, and keywords. Links between nodes represented correlations between parameters, and the thickness of links indicated their strength. Links were quantitatively assessed by total link strength (TLS).<sup>23</sup>

## Results

### Global Publication and Citation Trend

According to the search strategy, we extracted 2697 publications over the past 20 years from WoSCC. As displayed in



**Figure 2.** (A) Geographical distribution of global research publications; (B) Trend of top 10 countries/regions with the most annual publication number.

Figure 1(A), there was a steady increase in the number of GRE research publications worldwide from 2004 to 2023. Especially, from 2020, more than 200 publications have been published each year. Polynomial fitting curve in Figure 1(B) indicated a significant correlation between annual publication number and publication year, with a correlation coefficient  $R^2$  of 0.9635.

#### Analysis of Countries/Regions

A total of 94 countries/regions published articles in GRE field. Geographical distribution illustrated in Figure 2(A) indicates that the USA, China, and Germany had more than 250 publications. Besides, Figure 2(B) presents the trend from 2004 to 2023 of top 10 countries/regions with the most annual publication number. The USA ranked first with 851 papers (31.55%), followed by China with 387 papers (14.35%), Germany with 271 papers (10.05%), Italy with 245 papers (9.08%), and France with 203 papers (7.53%). See Table 1 for details. In addition, H-index 93 and TC (35,288) of the USA also ranked first. From Figure 3(A) who reported collaborations between different countries/regions, the USA had close collaborations with Germany, Netherlands and Italy. Countries/regions co-authorship analysis from VOSviewer was described in Figure 3(B), including 48 countries/regions with the minimum quantity of 5 publications. Top 5 countries/regions with the largest TLS were the USA (476), Germany (423), Netherlands (347), England (345), and Italy (342).

#### Analysis of Institutions

A total of 3268 institutions published articles in GRE field. Table 2 presents the top 5 institutions with the most publication number, among which Institut National de la Sante et de la Recherche Medicale (Inserm) made the greatest contribution with 139 publications, followed by University of California

**Table 1.** Top 10 countries/regions with the most publication number.

RANK	COUNTRY/REGION	TP (%)	TC	H-INDEX
1	USA	851 (31.55%)	35,288	93
2	China	387 (14.35%)	5463	35
3	Germany	271 (10.05%)	10,314	55
4	Italy	245 (9.08%)	8834	48
5	France	203 (7.53%)	9626	53
6	England	186 (6.89%)	7100	41
7	Japan	159 (5.90%)	2981	26
8	Netherlands	140 (5.19%)	7783	47
9	India	98 (3.63%)	786	16
10	Canada	95 (3.52%)	3937	30

TP, total publications; TC, total citations. 2697

system with 105 publications and Harvard University with 98 publications. Besides, Inserm had the highest H-index (41) and the most TC (6050 times). Institutions co-authorship analysis from VOSviewer was described in Figure 4(A) and (B), including 125 institutions with the minimum quantity of 10 publications. Top 3 institutions with the largest TLS were Massachusetts General Hospital (80), University of Amsterdam (80) and Harvard Medical School (77).

*Analysis of Journals.* A total of 695 journals published articles in GRE field. As shown in Table 3, top 5 journals with the most publications related to GRE were Journal of Neuro Oncology (IF = 3.2), Journal of Neurosurgery (IF = 3.5), World Neurosurgery (IF = 1.9), Epilepsia (IF = 6.6), and Neuro Oncology (IF = 16.4). We finally included 198 journals with at least 90 citations to develop co-citations network (Figure 5(A) and (B)). Top 3 journals with the most co-citations were Journal of Neurosurgery (4663 times), Epilepsia (3696 times) and Neurology (3685 times). Also, the above 3 journals had the largest TLS of 181,106, 171,205 and 171,420, respectively.

