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Global Bibliometric Analysis of Cell Death in Stroke: Unveiling Research Landscapes and Emerging Frontiers

Yuying Shao[1,#] ， Weibo Sun[2,#,] Shuhao Guo[3,#] Yuanyuan Qu[1], Chuwen Feng[1,4,*]
Tiansong Yang[1,4,*]

The First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine 150040

Harbin Medical Sciences University 150076

The First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine 150040

1Email：sharon_yuying@163.com

corresponding author：yangtiansong2006@163.com

Abstract

Background: In recent years, the intricate relationship between stroke and cell death has blossomed into a vibrant field within neuroscience. At present, there is no literature analyzing the current status of research on cell death in stroke, we conducted a systematic and multi-faceted bibliometric analysis of relevant literature published between 1990 and 2024.

Methods: We harvested stroke-related cell death literature from the Web of Science spanning 1990 to 2024. Advanced visualization tools, including CiteSpace (6.2.R4), VOSviewer (v1.6.18), HisCite Pro2.1, and Alluvial Generator, were employed to meticulously mine the data, unraveling influential factors and evolving research trends.

Results: Over the past three decades, our search yielded a rich tapestry of 12,097 papers, involving 6,470 institutions and 37,642 authors, all centered on cell death in stroke

within the Web of Science. Across different periods, 123 related disciplines and 1,148 keywords emerged, with 2,378 papers experiencing citation surges, indicating significant impact. In terms of publication volume, *Arteriosclerosis, Thrombosis, and Vascular Biology* stood as the most prolific journal, contributing 449 articles. The fourth cluster of keywords revealed nine burgeoning research areas. A keyword burst analysis unveiled #1aquaporin_4 as the most enduring research module in this field, encompassing directions such as ubiquitination and synaptic plasticity. Emerging keywords included network pharmacology, molecular docking, necroptosis, and the blood-brain barrier. Furthermore, the latest research, as revealed through reference clustering, highlighted six key domains: #1aquaporin_4, #2stroke, #3obesity, #4caspase_8, #5inflammatory_factors, and #6cerebral_small_vessel_disease.

Conclusion: The research on cell death in stroke is continuously advancing, providing a solid scientific foundation and theoretical guidance for future studies in the field of neuroscience.

Keywords: *cell death, bibliometrics, stroke, CiteSpace, VOSviewer,neuroscience.*

1. Introduction

Stroke, a devastating cerebrovascular disease, arises from various etiologies, leading to focal cerebral hemorrhage or infarction. It manifests as acute neurological deficits persisting beyond 24 hours and can, in severe cases, prove fatal[1]. Global epidemiological data across 31 regions reveal significant geographical disparities in stroke incidence, mortality, and subtype distribution (ischemic vs. hemorrhagic)[2]. Notably, hemorrhagic stroke accounts for a considerably higher proportion in Asian

countries (e.g., 33% in China) compared to Western nations[3]. While high-income countries exhibit a greater prevalence of ischemic stroke (71%), low-income countries see this figure at 63%, underscoring a notable increase in hemorrhagic stroke mortality within the latter[4]. Projections by Feigin et al. anticipate a substantial rise in the global stroke burden between 2020 and 2050, warning that without effective interventions, stroke mortality could surge by 50%, with a parallel increase in disability-adjusted life years (DALYs). Given its high incidence, recurrence, disability, and mortality rates, stroke stands as the second leading cause of death globally and the third leading cause of disability[5,6]. Clinical guidelines provide diagnostic assessments and treatment recommendations for ischemic stroke etiological subtypes, emphasizing the critical role of managing vascular risk factors (e.g., hypertension, diabetes) and lifestyle interventions (e.g., healthy diet, exercise) in disease prevention. Anticoagulation therapy and surgical interventions are viable options for many patients, with a strong emphasis on individualized treatment and multidisciplinary support[7].

Stroke is broadly classified into ischemic and hemorrhagic types, with ischemic stroke accounting for 68% of global cases and hemorrhagic stroke for 28%[4]. Ischemic stroke typically results from the occlusion of cerebral blood vessels by atherosclerotic plaques or atrial fibrillation emboli, leading to localized cerebral ischemia and necrosis. A smaller fraction involves venous infarction caused by the obstruction of cerebral veins or venous sinuses. Hemorrhagic stroke generally stems from the rupture of cerebral blood vessels due to hypertension or vascular malformations, forming intracerebral or subarachnoid hemorrhage. The resultant hematoma compresses

surrounding tissues, causing damage and neurological deficits[8]. The intricate pathological mechanisms of stroke encompass a cascade of events including inflammation, energy metabolism dysfunction, acidosis, calcium overload, oxidative stress, blood-brain barrier disruption, and glial cell activation. Following a stroke, cerebral tissue injury unleashes a torrent of pathophysiological responses, including cell death, inflammatory reactions, breakdown of the blood-brain barrier, mitochondrial dysfunction, and excitotoxicity. Among these, the reduction in cerebral blood flow leading to embolism-induced cell death stands as a central pillar in stroke pathology[9].

Cell death can be broadly categorized into accidental cell death (ACD) and regulated cell death (RCD). RCD, a core regulatory mechanism for maintaining organismal homeostasis, dynamically clears cells and continuously occurs in physiological systems to uphold tissue equilibrium[10]. RCD encompasses a diverse array of processes, including necroptosis, pyroptosis, ferroptosis, autophagy, NETosis, parthanatos, lysosome-dependent cell death, autophagy-dependent cell death, alkaliptosis, and oxeiptosis[11]. The intricate dance of RCD is intimately linked to the genesis and progression of various diseases, including cancer, neurodegenerative disorders, autoimmune diseases, inflammatory conditions, cardiovascular diseases, and central nervous system (CNS) disorders[12–14]. Notably, RCD plays a pivotal role in the pathological progression of stroke, and its targeted regulation offers multi-dimensional intervention strategies to ameliorate post-stroke brain tissue damage.

Among the various forms of cell death, apoptosis is a dominant force in neuronal death following ischemic stroke, and the inhibition of caspase activity significantly

mitigates brain injury[15]. Necroptosis, mediated by the RIPK1/RIPK3/MLKL pathway, also contributes to cell demise, with pathway inhibition demonstrating a reduction in ischemic brain injury[16]. In pyroptosis, activation of the NLRP3 inflammasome cleaves Gasdermin D (GSDMD) via activated Caspase-1, releasing inflammatory cytokines IL-1β and IL-18 and promoting the efflux of damage-associated molecular patterns (DAMPs), thereby amplifying the inflammatory cascade through the TLR4/NF-κB pathway. Concurrently, GSDMD pore formation induces K^+ efflux, which in turn reactivates the NLRP3 inflammasome, forging a positive feedback loop that exacerbates local and systemic inflammatory responses; inhibiting the NLRP3 inflammasome can improve prognosis[17,18]. Ferroptosis, through the lipid peroxidation-inflammation axis, exacerbates cerebral ischemia/reperfusion injury12/9/2025 7:28:00 AM. During cerebral ischemia, oxidation generates lipid peroxides (LPO), inducing iron-dependent membrane disintegration. Simultaneously, DAMPs released by ferroptosis activate the microglial TLR4/NF-κB pathway, leading to the release of IL-6 and TNF-α, thus forming an oxidative stress-inflammation positive feedback loop. Using ACSL4 inhibitors or iron chelators (e.g., Deferoxamine) can reduce LPO accumulation, improve blood-brain barrier integrity, and alleviate stroke injury[19–21]. Cuproptosis collaborates with oxidative stress to drive cardiovascular and cerebral ischemic injury: copper dyshomeostasis, through the inactivation of Fe-S cluster proteins and decoupling of the respiratory chain, induces massive reactive oxygen species (ROS) production. Oxidative stress further inhibits Akt phosphorylation, weakening its regulation of PRAS40 (Proline-rich Akt substrate),

blocking the mTORC1 survival signaling pathway, and aggravating neuronal apoptosis. Copper chelators (e.g., tetrathiomolybdate) combined with antioxidants (NAC) can reverse copper-dependent lipid peroxidation and mitochondrial damage, offering a strategic approach for targeted intervention[22–24].In summary, intervention strategies targeting the multi-modal RCD regulatory network not only directly reduce infarct size by inhibiting neuronal death but also indirectly improve prognosis by modulating the neurovascular microenvironment, thereby forging new pathways for neurorestoration in cerebrovascular diseases.

Bibliometric analysis, by quantitatively scrutinizing the literature on cell death in stroke, empowers scholars to swiftly grasp the field's historical trajectory, seminal works, and burgeoning research frontiers[25]. This analytical approach also facilitates the identification of high-impact publications and research teams, serving as a valuable reference for fostering scientific collaborations[26]. This paper leverages VOSviewer software for analyzing inter-author collaboration data. VOSviewer is adept at generating large-scale bibliometric visualizations, emphasizing graphical interpretability and capable of handling vast datasets[27]. CiteSpace is extensively employed in constructing knowledge graph visualizations. In this study, CiteSpace software and HistCite Pro 2.1 are utilized to assess cell death research in stroke, analyze keywords, citation patterns, and cluster structures within citation networks, identify the evolutionary paths and key nodes of the disciplinary field, and visualize national and institutional collaboration networks[28]. Therefore, this paper undertakes a multi-faceted bibliometric analysis of cell death in stroke, aiming to unveil the research field's

developmental history, hotspots, and trends, thereby addressing existing research gaps and propelling scientific advancement in this vital domain.

2. Methods

2.1. Data Collection and Statistics

The Web of Science Core Collection (WoSCC), a rich repository of knowledge, encompasses over 12,000 influential academic journals, which are vital to our exploration of cell death in stroke. For this study, WoSCC served as our target database. We employed a comprehensive search strategy encompassing the following terms for stroke: ((((((((((((TS=(Stroke)) OR TS=(Strokes)) OR TS=("Cerebrovascular Accident")) OR TS=("Cerebrovascular Stroke")) OR TS=("Cerebral Hemorrhage*")) OR TS=("Intracerebral Hemorrhage*")) OR TS=("Cerebrum Hemorrhage*")) OR TS=("Cerebral Brain Hemorrhage*")) OR TS=("Cerebral Parenchymal Hemorrhage*")) OR TS=("Parenchymal Hemorrhage, Cerebral")) OR TS=("Cerebral Infarction")) OR TS=("Cerebral Infarct")) OR TS=("Subcortical Infarctions")) OR TS=("Subcortical Infarction") AND ((((((((((((((((((((((((((((((TS=("Cell Death")) OR TS=("Death, Cell")) OR TS=(Apoptosis)) OR TS=("Classical Apoptosis")) OR TS=("Apoptosis, Classical")) OR TS=("Classic Apoptosis")) OR TS=("Classic Apoptoses")) OR TS=("Programmed Cell Death, Type I")) OR TS=("Apoptosis, Extrinsic Pathway")) OR TS=("Apoptoses, Extrinsic Pathway")) OR TS=("Extrinsic Pathway Apoptoses")) OR TS=("Apoptosis, Intrinsic Pathway")) OR TS=("Apoptoses, Intrinsic Pathway")) OR TS=("Intrinsic Pathway Apoptoses")) OR TS=("Intrinsic Pathway Apoptosis")) OR TS=("Programmed Cell Death")) OR TS=("Cell Death, Programmed")) OR

TS=("Caspase-Dependent Apoptosis")) OR TS=("Apoptosis, Caspase-Dependent")) OR TS=("Caspase Dependent Apoptosis")) OR TS=(Pyroptosis)) OR TS=(Pyroptoses)) OR TS=("Inflammatory Apoptosis")) OR TS=("Inflammatory Apoptoses")) OR TS=("Pyroptotic Cell Death")) OR TS=("Cell Death, Pyroptotic")) OR TS=("Cell Deaths, Pyroptotic")) OR TS=("Death, Pyroptotic Cell")) OR TS=("Pyroptotic Cell Deaths")) OR TS=("Caspase-1 Dependent Cell Death")) OR TS=("Caspase 1 Dependent Cell Death")) OR TS=(Necroptosis)) OR TS=(Endocytosis)) OR TS=(pan-apoptosis)) OR TS=(Ferroptosis)) OR TS=((Disulfidptosis))). The search period was set from 1990 to 2024. All retrieved literature records were downloaded and saved as plain text files in "Full Record and Cited References" format, forming the sample for our analysis. Ultimately, we amassed 12,097 literature entries, which were collectively designated as "DATA." Concurrently, raw data pertaining to publication countries/regions, institutions, journals, authors, and article types were collected and statistically analyzed using EXCEL (WPS 21019).

