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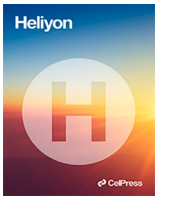

Research article

Ischemic stroke pathophysiology: A bibliometric and visualization analysis from 1990 to 2022

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ABSTRACT

Background: Pathophysiology plays a significant role in the scientific study of ischemic stroke, and has attracted increasing interest from researchers in the field. However, a comprehensive bibliometric analysis is lacking in this field. The purpose of this study is to identify the current research status and hotspots of ischemic stroke pathophysiology from a bibliometric perspective.
Methods: The Web of Science Core Collection database was searched for articles published from 1990 to 2022. CiteSpace, VOSviewer, and R package "bibliometrix" software were used to analyze countries/regions, institutions, journals, authors, papers, and keywords to predict the latest trends in ischemic stroke pathophysiology research.
Results: This analysis collected 7578 records of ischemic stroke pathophysiology. China and America emerged as the leading countries in this field, with Harvard University being the most active institution. Among journals and authors in this field, journal *Stroke* and author Gregory YH Lip published the most papers, while *Nature Medicine* was the journal with the highest citation per article. Keywords and co-citation clusters were closely related to "central nervous system", "mechanisms", "biochemistry & molecular biology" and "radiology, nuclear medicine & medical imaging", while other related fields, such as peripheral organs damage induced by the central nervous system and rehabilitation after ischemic stroke, require further research efforts.
Conclusion: This is the first bibliometric study that comprehensively mapped out the knowledge structure and development trends of ischemic stroke pathophysiology in recent 32 years, which may provide a reference for scholars to explore ischemic stroke pathophysiology.

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Abbreviations

ACPA	average citations per article
APY	average published year
PRC	People's Republic of China
USA	United States of America
WoSCC	Web of Science Core Collection

1. Introduction

Ischemic stroke is a cerebrovascular disease, whose pathological feature is occlusion of the middle cerebral artery induced by the central thrombosis or embolism [1]. Ischemic stroke is a prevalent and devastating disease, accounting for 5.9 million deaths and 102 million disability-adjusted life years lost worldwide. In 2016, there were 11.9 million new incidents of ischemic stroke globally [2]. At present, some high-quality papers have reviewed the pathophysiology of ischemic stroke. Some reviews outlined the relationship between the immune system and ischemic stroke for a better treatment strategy. Qin et al. summarized the molecular mechanisms and related pathways involved in ischemic stroke, highlighting the important role of excitotoxicity and its association with signaling pathways such as phosphatidylinositol 3-kinase-Akt and phosphatase and tensin homolog [3]. Furthermore, ischemic stroke may lead to specific immune depression, increasing susceptibility to infection and causing complications including poststroke dementia, poststroke depression, pneumonia, and urinary tract infection [4–6]. Drug therapy is also associated with ischemic stroke pathophysiology. Researchers have reviewed the potential of natural medicine for ischemic stroke due to its mild toxicity and multi-target properties, particularly in the context of neuroprotection [7]. Although contributing a lot to the field of ischemic stroke pathophysiology, these reviews remain shortcomings in that they may not reflect the research status of the entire field. For example, topics of reviews in ischemic stroke pathophysiology are most limited in the specific and detailed pathophysiologic processes like neuroinflammatory mechanisms [8], immune cells [9], cognitive dysfunction [10] and endothelial cell dysfunction [11] instead of macroscopic perspective of the whole field of ischemic stroke. Therefore, existing reviews cannot meet the needs of readers for comprehensive information on ischemic stroke pathophysiology, and new approaches are necessary to study the progress in this field.

Bibliometric analysis is an advanced literature research strategy that focuses on the features of literature, aiding in understanding knowledge frameworks through analyzing qualitative and quantitative papers [12]. Bibliometric analysis allows for the comprehensive analysis of enormous amounts of scientific information, enabling the understanding of the development of various disciplines and the identification of the state of knowledge and emerging trends of a research topic or field over time [13,14]. Besides, the contributions of different countries, institutions, journals, and scholars can also be analyzed by bibliometrics [15]. Therefore, this method provides the possibility to make a systematic analysis of the research state and trend on the ischemic stroke pathophysiology.

In this review, we conducted a scientometric study of ischemic stroke pathophysiology from 1990 to 2022 aiming to perform a bibliometric analysis with a concentration on countries/regions, journals, authors, keywords, and references. Since 1990, ischemic stroke pathophysiology has developed rapidly. The analysis of literature on ischemic stroke pathophysiology spanning the past 32 years allows for a comprehensive reflection of recent and current research trends within the field. Furthermore, this time frame provides insights into the evolutionary progression of the ischemic stroke pathophysiology. The results of this study may provide valuable insights into the current state and future directions of ischemic stroke pathophysiology research.

2. Materials and methods

2.1. Data source and search strategy

The Web of Science Core Collection (WoSCC) database is one of the most authoritative database platforms containing more than 12,000 international academic journals. Therefore, we chose this database to obtain comprehensive academic information for bibliometric analysis [16,17].

A literature search was conducted to analyze papers associated with the pathophysiology of ischemic stroke by using the WoSCC database from January 1, 1990 to June 30, 2022. In the present study, the search strategy was as follows: Topic Search (TS) = ischemic stroke, cryptogenic ischemic stroke or pathophysiology AND TS = pathophysiology or dysfunction AND Language (LA) = English AND Document types (DT) = article or review.

2.2. Data extraction

Data extraction and quality evaluation were performed independently. After searching the WoSCC database, the number of publications and the total and average citations were recorded. Retrieved publications meeting the following criteria were excluded: duplicate records; publications that could not be identified with DOI; article of proceedings paper or early access; review of proceedings paper; retracted publications.

