International Journal of Cerebrovascular Disease and Stroke
Shogren SL, et al. Int J Cerebrovasc Dis Stroke 7: 185
www.doi.org/10.29011/2688-8734.000085
www.gavinpublishers.com

Review Article

Bibliometric Analysis of the Composition of Landmark Cerebral Venous Sinus Thrombosis Research

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Citation: Shogren SL, Suarez JV, Castillo MG, Calienes AR, Anil S, et al. (2024) Bibliometric Analysis of the Composition of Landmark Cerebral Venous Sinus Thrombosis Research. Int J Cerebrovasc Dis Stroke 7: 185. DOI: 10.29011/2688-8734.100185

Received Date: 26 July, 2024; **Accepted Date:** 01 August, 2024; **Published Date:** 05 August, 2024

Abstract

Background: Cerebral Venous Sinus Thrombosis (CVST) is a relatively rare type of stroke, accounting for less than 3% of all stroke cases, and is associated with significant morbidity and mortality in young females. However, when promptly diagnosed and treated, it can have favorable outcomes. Several knowledge gaps remain regarding pathophysiology, diagnosis, and management of CVST, so critical assessment of past and present research could help close these gaps or establish targeted future research goals.

Methods: We screened Elsevier Scopus database articles with CVST as the primary topic. Clinical guidelines, abstracts, letters, and editorials were excluded. The top 100 articles, ordered by number of citations, were selected, and data collection and analysis were performed using Microsoft Excel, R software, and VOS viewer.

Results: Out of 4,832 documents, the top 100 most-cited articles spanned the years of 1973 to 2021 and had a total citation frequency of 18,208. France and the United States were the top-contributing countries, and Stroke had the highest number of manuscripts published in the top 100 (n=30). Analysis of word-use trends over time showed increases in the mention of "vaccination" since 2021, "mechanical thrombectomy" since 2017, and "fibrinolytic therapy" since 2015.

Conclusions: Our study detailed the 100 most-cited articles on CVST in the past 50 years. Understanding top-contributing countries, authors, and journals may help guide the direction of future research in CVST and encourage collaboration within the field. Areas of further research may include association with other pathologies (non-infectious and infectious) and advancements in acute therapies.

Keywords: Cerebral venous sinus thrombosis; Cerebral venous thrombosis; Bibliometric analysis; Biblioshiny, VOSviewer.

Introduction

Cerebral Venous Sinus Thrombosis (CVST) accounts for less than 3% of all stroke cases and can be associated with significant morbidity and mortality if not treated promptly [1-3]. Recent population-based studies have shown an annual incidence ranging from 1.32 to 2 per 100,000 adults [4]. Compared to strokes of arterial origin, CVST predominantly affects young female patients, has a gradual onset with a wide spectrum of clinical manifestations, and has multiple predisposing and precipitant conditions [5]. CVST can be challenging to diagnose because it does not present with typical stroke symptoms, and imaging findings can be subtle and overlooked on initial Computed Tomography (CT). However, evolution and availability of diagnostic imaging modalities, including CT venography, Magnetic Resonance Imaging (MRI), Magnetic Resonance Venogram (MRV), and digital subtraction angiography have prompted an earlier diagnosis of the pathology. Currently, MRI and MRV have become the imaging of choice due to their high sensitivity and specificity [6]. Despite this, diagnosis can still be challenging. For instance, a retrospective cohort study by Lieberman et al. showed that about 1 in 30 patients with CVST are initially misdiagnosed [7]. Standard of care involves anticoagulation, but advancements continue to be made in research for treatment alternatives [8].

Despite the growing clinical knowledge of CVST, there are still several areas of ongoing research regarding its pathophysiology, diagnosis, and management. Thus, critical assessment of past and present research could potentially help to establish targeted future research goals. We performed a bibliometric analysis of the top 100 most-cited CVST articles to determine the key contributions and contributors to this disease, assess content of the studies, and outline trends in research from the most influential articles in the field.

Methods

Search strategy

Utilizing the Elsevier Scopus database, we performed an electronic systematic search on index terms, titles, and abstracts with the advanced query function from inception to September 21, 2023. The search query used was conducted using the following terms: “cerebrum,” “venous thrombosis,” “cerebral venous thrombosis,” cerebral venous sinus thrombosis,” “cerebral vein thrombosis,” and “cerebral-vein thrombosis”. This effectively included all articles using the terms “cerebral venous sinus thrombosis,” “cerebral venous thrombosis,” and “cerebral vein thrombosis.” On initial review, two researchers (JVS and SA) independently searched and screened the database from inception to February 2023, eliminating articles that did not fit selection criteria. An updated database search was performed by a third researcher (SLS) in September 2023. Any discrepancies were solved with discussion between the authors.

