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SPECIALTY SECTION
This article was submitted to
Non-Neuronal Cells,
a section of the journal
Frontiers in Cellular Neuroscience

RECEIVED 22 June 2022
ACCEPTED 22 August 2022
PUBLISHED 08 September 2022

CITATION
Ding Z, Jiang N, Yang T, Han H, Hou M,
Kumar G, Wu Y, Song L, Li X, Ma C and
Su Y (2022) Mapping the research
trends of astrocytes in stroke:
A bibliometric analysis.
Front. Cell. Neurosci. 16:949521.
doi: 10.3389/fncel.2022.949521

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Mapping the research trends of astrocytes in stroke: A bibliometric analysis

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Background: Stroke, including ischemic stroke and hemorrhagic stroke, possesses complex pathological mechanisms such as neuroinflammation, oxidative stress and blood-brain barrier damage. Astrocyte functions have been reported during injury, neuroprotection and cell crosstalk. It plays a key role in exacerbating stroke injury, promoting neurological repair and enhancing neuroregeneration.

Aim: This holistic bibliometric analysis aimed to provide a general overview of the recent advancement and the hotspots in the field of stroke and astrocyte from 2001 to 2021.

Materials and methods: Publications between 2001 and 2021, related to stroke and astrocyte were retrieved from the Web of Science (WOS) and analyzed in Gephi and VOSviewer.

Results: In total, 3789 documents were extracted from the WOS databases. The publications showed stable growth since 2001. The United States and China were the most prolific countries and University of California San Francisco and Oakland University were the most influential institutes. The top four most productive journals were *Brain Research*, *Journal of Cerebral Blood Flow and Metabolism*, *Glia* and *Journal of Neuroinflammation*. Keywords frequency and co-occurrence analysis revealed that the topics related to “micro-RNA”, “toll like receptor”, “neuroinflammation”, “autophagy” and “interleukin” were research frontiers. The field of stroke and astrocyte focused on several aspects, such as the role of astrocytes in the treatment of stroke, metabolic changes in astrocytes, the protective role of apoptosis in astrocytes after oxidative stress injury and neurovascular units.

Conclusion: This comprehensive bibliometric study provides an updated perspective on the trend of research associated with stroke and astrocyte. It will benefit scientific community to identify the important issues, future directions and provide a novel understanding of stroke pathophysiology, hotspots and frontiers to facilitate future research direction.

KEYWORDS

stroke, astrocytes, bibliometric analysis, citation analysis, scientific outputs

Introduction

Stroke, broadly classified into ischemic stroke and hemorrhagic stroke, has been a serious public health problem worldwide. Several studies report that stroke is the second leading cause of death and major contributor of disability-adjusted life years (DALYs). In 2019, the global incidence of stroke events was around 101.47 million with 12.2 million new strokes (Collaborators, 2021). It is expected that there will be more than 200 million stroke survivors, almost 300 million DALYs, 25 million new strokes, and 13 million deaths from stroke annually by 2050 (Collaborators, 2021). It has been shown that the absolute numbers of stroke survivors have increased globally, partly due to rising numbers in low- and middle-income countries (Katan and Luft, 2018). Complex interwoven issues of inaccessibility to therapeutic management and interventions limit the effectiveness of primary and secondary prevention in stroke care (Kim et al., 2020). Abundant medical resource requirements for stroke treatment and follow-up management increase the financial burden on patients' families and healthcare systems.

Astrocytes are important component of neurovascular unit (NVU) structure composition and play a vital role in the regulation of central nervous system (CNS) functions. The onset of stroke activates astrocytes and contributes to differentiating astrocytes into several phenotypes. Neuroinflammation and neuroprotection effects in stroke are due to the activation of astrocytes into "A1s" and "A2s" (Zamanian et al., 2012). In acute phase of stroke, A1 reactive astrocytes predominate and secrete inflammatory factors that exacerbate neuronal and blood-brain barrier (BBB) damage and form glial scar to limit the spread of inflammation (Xu et al., 2020). Conversely, in the subacute and chronic phases, A2 reactive astrocytes play a protective role by secreting neurotrophic factors to promote neurogenesis, synaptogenesis (Yamagata, 2021), angiogenesis (Williamson et al., 2021), and BBB repair (Song et al., 2021). However, the categorization of reactive astrocytes in pathological conditions is controversial, and the understanding of astrocytic heterogeneity in response to ischemic stroke is limited and still needs

further discussion (Li et al., 2022; Ma et al., 2022). Extensive research on the pathological mechanisms, diagnosis, treatment, and prognosis of stroke has been conducted to provide new research perspectives in recent decades (Kuriakose and Xiao, 2020). Therefore, we have summarized the key findings and trends of stroke research in two decades (2001 to 2021) (Supplementary Table 1). We showed an overview of the mechanisms, functions, and potential therapeutic targets of astrocytes involved in the development of stroke. It is expected to help the scientific community to explore new research trends, track research hotspots and identify the novel research direction in future.

Bibliometric analysis is an effective tool used for mapping and identifying the published records. Currently, it has been widely recognized as an alternative method to evaluate the hot issues in several fields of neuroscience (Zhang et al., 2021; Miao et al., 2022). The methods included co-authorship network, co-occurrence of author keywords, highly cited paper analysis, impact factor and h-index. Therefore, comprehensive bibliometric methods and indicators were used to have a deeper insight into the research trends, the most concerned topics, and existing research gaps in the field of stroke and astrocyte. Our study showed a systematic and comprehensive analysis of the most contributing factors and development trends in this field through bibliometric analysis.

Materials and methods

Data source

The data in this study were extracted from the Web of Science (WOS) core collection, including the Science Citation Index-expanded (SCI-E), and Social Sciences Citation Index (SSCI). The WOS database provides comprehensive, multi-disciplinary citation data, and served as the major source of data for bibliometric analysis. The SCI-E and SSCI databases are the most frequently used databases for bibliometric studies (Peng et al., 2015). We conducted

a comprehensive online search in WOS database from 2001 to 2021, with restricted document types to original articles and reviews. The searched items are shown in [Supplementary Table 2](#). A total of 3789 published articles were retrieved and each contains author names, institutions, titles, abstracts, total citations, keywords, sources and cited references.