2.3. Bibliometric analysis and visualization

Raw data including the number of publications, country/region, journal, keyword, and title of papers were extracted using Bibliometrix [18]. VOSviewer (Leiden University, Leiden, The Netherlands) software was used for constructing and visualizing bibliometric networks of the publications in our present study [19]. Moreover, CiteSpace, developed by Professor Chen, was used to construct a dual-map overlay for journals, cluster analysis of co-cited keywords, and detection of references and keywords with intense citation bursts [20].

3. Results

3.1. General data

According to the defined search criteria, a total of 7578 pieces of literature were retrieved from the year 1990–2022. Finally, 7073 eligible papers were identified by excluding publications meeting the exclusion criteria. As shown in Fig. 1, the trend of global works of literature was increasing steadily year by year.

3.2. Countries and regions

A total of 19 countries/regions contributing to the highest publications are included in this study and presented in Fig. 2A and Table 1. The number of publications can serve as an indicator of national or regional attention to this field. Table 1 displays the countries/regions with the highest publications and citations. The United States of America (USA) (2275 papers), the People's Republic of China (PRC) (1629 papers), Germany (551 papers), Italy (411 papers), and Japan (403 papers) were the top 5 productive countries. Among the 19 countries/regions, the USA was the first and only country that conducted research on ischemic stroke pathophysiology from 1990 to 2000. In terms of citations, the most productive country, the USA, also had the highest total citation frequencies (107827). Germany ranked second in total citation frequencies (30388), followed by the PRC (28539), England (19119), and Italy (14651). Interestingly, although the USA ranked first in terms of the number of articles and total citations, the two highest average citations per article (ACPA) countries were Germany and England. Germany ranked first in ACPA (ACPA = 55.15), followed by England (48.90) and the USA (47.40).

As shown in Fig. 2B, visually, the USA published the most papers among 19 countries from 1990 to 2016. However, since 2016, the PRC had begun to publish as many papers as the USA until 2022. Notably, publications of each country/region presented an increasing long-term trend in Fig. 2B.

Regarding the intercountry/regional cooperation network analysis, the USA and the PRC both established the most partnerships with other 18 highly productive countries or regions as illustrated in Fig. 2C. Moreover, the USA, the PRC, and Australia collaborated closely with each other.

3.3. Institutions

The impact of institutions was assessed based on their ACPA, and the top 21 contributing institutions are presented in Table 2 and Fig. 3. Harvard University (115 papers) was the institution with the highest ACPA of 101.8, followed by Miami University (ACPA = 87.7, 52 papers), University of California (ACPA = 78.3, 87 papers), Heidelberg University (ACPA = 65.6, 54 papers) and University of Pittsburgh (ACPA = 63.5, 60 papers). Among the top 10 influential institutions, nine of the top 10 influential institutions were situated in the USA, except the ranked fourth Heidelberg University located in Germany. Furthermore, among the 21 institutions with the

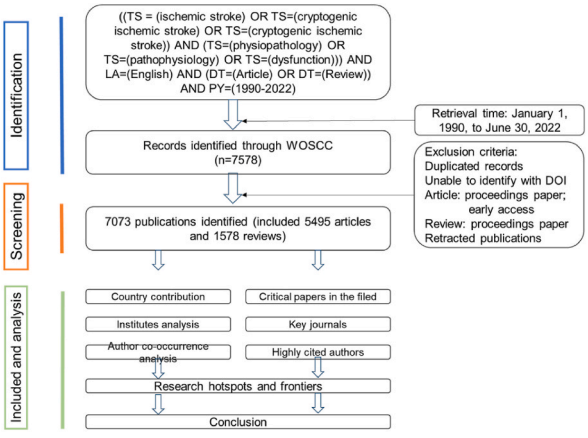

Fig. 1. Flowchart of the screening process.

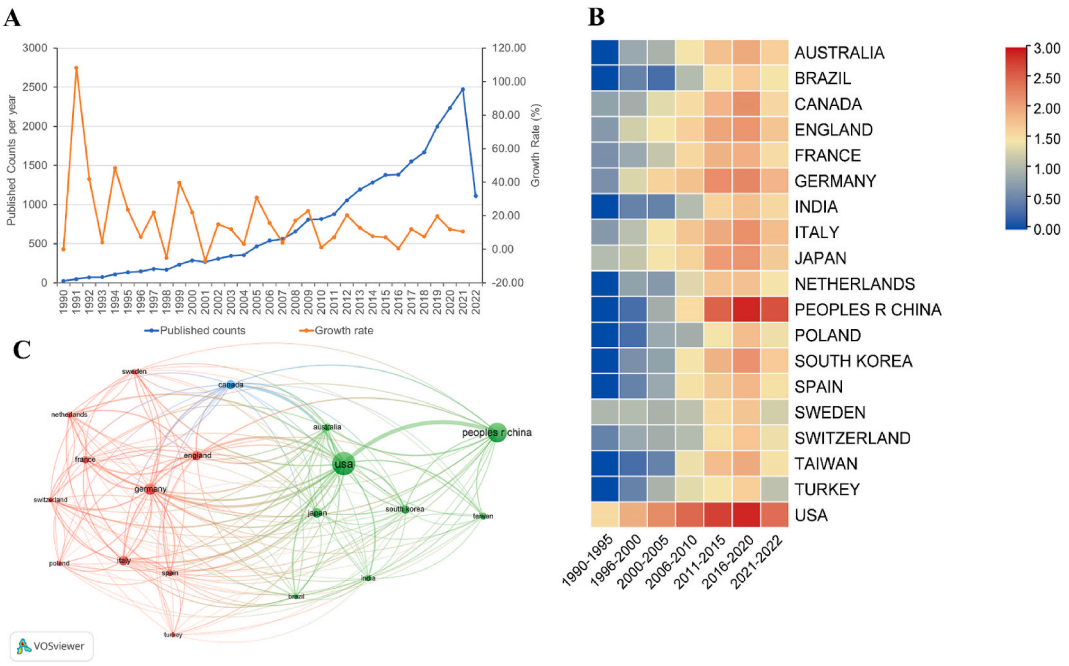

Fig. 2. Visualization of countries/regions. (A) The global number and growth rate of publications of ischemic stroke pathophysiology. (B) Several publications by countries/regions and years (C) Cooperation network.

