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SCIENTOMETRICS

Stem cell transplantation in cerebrovascular accidents: A global bibliometric analysis (2000-2023)

Jad El Masri, Ahmad Afyouni, Maya Ghazi, Karim Hamideh, Israe Moubayed, Abdo Jurjus, Hanine Haidar, Ruzanna Petrosyan, Pascale Salameh, Hassan Hosseini

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Jad El Masri, École Doctorale Sciences de la Vie et de la Santé, Université Paris-Est Créteil, Créteil 94010, France

Jad El Masri, Hassan Hosseini, INSERM U955-E01, Institut Mondor de Recherche Biomédicale, Université Paris-Est Créteil, Créteil 94000, France

Jad El Masri, Ahmad Afyouni, Maya Ghazi, Karim Hamideh, Israe Moubayed, Faculty of Medical Sciences, Lebanese University, Beirut 1533, Lebanon

Jad El Masri, Abdo Jurjus, Hanine Haidar, Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut 1107, Lebanon

Maya Ghazi, Department of Neurology, Faculty of Medicine, Lebanese American University, Beirut 1102, Lebanon

Ruzanna Petrosyan, Department of Pathology, Faculty of Medicine, Lebanese American University, Beirut 1102, Lebanon

Pascale Salameh, Faculty of Pharmacy, Lebanese University, Beirut 1102, Lebanon

Pascale Salameh, Faculty of Medicine, Lebanese American University, Beirut 1102, Lebanon

Pascale Salameh, Department of Primary Care and Population Health, University of Nicosia Medical School, Nicosia 2408, Cyprus

Pascale Salameh, Institut National de Santé Publique d'Épidémiologie Clinique et de Toxicologie-Liban, Beirut 1103, Lebanon

Hassan Hosseini, Department of Neurology, Henri Mondor Hospital, AP-HP, Créteil 94000, France

Corresponding author: Abdo Jurjus, PhD, Professor, Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Bliss Street, Hamra, Beirut 1107, Lebanon. aj00@aub.edu.lb

Abstract

BACKGROUND

Cerebrovascular accident (CVA) is a major global contributor to death and disability. As part of its medical management, researchers have recognized the importance of promising neuroprotective strategies, where stem cell transplantation (SCT) is thought to confer advantages *via* trophic and neuroprotective effects.

AIM

To evaluate the current state of research on SCT in patients with CVA, assess key trends and highlight literature gaps.

METHODS

PubMed was screened for SCT in CVA-related articles in October 2023, for each country during the period between 2000 and 2023. Using the World Bank data, total population and gross domestic product were collected for comparison. VOSviewer_1.6.19 was used to create the VOS figure using the results of the same query. Graphs and tables were obtained using Microsoft Office Excel.

RESULTS

A total of 6923 studies were identified on SCT in CVA, making 0.03% of all published studies worldwide. Approximately, 68% were conducted in high-income countries, with a significant focus on mesenchymal stem cells. The journal "*Stroke*" featured the largest share of these articles, with mesenchymal SCT having the highest rate of inclusion, followed by hematopoietic SCT. Over time, there has been a noticeable shift from *in vitro* studies, which assess stem cell proliferation and neurogenesis, to *in vivo* studies aimed at evaluating efficacy and safety. Additionally, the number of reviews increased along this approach.

CONCLUSION

This bibliometric analysis provides a comprehensive guide for physicians and researchers in the field through an objective overview of research activity, and highlights both current trends and gaps. Having a potential therapeutic role in CVA, more research is needed in the future to focus on different aspects of SCT, aiming to reach a better treatment strategy and improve life quality in patients.

Key Words: Bibliometric analysis; PubMed; Stem cell transplantation; Cerebrovascular accidents; Stroke

Core Tip: This study evaluated the research landscape of stem cell transplantation in patients with cerebrovascular accident, highlighting trends and gaps. Analyzing publications from 2000 to 2023, we found that high-income countries lead stem cell transplantation research, predominantly using mesenchymal stem cells. The journal "*Stroke*" published the most articles. Recent research has shifted from *in vitro* studies to patient-oriented *in vivo* studies focusing on safety and efficacy. This trend indicates a maturing field moving towards clinical application. This study provides a comprehensive overview, guiding future research to optimize clinical outcomes for patients with cerebrovascular accident through stem cell transplantation.