The keywords provided by the authors were considered in this study. Firstly, synonym terms were manually merged, e.g., “brain ischemia” and “cerebral ischemia”. Secondly, to improve the visualization, acronyms were generally favored, e.g., “GFAP” for “glial fibrillary acidic protein.” Similarly, “oxygen glucose deprivation” was shortened for “OGD.” The singular form and the plural form of the same noun (e.g., Astrocytes and Astrocyte) were grouped.

Methods

The scientific performance of an entity (e.g., an institution, a country or a journal) was measured on the basis of productivity and quality of research publications. We adopted the following four indicators in this study. The first indicator concerns the output. The second and third indicators focus on quality and the fourth indicator accounts for paper output and the citation impact:

- (1) Total publications (TP): Total number of publications of an entity during the observation period.
- (2) Total citations (TC): Total number of citations of articles published by an entity during the observation period.
- (3) TC/TP: Average citation per publication.
- (4) H-index served to reflect the academic influence of an institution, a country or a journal. The index of H means that an institution, a country or a journal has published H publications and each of which has been cited by other papers at least H times ([Hirsch and Buéla-Casal, 2014](#)).

VOSviewer is an optimal software tool to analyze the research collaboration among institutions. It is also used to map and visualize the network of keywords. VOSviewer can classify keywords into different clusters through co-occurrence analysis, and simultaneously color them by time course. Gephi is the leading visualization and exploratory software for network analysis. In this study, Gephi software was used to visualize the collaboration network among countries ([Bastian et al., 2009](#)). CitNetExplorer is a software tool for visualization and analysis of citation networks among scientific publications ([Eck and Waltman, 2014](#)). It was used to identify the critical findings in stroke and astrocyte research.

Results

General statistics

[Figure 1](#) shows the trend of publications related to stroke and astrocyte. The number of publications on stroke and astrocyte increased steadily during the past 20 years. The paper output increased by 251.1% (from 88 in 2001 to 309 in 2021), indicating that researchers are paying more attention to this field. The total citation frequency showed significant fluctuation before 2015, reached the peak of 11,134 in 2004, and declined steadily from 2015 to 2021. The average citation per paper significantly decreased by 97.6% (from 93.32 in 2001 to 2.24 in 2021).

Most productive and influential countries

From 2001 to 2021, 70 countries contributed to stroke and astrocyte research by publishing academic papers in WOS database. However, 95.51% of publications were contributed by the top 20 countries as shown in [Table 1](#). The United States published the highest number of papers (1191), accounting for 31.43%, followed by China (1108 papers, 29.24%), Japan (416 papers, 10.98%), Germany (287 papers, 7.57%), and South Korea (258 papers, 6.81%). The United States had the highest citation frequency (73,986), which is 2.91 times of China. Sweden had the highest average citation frequency (82.31 citations per paper), followed by Switzerland (72.27), and the United Kingdom (65.76).

[Figure 2](#) shows the trend of the top five prolific countries. Studies on astrocytes for stroke in the United States started relatively early. Before 2013, the number of articles published by the United States was higher than other countries. After a sudden decline in 2014, the number of articles began to increase steadily to 75 in 2021. China ranked second in total number of publications related to stroke and astrocyte and growing steadily. It has reached 138 in 2021 after surpassing the United States in 2014. Compared with the United States and China, the growth trend of papers in Japan, Germany and South Korea is not significant, and the number of papers has been at a low level.

In order to explore the characteristics of collaboration among countries in the field of stroke and astrocyte, a cross-border collaboration network was established by including countries with more than 10 publications. In the network, nodes represent countries and connections indicate collaborative relationships. Nodes size represents paper output, and color represents the region. [Figure 3](#) showed that the United States is at the center of the collaborative network with 34 different collaboration partners ([Supplementary Figure 1](#)). It is noticeable that among 36 different countries in the collaboration