Table 1
| Number of publications and citations by countries or regions.

Rank	Country or Regions	Publications	Citations	Average citations per article	Active period in the field (year)
1	USA	2275	107827	47.39648	1990–2022
2	PRC	1629	28539	17.51934	2006–2022
3	Germany	551	30388	55.15064	2000–2022
4	Italy	411	14651	35.6472	2006–2022
5	Japan	403	10138	25.15633	2006–2022
6	England	391	19119	48.8977	2006–2022
7	Canada	339	14410	42.50737	2006–2022
8	South Korea	311	5580	17.94212	2010–2022
9	France	258	10388	40.26357	2006–2022
10	Australia	245	7708	31.46122	2011–2022
11	Taiwan	214	4489	20.97664	2011–2020
12	Spain	198	7178	36.25253	2006–2022
13	Netherlands	173	7637	44.14451	2011–2020
14	India	155	3266	21.07097	2006–2022
15	Sweden	146	6225	42.63699	2011–2020
16	Switzerland	136	5543	40.75735	2011–2020
17	Poland	132	5289	40.06818	2016–2020
18	Brazil	125	2631	21.048	2011–2020
19	Turkey	117	2232	19.07692	2016–2020

highest ACPA, thirteen participated in the latest edition of the guidelines, with six in the USA, four in the PRC, one each in Germany, Australia, and Canada.

3.4. Authors

The top 10 authors contributed a total of 452 publications, accounting for approximately 6.4% of all included publications in the field of ischemic stroke pathophysiology. Gregory YH Lip was the top author with the most publications (papers = 40), followed by Joanna Wardlaw, Christoph Kleinschnitz, Xunming Ji, and David S. Liebeskind, all of whom published 27 papers respectively. (Table 3). The h-index assesses researchers' academic accomplishments or the publication output [21,22]. Gregory YH Lip, having published the most articles, also holds the highest h-index.

Table 2
| The most influential organizations in ischemic stroke pathophysiology.

Rank	Organization	Publication	Average citations per article	Located	Participation in the latest edition of the guidelines
1	Harvard University	115	101.8	USA	No
2	Miami University	52	87.7	USA	No
3	University of California, San Francisco	87	78.3	USA	No
4	Heidelberg University	54	65.6	Germany	Yes
5	University of Pittsburgh	60	63.5	USA	Yes
6	Massachusetts General Hospital	79	61.4	USA	Yes
7	Mayo Clinic	88	57.4	USA	No
8	Stanford University	52	53.5	USA	No
9	Columbia University	69	51.2	USA	Yes
10	University of Washington	54	49.6	USA	Yes
11	Johns Hopkins University	91	46.1	USA	No
12	University of California, Los Angeles	66	45.5	USA	Yes
13	University of Michigan	50	40.1	USA	No
14	University of Melbourne	58	31.6	Australia	Yes
15	Harvard Medical School	80	28.9	USA	Yes
16	University of Toronto	71	27.5	Canada	Yes
17	Shanghai Jiao Tong University	69	22.6	PRC	Yes
18	Huazhong University of Science and Technology	52	21.3	PRC	No
19	Fudan University	77	20.2	PRC	Yes
20	Nanjing Medical University	68	16.4	PRC	Yes
21	Capital Medical University	147	14.7	PRC	Yes

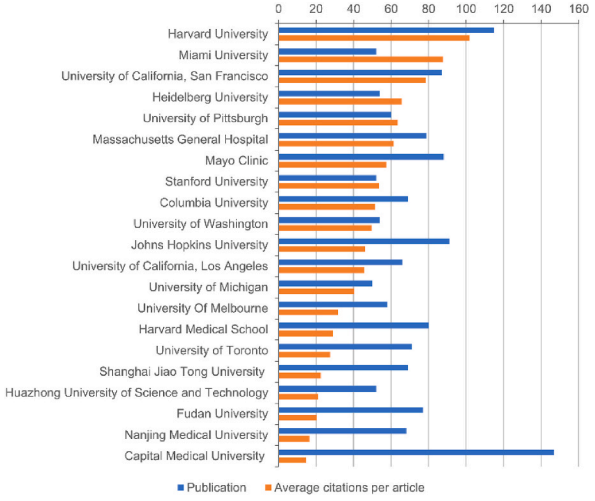

Fig. 3. The top 21 institutions of publication and average citations per article related to ischemic stroke pathophysiology.

3.5. Journals

Regarding ACPA as the ranking criteria, the top 20 cited journals are listed in Table 4. The top 3 cited journals were *Nature Medicine* (ACPA = 702.2, 5 papers), *The New England Journal of Medicine* (ACPA = 492.5, 4 papers), and *Jama-Journal of The American Medical Association* (ACPA = 4226.3, 12 papers). The latest impact factors of all the top 10 cited journals were higher than 5.000, and seven of them had the latest impact factors greater than 20.000. Besides, thirteen of the top 20 cited journals were in the Quartile in Category 1 of JCR, while twelve of the top 20 were top journals.

As shown in Fig. 4, the publication number of the top 18 journals with high productivity was measured by the circle size, and the average published year (APY) of these top 18 journals was from 2008 to 2016, visually distinguished from blue (earlier) to yellow (more recent). The top three paper-published journals were *Stroke* (379 papers, ACPA = 73.9), *Journal of Stroke & Cerebrovascular Diseases* (165 papers, ACPA = 10.5), and *Journal of Cerebral Blood Flow and Metabolism* (127 papers, ACPA = 46.1). As regards colors in this graph, papers published in the *International Journal of Molecular Sciences* (APY = 2019) and *Journal of Stroke & Cerebrovascular Diseases* (APY = 2017) were up to date, while papers published in *The New England Journal of Medicine* (APY = 2006) and *Circulation* (APY = 2007) were relatively early.