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INTRODUCTION

Cerebrovascular accident (CVA) is a major global contributor to death and disability[1]. Despite advancements in stroke prevention and care, the degree of neurological deficits following a stroke poses a significant medical challenge, underscoring the urgent need for efficient targeted treatments to reduce these profound site effects[2]. Intravenous and intra-arterial thrombolysis can help recanalize occluded arteries in the first hours after the onset of the infarction process which may lessen the severity of brain damage[2]. However, this process also has drawbacks that have prompted the implementation of mechanical thrombectomy, which breaks down the clot physically using stent retriever devices, rather than dissolving them chemically[3]. In parallel, researchers and clinicians have recognized the importance of promising neuroprotective strategies aimed at protecting brain cells from damage. Nevertheless, the discovery of effective cytoprotective agents has proven challenging[4,5].

The above results spurred efforts to find alternative treatments, which have recently focused on restoring brain function through cell transplantation. Adult stem cells serve as a promising source of cells for regenerative medicine, particularly in the context of neurological diseases such as stroke. Data from animal models suggest that these cells have the capacity to replace damaged or dysfunctional cells and contribute to tissue repair and functional recovery[6-9]. The spectrum of cells currently used in these studies includes bone marrow, mesenchymal, umbilical, fetal, and embryonic cells[10].

Beyond the replacement of infarcted tissues, transplanted cells are thought to confer advantages *via* trophic and neuroprotective effects. The release of trophic factors by neurons and nonneuronal cells in stumps of the denervated distal nerves enriches the local neural environment by sustaining synaptic connections and enabling host axonal regeneration[11]. Moreover, grafts have also been suggested to stimulate surviving cells to build new neural circuits by supplementing endogenous recovery mechanisms, which include neurogenesis and angiogenesis[12]. Although the immense success seen in preclinical models is uplifting, clinical trials have yet to yield the same results. Many issues still need to be addressed, and much research is still required before this treatment can be widely available[13].

Despite these challenges, stem cell transplantation (SCT) holds great promise for treating CVA. With continued research and innovative development in this dynamic domain, this treatment could in the near future revolutionize medicine and improve the lives of millions of people. Therefore, the purpose of this study is to evaluate the current state of research on SCT in patients with CVA and to assess trends as well as highlight any gaps in the literature.

MATERIALS AND METHODS

Database and search strategy

Searches for SCT in CVA-related articles were conducted on October 25, 2023, for each country worldwide, with a time limit between 2000 and 2023. We used PubMed, a free search engine that primarily accesses the MEDLINE database of references and abstracts on life sciences and biomedical topics. PubMed keywords search offers optimal update frequency and includes online early articles rendering it the optimal tool in biomedical electronic research[14]. Similar studies have been conducted in different specialty fields and for different regions[15-17].

Interpretation and comparison

The PubMed database was searched using the following keywords and free-text terms combined with boolean operators (AND, OR): ("Stem cells"[Medical Subject Headings (MeSH) Terms] OR "Stem Cell Transplantation"[MeSH Terms] OR "stem cells"[All Fields] OR "Stem cells transplantation"[All Fields] OR "stem cell therapy"[All Fields] OR "stem cell transfer"[All Fields]) AND ("Stroke"[MeSH Terms] OR "Cerebrovascular Trauma"[MeSH Terms] OR "Brain Ischemia"[MeSH Terms] OR "Intracranial Hemorrhages"[MeSH Terms] OR "brain hemorrhage, traumatic"[MeSH Terms] OR "Cerebrovascular Disorders"[MeSH Terms] OR "cerebrovascular accident"[All Fields] OR "Stroke"[All Fields] OR "traumatic brain hemorrhage"[All Fields] OR "ischemic brain injury"[All Fields]) AND 2000/01/01: 2023/12/31[Date - Publication]. The affiliation of authors was used to track the country of publication and create the map using mapchart.net[18]. Based on the World Bank classification, studies from each country were classified as high-income, upper-middle-income, low-middle-income, and low-income countries[19].

The gross domestic product (GDP) and the population size were acquired from the World Bank data website[20]. Taiwan's GDP was obtained from tradingeconomics.com and its population from macrotrends.net. We calculated the average GDP and population for the top 20 countries between 2000 and 2023 and obtained the publications per average GDP (in 100 billion USD) and the publications per million population.

