Heliyon 10 (2024) e26653

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Mapping the global research landscape and trends of autoimmune encephalitis: A bibliometric analysis

Song Ouyang[a,b,1], Zhenchu Tang[c,d,1], Weiwei Duan[e], Sizhi Tang[f], Qiuming Zeng[e], Wenping Gu[e], Miao Li[a], Hong Tan[a], Jiangying Hu[a], Weifan Yin[c,*]

[a] Department of Neurology, The Affiliated Changsha Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan, PR China
[b] The "Double-First Class" Application Characteristic Discipline of Hunan Province (Clinical Medicine), Changsha Medical University, Changsha, Hunan, PR China
[c] Department of Neurology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, PR China
[d] Hunan Key Laboratory of Tumor Models and Individualized Medicine, The Second Xiangya Hospital, Central South University, Changsha, Hunan, PR China
[e] Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan, PR China
[f] Department of Neurology, Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University, Zhuzhou, Hunan, PR China

ARTICLE INFO

Keywords:
Autoimmune encephalitis
Bibliometric analysis
VOSviewer
CiteSpace
Immunotherapy

ABSTRACT

Background: Autoimmune encephalitis (AE) is a neuroautoimmune disease featured by the presence of antibodies targeting neuronal surface, synaptic, or intracellular antigens. An increasing number of articles on its clinical manifestations, treatments, and prognosis have appeared in recent years. The objectives of this study were to summarize this growing body of literature and provide an overview of hotspots and trends in AE research using bibliometric analysis.
Methods: We retrieved AE-related articles published between 1999 and 2022 from the Web of Science Core Collection. Using bibliometric websites and software, we analyzed the data of AE research, including details about countries, institutions, authors, references, journals, and keywords.
Results: We analyzed 3348 articles, with an average of 32.83 citations per article and an H-index of 141. The USA (1091, 32.587%), China (531, 15.860%), Germany (447, 13.351%), England (266, 7.945%), and Japan (213, 6.362%) had the greatest numbers of publications. The top five institutions by numbers of publications were Oxford (143, 4.271%), the Udice French Research Universities (135, 4.032%), the University of Pennsylvania (135, 4.032%), l'Institut National de la Sante de la Recherche Medicale Inserm (113, 3.375%), and the University of Barcelona (110, 3.286%). The most productive authors were J. Dalmau (98, 2.927%), A. Vincent (65, 2.479%), H. Pruess (64, 1.912%), C. G. Bien (43, 1.284%), and F. Graus (43, 1.284%). "autoimmune encephalitis" was the most frequently used keyword (430), followed by "antibodies" (420), "NMDA receptor encephalitis" (383), and "limbic encephalitis" (368). In recent years, research hotspots have focused on the diagnosis and immunotherapy of NMDAR encephalitis and on limbic encephalitis.
Conclusion: Developed Western countries have made significant contributions to this field. China has shown a steady increase in the number of publications in recent years, but the quality and influence of these articles warrant efforts at improvement. Future directions in AE research lie in

* Corresponding author. Department of Neurology, The Second Xiangya Hospital, Central South University, Changsha, 410011, Hunan, PR China.
E-mail address: yinweifan1985@csu.edu.cn (W. Yin).

[1] Authors share the first authorship.

https://doi.org/10.1016/j.heliyon.2024.e26653
Received 11 July 2023; Received in revised form 22 January 2024; Accepted 16 February 2024
Available online 17 February 2024

two key areas: (i) the clinical manifestations, prevalence, and prognosis of AE (enabled by advances in diagnosis); and (ii) the efficacy and safety of targeted, individualized immunotherapy.

1. Introduction

Autoimmune encephalitis (AE) is a neuroimmune disease featured by the presence of aberrant antibodies targeting neuronal cell-surface, synaptic, or intracellular antigens [1]. It is a rare but severe neurological disorder with an incidence of approximately 0.8 every 100,000 persons per year and a prevalence of almost 13.7 in every 100,000 persons worldwide [2]. Although AE was first described in the mid-19th century, it has gained widespread attention and research focus in recent years [3]. Progress has been achieved in the diagnosis and treatment of AE due to a deeper understanding of the interactions between the immune and nervous systems. Clinical symptoms of AE include mental disturbances, seizures, cognitive impairment, decreased consciousness, and movement disorders [4]. The polysymptomatic neurological and neuropsychiatric manifestations of AE mainly depend on distinct autoantibodies [5]. With the continuous expansion of the repertoire of known AE antibodies, the associated clinical spectrum has also expanded [6].

As a heterogeneous entity, the exact etiology of AE remains incompletely understood but is expected to be closely associated with factors such as infection, tumors, and immune dysregulation [7]. In addition, owing to the atypical clinical syndromes of AE and the fact that testing for the causative antibodies can produce type-II errors, accurate diagnosis and therapeutic efficiency in clinical practice remain challenging [8]. The quantity of published research on this topic has grown significantly in recent years. However, significant gaps remain in our understanding and management of AE. Moreover, the cited challenges in accurate diagnosis and evaluation may lead to delays and difficulties in disease management, resulting in a poor prognosis [9]. Early diagnosis and immunotherapy hold promise for better clinical outcomes [10] but treatment-related adverse effects may impact the long-term outcome, and in patients with complex comorbidities, the choice of treatment regimens may be limited [11]. Although many qualitative studies and systematic reviews have been published, a comprehensive summary of AE research, including key authors, institutions, countries, and promising research trends, has been lacking.

Bibliometrics is an established bioinformatics tool for academic publication analysis and visualization that can provide quantitative and qualitative evidence in a defined field of research [12]. Through bibliometric analysis, researchers can obtain a quick understanding of the countries and institutions performing the research, contributing authors, publishing journals, and references in the field of interest. Additionally, the analysis of keyword timelines can indicate current hotspots and developing trends in related research areas [13]. To date, no bibliometric analyses have been conducted in the AE field. Bibliometric analysis of AE research can improve our knowledge of the status, hotspots, and developmental trends of this disease. The present study is the first bibliometric analysis of AE research, which aims to present a thorough analysis and academic mapping of articles on AE in terms of countries, institutions, references, citations, authors, and keywords using relatively objective and unbiased methods. Using bibliometric websites and CiteSpace and VOSviewer software, we analyzed relevant data on AE studies from 1999 to 2022.

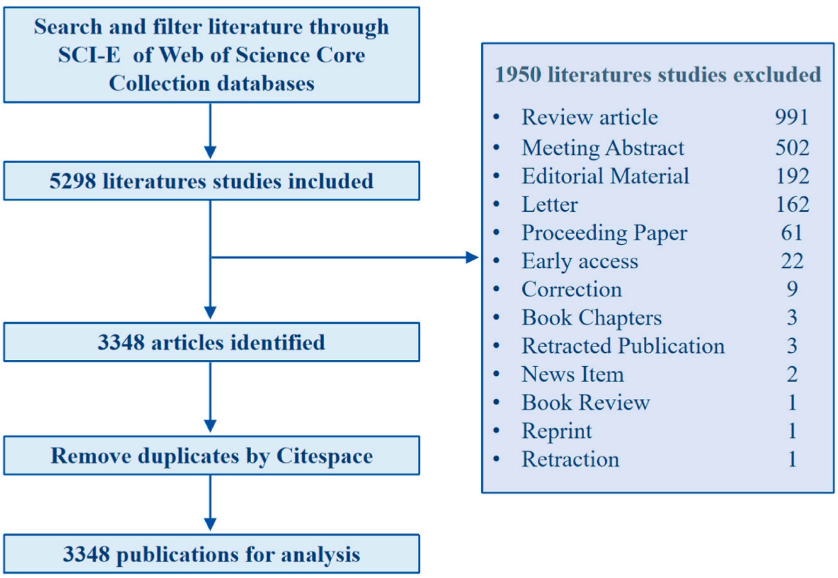

Fig. 1. Flowchart for literature retrieval.

2. Research methods

2.1. Data extraction

We conducted a comprehensive literature retrieval in Science Citation Index Expanded (SCI-E) of the Web of Science Core Collection (WoSCC) database utilizing the subsequent search strategy: Thematic Suffix (TS)= ((Autoimmune Encephalitis) OR (Autoimmune Encephalitides) OR (Encephalitis, Autoimmune) OR (Antibody Mediated Encephalitis) OR (Antibody-Mediated Encephalitis) OR (Antibody-Mediated Encephalitides)) AND LA = (English). All included literature searches and data were prior to December 31, 2022. A total of 5298 publications were retrieved, and 3348 relevant articles were identified after excluding reviews, meeting abstracts, editorials, letters, proceedings, early access records, and retractions. The details of the search procedure are presented in Fig. 1.