Selection criteria

Peer-reviewed journal publications focusing on CVST as the primary topic were considered, without any restrictions regarding the age of the participants, language of the article, or geographical area of the study. We included the most cited original research and review articles, as we aimed to characterize the most-cited articles regarding CVST. Clinical guidelines, abstracts, letters, and editorials were excluded.

Data extraction and bibliometric analysis

Articles were arranged from highest to lowest citation count, and the 100 most cited were selected and analyzed. The bibliometric parameters extracted were title, authors, journal, keywords, publication year, institution, country, and number of citations. Articles were classified by study type (observational, review, experimental) and study design (retrospective cohort, prospective cohort, case report, narrative review, systematic review, meta-analysis, pictorial review) based on individual review. These data were then imported into Microsoft Excel (Version 2302) and the Bibliometrix package (version 4.1.2) and Biblioshiny application in R software (version 4.3.1) [9]. Both were used to analyze the distribution of countries/regions, years of publication, all included authors, and trends in literature over time. An alluvial diagram was created to reflect the number of publications per country over time, and time periods were sectioned in 9- to 17-year groups to achieve representative quantities of publications [10]. Similarly, a Sankey diagram of thematic evolution grouped trends in keywords by 3- to 23-year groups to achieve representative quantities of keywords, accounting for differing numbers of publications during various time periods. Data were also imported into VOSviewer (version 1.6.19) to complete network maps and highlight collaboration between authors and countries [11]. In VOSviewer, node size positively correlates with number of articles, and width of connecting lines positively correlates with cooperation strength. Data were grouped into colors based on frequency of collaboration. Total link strength was measured within the software and indicates the number of collaboration events between groups and the strength of those associations. For example, an author with a high total link strength has likely collaborated with multiple authors many times. Subgroup analysis, stratified by 10-year clusters starting in 1973, was performed to classify the distribution of various study types over time.

Results

Overall study characteristics

Our initial search query yielded 4832 articles from which the 100 most cited articles were identified. The complete list of publications is detailed in Supplementary Table 1, and the top 10 most-cited articles are summarized in Table 1. The top 100 cited articles were published between 1973 and 2021 in 48 unique journals and originating from 26 countries. Considering these most cited articles over this approximately 50-year period, the total number of papers steadily increased in 10-year clusters and reached its peak between 2001 and 2010 (n=42), with the largest number of publications

occurring in 1996 (n=7) and 2005 (n=7) (Figure 1A). After this time point, publications decreased in frequency with just 24 occurring between 2011 and 2021. Similarly, the number of citations increased from 1973 onward and reached their peak between 2001 to 2010 (n=7581). Citations have steadily decreased since that point (n=3564). Most citations occurred in 1996 (n=1368) and 2006 (n=1421). The most cited article from 1996 discussed long-term prognosis in patients with CVST, [12] and the most cited article from 2005 covered diagnosis and management of CVST in children [13]. Most studies were observational studies (n=74), followed by reviews (n=22), and experimental studies (n=4) (Figure 1B). Further study design classification showed many retrospective cohort studies (n=58), with a smaller number of narrative reviews (n=11), case reports (n=8), prospective cohort studies (n=7), systematic reviews (n=5), pictorial reviews (n=4), meta-analyses (n=3), randomized controlled trials (n=3), and animal studies (n=1) (Figure 1C). Of the 74 observational studies, five utilized the same cohort group, outlined in Supplementary Table 2.

Rank	Title	Publication year	Journal	First author	Country	Citations per year	PubMed ID
1	Cerebral venous thrombosis: an update	2007	Lancet Neurology	Bousser M.G.	France	54.2	17239803
2	Cerebral venous thrombosis — a review of 38 cases	1985	Stroke	Bousser M.G.	France	17.3	3975957
3	Cerebral venous thrombosis	1992	Neurologic Clinics	Ameri A.	France	18.6	1557011
4	High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives	1998	New England Journal of Medicine	Martinelli I.	Italy	23	9632445
5	Cerebral venous sinus thrombosis in children: Risk factors, presentation, diagnosis and outcome	2005	Brain	Sébire G.	United Kingdom	23.3	15699061
6	Imaging of cerebral venous thrombosis: Current techniques, spectrum of findings, and diagnostic pitfalls	2006	Radiographics	Leach J.L.	United States	24.4	17050515
7	US Case Reports of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Ad26. COV2.S Vaccination, March 2 to April 21, 2021	2021	JAMA-Journal of the American Medical Association	See I.	United States	180	33929487
8	Cerebral venous thrombosis associated with pregnancy and puerperium: Review of 67 cases	1993	Stroke	Cantú C.	Mexico	11.9	8248971
9	Causes and predictors of death in cerebral venous thrombosis	2005	Stroke	Canhão P.	Portugal	18.4	16002765
10	Long-term prognosis in cerebral venous thrombosis: Follow-up of 77 patients	1996	Stroke	Preter M.	United States	12	8571417