The contribution of the top five active countries mentioning one type of SCT was obtained using the search strings mentioned above AND the "MeSH term" for different types of transplantation. The contribution of the top 20 clinical neurology journals according to Scimagojr.com was determined using the aforementioned search strings AND the term of each journal[21]. VOSviewer_1.6.19 was used to create the VOS figure using the results of the same query. Graphs and tables were obtained using Microsoft Office Excel.

RESULTS

Figure 1 shows the distribution of research articles published on SCT in CVA worldwide between 2000 and 2023. The United States and China had the highest productivities with several articles ranging between 1000 and 2000. By contrast, many countries had minimal productivity. Most African and some Asian countries, along with Greenland, had zero articles. According to Figure 2, approximately two-thirds (69%) of the articles related to SCT in CVA were contributed by high-income countries, while almost none (0.04%) by low-income countries. Besides, around one-third of the articles were contributed by upper-middle and lower-middle income countries (26.67% and 4.5%, respectively).

A total of 6923 studies were identified on SCT in CVA, making 0.03% of all published studies worldwide. The United States ranked first worldwide with respect to the number of articles on SCT in CVA, with 1681 articles (Table 1) accounting for 24.28% of the total research on SCT in CVA. China ranked second with 1476 articles accounting to 21.32%, followed by Japan with 543 articles accounting to 7.84% of total articles. Germany and Canada ranked fourth and fifth, respectively. On the other hand, research on SCT in CVA constituted less than 0.1% of the total articles in each of the top 20 countries, with South Korea having the highest percentage of 0.08%, Georgia second with 0.062%, and Taiwan third

Table 1 Top 20 performing countries with research articles on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023

Rank	Country	Number of articles on SCT in CVA	Percentage among total articles on SCT in CVA	Total number of articles	Percentage of articles on SCT in CVA among total articles	Number of articles per GDP (100 billion USD)	Number of articles per million population
1	United States	1681	24.28%	4522491	0.037%	10.30	6.53
2	China	1476	21.32%	2710209	0.054%	18.72	1.34
3	Japan	543	7.84%	1146807	0.047%	10.90	4.59
4	Germany	387	5.59%	1140393	0.034%	11.62	4.85
5	Canada	239	3.45%	804341	0.030%	16.20	8.52
6	Italy	163	2.35%	875969	0.019%	8.48	2.88
7	Taiwan	154	2.22%	261548	0.059%	32.63	6.66
8	Spain	151	2.18%	588135	0.026%	12.17	3.81
9	France	150	2.17%	780901	0.019%	6.13	2.57
10	Sweden	142	2.05%	325489	0.044%	29.79	16.27
11	Iran	136	1.96%	248208	0.055%	38.90	2.51
12	Australia	119	1.72%	682640	0.017%	10.97	6.80
13	Netherlands	113	1.63%	512315	0.022%	14.33	7.56
14	India	99	1.43%	654887	0.015%	5.79	0.11
15	Georgia	86	1.24%	137776	0.062%	692.04	20.68
16	Poland	83	1.20%	234641	0.035%	18.60	2.29
17	South Korea	83	1.20%	104065	0.080%	6.81	1.99
18	Brazil	82	1.18%	424567	0.019%	5.18	0.55
19	United Kingdom	79	1.14%	343056	0.023%	3.03	1.34
20	Belgium	64	0.92%	247924	0.026%	14.07	6.27

CVA: Cerebrovascular accident; GDP: Gross domestic product; SCT: Stem cell transplantation; USD: United States dollar.

with 0.059%[1]. This percentage was lowest in India (0.015%), and slightly higher in Australia, Brazil, and Italy (0.017%, 0.019%, and 0.019%, respectively). Georgia by far had the highest number of articles per GDP (100 billion USD) at 692.04. Second and third were Iran (38.90) and Taiwan (32.63). This number was the lowest in the United Kingdom (3.03). Regarding the number of articles per million population, Georgia again ranked first with 20.68 articles, followed by Sweden with 16.27 and India ranked last (20th) with only 0.11 articles.

Figure 3 shows the evolution of the number of articles between 2000 and 2023 among the top five countries with the highest contributions to SCT in CVA research. The United States exhibited a steady increase over the years, peaking at about 150 articles in 2019, followed by a steep decline to approximately 50 articles in 2023. China experienced a sharper increase, peaking at almost 175 articles in 2022, with a subsequent decline to slightly less than 150 in 2023. Japan, Germany, and Canada showed a modest increase over the years, each reaching 50 articles per year. These three countries also peaked in recent years and have seen a significant decline over the last 2 years. Overall, it appears that productivity, as measured by the number of articles, has declined in the last 3-4 years across all these countries.