2.2. Data analysis

We exported all the included articles and input them into CiteSpace software (version 6.2. R2), VOSviewer (1.6.19), and a bibliometric website for further investigation.

The particular CiteSpace parameters were as following: method, log-likelihood ratio; time slicing, January 1999–December 2022, years per slice, term source, title/abstract/author/keywords/keyword plus; node type, author/institution/keyword/country; and selection criteria, g-index K = 25. We conducted number, centrality, burst, and cluster analysis of AE research field using CiteSpace involving countries, institutions, journals, authors, and keywords. The centrality metric was employed as an index of the significance of nodes within the network. Nodes with a centrality value greater than 0.1 were deemed comparatively important. Burst analysis was used to reveal surges in citations within a specific research area during a particular period as well as the duration of these bursts, the latter reflecting the length of time during which focused research interest persisted. Cluster analyses showed similar characteristics with the same color.

We also used VOSviewer to assess and visualize research characteristics from countries, institutions, and keywords. The co-occurrence graph so obtained included nodes and links. The nodes indicated the quantities of items, and the links represented the connection strength between two nodes. The size of a node indicated its importance; larger nodes represented more influential literature, keywords, authors, and institutions. Clusters represented collections of nodes with similar themes. Similar nodes were grouped together to form clusters differentiated by color and shape. Larger clusters typically represented more important topics or areas.

The online platform for bibliometric analysis and visualization was used to illustrate international collaboration among countries. Microsoft Excel (2019) was used for graphing and statistical analyses.

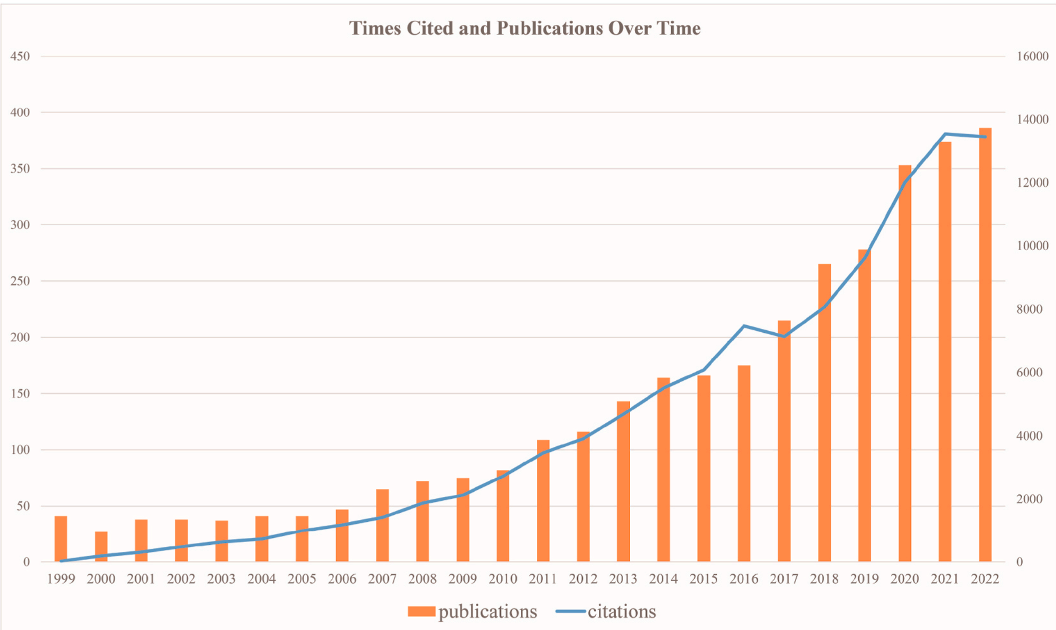

Fig. 2. Research in autoimmune encephalitis (AE), 1999–2022: Trends in publication volume and citations.

3. Results

3.1. Overall status and research trends

As depicted in Fig. 2, The quantity of AE publications exhibited a consistent upward trend throughout the years, from 41 in 1999 to 386 in 2022. Similarly, yearly citations showed a consistent upward trend, rising from 31 in 1999 to 13,447 in 2022. Notably, we observed two peaks in citation numbers in 2016 and 2021, possibly linked to important breakthroughs in AE research in these two periods. Overall, AE studies received 57,714 citations (55,204 after excluding self-citations), with an average of 32.83 citations per article and an H-index of 141. These results covered 93 research categories. The top three were clinical neurology (1375, 41.069%), neuroscience (980, 29.271%), and immunology (582, 17.384%). Others were pediatrics (267, 7.975%) and psychiatry (243, 7.258%) (Table 1).

3.2. Analysis of national research and collaborations

Among the 92 countries involved in AE research, the leading five countries in terms of publication numbers were the USA (1091, 32.587%), China (531, 15.860%), Germany (447, 13.351%), England (266, 7.945%), and Japan (213, 6.362%) (Table 1). Citation bursts were analyzed by country from 1999 to 2022 (Fig. 3**A**). Notably, China exhibited the greatest burst strength (49.26) during the years 2020–2022, indicating significant research interest in recent years. The USA (2004–2009), Germany (2001–2003), England (2013–2014), and Canada (2004–2011) followed with strong citation bursts. The majority of top 10 countries with the strongest burst were from developed countries. However, we found Turkey as another developing country in addition to China, with the burst strength 3.31 and duration time burst from 2016 to 2018. A collaboration analysis based on national productivities is shown in Fig. 3**B**, which displays a network map of 45 nodes and eight clusters using a threshold of 5. The leading three countries with the largest total link strength (TLS) were sequentially the USA (TLS = 642), Germany (TLS = 431), and England (TLS = 355). For less developed countries, China (TLS = 114) and Turkey (TLS = 49) showed relatively weak national collaboration compared with developed countries.

3.3. Institutional outputs and collaborations

The top five institutions by numbers of publications are shown in Table 1. Oxford (143, 4.271%) was the most productive institution, followed by the Udice French Research Universities (135, 4.032%), the University of Pennsylvania (135, 4.032%), l'Institut National de la Sante de la Recherche Medicale Inserm (113, 3.375%), and the University of Barcelona (110, 3.286%). The citation bursts of 25 institutions are shown in Fig. 4. The top five institutions by burst strength were the University of Washington (2007–2013), Oxford (2010–2014), the University of Barcelona (2012–2016), Capital Medical University (2020–2022), and the National Institutes of Health (2006–2011). Notably, five institutions of the recent burst duration were Shandong University (2020–2022), Capital Medical University (2020–2022), CNRS-National Institute for Biology (2019–2022), Universite Claude Bernard Lyon 1 (2019–2022), and Southern Medical University-China (2018–2020). Three of them were from China, which indicated institutions of China have active research atmosphere in the recent years.

Collectively, 3348 articles were selected and loaded into VOSviewer from institutions that published at least 15 articles. Based on this criterion, 96 institutions were identified and categorized into eight clusters based on their collaboration levels. The top five largest clusters were as follows: Mayo Clinic, Johns Hopkins University, Washington University, and Stanford University (Fig. 5, green);

Table 1
Top five ranked on publication volume (1999–2022).

