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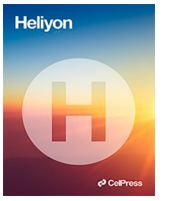

Research article

Bibliometric analysis of the gut microbiota and stroke from 2002 to 2022

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ABSTRACT

Stroke is the fifth leading cause of death worldwide, and the functional status of the gut plays a key role in patients' prognosis. Recent publications have explored the gut association with stroke, but few articles have been published that specifically address a comprehensive bibliometric analysis of the gut microbiota and its association with stroke. To address this gap, we used bibliometric methods to examine the landscape of research concerning the gut and stroke over approximately two decades, utilizing the Web of Science Core Collection (WoSCC). On November 1, 2022, a search was conducted for English-language articles published between 2002 and 2022, with only including original articles. Visual and statistical analyses were performed using CiteSpace, VOSviewer, and Bibliometrix 4.1.0 Package. After screening relevant articles, the results revealed that the number of articles published in this field has progressively increased during the last two decades. In particular, the total number of publications rapidly increased year by year from 2014. Among them, China ranked first in the world with a total of 227 publications. Authorship analysis highlighted Wang Z as the most prolific author, with 18 publications and an H-index of 14, highlighting significant contributions to this field. Meanwhile, the Southern Medical University of China was identified as the most productive institution. Moreover, analysis of keywords revealed that 'cerebral ischemia', 'intestinal microbiota', 'gut microbiota', and 'trimethylamine N-oxide' were popular topics searched, and research on the relationship between stroke and the gut continues to be a research hotspot. In summary, this study presents an overview of the progress and emerging trends in research on the relationship between stroke and gut health over the past two decades, providing a valuable resource for researchers aiming to understand the current state of the field and identify potential directions for future studies.

1. Introduction

Stroke is a cerebrovascular disease associated with a high mortality and disability rate worldwide. It is classified

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neuropathologically into two main types: ischemic and hemorrhagic strokes, with ischemic strokes constituting approximately 87 % of cases [1]. Ischemic stroke is a potentially fatal disease caused by narrowing or occlusion of the blood supply arteries to the brain, resulting in insufficient blood supply to the brain, and may eventually lead to necrosis of brain tissues and severe neurological symptoms [2]. In the peri-infarct area, although the cellular structures tend to be unchanged, the cellular functions become compromised. Thus, the potential for recovery exists if reperfusion to the tissue surrounding the infarct zone is promptly restored.

Ischemic strokes can also initiate a cascade of ischemic responses, culminating in neuronal dysfunction and cell death [3]. Effective stroke treatment options have long been lacking in clinical practice, and the only approved drug for the treatment for acute ischemic stroke is alteplase, a tissue plasminogen activator, which facilitates early arterial recanalization and reperfusion of ischemic tissues, thereby improving neurological outcomes. However, the therapeutic window for administering thrombolytic therapy is constrained to a brief period of 4–6 h post-stroke onset. Consequently, there exists a critical imperative to advance our understanding of the pathophysiological processes involved in ischemic stroke and to develop novel treatment strategies [4].

The gut and its microbiota are increasingly recognized as critical regulators of host health, either through direct interactions or via their metabolites [5]. In recent years, studies have established that the intestinal flora plays a significant role in the onset and progression of central nervous system disorders through the nervous, neuroendocrine, and immune systems [6]. Moreover, earlier investigations have highlighted the existence of bidirectional communication between the brain and the gut, encompassing the central nervous system, the autonomic nervous system and the enteric nervous system, which is known as the microbiome-gut-brain axis [7]. The relationship between gut microbiota and various neurological diseases has become a focal point of study. Gut microbiota has the potential to influence the host's metabolic state, including impacts on blood pressure, blood glucose levels, and atherosclerosis, all recognized risk factors for ischemic stroke. Additionally, intestinal bacteria may also play a role in determining outcomes following an ischemic stroke by modulating the immune system [8]. Although an increasing number of studies on the intestinal and gut-brain axis have found that the neurological, endocrine and immune systems respond to alterations in the bacterial flora and that these responses largely influence the occurrence and prognosis of ischemic stroke, the exact mechanism of action in ischemic stroke remains poorly understood.

The link between the gut and stroke has emerged as a significant area of interest in recent research. Despite this growing attention,

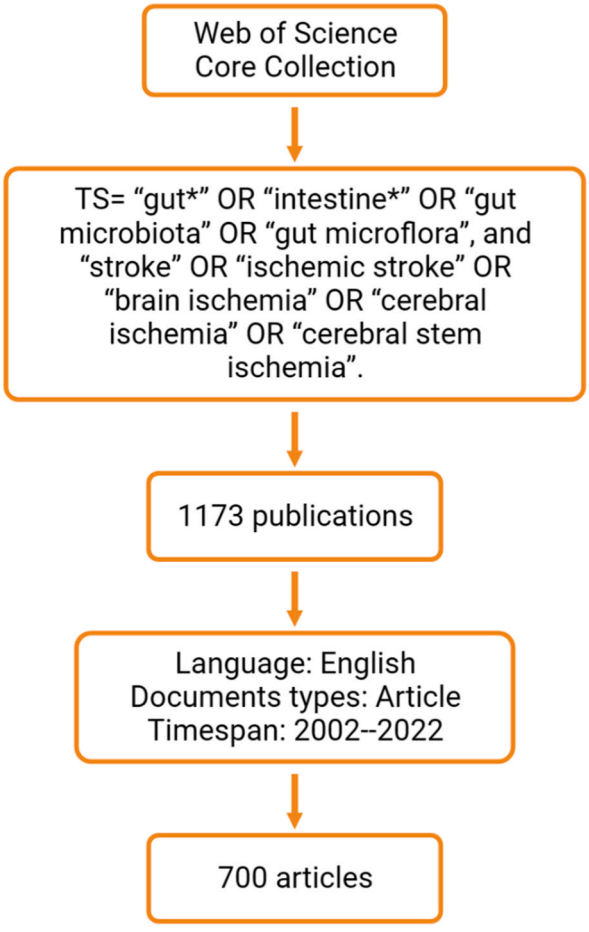

Fig. 1. The steps for the literature screening process.

there has not yet been a comprehensive and global assessment of the scientific research on this topic. Therefore, it is important to use advanced visualization techniques to outline the current research landscape, identify future research directions, and highlight key focus areas in the study of gut microbiota and stroke. Bibliometrics, a method widely used to analyze trends and patterns in various biomedical fields, provides clear insights by evaluating the contributions of countries, institutions, and authors, as well as the prevalence of certain keywords. For this purpose, we used tools such as VOSviewer and CiteSpace to perform a bibliometric analysis of the literature on gut health and stroke from 2002 to 2022 in this present study to systematically review and summarize the existing knowledge and trends, as well as offering guidance for future studies [9].

2. Materials and methods

2.1. Data collection and screening

A comprehensive literature search was conducted in the Web of Science Core Collection (WoSCC) (Clarivate Analytics, Boston, United States; https://www.webofscience.com/wos/woscc/basic-search) from January 1, 2002, to November 26, 2022, at Wuhan University. In order to obtain more accurate results, the following search terms were used: TS = "gut*" OR "intestine*" OR "gut microbiota" OR "gut microflora", and "stroke" OR "ischemic stroke" OR "brain ischemia" OR "cerebral ischemia" OR "cerebral stem ischemia". The search was limited to documents published in English, and only original articles were considered for inclusion. Data collection included the number of publications and citations, article titles, authors, affiliations, countries, keywords, journals, years of publication, and references. Ultimately, 700 original articles meeting the inclusion criteria were identified. A flowchart illustrating the entire search and selection process is presented in Fig. 1.