Table 1: The top 10 most cited articles in CVST.

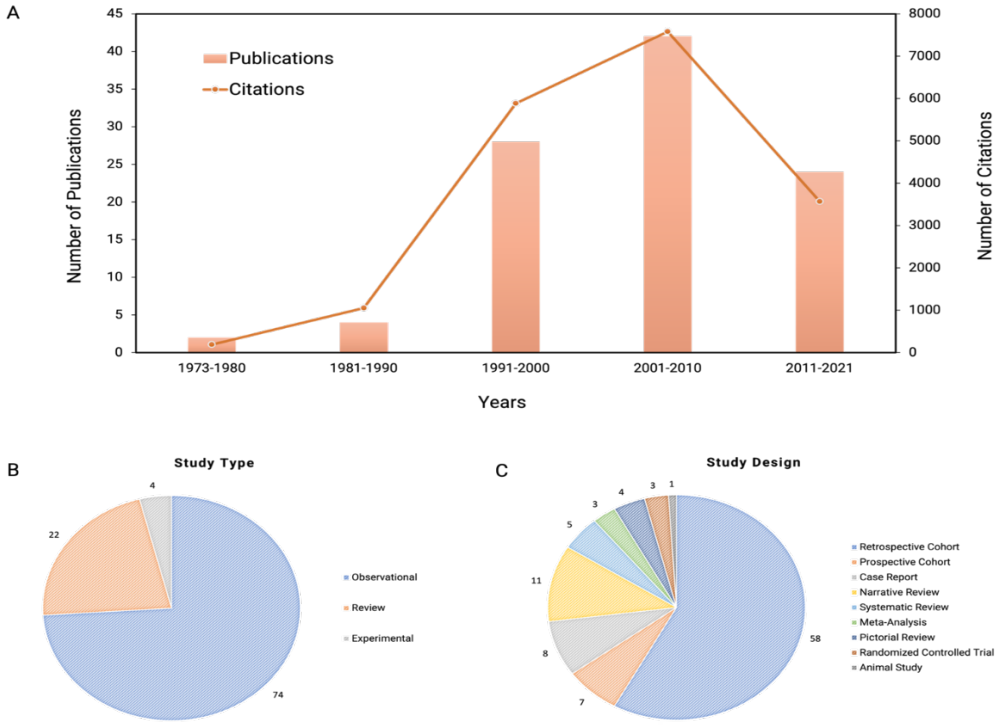

Figure 1: (A-C) (A) Number of publications and citations over time for the 100 most cited articles. (B) Distribution of study type and (C) design of the 100 most cited articles in CVST.

Highly cited articles

The 100 most cited articles had an average citation per document of 182 (range 90-867), and the median citation count per year was 7.4 (range 1.8-64.9). The most-cited publication to date by Bousser and Ferro is titled "Cerebral venous thrombosis: an update" and was published in Lancet Neurology in 2007 [14]. This review paper has accumulated 867 citations since publication and discusses diagnostic options, characterizes the radiological findings relevant to CVST, and highlights management for typical patients as well as higher-risk groups (children and the elderly). The paper with the most citations per year was "US case reports with cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021" by See et al. [15]. It was published in the Journal of the American Medical Association and has accumulated 121 citations/year since publication. This article is a case series of 12 patients with CVST and thrombocytopenia that developed after receiving the Ad26.COV2.S vaccine and aimed to highlight the possible relationship between these two entities.

Contributions by author

The most prolific author was M.G. Bousser of France, who coauthored 21 of the 100 most cited articles and was also the most cited author of the group (n=91) (Figure 2A). I. Martinelli was tied for the tenth most productive author (n=4) but had the highest number of citations per article of the group (n=13.5). Collaboration and co-authorship were visualized in a network presented in Figure 2B. Eighteen authors were included in the analysis with a minimum number of 3 documents per author. M.G. Bousser was the top collaborator with a total link strength of 68. J.M. Ferro of Portugal and J. Stam of the Netherlands shared the second highest total link strength of 49.