Field		Count	Percentage (%)
Research areas	Clinical Neurology	1375	41.07
	Neurosciences	980	29.27
	Immunology	582	17.38
	Pediatrics	267	7.98
	Psychiatry	243	7.26
Countries	USA	1091	32.59
	China	531	15.86
	Germany	447	13.35
	England	266	7.95
	Japan	213	6.36
Institutions	University of Oxford	143	4.27
	Udice French Research Universities	135	4.03
	University of Pennsylvania	135	4.03
	Institut National de la Sante de la Recherche Medicale Inserm	113	3.38
	University of Barcelona	110	3.29
Authors	Dalmau Josep	98	2.93
	Vincent Angela	65	2.48
	Pruess Harald	64	1.91
	Bien G Christian	43	1.28
	Graus Francesc	43	1.28

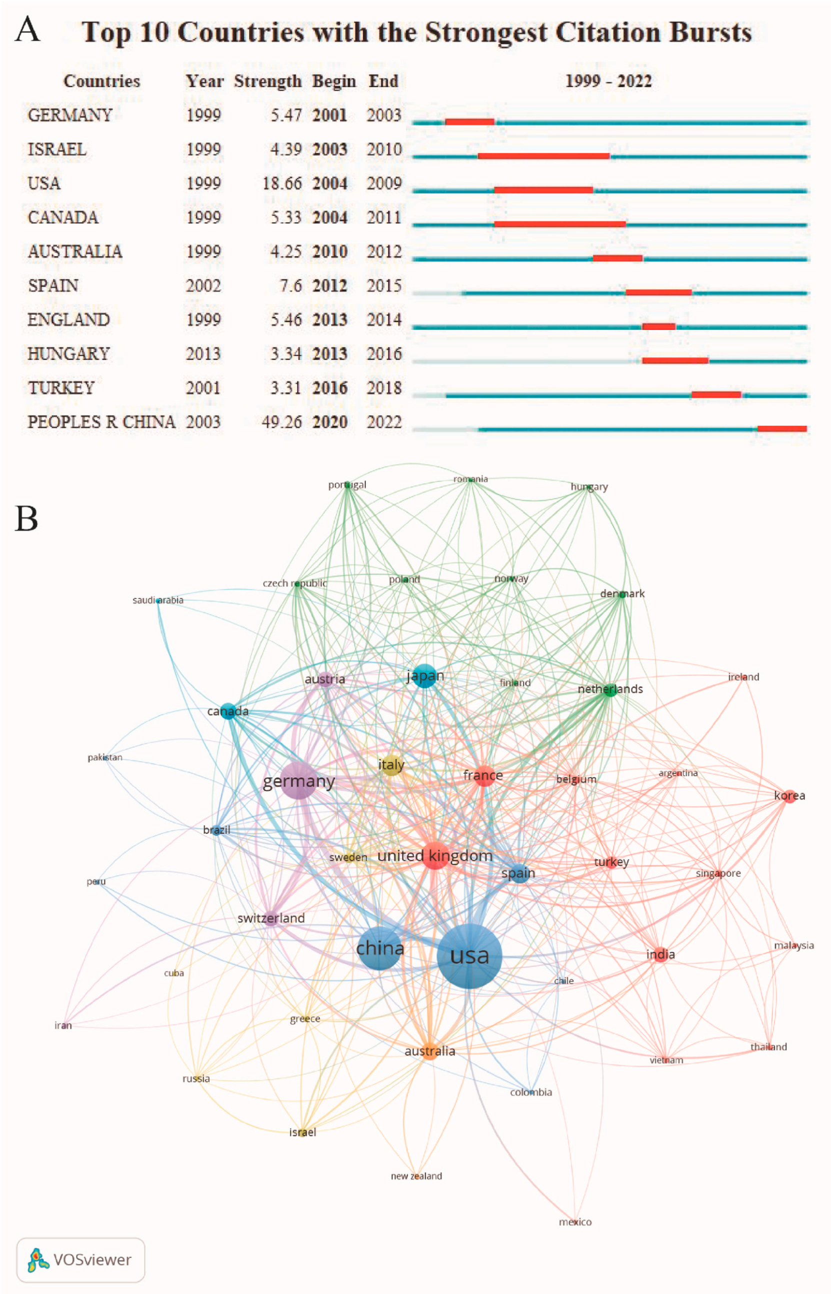

Fig. 3. Citation-burst and cluster analysis by country
(**A**) Shown are the top ten countries by citation-burst strength from 1999 to 2022. Red lines represent duration of the citation bursts, which indicate an escalation of research intensity in a particular country. (**B**) A graphical representation of the current state of international collaboration. Distinct colors symbolize distinct collaborative clusters; links demonstrate the level of cooperation, and the thickness of the links indicates the proximity of the collaboration.

Charité Universitätsmedizin Berlin, Medical University of Vienna, University of Freiburg, and University of Bonn (red); Oxford, University of Sydney, John Radcliffe Hospital, and Karolinska Institute (blue); University of Pennsylvania, University of Barcelona, and the Clinical Hospital of Barcelona (purple); and Capital Medical University, Sichuan University, Shandong University, and Chongqing Medical University (yellow).

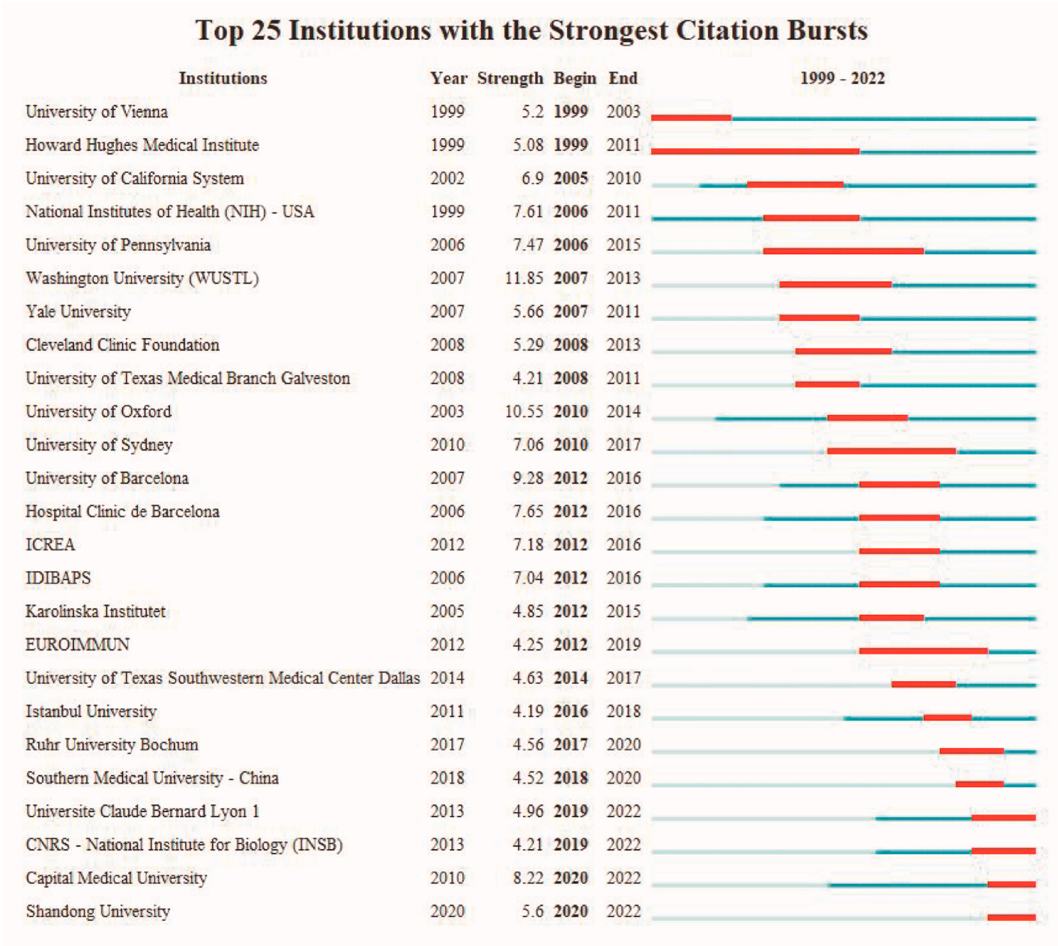

Fig. 4. The top 25 institutions by citation-burst strength.
The red lines indicate the duration of citation bursts.

3.4. Analysis of author output and collaboration

Among the 873 authors analyzed, the top five by productivity were J. Dalmau (98 publications, 2.927%), A. Vincent (65 publications, 2.479%), H. Pruess (64 publications, 1.912%), C. G. Bien (43 publications, 1.284%), and F. Graus (43 publications, 1.284%) (Table 1). As shown in Fig. 6**A**, the authors who exhibited the strongest bursts in their publication activity were A. Vincent (2010–2015), Michael S. D (2007–2012), J. Dalmau (2010–2015), Russell C. D (2010–2017), and H. Pruess (2018–2020). However, the centrality index was <0.1 for all authors, and the network map revealed a limited number of connections, suggesting minimal collaboration among researchers in this research field. The authors were categorized into six clusters based on the research area of the published articles. Succeeded by cluster #1 and subsequent clusters, arranged in descending order based on their respective sizes (Fig. 6**B**).