#### Analysis of authors

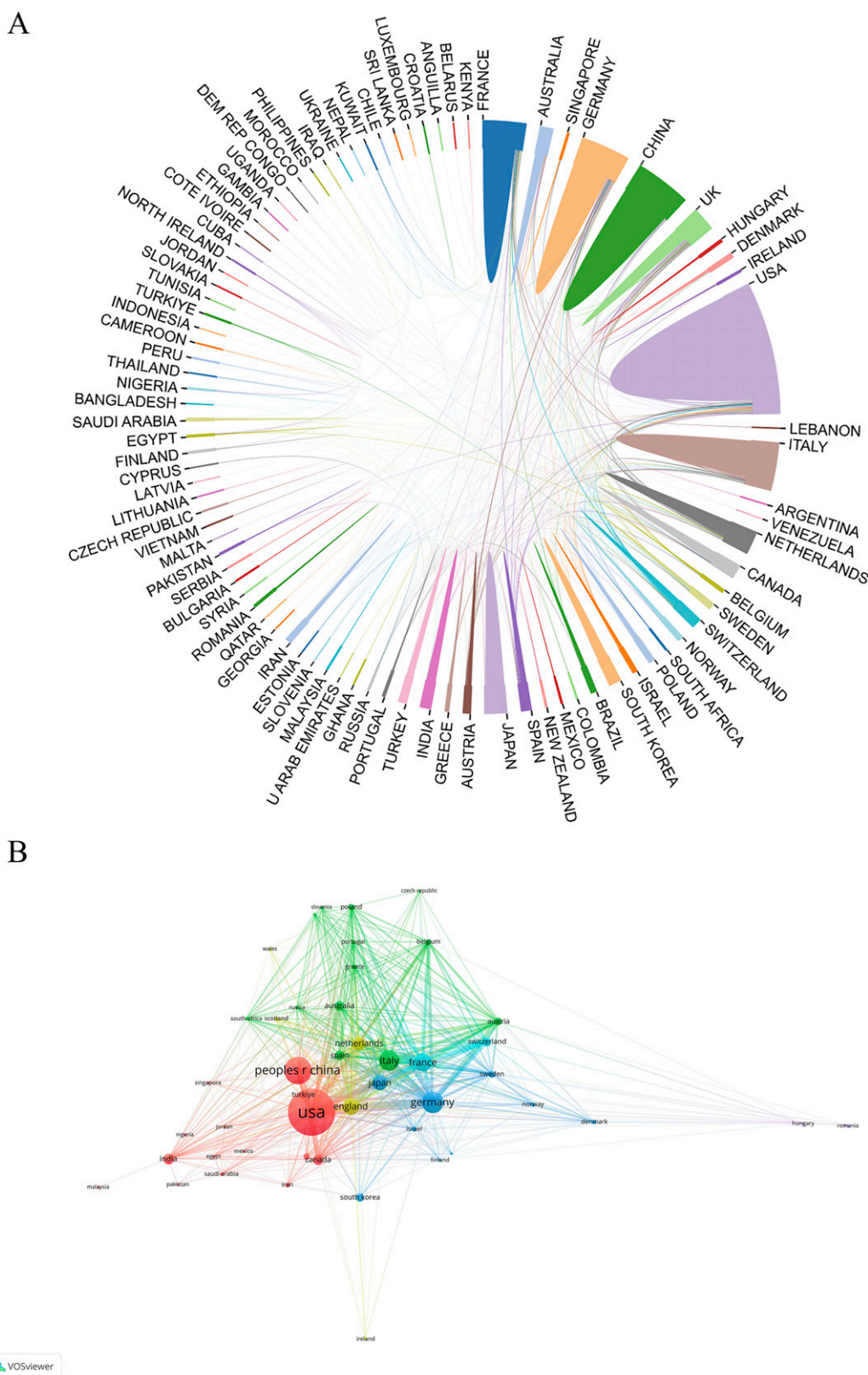
Table 4 presents the top 5 authors with the most publications related to GRE over the past 20 years. Duffau, Hugues was the most productive author with 53 papers, followed by Taphoorn, Martin J. B. with 25 papers, Reijneveld, J. C. with 23 papers, Berger, Mitchel Stuart with 23 papers, and Jiang, Tao with 22 papers. In addition, Duffau, Hugues had the highest H-index (30) and the most TC (2875 times). We finally included 229 authors with at least 5 publications to develop co-authorship analysis (Figure 6(A)). Top 3 authors with the largest TLS were Reijneveld, J. C. (120), Taphoorn, Martin J. B. (110) and Koekkoek, Johan A. F. (109). In terms of authors co-citation analysis, we analyzed 189 authors with at least 50 citations (Figure 6(B)). Top 3 authors with the largest TLS were Duffau, Hugues (14,812), Pallud, Johan (9070) and Maschio, Marta (7764).

#### Analysis of Co-Cited References

Table 5 presents the top 5 references with the most co-citations, among which 1 were published on Acta Neuropathol, 1 on Lancet Neurol, 1 on J Neurosurg, 1 on N Engl J Med, and 1 on Brain. We finally included 183 references with at least 35 citations to develop references co-citation analysis (Figure 7(A) and (B)). Reference titled "Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management" on Lancet Neurol by Van Breemen MS et al.<sup>24</sup> had the most TC (257 times) and the largest TLS (2535).