Table 3
| The 20 authors with the highest number of publications.

Author name	Institutes	Countries	Number of articles	Citations	H-index	Average citations per article
Gregory YH Lip	Aalborg University	Denmark	40	1830	189	45.8
Joanna Wardlaw	The University of Edinburgh	England	27	2638	121	97.7
Christoph Kleinschnitz	University Hospital Essen	Germany	27	1609	78	59.6
Xunming Ji	Capital Medical University	PRC	27	751	61	27.8
David S. Liebeskind	University of California, Los Angeles	USA	27	549	91	20.3
Eng H Lo	Hospital Essen General Hospital	Germany	26	1771	97	68.1
Matthias Endres	Charité University Medicine	Germany	26	1054	91	40.5
Yuchuan Ding	Wayne State University	USA	24	534	47	22.3
Peter Kraft	Harvard University	USA	23	937	113	40.7
Louise D. McCullough	McGovern Medical School	USA	19	771	74	40.6
Bruce Ovbiagele	University of California, San Francisco	USA	18	870	73	48.3
Adam Kirton	University of Calgary	Canada	18	503	47	27.9
John H. Zhang	Loma Linda University	USA	18	479	90	26.6
Ralph L. Sacco	University of Miami	USA	17	4122	144	242.5
Jian Wang	Wuhan University	PRC	17	639	55	37.6
Argye E. Hillis	Johns Hopkins Hospital	USA	17	474	68	27.9
Wei Wang	University of Pittsburgh	USA	17	314	13	18.5
Martin Dichgans	Ludwig Maximilian University	Germany	16	1768	113	110.5
Michael K Schuhmann	University of Wuerzburg	Germany	16	810	30	50.6
Li Zhang	University of Maryland	USA	16	495	38	30.9
Rebecca F. Gottesman	National Institute of Neurological Disorders and Stroke	USA	16	383	75	23.9

Table 4
| Ranking of the top 20 journals by citations.

Rank	Source	Publication	Citations	Average Citations per Article	Average Published Year	Lastest Impact Factor	JCR	Top journal
1	Nature Medicine	5	3511	702.2	2009	87.241	Q1	Yes
2	The New England Journal of Medicine	4	1970	492.5	2006	176.079	Q1	Yes
3	Jama-Journal of The American Medical Association	12	2715	226.3	2011	157.335	Q1	Yes
4	Lancet Neurology	15	3210	214.0	2011	59.935	Q1	Yes
5	Circulation	43	6895	160.3	2007	39.918	Q1	Yes
6	Annals of Neurology	31	3777	121.8	2008	11.274	Q1	Yes
7	Journal of Neuroscience	21	1886	89.8	2011	6.709	Q1	Yes
8	Journal of The American College of Cardiology	39	3314	85.0	2011	27.203	Q1	Yes
9	Stroke	379	28025	73.9	2010	10.170	Q1	Yes
10	Neurology	88	6297	71.6	2010	11.800	Q1	Yes
11	Journal of Neurochemistry	32	1620	50.6	2012	5.546	Q2	Yes
12	Journal of Cerebral Blood Flow and Metabolism	127	5854	46.1	2012	6.960	Q1	No
13	American Journal of Cardiology	49	1936	39.5	2008	3.133	Q3	No
14	International Journal of Stroke	50	1784	35.7	2015	6.948	Q1	No
15	Brain Research	78	2308	29.6	2011	3.610	Q3	No
16	Cerebrovascular Diseases	117	3458	29.6	2010	3.104	Q3	No
17	Journal of The Neurological Sciences	88	2128	24.2	2011	4.553	Q2	No
18	Plos One	115	2518	21.9	2015	3.752	Q2	No
19	International Journal of Molecular Sciences	100	1940	19.4	2019	6.208	Q1	Yes
20	Journal of Stroke & Cerebrovascular Diseases	165	1726	10.5	2017	2.677	Q3	No

3.6. Cited references

The twenty most frequently cited references from 1990 to 2022 are summarized in Table 5. All references were cited more than 725 times, with the top two references “Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease” and “Ischemia and reperfusion–from mechanism to translation” cited 2031 and 1915 times each.

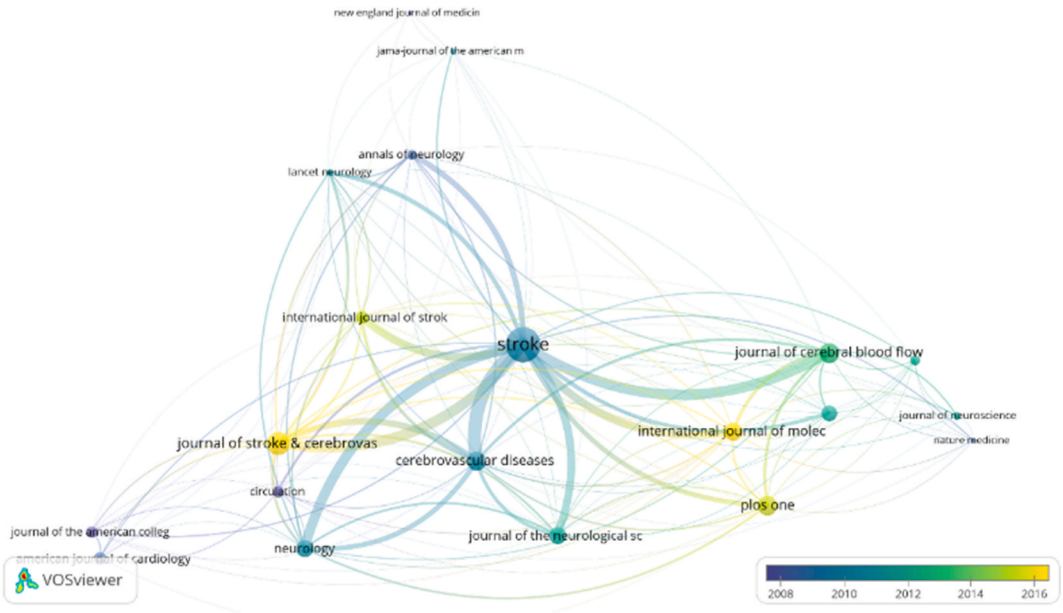

Fig. 4. Distribution of journals according to ACPA; journals in yellow appeared later than those in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.7. Co-citation clusters