3.5. Present status of journal publication and dissemination

Table 2 presents the top five journals in terms of publication count. The order of the publication counts was as follows: Journal of Neuroimmunology (134, 4.002%) > Frontiers in Neurology (125, 3.734%) > Frontiers in Immunology (94, 2.808%) > Journal of Virology (94, 2.808%) > BMC Neurology (69, 2.061%). The order of the average number of citations per article was Journal of Neuroimmunology (20.66) > Journal of Virology (73.31) > Frontiers in Neurology (6.58) > Frontiers in Immunology (6.68) > BMC Neurology (5.93). The order of the H-index values was Journal of Virology (47) > Journal of Neuroimmunology (31) > Frontiers in Neurology (17) > Frontiers in Immunology (15) > BMC Neurology (10).

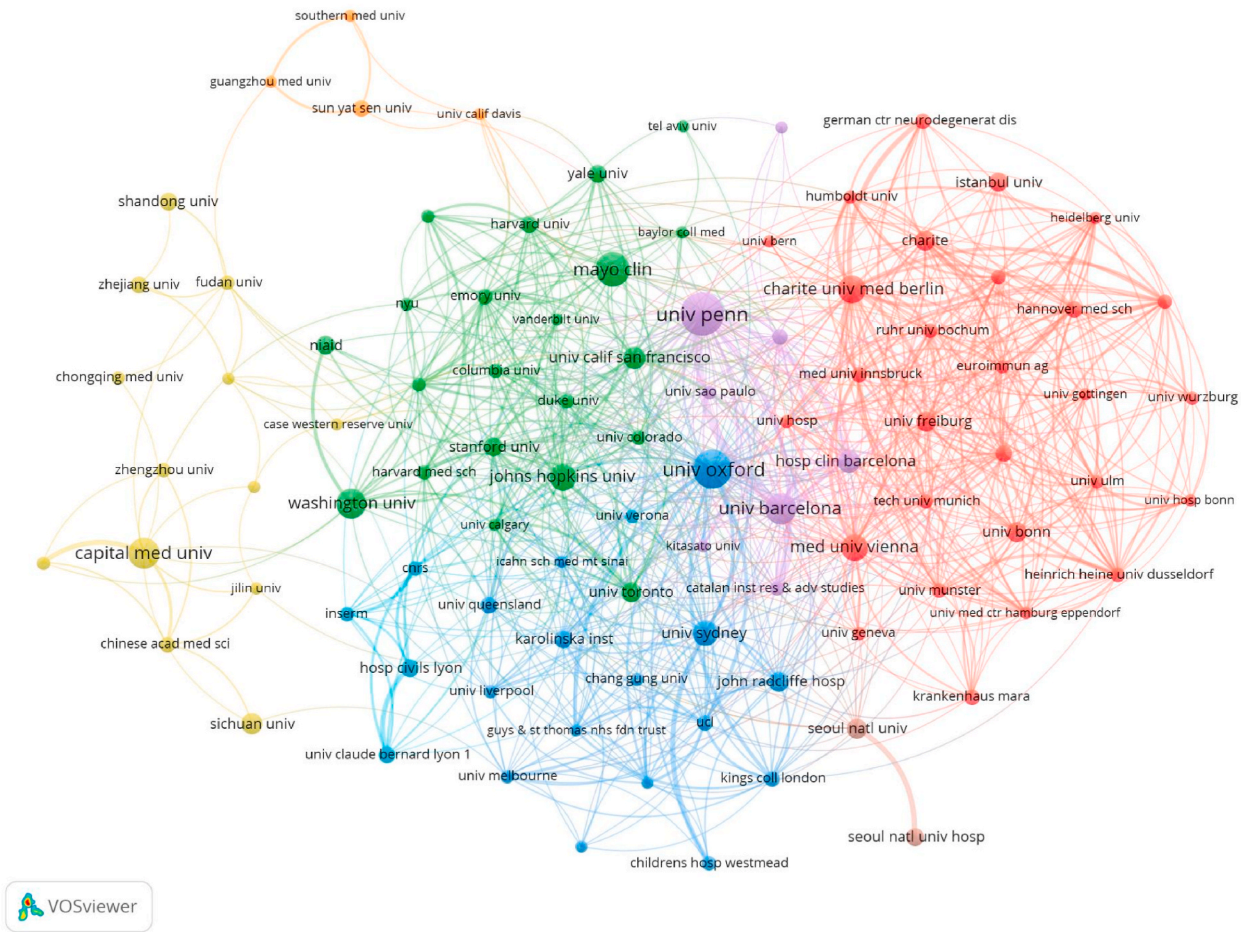

Fig. 5. Institutional collaborations.
Different hues represent different institutional collaborations, and links indicate the degree of cooperation. The thickness of the links reflects the closeness of the collaboration of individual institutions.

3.6. Current status of references

Table 3 presents a compilation of the top 10 most highly cited references of 1999–2022 that would be of particular interest to AE researchers. Fig. 7 presents the top 30 references with the most notable citation bursts. Among all the cited references, the strongest burst (102.93) was that of "A clinical approach to diagnosis of autoimmune encephalitis" published by F. Graus during the period 2017–2022. This study developed a practical syndrome-based diagnostic approach for AE and provided guidelines for navigating the process of differential diagnosis. The second-strongest burst (63.79) was that of "A multi-center study of treatment and prognostic factors for long-term outcomes in patients with anti-NMDA receptor encephalitis" published by M. J. Titulaer during the period 2014–2018. This was a large, multi-center, observational study on therapy and long-term outcomes in patients with anti-NMDA receptor encephalitis.

3.7. Analysis of keywords

3.7.1. Keyword bursts and timelines

Table 4 lists the 30 most frequently used keywords and their centrality indices. The top five by frequency were "autoimmune encephalitis" (430), "antibody" (420), "NMDA receptor encephalitis" (383), and "limbic encephalitis" (368). The top five by centrality were "cells" (0.1), "antibody" (0.09), "encephalitis" (0.09), "disease" (0.09), and "expression" (0.08). A keyword timeline graph was generated using the timeline view in CiteSpace (Fig. 8**A**) to visualize the clustering of keywords by plotting them against their years of occurrence. In timeline view, keywords are arranged within their respective clusters, and the length of the horizontal line for each cluster represents its timeframe. This graphical representation allows for a visual understanding of the historical evolution of the literature and facilitates the tracking of research trends over time. As presented in Fig. 8**A**, most of the study clusters started in 1999, including #0 "multiple sclerosis," #1 "dengue virus," #3 "limbic encephalitis," #7 "cerebrospinal fluid," and #5 "autoimmune

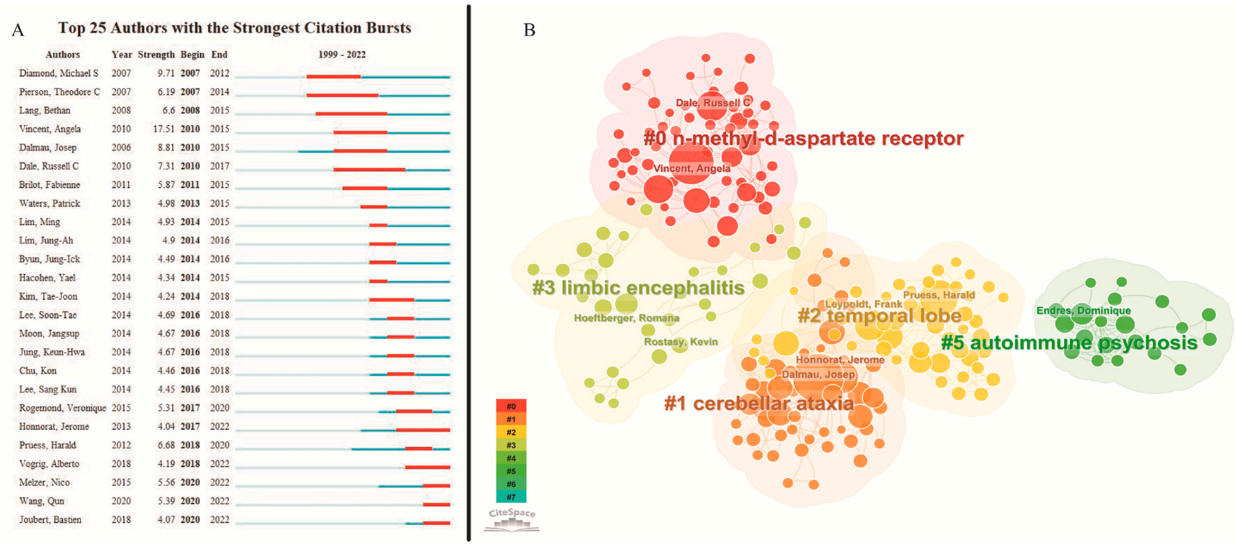

Fig. 6. Citation-burst and cluster analysis of author collaborations
(**A**) Shown are the leading 25 authors by citation-burst strength. Red lines indicate burst duration. (**B**) Author co-citation, indicating authors who conducted research in similar directions. Shown are five clusters identified by the maximum log-likelihood ratio method of cluster analysis.