2.2. Statistical analysis

In this study, the bibliometric analysis was performed using CiteSpace (version 6.6.R2), VOS viewer (version 1.6.18.0), Excel 2019, and the Bibliometrix 4.1.0 Package (https://www.bibliometrix.org), which operates using the R programming language.

CiteSpace, developed at Drexel University (Philadelphia, PA, USA), is a Java-based bibliometric and visualization software designed for scientometric analysis and data visualization [10]. It can be used to construct a dual-map overlay of journals and detect references and keywords with strong bursts [11]. These bursts of keywords and references are typically used to detect new research trends in a specific research field [12]. The specific settings used in CiteSpace were as follows: the analysis was divided into annual segments (time slicing) over a period from 2002 to 2022, with all other parameters maintained at their default values.

The Bibliometrix package, an established tool for bibliometric analysis based on R, facilitates a comprehensive understanding of seminal works, leading researchers, and future trends within a given field of study [13]. Utilizing this program, researchers can rapidly identify key literature and contributors in their area of interest and effectively visualize research outcomes.

VOS viewer (Leiden University, Leiden, Netherlands, https://www.vosviewer.com) can be used to generate various bibliometric relationship-based graphs, such as author or journal co-citation relationship maps, keyword co-occurrence relationship maps, etc. [14] In the network maps generated by VOSviewer, different nodes symbolize various entities, including nations/regions, organizations, and journals. The size of each node indicates the frequency of co-occurrence, while the lines connecting nodes depict the associations between these occurrences [15].

Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, United States) was used to evaluate the top 10 countries, institutions and authors for the number of published articles, as well as the top 10 cited articles and references. In addition, international cooperation networks were examined using an online bibliometric platform (https://bibliometric.com).

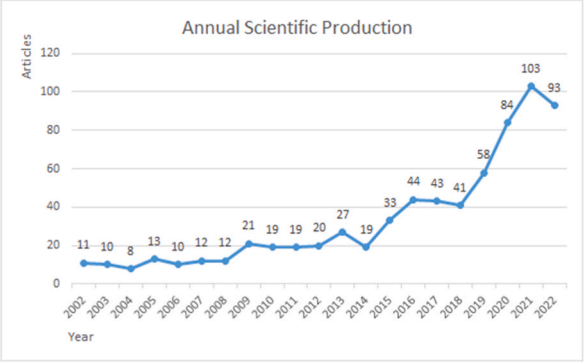

Fig. 2. Annual scientific production.

3. Results

3.1. Analysis of publication trends

Our results showed that a total of 700 articles meeting the inclusion criteria were published between 2002 and 2022. Fig. 2 illustrates the overall increasing trend in the number of publications in the last two decades, although it fluctuated during a certain time period. In the last two decades, two specific trends can be observed in the volume of publications: firstly, there was a general fluctuating trend in the volume of publications and a low total number of articles published until 2014. Then, the number of published articles per year rapidly increased after 2014, highlighting a growing global interest in the interplay between gut health and ischemic stroke. The concept of a connection between the brain and the gut was first proposed in the late 18th century, but it initially garnered minimal attention. The advent and advancement of metabolomics and sequencing technologies, particularly 16s rRNA gene sequencing, have since facilitated deeper investigations into gut microbes and their metabolites. A pivotal moment occurred in 2014 with the publication of a significant study in the New England Journal titled "Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk." [16] This study monitored 4007 patients undergoing elective coronary angiography for up to three years to explore the potential link between fasting plasma levels of Trimethylamine N-oxide (TMAO) and the incidence of major adverse cardiovascular events, finding a correlation between elevated TMAO levels and increased cardiovascular risk, which spurred a surge in research focusing on TMAO. Subsequently, in 2016, discoveries were made regarding the presence of ectopic gut-derived microbes post-stroke [17]. That same year, Corinne Benakis and colleagues established a connection between the immune response, gut flora, and stroke outcomes [8]. In 2017, a study published in Nature titled "Endothelial TLR4 and the microbiome drive cerebral cavernous malformations" enriched the discussion on the brain-gut axis by demonstrating the significant roles of endothelial Toll-like receptor 4

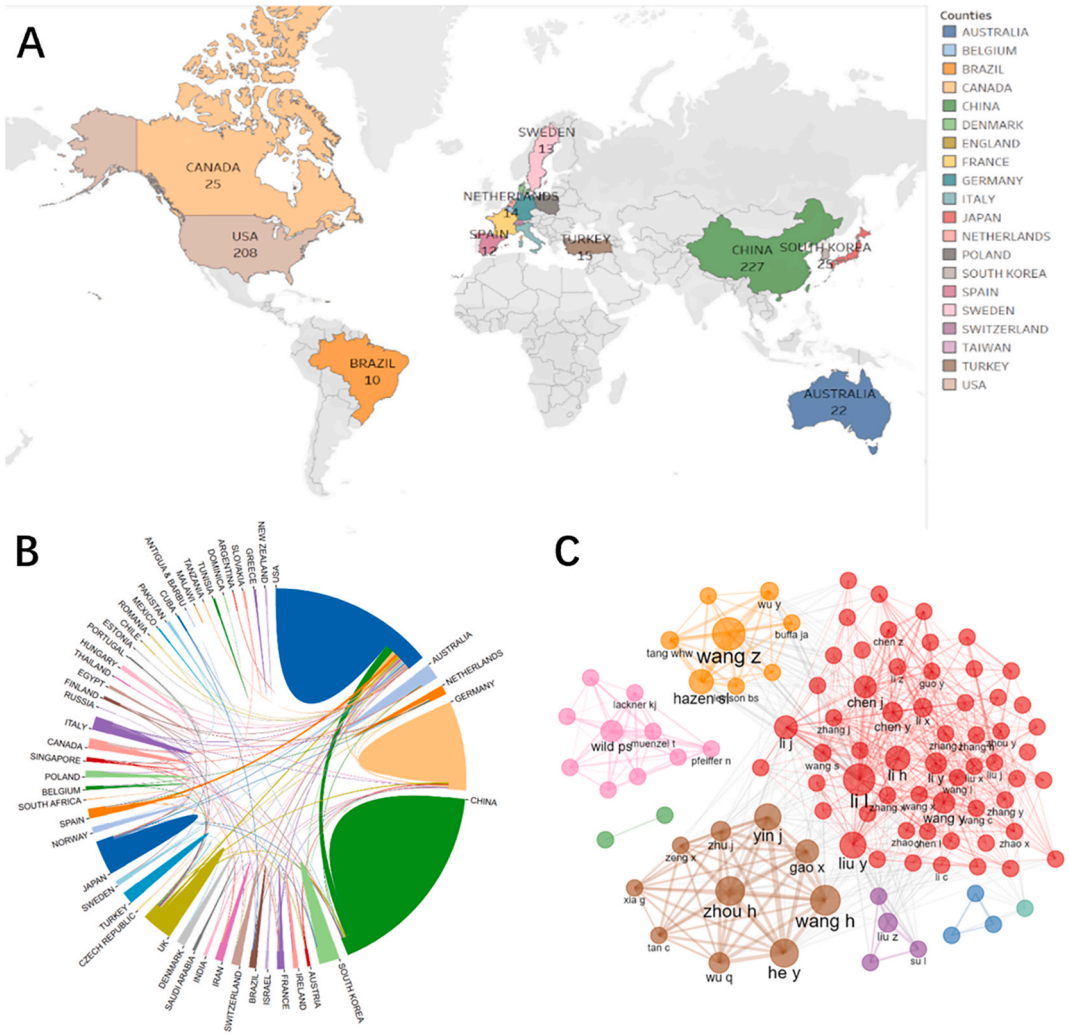

Fig. 3. Analysis by country and author. (A) The annual publication was indexed in the WOSCC from 2002 to 2022 by an online bibliometric analysis. The article number of the top 20 countries was presented. (B) Cooperation between countries. (C) Cooperation between authors.