2.2. Bibliometric Analysis Tools

2.2.1. CiteSpace

2.2.1.1. Co-occurrence Network

Scientific partnership is defined as the simultaneous appearance of multiple authors, institutions, or countries/regions within the same publication. Scientific research often thrives on extensive collaboration, and examining these cooperative ties can illuminate the research landscape of a specific scientific domain, a reflection observable across author, institutional, and national dimensions. When articles from a particular research

field are imported into CiteSpace software as a dataset, these collaborative relationships and scientific concepts can be visualized as a co-occurrence network. CiteSpace employs color-coded nodes and edges to distinguish merged networks, assigning a unique color to each year within the dataset. The color of a network's edge signifies the inaugural year in which the co-occurrence link was established. Nodes are composed of different colored "tree rings," with their thickness indicating the volume of co-occurrence in a given year. In this study, red rings denote a citation burst in a particular year, signifying a surge in citations. Purple rings symbolize the degree of betweenness centrality among nodes. A node exhibiting high betweenness centrality is particularly meaningful as it acts as a crucial bridge connecting other nodes within the network.

2.2.1.2. Burst Detection

Jon Kleinberg posited that a stream of documents, such as emails or articles, exhibits specific themes for a certain duration before gradually fading[29]. Specialized text mining algorithms can identify such thematic shifts over time, representing them as "activity bursts." Building upon Kleinberg's algorithm[30], Chen et al. defined citation bursts as indicators of active themes. Citation burst detection identifies sudden increases in citations, which can persist for several years or even a single year. CiteSpace offers citation burst detection for disciplines, keywords, and references. The emergence of a citation burst signifies that a particular discipline, keyword, or reference has garnered significant attention from the scientific community.

2.2.1.3. Cluster Analysis

CiteSpace provides three clustering algorithms—based on titles, abstracts, and

keywords—to group publications into conceptual clusters exhibiting distinct research characteristics. Depending on the slice settings, the clustering map reflects the temporal evolution of conceptual clusters. Furthermore, the timeline map vividly portrays the ebb and flow of a cluster's lifespan, as well as the nodes associated with other clusters.

The specific steps are as follows: The "DATA" dataset on cell death in stroke was imported into CiteSpace software (6.2.R4). "Time slicing" was set to "1990-2024" with "1 year per slice." For keyword analysis, "author keywords" were selected, and the word sources were set to "title," "abstract," "author keywords," and "keywords+." Node types were chosen as needed, with other settings remaining at their default values. This process automatically generated knowledge maps for national (regional), institutional, or author collaboration networks, which were then manually adjusted for clarity and aesthetic appeal. Using the same methodology, we depicted keyword cluster maps; however, for these, "keywords" were selected as nodes, and time slicing was set to 1990-1998, 1999-2007, 2008-2016, and 2017-2024. Additionally, when generating cluster maps for "references," we navigated to the "Layout" tab within the "Control Panel" and further selected the "Timeline View" to produce a citation timeline map. Furthermore, by selecting the "Burstness" tab in the "Control Panel" and clicking "View," burst detection maps for keywords, categories, or references were generated.

2.2.2. HisCite

Each piece of literature, much like a solitary spark in the darkness, gains luminosity with every citation it receives, akin to adding fuel to a flame. The more citations, the brighter and more readily discernible the literature becomes. The HistCite Pro 2.1

software is designed to chart this digital constellation, pinpointing the most luminous works and immediately revealing which articles have been cited most frequently. HistCite ranks articles using a Local Citation Score (LCS) and a Global Citation Score (GCS). LCS refers to the number of times a study is cited within the software's dataset, while GCS indicates its citation frequency within the broader WoSCC database. We imported the "DATA" research articles on cell death in stroke (12,097 papers) into Hiscite Pro 2.1, set the "limit" to 30, kept other settings at their default values, and selected "Make Graph" to chart the intellectual lineage of cell death research in stroke, thereby swiftly identifying pivotal literature.

2.2.3. The Alluvial Generator

Alluvial flow diagrams are designed to illuminate temporal patterns within evolving networks. To generate these diagrams, we leveraged CiteSpace to produce a series of individual networks for co-occurring keywords. These networks, once exported from CiteSpace, were then loaded into the Alluvial Generator (http://www.mapequation.org/apps/AlluvialGenerator.html). Each keyword was treated as a node, and nodes were clustered into modules within each time slice. As time progressed, nodes were observed to split and merge across different time slices, forming new modules, with the most recent modules often emerging from the intersection of prior nodes.

2.2.4. R

Figure 10, a donut chart, was rendered using R 4.2.2. The **geom_bar** function from the **ggplot2** (3.4.4) package in R was utilized for its creation.

The flowchart for this research is presented in Figure 1.

3. Results

3.1. The Historical Features of the Literature on Cell Death in Stroke

3.1.1. Distribution of Publications

The relentless march of time precisely maps the dynamic accumulation of knowledge within the neuroscientific landscape. Bibliometrics quantifies the trajectory of a research field's maturity, offering crucial parameters for understanding the evolutionary path of cell death research in stroke. In this study, we identified a total of 12,097 publications related to cell death in stroke, involving 37,642 authors and 6,470 institutions, published across 1,398 journals spanning 123 scientific categories (Table 1).

The annual output of research is depicted in Figure 2. In 1990, 16 papers related to cell death in stroke were published. This number increased to 35 papers in 1991. The publication volume remained relatively low from 1990 to 1993, then experienced a rapid increase from 1994 to 2011. Publications continued to climb after 2011, reaching a peak in 2021.

Arteriosclerosis, Thrombosis, and Vascular Biology led the publication volume with 449 articles, followed by *Atherosclerosis* (436 articles) and *Circulation* (223 articles). Figure 3 presents the top 20 most prolific journals, serving as a valuable guide for researchers considering submission venues.

3.1.2. The Vein of Research on Cell Death in Stroke

The co-citation network vividly illustrates the intricate relationships among

literature in the field of cell death in stroke over the past three decades (Fig4). The network comprises 2,513 nodes and 11,616 links, signifying extensive connections among the publications in this research domain. In the nascent stages of the literature (1990-2005), nodes marked in grey, with their dense clustering and abundant inter-node connections, formed the very root system of the field, providing vital nourishment for its sustainable growth. During the mid-period (2006-2017), blue-marked nodes gradually dispersed, forming the primary branches of research. In the later period (2018-2024), these nodes further developed into twigs, forming tighter clusters, signaling a convergence and differentiation within the research landscape. Among these seminal works, ten papers—Campbell BCV (2019)[31], Feigin VL (2021)[32], Jayaraj RL (2019)[33], Benjamin EJ (2017)[34], Radak D (2017)[35], Tuo QZ (2022)[36], Broughton BRS (2009)[15], Paul S (2021)[37], Benjamin EJ (2019) and Uzdensky AB (2019)[38]—stood out with significantly higher co-citation frequencies of 172, 142, 139, 136, 123, 120, 107, 103, 102, and 95, respectively, underscoring their pivotal roles in cell death in stroke research. This concentration and differentiation of research clusters will be further elucidated in the subsequent reference timeline maps. Additionally, we utilized HisCite Pro 2.1 to generate a citation history map of the research articles. These landmark articles are highlighted in Table 2, with the top three being "Apoptotic Mechanisms After Cerebral Ischemia"[15],"*Mechanismsofischemicbraindamage*"[39],*and*"*Evidenceforapoptosisa fterintracerebralhemorrhageinratstriatum*"[40]. Larger nodes signify more important references, and more connections indicate higher betweenness centrality of a node. By

employing these two methods, we not only gained an intuitive understanding of the literature's citation network structure but also precisely focused on the highly influential publications in this field.

The aforementioned articles represent classic works in the field. Doyle KP[39] primarily delves into the myriad mechanisms of ischemic brain damage, including excitotoxicity, acidosis, oxidative stress, inflammatory responses, and apoptosis—all contributors to neuronal death post-stroke. Broughton BRS[15] found that while cell death after cerebral ischemia was initially considered necrotic, research over the past decade has revealed that neurons in ischemic regions undergo apoptosis, indicating that cell death is not solely confined to necrosis. The two main apoptotic pathways—the intrinsic pathway stemming from mitochondrial cytochrome c release and caspase-3 activation, and the extrinsic pathway stemming from cell surface death receptor activation leading to caspase-8 activation—are not limited to neurons and caspase-dependent mechanisms. Matsushita K's[40] experiment confirmed that neuronal and glial cell apoptosis following cerebral hemorrhage is mediated by the caspase pathway, and inhibiting this pathway can mitigate injury. Currently, therapeutic options for stroke are quite limited; thus, developing novel treatments necessitates a comprehensive understanding of the diverse mechanisms underlying ischemic/hemorrhagic brain injury.

Feigin VL (2021)[32] systematically analyzed stroke incidence and risk factors across 204 countries and territories from 1990 to 2019. The study revealed a global increase in stroke incidence, with ischemic stroke accounting for 62.4% of all new cases

in 2019, intracerebral hemorrhage for 27.9%, and subarachnoid hemorrhage for 9.7%. The burden of various pathological types differed across countries and regions, with a higher proportion of intracerebral hemorrhage in low- to middle-income countries and a higher proportion of subarachnoid hemorrhage in high-income countries. Stroke mortality and DALY rates were significantly higher in low-income countries compared to high-income countries, with an increasing prevalence and incidence in individuals under 70 years old. In 2019, stroke DALYs were attributed to 19 risk factors, including high systolic blood pressure, high BMI, high fasting plasma glucose, environmental particulate matter pollution, and smoking. The study underscored the need to strengthen primary prevention strategies, control risk factors, and narrow the gap in stroke care and prevention between different countries. Additionally, Benjamin EJ (2017)[41] noted the significant health and economic burden imposed by cardiovascular diseases in the United States and globally. Approximately 92.1 million adults in the U.S. suffer from one or more cardiovascular diseases, and this proportion is projected to continue rising by 2030, with cardiovascular diseases also being one of the leading causes of death worldwide. The direct and indirect costs of cardiovascular diseases and stroke were estimated at 316.1 billion in 2012-2013, with direct medical costs projected to increase substantially by 2030. Cultivating healthy lifestyle habits can effectively reduce the risk of incidence. An updated 2019 dataset[34] revealed that approximately 7 million Americans aged ≥ 20 have experienced a stroke, with an overall prevalence of 2.5%. Hospitalizations for acute ischemic stroke patients aged 18-54 are on the rise, with a notable increase in hospitalization rates for men aged 35-44. Stroke risk is

attributed to 90% modifiable risk factors (e.g., hypertension, obesity, hyperglycemia, hyperlipidemia, and renal dysfunction) and 74% behavioral risk factors (e.g., smoking, sedentary lifestyle, dietary habits, and air pollution). Although global stroke mortality declined from 1990 to 2015, the absolute number of strokes, deaths, and DALYs continues to increase.

Campbell BCV (2019)[31] emphasized the critical importance of timely intervention and systemic regulation in improving stroke patient outcomes. Most strokes are ischemic, caused by arterial occlusion. For patients with infarction, enhancing the efficacy of reperfusion therapy and reducing treatment delays are key. Intravenous thrombolysis performed within 4.5 hours of stroke onset can reduce disability; for comatose patients, this window can extend to 9 hours. For patients with intravascular thrombus, thrombectomy within 6 hours of stroke onset can reduce disability; for patients post-perfusion imaging, the thrombolysis window can extend to 24 hours, alongside blood pressure control, cholesterol management, and antithrombotic medication. Other preventive measures are guided by the stroke mechanism, such as anticoagulation for atrial fibrillation patients and carotid endarterectomy for severe carotid stenosis. Tuo QZ (2022)[36] highlighted the susceptibility to ischemic reperfusion injury (IRI) during thrombolytic therapy, which triggers a burst of free radicals, calcium overload, and inflammatory cascades, thereby exacerbating tissue damage. Furthermore, cell death pathways involved in stroke include apoptosis, necroptosis, autophagy, ferroptosis, and pyroptosis. Future research should continue to explore potential drug targets and develop animal models based on

these cell death mechanisms. Jayaraj RL (2019)[33] discussed the dynamic biphasic regulation characteristic of neuroinflammation post-stroke. Rapid activation of microglia and astrocytes after stroke drives peripheral inflammatory cells, such as neutrophils and monocytes/macrophages, to infiltrate the ischemic area by releasing IL-1β, TNF-α, and MCP-1, thereby exacerbating blood-brain barrier disruption and neural damage. Simultaneously, Treg cells, TGF-β, and IL-10 exert neuroprotective effects by clearing necrotic debris and promoting vascular repair. Future strategies could focus on precise regulation of inflammatory cells and multi-target combined therapies, with targeting molecular pathways like MMPs, HMGB1, and MAPK offering multi-stage intervention strategies for stroke treatment.

