


The Clinical Research Landscape of Intracranial Nicardipine for Aneurysmal Subarachnoid Hemorrhage: Insights From Bibliometric Analysis

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Background: The 2023 American Heart Association/American Stroke Association guideline and Wessels et al's 2024 randomized controlled trial highlight the potential benefits of intracranial nicardipine for aneurysmal subarachnoid hemorrhage (aSAH). This study aims to systematically identify the publication trends and research hotspots in this field through bibliometric analysis.

Methods: Relevant publications were sourced from the Web of Science Core Collection (WoSCC). Bibliometric and visualization analyses were conducted using the online tools of the WoSCC database and CiteSpace 6.2.R6.

Results: Analysis of 28 articles published by 158 researchers from 55 institutions across 8 countries revealed an intermittent small-scale growth in annual publication volume from 1994 to 2024, with a continuous rise in annual citation volume since 2005, indicating growing interest in the field. Japan, Germany, and the United States of America (USA) were the most prolific and influential countries. Institutions such as Tokyo Women's Medical University showed particularly significant contributions. Kasuya Hidetoshi was the most prolific author. There was little global collaboration among countries, institutions, and authors, with distinct regional research characteristics: Japan and Germany focused on intracranial implants, while the USA concentrated on intrathecal injections. Major publishing and co-cited journals included *Neurocritical Care*, *Acta Neurochirurgica*, *Journal of Neurosurgery*, and *Stroke*. Popular keywords in 2024 included "preventing cerebral vasospasm", "delayed cerebral ischemia", "outcome events", and "clinical trials", revealing current research hotspots.

Conclusion: This study maps the global clinical research landscape of intracranial application of nicardipine for aSAH from 1994 to 2024, providing valuable references and guidance for future research.

Keywords: aneurysm subarachnoid hemorrhage, intrathecal, intraventricular, nicardipine, NPRI

Introduction

Nicardipine exerts its vasodilatory effect by inhibiting the influx of Ca^{2+} into vascular smooth muscle cells, and it is primarily used clinically for patients with hypertensive emergencies. In recent years, an increasing number of researchers have gradually recognized the potential role of intracranial application of nicardipine in both the prevention and treatment of vasospasm following aneurysmal subarachnoid hemorrhage (aSAH).^{1–3} Recently, the updated 2023 guideline for the management of patients with aSAH by the American Heart Association/American Stroke Association mentioned for the first time the potential benefits of intracranial application of nicardipine for treating aSAH, but pointed out the need for further research to validate its feasibility.³ The release of this guideline suggests that more research findings on the intracranial application of nicardipine will emerge in the future. Shortly thereafter, a randomized controlled trial published by Wessels et al in August 2024 indicated that the use of nicardipine prolonged release implants (NPRI) intracranially could safely and effectively reduce angiographic vasospasm and possibly improve clinical outcomes following aSAH, warranting further investigation in Phase III trials.⁴ The

publication of this clinical trial has once again brought the potential benefits of intracranial application of nicardipine for treating aSAH into the spotlight. In fact, there remains a lack of effective medications for treating aSAH, particularly interventions that effectively address aSAH-related vasospasm and delayed cerebral ischemia (DCI), which are still in preclinical and clinical trial phases.⁵ However, the clinical trial results of the previously highly anticipated potential drug clazosentan, which were released in 2024, were not satisfactory.⁶ At this point, the publication of Wessels et al's study has renewed hope and may spark a new wave of research interest.

Generally, the direct delivery of nicardipine to the intracranial space for the treatment of aSAH through three methods—intrathecal administration, intraventricular administration, and the implantation of NPRI—is referred to as “intracranial application of nicardipine for the treatment of aSAH.”² Currently, only three review articles specifically assessing the intracranial application of nicardipine for aSAH have been published, including a systematic review published in 2019,¹ a literature review published in 2019,² and a meta-analysis published in 2021.⁷ These review articles generally conclude that the intracranial application of nicardipine is effective in reducing cerebral vasospasm, but whether it can improve prognosis remains inconclusive. Furthermore, these reviews particularly focus on the safety issues associated with the intracranial application of nicardipine, especially concerning the risk of intracranial infections following intrathecal administration. Thus, existing review literature mainly concentrates on the efficacy and safety of intracranial nicardipine, leaving a gap in comprehensively understanding the research landscape. In particular, there is a lack of relevant materials tracking the development and background of intracranial use of nicardipine in aSAH, which is crucial for scholars aiming to advance this field.

Bibliometrics offers a distinct perspective that differs from traditional review methods by systematically assessing the evolution and trends within a research field through mathematical and statistical techniques.⁸ This approach allows for the analysis and quantification of academic literature characteristics, thus mapping the current state and trends of research and enabling visualization based on objective data.⁹ To date, there has been no bibliometric study visualizing the application of intracranial nicardipine in aSAH. Therefore, this study aims to systematically review the publication trends and research hotspots related to intracranial nicardipine in aSAH through bibliometric analysis. Our work not only seeks to address this significant research gap but also aims to provide guidance for future research in the field and inspire interest among researchers in various countries.

Materials and Methods

Data Collection

We retrieved relevant publications from the Web of Science Core Collection (WoSCC) database. Based on the research topic “Intracranial nicardipine for aSAH”, we formulated the following search string: Topic = (((intrathecal nicardipine) OR (intraventricular nicardipine) OR (nicardipine prolonged release) OR (nicardipine release implant)) AND (subarachnoid hemorrhage)). A total of 152 articles were retrieved in the search box. The search period ranged from the establishment of the WoSCC in 1964 to October 26, 2024. There were no geographical or language restrictions on the retrieved literature. Initially, one researcher read the titles and abstracts to exclude articles not related to the research topic (n=89). Subsequently, two researchers independently screened the selected articles, then excluded conference abstracts (n=14), animal studies (n=17), reviews (n=14), commentaries (n=6), and meta-analyses (n=1). Conference abstracts were excluded as data could not be obtained. Animal studies were excluded as they could not realistically simulate aSAH. Reviews, commentaries, and meta-analyses were excluded as they do not represent primary literature. Any disagreements were resolved by the principal investigator. Ultimately, 28 papers meeting the study topic were selected from the 152 articles, with publication dates spanning from 1994 to 2024. To reduce bias resulting from daily updates of the WoSCC database, we completed the literature search and data download on October 26, 2024. Bibliometric analysis was conducted using the WoSCC online analysis tool and CiteSpace (version 6.2.R6) software (Figure 1). Considering that the data we used were publicly available literature search data and did not involve personal private information, ethical review by an institutional review board was not required.