#### Analysis of keywords

We extracted a total of 4586 keywords plus from the 2697 publications. Table 6 lists the top 20 keywords with the most co-



**Figure 3.** (A) Visualized network map for countries/regions collaboration; (B) Countries/regions co-authorship analysis.

occurrence frequency. We finally included 84 keywords with at least 30 co-occurrence frequencies to develop network graphs of co-occurrence analysis (Figure 8(A)), which comprises 4 clusters. Cluster 1 (red) primarily focuses on the basic research

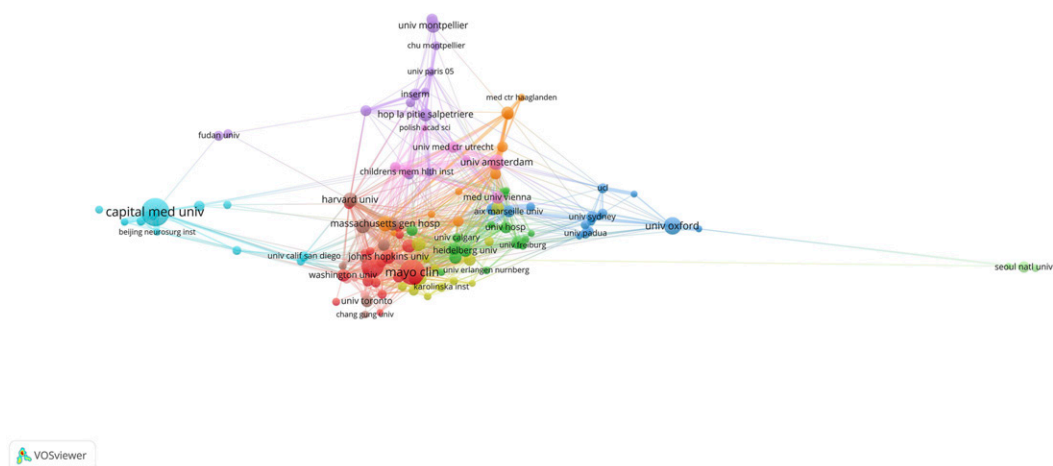
concerning the pathogenesis of GRE, particularly on IDH1 mutation. Cluster 2 (green) is centered on non-surgical treatments, prognosis, and survival outcomes of GRE. Cluster 3 (blue) emphasizes the diagnosis, cognitive impairment, and

**Table 2.** Top 5 institutions with the most publication number.

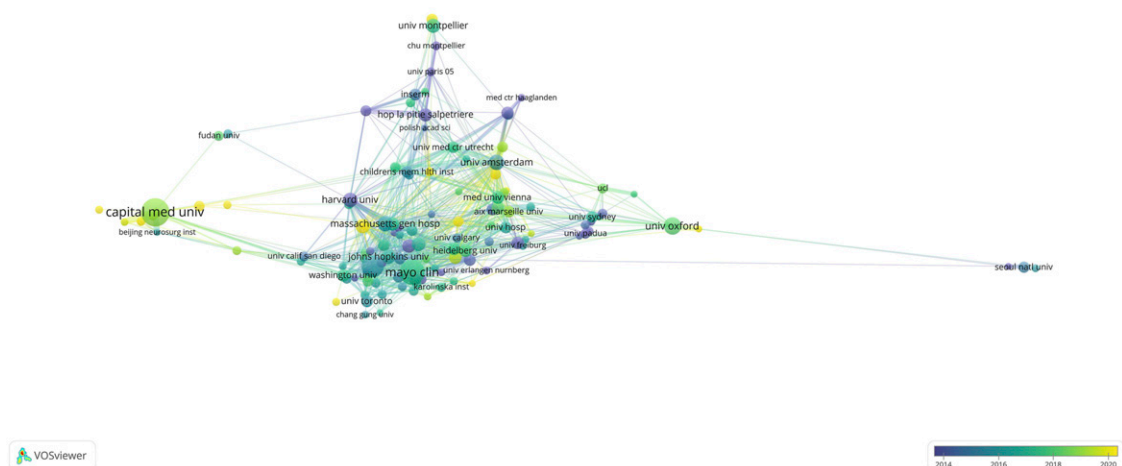
RANK	AFFILIATIONS	COUNTRY	TP	TC	H-INDEX
1	Institut National de la Sante et de la Recherche Medicale (Inserm)	France	139	6050	41
2	University of California system	USA	105	5510	36
3	Harvard University	USA	98	4184	34
4	Assistance Publique Hopitaux Paris (APHP)	France	80	4120	34
5	Capital Medical University	China	79	1418	22

TP, total publications; TC, total citations.