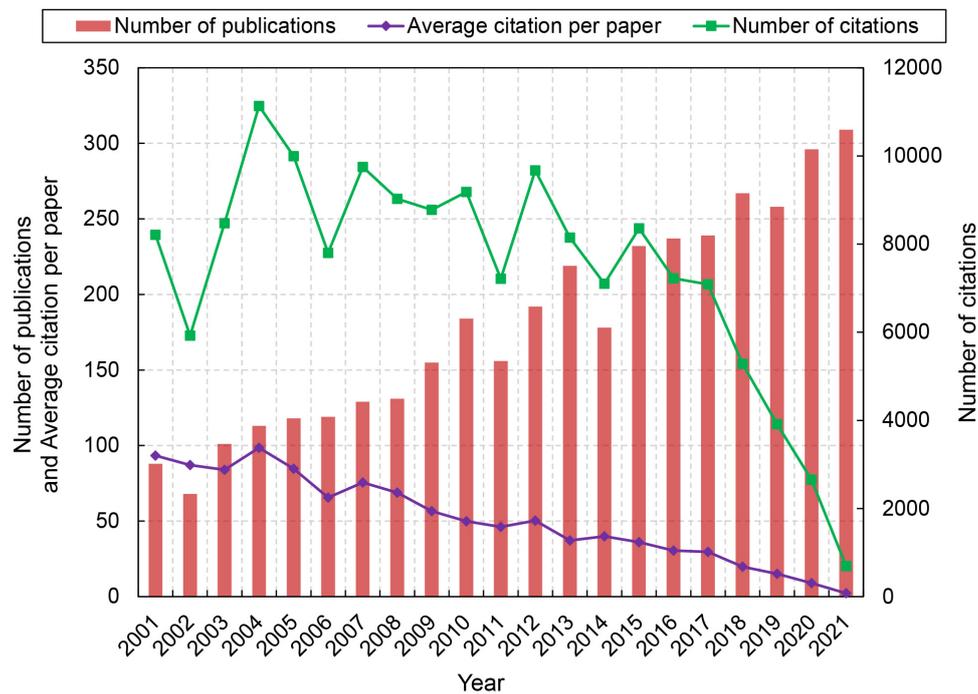


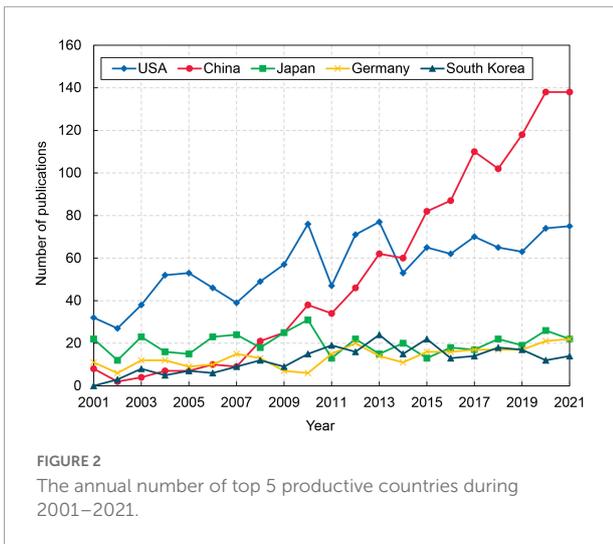
FIGURE 1

Trend in the number of publications in the field of stroke and astrocyte during the period 2001–2021.

TABLE 1 Top 20 most productive countries in the field of stroke and astrocyte.

Rank	Country	TP	Percentage (%)	TC	ACPP	H-index
1	United States	1191	31.43	73986	62.12	129
2	China	1108	29.24	25457	22.98	66
3	Japan	416	10.98	15171	36.47	67
4	Germany	287	7.57	14211	49.52	66
5	South Korea	258	6.81	9108	35.3	48
6	Canada	167	4.41	8161	48.87	50
7	United Kingdom	164	4.33	10785	65.76	58
8	Spain	116	3.06	5517	47.56	40
9	Italy	106	2.8	5122	48.32	40
10	Australia	105	2.77	4571	43.53	33
11	Sweden	104	2.74	8560	82.31	45
12	France	96	2.53	3710	38.65	34
13	Brazil	61	1.61	1505	24.67	21
14	Switzerland	60	1.58	4336	72.27	31
15	Poland	57	1.5	1477	25.91	21
16	Netherlands	51	1.35	2584	50.67	26
17	Russia	45	1.19	1353	30.07	13
18	Denmark	38	1	1277	33.61	18
19	Finland	34	0.9	1866	54.88	24
20	Hungary	30	0.79	1123	37.43	14

TP, total number of publications; TC, total citations; ACP, average citation per paper.



network, 21 from Europe and Central Asia, 6 from East Asia and Pacific, and a few from other regions. Among the network, the United States and China have the closest collaborative relationship, publishing 200 papers together, much higher than those of the second and third ranking of the United States–Japan (48) and the United States–United Kingdom (44), as presented in [Supplementary Table 3](#).

Most productive and influential institutions

We further identified the most productive and influential institutions in the field of stroke and astrocyte, as shown in [Table 2](#). Seoul National University and Kangwon National University ranked first and second with 62 and 60 papers respectively, followed by Stanford University with 59 papers. In terms of total citations, University of California San Francisco ranked first with 5,727 citations, followed by Oakland University with 5,145 citations. For average citation per article, University of California San Francisco and Oakland University also ranked the top two positions, with an average citation per article of 119.31 and 111.85 respectively. Regarding H index, the University of California San Francisco ranked first with an H index of 35, followed by Oakland University and Stanford University with 32. In general, among the top 20 institutions, 8 from the United States, 5 from China, 4 from South Korea, 2 from Japan, and 1 from Sweden.

The collaborative relationships among the top 200 productive institutions were also analyzed. As shown in [Figure 4](#), Hallym University and Kangwon National University, both from South Korea, have a strong collaborative relationship. They have published 48 co-authored papers, as shown in [Supplementary Table 4](#). It is