Online Analysis of the WoSCC Database

Using the WoSCC online analysis tool, we analyzed the 28 retrieved article datasets to obtain various bibliometric parameters, including annual publication counts, annual citation volumes, publication journals, total citations, Citations

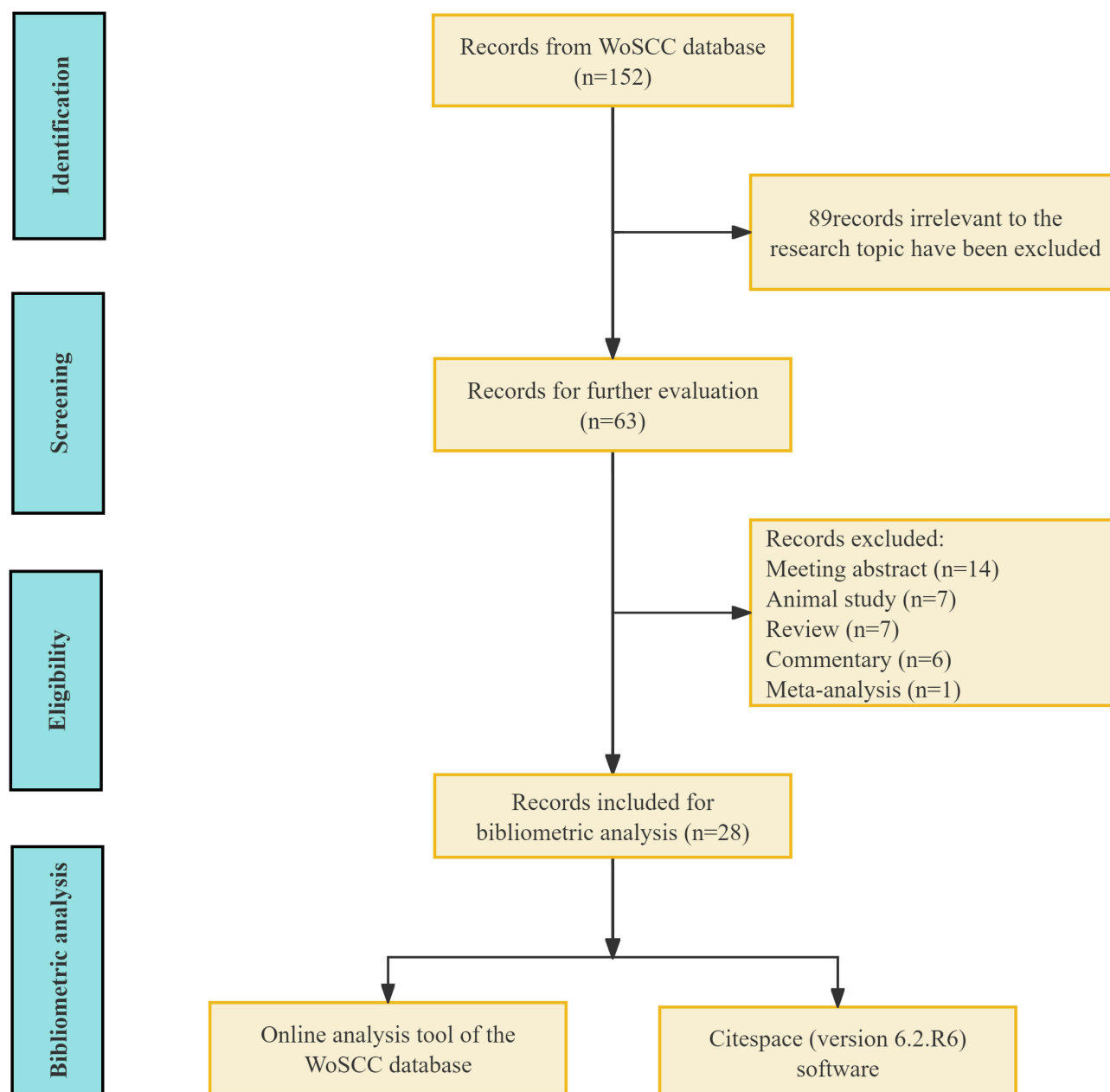


Figure 1 Study flow chart.

Per Publication (CPP), Annual Citation Rate (ACR), and H-index. Additionally, we also collected the 2023 Impact Factor (IF) and Journal Citation Reports (JCR) quartiles for the publication journals. CPP refers to the average number of times each article is cited, which is used to measure the influence and citation status of an article within the academic field. A higher CPP value indicates greater article influence. ACR is the ratio of the number of times a paper is cited to the number of years since its publication, serving as one of the indicators to measure paper influence and citation frequency. A higher ACR value indicates greater paper influence. The H-index is an indicator used to evaluate the academic achievements of researchers and can accurately reflect the scientific achievements of a country or institution. A higher H-index value indicates higher scientific influence for researchers or countries/institutions. The IF of journals is an important index for assessing journal influence, with a higher IF value indicating greater journal influence. JCR quartiles classify journals into four levels based on their influence and citation frequency: Q1, Q2, Q3, and Q4. Q1 represents the top 25% in terms of IF ranking, ie, journals with the highest influence; Q2 represents the ranking from 25–50%; Q3

represents the ranking from 50–75%; Q4 represents the ranking from 75–100%. Generally, Q1 and Q2 journals are considered to have high influence, while Q3 and Q4 journals have relatively lower influence.^{10,11}

CiteSpace Software Analysis

CiteSpace is a feature-rich bibliometric analysis software used for visualizing and analyzing academic literature in specific research fields or disciplines, facilitating a better understanding of research trends and hotspots.^{12,13} CiteSpace primarily encompasses three major analysis modules: 1. Collaboration network analysis (Author, Institution, Country); 2. Co-occurrence network analysis (Term, Keyword, Source, Category); 3. Co-citation network analysis (Reference, Cited Author, Cited Journal). In this study, data downloaded from the WoSCC database were exported into CiteSpace for analyzing various essential bibliometric parameters, ultimately generating visual knowledge graphs. Specifically, the authors conducted a collaboration network analysis of the Author, Institution, and Country to understand not only the number of published papers but also the collaborative relationships among them. Secondly, they performed Keyword clustering and Keyword burst analysis to reveal changes in research hotspots from the past to the present. Additionally, they conducted a co-citation network analysis of References, Cited Authors, and Cited Journal to further understand the influence of papers, authors, and journals related to the research topic. In CiteSpace, the Reference function pertains to co-citation analysis, where two references are cited by the same paper. The Cited Author function involves co-citation analysis of authors, indicating instances where two authors are jointly cited by other papers. The Cited Journal function focuses on co-citation analysis of journals, showing instances where two journals are cited by the same paper. Through these functionalities, deeper insights into the interrelationships and influence among literature, authors, and journals can be gained.

CiteSpace Result Interpretation

The visual knowledge graph generated by CiteSpace consists of nodes and links. Each node in the graph represents an element, including Author, Institution, Country, Keyword, Reference, Cited Author, and Cited Journal. The size of the nodes (indicated by the Count value) represents their frequency of occurrence or citation. The color of the nodes indicates different years, with circles of varying colors representing the period from 1994 to 2024. Nodes with a purple ring indicate a higher betweenness centrality. Betweenness centrality measures the importance of a node's position within the network and is typically considered a key point in a specific research field. Its value ranges from 0 to 1, with nodes having a centrality greater than 0.1 regarded as having a significant central position. The lines connecting the nodes represent collaborative, co-occurrence, or co-citation relationships among them.

Results

Annual Number of Publications and Citations

This bibliometric analysis covers 28 unique publications from 1994 to 2024.^{4,14–40} The total number of citations for these 28 articles is 871, with 763 citations being non-self-citations. The CPP is 31.11, the ACR is 28.10, and the H-index is 15. According to the data from this study, the first report on the use of Nicardipine for treating aSAH was published by Japanese researchers in 1994.¹⁴ From 1994 to 2024, the number of relevant publications experienced several periods of slight intermittent growth, particularly with two peaks in publication numbers during 2007–2012 and 2020–2024 (Figure 2). Although the total number of publications reached its highest point in 2011, it was only 4 articles. Furthermore, we noted that researchers from only 6 countries have published relevant studies as first authors. Figure 2 demonstrates the distribution of publications by country over different years, listed chronologically from earliest to latest as follows: Japan (n=8), Germany (n=7), the United States of America (USA) (n=9), Austria (n=2), South Korea (n=1), and Switzerland (n=1). Despite the limited number of publications each year, the annual citation count gradually rose after 2005, peaking in 2021 with a total of 85 citations (Figure 3). Overall, while there have been fluctuations in the annual citation count from 2005 to 2024, there is a general upward trend, reflecting the growing attention from researchers in this field and the sustained enthusiasm for research in this area.