A



B



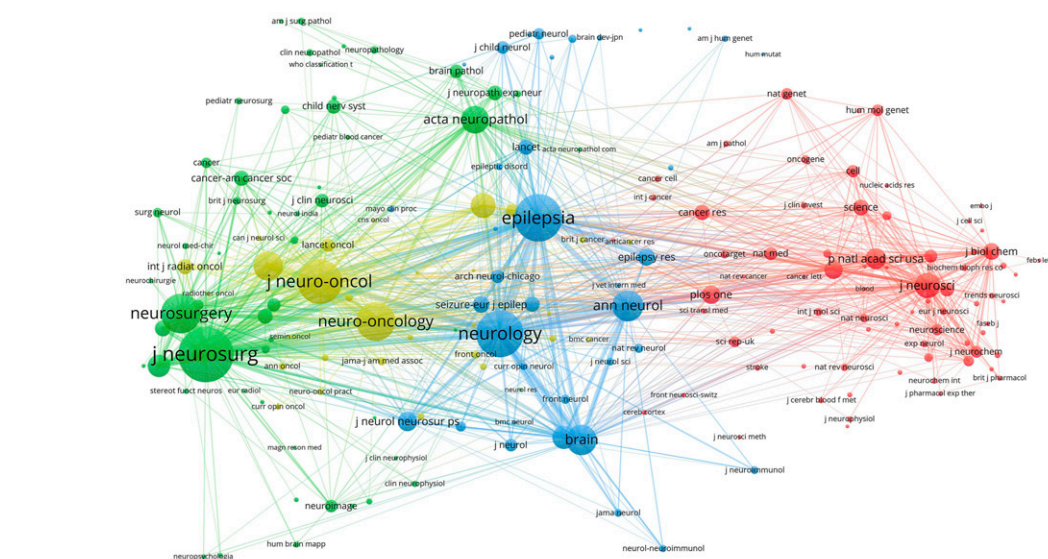
**Figure 4.** (A) Institutions co-authorship analysis; (B) Visual analysis of institutions according to average publication year.

**Table 3.** Top 5 journals with the most publication number.

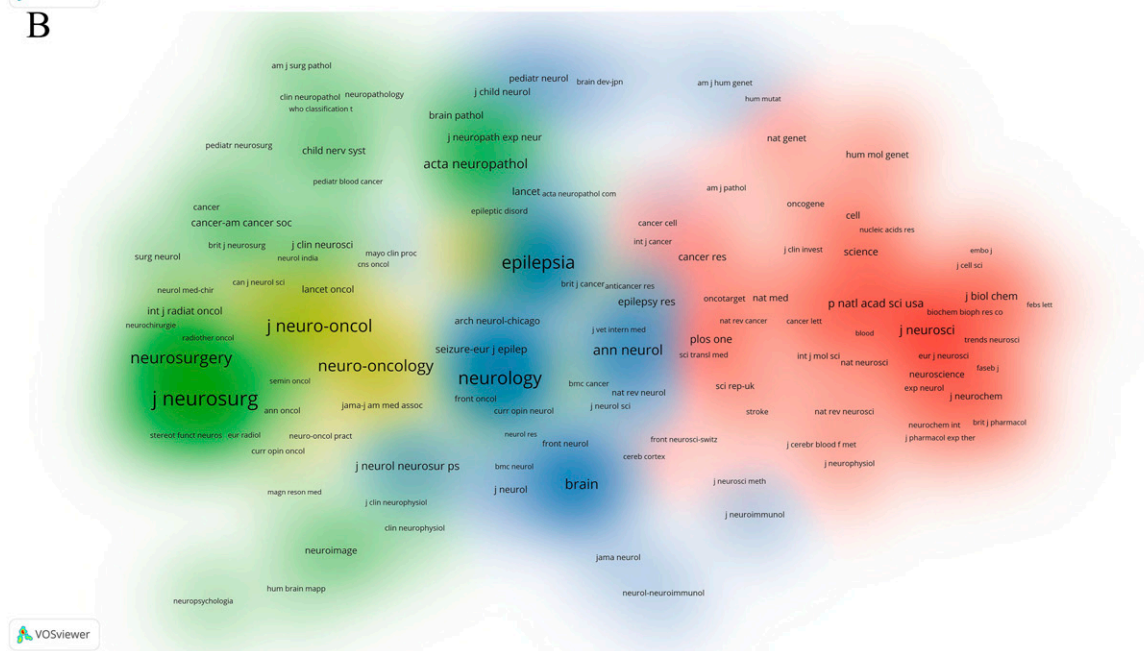
RANK	JOURNAL	TP	TC	H-INDEX	IF (2022)
1	Journal of Neuro Oncology	139	3977	34	3.2
2	Journal of Neurosurgery	85	4232	36	3.5
3	World Neurosurgery	84	1021	18	1.9
4	Epilepsia	55	2016	25	6.6
5	Neuro Oncology	50	3007	32	16.4