Table 2 shows the number of retrieved articles published in each of the top 20 clinical neurology journals. "*Stroke*" had the highest number of articles, totaling 165. In comparison, "*Annals of Neurology*" and "*Brain*" were ranked second and third, with a maximum of 27 and 22 articles, respectively. Notably, 6 of the top 20 journals had no articles published on SCT in CVA. On the other hand, Figures 4 and 5 depict the frequency of inclusion of each type of SCT in CVA research. Mesenchymal SCT was the most frequently mentioned term among these articles (63.0%). It accounted for 140 articles by the United States, 270 by China, 80 by Japan, 30 by Germany, and 20 by Canada. Hematopoietic SCT was the second most frequently used term (24.1%). The United States contributed with about 90 articles, Japan with 30 and China, Germany, and Canada with 20 articles each. Cord blood SCT was mentioned in 10.4% of articles, mainly by the United States and China, whereas peripheral blood SCT was included in 2.5% of articles, mostly contributed by Japan.

Network of co-occurrence of clusters

Network visualization of MeSH keywords co-occurrence revealed four main clusters. The first one, in red color, focused

Table 2 Distribution of articles published on stem cell transplantation in patients with cerebrovascular accident by journal between 2000 and 2023

Ranking	Journal	Number of articles
1	*The Lancet Neurology*	9
2	*JAMA Neurology*	1
3	*Nature Reviews Neurology*	3
4	*Molecular Neurodegeneration*	2
5	*Acta Neuropathologica*	4
6	*Neuro-Oncology*	3
7	*Brain*	22
8	*Annals of Neurology*	27
9	*Alzheimer's and Dementia*	0
10	*Journal of Neurology, Neurosurgery and Psychiatry*	4
11	*Autism in Adulthood*	0
12	*Sleep Medicine Reviews*	0
13	*Stroke*	165
14	*European Stroke Journal*	0
15	*Annual Review of Vision Science*	0
16	*Alzheimer's Research and Therapy*	1
17	*Movement Disorders*	1
18	*Translational Neurodegeneration*	0
19	*Neurology*	20