Radak D (2017)[35] posited that apoptosis likely accounts for a significant proportion of neuronal death following acute brain ischemia (ABI), though its specific mechanisms remain to be fully elucidated. Key triggers for apoptosis include excessive generation of free radicals, Ca2+ overload, and excitotoxicity. Future research could explore potential neuroprotective drugs, such as statins, which may regulate apoptotic pathways and contribute to stroke prevention and treatment. Paul S (2021)[37] primarily explored neuroprotective combination therapy strategies for ischemic stroke, introducing the U.S. National Institute of Neurological Disorders and Stroke's Stroke Preclinical Assessment Network (SPAN) program, which aims to protect brain tissue before and during reperfusion, extending the therapeutic window. Within SPAN, the peptide adropin exerts neuroprotective effects by activating the eNOS signaling pathway, while STEP-mimetics can intervene in the ischemic cascade to promote

recovery. The pharmaceutical compound verapamil reduces excitotoxic damage by inhibiting L-type calcium channels. In terms of epigenetic factors, various MicroRNAs exhibit diverse functions, such as regulating excitotoxicity, mitigating oxidative stress, modulating inflammatory responses, and improving blood-brain barrier function, offering new directions for ischemic brain injury treatment. Uzdensky AB (2019)[38] focused on reducing the area of brain infarction by mitigating cell death in the potentially salvageable transition zone (penumbra) within 24 hours of ischemic stroke. In the penumbra region, neuronal cell death types include necrosis, apoptosis, pyroptosis, ferroptosis, and autophagy-dependent cell death. Currently, pro-apoptotic proteins (e.g., caspase 3/6/7, Bcl-10, SMAC/DIABLO, AIF, PSR) and anti-apoptotic proteins (e.g., Bcl-x, ERK1, MDM2, p63, PKBα, RAF1, ERK5, MAKAPK2) bidirectionally regulate cell death. Direct executors of apoptosis, such as caspases 3, 6, and 7; signaling proteins regulating different apoptotic pathways, such as p38 and JNK; transcription factors controlling apoptotic protein expression, such as E2F1 and p53; and proteins that stimulate apoptosis under specific circumstances, such as NMDAR2a and Par4, all present targets. Synergistic upregulation of the inhibition of these proteins can improve penumbra injury area. Elucidating the molecular mechanisms of cell death, associated signaling pathways, and the regulatory roles of transcription factors is crucial. Some proteins hold promise as potential targets for anti-stroke therapy, and future exploration of multi-target neuroprotective agents for stroke will provide direction for subsequent research and treatment.

The mechanisms of cell death in stroke are generally intertwined with energy

metabolism, mitochondrial dysfunction, excitotoxicity, oxidative stress, inflammatory responses, blood-brain barrier damage, and diverse forms of cell death. Modulating cell death can significantly ameliorate neurological damage in the ischemic penumbra. Initially, cell death after cerebral ischemia was believed to be purely necrotic, but recent decade-long research has revealed the presence of apoptosis in ischemic regions, indicating that cell death is not solely confined to necrosis. Subsequently, cell death pathways involved in stroke were found to include apoptosis, necroptosis, autophagy-dependent cell death, ferroptosis, and pyroptosis, with the latest research supplementing modes like cuproptosis.[41] Based on the aforementioned and recent studies,necrosis typically results from cell swelling and rupture due to ischemia; necroptosis may be mediated by RIPK1/RIPK3; the mitochondrial pathway (caspase-3/9) and death receptor pathway (caspase-8) constitute the core apoptotic pathways, with free radical bursts and calcium overload being critical triggers for the cascade; ferroptosis is driven by the accumulation of lipid peroxidation due to glutathione peroxidase 4 (GPX4) inactivation; pyroptosis is closely associated with the activation of inflammasomes like NLRP3; while positive autophagy has neuroprotective effects in the early stages of onset, autophagy-dependent cell death may lead to cell demise[42].

An ideal stroke prevention and treatment strategy within the realm of cerebrovascular diseases should encompass multi-dimensional regulation, precise risk factor management, and dynamic therapeutic interventions. Current research, driven by the continuous optimization of targeted protein technologies, is shifting from molecular mechanism studies of cell death's impact on stroke to clinical intervention validation.

Most neuroprotective agents for ischemic stroke, based on cell death as a theoretical foundation, have unfortunately terminated at Phase III trials due to insufficient blood-brain barrier penetration and other reasons. Current drug delivery technologies include Intranasal Administration, Focused Ultrasound (FUS), and Liposomes. Transporters represent the next frontier in drug delivery, with examples like Organic Cation Transporters (OCTs) and Multidrug and Toxin Extruders (MATEs), as well as Organic Anion Transporting Polypeptides (OATPs), participating in drug transport across the blood-brain barrier (BBB), influencing the brain's blood supply mechanisms. Currently, only Edaravone[43,44] and Nimodipine[45,46] are partially recommended by some countries for the treatment of neurological dysfunction. The efficacy and mechanisms of action of such novel drugs require further investigation in the future. Optimizing transporter-mediated drug delivery pathways will contribute to advancing stroke drug development[47].

3.1.3. Scientific Cooperation

As depicted in Figure 5, the abundance of nodes and rich interconnections strongly indicates robust scientific cooperation across national, institutional, and author dimensions. The national collaboration network features 89 nodes and 648 connecting lines, with node scale ranging from China to the United States, Japan, South Korea, and Germany (Figure 5A). The institutional collaboration network comprises 742 nodes and 983 connecting lines, with node prominence in the order of Capital Medical University, University of California System, Fudan University, and Shanghai Jiao Tong University, as shown in Figure 5B. The author collaboration map is presented in Figure 5C. Chen,

Gang; Li, Haiying; Zhang, John H; and Li, Xiang are at the forefront in terms of publication volume in this field, with dense connections representing extensive research collaborations among researchers.

Notably, a clustering effect was observed among the nodes of authors Chen, Gang; Li, Xiang; Shen, Haitao; and Wang, Zhong, forming a cohesive cluster. Similarly, nodes like Zhang, Li; Liu, Yang; and Wang, Wei clustered together, indicating strong collaboration and communication within each author cluster (Supplementary Table S1).

In the study of cell death in stroke, 89 countries have participated in research, with the top five being China, the United States, Japan, South Korea, and Germany, and China accounting for a significant proportion of publications. Among the 742 institutions, a clustering effect was observed among the nodes of authors Chen, Gang; Li, Xiang; Shen, Haitao; and Wang, Zhong, forming a cohesive cluster. Similarly, nodes like Zhang, Li; Liu, Yang; and Wang, Wei formed another cluster, indicating strong collaboration and communication within each author cluster.

3.2. Variation of the Most Active Topics

3.2.1. Subject Category Burst

From 1990 to 2024, a remarkable 117 out of 123 relevant subject categories experienced citation bursts. The blue line delineates this entire time span, while red segments mark the specific duration of a subject category's burst, indicating its commencement and conclusion years. Figure 6 illustrates the top 50 categories with the highest burst strength across different periods. The subject category MEDICINE, RESEARCH & EXPERIMENTAL exhibited its most intense burst between 2017 and

2021, with a burst strength of 38.11. Notably, as time progressed, the trending subject categories diversified, encompassing fields such as CRITICAL CARE MEDICINE (2004-2012), SURGERY (2009-2013), MULTIDISCIPLINARY SCIENCES (2012-2015), TRANSPLANTATION (2018-2019), and ENGINEERING, BIOMEDICAL (2023-2024). The evolving landscape of burst categories on the timeline underscores the multidisciplinary nature of this field. Furthermore, starting from 2024, a total of 20 burst categories emerged (Supplementary Table S2), with CHEMISTRY, MEDICINAL (2023-2024), PLANT SCIENCES (2022-2024), and NANOSCIENCE & NANOTECHNOLOGY (2022-2024) leading the way.

In the early period (2004-2012), the core of research centered on CRITICAL CARE MEDICINE, gradually integrating disciplines such as SURGERY (2009-2013), MULTIDISCIPLINARY SCIENCES (2012-2015), and TRANSPLANTATION (2018-2019). Between 2017 and 2021, research into the mechanisms of cell death in stroke exhibited significant interdisciplinary characteristics, evolving from an initial foundation in critical care medicine, through surgical interventions for thrombus removal and hemorrhage control, to a later synergy of multidisciplinary approaches for optimizing treatment plans. The collaboration with transplantation in 2018, leveraging organ regeneration techniques for neural function remodeling, marked a paradigm shift in treatment modalities. Significantly, the involvement of BIOMEDICAL ENGINEERING (2023-2024) heralded technological innovation in this domain. Entering 2024, a groundbreaking shift in research paradigms is evident, with the emergence of 20 new interdisciplinary fields. Among these, CHEMISTRY,

MEDICINAL, PLANT SCIENCES, and NANOSCIENCE & NANOTECHNOLOGY ranked in the top three, signaling a profound expansion from traditional medicine into chemical biology, materials science, and ecological medicine. These interdisciplinary intersections not only propel the elucidation of stroke pathological mechanisms but also forge innovative pathways for targeted therapies and regenerative medicine.

3.2. Variation of the Most Active Topics

3.2.2. Keywords Burst

At a finer level, the detection of keyword burst patterns illuminates the active content within the realm of cell death in stroke across the entire time span (1990-2024). Among the 1,148 keywords, bursts occurred at various points, with the top 50 keywords exhibiting the highest burst strengths presented in Figure 7. The keyword "ischemic stroke" showed the highest burst strength of 133.35 between 2021 and 2024. "Cell death" burst between 2000 and 2009 with a strength of 74.85, while "focal cerebral ischemia" burst between 1996 and 2013 with a strength of 72.82. This indicates that among the core terms related to stroke, ischemic stroke is the latest research hotspot, with focal ischemia as a branching area, and the research focus in 2000-2009 centered on cell death.

Furthermore, we paid particular attention to 20 keywords that continued to burst into 2024, as these are likely to be future research hotspots in the field. For instance, ischemic stroke had a burst strength of 133.35 from 2021 to 2024; neuroinflammation showed a burst strength of 31.61 from 2021 to 2024; cerebral ischemia-reperfusion injury exhibited a burst strength of 30.5 from 2021 to 2024; and nlrp3 inflammasome

had a burst strength of 27.75 from 2020 to 2024. Stroke research, initially centered on ischemia-reperfusion injury, subsequently identified neuroinflammation as a crucial pathological link. In recent years, the NLRP3 inflammasome has emerged as a focal point due to its core regulatory role in the inflammatory cascade. Research is progressively shifting from mere thrombus clearance to the modulation of neuroinflammation, aiming for post-ischemic neuroprotection by targeting the NLRP3 pathway. This evolution exemplifies a leap from macroscopic pathological mechanisms to precise molecular interventions, offering new targets for developing anti-neuroinflammatory drugs (Supplementary Table S2).

3.2.3. Reference Burst

Calculations revealed a total of 2,378 burst articles. Table 3 lists the top 30 most frequently cited references with bursts between 1990 and 2024.

"Apoptotic Mechanisms After Cerebral Ischemia" was the article with the highest citation burst rate, sustained from 2010 to 2014. This paper posited that while cell death following cerebral ischemia was traditionally considered entirely necrotic, research over the past decade revealed that many neurons in the ischemic penumbra after stroke undergo apoptosis. Cerebral ischemia triggers two general apoptotic pathways: an intrinsic pathway stemming from mitochondrial cytochrome c release and subsequent caspase-3 activation, and an extrinsic pathway originating from the activation of cell surface death receptors, leading to caspase-8 stimulation. Despite the identification of many key apoptotic proteins, our understanding of their intricate intrinsic mechanisms remains limited, making the therapeutic manipulation of apoptotic pathways in stroke

patients a formidable task. However, recent advancements in the field have broadened our comprehension of apoptosis after cerebral ischemia. Beyond the simplistic notion that stroke-induced apoptosis primarily occurs in neurons and is caspase-dependent, there is now increasing evidence that apoptosis is also prevalent in non-neuronal cells, and caspase-independent mechanisms also play a crucial role. "The Science of Stroke: Mechanisms in Search of Treatments"[48] showed a burst from 2011 to 2015. A significant proportion of neuronal death after acute brain ischemia (ABI) may be due to apoptosis, but its fundamental mechanisms are still not fully understood. Cerebral ischemia can lead to stroke, which is one of the main causes of long-term morbidity and mortality in developed and developing countries. Therefore, stroke prevention and treatment are clinically very important. During ABI, the brain has two important independent regions: the ischemic core and the ischemic penumbra. Within minutes of an ischemic attack, blood flow to the ischemic core of the brain is suddenly reduced, causing irreversible damage and subsequent cell death. On the other hand, apoptosis within the ischemic penumbra may occur hours or days later, while necrosis in the ischemic core begins within hours of the ischemic attack. Ischemia-hypoxia is characterized by many cells undergoing key molecular events that initiate apoptosis, such as excessive free radical production, Ca2+ overload, and excitotoxicity. These changes in cellular homeostasis can trigger cell necrosis or apoptosis, which often depends on cell type, cell age, and location in the brain. Apoptosis leads to DNA fragmentation, degradation of cytoskeleton and nuclear proteins, protein cross-linking, apoptotic body formation, expression of phagocytic receptor ligands, and eventual

absorption by phagocytes. This review focuses on recent findings, based on animal and human studies, concerning the apoptotic mechanisms of neuronal death after ABI, and the development of potential neuroprotective agents that can reduce morbidity. In addition, the effects of statins on stroke prevention and treatment, and on apoptotic mediators, are also considered.