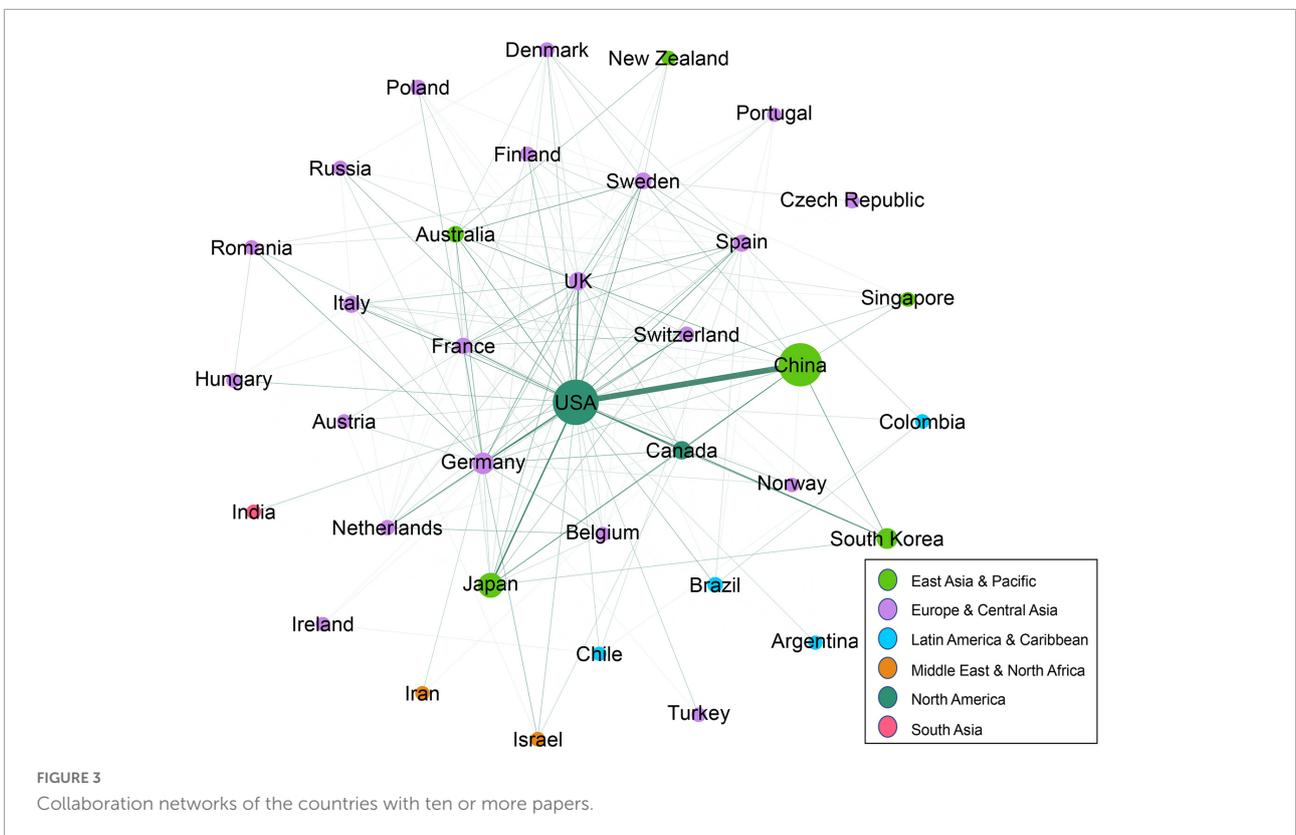


TABLE 2 Top20 most productive institutes in the field of stroke and astrocyte.

Rank	Institution	Country	TP	TC	ACPP	H-index
1	Seoul National University	South Korea	62	2075	33.47	25
2	Kangwon National University	South Korea	60	991	16.52	18
3	Stanford University	United States	59	4642	78.68	32
4	Hallym University	South Korea	57	1118	19.61	19
5	Massachusetts General Hospital	United States	56	3228	57.64	31
6	University of California San Francisco	United States	48	5727	119.31	35
7	Oakland University	United States	46	5145	111.85	32
8	Loma Linda University	United States	44	1570	35.68	24
9	University of Gothenburg	Sweden	41	4116	100.39	26
10	Fudan University Huashan Hospital	China	39	1135	29.1	18
11	Tongji Hospital, Huazhong University of Science and Technology	China	39	1287	33	22
12	Shanghai Jiao Tong University	China	38	1273	33.5	17
13	Harvard University	United States	37	3423	92.51	31
14	Kyoto University	Japan	37	1473	39.81	20
15	Zhejiang University	China	36	1196	33.22	23
16	Johns Hopkins University	United States	35	2765	79	26
17	Ruijin Hospital Shanghai Jiao Tong University	China	35	1301	37.17	17
18	Okayama University	Japan	33	1588	48.12	18
19	Emory University	United States	33	1765	53.48	21
20	Yonsei University	South Korea	32	2274	71.06	19

TP, total number of publications; TC, total citations; ACP, average citation per paper.