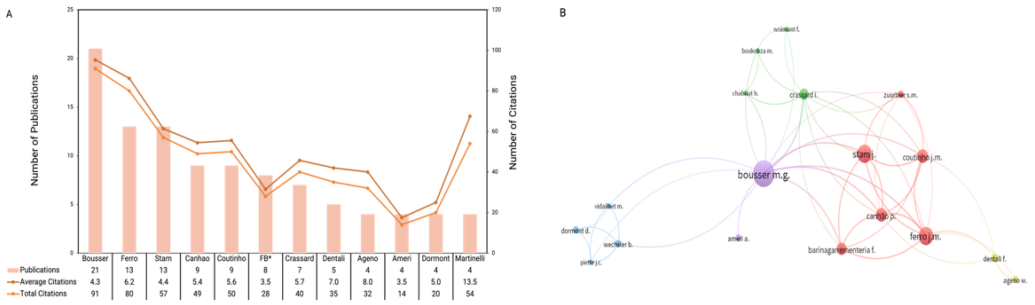

Figure 2: (A-B) The 10 most productive authors and collaboration among them. (A) Number of publications, total citations, and citations per publication for the top 10 prolific authors. (B) Collaboration among the most prolific and other top-cited authors. Node size indicates the number of articles, and width of links shows cooperation strength. Color groupings designate authors who frequently collaborate.

Contributions by country

There were 26 countries involved in authorship of 100 most cited articles. The countries with highest contributions were France (n=23), United States (n=20), Netherlands (n=9), and Germany (n=7) (Figure 3A). France also claimed the highest number of total citations (n=5028) and citations per article (n=218.6) (Figure 3B). Sixteen countries with greater than two published articles were included in the network map in Figure 3C, which showed that France, Portugal, and the Netherlands, shared the highest total link strength of 31. The United States had the second highest total link strength of 25, followed by Mexico with 21.

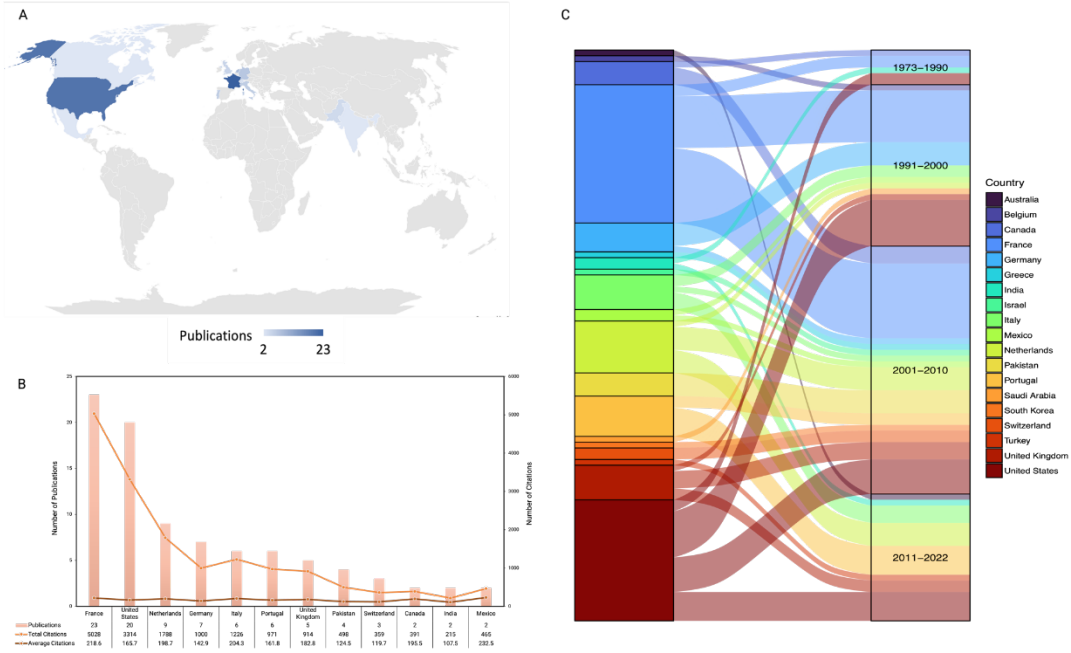

Figure 3: (A-C) The 10 most prolific countries of CVST research. (A) Number of publications for each country. (B) Number of publications and total citations for each country. (C) An alluvial diagram reflecting the number of publications per country, divided by time period.