As of 2024, there were 259 burst articles, and the top 20 articles by burst strength are presented in Table 4. Among these, 18 were "review" articles and 2 were "article" types. All these articles entered their citation burst period either in the year of publication or the following year. Tuo QZ's article[36], ranked first, comprehensively reviewed the mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications. Ischemic stroke is highly detrimental and involves multiple cell death pathways, including apoptosis, necroptosis, autophagy, and ferroptosis. The paper also discussed potential therapeutic targets for these pathways, such as strategies to modulate excitotoxicity, calcium overload, and various death pathways. Furthermore, it summarized relevant clinical trials, noting that only a few antioxidants and statins have shown clinical efficacy. Qin C's work[49] systematically elucidated stroke pathogenesis, related signaling pathways, and therapeutic interventions. Ischemic stroke, triggered by the interruption of cerebral blood flow, causes severe neurological damage. The paper detailed signaling pathways involved in pathological processes like energy deficiency, excitotoxicity, oxidative stress, cell death, and neuroinflammation, such as PI3K-Akt, PTEN, and Nrf2/ARE, which play promoting or inhibitory roles in different pathological stages. It also explored therapeutic approaches targeting these

pathways, such as inhibiting excitotoxicity by targeting the GluN2B-PSD95-nNOS complex and alleviating oxidative stress injury by activating the Nrf2/ARE signaling pathway. Despite current limited treatment options, in-depth research into signaling pathways is crucial for developing novel therapeutic strategies. Paul S's study[37] primarily explored neuroprotective strategies for ischemic stroke, encompassing both clinical and preclinical research. Stroke is a major cause of global disability and death, with ischemic stroke being the most common type. The authors summarized clinical trials completed and ongoing from 2015-2020, involving various drugs such as human urinary kininogenase and statins. The SPAN program, initiated by the National Institute of Neurological Disorders and Stroke, evaluated potential neuroprotective agents like fasudil. Additionally, emerging neuroprotective agents like adropin and STEP-mimetic peptides were introduced. Future efforts should focus on developing multi-target drugs or combination therapies for effective ischemic stroke treatment. Franziska H's research[50] provided guidance for the management of cerebrovascular diseases, analyzing how stroke mortality has declined in recent decades but has reversed in some parts of the United States. The treatment of acute ischemic stroke employs a multidisciplinary approach, with early identification and revascularization being critical. Treatment modalities include intravenous thrombolysis and endovascular therapy, with continuous advancements, such as research into drugs like tenecteplase. In ICU management, attention must be paid to blood oxygen, blood pressure, blood glucose, cerebral edema, fever, and comprehensive rehabilitation, nutritional support, and risk factor interventions. Future endeavors should prioritize patient education and

prevention to reduce the incidence of severe disability or death caused by stroke. Cui Y's article[51] reported that ACSL4 expression is inhibited by HIF-1α in the early stages of cerebral ischemia. Overexpression of ACSL4 exacerbates ischemic brain injury, manifested by increased infarct volume, neurological deficits, neuronal death, and exacerbated neuroinflammation; conversely, knocking down ACSL4 confers protection and alleviates brain injury. ACSL4 exacerbates ischemic stroke injury by promoting neuronal ferroptosis and enhancing microglia-mediated inflammation. This study revealed the critical role of ACSL4 in ischemic stroke, providing a potential therapeutic target for intervention. Review articles offer guiding insights into cell death in stroke research, while original articles provide significant reference value for its application. This also reminds researchers in the field of cell death in stroke to pay closer attention to this information.

3.3. Emerging Trends and New Developments

3.3.1. The Temporal Variation of Keyword Clusters

Keywords exhibit intimate intrinsic connections, with certain keywords forming distinct clusters based on their affinities. Identifying these clusters provides a more intuitive delineation of the hotspot sub-fields in cell death in stroke research. The nearly three decades were divided into four stages, each spanning 6 years, and snapshots of keyword clusters for each stage are presented in Figure 8. The first cluster (1990-1998) analyzed 179 papers, yielding 9 clusters, including #0 DNA fragmentation, #1 glutamate neurotoxicity, and #2 reperfusion (Figure 8A). The second cluster (1999-2007) analyzed 1,416 papers, generating 8 clusters, such as #0 intracerebral hemorrhage,

#1 cerebral ischemia, and #2 oxidative stress (Figure 8B). The third cluster (2008-2016) analyzed 3,789 papers, producing 8 clusters, including #0 hippocampal neurons, #1 neurogenesis, and #2 endoplasmic reticulum stress (Figure 8C). In the fourth cluster (2017-2024), 6,713 papers were included, resulting in 9 clusters: 0# cerebral infarction, 1# heat stroke, 2# mesenchymal stem cells, among others (Figure 8D). Compared to the preceding 15 years, classic research topics like cerebral infarction remain hotspots, while emerging research clusters such as 1# heat stroke, 2# mesenchymal stem cells, 3# myocardial infarction, 4# blood-brain barrier, 5# ferroptosis, 6# neural regeneration, 7# oxidative stress, and 8# network pharmacology have garnered increased attention from researchers.

Our interpretation of the emerging cluster literature reveals that these clusters aim to explore the hotspots of cell death in stroke research. 1# heat stroke comprises 116 articles related to high fever in stroke. 2# mesenchymal stem cells and 6# neural regeneration collect 104 and 76 articles, respectively, focusing on mesenchymal stem cells in post-stroke neural regeneration. 3# myocardial infarction contains 100 articles focusing on the link between myocardial infarction and stroke. 4# blood-brain barrier includes 96 articles on the blood-brain barrier's role in cell death and stroke. 5# ferroptosis gathers 78 articles on ferroptosis in stroke. 7# oxidative stress comprises 58 articles focusing on oxidative stress in stroke. 8# network pharmacology collects 43 articles on network pharmacology studies related to stroke. Table S3 (Supplementary Material) provides detailed data for the fourth cluster (2017-2024), with "Representative Keywords within the Cluster" aiding in pinpointing the core research

areas of cell death in stroke during the most recent phase (2017-2024).

Research into stroke cell death mechanisms exhibits a multi-dimensional evolutionary trend. Early studies focused on the pathophysiological elucidation of single cell death types, such as ferroptosis and oxidative stress. In recent years, with breakthroughs in mesenchymal stem cell intervention techniques and the application of network pharmacology modeling, the research focus has shifted to mechanisms linking multi-system injuries, such as the interplay of blood-brain barrier disruption, oxidative stress imbalance, myocardial diseases, and neural damage. Clinical translational research has expanded from basic treatment scenarios like neuroregeneration and repair to precise treatment fields such as ischemia-reperfusion injury protection and multi-organ complication prevention. Current core challenges include the regulation of cell death, precise grasp of the therapeutic window, and optimization of multi-modal intervention strategies. Future research will integrate artificial intelligence algorithms and single-cell sequencing technologies to achieve a leap forward from mechanistic research to clinical translation.

3.3.2. The Keyword Alluvial Flow Visualization

As shown in Figure 9, associated keywords can coalesce into specific research modules. These modules, through the dynamic recombination of keywords, may differentiate or merge across different time periods, giving rise to new formations.

Over these 25 years, some keyword flows have demonstrated remarkable vitality, some have blossomed into new research trends, while others have gracefully faded into the historical currents of the research landscape. Supplementary Table S4 lists the top

five largest keyword modules each year.

It is evident that the keywords contained within Module 1 in 2024, either diverging or converging within this research river basin, formed the largest research tributary (marked in red). This suggests that Module 1 is the most enduring research module. Furthermore, we depicted all keywords for the top 6 modules in 2024 (Figure 10). Module 1, named "aquaporin_4," gathered 21 keywords such as disruption, regeneration, and ubiquitination (Figure 10A). Module 2, named "stroke," collected 18 keywords including oxidative_stress, activation, apoptosis, and cell_death (Figure 10B). Module 3, named "obesity," comprised 15 keywords such as cardiac_function, heart_failure, atrial_fibrillation, and mortality (Figure 10C). Module 4, named "caspase_8," included 13 keywords like necrosis_factor_alpha, inflammatory_responses, clearance, and necroptosis (Figure 10D). Module 5, named "inflammatory_factors," contained 13 keywords such as pathways, animal_model, and cell_viability (Figure 10E). Module 6, named "cerebral_small_vessel_disease," collected 12 keywords including increases, surgery, fatty_acid_oxidation, and quercetin (Figure 10F). These modules are likely to represent emerging trends in the field of cell death in stroke for the next 5 years and potentially beyond.

The most frequently appearing phrase in the above data is "ischemia-reperfusion injury," revealing its pivotal role in the pathological process of stroke. This is followed by discussions surrounding the "blood-brain barrier," "inflammatory factors," and their related mechanisms, as changes in blood-brain barrier permeability and the inflammatory cytokine cascade significantly influence post-stroke prognosis. Research

on cell death in stroke is rapidly progressing from mechanistic studies to targeted therapies, forming clinical translational solutions based on cell death mechanisms and synergistic multi-target interventions. At the mechanistic level, oxidative stress and inflammatory activation triggered by ischemic stroke initiate a cascade of apoptosis and necroptosis via pathways such as mitochondrial damage and calcium overload. The predominant future direction should focus on targeted inhibition of cell death pathways to enhance neuronal survival rates and reduce infarct size. Research into drugs that regulate immediate characteristics will be crucial in overcoming existing therapeutic bottlenecks.

3.3.3. The Timeline Visualization of References

The timeline visualization, constructed based on the temporal span of citations, can predict which topics are emerging, which are classic, and which are relatively outdated. The timeline map of cell death in stroke research within the given period consists of 15 clusters, arranged from top to bottom by size (Figure 11a). Among these, Cluster 0 neuroprotection, Cluster 4 ischemic stroke, Cluster 5 matrix metalloproteinases, Cluster 9 estrogen, and Cluster 15 permanent ischemic injury are classic topics. While perhaps not the very latest, they maintain intimate connections with other clusters. Cluster 7 DNA fragmentation, Cluster 10 Alzheimer's disease, Cluster 11 almitrine-raubasine, Cluster 12 ischemic penumbra, Cluster 13 human primary neuron cultures, Cluster 14 animal models, Cluster 16 plasminogen activator, and Cluster 17 ischemic stroke are relatively outdated topics, exhibiting few connections with other clusters and lacking subsequent development on their own

timelines. Cluster 0 shear stress, Cluster 1 ferroptosis, Cluster 8 nanomedicine, and Cluster 10 optical coherence tomography are emerging topics, as they have remained active on the timeline since their appearance, foreshadowing their status as future research hotspots. Supplementary Table S5 provides a more detailed overview of these emerging clusters. Furthermore, some classic papers (large nodes with red circles) have played a profoundly significant role in advancing sub-fields (Figure 11b).

"Mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications" by Tuo QZ, published in 2022, belongs to Cluster 1 and has a co-citation frequency of 120. Ischemic stroke, caused by arterial occlusion, is the most common type of stroke and a leading cause of global disability and death. Current treatments involve rapid reperfusion through drugs or surgery, both of which are time-sensitive; moreover, restoring blood flow often leads to ischemia/reperfusion injury. However, despite the urgent need for neuroprotective interventions in stroke, the exact mechanisms of neuronal death during ischemic stroke remain unclear, thus limiting drug development capabilities. The pathogenesis of ischemic stroke is linked to various cell death pathways. Here, we review these potential neuronal death pathways, including intrinsic and extrinsic apoptosis, necrosis, autophagy, ferroptosis, parthanatos, efferocytosis, and pyroptosis. We also review the latest advancements in pharmacological research for ischemic stroke and summarize emerging drug targets, with a focus on clinical trials. These observations may contribute to a further understanding of pathological events in ischemic stroke and bridge the gap between basic and translational research, revealing novel neuroprotective interventions.