CiteSpace can be applied to conducting a statistical and correlation analysis of co-cited references into clusters. In this study, we identified eight different clusters in the network of co-cited references, with significant modularity and silhouette scores, indicating highly credible clusters (Q = 0.4463, S = 0.8224). The eight clusters are displayed in Fig. 5, including #0 Neurosciences, #1 Peripheral Vascular Disease, #2 Pharmacology & Pharmacy, #3 Medicine, General &Internal, #4 Medicine, Research & Experimental, #5 Biochemistry & Molecular Biology, #6 Multidisciplinary Sciences and #7 Radiology, Nuclear Medicine & Medical Imaging.

3.8. Keywords

Hot keywords of ischemic stroke pathophysiology from 2013 to 2016 were analyzed by VOSviewer and presented in Fig. 6. Keywords with the strongest citation bursts are shown in Fig. 7, indicating the earliest year of their appearance, burst start and end dates. The red bar represents the time when the keywords occur frequently, the blue bar denotes the time when the keywords occur infrequently and the light blue bar represents periods when keywords have not appeared yet. The keyword "tissue plasminogen activator" (Strength = 35.28) was the longest and earliest keyword burst that lasted for 16 years from 1996 to 2011, followed by the other four longest and earliest keyword bursts, which were "acute stroke" (43.73, 1996–2010), "nitric oxide" (42.01, 1999–2014), "consecutive patient" (34.28, 1999–2011) and "karger ag basel" (40.07, 2000–2014). Additionally, several keywords including "endothelial cell" (26.42, 2015–2022), "blood brain barrier" (32.45, 2016–2022), "neuroprotective effect" (25.36, 2016–2022), "blood-brain barrier" (29.43, 2017–2022), "inflammation" (24.28, 2017–2022), "cognitive dysfunction" (28.44, 2019–2022), "mechanism" (24.53, 2019–2022), "signaling pathway" (40.02, 2020–2022), "mitochondrial dysfunction" (37.76, 2020–2022), "underlying mechanism" (37.32, 2020–2022), "leading cause" (35.68, 2020–2022) and "positive effect" (27.26, 2020–2022) continued to have ongoing citation bursts in 2022. Notably, there was little overlap between the keyword citation bursts from 1996 to 2016 and those from 2016 to 2022.

4. Discussion

4.1. General data

Over the past few decades, researchers have put enormous efforts into the research of ischemic stroke pathophysiology [23]. The number of publications related to this field was increasing year by year. In the present study, the leading countries/regions, institutions, journals, authors, articles, and keywords were presented, and ischemic stroke pathophysiology-related research hotspots and trends were analyzed by using CiteSpace and VOSviewer software.

Table 5
| Top 20 cited papers.

Rank	Title	Corresponding Author	Institute	Journal	Published Year	Cited Frequency
1	Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease	Volker Schächinger	Goethe University	Circulation	2000	2031
2	Ischemia and reperfusion–from mechanism to translation.	Holger K. Eltzschig	University of Colorado	Nature Medicine	2013	1915
3	Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease	Thomas Heitzer	University Hospital Hamburg-Eppendorf	Circulation	2001	1520
4	An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association	Ralph L. Sacco	University of L'Aquila	Stroke	2013	1491
5	Treatment of stroke with erythropoietin enhances neurogenesis and angiogenesis and improves neurological function in rats	Michael Chopp	Oakland University	Stroke	2004	1126
6	Definition and evaluation of transient ischemic attack	Donald J. Easton	University of California, San Francisco	Stroke	2010	1120
7	Inflammatory mechanisms in ischemic stroke: role of inflammatory cells	Rong Jin	Louisiana State University	Journal of Leukocyte Biology	2011	1053
8	Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke	Randall T. Higashida	University of California, San Francisco	Stroke	2003	1015
9	Time is brain–quantified	Jeffrey L. Saver	University of California, Los Angeles	Stroke	2009	1010
10	Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention randomized controlled trial	James F. Toole	Wake Forest University	JAMA	2006	1000
11	Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers	Helena Chang Chui	University of Southern California, Los Angeles	Neurology	1992	951
12	Prognostic significance of endothelial dysfunction in hypertensive patients	Francesco Perticone	University of Catanzaro Magna Græcia	Circulation	2001	877
13	Thrombolysis for acute ischaemic stroke	Joanna M. Wardlaw	University of Edinburgh	Cochrane Database of Systematic Reviews	2014	865
14	Mean platelet volume: a link between thrombosis and inflammation?	Armen Y. Gasparyan	University of Birmingham	Current Pharmaceutical Design	2011	857
15	Embolic strokes of undetermined source: the case for a new clinical construct	Robert G Hart	McMaster University	Lancet Neurology	2014	832
16	Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging	Steven Warach	Beth Israel Hospital	Annals of Neurology	1995	827
17	Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women	Teresa S. M. Tsang	Mayo Clinic	Journal of The American College of Cardiology	2002	820
18	Angiotensin II attenuates endothelium-dependent responses in the cerebral microcirculation through nox-2-derived radicals	Helene Girouard	Cornell University	Arteriosclerosis, Thrombosis, and Vascular Biology	2006	809
19	Fibrinolysis for patients with intermediate-risk pulmonary embolism	Guy Meyer	Paris Descartes University	The New England Journal of Medicine	2014	771
20	Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis	Peter Langhorne	Royal Infirmary Glasgow	Stroke	2014	725