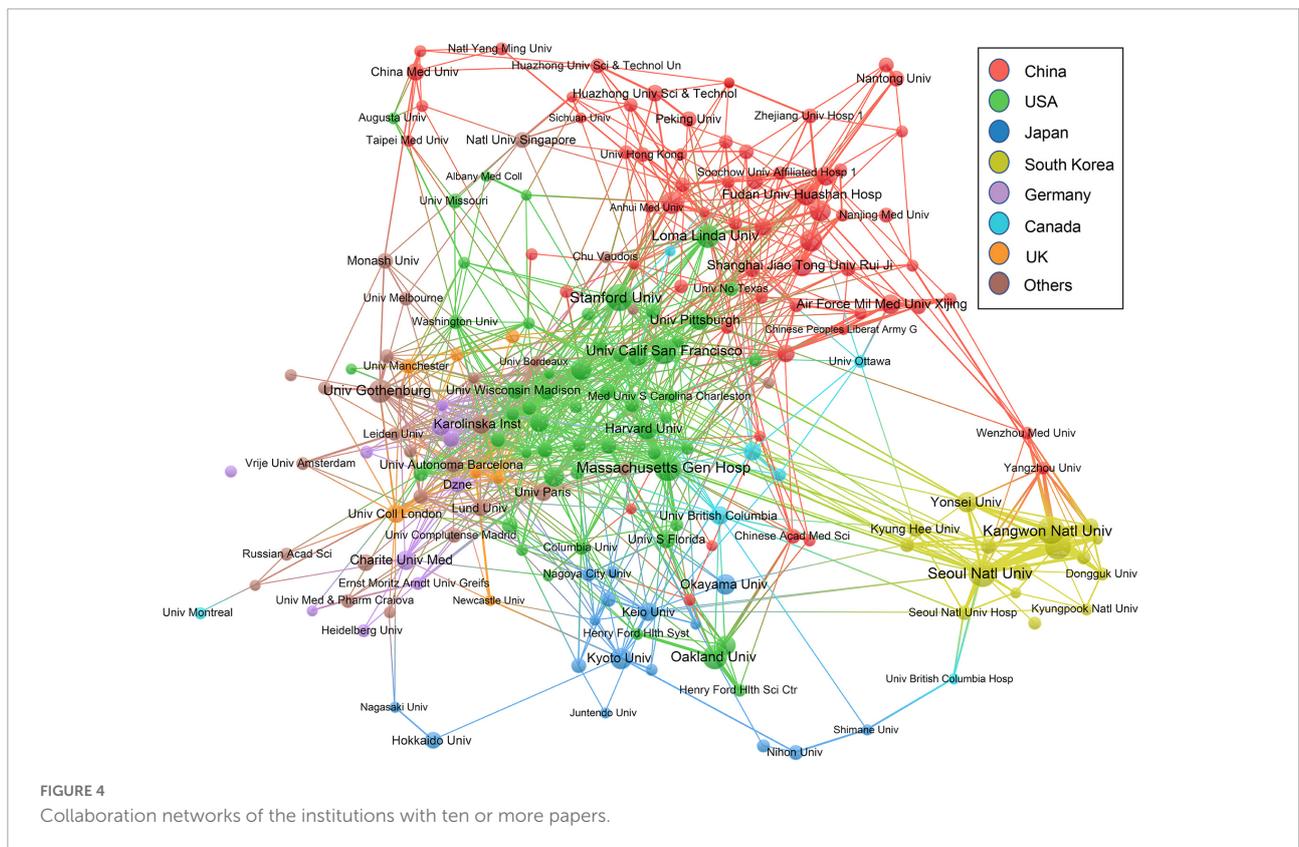


TABLE 3 Top 20 most productive journals in research on stroke and astrocyte.

Rank	Journal	TP	TC	ACPP	H	IF (2020)	WOS category (rank/total number of journals in WOS category)
1	Brain Research	146	5475	37.5	40	3.252	Neurosciences (170/273)
2	Journal of Cerebral Blood Flow and Metabolism	145	11762	81.12	62	6.2	Endocrinology and Metabolism (24/146) Hematology (16/76) Neurosciences (50/273)
3	Glia	102	6850	67.16	47	7.452	Neurosciences (33/273)
4	Journal of Neuroinflammation	96	3061	31.89	34	8.322	Immunology (21/162) Neurosciences (23/273)
5	Stroke	93	7674	82.52	54	7.914	Clinical Neurology (16/208) Peripheral Vascular Disease (6/65)
6	Neuroscience	92	3243	35.25	34	3.59	Neurosciences (141/273)
7	PLoS One	84	3199	38.08	35	3.24	Multidisciplinary Sciences (26/72)
8	Neuroscience Letters	80	2457	30.71	28	3.046	Neurosciences (186/273)
9	Journal of Neurochemistry	75	3423	45.64	34	5.372	Biochemistry and Molecular Biology (78/295) Neurosciences (67/273)
10	Neurochemical Research	73	2195	30.07	21	3.996	Biochemistry and Molecular Biology (139/295) Neurosciences (118/273)
11	Journal of Neuroscience Research	65	2574	39.6	29	4.164	Neurosciences (105/273)
12	Neurochemistry International	61	2238	36.69	26	3.921	Biochemistry and Molecular Biology (145/295) Neurosciences (122/273)
13	Experimental Neurology	60	3043	50.72	29	5.33	Neurosciences (70/273)
14	International Journal of Molecular Sciences	57	876	15.37	16	5.924	Biochemistry and Molecular Biology (67/295) Chemistry, Multidisciplinary (49/178)
15	Journal of Neuroscience	54	5815	107.69	36	6.167	Neurosciences (52/273)
16	Molecular Neurobiology	50	1170	23.4	21	5.59	Neurosciences (61/273)
17	Frontiers In Cellular Neuroscience	49	906	18.49	15	5.505	Neurosciences (63/273)
18	Neurobiology of Disease	42	3007	71.6	27	5.996	Neurosciences (54/273)
19	Neural Regeneration Research	40	357	8.93	11	5.135	Cell Biology (78/195) Neurosciences (78/273)
20	Translational Stroke Research	37	723	19.54	17	6.829	Clinical Neurology (24/208) Neurosciences (40/273)

TP, total number of publications; TC, total citations; ACPP, average citation per paper; H, H-index of a journal.

worth noting that most closed collaboration relationships are among South Korean institutions. Massachusetts General Hospital located in the United States is at the center of the collaboration network, having collaboration relationships with other 33 institutes, especially with Harvard University, United States. These two United States institutes have produced 22 co-authored publications. The German Center for Neurodegenerative Diseases and University of Washington also have close collaborative relationships with other 32 institutes, as shown in [Supplementary Table 5](#). Within the network, 62 (31%) and 54 (27%) institutions are from China and United States, respectively.

Analysis of core journals

With respect to source journals, 3,789 articles of our sample have been published in 710 journals. Among 710 journals, 349 journals published only one paper. The top 20 most productive journals in the research domain of stroke and astrocyte, account for 39.61% of the total published articles in our dataset (1,501 out of 3,789) as presented in [Table 3](#). Based on our results, Brain Research is the most productive journal with 146 articles and plays a significant role in the domain. The second and third most productive journals are Journal of Cerebral Blood Flow and Metabolism and Glia with 145 and 102 publications, respectively. In terms of total citation frequency and average

TABLE 4 Top 10 most cited papers in the field of stroke and astrocyte during 2001–2021.

Title	Author	Journal	TC	PY	TC/Y
The blood-brain barrier: an overview - Structure, regulation, and clinical implications	Ballabh, P; Braun, A; Nedergaard, M	Neurobiology of Disease	1373	2004	72.26
Astrocyte activation and reactive gliosis - A new target in stroke?	Pekny, M; Nilsson, M	Glia	1122	2005	62.33
Genomic Analysis of Reactive Astrogliosis	Zamanian, JI; Xu, LJ; Foo, Lc, etc.	Journal of Neuroscience	1089	2012	99
Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats	Chen, JI; Sanberg, PR; Li, etc.	Stroke	894	2001	40.64
Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1 alpha/CXC chemokine receptor 4 pathway	Imitola, J; Raddassi, K; Park, Ki, etc.	Proceedings of the National Academy of Sciences	838	2004	44.11
Apolipoprotein E controls cerebrovascular integrity via cyclophilin A	Bell, Rd; Winkler, Ea; Singh, I, etc.	Nature	738	2012	67.09
Astrocytes and brain injury	Chen, Ym; Swanson, Ra	Journal of Cerebral Blood Flow and Metabolism	685	2003	34.25
The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease	Iadecola, C	Neuron	661	2017	110.2
The Glymphatic System: A Beginner's Guide	Jessen, Na; Munk, Asf; Lundgaard, I, etc.	Neurochemical Research	651	2015	81.38
Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats	Zhao, Lr; Duan, Wm; Reyes, M, etc.	Experimental Neurology	640	2002	30.48

TC, total citations; TC/Y, average citation per year.

citation per paper, Journal of Cerebral Blood Flow, Metabolism, Stroke and Glia ranked relatively high. In addition, 13 of the top 20 productive journals have an impact factor greater than 5. The top 20 prolific journals are mainly distributed in neuroscience discipline.