"Autophagy in ischemic stroke" by Wang P belongs to Cluster 2, with a co-citation frequency of 74. Autophagy is an autophagic cellular catabolic pathway through which long-lived proteins, damaged organelles, and misfolded proteins are degraded and recycled to maintain cellular balance and normal cell function. Autophagy plays a crucial balancing role in regulating cell survival. Increasing evidence suggests that when ischemic stroke occurs, autophagy is activated in various cell types in the brain, including neurons, glial cells, and brain microvascular cells. However, the exact role and molecular mechanisms of the autophagic process in ischemic stroke remain to be elucidated. This review aims to comprehensively describe the regulation of autophagy in neurons, glial cells, and brain microvascular cells in response to ischemic stress. We also review the latest progress regarding autophagy's involvement in the pathological processes of brain ischemia preconditioning, post-conditioning, and post-treatment. We propose the mutual influence among autophagy, necrosis, and apoptosis, which collectively contribute to ischemic stroke. Furthermore, we discuss the interactions among autophagy, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress. "Neuroinflammation after Intracerebral Hemorrhage and Potential Therapeutic Targets" belongs to Cluster 6, with a co-citation frequency of 59. Spontaneous intracerebral hemorrhage (ICH) is a catastrophic disease leading to severe morbidity and mortality. Despite continuous advancements in surgical techniques for treating primary brain injury caused by ICH, little progress has been made in addressing the subsequent inflammatory cascade. Preclinical studies have advanced, identifying components of neuroinflammation, including microglia, astrocytes, and T lymphocytes.

After brain injury, inflammation is initially driven by M1 microglia, which secrete cytokines (e.g., interleukin-1β (IL-1β) and tumor necrosis factor-α) involved in the breakdown of the extracellular matrix, cellular integrity, and the blood-brain barrier. Furthermore, inflammatory factors recruit and induce the differentiation of A1 reactive astrocytes and T helper 1 (Th1) cells, thereby promoting the secretion of inflammatory cytokines, enhancing M1 polarization, and exacerbating inflammation. Within 7 days of ICH onset, the M1 phenotype transforms into the M2 phenotype, which is crucial for hematoma clearance, tissue healing, and overall resolution of inflammation. The secretion of anti-inflammatory cytokines (e.g., IL-4, IL-10) can promote Th2 cell differentiation. Th2 cells secrete more anti-inflammatory cytokines, inhibiting M1 and Th1 phenotypes, thereby maintaining M2 polarization. Elucidating the timing and triggers of anti-inflammatory phenotypes may be indispensable for improving clinical outcomes. A current challenge in translational research is the lack of equivalent disease animal models that reflect patient populations and co-morbid pathophysiological states. We reviewed existing data and described potential therapeutic targets, and we are developing a bench-to-bedside translational research model around these targets to better reflect the pathophysiology of ICH patients. "Selenium Drives a Transcriptional Adaptive Program to Block Ferroptosis and Treat Stroke," belonging to Cluster 8, ferroptosis is a non-apoptotic form of programmed cell death triggered by oxidative stress in cancer, heat stress in plants, and hemorrhagic stroke. The balanced transcriptional response to ferroptosis stimuli is not yet understood. Our study demonstrated that neurons respond to ferroptotic stimuli by inducing selenoproteins,

including the antioxidant glutathione peroxidase 4 (GPX4). Pharmacological selenium (Se) protects neurons by coordinately activating transcription factors TFAP2c and Sp1, enhancing GPX4 and other genes in this transcriptional program (the selenosome). Notably, in a hemorrhagic stroke model, administering a single dose of selenium into the brain promoted GPX4 expression, protected neurons, and improved behavior. In summary, our study indicates that pharmacological Se supplementation effectively inhibits GPX4-dependent ferroptosis as well as cell death-induced toxicity or ER stress, which are independent of GPX4. Systemic administration of brain-penetrant selenium peptides after hemorrhagic or ischemic stroke can activate homologous transcription of cell death and improve function.

We further analyzed the recent citation distribution of these four articles (Figure 11c), predicting that they are likely to be revisited in the coming years.

Discussion

Stroke, a devastating neurological event, remains a leading cause of long-term disability and mortality globally[32,52]. Our comprehensive bibliometric analysis, encompassing 12,097 publications from 1990 to 2024, meticulously maps the dynamic evolution of research on cell death in stroke. This study not only quantifies the growth trajectory of the field but also illuminates its intellectual landscape, identifying key scientific collaborations, influential research topics, and emerging frontiers. The observed exponential increase in publications, particularly after 2011 and peaking in 2021, underscores the burgeoning scientific interest and the escalating global health burden associated with stroke[53]. This trend aligns with epidemiological data

highlighting a worldwide rise in stroke incidence, necessitating intensified research efforts into its multifaceted pathophysiology and therapeutic interventions[54].

The intricate co-citation network vividly portrays the foundational works that have shaped our understanding of cell death in stroke. Early research, epitomized by works published between 1990 and 2005, laid the groundwork by focusing on fundamental mechanisms of neuronal damage[55]. The seminal contributions by Broughton BRS (2009) and Matsushita K[40], for instance, were pivotal in shifting the paradigm from an exclusive focus on necrosis to recognizing the significant role of apoptosis in ischemic brain injury[15]. This recognition has opened new avenues for neuroprotective strategies targeting specific apoptotic pathways, such as those involving mitochondrial cytochrome c release and caspase activation[36]. Subsequent studies, including those by Doyle KP[39], further elucidated the complex interplay of excitotoxicity, oxidative stress, and inflammatory responses in post-stroke neuronal demise, emphasizing the multifactorial nature of ischemic brain damage. The sustained high co-citation frequencies of these early works signify their enduring impact and continued relevance in guiding contemporary research.

The burden of stroke extends beyond mere incidence, encompassing significant health and economic costs, as highlighted by Benjamin EJ (2017; 2019)[34,56]. The global disparity in stroke outcomes, with low-income countries facing higher mortality and DALY rates, underscores the critical need for equitable access to prevention and care strategies [57]. Effective prevention hinges on rigorous control of modifiable risk factors, including hypertension, obesity, and hyperglycemia[58]. Furthermore, timely

and effective intervention, particularly reperfusion therapy for ischemic stroke, is paramount for improving patient outcomes[59]. Campbell BCV (2019) elegantly demonstrated the time-sensitive nature of thrombolysis and thrombectomy, extending therapeutic windows based on advanced imaging to mitigate disability[60]. However, the challenge of ischemia-reperfusion injury (IRI) remains, often exacerbating tissue damage through the burst of free radicals, calcium overload, and inflammatory cascades triggered upon reperfusion[61]. This complex interplay necessitates a deeper understanding of diverse cell death pathways beyond traditional necrosis and apoptosis, including necroptosis, autophagy, ferroptosis, and pyroptosis, as well as more recently identified mechanisms such as cuproptosis[62].

Our analysis of scientific cooperation reveals a robust and expanding network, with China, the United States, Japan, South Korea, and Germany leading in publication volume and collaborative endeavors[63]. The observed clustering among authors and institutions, such as Capital Medical University and the University of California System, indicates the formation of established research hubs and strong collaborative ties. These collaborative networks are crucial for facilitating knowledge exchange, fostering interdisciplinary approaches, and accelerating research progress in a field as complex as stroke.

The temporal shifts in active subject categories and keywords provide invaluable insights into the evolving research landscape. The initial focus on "CRITICAL CARE MEDICINE" and "SURGERY" reflects the early emphasis on immediate clinical management and intervention[64]. The subsequent diversification into

"MULTIDISCIPLINARY SCIENCES" and "TRANSPLANTATION" signals a broadening scope, incorporating advanced treatment modalities like regenerative medicine and neural function remodeling. The most recent emergence of "CHEMISTRY, MEDICINAL," "PLANT SCIENCES," and "NANOSCIENCE & NANOTECHNOLOGY" indicates a groundbreaking shift towards novel therapeutic development, material science applications, and a deeper integration of chemical biology[65]. This multidisciplinary expansion is crucial for deciphering complex pathological mechanisms and forging innovative pathways for targeted therapies and regenerative medicine[66,67].

Keyword burst analysis further refines our understanding of research hotspots. The sustained burst of "ischemic stroke," coupled with emerging bursts in "neuroinflammation" and "NLRP3 inflammasome," underscores a progressive shift from broad pathological mechanisms to precise molecular interventions[68]. The NLRP3 inflammasome, in particular, has garnered significant attention due to its central role in mediating inflammatory cascades post-stroke, representing a promising target for anti-neuroinflammatory drug development[49,69]. Furthermore, the identification of topics like "mesenchymal stem cells," "ferroptosis," and "network pharmacology" as emerging clusters highlights the forefront of current investigations[51,70]. Mesenchymal stem cells offer immense potential for neural regeneration and repair, while the recognition of ferroptosis, a distinct form of regulated cell death, provides new avenues for therapeutic intervention[21]. The application of network pharmacology signifies a move towards understanding complex drug-target

interactions and identifying multi-target therapies, which are increasingly seen as essential for managing multifactorial diseases like stroke[71].

Despite significant advancements, challenges persist in translating basic research into clinically efficacious treatments. Most neuroprotective agents, based on cell death mechanisms, have unfortunately failed in advanced clinical trials, often due to poor blood-brain barrier penetration or a lack of precise targeting[72]. The current therapeutic landscape largely relies on drugs like Edaravone and Nimodipine, whose mechanisms and efficacy require further elucidation[73]. Future research must prioritize optimizing drug delivery technologies, including intranasal administration, focused ultrasound, and transporter-mediated approaches, to enhance drug bioavailability in the brain[74].

The timeline visualization of references offers a discerning perspective on the longevity and impact of various research themes. While "neuroprotection," "ischemic stroke," and "matrix metalloproteinases" remain classic and interconnected topics, newer concepts like "ferroptosis" and "nanomedicine" have demonstrated sustained activity, signaling their ascendancy as future research hotspots[75]. The insights from Tuo QZ (2022) regarding the multifaceted neuronal death pathways in ischemic stroke and potential therapeutic targets, and Wang P's review on the dual role of autophagy, are exemplary of contemporary efforts to bridge basic science with translational research[76]. Similarly, understanding neuroinflammation post-intracerebral hemorrhage, including the dynamic shifts in microglial phenotypes, is critical for developing targeted anti-inflammatory strategies[77]. The discovery that selenium can

inhibit ferroptosis and improve stroke outcomes, as presented in Cluster 8, opens exciting avenues for nutritional and pharmacological interventions[78].

Conclusion

Our bibliometric analysis reveals a dynamic and rapidly evolving field of cell death in stroke research, characterized by increasing publication output, robust international collaboration, and a continuous shift towards more precise, multidisciplinary, and clinically translational approaches. The transition from fundamental mechanistic studies of single cell death types to an integrated understanding of multi-system injuries and multi-target interventions represents a significant maturation of the field. Future endeavors must focus on overcoming translational hurdles, particularly in drug delivery and the development of animal models that accurately reflect human stroke pathophysiology. The integration of cutting-edge technologies, such as artificial intelligence algorithms for drug discovery and single-cell sequencing for detailed mechanistic insights, holds immense promise for realizing effective neuroprotective strategies and ultimately improving outcomes for stroke patients worldwide.