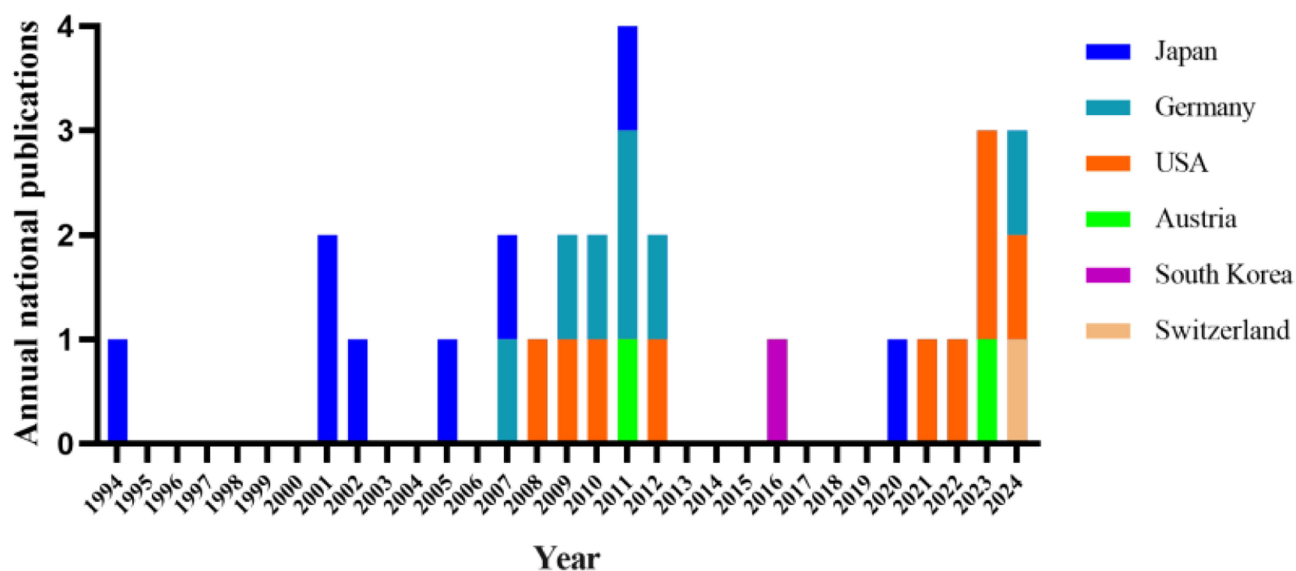


Figure 2 Trends in the number of annual publications from 1994 to 2024 on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage. The data are from online analysis of the WoSCC database, visualized using GraphPad Prism (version 8.0.2).

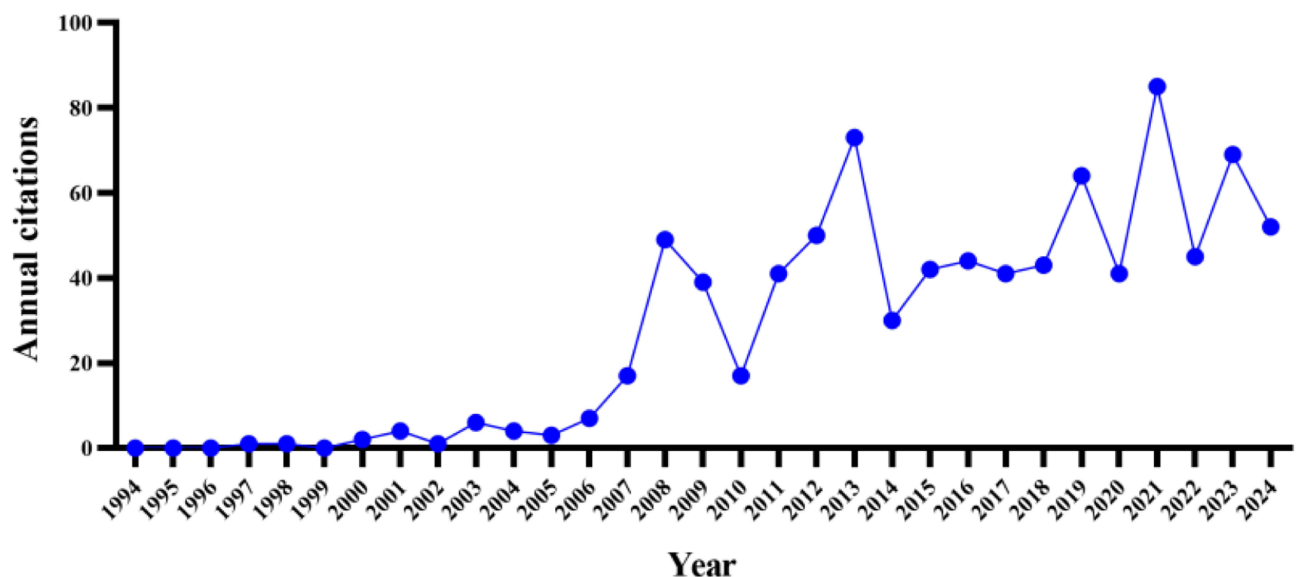


Figure 3 Trends in the number of annual citations from 1994 to 2024 on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage. The data are from online analysis of the WoSCC database, visualized using GraphPad Prism (version 8.0.2).

Distribution of Countries

According to the CiteSpace country collaboration network analysis (Figure 4), only 8 countries have been involved in this research. Ranked in order of the number of publications from most to least, these countries are Japan (Count=15), USA (Count=10), Germany (Count=10), Austria (Count=4), Switzerland (Count=1), Canada (Count=1), South Korea (Count=1), and Brazil (Count=1). Although USA does not have the highest number of publications, it exhibits high centrality (Centrality=0.48), indicated by a purple outer circle. This suggests that USA has a significant influence in this research field. Austria has the most extensive collaboration network, having conducted research with 5 countries, which makes it the most cooperative country and gives it the highest centrality (Centrality=0.76), also marked by a purple outer circle. Additionally, a statistical analysis of the first author's country affiliation in the 28 publications (Table 1) shows that only 6 countries have published relevant studies with the first author affiliation from these countries: USA, Japan,

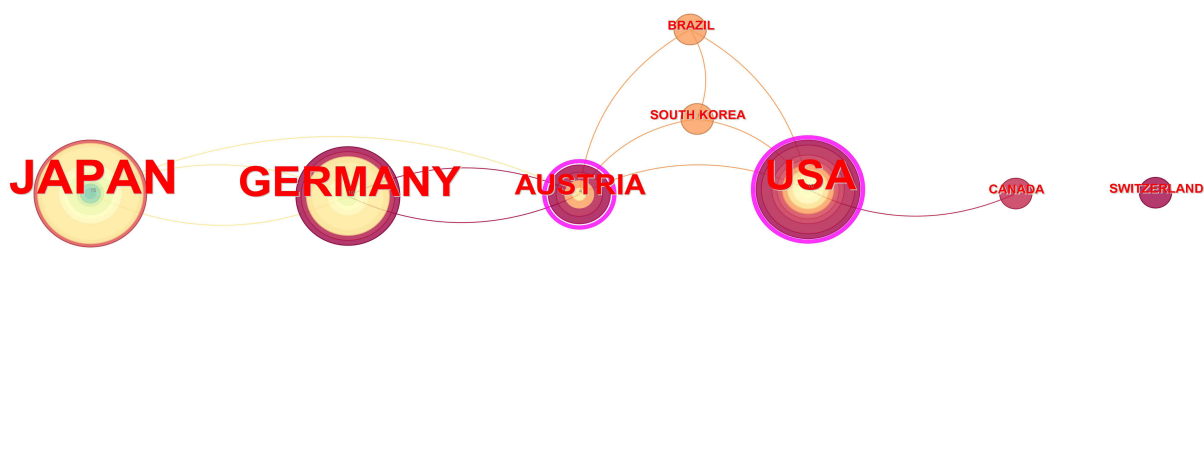


Figure 4 CiteSpace collaboration network analysis of countries on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage.