Contributions by Journal

The three most prolific journals were Stroke (n=30), followed by Neurology (n=7), and the American Journal of Neuroradiology (n=6) (Figure 4A). These three journals were also the most cited, with 480, 101, and 92 total citations, respectively (Figure 4B). As previously mentioned, the most-cited publication was published in Lancet Neurology. Journals with the highest total link strength are Stroke, Lancet Neurology, and Archives of Neurology (Figure 4C).

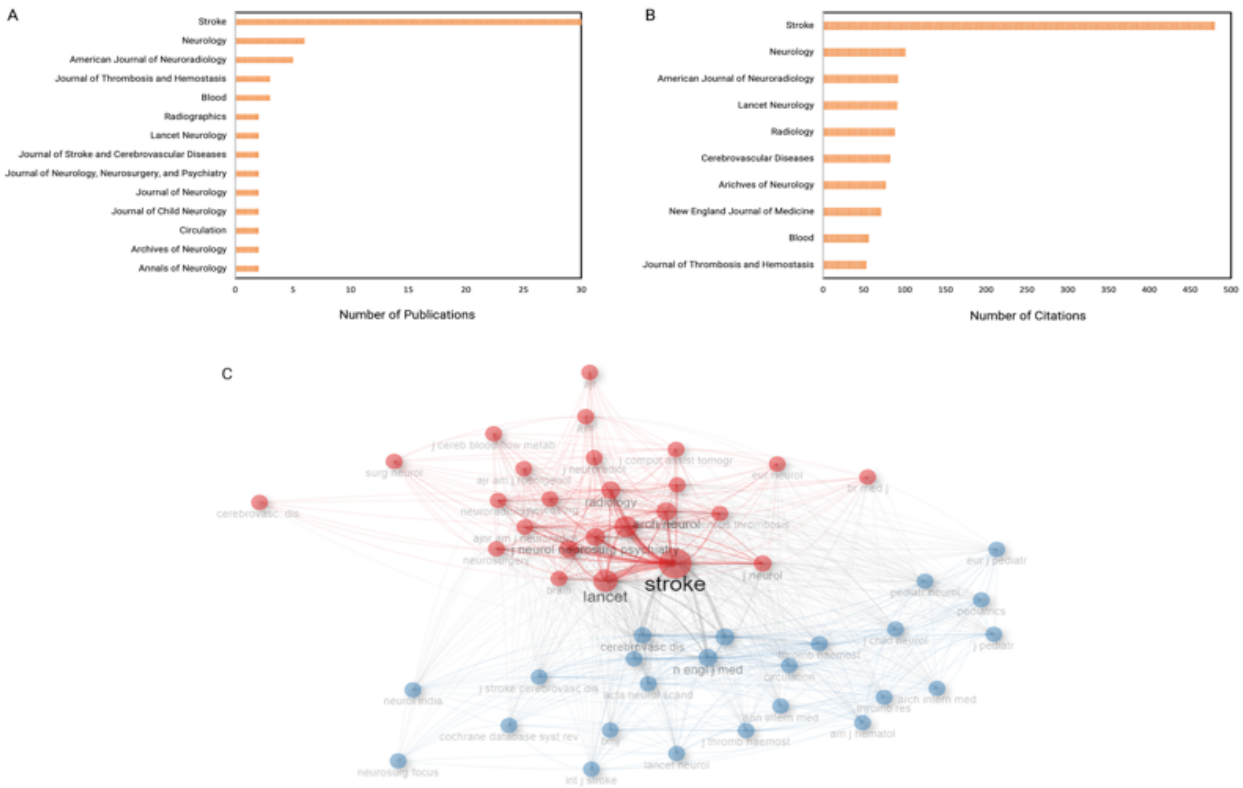

Figure 4: (A-C) (A) Ranking of the 14 most prolific journals containing the 100 most cited articles in CVST. (B) The top 10 most cited journals. (C) Co-citation network of the most prolific journals. Node size indicates the number of articles, and width of links shows cooperation strength. Color groupings designate journals that frequently cite articles from each other.