4.2. Research strength analysis

In terms of the number of publications, particularly, the USA emerged as the most prolific country in the field of ischemic stroke pathophysiology, contributing 2275 papers, which accounted for 28.33% of the top 19 productive countries/regions. This was followed by the People's Republic of China (PRC) with 1629 papers (20.29%), Germany with 551 papers (6.86%), Italy with 411 papers (5.12%), Japan with 403 papers (5.02%), and England with 391 papers (4.87%). The publication counts from other countries over five-year intervals were lower than those from the USA, reflecting the continuous attention to research in ischemic stroke pathophysiology

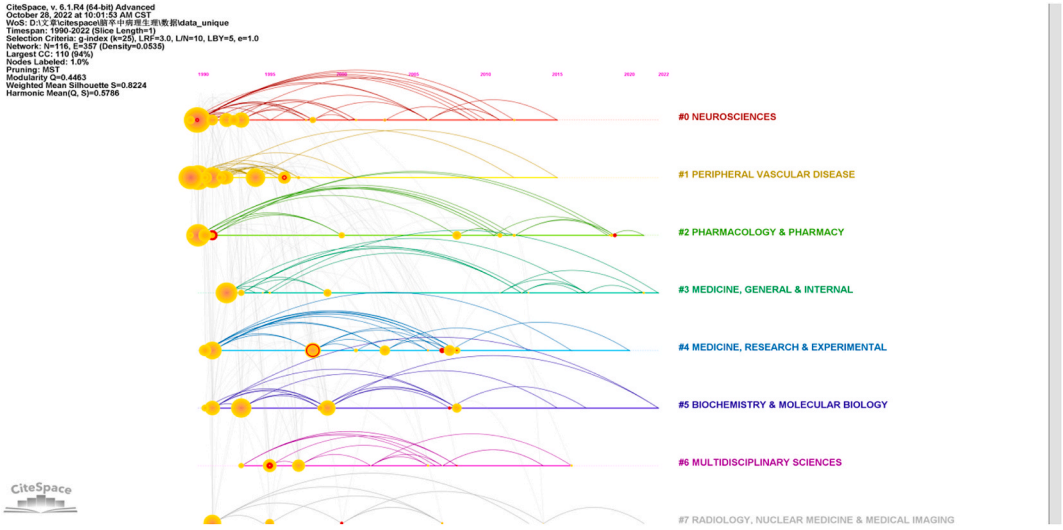

Fig. 5. Timeline visualization of co-cited references.

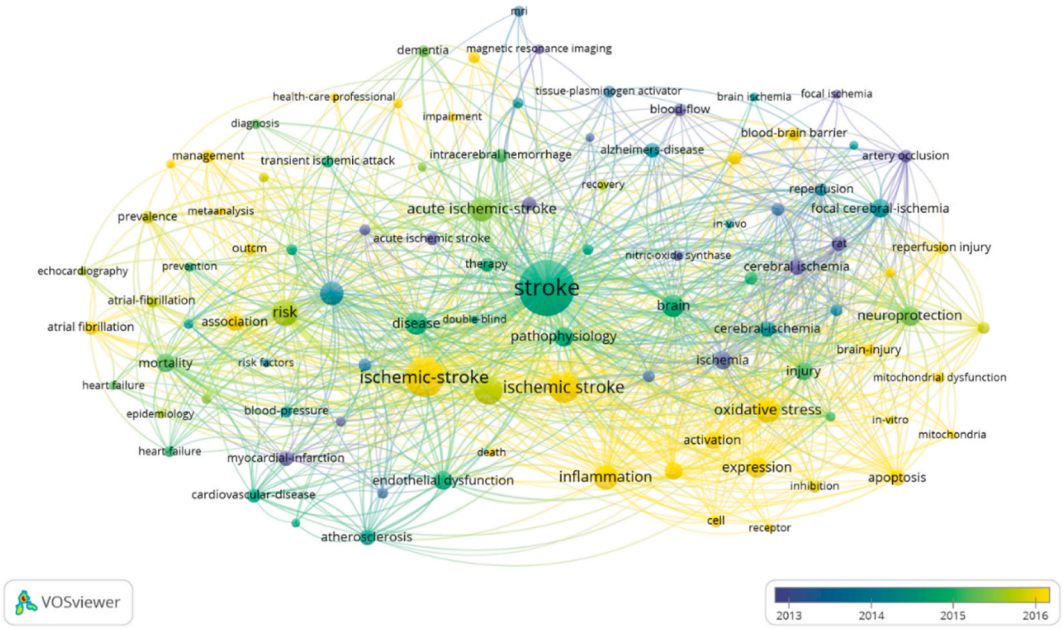

Fig. 6. Keyword analysis regarding ischemic stroke pathophysiology.

paid by the USA. Besides, total citations and ACPA are also critical parameters in the bibliometric study, which represent the quality and academic impact of different countries/regions. The USA not only produced the most publications but also received the highest total citations (107827).

Considering the prominent and predominant role that institutions play in a field, we analyzed the top 21 influential organizations in ischemic stroke pathophysiology. Of these, nine of the top 10 institutions were based in the USA, with the fourth-ranked institution being Heidelberg University in Germany. Based on these results, it can be indicated that the USA was a consistently leading country of ischemic stroke pathophysiology in the aspect of high productivity and paper quality.