Germany, Austria, South Korea, and Switzerland. Regarding the total citations for these 6 countries, Germany leads, followed by Japan and USA. Austria, South Korea, and Switzerland follow in the rankings. Overall, based on the CiteSpace statistical analysis results and Table 1, which presents the counts, total citations, CPP, ACR, and H-index, it is evident that Japan, Germany, and USA are the countries with the highest number of publications and the most significant influence in this research field. However, we also observed that research on the intracranial use of Nicardipine for treating aSAH is limited to a few countries, with an uneven geographical distribution, and the level of collaboration among these countries is not sufficiently close.

Distribution of Institutions

The CiteSpace institution collaboration network reveals that 55 institutions have been dedicated to clinical research on the intracranial application of Nicardipine for treating aSAH (Figure 5). The top five institutions with the highest number of publications are Tokyo Women's Medical University (Count=12), Ruprecht Karls University Heidelberg (Count=9), Charité Universitätsmedizin Berlin (Count=5), Emory University (Count=5), and Berlin Institute of Health (Count=5). We note that the Medical University of Innsbruck (Centrality=0.15), marked by a purple ring node, indicates high betweenness centrality, suggesting it is an authoritative institution in this research field. Additionally, we observe that the 55 institutions in this research field form many separate clusters with little connection among them. For example, Tokyo Women's Medical University in Japan and the Medical University of Innsbruck in Germany form a separate cluster. Emory University, with itself as the research center, forms another independent cluster. These results suggest a lack of close collaboration among institutions.

Table 1 Analysis of the Country Affiliations of the First Authors of 28 Papers. Total Citations, CPP, ACR, and H-Index are From Online Analysis of the WoSCC Database

Rank	Country	Counts	% of 28	Total Citations	CPP	ACR	H-index
1	USA	9	0.32	161	17.89	9.47	6
2	Japan	8	0.28	309	38.63	9.97	7
3	Germany	7	0.25	372	53.14	20.67	6
4	Austria	2	0.07	13	6.5	0.93	2
5	South Korea	1	0.04	13	13	1.44	1
6	Switzerland	1	0.04	3	3	3	1

Abbreviations: CPP, citations per publication; ACR, annual citation rate.



Figure 5 CiteSpace collaboration network analysis of institutions on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage.

Distribution of Authors and Co-Cited Authors

The CiteSpace author collaboration network shows that 28 papers involve 158 authors (Figure 6). However, these authors form their own independent clusters, indicating that although they are all dedicated to researching the same topic, their collaborative ties are not strong enough. In terms of publication volume, the most prolific author is Kasuya Hidetoshi (Count=9), followed by

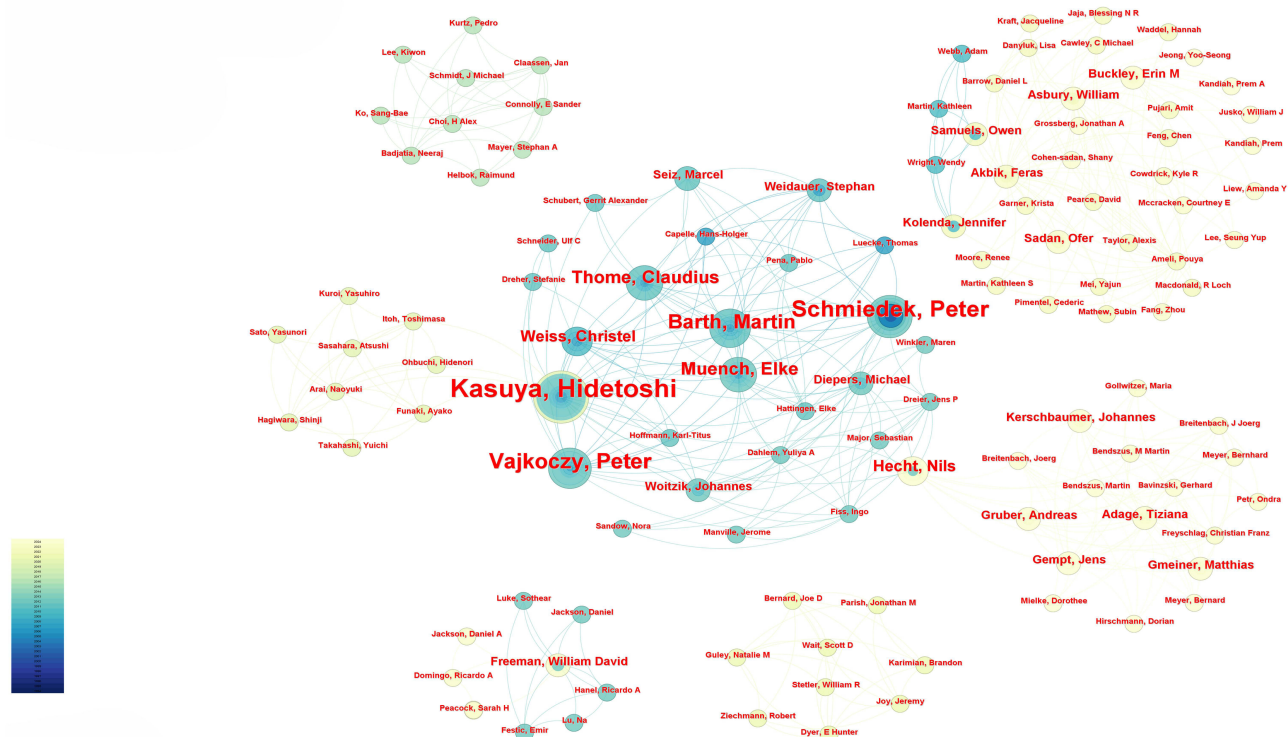


Figure 6 CiteSpace network analysis of authors on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage.

Schmiedek Peter (Count=7), Vajkoczy Peter (Count=6), Barth Martin (Count=5), and Thome Claudius (Count=4). However, none of the 158 authors have a centrality greater than 0.1, and there are no nodes with a purple outer circle, suggesting a lack of sufficiently influential authors in this research field. Furthermore, the CiteSpace cited author network reveals that the top five most frequently cited authors are BARTH M (Count=16), KASUYA H (Count=15), HALEY EC (Count=12), MACDONALD RL (Count=10), and SHIBUYA M (Count=9) (Figure 7). Overall, the CiteSpace author collaboration network highlights the lack of closeness in collaboration among authors, while also providing information about influential researchers and potential collaborators, which may contribute to future collaborative research.