Keywords and trends over time

Evolution of themes in CVST literature from 1973 to 2021 is seen in Figure 5. Each featured word or phrase was mentioned at least five times in articles published during the four-year timeframe. “Female” was one of the highest used words from 1973 to 2012 due to the higher frequency of CVST in women. “Nuclear magnetic resonance imaging” appeared as a common theme from 2003 to 2012 as use of MRI and MRV became more common and ultimately, the gold standard for diagnosing CVST [16]. Emerging themes from 2013 to 2021 include “thrombectomy,” “blood clot lysis,” and “vaccination.” Since 2013, three highly cited articles have been published about endovascular therapy in the setting of CVST, which is an area of ongoing research [17-19]. Since the advent of COVID-19, three highly cited articles have been published about CVST after vaccination against the infection [20-21] and two highly cited articles have been published about CVST in the setting of active infection [15,22,23].

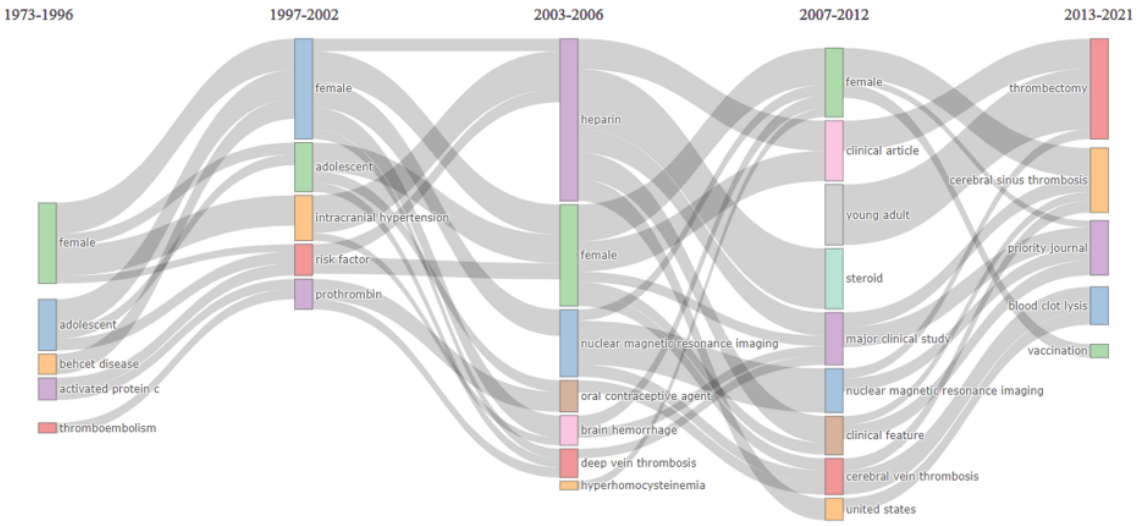

Figure 5: Evolution of themes in CVST literature from 1973 to 2021 based on keyword identification. The size of each node is proportional to the number times an article published in the allotted timeframe used a particular keyword. Only keywords used at least 5 times during the period shown were included. The gray line indicates flow between each node and the evolutionary direction of each theme (whether its use increased or decreased between periods). The width of the gray line is proportional to the number of times two keywords were identified in the same publication.

Subgroup analysis

Subgroup analysis of 10-year clusters since 1973 showed an increasing number of observational studies, with the most being published between 1991 and 2010, and a decrease since 2010 (Supplementary Figure 1). Despite a decreasing number of publications since 2001 to 2010, the number of review articles being published has stayed consistent since 2011 to 2021 (n=9 versus n=10). This is likely due to continued updates in diagnosis and alternative treatment strategies, as 8 out of 10 of the reviews published between 2011 and 2021 highlighted advancements in management, including anticoagulation and mechanical thrombectomy [8,16,18,19,22,24-28].

Discussion

General trends in CVST research

Clinical recognition and awareness of CVST increased in the late 1980's and early 1990's due to its increasing identification and diagnosis guided by the advancements in diagnostic imaging [29]. In addition, a systematic review from 2014 showed declining mortality over time, likely secondary to the identification of less severe cases due to the availability of CT venography and MRI/MRV and improvements in therapeutic management *(i.e.*, anticoagulation and decompressive hemicraniectomy for severe cases) [30]. These findings correspond with changes over time in the number of publications and citations of the 100 most cited CVST articles. For instance, between the years of 1991 and 2000, common article topics included neuroimaging, updates in diagnosis and management, and endovascular thrombolysis. Then, between 2001 and 2010, publications and citations reached their peak, and the articles highlighted changes in risk factors, such as oral contraceptive use, and the diagnostic value of different MRI sequences. Of note, the most highly cited article, "Cerebral venous thrombosis: an update" by Bousser and Ferro, was also published during this period, which likely contributed to the high citation count observed during this time frame.