(TLR4) and gut bacteria in the development of Cerebral Cavernous Malformations (CCMs).

The increasing volume of literature from 2018 onwards suggests that the exploration of gut health and its impact on stroke remains a hot and expanding field of research, indicating its continuing relevance and potential for future discoveries.

3.2. Analysis of countries

The bibliometric analysis revealed that 58 countries and regions around the globe contributed to the collection of 700 articles on the topic. The top five contributors by the number of publications were China (n = 227), the United States (n = 208), Germany (n = 66), the United Kingdom (n = 56), and Japan (n = 39) (Fig. 3A, Table 1). Early research efforts were predominantly seen in countries like the United States, the United Kingdom, and Canada. China entered this research domain around 2004 and, by approximately 2017, had surpassed the United States in the total number of publications, positioning itself as the leading country in this research area. The concept of "between centrality" is often used to gauge the influence or importance of a country's contributions within a research network. According to the data (Table 1), although the United States published fewer articles than China, it achieved the highest between centrality score, indicating that research articles from the United States might have had a marginally higher impact or quality compared to those from China. Based on the volume of publications, China and the United States are the most active countries in this field of research. The geographical distribution of research indicates a concentration of activity in developed countries (Fig. 3A), suggesting a correlation between a country's development status and its scientific output in this area. Fig. 3B illustrates the international collaboration network, with the size of each sector representing the volume of publications from each country. A larger sector size corresponds to a greater number of publications. The thickness of the lines between countries signifies the level of collaboration; denser lines indicate more extensive cooperation. Notably, the United States emerged as having the most extensive international collaborations, with China and the United States being each other's largest collaborators.

3.3. Analysis of the author and institutions

Analysis of authorship among the 700 identified articles reveals significant contributions from a diverse group of 3797 researchers, highlighting the global engagement in the intersection of stroke and intestinal health research. Wang Z was identified as the most productive author, with a total of 18 publications, closely followed by Li H, Li X, and Chen Y, each with 17 publications. Notably, Wang Z also emerged as the most influential author, with an H-index of 14, underscoring the impact of contributions to the field. A significant observation is the prominent representation of Chinese authors among the top contributors, which aligns with the broader trend of China's substantial involvement in this area of research (Table 2).

Several academic groups have emerged in the field of stroke and intestinal research. Cluster analysis revealed four distinct groups based on cooperative relationships among relevant authors (Fig. 3C). Within these groups, notable collaborations, such as between Liu Y and Chen Y, were identified. Furthermore, active collaborations were observed between clusters, such as the partnership between Zhou Y and Liu J. As listed in Table 3, the top 10 publications were from China, Germany, and the United States. Moreover, we observed that the three institutions with the highest number of publications were Southern Medical University in China with 114 articles, Johannes Gutenberg University in Germany with 86 articles, and Wenzhou Medical University in China with 50 articles.

3.4. Articles citation analysis

A citation analysis of 700 articles conducted using VOSviewer software revealed that 269 articles had been cited more than 20 times. The most cited article, published in 2013 by Koeth et al. [18], titled "Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis" in Nature Medicine, had a total of 2502 citations (Table 4). This study elucidated how microorganisms residing in the human gut are influenced by long-term dietary patterns. It demonstrated that diets rich in carnosine can alter the composition of gut bacteria, leading to the conversion of carnosine into TMAO, which in turn increases the risk of atherosclerosis, an independent risk factor for stroke.

Table 1
Total number of publications in the top 10 countries.

Rank	Year	Counties	Count	Percentage
1	2004	CHINA	227	32.15 %
2	2002	USA	208	29.46 %
3	2003	GERMANY	66	9.35 %
4	2002	ENGLAND	56	7.93 %
5	2003	JAPAN	39	5.52 %
6	2002	CANADA	25	3.54 %
7	2004	SOUTH KOREA	25	3.54 %
8	2004	ITALY	23	3.26 %
9	2003	AUSTRALIA	22	3.12 %
10	2002	TURKEY	15	2.12 %

Table 2
The number of publications by the top 10 authors.

Rank	Author	H-index	Article count	Affiliation
1	Wang Z	14	18	Metabolic Sciences, Lerner Research Institute, USA
2	LI H	9	17	Capital Medical University, China
3	LI X	8	17	China Pharmaceutical University, China
4	CHEN Y	8	17	Peking Union Medical College, China
5	LI J	9	16	Peking Union Medical College, China
6	LI L	12	16	Beijing Chaoyang Integrative Medicine Emergency Medical Center, China
7	LIU Y	11	15	Xi'an Jiao Tong University, China
8	WANG H	10	14	Southern Medical University, China
9	WANG Y	7	14	Peking Union Medical College, China
10	LI Y	9	14	Harbin Medical University, China

Table 3
Top 10 most productive organizations.

Rank	Affiliation	Counties	Articles	Percentage
1	SOUTHERN MED UNIV	China	114	23.75 %
2	JOHANNES GUTENBERG UNIV MAINZ	Germany	86	17.92 %
3	WENZHOU MED UNIV	China	50	10.42 %
4	PEKING UNIV	China	43	8.96 %
5	UNIV MED CTR MAINZ	Germany	41	8.54 %
6	BAYLOR COLL MED	America	33	6.88 %
7	ZHEJIANG UNIV	China	33	6.88 %
8	SHANDONG UNIV	China	29	6.04 %
9	SHANGHAI JIAO TONG UNIV	China	26	5.42 %
10	UNIV FLORIDA	America	25	5.21 %

Table 4
The 10 most cited documents from 2002 to 2022.

Rank	Title	First author	Journal	Year	Citation
1	Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis	Robert A Koeth	Nature Medicine	2013	2502
2	Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk	W.H. Wilson Tang	The New England Journal of Medicine	2013	1889
3	Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk	WeifeiZhu	Cell	2016	908
4	Human metabolic phenotype diversity and its association with diet and blood pressure	Elaine Holmes	Nature	2008	793
5	Goal-directed Intraoperative Fluid Administration Reduces Length of Hospital Stay after Major Surgery	Tong J. Gan	Anesthesiology	2002	652
6	Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells	Corinne Benakis	Nature Medicine	2016	507
7	Liberal or Restrictive Transfusion after Cardiac Surgery	Gavin J. Murphy	The New England Journal of Medicine	2015	497
8	Influence of maternal obesity on the long-term health of offspring	ProfKeith Mgodfrey	The Lancet	2017	456
9	Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery	H.G.Wakeling	British Journal of Anaesthesia	2005	431
10	Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-N-oxide	Zeneng Wang	European Heart Journal	2014	393

3.5. Reference citation analysis

A co-citation analysis of the cited references was conducted to assess the citation frequency of publications. Co-cited references are those simultaneously cited by one or more publications on a specific topic [19]. Table 5 presents the top 10 co-cited references. The article by Benakis C et al. [8] in Nature Medicine received the highest number of citations, followed by the works of Singh V et al. [20] in the Journal of Neuroscience and Wang Z et al. [21] in Cell. Notably, these findings align with the analysis results presented in Table 6.