Influential articles analysis

The citation frequency of scientific papers is commonly used to measure their influence on the related research field. The most highly cited articles were analyzed with parameters such as the total citations, average annual citations, and the authors of the articles for 2001–2021. As shown in **Table 4**, the most highly cited article with 1373 citations is a comprehensive review paper conducted by [Ballabh et al. \(2004\)](#), describing the role of BBB in neurological diseases. Astrocytes as the component of BBB, also participate in the induction of tight junction disorganization and BBB breakdown in hypoxic-ischemic. [Pekny and Nilsson \(2005\)](#) showed the second highest citation (1,122), focused on several functions of astrocytes in acute, postacute, and chronic stroke phases and elucidates its role as novel target in trauma and ischemia of CNS. In the third highest citation (1,089) [Zamanian](#) provided transcriptome databases for two subtypes of reactive astrocytes and suggested that reactive astrocytes in ischemia exhibited a protective molecular phenotype ([Zamanian et al., 2012](#)).

Analysis of keywords frequency and co-occurrence network

The underlying justification for performing keywords frequency and co-occurrence analysis is that authors' keywords effectively represent the main topic and broader scope of articles and their themes ([Agnusdei and Coluccia, 2022](#)). **Table 5** lists the top 30 highest frequently used keywords. The hot topics related to stroke and astrocyte were astrocyte reactivity including inflammatory response of astrocytes, neuroprotection, apoptosis, oxidative stress, and homeostasis of neurovascular units. It suggests that reactive astrocyte plays an important role in the pathogenesis of stroke. *In vivo* model, MCAO (Middle Cerebral Artery Occlusion) is frequently used to mimic the human ischemic stroke and displays similar penumbra ([Kuriakose and Xiao, 2020](#)), while *in vitro* model, OGD (Oxygen-Glucose Deprivation) allows the investigation of specific basic biochemical and molecular mechanisms under conditions of energy deficiency similar to ischemia ([Sommer, 2017](#)). Both models showed rapid growth in the frequency of publications in the last 20 years.

A total of 6,704 keywords were extracted from our dataset, and **Figure 5** presents the co-occurrence network of 201 keywords with a frequency of 20 and above. For research topic analysis, all the keywords were grouped into 7 major clusters. The first and biggest cluster (red color) containing the most

TABLE 5 Frequency of top 30 most used author keywords in each period.

Keyword	Frequency			
	All years	2001–2007	2008–2014	2015–2021
Astrocyte	1,484	280	508	696
Cerebral ischemia	848	193	294	361
Stroke	766	138	271	357
Ischemic stroke	433	27	109	297
Microglia	391	66	135	190
Inflammation	353	44	112	197
Neuron	339	71	128	140
Neuroprotection	336	57	106	173
Ischemia	330	96	124	110
Brain Injury	319	54	105	160
Blood brain barrier	311	44	94	173
Rat	288	81	101	106
Middle cerebral artery occlusion	249	49	92	108
Mouse	229	50	82	97
Neuroinflammation	221	9	37	175
Apoptosis	218	47	74	97
Reperfusion	204	29	50	125
Therapy	200	34	66	100
Brain	196	39	74	83
GFAP	182	51	72	59
Intracerebral hemorrhage	174	21	49	104
Oxidative stress	161	30	44	87
OGD	160	10	46	104
Dementia	156	36	42	78
Neurogenesis	139	23	53	63
Hippocampus	139	30	55	54
Neurodegenerative disease	138	39	40	59
Neurovascular unit	133	7	36	90
Brain endothelial cell	119	17	53	49
CNS	116	31	47	38

keywords (45) focused on the role of astrocytes in the treatment of stroke, including neural cell development, proliferation, differentiation, regeneration, clinical and basic research in human, animal, and cellular levels. Cluster 2 (green) refers to metabolic changes in astrocytes, including energy metabolism, glutamate metabolism, lactic acid metabolism, etc. Cluster 3 (blue) involves the protective role of apoptosis in astrocytes after oxidative stress injury, including neurotrophic factor secretion, oxidative stress, autophagy, cell death, apoptosis and

signaling pathway-related protein kinases. Cluster 4 (yellow) focuses on neurovascular units, including cerebrovascular, cerebral blood flow, BBB, endothelial cells, tight junctions and central homeostasis. Cluster 5 (purple), cluster 6 (light blue), and cluster 7 (orange) represent the assessment of cerebral infarction, neuroinflammation, and reactive astrocyte biomarkers, respectively.

Next, we calculated the average occurrence of keywords per year. As shown in Figure 6, the keywords colored from blue to green, and further to yellow denote that the average per year is diminishing. Few keywords such as micro-RNA, toll like receptor, neuroinflammation, autophagy and interleukin with a yellow color indicate research hotspots in recent years in the field of stroke and astrocyte.

Discussion

The general characteristics of the papers

This bibliometric analysis thoroughly examines the research trends and advancement in the field of stroke and astrocyte from 2001 to 2021 by using social network analysis involving country, institution and author keywords, which provides a comprehensive description of the field for the first time. This temporal analysis revealed that the scientific output in the field of stroke and astrocyte showed substantial growth in publications. At the global level, the United States has been taking a leadership position in stroke and astrocyte research with the largest number of publications as well as the greatest academic influence in this field. Notably, China exceeded the United States in the number of publications since 2014. At the institutional level, the Seoul National University was the most productive institution, followed by Kangwon National University, Stanford University and Hallym University. The top 20 journals contributed 39.61% of total publications related to stroke and astrocyte. Brain Research was the most productive journal followed by Journal of Cerebral Blood Flow and Metabolism, Glia, Journal of Neuroinflammation and Stroke.