Table 2
Top 5 Journals based on publication volumes.

Journal	Number of publications	Citing articles		Times cited		Average per item	H-index
		Total	Without self citations	Total	Without self citations		
Journal of Neuroimmunology	134	2434	2395	2769	2717	20.66	31
Frontiers in Neurology	125	672	637	823	772	6.58	17
Frontiers in Immunology	94	557	532	628	583	6.68	15
Journal of Virology	94	5761	5721	6891	6816	73.31	47
BMC Neurology	69	386	380	409	403	5.93	10

Table 3
Top 10 references ranked by citation times.

Rank	Title	Journal	Country	Author	Years	Number of citations
1	A clinical approach to diagnosis of autoimmune encephalitis	Lancet Neurology	Spain	Francesc Graus	2016	378
2	Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study	Lancet Neurology	USA	Maarten J Titulaer	2013	191
3	Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis	Lancet Neurology	USA	Josep Dalmau	2011	140
4	Antibody-Mediated Encephalitis	The New England Journal of Medicine	USA and Spain	Josep Dalmau	2018	138
5	Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis	Annals of Neurology	USA	Divyanshu Dubey	2018	87
6	N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes	Brain	The United Kingdom	Sarosh R Irani	2010	85
7	Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study	Lancet Neurology	Spain	Nuria Gresa-Arribas	2014	82
8	Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies.	Lancet Neurology	USA	Josep Dalmau	2008	81
9	An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models	Lancet Neurology	Spain	Josep Dalmau	2019	73
10	Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia	Brain	The United Kingdom	Sarosh R Irani	2010	71

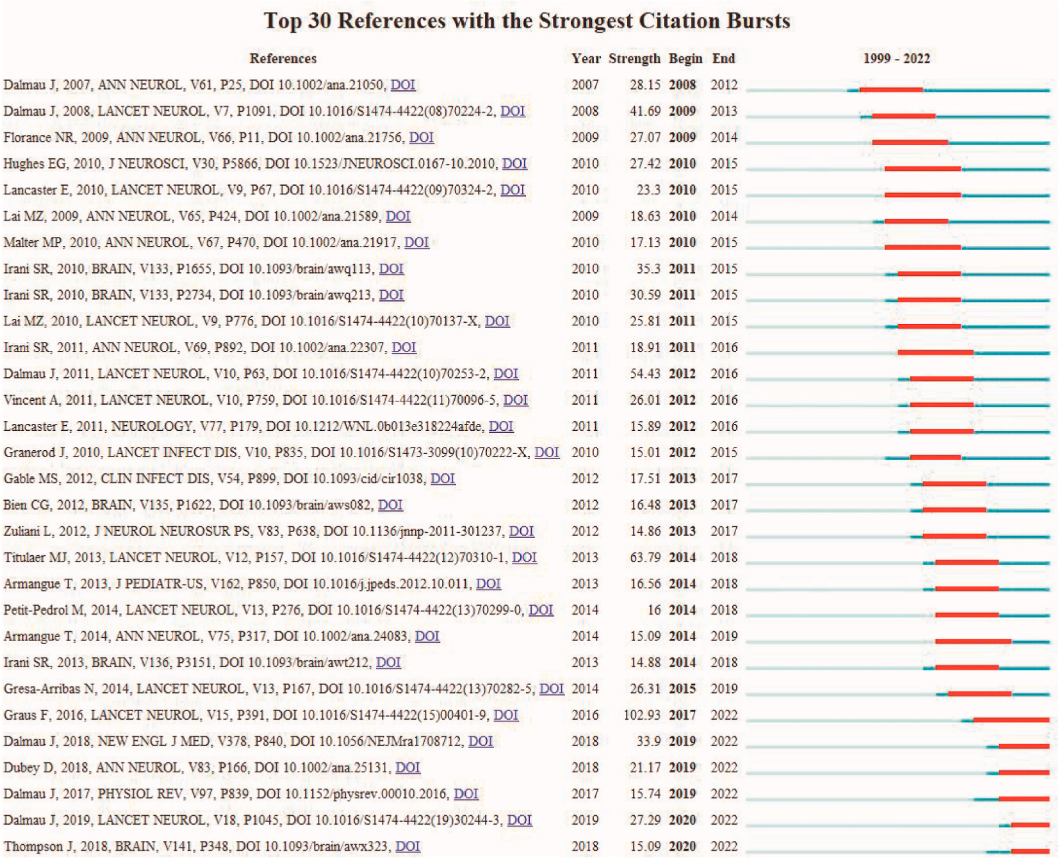

Fig. 7. The top 30 references by citation-burst strength.
The red lines indicate the duration of citation bursts.

disease." A study of AE model was initiated in 2004.

In addition, we analyzed the top 25 keyword citation bursts using CiteSpace. As illustrated in Fig. 8**B**, the top 25 keyword bursts emerged between 1999 and 2022, with "central nervous system" (25.58) having the highest intensity. The keyword bursts in the most recent five years were "outcome" (2020–2022), "case report" (2020–2022), "prevalence" (2018–2022), "diagnosis" (2019–2022), and "autoimmune" (2019–2022). Those lasting more than 4 years included "central nervous system" (1999–2011), "monoclonal antibody" (1999–2009), "experimental autoimmune encephalitis" (1999–2011), "mice" (1999–2011), "interferon gamma" (1999–2011), "infection" (2000–2011), "immune responses" (2000–2011), "experimental anergic encephalomyelitis" (2000–2013), "borne encephalitis virus" (2000–2011), "identification" (2002–2015), "dengue virus" (2005–2013), "potassium channel antibody" (2006–2013), and "ovarian teratoma" (2010–2018). The results suggest that these research directions have garnered considerable attention from researchers and maintained a sustained level of popularity over an extended period.

3.7.2. Keyword co-occurrence and clustering

A VOSviewer analysis was employed to visualize keyword co-occurrence and overlay networks, providing insights into prominent areas of research and emerging trends within the field. A network mapping visualization was constructed specifically for keywords that exhibited a co-occurrence value greater than 35 ×. The visualization map consisted of 123 nodes divided into three clusters. These nodes were connected by 8832 links with a cumulative link strength of 54,262. (Fig. 8**C**). The term "encephalitis" was the node of greatest centrality, followed by "autoimmune encephalitis." The overlay visualization map summarizes keyword occurrences from a temporal-epoch perspective. In Fig. 8**D**, blue and yellow nodes represent keywords that have appeared recently, indicating that research hotspots in recent years have involved the diagnosis and immunotherapy of NMDAR encephalitis as well as limbic encephalitis.

In summary, the AE research conducted over the past decade has primarily focused on rare cases. However, as more cases have been reported, clinical researchers have increasingly focused on the diagnostic patterns, clinical outcomes, immunotherapy, and prevalence of AE.

Table 4
Top 30 keywords ranked by occurrence frequency (in count order, 1999–2022).