Distribution of Journals and Co-Cited Journals

The 28 papers retrieved in this study were published in 20 journals, with the top five journals that published the most research on the intracranial application of Nicardipine for treating aSAH being *Neurocritical Care*, *Acta Neurochirurgica*, *Journal of Neurosurgery*, *Stroke*, and *Acta Neurochirurgica Supplement* (Table 2). Evaluating the IF and JCR data for these 20 journals, it was found that the overall influence of these journals for publishing papers in this field was not high. Furthermore, considering the Total citations, CPP, ACR, and H-index data, it was found that the academic influence of papers in this research area published in these journals was not high. Notably, the highest individual IF for a paper in this field appeared in a paper published in *JAMA Neurosurgery* in August 2024, indicating that this research area has begun to attract the interest of high-quality journals. Additionally, the CiteSpace cited journal network shows (Figure 8) that the top five journals with the most co-citations are *Journal of Neurosurgery* (Count=28), *Stroke* (Count=27), *Neurosurgery* (Count=27), *Acta Neurochirurgica* (Count=17), and *Neurocritical Care* (Count=13). We found significant overlap between the Top 5 journals where papers were published and the Top 5 journals most frequently co-cited. This suggests that the research area primarily focuses on the journals *Neurocritical Care*, *Acta*

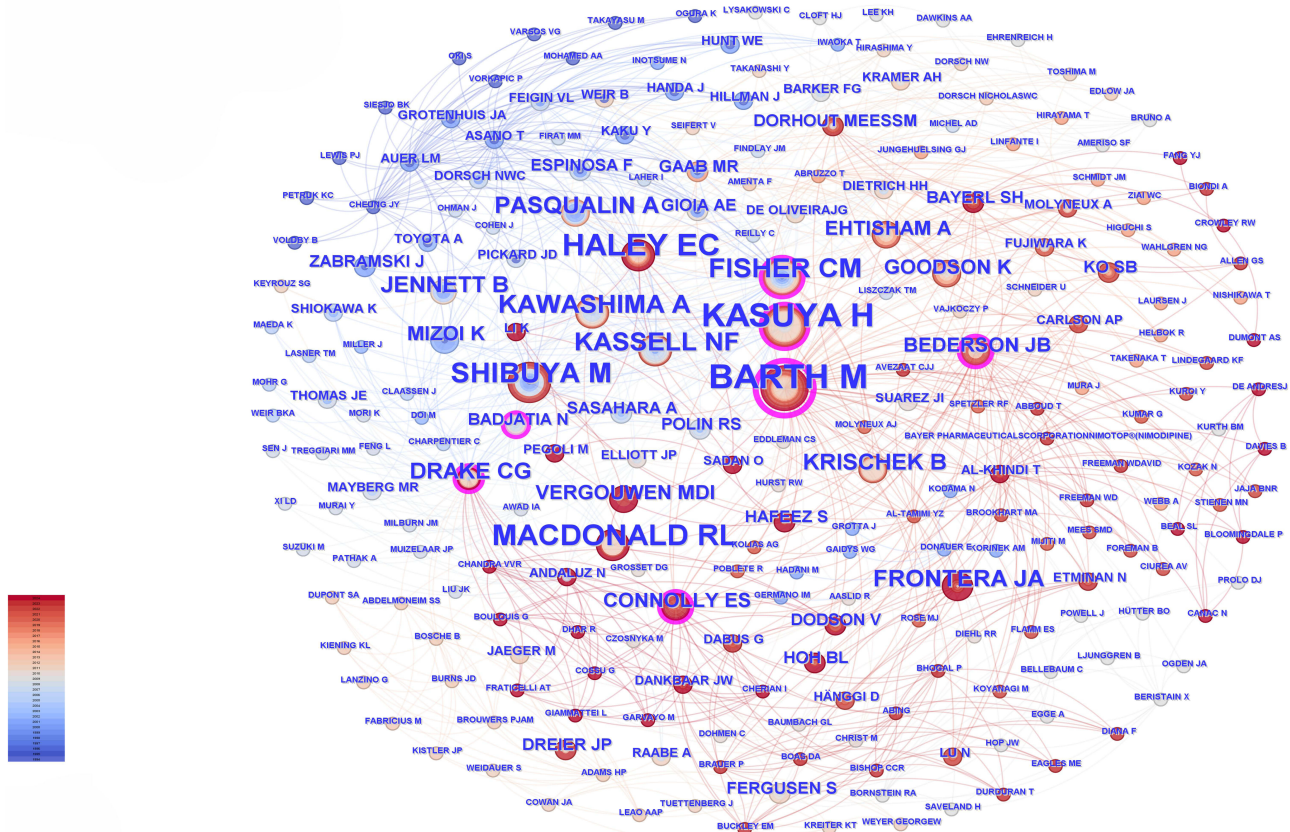


Figure 7 CiteSpace network analysis of co-cited authors on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage.

Table 2 Analysis of the 20 Scholarly Journals in Which the 28 Articles Were Published. Total Citations, CPP, ACR, and H-Index are From Online Analysis of the WoSCC Database

Rank	Journal	Count	IF	JCR	Total Citations	CPP	ACR	H-Index
1	Neurocritical Care	4	3.1	Q2	151	37.75	8.88	4
2	Acta Neurochirurgica	3	1.9	Q2	59	19.67	1.90	3
3	Journal of Neurosurgery	2	3.5	Q1	48	24	3	2
4	Stroke	2	7.9	Q1	190	95	8.26	2
5	Acta Neurochirurgica Supplement	2	NA	NA	24	12	1.71	2
6	No Shinkei Geka. Neurological Surgery	1	NA	NA	12	12	0.5	1
7	Neurosurgical Review	1	2.5	Q1	38	38	1.58	1
8	Neurosurgery	1	3.9	Q1	91	91	4.55	1
9	Neurologia Medico-chirurgica	1	2.4	Q2	29	29	1.61	1
10	Southern Medical Journal	1	1.0	Q3	24	24	1.5	1
11	British Journal of Neurosurgery	1	1.0	Q3	23	23	1.64	1
12	Journal of Cerebral Blood Flow and Metabolism	1	4.9	Q1	148	148	11.38	1
13	Clinical Neurology and Neurosurgery	1	1.8	Q2	13	13	1.44	1
14	Journal of Neurointerventional Surgery	1	4.5	Q1	7	7	1.4	1
15	Interdisciplinary Neurosurgery: Advanced Techniques and Case Management	1	0.4	Q4	1	1	0.25	1
16	Journal of Personalized Medicine	1	3.0	Q1	1	1	0.5	1
17	Frontiers in Neurology	1	2.7	Q2	7	7	3.5	1
18	Brain Spine	1	1.9	Q3	3	3	1.5	1
19	Journal of Clinical Pharmacology	1	2.4	Q3	2	2	2	1
20	JAMA Neurology	1	20.9	Q1	0	0	0	0

Abbreviations: IF, impact factors; JCR, journal citation reports; CPP, citations per publication; ACR, annual citation rate; NA, not available.

Neurochirurgica, *Journal of Neurosurgery*, and *Stroke*. Additionally, we identified 7 cited journals with purple outer rings (Table 3), all of which had a Centrality > 0.1, indicating a significant central position. When these 7 cited journals were categorized by their country of publication, it was found that the majority were from USA, followed by the England. In summary, although the IFs of the 20 journals in this research area are generally low, the highest IFs for recent publications have been achieved. The main journals where papers are published and frequently co-cited are concentrated in *Neurocritical Care*, *Acta Neurochirurgica*, *Journal of Neurosurgery*, and *Stroke*.

Distribution of Highly Cited Papers

The most cited paper was published by a German research team in the journal *Journal of Cerebral Blood Flow And Metabolism* (2023 IF: 4.9, Q1) in 2012, titled “Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage”, which has been cited a total of 148 times, with an ACR of 11.38 times per year.³⁰ The second most cited article was also published by a German research team in *Stroke* (2023 IF: 7.9, Q1) in 2007, titled

Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study,

which has been cited 115 times, with an ACR of 6.39 times per year.¹⁹ The top 10 most cited papers are shown in Table 4. We found that although there are few articles published on the intracranial application of Nicardipine for treating aSAH, the citation counts of these articles are quite significant. This suggests that the intracranial application of Nicardipine for treating aSAH has attracted the attention of researchers. Additionally, among the top 10 most cited papers, Japan (4 articles, 247 citations), Germany (3 articles, 313 citations), and USA (3 articles, 101 citations) are the dominant countries. This again indicates that Japan, Germany, and USA are the three countries with the highest influence in this research area.