Analyzing references with significant citation bursts can shed light on how research interests have shifted over time and indicate potential future directions in a specific field [22]. Fig. 4 shows the top 10 references with the most pronounced citation bursts. Yin J et al. [23] achieved the highest burst strength of 7.05 for articles published between 2019 and 2020, which indicates a surge in citations for numerous references, suggesting a shifting trend.

Table 5
Top 10 co-citations of cited references from 2002 to 2022.

Rank	Cited References	Citations	DOI
1	BENAKIS C, 2016, NAT MED, V22, P516	79	DOI 10.1038/NM.4068
2	SINGH V, 2016, J NEUROSCI, V36, P7428	78	DOI 10.1523/JNEUROSCI.1114-16.2016
3	WANG ZN, 2011, NATURE, V472, P57	75	DOI 10.1038/NATURE09922
4	YIN J, 2015, J AM HEART ASSOC, V4	68	DOI 10.1161/JAHA.115.002699
5	TANG WHW, 2013, NEW ENGL J MED, V368, P1575	64	DOI 10.1056/NEJMOA1109400
6	KOETH RA, 2013, NAT MED, V19, P576	60	DOI 10.1038/NM.3145
7	ZHU WF, 2016, CELL, V165, P111	54	DOI 10.1016/J.CELL.2016.02.011
8	STANLEY D, 2016, NAT MED, V22, P1277	46	DOI 10.1038/NM.4194
9	SPYCHALA MS, 2018, ANN NEUROL, V84, P23	36	DOI 10.1002/ANA.25250
10	CAPORASO JG, 2010, NAT METHODS, V7, P335	35	DOI 10.1038/NMETH.F.303

Table 6
The top ten most cited articles.

Rank	Document	DOI	Citations
1	BENAKIS C, 2016, NAT MED	10.1038/nm.4068	78
2	SINGH V, 2016, J NEUROSCI	10.1523/JNEUROSCI.1114-16.2016	77
3	YIN J, 2015, J AM HEART ASSOC	10.1161/JAHA.115.002699	66
4	KOETH RA, 2013, NAT MED	10.1038/nm.3145	58
5	STANLEY D, 2016, NAT MED	10.1038/nm.4194	45
6	SPYCHALA MS, 2018, ANN NEUROL	10.1002/ana.25250	36
7	YAMASHIRO K, 2017, PLOS ONE	10.1371/journal.pone.0171521	30
8	WINEK K, 2016, STROKE	10.1161/STROKEAHA.115.011800	26
9	HOULDEN A, 2016, BRAIN BEHAV IMMUN	10.1016/j.bbi.2016.04.003	25
10	XIA GH, 2019, FRONT NEUROL	10.3389/fneur.2019.00397	25

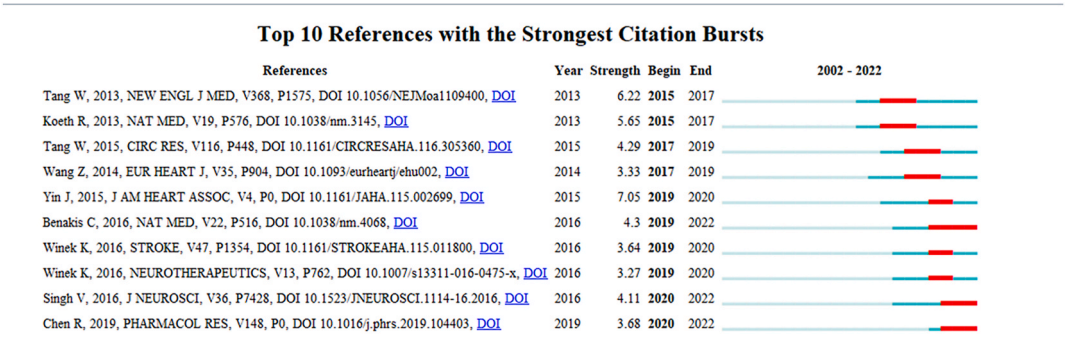

Fig. 4. Top 10 references with the strongest citation bursts. The timeline represents the year in which the reference appeared burst. Strength indicates the intensity of burst.

3.6. Journals analysis

The double mapping overlay of journals illustrated the thematic relationships among journals, with citing journals positioned on the left side of the map and cited journals on the right. There were four main citation pathways identified in Fig. 5. The two paths highlighted in green indicated that research from health, nursing and medicine journals, as well as papers from molecular biology and genetics journals, were frequently cited by journals in the medical, clinical and medicinal fields. Conversely, the two paths marked in orange showed that articles from molecular biology and immunology journals were commonly cited by journals in molecular biology, genetics, health, nursing, and medicine. Overall, the research landscape in this area was primarily composed of studies in molecular biology, immunology, and medical disciplines.

Academic journals are an essential platform for sharing the findings of scientific studies. Among the 700 papers reviewed, they were distributed across 412 distinct journals. Utilizing VOSviewer, an analysis was performed on these journals with the criteria set to include only those with a minimum of two papers relevant to the study area, ranging from 2002 to 2022. In this analysis, a total of 129 journals were examined. The visualization presented in the figure uses circle sizes to indicate the number of articles published by each journal. PLOS ONE was identified as the leading journal, with a total of 11 articles. Additionally, the Frontiers series of journals also played a significant role in this field, with Frontiers in Neurology publishing 8 articles, and both Frontiers in Pharmacology and Frontiers in Neuroscience each publishing 10 articles. These results can guide future researchers to consider these journals when seeking publication opportunities for their work on related topics (Fig. 6).

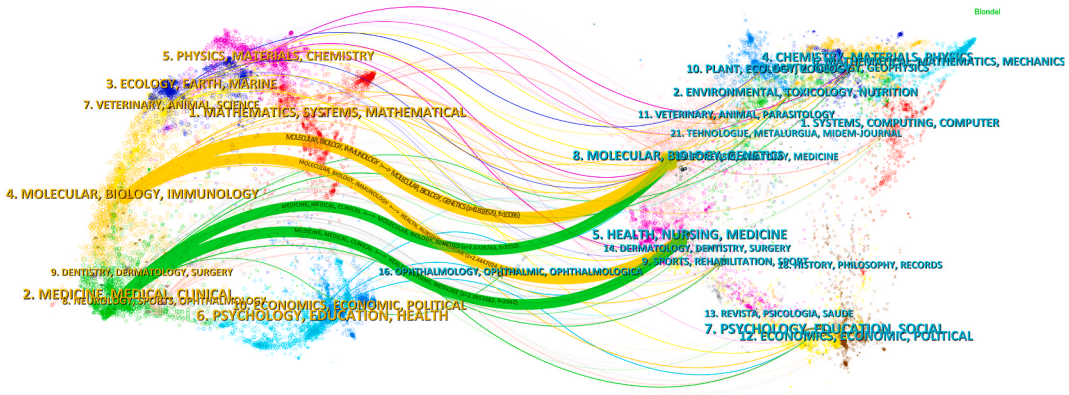

Fig. 5. The dual-map overlay of journals. The citing journals are located on the left side of the map, whereas the cited journals are located on the right side. The map shows the four primary citation pathways.