Keywords	Centrality	Count	First appearance year
Autoimmune encephalitis	0.01	430	2010
Antibody	0.09	420	1999
NMDA receptor encephalitis	0.01	383	2010
Limbic encephalitis	0.04	368	2005
Encephalitis	0.09	297	1999
Diagnosis	0.02	287	2004
Multiple sclerosis	0.06	274	1999
Central nervous system	0.05	249	1999
Autoantibody	0.06	205	1999
Infection	0.05	169	1999
Disease	0.09	153	1999
Children	0.03	152	2003
Expression	0.08	144	1999
Cerebrospinal fluid	0.07	133	1999
Experimental autoimmune encephal- omyelitis	0.06	129	1999
T cells	0.06	107	1999
NMDA receptor	0.03	106	2011
Case series	0.02	105	2013
Monoclonal antibody	0.05	98	1999
Epilepsy	0.03	96	1999
Mice	0.06	95	1999
Brain	0.07	84	2000
Protein	0.06	83	1999
Immune responses	0.06	78	2000
Cells	0.1	74	1999
Receptor encephalitis	0.01	73	2011
Disorders	0.02	70	2002
Mechanisms	0.02	68	2006
Immunotherapy	0.01	68	2011
West nile virus	0.03	67	2005

4. Discussion

Bibliometrics is an effective method for providing a thorough overview of current research progress and future trends within a particular field [14,15]. To the best of our comprehension, this is the primary bibliometric analysis to specifically examine the evolutionary direction of AE research from 1999 to 2022. We assessed 3348 articles from 873 authors, 735 journals, 3531 institutions, and 93 countries.

In general, this study showed that the number of AE-associated articles and the number of citations of publications increased each year. The possible reasons for this are as follows: First, with the advance of diagnostic technology, notably the improvement of diagnosis and treatment in developing countries, an increasing number of neuroimmune diseases are being diagnosed and treated in a timely manner [16,17]. Second, increased research interest and funding have led to the development of new diagnostic tools and therapies for AE, leading to more studies and publications [18]. Third, greater collaboration and information sharing among healthcare providers, researchers, and patient advocacy groups has led to more effective treatment and management of rare neuro-immune diseases [19,20].

Distinctive patterns were identified in the distribution of the countries and institutions contributing to AE research. Table 1 indicates that the USA accounted for the greatest number of publications globally. These results are consistent with those of previous bibliometric studies on other neurological autoimmune diseases such as myasthenia gravis [21,22] and multiple sclerosis [23]. The reasons for the large number of AE studies from the USA are multifaceted. First, the US government and private institutions invest a significant amount of funding in the research and development of neuroimmunology, enabling US researchers and institutions to conduct research and publish papers [24]. Second, the USA has several excellent research teams and facilities devoted to the field of neuroimmunology. These assets can attract outstanding international researchers and students. In addition, extensive collaboration between American institutions and researchers and their counterparts in other countries facilitates the sharing of research findings and practices, allowing US researchers to utilize this knowledge to further their own research endeavors. Third, the USA has a strong research culture that encourages innovation and the exploration of unknown areas, which leads researchers to try new research directions and conduct in-depth studies [25]. However, in terms of institutions, it is noteworthy that only one of the top five institutions by numbers of publications originated from the USA, while the remaining four were based in Europe. This indicates that Europe is a strong contributor to AE research and publishing, with several institutions producing a significant number of publications, such as Oxford and the Udice French Research Universities. We observed that China was the second-largest country in terms of AE literature. Furthermore, China had the strongest citation burst, with a duration from 2020 to 2022, indicating that China has recently prioritized research in this area. The reason for this might be that the Chinese government's expenditure and financing for medicine and healthcare have been rising as the economy grows at a rapid pace, in parallel with an increasing need for medical attention and healthcare [26,27]. There were no other developing countries ranked in the top 10 countries in literature volumes, citations, and total

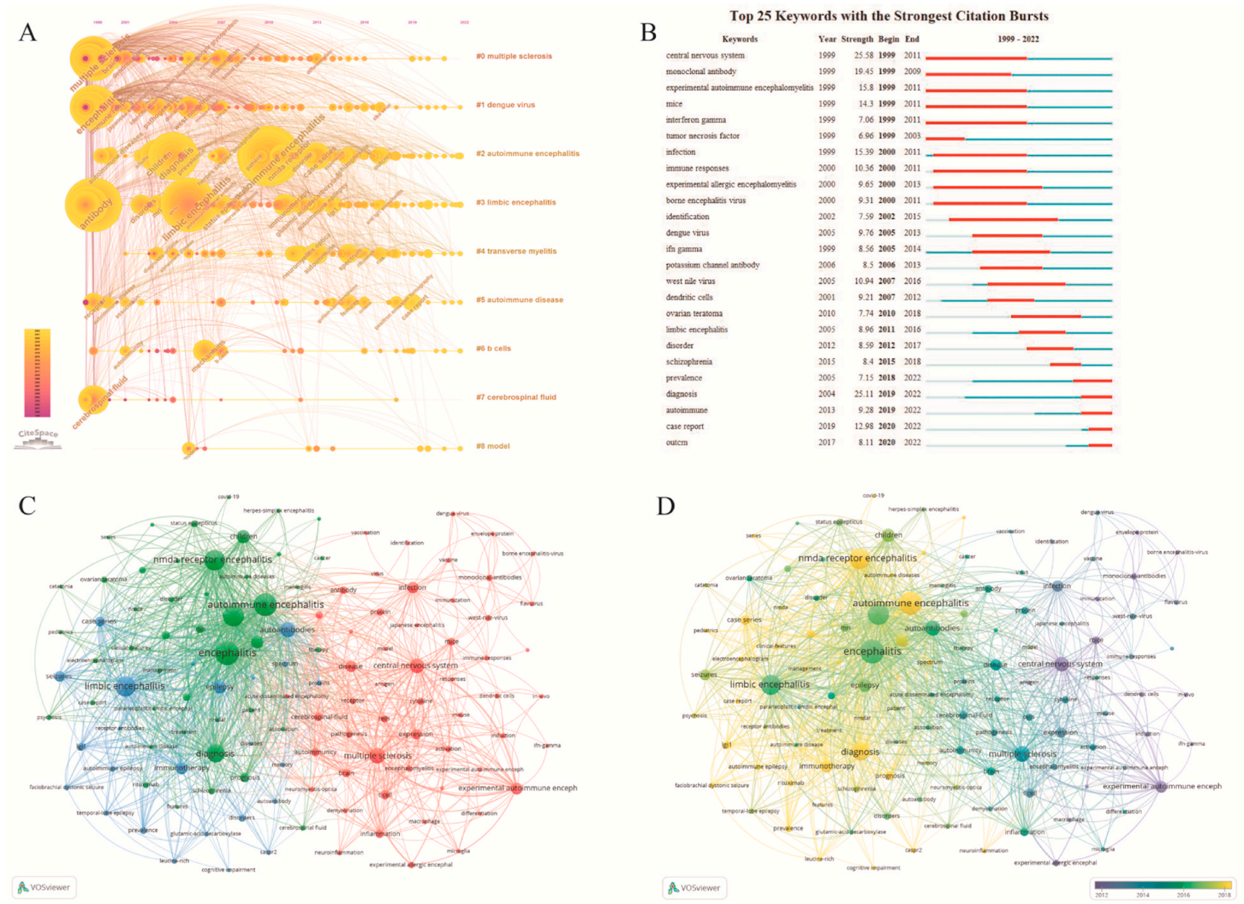

Fig. 8. Keyword analysis
(**A**) A timeline view the results of keyword clustering analysis, showing the progression of research hotspots over time. The duration of each cluster is represented by the length of the horizontal straight line, while the frequency of citations is indicated by the diameter of the circle. Purple circles: early period of 1999–2022; yellow circles: recent period of 1999–2022. (**B**) The 25 most prominent keywords by citation-burst strength, highlighting the hotspots in specific research domains; red lines, duration of bursts. (**C**) Network visualization of keywords; keywords with strong associations are grouped into clusters of the same color: cluster 1 (red), cluster 2 (green), and cluster 3 (blue). (**D**) Overlay visualization of keywords; the nodes colored purple or blue indicate keywords that appear in earlier research, while those colored yellow or green represent current research foci.

link strength, which revealed disparity in academic research between developed and developing countries.

The top five most productive authors were from Europe and the USA, comprising J. Dalmau from the University of Pennsylvania, F. Graus from the University of Barcelona, H. Pruess from the University of Erlangen-Nuremberg, C. G. Bien from the University of Marburg, and A. Vincent from the Oxford University Neuroscience Center. Notably, despite China holding second place in terms of publication volume, none of the five leading research institutions or authors originated from China. Likewise, as indicated in Table 3, none of the top ten highly cited references were authored by Chinese scholars. These findings suggest that in this field, the impact of scholars and research institutions in China is less significant than in developed Western countries.