Conflict of Interest

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

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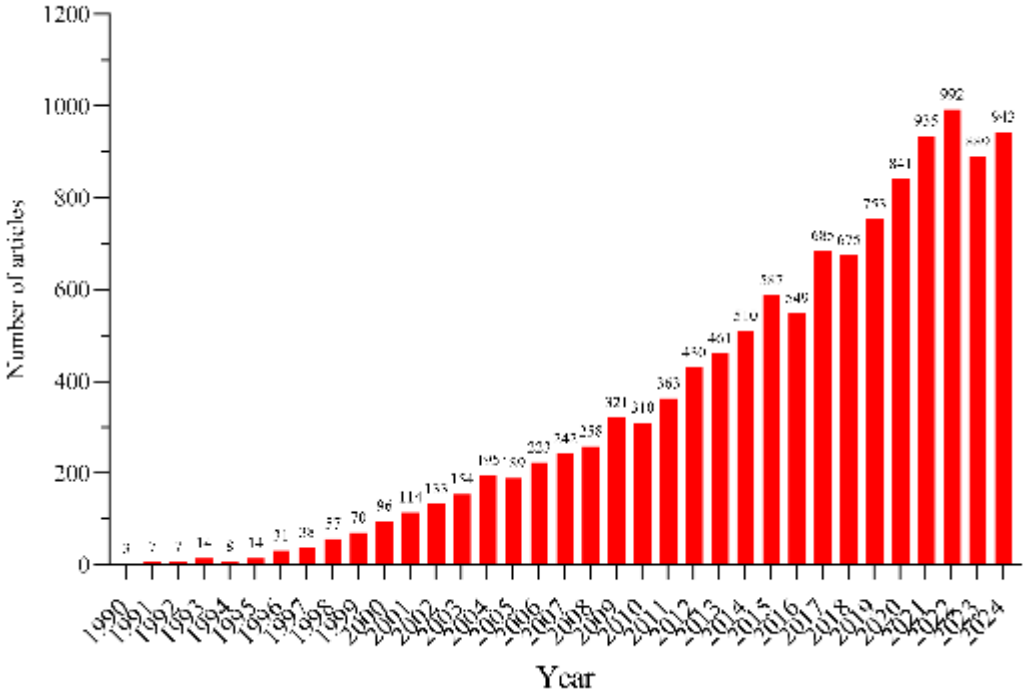

Fig2. The annual distribution of publications

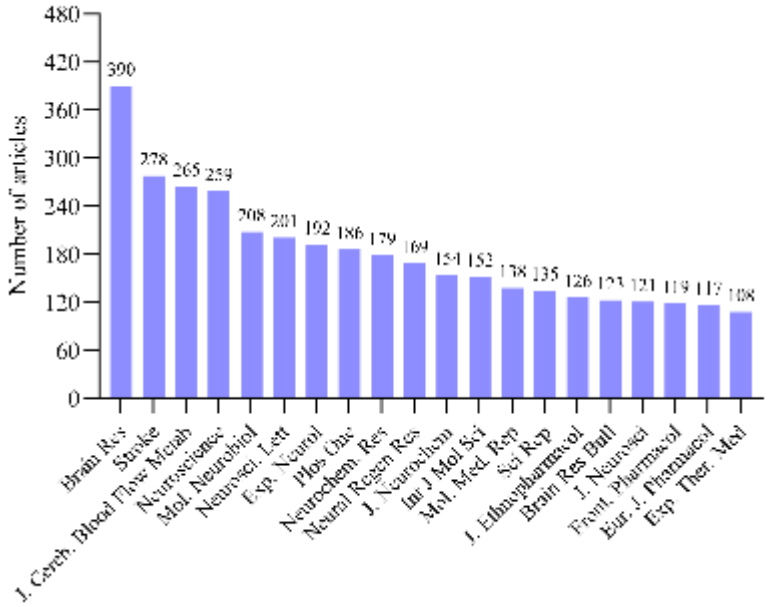

Fig3. The top 20 fruitful journals (Red columns). Y-axis: Publication’ s quantity.

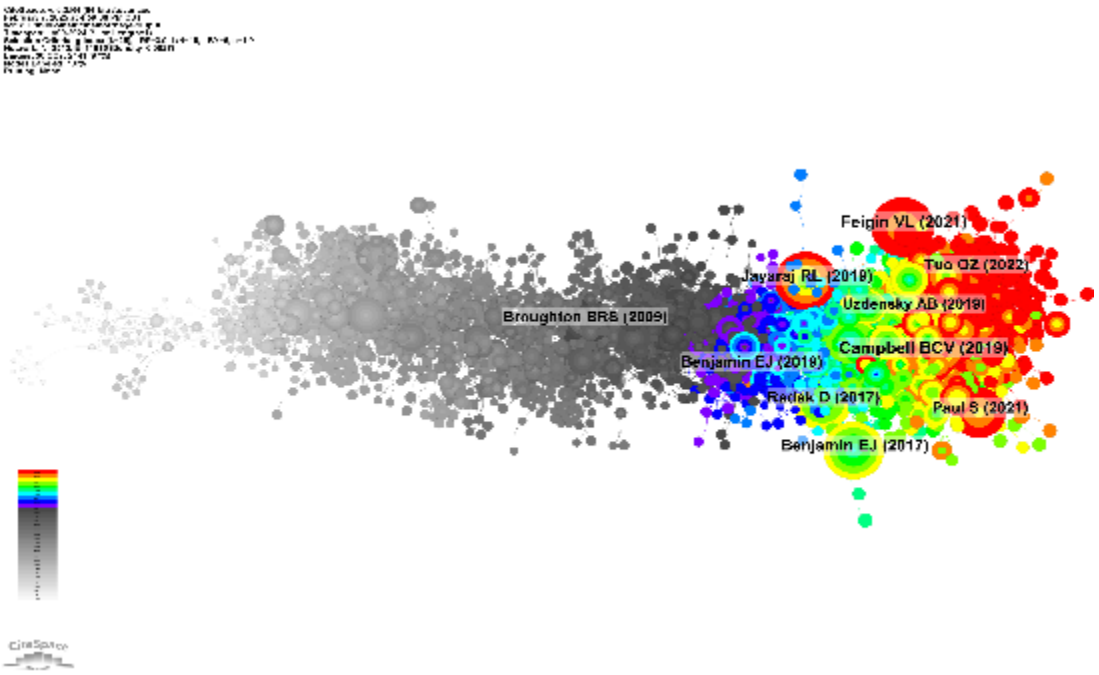

Fig4. The citation co-occurrence network. The color bar from left(white) to right(red) indicates the year from 1990 to 2024.

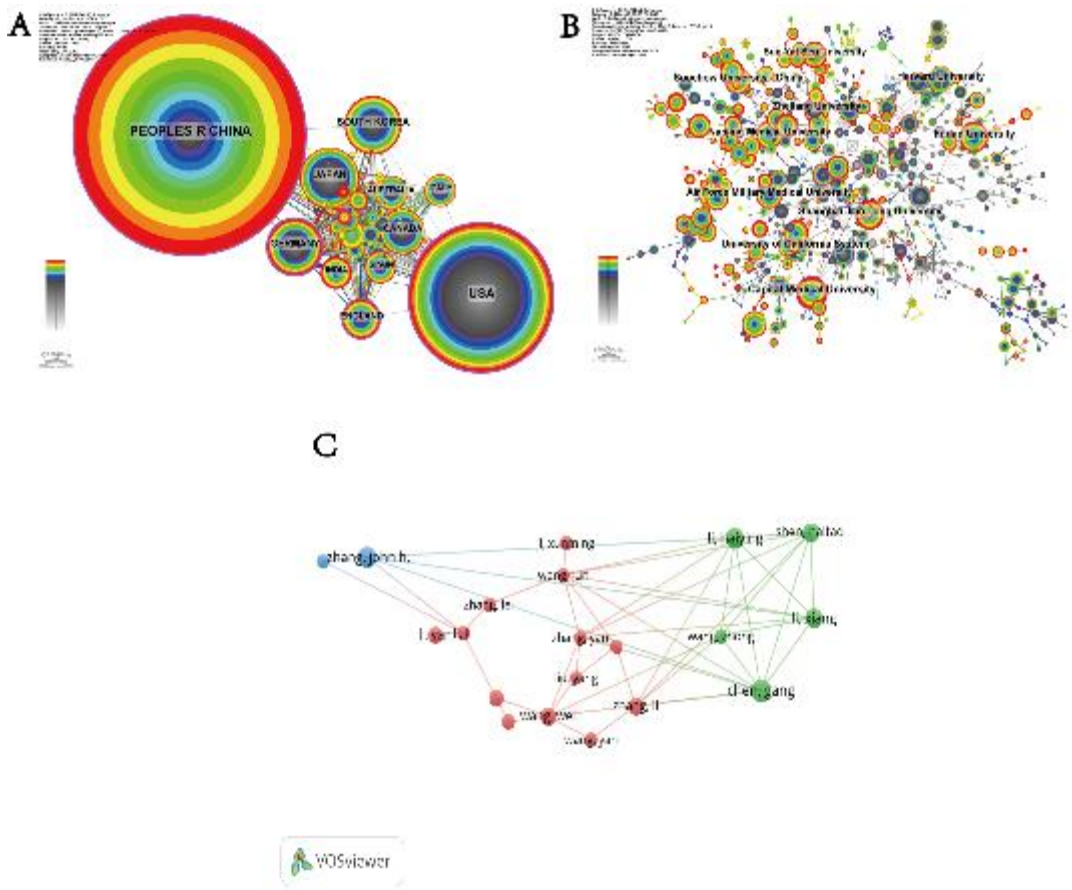

Fig 5. The scientific cooperation network. A: Country cooperation, B: Institution cooperation, C: Author cooperation, i: Author clustering as represented by

Top 50 Subject Categories with the Strongest Citation Bursts

Subject Categories	Year	Strength	Begin	End	1990 - 2024
CRITICAL CARE MEDICINE	1992	13.95	**2004**	2012	
NEUROIMAGING	1992	1.78	**2006**	2008	
CARDIAC & CARDIOVASCULAR SYSTEMS	1995	3.19	**2007**	2007	
SURGERY	1993	13.12	**2009**	2013	
HEMATOLOGY	1995	5.72	**2010**	2011	
ENDOCRINOLOGY & METABOLISM	1995	1.58	**2010**	2011	
CLINICAL NEUROLOGY	1990	11.64	**2011**	2011	
PERIPHERAL VASCULAR DISEASE	1992	3.04	**2011**	2011	
MULTIDISCIPLINARY SCIENCES	1991	17.42	**2012**	2015	
GASTROENTEROLOGY & HEPATOLOGY	2003	2.19	**2014**	2015	
OPHTHALMOLOGY	2003	2.59	**2015**	2016	
RESPIRATORY SYSTEM	2001	2.55	**2016**	2016	
PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	2007	2.02	**2016**	2018	
MEDICINE, RESEARCH & EXPERIMENTAL	1991	38.11	**2017**	2021	
PHYSIOLOGY	1991	7.9	**2017**	2018	
TRANSPLANTATION	2005	3.72	**2018**	2019	
BIOPHYSICS	1997	2.35	**2018**	2018	
CELL & TISSUE ENGINEERING	2005	2.1	**2018**	2020	
PSYCHIATRY	1991	6.71	**2019**	2021	
HEALTH CARE SCIENCES & SERVICES	2016	2.67	**2019**	2022	
OPTICS	2009	2.23	**2019**	2019	
BIOTECHNOLOGY & APPLIED MICROBIOLOGY	1998	12.36	**2020**	2022	
GERIATRICS & GERONTOLOGY	1993	11.24	**2020**	2021	
ONCOLOGY	1997	8.57	**2020**	2021	
DEVELOPMENTAL BIOLOGY	1996	4.88	**2020**	2021	
MATERIALS SCIENCE, MULTIDISCIPLINARY	2006	19.48	**2021**	2024	
INTEGRATIVE & COMPLEMENTARY MEDICINE	2001	16.88	**2021**	2024	
MATHEMATICAL & COMPUTATIONAL BIOLOGY	2004	1.8	**2021**	2024	
POLYMER SCIENCE	2018	1.73	**2021**	2024	
PLANT SCIENCES	2000	25.05	**2022**	2024	
NANOSCIENCE & NANOTECHNOLOGY	2006	24.67	**2022**	2024	
CHEMISTRY, MULTIDISCIPLINARY	1999	24.59	**2022**	2024	
IMMUNOLOGY	1993	10.95	**2022**	2024	
FOOD SCIENCE & TECHNOLOGY	2004	10.14	**2022**	2024	
CHEMISTRY, PHYSICAL	2005	7.73	**2022**	2024	
ENGINEERING, CHEMICAL	2022	5.88	**2022**	2024	
ENGINEERING, ENVIRONMENTAL	2012	5.61	**2022**	2024	
MEDICINE, GENERAL & INTERNAL	1991	5.44	**2022**	2024	
WATER RESOURCES	2022	3.62	**2022**	2024	
MICROBIOLOGY	2006	2.17	**2022**	2024	
NUTRITION & DIETETICS	2004	2.12	**2022**	2022	
ZOOLOGY	2001	1.84	**2022**	2024	
GENETICS & HEREDITY	1998	1.7	**2022**	2024	
CHEMISTRY, MEDICINAL	1997	28.67	**2023**	2024	
MATERIALS SCIENCE, BIOMATERIALS	2011	6.64	**2023**	2024	
BEHAVIORAL SCIENCES	2002	6.64	**2023**	2024	
ENGINEERING, BIOMEDICAL	2003	3.92	**2023**	2024	
PHYSICS, CONDENSED MATTER	2014	3.67	**2023**	2024	
PHYSICS, APPLIED	2014	3.34	**2023**	2024	
VETERINARY SCIENCES	2003	1.77	**2023**	2024	

Fig6. The top 50 subject categories with the strongest citation bursts. Year: Year of the first occurrence, Strength: Burst’s strength, Begin: Burst’s beginning year, End: Burst’s ending year.