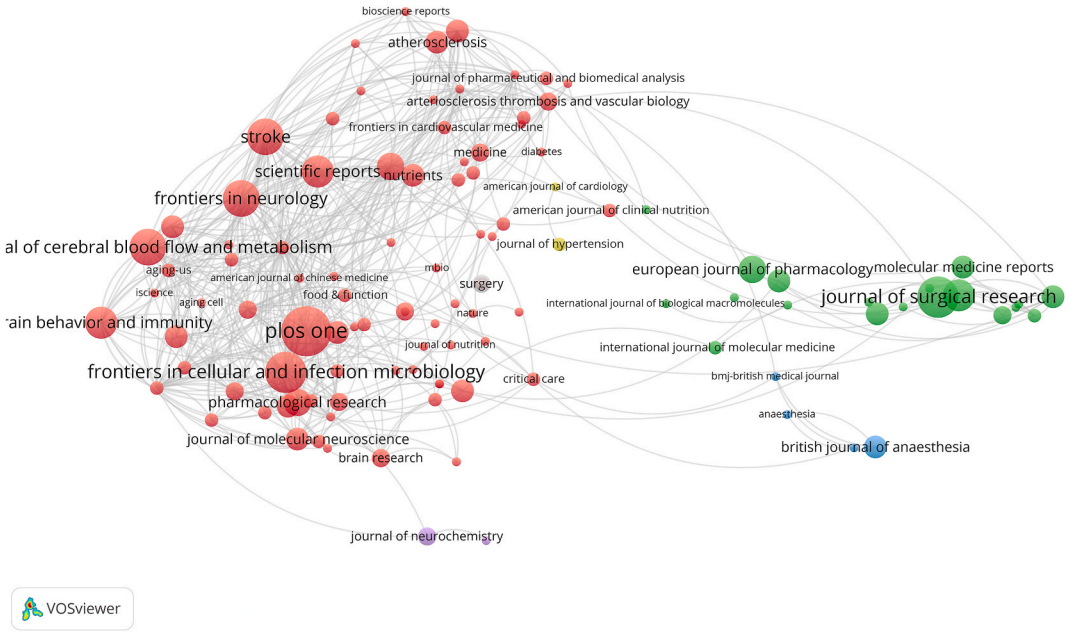

Fig. 6. Journal analysis. The circles represent different journals. The size of the circle represents how many articles the journal has published. The color of the circle indicates clustering of journals based on article content. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.7. Analysis of keywords

The analysis of keyword co-occurrences serves as a pivotal tool for identifying hot topics within a research domain [24], facilitating the prediction of research trends and content directions based on the affinity between words. From a dataset comprising 6284 keywords, 117 were identified, with occurrences surpassing the threshold of 10. The visualization of keyword co-occurrence and cluster analysis, as shown in Fig. 7A, uses node sizes to reflect the frequency of keyword occurrences, with larger nodes signifying higher frequencies. The interconnecting lines between nodes illustrate the correlation levels between keywords, with the strength of these links indicating the degree of keyword co-occurrence. Based on the strength of keyword co-occurrence links, this study clustered keywords appearing more than 10 times into four distinct groups, with each group denoted by a specific color. These clusters represent divergent research directions within the field. Notably, the keywords with the highest frequency of co-occurrence were “stroke” (187 occurrences), “gut microbiota” (140 occurrences), and “inflammation” (86 occurrences). These keywords indicate their fundamental role in driving the progression and focus of research in this discipline and contribution to the field’s development.

The density of keyword co-occurrence serves as an effective indicator of current research hotspots, with areas of greater brightness signifying more intense research activity. Fig. 7B demonstrates that “stroke,” “gut microbiota,” and “inflammation” were the primary

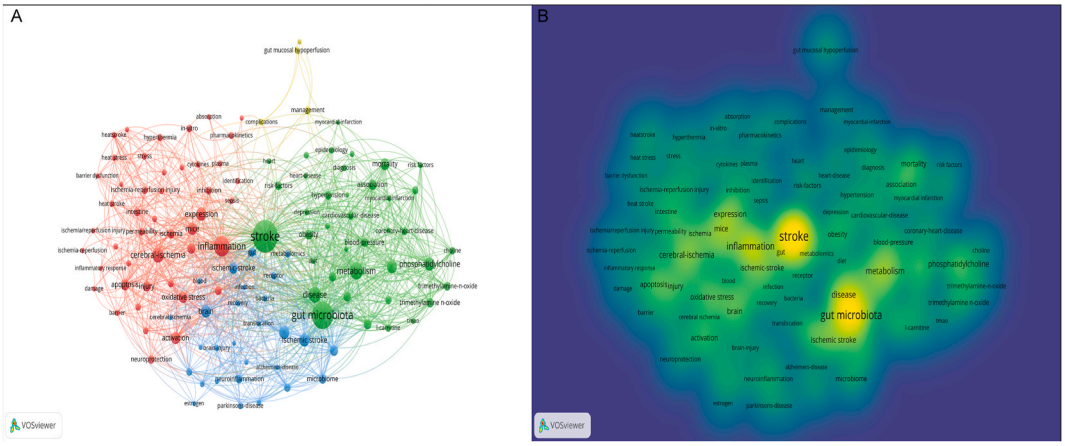

Fig. 7. Analysis of keywords co-occurrence. (A) Keyword co-occurrence map. Circles represent different keywords. The size of the circle represents the frequency of co-occurrence of the keyword. The colors of the circles indicate different types of keywords. (B) Keywords co-occurrence density visualization. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

focal points of current research, which aligns with the findings shown in Fig. 7A. Thus, it can be confirmed that the keywords "stroke," "gut microbiota," and "inflammation" represent the core themes and hot topics in gut and stroke research.

Keyword burst analysis, which identifies terms that surge in frequency over a specified time frame, pinpoints emerging topics in a research field. This approach is based on the analysis of keyword co-occurrences, offering a graphical depiction of the shifts in research focus, thereby identifying both current and evolving hotspots and frontiers. It also evaluates the intensity and temporal spread of keyword occurrences, providing insights into the research domain's evolving trends and pioneering areas over selected periods. Fig. 8 presents a detailed visualization of when keywords first emerged and the periods during which they experienced significant bursts. It highlights the top 15 keywords with the most substantial citation bursts related to the study of gut microbiota in stroke from 2002 to 2022. 'Cerebral ischemia' stands out with the highest burst intensity of 8.5, first appearing in 2003 and maintaining relevance until 2015. Moreover, the continuous study of terms like 'phosphatidylcholine,' 'intestinal microbiota,' 'gut microbiota,' and 'trimethylamine n-oxide' up to 2022 signifies their ongoing importance in current research.

A time-zone view of keyword co-occurrence was also developed (Fig. 9) to assist in the visualization of the hotspots and directions of the phased study from the time dimension.