Despite 20% of articles published between 2011 and 2021 being related to CVST in the setting of COVID-19 vaccination or active infection, the overall number of publications and citations decreased. This may be due to relative stability in diagnostic and treatment methods over this time. Seventy-four of the top 100 most cited articles were observational studies, the majority of which were retrospective cohort studies. Of note, five of the observational studies utilized the same cohort group from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), a multinational study that characterized the natural history and prognosis of CVST [31]. When it went to print in 2004, it was the largest cohort group ever published, so it is not surprising some of the top 100 most-cited articles in CVST also utilized this cohort. Only three of the articles involved experimental or interventional studies-which were focused on neuroimaging techniques and anticoagulation selection-highlighting the lack of randomized controlled trials in this group of top-cited articles.

Analysis of top articles, authors, countries and journals

In our study, the most cited publication was a review article by Bousser and Ferro published in 2007 that outlined the development

in characterization, diagnosis, and management of CVST [14]. The study with more citations per year was directly related to the COVID-19 pandemic [15], which depicts how the pandemic influenced CVST literature by becoming a primary risk factor to consider for CVST. It also highlighted the need to characterize the role of CVST in the clinical evolution of COVID-19 patients. Although the article by See et al. is highlighted due to its significant number of citations after publication, it does not bring forth novel concepts or a difference in the understanding of CVST before the onset of the COVID-19 pandemic.

Our findings also confirm the fundamental contributions of Dr. M.G. Bousser (1943–present day) to the current understanding of CVST. From the articles included in our analysis, her initial paper published in 1985 included 38 CVST cases [32] and demonstrated the challenges faced during the diagnostic process and described the clinical outcomes after prescribing anticoagulation (which at that time had limited evidence). Her subsequent studies focused on the evaluation of risk factors, patient subgroups with higher risk factors, diagnostic approaches (clinical presentation, laboratory results, and imaging findings), predictors of clinical outcome, therapeutic approaches, and several review papers (including the most cited paper). We expect her efforts to expand and guide the next steps in CVST research.

Unsurprisingly, the most prolific country was France (n=23) which is the country of residence of Dr. Bousser, and a close follower was the United States (n=20). The difference was larger between the top two and remaining 17 contributing countries, which demonstrates the incremental global effort in the study of CVST. However, the main contributing continents were North America and Europe. It must be acknowledged that in the most cited papers were written in English, so our characterization of literature including other regions of the world may be limited. We expect that with continual development of tools that allow communication between different regions and languages, the globalization of research will continue to expand. Considering the journals represented in the included studies, our findings confirm that the authors chose to present their work primarily in clinical journals to bring forth valuable insights to the audience of experts who are managing CVST cases on a regular basis. We found a considerable difference between the journal with most publications (Stroke with 30 articles) and the second in order (Neurology with 7). Of note, basic science journals had a weak presence among the included studies, which suggests a limited role of basic science research in CVST.

Evolution of CVST diagnosis and management

Analysis of CVST literature over the past 50 years distinctly shows the influence of the evolving management and diagnostic approaches in the research trends. Studies from the early 1970's to late 1990's focused on the characterization of the patient population affected by CVST, including adult women (particularly those who were pregnant) and documentation of clinical findings in rarer cases, like those in neonates, children, and young adults. "Risk factor" was a commonly used word in top cited articles published between 1997 and 2002, likely reflecting additions to and changes in the list of known risk factors for CVST as knowledge about the disease grew. From a diagnostic standpoint, articles about MRI first appeared in the mid-1980's (a time when cerebral angiography was primarily used) and became most prevalent in the mid-1990's to late 2000's as it became the gold standard for diagnosis of CVST. Although angiography can show characteristics such as a lack of filling and delayed emptying from the cerebral veins, MRI came into favor due its high sensitivity for demonstrating the thrombus or occluded sinus or vein; in addition, MRI is less invasive than angiography, making it an advantageous diagnostic tool. Evolution of anticoagulation guidelines are also evident in the literature, as they were first described in 1973 as "for select cases," [33] later on as possibly beneficial with unclear necessary treatment duration in 1985 [32]and more recently, requiring either unfractionated heparin or low molecular weight heparin as initial therapy for all CVST patients [34].