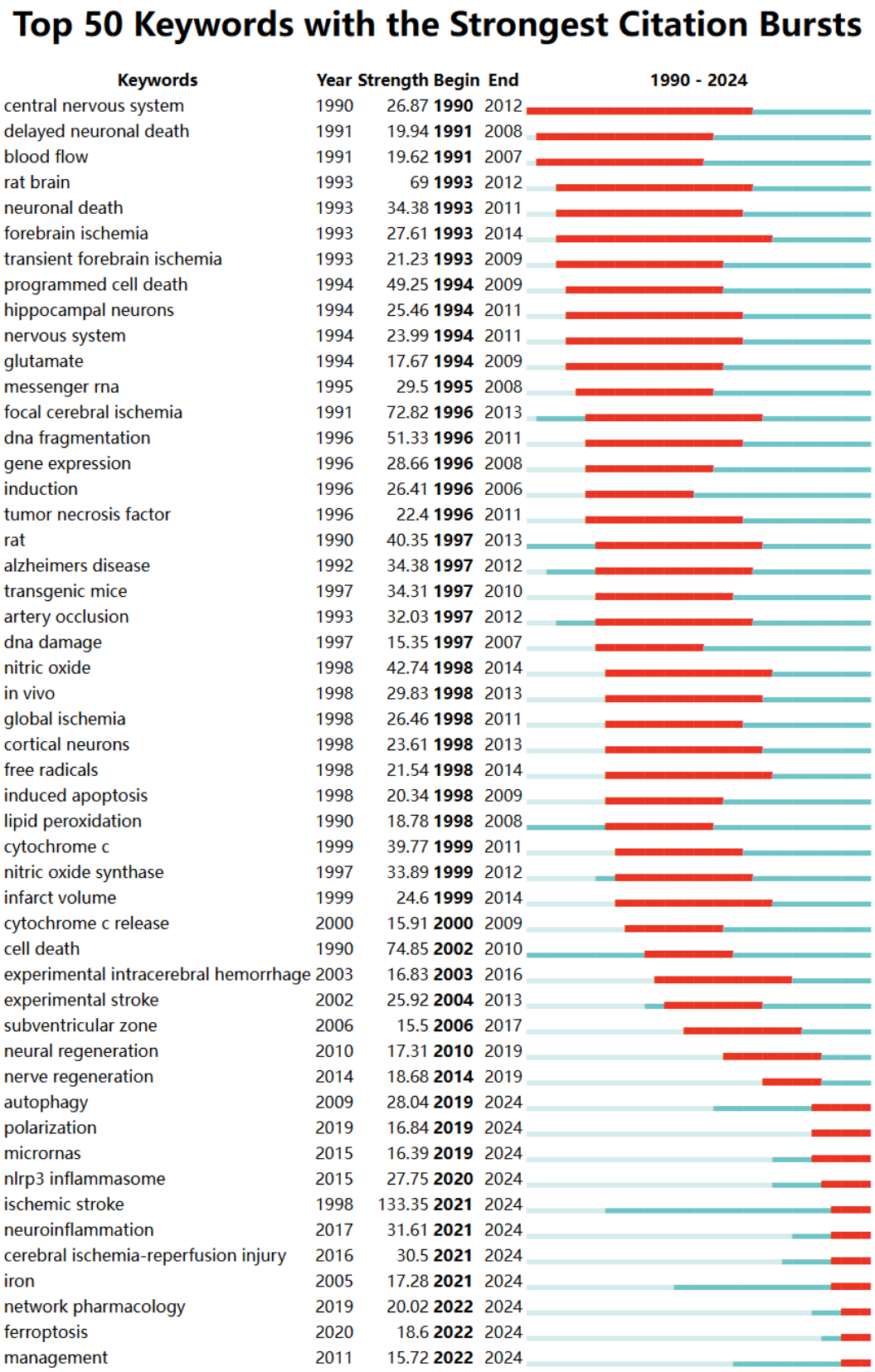

Fig 7. The top 30 keywords with the strongest citation bursts.

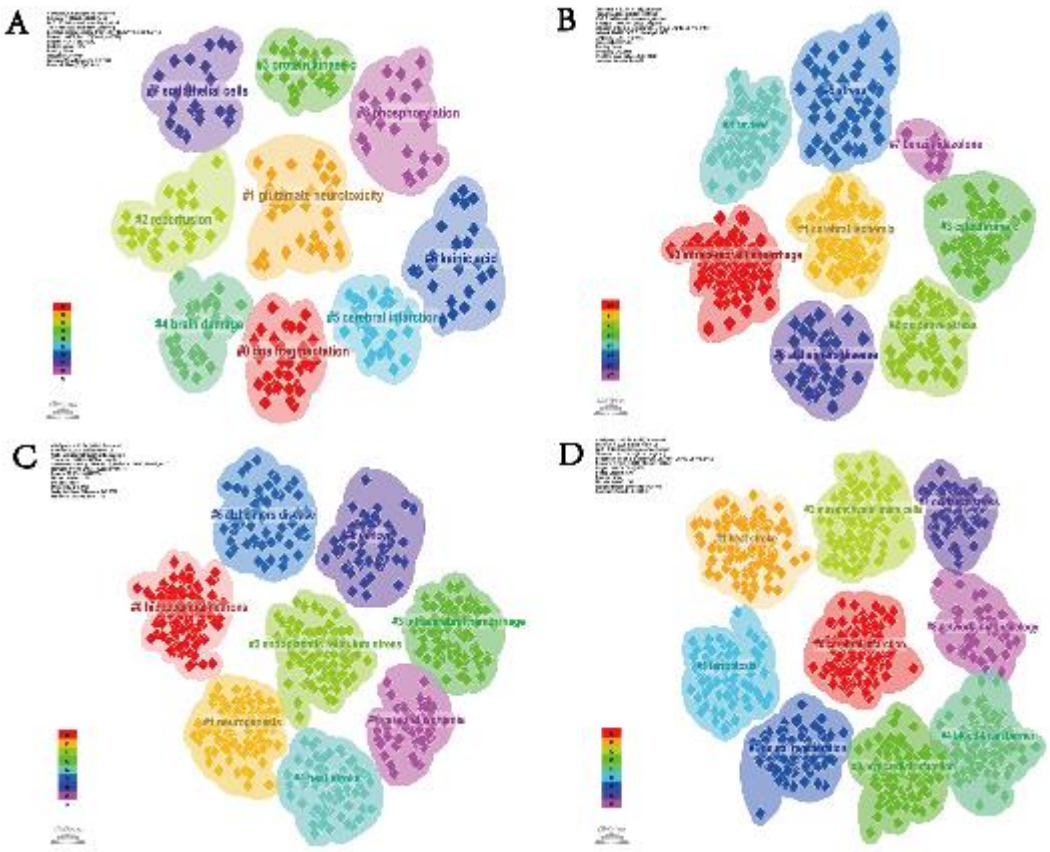

Fig 8. The keyword clusters snapshots in four periods. A: 1990 – 1998, B: 1999 – 2007, C: 2008 – 2016, D: 2017 – 2024.

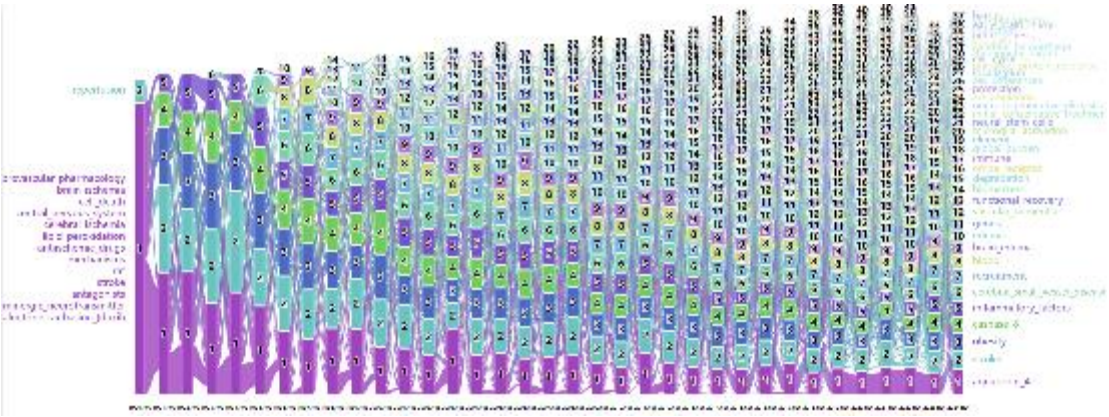

Fig9. The keywords alluvial map 1990 – 2024. X axis: Time slice. Y axis: Counting of modules. Number: Order of modules on each time slice sorted by the number of nodes.

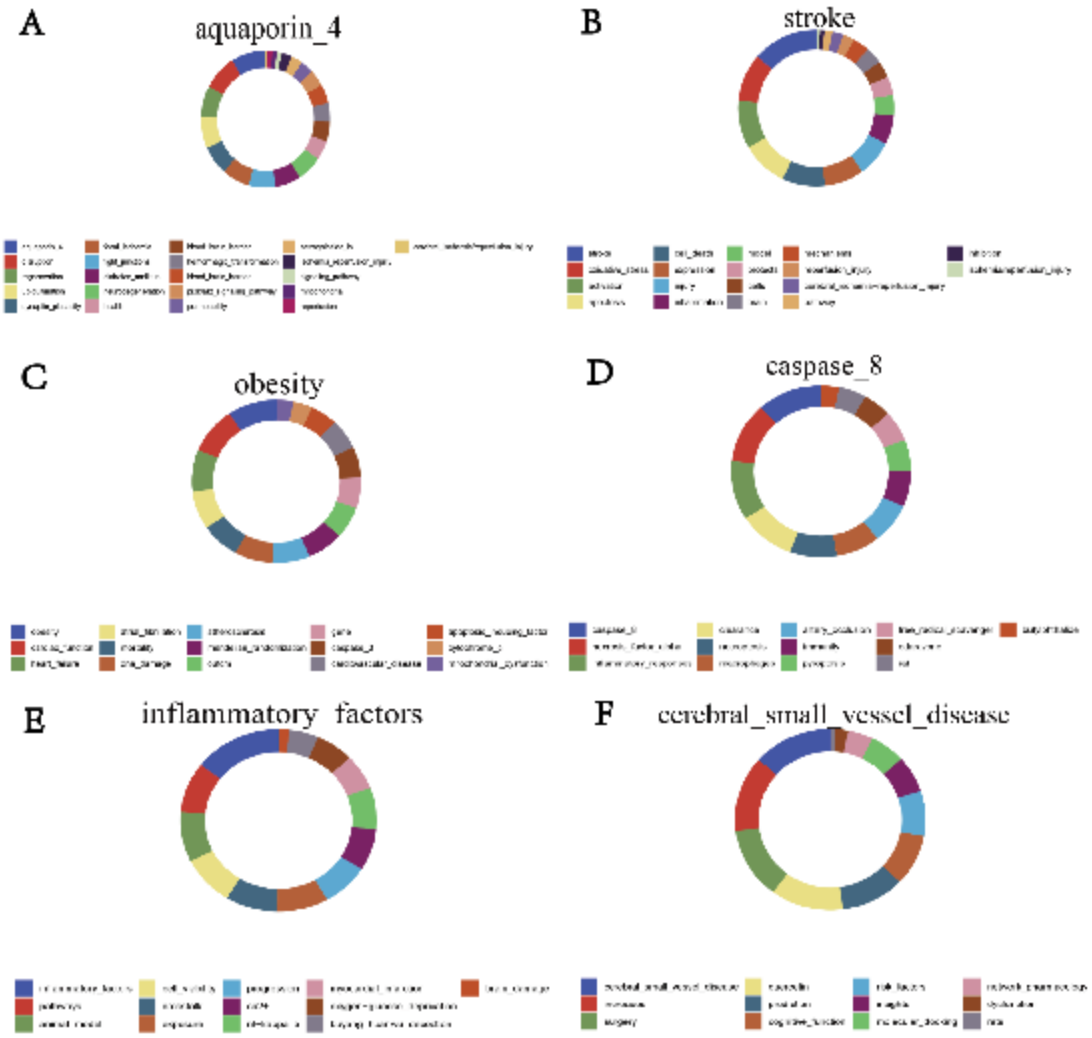

Fig10. The keywords of top 5 modules in 2024. A: Module 1. B: Module 2. C: Module 3. D: Module 4. E: Module 5. F: Module 6.