TP, total publications; TC, total citations.

A



B



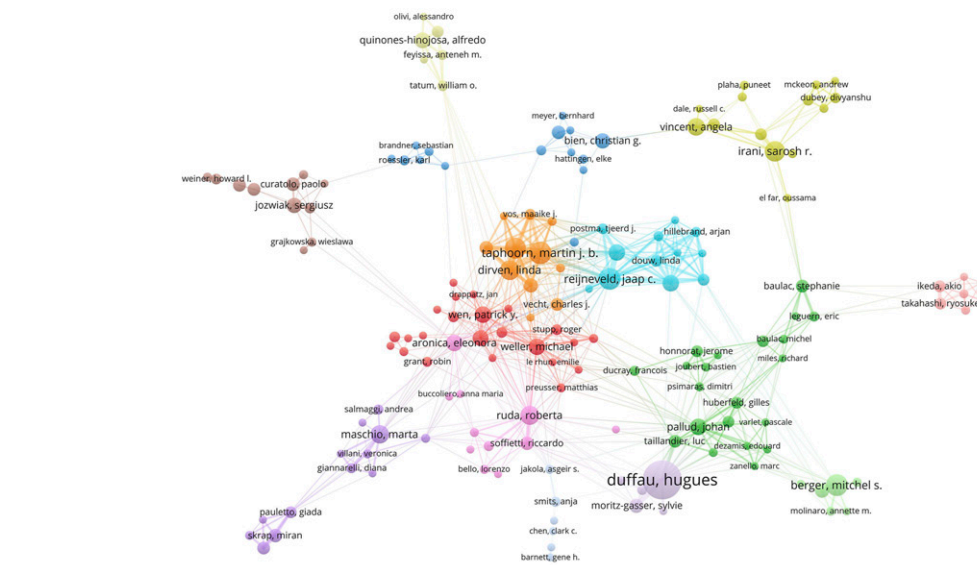
**Figure 5.** (A) Journals co-citation analysis; (B) Density map of journals.

**Table 4.** Top 5 authors with the most publication number.

RANK	AUTHOR	COUNTRY	TP	TC	H-INDEX
1	Duffau, Hugues	France	53	2875	30
2	Taphoorn, Martin J. B	Netherlands	25	786	14
3	Reijneveld, J. C	Netherlands	23	1231	20
4	Berger, Mitchel Stuart	USA	23	1494	16
5	Jiang, Tao	China	22	557	13

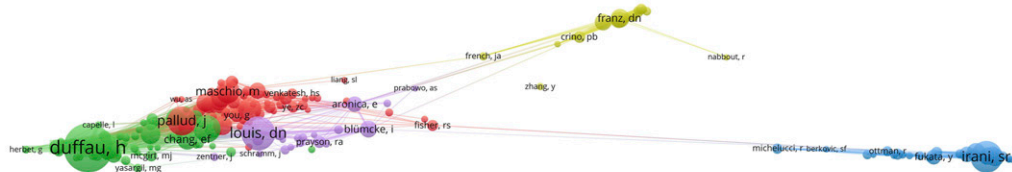
TP, total publications; TC, total citations.

A



VOIviewer

B



VOIviewer

**Figure 6.** (A) Co-authorship analysis between authors; (B) Authors co-citation analysis.



**Table 5.** Top 5 references with the most co-citations.

RANK	ARTICLE TITLE	FIRSTAUTHOR/YEAR/JOURNAL	NC
1	Epilepsy in patients with brain tumours: Epidemiology, mechanisms, and management	van Breemen MS/2007/Lancet Neurol	257
2	Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma	Stupp R/2005/N Engl J Med	236
3	The 2016 World Health Organization classification of tumors of the Central Nervous system: a Summary	Louis DN/2016/Acta Neuropathol	217
4	Seizure characteristics and control following resection in 332 patients with low-grade gliomas	Chang EF/2008/J Neurosurg	188
5	Epileptic seizures in diffuse low-grade gliomas in adults	Pallud J/2014/Brain	152

NC, number of citations.