Distribution of Co-Cited References

The CiteSpace reference time zone map displays the top 10 most co-cited references (Figure 9), and Table 5 analyzes these 10 references. The most co-cited reference is

Table 4 The Top 10 Most Cited Publications. The Citations and ACR are From Online Analysis of the WoSCC Database

Rank	Title	First Author	Journal	Country	IF	JCR	Publication Year	Citations	ACR
1	Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage	Johannes Woitzik	Journal of Cerebral Blood Flow And Metabolism	Germany	4.9	Q1	2012	148	11.38
2	Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study	Martin Barth	Stroke	Germany	7.9	Q1	2007	115	6.39
3	Application of nicardipine prolonged-release implants: Analysis of 97 consecutive patients with acute subarachnoid hemorrhage	Hidetoshi Kasuya	Neurosurgery	Japan	3.9	Q1	2005	91	4.55
4	Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans	Hidetoshi Kasuya	Stroke	Japan	7.9	Q1	2002	75	3.26
5	Correlation of Clinical Outcome with Pressure-, Oxygen-, and Flow-Related Indices of Cerebrovascular Reactivity in Patients Following Aneurysmal SAH	Martin Barth	Neurocritical Care	Germany	3.1	Q2	2010	50	3.33
6	Effects of prophylactic intrathecal administrations of nicardipine on vasospasm in patients with severe aneurysmal subarachnoid haemorrhage	M Shibuya	Acta Neurochirurgica	Japan	1.9	Q2	1994	43	1.39
7	Intrathecal administration of nicardipine hydrochloride to prevent vasospasm in patients with subarachnoid hemorrhage	M Suzuki	Neurosurgical Review	Japan	2.5	Q1	2001	38	1.58
8	Intraventricular Nicardipine for Aneurysmal Subarachnoid Hemorrhage Related Vasospasm: Assessment of 90 Days Outcome	Na Lu	Neurocritical Care	USA	3.1	Q2	2012	36	2.77
9	The Effect of Intraventricular Administration of Nicardipine on Mean Cerebral Blood Flow Velocity Measured by Transcranial Doppler in the Treatment of Vasospasm Following Aneurysmal Subarachnoid Hemorrhage	Adam Webb	Neurocritical Care	USA	3.1	Q2	2010	33	2.2
10	Intraventricular nicardipine for refractory cerebral vasospasm after subarachnoid hemorrhage	Kelly Goodson	Neurocritical Care	USA	3.1	Q2	2008	32	1.88

Abbreviations: IF, impact factors; JCR, journal citation reports; ACR, annual citation rate.

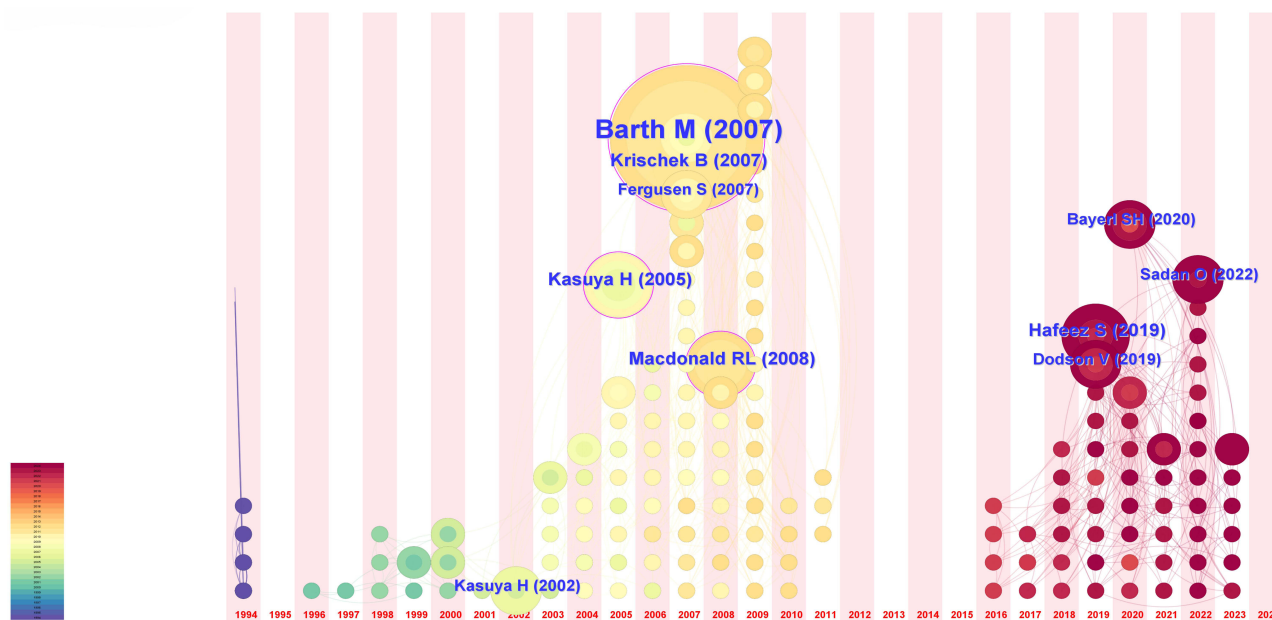


Figure 9 CiteSpace timezone view of top eight co-cited references on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage.

Distribution of Keyword Clusters and Keyword Bursts

Using CiteSpace, 135 keywords in this research field were generated. These 135 keywords were clustered to form 8 keyword clusters: #0 outcome; #1 delayed cerebral ischemia; #2 drug delivery system; #3 transcranial doppler; #4 neurovascular coupling; #5 intrathecal administration; #6 multimodality monitoring; #7 functional outcome (Figure 10). This suggests that research on the intracranial application of Nicardipine for treating aSAH worldwide from 1994 to 2024 has been focused on these 8 hotspots. Additionally, we also counted the top 20 keywords with the strongest citation

Table 5 The Top 10 Co-Cited References

Rank	References	Journal	IF	JCR	First Author	Publication Year	Total Citations
1	Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans	Stroke	7.9	Q1	Hidetoshi Kasuya	2002	75
2	Application of nicardipine prolonged-release implants: analysis of 97 consecutive patients with acute subarachnoid hemorrhage	Neurosurgery	3.9	Q1	Hidetoshi Kasuya	2005	91
3	Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study	Stroke	7.9	Q1	Martin Barth	2007	115
4	Nicardipine prolonged-release implants for preventing cerebral vasospasm after subarachnoid hemorrhage: effect and outcome in the first 100 patients	Neurologia Medico-chirurgica	2.4	Q2	Boris Krischek	2007	29
5	Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage	Neurosurgery	3.9	Q1	Sherise Ferguson	2007	211
6	Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1) Randomized, Double-Blind, Placebo-Controlled Phase 2 Dose-Finding Trial	Stroke	7.9	Q1	R Loch Macdonald	2008	501

(Continued)

Table 5 (Continued).