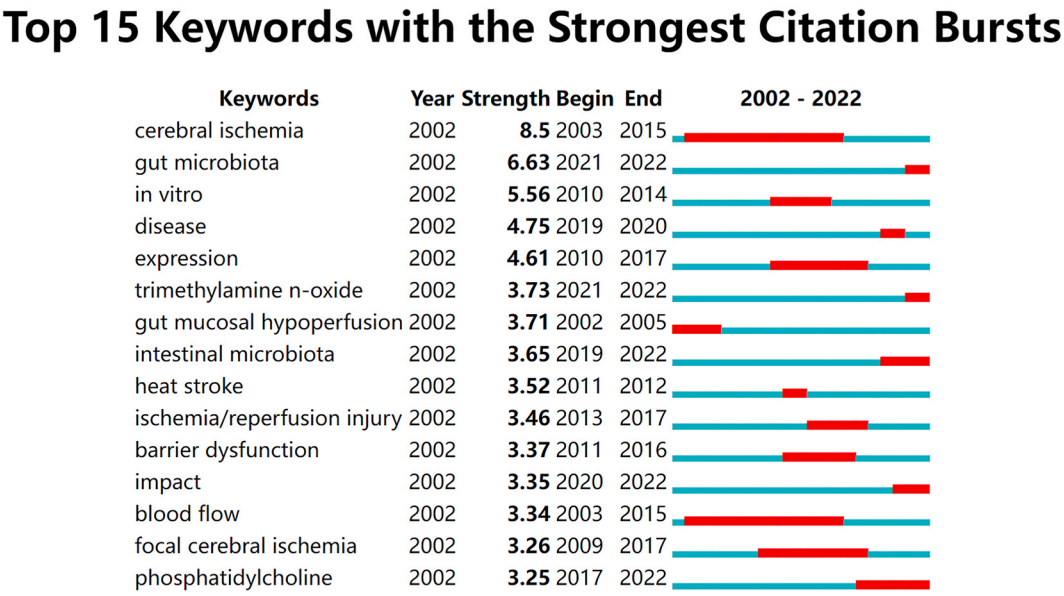

Fig. 8. Top 15 keywords with the strongest citation bursts related to gut microbiota in stroke.

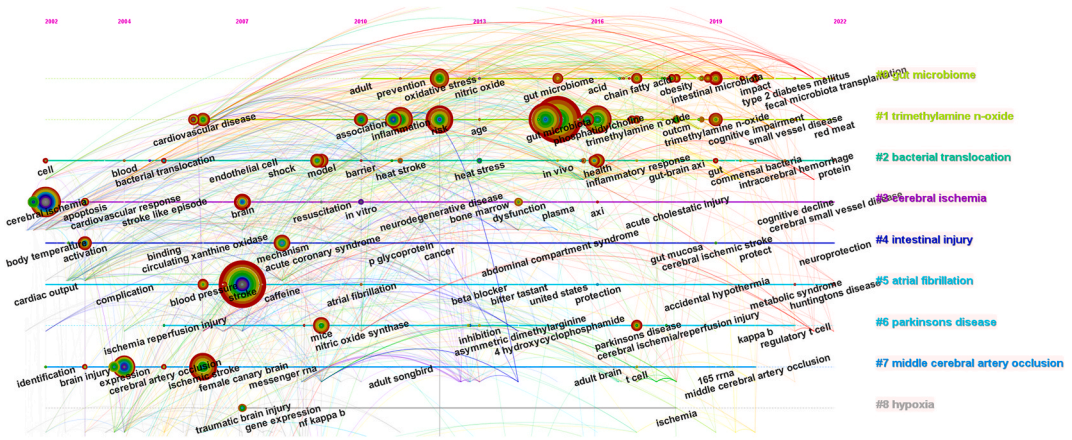

Fig. 9. Time-zone view of keyword co-occurrence related to gut microbiota in stroke. (2002–2022).

4. Discussion

The rising incidence of stroke, increasingly affecting younger populations, has escalated into a global health crisis [4]. Concurrently, the gut, often referred to as the second brain, has been linked to a broad spectrum of diseases through the concept of the brain-gut axis [25]. This axis, a bidirectional neurohumoral communication system between the nervous system and the gastrointestinal tract, is crucial in disease development, including stroke [26]. Using a bibliometric analysis based on the WoSCC database, combined with Citespace, VOSviewer and bibliometric tools, this study systematically analyzes data on countries, institutions, authors, keywords, journals and references, with the aim to map out the principal research themes, identify the focal points of current investigations, and forecast emerging trends in the nexus between gut health and stroke. Overall, this investigation represents the first effort to assess the gut-stroke relationship through bibliometric methodologies.

Assessment of the WoSCC database from 2002 to 2022 identified 700 articles from 58 countries and regions focused on ischemic stroke and intestinal flora. The trend analysis indicates a significant surge in research interest in this area starting from 2002, with a notable increase after 2014, which marks the integration of intestinal flora studies into ischemic stroke research, highlighting its emerging significance in treatment methodologies. The sustained growth in publications underscores the high interest in this field, projecting its continued relevance and expanding research focus in the years ahead. To perform a more thorough bibliometric study on the relationship between gut microbiota and stroke, we selected the literature from 2002 to 2022. Employing advanced analysis technologies, including CiteSpace, VOSviewer, and the Bibliometrix 4.1.0 Package, this study assessed the evolving trends of publications in this domain. The analysis extends beyond merely tracking the annual publication count; it also explores the underlying factors driving the observed trends. Our findings reveal a significant increase in the volume of research articles on gut microbiota and stroke as from 2014. The advancement of metabolomics and sequencing technologies, particularly the use of 16s rRNA gene sequencing, has provided valuable tools for investigating the gut microbiota and its metabolites. This field gained significant attention following the publication of a pivotal study in the New England Journal of Medicine titled “Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk,” which highlighted the link between gut microbiota metabolites and cardiovascular disease. Subsequently, research into the gut microbiota, especially its metabolites, in relation to stroke has rapidly increased. Analysis of publication trends and the underlying reasons reveals that the advent and adoption of new technologies play a crucial role in the emergence of new research areas. Thus, for researchers, the exploration of experimental technologies remains a key focus. The time-zone view of keyword co-occurrence offers insights beyond those provided by keyword bursts, allowing us to not only identify the periods during which certain keywords were most frequent but also to observe the frequency of these keywords during peak years and their relationships with other terms. From this perspective, we observed that before 2013, research predominantly concentrated on traditional stroke-related topics such as oxidative stress, inflammation and NF-kB pathways. Although there were investigations into bacterial translocation, this topic was not comprehensively investigated. Since 2013, there has been a notable increase in studies focusing on the gut microbiota, aligning with our analysis of publication trends and the growing interest in topics such as gut microbiota, phosphatidylcholine, TMAO, and short-chain fatty acids (SCFAs). The time-zone view of keyword co-occurrence and cluster analysis over the past decade identified nine key research clusters, with gut microbiome, phosphatidylcholine, TMAO, and bacterial translocation emerging as the top clusters. This indicates a research shift towards the gut microbiota and its metabolites, particularly TMAO, with bacterial translocation also highlighted as a significant area of interest for ischemic stroke research. The insights gained from this analysis suggest that future research should concentrate on a more in-depth examination of gut flora metabolites and the identification of metabolites that are significant for stroke treatment or diagnosis. This direction necessitates advancements in analytical technology, similar to the breakthroughs enabled by the advent of 16s rRNA gene sequencing technology, which revolutionized the study of gut flora.