The USA's central position in the field of ischemic stroke pathophysiology was attributed to several factors, including early and in-depth research, a well-established medical system, and extensive clinical trials [24,25]. The USA has been at the forefront of ischemic stroke pathophysiology research for at least a decade longer than any other highly productive countries or regions [26,27]. In the 1990s, the USA had begun to explore the pathophysiology of ischemic stroke in aspects of subtype of acute ischemic stroke, diagnosis, treatment, and clinical case [28–30]. In 1990, the University of Texas Health Science Center conducted an analysis of case reports of ischemic stroke patients and discovered that ischemic stroke was associated with more than a dozen primary hematologic disorders

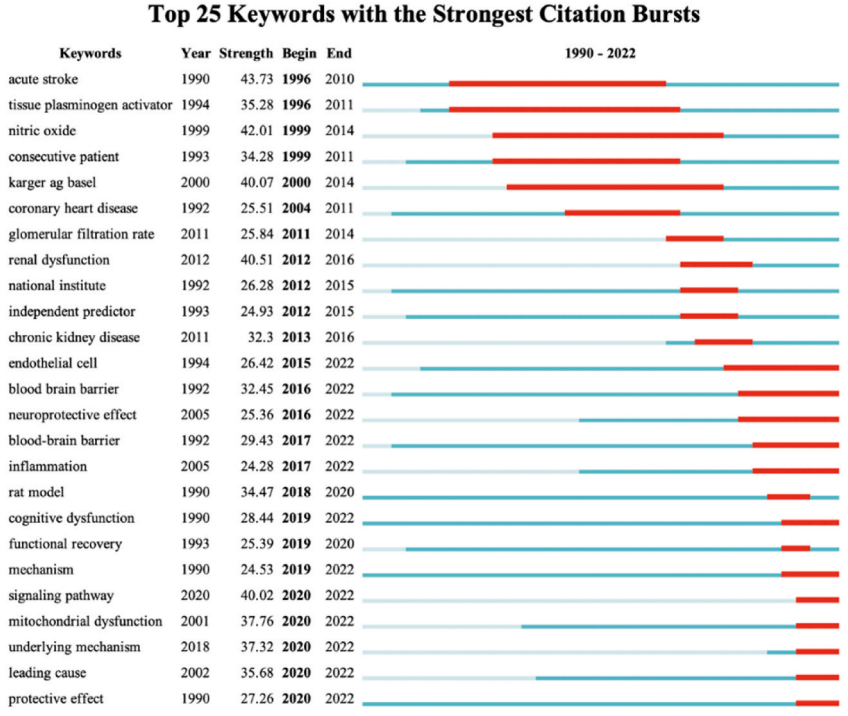

Fig. 7. Top 25 keywords with strongest citation bursts in ischemic stroke pathophysiology.

such as hereditary abnormalities of fibrinolysis and platelet disorders [31]. In 1994, an article reported an algorithm for the clinical assessment and treatment of patients with minor ischemic stroke. Furthermore, the healthcare system of the USA is well-developed, with higher healthcare expenditure per person ($59,900 per patient per year) than any other country [32,33]. Besides, Americans always mount healthcare reforms to promote the efficiency and fairness of the system. For instance, Affordable Care Act introduced by senator Bernard Sanders can ensure healthcare access for all American citizens, allowing patients who are covered by the USA healthcare system to participate in clinical research and promote the development of ischemic stroke pathophysiology [34]. Moreover, recently, scholars of the USA in the ischemic stroke pathophysiology field began to pay precise attention to clinical cohort studies, meta-analyses and those particular ischemic stroke patients, like rural folks and veterans [35,36]. This precise attention to clinical research and specific patient populations demonstrates the USA's continued commitment to advancing the understanding and treatment of ischemic stroke pathophysiology.

Currently, the PRC held the second rank in the number of publications on ischemic stroke pathophysiology, which was closely attributed to the PRC's rapid development in recent years [37–40]. The PRC's emerging and active research in ischemic stroke pathophysiology may be related to the development of Chinese Brain Projects launched in 2016, which has provided impetus for neuroscience research in the country [41]. The PRC continues to be active in ischemic stroke pathophysiology research, as evidenced by the increasing number and quality of publications [42].

The majority of high-impact authors in the field of ischemic stroke pathophysiology were clinicians affiliated with medical schools across various institutions, and they played a vital role in formulating guidelines for this disease in their respective countries. It is of strong clinical value to track the research results of these authors. In terms of specific authors, Gregory YH Lip from Denmark, Joanna Wardlaw from England, Christoph Kleinschnitz from Germany, Xunming Ji from the PRC, and David S. Liebeskind from the USA were the top 5 authors with the most publications. Regarding the proportion, authors from the USA accounted for 55% and authors from Germany accounted for 25% of the top 20 authors with the most publications. This result was consistent with the conclusion that the USA and Germany were the most productive countries in publications. Notably, except the most productive author Gregory YH Lip is Danish, all other top 19 authors came from the top 4 productive countries, while 30% of the top 20 authors were affiliated with the most influential institutions, indicating that high-yielding countries/regions have more potential to build influential institutions that can ensure better output of researchers. Consequently, excellent researchers in ischemic stroke pathophysiology can elevate the status of their institutions or even their countries/regions.

4.3. Hotspots analysis

The ranking of journals based on the ACPA index reveals that *Nature Medicine*, *The New England Journal of Medicine*, and *Jama-Journal of The American Medical Association* were the top 3 journals with the highest citation frequency, which represented the international attention and recognition of these journals in this field [43–47]. However, the APY of all top 10 journals dates back to

before 2012. Regarding the bottom 10 journals, they were more active in publishing papers recently, while their impact factors were all below 10 points. Furthermore, only two of the bottom 10 journals ranked in the first Quartile in the Category of JCR, while the rest of them were in the second or third Quartile in the Category of JCR, suggesting that researchers in ischemic stroke pathophysiology are increasingly publishing their research in journals that may cover a wider range of research topics, rather than those that exclusively focus on experimental research.