Future directions

Management of CVST typically involves anticoagulation with subcutaneous low molecular weight heparin or intravenous heparin for symptomatic patients without contraindication [5]. Interestingly, recent keyword and trend analysis between the years of 2013 to 2021 showed emerging themes of "blood clot lysis" and "thrombectomy," two methods of treatment that are generally reserved for patients that experience neurologic decline despite treatment with anticoagulation [35,36]. A systematic review from 2015 evaluated 185 patients with CVST, and of those who underwent mechanical thrombectomy, there was 14% mortality and new intracranial hemorrhage in 9% [18]. Complete recanalization occurred in 69% (and partial recanalization in 26%), and 35% achieved complete recovery. In addition, mechanical thrombectomy with intra-sinus thrombolysis did not show additional harm or benefit. However, the patients that were studied typically had a poorer clinical exam, as 47% were stuporous or comatose.

The thrombolysis or anticoagulation for cerebral venous thrombosis (TO-ACT) trial, conducted from 2011 to 2016, aimed to assess the safety and efficacy of endovascular treatment, but the study did not show that endovascular therapy (plus standard care with anticoagulation) improved functional outcomes in patients with CVST [37]. However, there was a small sample size (n=67), which could have influenced these results. Since that point, multiple systematic reviews and meta-analyses have reported mixed results about endovascular thrombolysis or mechanical thrombectomy for CVST [38-45]. More trials are needed to determine exact indications and the best timing, approach, and device use for endovascular therapy with or without intra-sinus thrombolysis.

Keyword analysis also highlighted the word "vaccination" being commonly used since 2020, which coincides with the COVID-19 pandemic starting in 2019 and vaccinations being established in late 2020. Multiple case series and a retrospective cohort study identified CVST caused by vaccine-induced immune thrombotic thrombocytopenia (VITT), and these studies were used to develop treatment guidelines to this rare side effect. These patients were

found to develop vaccine-induced autoantibodies against a PF4 platelet antigen (like those in patients with heparin-induced thrombocytopenia), and management consisted of anticoagulation and Intravenous Immune Globulin (IVIg), the latter of which reduced mortality [46,47]. These findings of immunomodulation being essential to mortality reduction may influence future management of patients with CVST in the setting of VITT or autoimmune disease. CVST with thrombocytopenia–typically caused by an autoimmune disease–is treated differently than CVST alone, as IVIg or steroid therapy is necessary, and lower platelet levels may require anticoagulation dose adjustment [48]. In addition, recent literature indicates there are no standard guidelines for autoimmune disease-associated CVST treatment [49]. For this reason, individual pathologies of various types of autoimmune disease-associated CVST may need to be studied in the future to ascertain most effective therapies.

Limitations

Though we utilized the Scopus database, which has previously been used to perform bibliometric analyses [50], we acknowledge the potential omission of literature from other sources or databases. We also constricted our study to the top 100 most cited articles, which results in limited coverage of the scientific literature. Importantly, articles not included in this list do not have an inferior scientific contribution. Although the included studies represent the current most cited papers, citations take time to accumulate, and often, there is a lag between publication and increase in citation number. Furthermore, the number of citations was not adjusted for self-citations versus collaborative group citations, which could be a potential confounder in the total number. Additionally, the onset and impact of the COVID-19 pandemic in the clinical and scientific community should be considered as an altering factor in the bibliometric trends of CVST. Due to the bibliometric design of this study, establishing causality or clinical implications is not possible and was not attempted. However, we were able to analyze the characteristics, impact, and quality of CVST literature.

Conclusion

Our results demonstrate that most CVST research has been focused on its clinical aspect, with diagnosis and management as the most studied topics. Though France and the United States were the most prolific contributors, a tendency towards a more global effort was evidenced. Basic science research was not found to have a prominent position when considering the most cited literature. Further research with prospective and collaborative efforts is needed to optimize the limited amount of data and increase the power to improve our understanding and management of this condition.

Funding

This research is supported by the by the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) through an RO3NS126804-01 grant. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Acknowledgements: None.

Ethical Guidelines: IRB or ethics committee approval was not required for this bibliometric analysis.

Competing Interests

Shogren-None

Vivanco-Suarez-None

Galecio-Castillo-None

Rodriguez-Calienes-None

Anil-None

Alva-None

Weng-None

Smith-None

Torner-None

Mohr-None

Cano Nigenda-None

Arauz-None

Ortega-Gutierrez-Grants: NIH-NINDS (R01NS127114-01, RO3NS126804-01), Stryker, Medtronic, Microvention, Methinks,Viz. ai. Consulting fees: Medtronic, Stryker Neurovascular.

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