The visual data analysis indicates that China and the United States have been the leading contributors to research on the impact of gut health on ischemic stroke. Notably, China was the only developing nation among the top 10 contributing countries, with 227

articles published in this domain from 2002 to 2022, which could be reflective of China's economic and scientific strength. The United States, being the world's leading developed nation, is equipped with the most sophisticated scientific research infrastructure and hosts a vast community of medical researchers globally. On the other hand, China, as one of the world's most rapidly advancing countries, has seen its government make significant efforts to improve its scientific sector in recent years. The visualization tool CiteSpace highlighted the contributions of authors and institutions in gut microbiota and stroke research. Among the 3797 researchers identified, Wang Z, Li H, Li X, Chen Y and Li J were the most productive authors globally and had significant collaboration among themselves. The analysis also identified approximately 1258 institutions worldwide in this research area. The Southern Medical University in China was distinguished as the leading institution with a total of 114 publications. Remarkably, six of the top ten institutions with the most publications were based in China, underscoring the country's growing focus on this research domain. Most of these leading Chinese institutions are situated in major economic zones such as Beijing, Zhejiang, and Shanghai, hinting at the considerable experimental funding likely required for research in this field. The investigation into intestinal flora often necessitates advanced sequencing and multi-omics approaches, which are more expensive than traditional experimental methods, highlighting the importance of ongoing innovation in methodologies for studying gut microbiota. A visual analysis of the distribution of journal types indicated a primary association with the fields of medicine, molecular biology, and immunology. The frequency of citations of scientific articles often reflects their significance within their respective domains. Thus, using VOSviewer software, the 10 most cited articles between 2002 and 2022 were examined. The article titled "Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells," [8] published in Nature Medicine in 2016, emerged as the most cited work. It revealed the microbiota-gut-brain axis, marking the first demonstration of how gut microbes can affect the prognosis of ischemic stroke by modulating intestinal γδ T cells. The emergence of specific keywords such as 'phosphatidylcholine,' 'intestinal microbiota,' 'gut microbiota,' and 'trimethylamine n-oxide' signifies evolving research interests. A recent nested case-control study highlighted an association between elevated TMAO levels and increased stroke risk. Conversely, no significant relationship was observed between TMAO precursors (carnitine, choline, betaine, and TML) and stroke risk in one study [27], while another study contradicted these findings, showing an inverse correlation between plasma levels of choline and betaine and cognitive impairment in 617 patients with cognitive issues and acute ischemic stroke [28] Therefore, the analysis of keywords can guide researchers to effectively target research directions for future clinical trials.

The analysis of citations identified in Table 4 highlights the top 10 cited articles in the field. Notably, the study "Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis," published in Nature Medicine, ranks as the most cited, underscoring its pivotal role in this research area. This groundbreaking work was the first to link dietary L-carnitine consumption to accelerated atherosclerosis in mice, mediated by the gut microbiota's metabolism to produce TMAO. This finding aligns with the insights from "Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk," which implicated dietary phosphatidylcholine in TMAO production, reliant on gut microbiota metabolism, and associated elevated TMAO levels with a heightened risk of major adverse cardiovascular events. Further analysis of the publication years of the most highly cited articles reveals an initial focus on metabolites, particularly TMAO. Over time, research has broadened to explore the links between gut microbiota and neuroinflammation. A significant contribution to this expanding research landscape was made in 2016 with a publication in Nature Medicine, titled "Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells." This study marked a pioneering discovery that dysbiosis in the gut microbiota can influence ischemic brain injury by modulating dendritic cell activity, leading to an increase in regulatory T cells and a reduction in interleukin (IL)-17-positive γδT cells.

The bibliometric analysis highlights that recent research has increasingly focused on intestinal flora, immunity, and metabolites. A significant pathway facilitating communication between gut flora and the brain is the immune pathway. The gut flora and its metabolites exert a profound influence not just on the gut's local immune microenvironment but also on the development, maturation, and functionality of the brain's immune cells, microglia. Moreover, the presence of neuroinflammation can alter the intestinal flora's composition, indicating a complex interaction where a dysregulated gut flora can intensify the neuroimmune response. Consequently, targeting the intestinal flora-immune pathway emerges as a promising strategy for enhancing stroke prognosis. The development of stroke is intricately linked to the intestinal flora, underscoring a bidirectional communication channel known as the "microbe-gut-brain axis" [25].

The intestinal microbiota significantly influences the inflammatory and immune responses following ischemic stroke. Such events alter the microbiota's composition and functionality, consequently modifying the intestinal environment [29]. Enterobacteriaceae, a group of pathogenic bacteria, are implicated in elevating inflammatory mediator levels in the bloodstream and initiating immune responses [30]. An increased presence of Enterobacteriaceae marks a distinctive alteration in the gut microbiota after acute stroke [31]. Furthermore, dysregulation of the gut microbiota can be observed after a stroke, characterized by a reduction in beneficial bacteria like bifidobacteria and an increase in detrimental bacteria, including enterococci. This imbalance amplifies the production and activity of inflammatory agents, adversely affecting stroke outcomes [32]. Additionally, stroke-induced enhanced intestinal permeability may facilitate the translocation of gut bacteria. Immunogenic components such as lipopolysaccharide (LPS), derived from the gut microbiota, are known to exacerbate neuroinflammation by driving the infiltration of peripheral immune cells into the brain [33]. Studies indicate that fecal flora transplantation (FMT) to restore the normal gut microbiota in stroke patients can significantly improve their prognosis [34]. For instance, Chen et al. demonstrated that FMT provides neuroprotection in mouse ischemic stroke models by modifying the gut microbiota, subsequently reducing neurological deficits, brain edema, and infarct volume [35]. Additionally, age significantly influences stroke prognosis. Spychala MS et al. reported that gut microbiota from young mice lessened the extent of brain damage post-MCAO in older mice, whereas microbiota from older mice worsened brain damage in young mice after MCAO [36]. Kaiyu Xu et al. explored the dynamics of gut microbiota dysbiosis and its association with stroke prognosis through 16SrRNA sequencing in two distinct cohorts of patients with ischemic stroke. Their research identified significant enrichments in Enterobacteriaceae, Ruminococcaceae, Veillonellaceae, and Lachnospiraceae after stroke, with Enterobacteriaceae emerging as an

independent risk factor for stroke. Following these findings, they utilized a mouse MCAO model to investigate the specific molecular mechanisms involved. They found that cerebral ischemia promptly causes intestinal ischemia, leading to an overproduction of nitrate through free radical reactions, which results in dysbiosis of the gut microbiota. This dysbiosis, characterized by the enrichment of Enterobacteriaceae, aggravates cerebral infarction by enhancing systemic inflammation, thereby constituting an independent risk factor for adverse prognosis in stroke patients [31]. Hemorrhagic transformation (HT) is identified as a severe post-stroke complication [37]. In a preclinical investigation into the gut microbiome's role in HT following stroke, it was found that the gut of HT rats exhibited a higher relative abundance of Aspergillus and Actinobacteria compared to non-HT rats. Additionally, metabolite analysis revealed reduced concentrations of butyrate and valeric acid in the cecum of HT rats. Gender differences also appear to indirectly influence stroke outcomes through alterations in the gut microbiota. Fecal transplantation experiments showed that male mice receiving gut flora from female mice exhibited lower inflammation levels post-stroke [38]. Furthermore, the stroke-induced decrease in gut microbiota abundance and diversity could be counteracted by administering a moderately reduced protein diet (PRD) containing 8 % protein to mice subjected to MCAO [39]. Prebiotics have been shown to improve stroke outcomes by modifying the gut microbiota and its metabolites. Specifically, Puerariae Lobatae Radix-resistant starch (PLR-RS), a novel prebiotic, was found to increase the populations of Akkermansia and Bifidobacterium in post-stroke mice. PLR-RS also enhanced the production of melatonin by the gut flora, offering protective effects against ischemic stroke damage [40].