Examining journals and co-cited journals can offer valuable insights for researchers trying to decide which journals to submit [28]. The Journal of Neuroimmunology (impact factor = 3.478) was the most productive journal in this field, followed by Frontiers in Neurology (impact factor = 4.086) and Frontiers in Immunology (impact factor = 8.787). The top two journals by H-index were the Journal of Virology and the Journal of Neuroimmunology. Researchers interested in AE can remain informed about research trends and frontiers by focusing on comprehensive immunology or neurology journals. These journals can also be useful for researchers seeking to avoid delays in the study timeline by submitting manuscripts where they will receive timely processing [21].

The significance of an article in a specific field is directly correlated with its citation frequency. Among the top ten most-cited articles were four reviews, one case series, and five clinical research studies (Table 3). Nine out of ten of the articles were published between 2010 and 2020, with only one article published before 2010. The Graus paper titled "A clinical strategy for the diagnosis of autoimmune encephalitis" has witnessed an exceptional surge in citations, making it the most impactful article in recent years with the greatest citation count. The main contribution of this study was the establishment of a diagnostic approach for AE that considers the presence or absence of specific antibody types [29]. Six articles with the nearest citation burst times were published in high-quality journals such as Lancet Neurology, the New England Journal of Medicine, Annals of Neurology, Brain, and Physiological

Reviews (Table 3). This indicates that AE researchers are gradually shifting their focus from quantity to quality in terms of the number of published articles [30,31].

Among the most frequently mentioned keywords, "autoimmune encephalitis" ranks highest with 430 occurrences, followed by "antibody" and "NMDA receptor encephalitis" with 420 and 383 occurrences, respectively. AE is an antibody-mediated autoimmune disease. Since the discovery of anti-NMDAR antibodies, a growing number of antibodies have been comprehensively studied, including antibodies against intracellular or membrane-bound neuronal proteins such as GABAR, LGI1, and AMPAR [32]. This might be the reason for the keyword “antibody” ranking second in the occurrence ranking. Multiple in-depth studies on the pathogenesis, clinical manifestations, and therapy of anti-NMDAR encephalitis have been reported [33]. The misdiagnosis and differential diagnosis of anti-NMDAR encephalitis in relation to catatonia and schizophrenia have been well analyzed [34,35]. Among the top 30 keywords occurrence frequency, we identified three categories as the most popular research topics. Firstly, diagnosis was one of the mostly interested research topic. Keywords of “diagnosis”, “multiple sclerosis”, “infection”, “epilepsy”, “cerebrospinal fluid” and “autoantibody” represent diagnostic methods and differential diagnosis for AE. Secondly, pathogenically mechanism was intensively investigated, which represent with keywords “immune responses”, “mechanisms”, “protein”, “T cells”. Antigen-specific CD4^{+}T cells play central roles in contributing actively to AE development, which induce blood brain barrier leakage, microglial activation, and antibody infiltration into the central nervous system [36]. As the exploration of immune mechanism of AE, and increasing refractory AE cases, immunotherapy, especially monoclonal antibody, has showed great promise in treatment for refractory AE cases Keywords “immunotherapy”, “monoclonal antibody”, “case series” appeared in the recent years, which may indicate immunotherapy of monoclonal antibodies as individualized treatments might be research hotpots in the future.

A timeline view of keyword appearances represents the evolution of research hotspots. Previously, researchers believed that the onset of autoimmune encephalitis was closely related to viral infection. Keywords around virus infection in the pathogenesis of AE became popular, as represented by the keyword bursts “dengue virus” (2005–2013) [37], “air-borne encephalitis virus” (2000–2011), and “West Nile virus” (2007–2016) [38]. In recent years, “limbic encephalitis” (2011–2016) has become a popular research topic [39]. It is a major component of AE and is due to autoantibodies targeting specific neuronal receptors, causing inflammation in the temporal lobes and leading to clinical symptoms of immediate memory impairment, epileptic episodes, or psychological manifestations [40]. Limbic encephalitis has atypical clinical manifestations and a poor prognosis and is often misdiagnosed [41]. Therefore, early diagnosis and treatment play a key role in improving the prognosis of this disease. It is noteworthy that the most recently mentioned keywords in AE research were "prevalence," "rituximab," "spectrum," "immunotherapy," "diagnosis," and “prognosis.” With advances in diagnostic techniques for AE, an increasing number of cases have been reported as researchers have shifted focus from the diagnosis and treatment efficacy of individual disease to disease spectrum alterations, epidemiology, and targeted immunotherapy [42].

Although this study provides objective information on the present global research status and developmental trends in the field of AE, some limitations remain. First, the inclusion of English-only articles may have introduced a bias into the selection process and the exclusion of recently published literature could also have introduced bias as it may have contained important information. Second, bibliometric analysis has inherent limitations, tending to emphasize the volume of articles produced rather than their quality and impact. Consequently, this study may have overestimated certain research accomplishments in the field of AE. Additionally, researchers may artificially inflate their influence and citation counts by engaging in self-citation practices. Consequently, the use of bibliometric methods may overestimate the influence of certain researchers or research teams. It is important to consider these limitations when interpreting bibliometric data. Despite the innate limitations of bibliometric methods, this study remains a valuable resource for gaining insight into emerging trends and popular topics in AE research.

5. Conclusions

We conducted a bibliometric investigation of 3348 primary articles on AE published between 1999 and 2022, identifying the leading five countries, institutions, authors, journals, references, and keywords related to these articles. Our research reveals the considerable impact and contribution of advanced Western countries such as the USA in this field. As a developing country, China has steadily increased its number of publications over the years. However, a gap remains in the quality and influence of these articles compared with those from Western countries. Future research foci for AE are predicted to be the following: (i) the clinical manifestations, prevalence, and prognosis of specific antibody-related AEs following advances in diagnostic methods, and (ii) the efficiency and safety of targeted immunotherapy in individual patients. This study will be valuable to scholars wishing to survey the frontiers and emerging patterns of AE research as well as to locate core authors and potential research collaborators. It will also help investigators to recognize the most impactful institutions and references in the AE research field.

Funding

This study was supported by grants from the Natural Science Foundation of Hunan Province (Grant Numbers: 2022JJ40724, 2023JJ30062, and 2023JJ30868), the Science and Technology Innovation Guidance Project of Hunan Province (Grant Number: 2020SK53009), and the Changsha Municipal Natural Science Foundation (Grant Number: kq2007037).

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Song Ouyang: Writing – review & editing, Writing – original draft, Funding acquisition. **Zhenchu Tang:** Formal analysis, Data curation. **Weiwei Duan:** Data curation. **Sizhi Tang:** Writing – review & editing. **Qiuming Zeng:** Data curation. **Wenping Gu:** Writing – review & editing. **Miao Li:** Writing – review & editing. **Hong Tan:** Writing – review & editing. **Jiangying Hu:** Writing – review & editing. **Weifan Yin:** Writing – original draft, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AE	autoimmune encephalitis
NMDA	N-methyl-D-aspartate
NMDAR	NMDA receptor
TLS	total link strength