Rank	References	Journal	IF	JCR	First Author	Publication Year	Total Citations
7	Systematic Review of Intrathecal Nicardipine for the Treatment of Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage	Neurocritical Care	3.1	Q2	Shaheryar Hafeez	2019	26
8	Intracranial Administration of Nicardipine After Aneurysmal Subarachnoid Hemorrhage: A Review of the Literature	World Neurosurgery	1.9	Q2	Vincent Dodson	2019	14
9	In vitro and in vivo testing of a novel local nicardipine delivery system to the brain: a preclinical study	Journal of Neurosurgery	3.5	Q1	Bayerl SH	2020	9
10	Does intrathecal nicardipine for cerebral vasospasm following subarachnoid hemorrhage correlate with reduced delayed cerebral ischemia? A retrospective propensity score-based analysis	Journal of Neurosurgery	3.5	Q1	Sadan O	2022	25

Abbreviations: IF, impact factors; JCR, journal citation reports.

bursts to identify research hotspots that have changed over time and current hotspots (Figure 11). We found that the hot keywords in research have gradually changed over the past 30 years, shifting from keywords in 1994 such as rabbit basilar artery, prevention, ischemia, chronic cerebral vasospasm, and therapy to keywords in 2024 like preventing cerebral vasospasm, delayed cerebral ischemia, outcome event, and clinical trials, revealing the current direction of research.

Discussion

The First Decade

Between 1994 and 2004, a total of four studies were published, accounting for only 14.3% of all included literature.^{14–17} In 1994, the first clinical trial in this field was published by Shibuya and et.al. from Japan, indicating that intrathecal administration could effectively reduce the incidence of cerebral vasospasm, although side effects such as headache and bacterial meningitis were observed.¹⁴ All studies published between 1994 and 2004 were conducted by Japanese researchers. The initial method of administration was repeated intrathecal dosing,^{14–16} followed by a one-time intracranial insertion of NPRI.¹⁷ While both methods are reported to prevent cerebral vasospasm, the former has been associated with

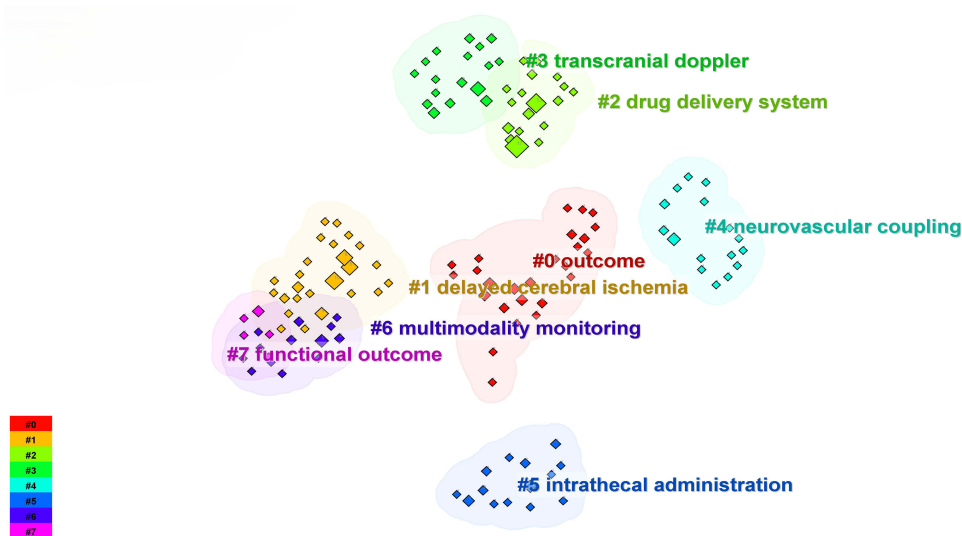


Figure 10 CiteSpace keywords clusters analysis on intracranial administration of nicardipine for the treatment of aneurysmal subarachnoid hemorrhage.

Top 20 Keywords with the Strongest Citation Bursts

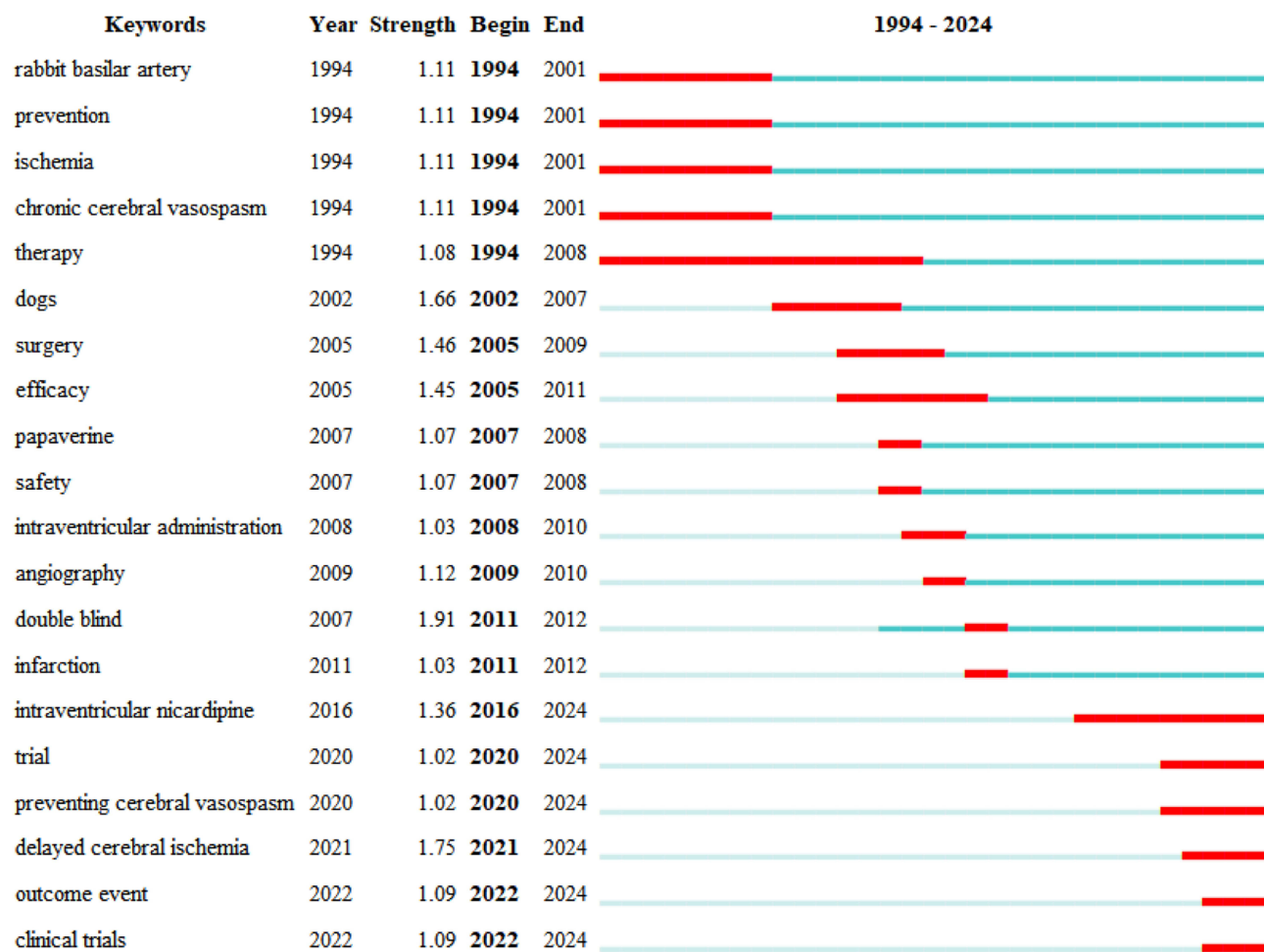


Figure 11 The change distribution of top 20 keywords with the strongest citation bursts from 1994 to 2024.

an increased risk of intracranial infections.^{14–16} At this stage, the intracranial use of nicardipine was still being explored for the prevention of post-aSAH cerebral vasospasm (prophylactic use) and had not yet shifted to treating already occurring vasospasm (therapeutic use). Japanese scholars developed NPRI in this research field, attempting to enhance the efficacy of intracranial nicardipine application while reducing side effects such as intracranial infections and hydrocephalus.¹⁷ In the subsequent second decade, multiple studies were published that demonstrated the efficacy and safety of this approach.