A



B



**Figure 7.** (A) Network graphs of references co-citation; (B) Density map of references.

**Table 6.** Top 20 keywords with the most co-occurrence frequency.

RANK	KEYWORD	OCCURRENCES	RANK	KEYWORD	OCCURRENCES
1	Seizure	644	11	Trial	177
2	Surgery	475	12	Expression	166
3	Tumor	440	13	Children	153
4	Brain tumor	369	14	Management	145
5	Glioblastoma	296	15	Classification	138
6	Glioma	242	16	Encephalitis	137
7	Low-grade glioma	236	17	Brain	131
8	Radiotherapy	229	18	Central-nervous-system	130
9	Survival	211	19	Prognosis	127
10	Temozolomide	185	20	Extent	127

immunotherapy associated with GRE. Cluster 4 (yellow) mainly focuses on the surgical treatment of GRE. As shown in Figure 8(B), based on average publication year (APY), we conducted visual analysis by VOSviewer to divide the colors of all keywords. In recent years, the following keywords have shown a higher frequency of co-occurrence: IDH1 mutation (cluster 1, APY: 2019.67), cognitive impairment (cluster 3, APY: 2019.08), immunotherapy (cluster 3, APY: 2018.89), and awake craniotomy (cluster 4, APY: 2018.86).

## Discussion

This is the first study using bibliometrics to systematically analyze 2697 publications on GRE over the past 2 decades in WoSCC. In general, the number of publications on GRE studies has been steadily increasing year by year from 2004 to 2023. Since 2020, annual number of publications exceeds 200, suggesting more published articles in the coming years due to the increasing concern about GRE.

From 2004 to 2023, the USA, China, and Germany published more than 250 articles and were also the top 3 countries with the most publication number. The USA ranked first in terms of publication number, TC and H-index, followed by China and Germany with much less publication number, TC and H-index, indicating the leading position of the USA for GRE research. Although ranked second in publication number, H-index (35) and TC (5463 times) of China were lower than those of Germany (H-index = 55, TC = 10,314 times), pointing out the significant room for development on GRE research in China. Collaborations between countries/regions were close, and the USA, Germany, England, Netherlands, and Italy were at the core position.

With regard to the geographical distribution of institutions, 2 of the top 5 institutions with the most publication number were in France, 2 were in the USA and 1 was in China. Inserm, University of California system and Harvard University were the