References

[1] M.S. Nissen, M. Ryding, M. Meyer, M. Blaabjerg, Autoimmune encephalitis: current knowledge on subtypes, disease mechanisms and treatment, CNS Neurol. Disord.: Drug Targets 19 (8) (2020) 584–598.
[2] D. Dubey, S.J. Pittock, C.R. Kelly, A. McKeon, A.S. Lopez-Chiriboga, V.A. Lennon, et al., Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis, Ann. Neurol. 83 (1) (2018) 166–177.
[3] J. Dalmau, F. Graus, Antibody-mediated encephalitis, N. Engl. J. Med. 378 (9) (2018) 840–851.
[4] H. Abboud, J.C. Probasco, S. Irani, B. Ances, D.R. Benavides, M. Bradshaw, et al., Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management, J. Neurol. Neurosurg. Psychiatry 92 (7) (2021) 757–768.
[5] S. Ramanathan, A. Al-Diwani, P. Waters, S.R. Irani, The autoantibody-mediated encephalitides: from clinical observations to molecular pathogenesis, J. Neurol. 268 (5) (2021) 1689–1707.
[6] C.E. Uy, S. Binks, S.R. Irani, Autoimmune encephalitis: clinical spectrum and management, Practical Neurol. 21 (5) (2021) 412–423.
[7] S. Esposito, G. Autore, A. Argentiero, G. Ramundo, N. Principi, Autoimmune encephalitis after herpes simplex encephalitis: a still undefined condition, Autoimmun. Rev. 21 (12) (2022) 103187.
[8] T. Cellucci, H. Van Mater, F. Graus, E. Muscal, W. Gallentine, M.S. Klein-Gitelman, et al., Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient, Neurol Neuroimmunol Neuroinflamm 7 (2) (2020). Epub 20200117.
[9] S. Pradhan, A. Das, A. Das, M. Mulmuley, Antibody negative autoimmune encephalitis- does it differ from definite one? Ann. Indian Acad. Neurol. 22 (4) (2019) 401–408. Epub 20191025.
[10] B.P. Trewin, I. Freeman, S. Ramanathan, S.R. Irani, Immunotherapy in autoimmune encephalitis, Curr. Opin. Neurol. 35 (3) (2022) 399–414.
[11] G. Harutyunyan, L. Hauer, M.W. Dünser, A. Karamyan, T. Moser, S. Pikija, et al., Autoimmune encephalitis at the neurological intensive care unit: etiologies, reasons for admission and survival, Neurocrit Care 27 (1) (2017) 82–89.
[12] A. Ninkov, J.R. Frank, L.A. Maggio, Bibliometrics: methods for studying academic publishing, Perspect Med Educ 11 (3) (2022) 173–176.
[13] D.F. Thompson, C.K. Walker, A descriptive and historical review of bibliometrics with applications to medical sciences, Pharmacotherapy 35 (6) (2015) 551–559.
[14] X. Li, P. Xiang, J. Liang, Y. Deng, J. Du, Global trends and hotspots in esketamine research: a bibliometric analysis of past and estimation of future trends, Drug Des Devel Ther 16 (2022) 1131–1142.
[15] F. Wu, J. Gao, J. Kang, X. Wang, Q. Niu, J. Liu, et al., Knowledge mapping of exosomes in autoimmune diseases: a bibliometric analysis (2002-2021), Front. Immunol. 13 (2022) 939433.
[16] F. Zhu, W. Shan, R. Lv, Z. Li, Q. Wang, Clinical characteristics of anti-GABA-B receptor encephalitis, Front. Neurol. 11 (2020) 403.
[17] N. Papri, Z. Islam, S.E. Leonhard, Q.D. Mohammad, H.P. Endtz, B.C. Jacobs, Guillain-Barré syndrome in low-income and middle-income countries: challenges and prospects, Nat. Rev. Neurol. 17 (5) (2021) 285–296.
[18] M. Nosadini, T. Thomas, M. Eyre, B. Anlar, T. Armangue, S.M. Benseler, et al., International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis, Neurol Neuroimmunol Neuroinflamm 8 (5) (2021) e1052.
[19] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, et al., MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome, J. Neuroinflammation 13 (1) (2016) 280, acceptance Wassmer E, Chitnis T, Pohl D, Amato MP, Banwell B, Ghezzi A, et al. International Pediatric MS Study Group Global Members Symposium report. Neurology (2016) 87(9 Suppl 2):S110-S116.
[20] Y. Su, Z. Ruan, R. Wang, S. Hao, Y. Tang, X. Huang, et al., Knowledge mapping of targeted immunotherapy for myasthenia gravis from 1998 to 2022: a bibliometric analysis, Front. Immunol. 13 (2022) 998217.
[21] F. Jiang, Y. Su, T. Chang, Knowledge mapping of global trends for myasthenia gravis development: a bibliometrics analysis, Front. Immunol. 14 (2023) 1132201.
[22] S. Aykaç, S. Eliaçık, What are the trends in the treatment of multiple sclerosis in recent studies? - a bibliometric analysis with global productivity during 1980-2021, Mult Scler Relat Disord 68 (2022) 104185.
[23] R. Marignier, Y. Hacohen, A. Cobo-Calvo, A.K. Pröbstel, O. Aktas, H. Alexopoulos, et al., Myelin-oligodendrocyte glycoprotein antibody-associated disease, Lancet Neurol. 20 (9) (2021) 762–772.
[24] W.R. Garney, K.L. Wilson, K.M. Garcia, D. Muraleetharan, C.H. Esquivel, M.N. Spadine, et al., Supporting and enabling the process of innovation in public health: the framework for public health innovation, Int J Environ Res Public Health 19 (16) (2022) 10099.
[25] W. Tao, Z. Zeng, H. Dang, P. Li, L. Chuong, D. Yue, et al., Towards universal health coverage: achievements and challenges of 10 years of healthcare reform in China, BMJ Glob. Health 5 (3) (2020) e002087.
[26] X.L. Feng, Y. Zhang, X. Hu, C. Ronsmans, Tracking progress towards universal health coverage for essential health services in China, 2008-2018, BMJ Glob. Health 7 (11) (2022) e010552.

[27] M. Wilson, M. Sampson, N. Barrowman, A. Doja, Bibliometric analysis of neurology articles published in general medicine journals, JAMA Netw. Open 4 (4) (2021) e215840.
[28] F. Graus, M.J. Titulaer, R. Balu, S. Benseler, C.G. Bien, T. Cellucci, et al., A clinical approach to diagnosis of autoimmune encephalitis, Lancet Neurol. 15 (4) (2016) 391–404.
[29] J. Thompson, M. Bi, A.G. Murchison, M. Makuch, C.G. Bien, K. Chu, et al., The importance of early immunotherapy in patients with faciobrachial dystonic seizures, Brain 141 (2) (2018) 348–356.
[30] J. Dalmau, T. Armangué, J. Planagumà, M. Radosevic, F. Mannara, F. Leypoldt, et al., An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models, Lancet Neurol. 18 (11) (2019) 1045–1057.
[31] J. Dalmau, A.J. Gleichman, E.G. Hughes, J.E. Rossi, X. Peng, M. Lai, et al., Anti- NMDA-receptor encephalitis: case series and analysis of the effects of antibodies, Lancet Neurol. 7 (12) (2008) 1091–1098.
[32] N. Seery, H. Butzkueven, T.J. O'Brien, M. Monif, Contemporary advances in anti-NMDAR antibody (Ab)-mediated encephalitis, Autoimmun. Rev. 21 (4) (2022) 103057.
[33] Y. Jia, M. Li, S. Hu, H. Leng, X. Yang, Q. Xue, et al., Psychiatric features in NMDAR and LGI1 antibody-associated autoimmune encephalitis, Eur Arch Psychiatry Clin Neurosci (2023). Epub 20230408.
[34] M. Espinola-Nadurille, J. Flores-Rivera, V. Rivas-Alonso, S. Vargas-Cañas, G.L. Fricchione, L. Bayliss, et al., Catatonia in patients with anti-NMDA receptor encephalitis, Psychiatry Clin Neurosci 73 (9) (2019) 574–580.
[35] S. Krishnarajah, B. Becher, TH cells and cytokines in encephalitogenic disorders, Front. Immunol. 13 (2022) 822919.
[36] F.J. Carod-Artal, O. Wichmann, J. Farrar, J. Gascón, Neurological complications of dengue virus infection, Lancet Neurol. 12 (9) (2013) 906–919.
[37] A.J. Aksamit Jr., Treatment of viral encephalitis, Neurol. Clin. 39 (1) (2021) 197–207.
[38] A. Budhram, A. Leung, M.W. Nicolle, J.G. Burneo, Diagnosing autoimmune limbic encephalitis, CMAJ (Can. Med. Assoc. J.) 191 (19) (2019) E529-e34.
[39] P. Štourač, J. Bednářová, P. Zicháček, Z. Čermáková, Z. Pavelek, M. Vališ, Autoimmune and limbic encephalitis: case series with some atypical variables in clinical practice, Neurol. Sci. 43 (1) (2022) 687–690.
[40] J.Y. Yoo, L.J. Hirsch, Limbic encephalitis associated with anti-voltage-gated potassium channel complex antibodies mimicking Creutzfeldt-Jakob disease, JAMA Neurol. 71 (1) (2014) 79–82.
[41] T. Armangue, M. Spatola, A. Vlagea, S. Mattozzi, M. Cárceles-Cordon, E. Martinez-Heras, et al., Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis, Lancet Neurol. 17 (9) (2018) 760–772.