Astrocytes in therapies

Our results showed that the functional recovery mechanisms of neurological injury attract more attention in the recent decade. Astrocyte has been shown in promoting the development of neurocytes by alleviating cell death and promoting neuroregeneration in ischemic stroke injury. Figure 5 shows that research on stem cell therapy have been popular for more than 10 years. Neural stem cells trigger and amplify the endogenous neural recovery process (Zhang et al., 2019). Bone marrow mesenchymal stem cells

(BMMSCs) (Li et al., 2021b) and endothelial progenitor cells (EPCs) (Bayraktutan, 2019) have emerged and gradually became the promising candidates for clinical translations. The transplantation of stem cells through intravenous, intra-arterial, and stereotactic approaches confirms the safety and feasibility in clinical application for the treatment of ischemic stroke (Kawabori et al., 2020; Yang et al., 2020).

Astrocytes in substance-energy metabolism

Astrocytic gap junctions and hemichannels facilitate metabolites exchange and information communication with neurons and oligodendrocytes and maintain intracellular and extracellular homeostasis. Changes in astrocyte substance-energy metabolism indirectly reflect neuronal energy supply. Connexins and pannexins in cerebral ischemia are involved in excitotoxicity, BBB disruption and neuroinflammatory response (Kim et al., 2018). Ischemic stroke decreases cerebral perfusion and reduces the production of ATP, which severely changes neuronal energy homeostasis. Explosive release of excitatory amino acids (such as glutamate) induces calcium influx and thus triggers the release of ROS, NO, and inflammatory factors. These factors may cross the damaged neurons to healthy astrocytes *via* Cx43/Cx36, a major component of astrocyte gap junctions, reducing the load of neurons and activating astrocytes (Liang et al., 2020). However, the mechanism of ischemia induced by astrocytic Cx43 expression remains controversial.

Astrocytes in oxidative stress

After stroke, astrocytes and microglia release inflammatory factors and ROS through the activation of NF- κ B and NADPH oxidase pathways, causing damage to glial cells and neurons (Zhu et al., 2022). Research on nucleic acid therapy bursting (Henninger and Mayasi, 2019) suggests that miRNAs regulate cellular pathways and mitochondrial function in stroke (Jiang et al., 2021; Li et al., 2021a; Halurkar et al., 2022). It provides an efficient and precise method to control these pathways. In addition, various neurotrophic factors secreted by astrocytes, such as nerve growth factor (NGF), brain-derived growth factor (BDNF), erythropoietin (EPO), vascular endothelial growth factor (VEGF), and glial derived neurotrophic factor (GDNF), are increased after stroke (Linnerbauer and Rothhammer, 2020).

Astrocytes in neurovascular unit

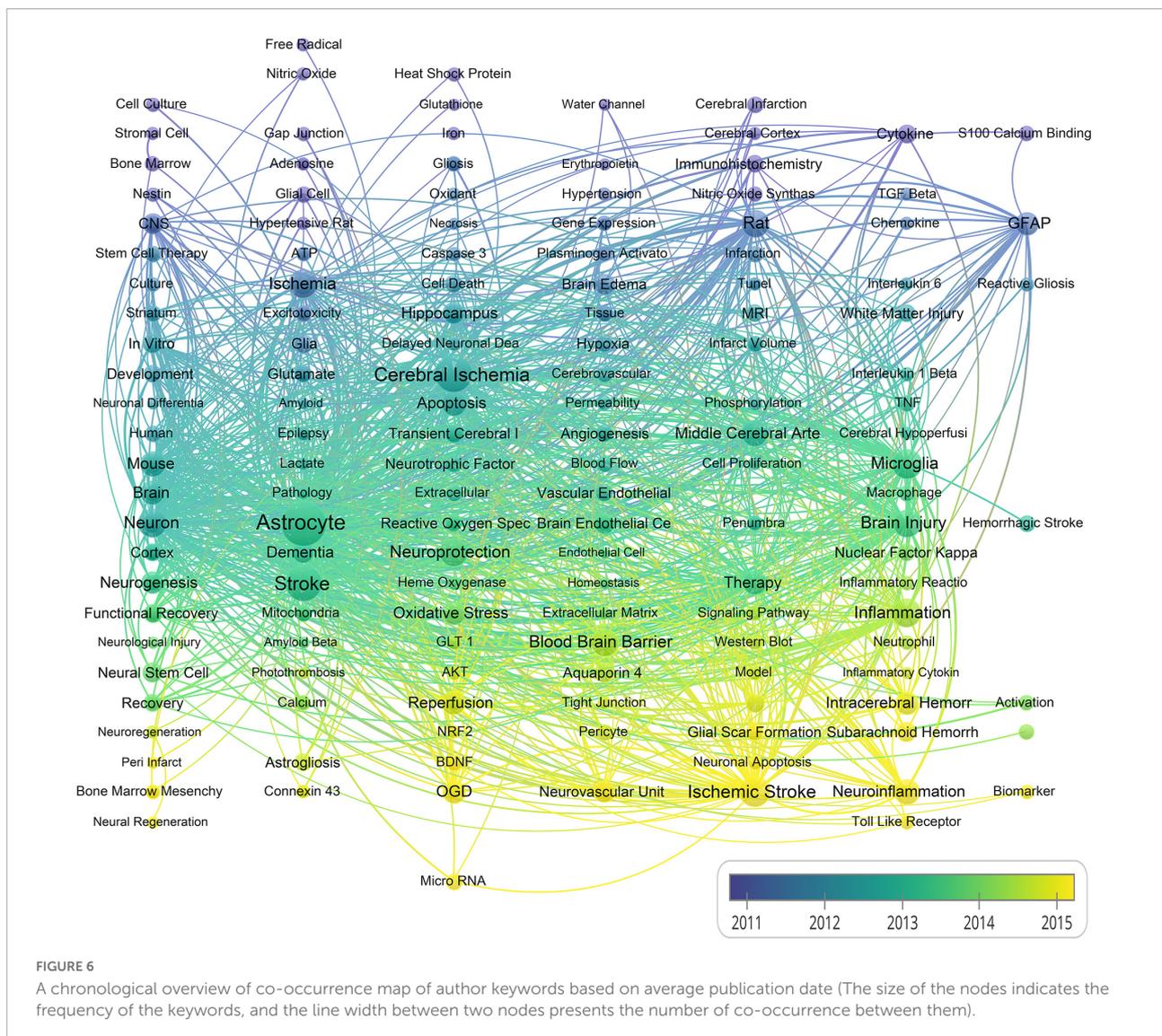
Neurovascular unit consists neuron-glia-vasculature and plays an important role in maintaining the normal physiological