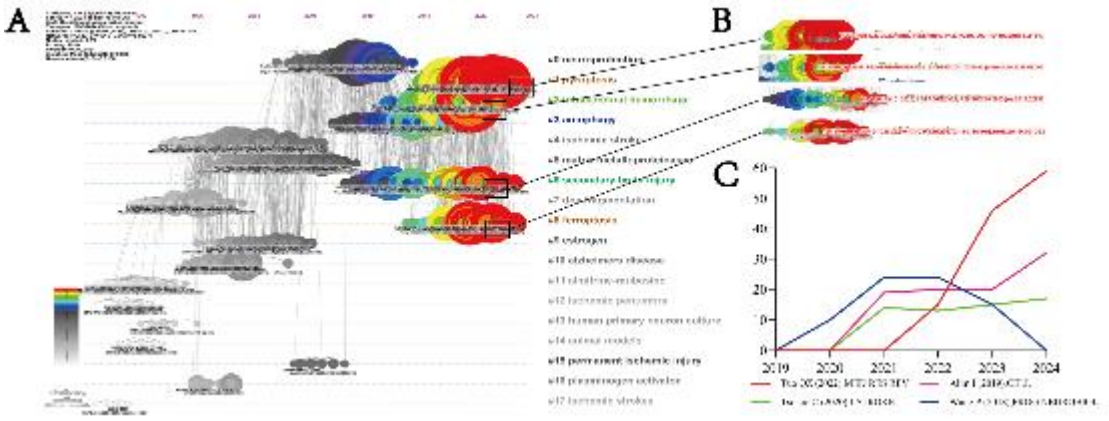

Fig11. The reference clusters map. a. the citation timeline visualization, b. The burst citation in #1, #2, #6, and #8, c. citation frequency distribution of the burst citation, X-axis: Year, Y-axis: Cited frequency

Table 1. Overview of publication distribution.

Categories	Publication	Authors	Institutions	Journals	Subject categories
Amount	12097	37642	6470	1398	123

Table 2. Details of the top 30 publications ranked by LCS (Local Citation Score).

NO.	Article information	Journal	LCS	GCS
2005	Apoptotic Mechanisms After Cerebral Ischemia	STROKE	384	1037
1769	Mechanisms of ischemic brain damage	NEUROPHARMACOLOGY	149	677
267	Evidence for apoptosis after intracerebral hemorrhage in rat striatum	J CEREBR BLOOD F MET	130	490
1057	Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury	NAT CHEM BIOL	120	224
202	NF-κB is activated and promotes cell death in focal cerebral ischemia	NAT MED	111	2319
647	Apoptosis as a form of cell death in intracerebral hemorrhage	NEUROSURGERY	109	585
29	EVIDENCE SUPPORTING A ROLE FOR PROGRAMMED CELL-DEATH IN FOCAL CEREBRAL-ISCHEMIA IN RATS	STROKE	107	682
5645	Neuronal Death After Hemorrhagic Stroke In Vitro and In Vivo Shares Features of Ferroptosis and Necroptosis	STROKE	107	182
5975	Tau-mediated iron export prevents ferroptotic damage after ischemic stroke	MOL PSYCHIATR	107	401
7054	Selenium Drives a Transcriptional Adaptive Program to Block Ferroptosis and Treat Stroke	CELL	106	508
6331	Autophagy in ischemic stroke	PROG NEUROBIOL	94	688
97	Inhibition of interleukin 1 beta converting enzyme family proteases reduces ischemic and excitotoxic neuronal damage	P NATL ACAD SCI USA	93	317
1755	Neuronal injury in rat model of permanent focal cerebral ischemia is associated with activation of autophagic and lysosomal pathways	AUTOPHAGY	89	754
60	Very delayed infarction after mild focal cerebral ischemia: A role for apoptosis?	J CEREBR BLOOD F MET	84	354
3365	Molecular Mechanisms of Ischemia-Reperfusion Injury in Brain: Pivotal Role of the Mitochondrial Membrane Potential in Reactive Oxygen Species Generation	MOL NEUROBIOL	82	529
8570	ACSL4 exacerbates ischemic stroke by promoting	BRAIN BEHAV	80	508

	ferroptosis-induced brain injury and neuroinflammation	IMMUN		
2275	miR-497 regulates neuronal death in mouse brain after transient focal cerebral ischemia	NEUROBIOL DIS	79	327
646	Bcl-2 overexpression protects against neuron loss within the ischemic margin following experimental stroke and inhibits cytochrome c translocation and caspase-3 activity	J NEUROCHEM	78	270
2195	Brain and blood microRNA expression profiling of ischemic stroke, intracerebral hemorrhage, and kainate seizures	J CEREBR BLOOD F MET	77	283
7390	Global brain inflammation in stroke	LANCET NEUROL	76	445
390	Intracerebral hemorrhage-induced neuronal death	NEUROSURGERY	75	152
118	Ischemic brain injury is mediated by the activation of poly(ADP-ribose)polymerase	J CEREBR BLOOD F MET	75	562
287	Intracerebral injection of autologous whole blood in rats: time course of inflammation and cell death	NEUROSCI LETT	71	529
695	A peptide inhibitor of c-Jun N-terminal kinase protects against excitotoxicity and cerebral ischemia	NAT MED	70	215
6241	Melatonin Alleviates Intracerebral Hemorrhage-Induced Secondary Brain Injury in Rats via Suppressing Apoptosis, Inflammation, Oxidative Stress, DNA Damage, and Mitochondria Injury	TRANSL STROKE RES	70	591
429	Specific caspase pathways are activated in the two stages of cerebral infarction	J NEUROSCI	67	214
495	Cell death in experimental intracerebral hemorrhage: The black hole" model of hemorrhagic damage"	ANN NEUROL	67	166
2217	DAPK1 Interaction with NMDA Receptor NR2B Subunits Mediates Brain Damage in Stroke	CELL	67	228
1960	Neuroprotective strategies targeting apoptotic and necrotic cell death for stroke	APOPTOSIS	66	397
1680	A new penumbra: transitioning from injury into repair after stroke	NAT MED	65	471

Table 3 The references with citation bursts at different period.

References	Year	Strength	Begin	End	2004 - 2024
LI Y, 1995, J CEREBR BLOOD F MET, V15, P389, DOI 10.1038/jcbfm.1995.49, [1]	1995	26.15	**1996**	2000	
Du C, 1996, J CEREBR BLOOD F MET, V16, P195, DOI 10.1097/00004647-199603000-00003, DOI	1996	24.54	**1997**	2001	
Endres H, 1998, J CEREBR BLOOD F MET, V18, P238, DOI 10.1097/00004647-199803000-00002, DOI	1998	24.71	**1998**	2003	
Namura S, 1998, J NEUROSCI, V18, P3659	1998	34.92	**1999**	2003	
Dirnagl U, 1999, TRENDS NEUROSCI, V22, P391, DOI 10.1016/S0166-2236(99)01401-0, DOI	1999	38.06	**2000**	2004	
Lipton P, 1999, PHYSIOL REV, V79, P1431, DOI 10.1152/physrev.1999.79.4.1431, DOI	1999	28.97	**2000**	2004	
Graham SH, 2001, J CEREBR BLOOD F MET, V21, P99, DOI 10.1097/00004647-200102000-00001, DOI	2001	27.89	**2001**	2006	
Donnan GA, 2008, LANCET, V371, P1612, DOI 10.1016/S0140-6736(08)60694-7, DOI	2008	31.84	**2009**	2013	
Wang Q, 2007, J NEUROIMMUNOL, V184, P53, DOI 10.1016/j.jneuroim.2006.11.014, DOI	2007	24.64	**2009**	2012	
Broughton BRS, 2009, STROKE, V40, PE331, DOI 10.1161/STROKEAHA.108.531632, DOI	2009	61.86	**2010**	2014	
Moskowitz MA, 2010, NEURON, V67, P181, DOI 10.1016/j.neuron.2010.07.002, DOI	2010	47.94	**2011**	2015	
Jin R, 2010, J LEUKOCYTE BIOL, V87, P779, DOI 10.1189/jlb.1109766, DOI	2010	24.76	**2011**	2015	
Lakhan SE, 2009, J TRANSL MED, V7, P0, DOI 10.1186/1479-5876-7-97, DOI	2009	24.21	**2011**	2014	
Iadecola C, 2011, NAT MED, V17, P796, DOI 10.1038/nm.2399, DOI	2011	42.54	**2012**	2016	
Keep RF, 2012, LANCET NEUROL, V11, P720, DOI 10.1016/S1474-4422(12)70104-7, DOI	2012	33.85	**2014**	2017	
Lai TW, 2014, PROG NEUROBIOL, V115, P157, DOI 10.1016/j.pneurobio.2013.11.006, DOI	2014	30.04	**2015**	2019	
Zhou Y, 2014, PROG NEUROBIOL, V115, P25, DOI 10.1016/j.pneurobio.2013.11.003, DOI	2014	26.28	**2015**	2019	
Feigin VL, 2014, LANCET, V383, P245, DOI 10.1016/S0140-6736(13)61953-4, DOI	2014	24.13	**2015**	2019	
Mozaffarian D, 2015, CIRCULATION, V131, PE29, DOI 10.1161/CIR.0000000000000152, DOI	2015	26.12	**2016**	2020	
Chamorro A, 2016, LANCET NEUROL, V15, P869, DOI 10.1016/S1474-4422(16)00114-9, DOI	2016	38.08	**2017**	2021	
Mozaffarian D, 2016, CIRCULATION, V133, PE38, DOI 10.1161/CIR.0000000000000350, DOI	2016	27.41	**2017**	2019	
Benjamin EJ, 2017, CIRCULATION, V135, PE146, DOI 10.1161/CIR.0000000000000530, DOI	2017	47.59	**2018**	2022	
Khoshnam SE, 2017, NEUROL SCI, V38, P1167, DOI 10.1007/s10072-017-2938-1, DOI	2017	31.41	**2018**	2022	
Hankey GJ, 2017, LANCET, V389, P641, DOI 10.1016/S0140-6736(16)30962-X, DOI	2017	31.06	**2018**	2022	
Radak D, 2017, CURR VASC PHARMACOL, V15, P115, DOI 10.2174/1570161115666161104095522, DOI	2017	47.26	**2019**	2022	
Jayaraj RL, 2019, J NEUROINFLAMM, V16, P0, DOI 10.1186/s12974-019-1516-2, DOI	2019	26.06	**2020**	2024	
Campbell BCV, 2019, NAT REV DIS PRIMERS, V5, P0, DOI 10.1038/s41572-019-0118-8, DOI	2019	40.68	**2022**	2024	
Paul S, 2021, EXP NEUROL, V335, P0, DOI 10.1016/j.expneurol.2020.113518, DOI	2021	35.54	**2022**	2024	
Herpich F, 2020, CRIT CARE MED, V48, P1654, DOI 10.1097/CCM.0000000000004597, DOI	2020	26.19	**2022**	2024	
Maida CD, 2020, INT J MOL SCI, V21, P0, DOI 10.3390/ijms21186454, DOI	2020	23.76	**2022**	2024	

Table4. The references with citation bursts from beginning to 2024.

be'gin	end	Strebgth	Year	Type	Title
2023	2024	44.67	2022	Review	Mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications
2022	2024	35.54	2019	Review	Emerging neuroprotective strategies for the treatment of ischemic stroke: An overview of clinical and preclinical studies
2023	2024	30.23	2021	Review	Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions
2023	2024	27.87	2022	Article	ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation
2022	2024	26.19	2021	Review	Management of Acute Ischemic Stroke
2020	2024	26.06	2021	Review	Neuroinflammation: friend and foe for ischemic stroke
2022	2024	23.76	2020	Review	Neuroinflammatory Mechanisms in Ischemic Stroke: Focus on Cardioembolic Stroke, Background, and Therapeutic Approaches
2020	2024	23.2	2019	Review	Autophagy in ischemic stroke
2020	2024	22.89	2020	Review	Global Burden of Stroke
2021	2024	22.68	2018	Article	Selenium Drives a Transcriptional Adaptive Program to Block Ferroptosis and Treat Stroke
2022	2024	22	2018	Review	Pathophysiology of Ischemic Stroke: Role of Oxidative Stress
2020	2024	20.68	2019	Review	Free Radical Damage in Ischemia-Reperfusion Injury: An Obstacle in Acute Ischemic Stroke after Revascularization Therapy
2022	2024	19.91	2020	Review	Cell Death Pathways in Ischemic Stroke and

					Targeted Pharmacotherapy
2023	2024	19.67	2018	Review	Neuroinflammation in Cerebral Ischemia and Ischemia/Reperfusion Injuries: From Pathophysiology to Therapeutic Strategies
2023	2024	19.67	2020	Review	Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment (Review)
2020	2024	19.43	2022	Review	Blood-brain barrier dysfunction and recovery after ischemic stroke
2020	2024	19.43	2022	Review	Current Mechanistic Concepts in Ischemia and Reperfusion Injury
2022	2024	19.27	2018	Review	Ferroptosis: mechanisms, biology and role in disease
2020	2024	19.11	2018	Review	Neuronal Cell Death
2021	2024	18.8	2021	Review	Apoptosis regulation in the penumbra after ischemic stroke: expression of pro- and antiapoptotic proteins