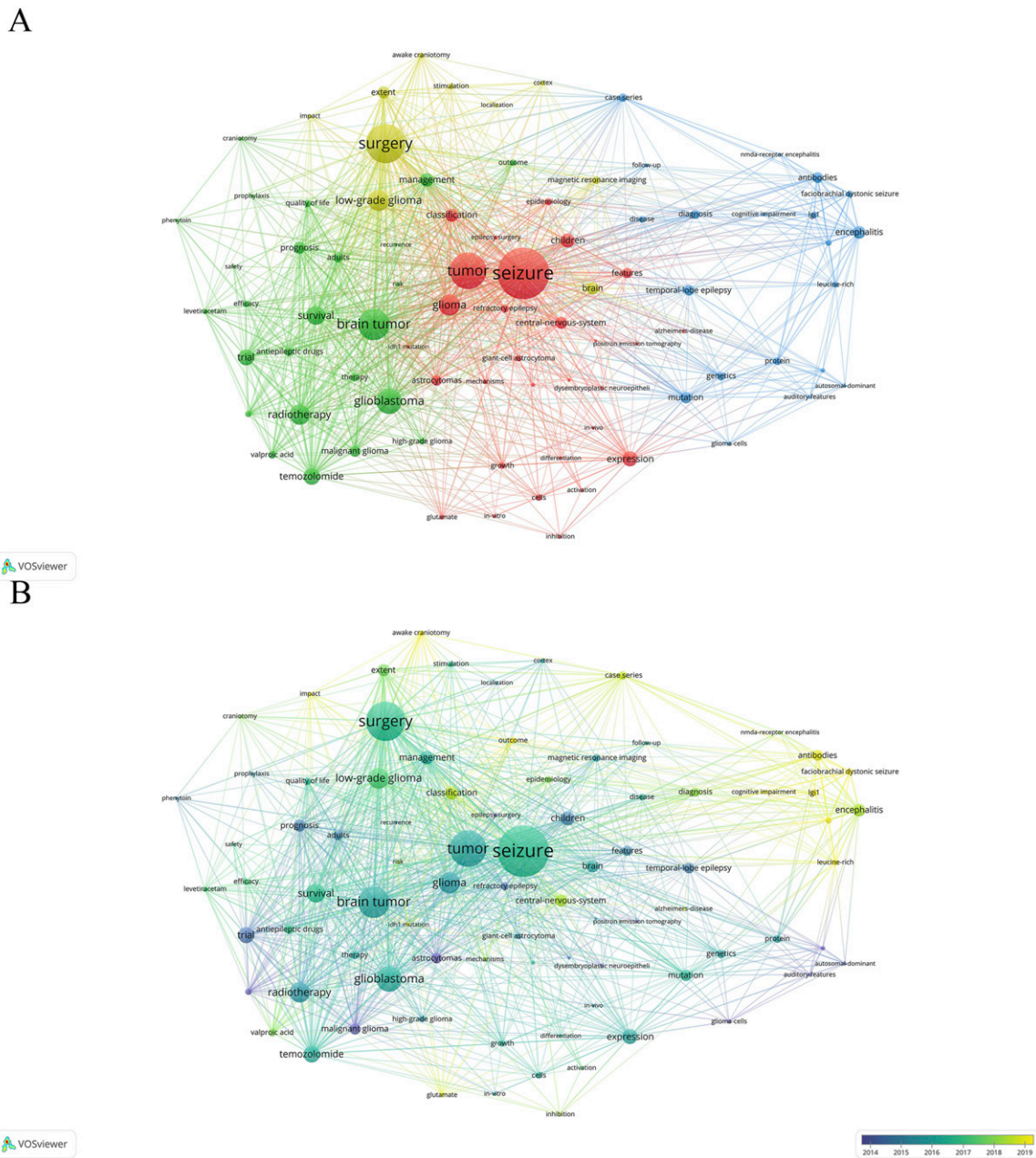
3 institutions with most GRE-related publications. Further, Massachusetts General Hospital, University of Amsterdam and Harvard Medical School actively collaborated with other institutions, meaning their outstanding contribution to the GRE field.

Top 5 journals with the most publications related to GRE were Journal of Neuro Oncology (IF = 3.2), Journal of Neurosurgery (IF = 3.5), World Neurosurgery (IF = 1.9), Epilepsia (IF = 6.6), and Neuro Oncology (IF = 16.4), indicating that these journals were particularly interested in GRE-related research. In addition, we conducted journals co-citations analysis to identify core journals in the field of GRE. Top 3 journals with the most co-citations were Journal of Neurosurgery (4663 times), Epilepsia (3696 times) and Neurology (3685 times), with the largest TLS, reflecting the high quality of scientific output in these journals.

Among the top 5 authors with the most publications related to GRE, Duffau, Hugues from CHU de Montpellier was the most productive author (TP = 53), with the most TC (2875) and the highest H-index (30), proving his prominent contribution to GRE research.

Results from references co-citation analysis noted that review on Lancet Neurol in 2007 by Van Breemen MS et al.<sup>24</sup> had the most TC (257 times) and the largest TLS (2535), indicating its significant influence. In this review, the authors elaborated clinical features of seizures in patients with brain tumors (including gliomas), potential mechanisms of refractory epilepsy, and the interaction between antiepileptic and chemotherapeutic agents, thereby providing management guidelines.<sup>24</sup>

Epileptic seizures may be the sole or initial clinical symptom in patients with glioma. The preoperative incidence of epilepsy in patients with LGG ranges from approximately 70% to 90%,<sup>25-27</sup> whereas in patients with HGG, the preoperative incidence is about 30% to 50%.<sup>28-30</sup> The pathogenesis of GRE is complex and primarily involves tumor location, peritumoral edema,



**Figure 8.** (A) Network graphs of keywords co-occurrence analysis; (B) Visual analysis of keywords according to average publication year.

intrinsic genetic alterations of the tumor, and modifications in the tumor microenvironment.<sup>8-12</sup> Studies indicate that patients with gliomas located in the frontal lobe exhibit a higher incidence of preoperative epilepsy, whereas those with tumors in the occipital lobe demonstrate a lower incidence.<sup>8,31</sup> Peritumoral edema is significantly associated with postoperative seizures in glioma patients,<sup>32</sup> potentially due to its disruption of neurotransmitter pathways.<sup>33</sup> Additionally, genetic alterations within gliomas, such as IDH1 mutations and elevated expression of aquaporin-4, may contribute to the development of epilepsy.<sup>34,35</sup> Furthermore, interactions among microglia, neurons, and tumor cells in the microenvironment surrounding gliomas are critical factors that can lead to the onset of epilepsy.<sup>12</sup>