function of neurons. After stroke, AQP4 on the surface of astrocytes cause astrocyte swelling and compression of blood vessels, disrupting the BBB integrity and neurovascular unit homeostasis (Ji et al., 2021). Studies have reported that excessive VEGF reduces the expression of tight junctions in endothelial cells, thereby exacerbating BBB injury and neurological deficits (Wen et al., 2017). Furthermore, astrocyte-derived VEGF accelerates the infiltration of peripheral immune cells into the CNS by increasing the expression of ICAM-1 and VCAM-1 in endothelial cells (Moon et al., 2021; Qiu et al., 2021). Conversely, astrocyte-secreted angiopoietin 1 promotes endothelial cell proliferation and BBB formation, thereby improving post-stroke revascularization, enhancing endogenous angiogenesis and promoting neurological functional recovery after cerebral ischemia (Patabendige et al., 2021). Therefore, astrocytes act as mediators of angiogenesis and may provide therapeutic targets for the development of novel neuroprosthetic therapies for stroke.

Assessment method, glial scar formation, neuroinflammation, biomarkers in stroke

We observed an interesting finding, where MRI was a vital diagnostic tool and assessment method shown in **Figure 5**. Diffusion-weighted MRI allows earlier detection for clinical intervention as compared to conventional CT diagnosis (Bhat et al., 2021). MRI offers accurate and precise estimation of cellular level neuroenergetic abnormality. Metabolic MRI monitors the process of astrogliosis and its correlation with the neuronal connective pathway over a period (Hao et al., 2016; Alamyran et al., 2020). Laboratory methods assess the reactive astrocytes proliferation, glial scar formation for monitoring subtle changes during pathogenesis.

Reactive astrocytes microglia aggregate to form the glial scars and increase the inhibitory environment by secreting extracellular matrix proteins (such as chondroitin sulfate proteoglycans) into the peri-infarct region (Dzyubenko et al., 2018; Pekny et al., 2019). Although glial scars limit tissue damage during the peak of inflammation and act as the major obstacle for axonal growth during cerebral ischemic stroke recovery. Whether astrocyte scar formation aids axon regeneration needs further exploration (Bradbury and Burnside, 2019). Interestingly, Shi et al. (2021) demonstrated that reactive microgliosis and astrogliosis hinder brain repair by engulfing synapses, and specific inhibition of this phagocytosis before glial scar maturation has beneficial consequences. Several signaling pathways and targets related to astrogliosis and glial scar formation have also been identified (Zhang et al., 2018; Zhu et al., 2021), which indicates that astrocytes and glial scars have great research prospects. In addition to glial scars, the function and role of fibrotic scars, which contains a rich deposit of



crossing from the BBB could be potential biomarker for stroke prognosis and potentially predict the outcome of post-stroke rehabilitation.

Limitations

The purpose of this study is to summarize the literature in the field of stroke and astrocyte, projects the recent trends and research hotspots. However, the major limitation of this study is inclusion of only WOS database, while other databases such as Scopus or PubMed have not been considered. Multiple databases could be included in the future study to verify the robustness of this study. Also, this study involved only articles and reviews. The analyses of different types of publications, including book chapters, conference

proceedings and other documental types may be considered in future studies.

Conclusion

In this study, we provided a panorama-to-profile up-to-date analysis on the research trends and hot issues of stroke and astrocyte, based on the bibliometric analysis of publications from 2001 to 2021. Statistical results showed significantly increased concern of stroke and astrocyte in the past two decades and China contributed 50% increase in the last seven years. The increased publications in other countries are relatively slow. The United States and China were the most productive and influential countries with the highest number of total citations, high publications and the most collaborative

countries. The University of California San Francisco has a significant academic influence in the field. The research issues can be categorized into seven aspects: (1) the role of astrocytes in the treatment of stroke; (2) metabolic changes in astrocytes; (3) the protective role of apoptosis in astrocytes after oxidative stress injury; (4) neurovascular units; (5) the assessment of cerebral infarction; (6) neuroinflammation; and (7) reactive astrocyte biomarkers. Items such as Micro-RNA, TLR, neuroinflammation, autophagy and interleukin related topic were the emerging research hotspots.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

ZD and YS: conceptualization. ZD, NJ, TY, HH, YW, LS, and YS: data collection and analysis. ZD, XL, and YS: writing—original draft preparation. ZD, GK, YS, and CM: writing—review and editing. YS: visualization. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Natural Science Foundation of China (81473577 to CM and 82004028 to LS), China Postdoctoral Science Foundation (2020M680912 to

LS), Shanxi Applied Basic Research Project (20210302123408 to ZD), Leading Team of Medical Science and Technology, Shanxi Province (2020TD05 to CM), 136 Revitalization Medical Project Construction Funds, Shanxi Province (2021YZ09 to YS), and Shanxi Medical University Third Hospital Talent Introduction Research Fund Project (2021RC026 to YS and 2021RC033 to ZD).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fncel.2022.949521/full#supplementary-material>

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