The Second Decade

The period from 2004 to 2014 saw a surge in the number of publications on the intracranial application of nicardipine for aSAH, with 14 relevant articles published,^{18–31} accounting for approximately 50% of all related literature. Remarkably, out of these 14 studies, 10 focused on NPRI.^{18–20,23,25–30} During this second decade, the research field began to gain attention from researchers in other countries, including Germany, USA, and Austria.^{19,21,27} Germany emerged as the leading country during this period, publishing the highest number of studies (n=6).^{19,23,25,28–30} The efficacy and safety of NPRI were thoroughly discussed and confirmed during this time. However, the safety of ventricular/intrathecally administered nicardipine for the treatment of aSAH had not been well-explored. Research on NPRI was primarily conducted by researchers from Germany, Japan, and Austria. In contrast, USA researchers did not publish studies on NPRI but focused on ventricular and intrathecal administration methods; however, these studies had relatively small sample sizes (6–42 cases). As a result, many USA researchers expressed a desire to conduct large-scale randomized controlled trials to

validate the safety and efficacy of ventricular/intrathecal nicardipine administration for aSAH.^{21,22,24,31} During this second decade, the application of nicardipine began to shift towards treating patients with established cerebral vasospasm,^{21,22} while there was a notable research shift from a focus on vasospasm to DCI and then to prognosis.^{18,19,23,30,31}

The Third Decade

From 2014 to 2024, ten relevant articles were published,^{4,32–40} accounting for approximately 35.7% of all related literature. Among these ten studies, seven were related to the treatment of aSAH with nicardipine administered either intrathecally or into the ventricles (USA=5, Korea=1, Switzerland=1);^{32,34–37,39,40} three studies were related to NPRI research (Germany=1, Japan=1, Austria=1).^{4,33,38} Thus, the third decade was primarily dominated by USA researchers, who continued to focus only on the administration of nicardipine via the ventricular or intrathecal route for treating aSAH. The sample sizes reported in studies on ventricular/intrathecal nicardipine treatment for aSAH during this decade increased compared to the previous one (3–1351 cases), yet many published studies were single-center retrospective analyses.^{32,35–38,40} There remains a lack of large-scale prospective randomized controlled trials to robustly confirm the safety and efficacy of ventricular/intrathecal nicardipine treatment for aSAH. Additionally, USA researchers also undertook the first pharmacokinetic study of cerebrospinal fluid after intrathecal administration in aSAH patients during this period.⁴⁰

Comparison of Nicardipine Intracranial Application Methods

The treatment of cerebral vasospasm following aSAH has long been deficient in effective methods. Recent aSAH clinical management guidelines no longer recommend the routine use of statins or intravenous magnesium to improve outcomes. Many previously recommended methods are gradually being abandoned, and alternative approaches, such as intrathecal nicardipine administration, are being considered.³ Some retrospective single-center studies have confirmed that this method can reduce the incidence of cerebral vasospasm, but its ability to improve outcomes urgently requires clinical trials.^{1,2,7} This aligns with the hotspot keyword analysis results of our bibliometric analysis, which enhances the reliability of our analysis. NPRI has published sufficient research to demonstrate its effectiveness and safety in preventing cerebral vasospasm, although its ability to improve outcomes remains uncertain. Therefore, the publication quantity in the third decade has decreased, but the studies have been published in high-quality journals, indicating the scientific community's recognition of this method. Compared to intraventricular/intrathecal administration, NPRI appears to have a lower risk of intracranial infection, as it only requires a single intracranial implantation, whereas intraventricular/intrathecal administration requires repeated dosing, potentially increasing the risk of intracranial infection. However, intraventricular/intrathecal administration seems more universally applicable and feasible. Firstly, NPRI can mostly only be used prophylactically, while intraventricular/intrathecal administration can be used both prophylactically and therapeutically. Secondly, with the popularization of minimally invasive treatment concepts, more and more aSAH patients are choosing interventional treatments, limiting the use of NPRI, which requires craniotomy for implantation. Additionally, the specific materials for NPRI are not globally available, whereas intraventricular/intrathecal administration can be used worldwide based on patient preference. Therefore, compared to NPRI, intraventricular/intrathecal administration may have greater potential in the future.⁴¹

Research Significance

Although the current study included a relatively small number of articles, which might not seem suitable for bibliometric analysis, we found that applying this method to these articles unearthed many key insights that had not been mentioned in previously published review articles. These insights could potentially facilitate rapid advancements in the field. For instance, the intracranial use of nicardipine for the treatment of aSAH has a history of at least 30 years, yet only researchers from eight countries globally are focusing on this area. This indicates that many regions and countries have yet to explore this potentially beneficial therapy. The efficacy of intracranial nicardipine in reducing vasospasm after aSAH has already been confirmed. Another example is the apparent regional research characteristics in the field. Between 1994 and 2024, researchers from Germany and Japan focused on the study of NPRI, while USA researchers exclusively investigated intrathecal nicardipine. This intriguing finding helps researchers understand the research

expertise of different countries and identify potential collaborators. Additionally, we observed a continuous increase in researchers' interest in this field, with expectations for clinical trials evaluating clinical outcomes. However, there were issues such as uneven regional distribution of research and a lack of research collaboration. Therefore, our findings could aid subsequent researchers in advancing the field, enabling more researchers worldwide to recognize the significant gaps and regional imbalances in this area. This is why we insisted on using bibliometric methods to study this field.

Future Research

Based on the bibliometric analysis conducted in this study, intracranial nicardipine application has demonstrated potential in reducing cerebral vasospasm. However, several critical research gaps remain to be addressed in future studies. These include the need for high-quality clinical trials, direct comparisons of different administration routes, assessments of long-term prognosis and quality of life, evaluations of efficacy and safety in diverse patient populations, mechanistic studies, and cost-effectiveness analyses. Addressing these research directions will not only provide a stronger scientific basis for the clinical application of intracranial nicardipine but also significantly advance the development of this field.

Limitation

This study has several limitations. Firstly, it only utilized literature from the WoSCC database, potentially excluding articles from other databases. Secondly, meeting abstracts were excluded, which could impact the study's findings. Although many meeting abstracts eventually lead to published research papers, some may not, leading to a possible oversight of their contributions to the research field. Lastly, the study organized the research field based on publication years rather than the actual commencement of studies in the real world. Therefore, it is important to consider these factors when interpreting the results of this study.

Conclusion

This study uses bibliometric methods to depict the landscape of global clinical research on the intracranial application of nicardipine for the treatment of aSAH from 1994 to 2024. It reveals that during this specific period, the research field has experienced a scarcity of studies, intermittent research progress, a sustained increase in attention, regional imbalances in research, limited research collaboration, distinctive regional research characteristics, and a current need for clinical trials evaluating clinical outcomes. These findings can serve as a reference for future research efforts.

Data Sharing Statement

The data for this article were sourced from Web of Science, a publicly accessible database of scholarly literature, and were gathered and utilized in accordance with established practices.

Ethics Approval

Ethical approval was not required for this study, as all data were downloaded from public databases and did not involve any human or animal participants.

Author Contributions

Each author provided substantial contributions to this work, encompassing conception, study design, execution, data acquisition, analysis, interpretation, or a combination thereof. They participated in drafting, revising, and critically reviewing the manuscript. All authors approved the final version to be published, agreed on the journal for submission, and are accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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