When considering publications, as shown in Table 5, the most cited article written by Volker Schächinger confirmed that coronary endothelial dysfunction can predict long-term atherosclerotic disease progression and the rate of a cardiovascular event, such as the ischemic stroke [48,49]. The second-cited study, titled "Ischemia and reperfusion–from mechanism to translation" and published in Nature Medicine, is a review focused on the mechanism and translation of ischemia and reperfusion. Ischemia and reperfusion-elicited tissue injury and destruction result in morbidity and mortality of ischemic stroke. Therefore, the author, Holger K. Eltzschig, summarized the molecular and immunological consequences of ischemia and reperfusion. Besides, the author emphasized that it is pivotal to understand the mechanisms of reperfusion injury in developing strategies to make tissues more resistant to ischemia or to mitigate reperfusion injury [50].

Keywordsare the core of a scientific article and their clusters can reflect the most widely well-represented research areas of a field. Thus, by analyzing high-frequency keywords, we can track the knowledge evolution, hotspots, and future directions of research works [51,52]. As shown in Fig. 7, keywords burst terms can be divided into two stages by year: the first stage lasted from 1996 to 2016, and the second stage spanned from 2016 to today. In the first stage, as shown in Fig. 7, "tissue plasminogen activator" and "acute stroke" were the keywords with the earliest citation outbreaks, which represent the initial status of two keywords in ischemic stroke research [53]. From 2016 to 2022, the second stage, the citation bursts of keywords, such as "endothelial cell", "blood brain barrier", "neuroprotective effect", "blood-brain barrier", "inflammation", "cognitive dysfunction" and "mitochondrial dysfunction" reflect the potential in these directions, focus on basic experiments as well as molecular biology mechanism studies [54–58]. Additionally, "mechanism", "signaling pathway", "underlying mechanism", "leading cause" and "positive effect" are also citation bursts keywords related to mechanisms that have been widely concerned by scholars in recent years [59,60]. Besides, as shown in Fig. 5, the research clusters out of date mainly referred to #0 Neurosciences, #1 Peripheral Vascular Disease, and #6 Multidisciplinary Sciences. Popular research clusters until 2022 were #2 Pharmacology & Pharmacy, #3 Medicine, General &Internal, #5 Biochemistry & Molecular Biology, and #7 Radiology, Nuclear Medicine & Medical Imaging, which are the hotspots in the exploration of ischemic stroke pathophysiology [61–65]. In general, the top 25 keywords, as well as their eight clusters, reflect a transition trend in ischemic stroke pathophysiology from the central system like cluster #0 Neurosciences to focusing on a holistic system like cluster #3 medicine, general & internal and mechanism-related keywords. Besides, #5 Biochemistry & Molecular Biology and #7 Radiology, Nuclear Medicine & Medical Imaging are also at the forefront of research in this field. However, there may be some problems regarding these two clusters (cluster #5 and cluster #7) as frontier research directions in ischemic stroke pathophysiology. In terms of #5 Biochemistry & Molecular Biology, excessive attention to the microscopic pathophysiology of ischemic stroke may ignore the overall pathophysiology process, resulting in biased conclusions drawn from studies. For #7 Radiology, Nuclear Medicine & Medical Imaging, most of the research of this part is still focused on central system research instead of holistic research, which lags behind the trend of ischemic stroke pathophysiology [66].

4.4. Trend and perspective

Based on the results of this present study, it can be inferred that the USA, the PRC, Germany, and England, as well as their respective academic institutions, are at the leading edge of ischemic stroke pathophysiology. This preeminent position is attributed to their establishment of large-scale stroke clinical trials and implementing related Brain Projects. The consistency of these research inputs with the published results of the article suggests that the research cycle in these countries and institutions has entered a virtuous cycle. This positive feedback model may serve as a valuable blueprint for other countries seeking to establish similar investigation systems in this field.

Nevertheless, the field of post-stroke pathophysiology has suffered from bottlenecks in its development. On the one hand, according to the hotspot analysis, there has been a decrease in the activity of high-quality journals and highly cited articles in this field since 2012. This decline suggests that in-depth studies on the pathophysiology of ischemic stroke have encountered technical challenges, which could be linked to the stagnation of high-throughput monitoring techniques used in the field of neurobiology in recent years. The result is consistent with the fact that clusters "#1 neuroscience" and "#2 peripheral vascular disease" are no longer considered hot categories after 2016. Moreover, "Pharmacology & Pharmacy," "Medicine, general & internal," and "Biochemistry & Molecular biology" have emerged as the frontier directions in this field. Whether the progress in these directions will lead to substantial breakthroughs in this area remains to be seen.

On the other hand, research in ischemic stroke pathophysiology requires novel investigative strategies. Most current clinical guidelines maintain that ischemic stroke is an acute cerebrovascular disease [1,3]. This statement has focused on the central nervous system in ischemic stroke investigations. However, the extent to which the patient recovers during the rehabilitation period is a decisive factor affecting the perspective of social burden and the patient's prognosis of quality of life [67–69]. Thus, it is warranted to acknowledge ischemic stroke as a systemic disease. For this objective to be achieved, more pathophysiological studies on the secondary damage induced by the CNS to peripheral organs after the acute phase should further be complemented in the knowledge system of ischemic stroke.

5. Conclusion

In conclusion, this study summarizes the progress in the pathophysiology of ischemic stroke over the past 30 years. Accordingly, we speculate that the application of multidisciplinary techniques in this field and the study of secondary damage to peripheral organs after the onset of ischemic stroke could become an increasing trend in the pathophysiology of ischemic stroke.

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Data availability statement

Data is contained within the article and supplementary material.

CRediT authorship contribution statement

Yiwen Bao: Writing – original draft. **Hu Qi:** Writing – original draft. **Dejian Wang:** Writing – original draft. **Meiling Ding:** Supervision. **Wenjing Li:** Supervision. **Li Chen:** Supervision. **Ziqin Lei:** Visualization. **Ruocong Yang:** Investigation, Data curation, Conceptualization. **Nan Zeng:** Writing – review & editing, Supervision, Formal analysis, 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.

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