Keywords co-occurrence analysis can recognize the development trend and hot issues in a certain research field. Our results demonstrated 4 main concerns on GRE research: (1) basic research on pathogenesis, particularly on IDH1 mutation; (2) non-surgical treatments, prognosis, and survival outcomes; (3) diagnosis, cognitive impairment, and immunotherapy; (4) surgical treatments. The evolution of research trends could be visually demonstrated by superimposing keywords with publication year information. Keywords with high-frequency recent years were awake craniotomy, IDH1 mutation, cognitive impairment, and immunotherapy. Surgical treatment plays the most fundamental, critical, and irreplaceable role in the process of treating GRE. Xu et al.<sup>36</sup>

studied 128 LGG patients with seizures and found that when extent of resection was greater than 80%, both postoperative seizure-free proportion and duration significantly prolonged. Still et al.'s study<sup>37</sup> included 346 LGG patients with seizures and showed that when extent of resection was no less than 91% or residual tumor volume was no more than 19cc, postoperative seizure control was easier. The above 2 studies indicated that the likelihood of seizure control had a positive correlation with the extent of surgical resection of gliomas. Therefore, maximal resection of gliomas is effective in controlling postoperative seizures under the premise of safety and feasibility. Gliomas causing epilepsy are mostly located in functional areas of the brain, while intraoperative wake-up allows maximal tumor resection with protection of neurological function.<sup>38-40</sup> Wang et al.<sup>41</sup> performed awake craniotomy on 41 glioma patients with epilepsy and reported good neurological function after surgery, which was beneficial for long-term control of epilepsy symptoms. Surgery and chemoradiotherapy help improve the prognosis of glioma patients, but those with epilepsy may still continue to suffer from epilepsy after surgery, which can seriously affect their quality of life. Furthermore, the use of anti-epileptic drugs may result in cognitive impairment among glioma patients.<sup>42</sup> Thus, studying the mechanism of GRE at the genetic level and performing related target therapy may provide new treatments options. By meta-analysis, Li et al.<sup>43</sup> found LGG patients with IDH1 mutations had a higher incidence of preoperative epilepsy, which might be related to the similar structure of metabolites and glutamate after IDH1 mutations, leading to increased neuronal activity and finally epilepsy. Additionally, Drumm et al.<sup>44</sup> demonstrated that IDH-mutant inhibitors can mitigate the onset of GRE by utilizing an in vivo mice model. Immunotherapy, known for its significant effectiveness in treating a range of tumors, is considered a viable strategy for the treatment of gliomas.<sup>45</sup> Within the realm of glioma immunotherapy, peptide vaccines that target IDH mutations have emerged as a promising therapeutic option, potentially leading to a reduction in seizures among glioma patients.<sup>46</sup>

There are some limitations in this study. First, we only included articles and review articles published in English and did not consider those in non-English language. Second, bibliometrics was the general trend description of a certain field, and errors might be generated according to different software statistical algorithms. Finally, only WoSCC was used for searching. However, it is worth noting that WoSCC is the most common database in scientometrics, where the majority of bibliometric software can extract information.<sup>47,48</sup> Despite these uncontrollable factors, this study is committed to presenting the publication of GRE publications during 2004-2023 and analyzing the hotspots of related research, with considerable reliability and reference value.

## Conclusion

In summary, this is the first study using bibliometrics to analyze GRE-related scientific outputs over the past 2 decades. The number of publications has been generally increasing from 2004

to 2023. The USA ranked first in publication number, TC and H-index. Inserm, University of California system and Harvard University were the 3 institutions with the greatest contribution. Core journals were Journal of Neurosurgery, Epilepsia and Neurology. Duffau, Hugues was the most productive authors. The latest research focus of GRE were awake craniotomy, immunotherapy, cognitive impairment, and basic research on pathogenesis, with particular emphasis on the IDH1 mutation.

## Author Contributions

**R.L.:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft. **C.H.:** Data curation; Formal analysis; Investigation; Methodology; Software; Writing – review & editing. **H.L.:** Data curation; Formal analysis; Writing – review & editing. **X.T.:** Conceptualization; Methodology; Supervision; Writing – review & editing.

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## Data Availability Statement

The data and materials supporting the results of this study are available from the corresponding author on reasonable request.

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