The gut microbiota harbors numerous immune cells, including Peyer's patches (PP) and lamina propria (LP) immune cells, which play a critical role in stroke development [41]. Post-stroke, there is an increase in γδ T cells within the intestine, which migrate to the meninges, amplifying the inflammatory response through the production of interleukin-17 (IL-17) [8]. Moreover, regulatory T cells (Treg) contribute to the protection of post-ischemic brain tissue by dampening inflammation, inhibiting lesion progression, and facilitating tissue repair [42]. These cells also provide neuroprotection against stroke by emitting cytokines such as IL-10 and IL-33, encouraging a shift in microglia towards an M2 phenotype. Consequently, M2 microglia release IL-10 and TGF-β, enhancing Treg cell polarization, thereby establishing a beneficial cycle that mitigates neuroinflammatory reactions [43]. Additionally, Tregs prevent the differentiation of IL-17-producing Th17 cells, preserving an anti-inflammatory state within the gut [44]. In aged mice subjected to MCAO, the transplantation of intestinal epithelial stem cells (IESC) from young donors not only repaired the intestinal barrier and improved gut permeability but also lowered circulating levels of IL-17A and LPS. This intervention alleviated post-stroke depressive-like behavior and cognitive deficits [45].

Gut metabolites significantly affect stroke prognosis. The intestinal microbiota metabolizes consumed nutrients, generating metabolites such as SCFAs, TMAO, tryptophan metabolites, and secondary bile acids (2BAs). These substances are intricately linked with the pathogenesis of ischemic stroke. Research has demonstrated that TMAO is crucially involved in atherosclerosis development, which is an independent predictor of stroke. TMAO facilitates atherosclerosis progression through several mechanisms, including macrophage cholesterol accumulation, thrombosis augmentation, and vascular inflammation promotion [46]. Comparatively, atherosclerosis was identified as an independent risk factor for stroke. Zhu et al. [47] demonstrated that gut microbes significantly impact the extent of cerebral infarctions and subsequent adverse outcomes following stroke through the synthesis of dietary choline and TMAO in a mouse model of stroke. SCFAs, primarily acetic acid, propionic acid, and butyric acid, produced by anaerobic bacteria, have been shown to mitigate hippocampal neuroinflammation and neuronal apoptosis. They achieve this by inhibiting the NF-κB signaling pathway through GPR41 and activating the ERK1/2 cascade, thereby enhancing cognitive functions and reducing depression-like behaviors in rats [48]. Stroke pathology often includes disruption of the blood-brain barrier (BBB). During a stroke, impairment of the BBB allows a significant influx of inflammatory cells and factors into the brain, which exacerbates the inflammatory cascade and deteriorates stroke prognosis. SCFAs have been found to enhance the expression of tight junction proteins, preserve BBB integrity, decrease BBB permeability, and ameliorate ischemic symptoms [49]. Furthermore, SCFAs influence microglial polarization (by inhibiting pro-inflammatory M1 microglia) and increase the population of regulatory T (Treg) cells, thus dampening the immune response and minimizing neuronal damage [50]. Additionally, Indole-3-propionic acid (IPA), a tryptophan metabolite produced by the gut flora, showed increased serum levels in MCAO/R mice. Subsequent research indicated that IPA treatment altered the gut microbiota composition, enhanced gut barrier integrity, and modulated the activity of regulatory T cells and TH17 cells [51].

Research on the brain-gut-microbiota axis faces several significant challenges. Firstly, the substantial inter-individual variability in the gastrointestinal microbiome introduces complexities in conducting clinical trials. Factors such as geographic location, diet, age and gender must be accounted for to identify potential diagnostic markers related to gut microbiota and formulate personalized therapeutic approaches. Furthermore, stroke is characterized by complex pathophysiological mechanisms, including oxidative stress, neuroinflammation, and apoptosis. There is no singular mechanism that solely dictates the progression of stroke. The interactions between the intestinal flora and its metabolites, potentially mediated through the brain-gut axis, are implicated in these pathophysiological processes, suggesting that the gut microbiota and its metabolic products may play a crucial role in modulating the prognosis of stroke through their influence on oxidative stress and neuroinflammation.

While the conceptual framework of the brain-gut axis has seen considerable advancement over the years, the precise molecular mechanisms underlying the brain-gut axis remain largely elusive, suggesting the necessity to identify specific cells and receptors that play pivotal roles in the brain-gut axis. Furthermore, discrepancies in findings from basic experimental and clinical cohort studies on the brain-gut microbial axis highlight the need for more advanced sequencing technologies to elucidate the gut microbiome's complexity. Currently, 16S rRNA sequencing remains the predominant method, focusing primarily on the composition of species within communities, the evolutionary relationships among species, and the diversity of microbial communities. In the future, research could pivot towards macro-genome sequencing to build upon the foundational insights provided by 16S sequencing, which could provide more detailed investigations at both genetic and functional levels (e.g., Gene Ontology (GO), pathways), offering a deeper understanding of the brain-gut microbial interactions.

4.1. Strengths and limitation

This study represents the first comprehensive bibliometric analysis of the literature from 2002 to 2022 concerning stroke and gut flora. It explores the evolution of this field through various perspectives, including publication characteristics, contributions from institutional authors, co-citations of authors' works, and keyword trends, utilizing diverse visualization tools. As the first bibliometric investigation into the relationship between gut health and stroke, this study holds significant value but with certain limitations that warrant consideration. First, the only data source for this paper was articles indexed in WoSCC, with no exploration of additional databases. This exclusion may have overlooked articles from other databases, introducing potential incompleteness and bias. Currently, bibliometric analyses are confined to the WoSCC database, underscoring the need for the development of analysis software compatible with a broader range of databases to encompass a wider selection of articles. Second, although English is the most widely used language globally, valuable insights can be derived from literature in other languages. Incorporating more languages in future analyses could enhance the article's credibility. Third, we performed a thorough search using the terms "stroke" and "gut microbiota". However, we acknowledge the possibility of employing alternative search strategies, such as "Gastrointestinal Microflora." As a next step, we aim to expand our focus to include content related to cerebrovascular diseases and the gastrointestinal tract to enrich our research scope.

5. Conclusion

This study analysed trends in research between gut health and stroke and identified key publications from the past two decades that may serve as valuable references for subsequent research teams. The topic of gut health and stroke research is becoming increasingly popular among clinical practitioners and researchers. Despite the mentioned limitations, this study provides an important foundation for future investigations, offering insights into emerging topics, potential research goals, and trends in the field of gut health and stroke.

Contributions

Wang CQ conceived the study. Zhu H collected the data. Li YT and Zhang YG re-examined and analysed the data. Wang CQ wrote the manuscript. Ye YZ, Zhong Y, and Qiu S revised the manuscript. Jian ZH and Xiong XX prepared the final version. All authors contributed to the article and approved the submitted version.

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Data availability statement

The data analysed in this study are included in the article, further data will be made available on request.

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because all data were obtained in public databases and the data type was article.

CRediT authorship contribution statement

Chaoqun Wang: Writing – review & editing, Writing – original draft, Conceptualization. **Hua Zhu:** Visualization, Supervision, Methodology. **Yuntao Li:** Writing – review & editing, Visualization. **Yonggang Zhang:** Software. **Yingze Ye:** Project administration. **Yi Zhong:** Validation. **Sheng Qiu:** Methodology. **Xiaoxing Xiong:** Project administration, Funding acquisition, Conceptualization. **Zhihong Jian:** Project administration, Funding acquisition, Conceptualization.

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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