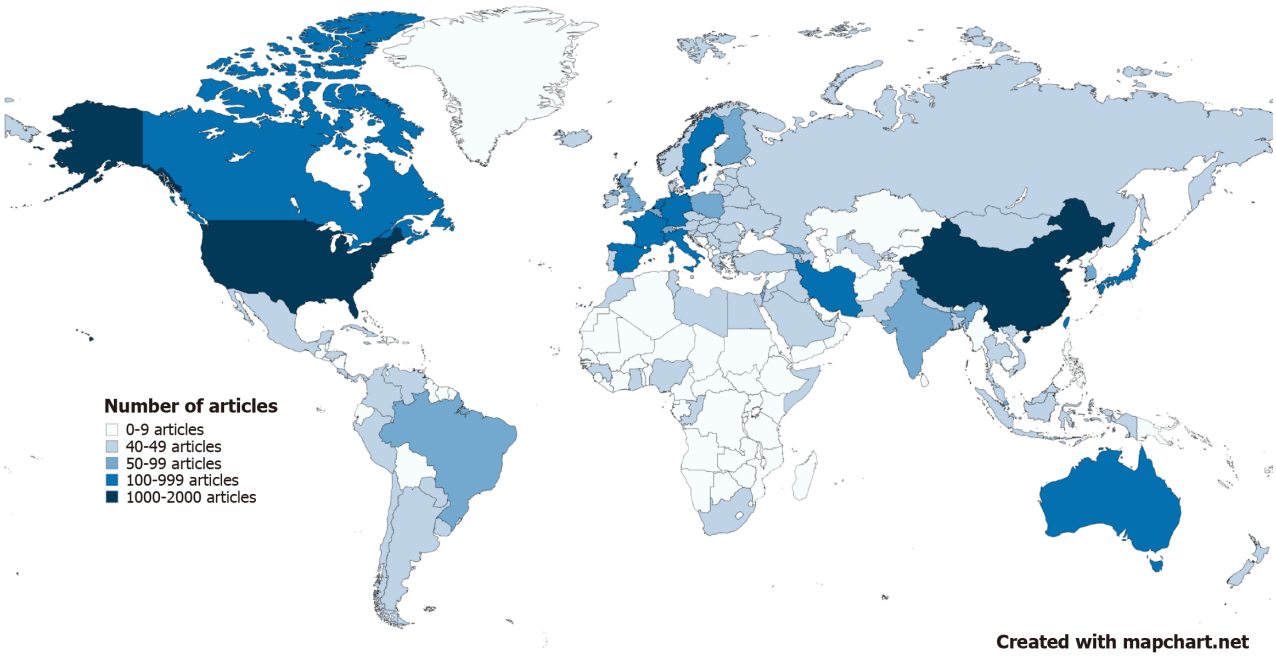

Figure 1 Global research productivity on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023.

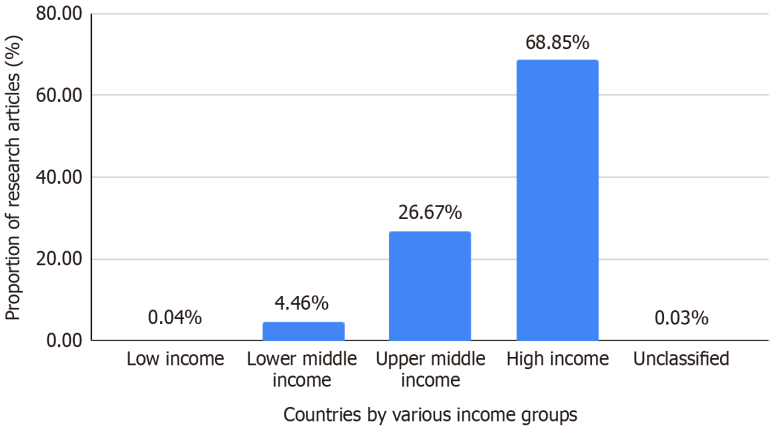

Figure 2 Proportion of research articles on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023 by various income group countries.

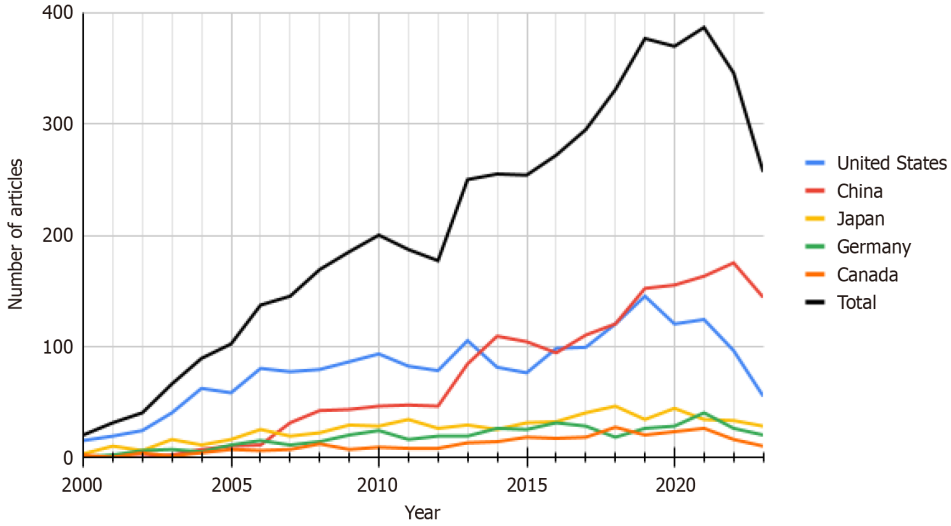

Figure 3 Publication trend among the top five countries on stem cell transplantation in patients with cerebrovascular accident between 2000 and 2023.

on neurogenesis-related keywords and comprised the terms: proliferation, neural progenitor cell, subventricular zone, and apoptosis. The second cluster, shown in blue, focused on the patient and contained the terms: Study, trial, efficacy, safety, acute myocardial infarction, and heart failure. The third cluster, in green, addressed the disease and included the following keywords: Hematopoietic stem cell transplant, review, research, progress, risk, and neurological disease. The last cluster, colored in yellow, targeted SCT and included the terms: Meta-analysis, systemic review, mesenchymal stem cell therapy, and stroke patient (Figure 6). The co-occurrence of MeSH keywords using the overlay visualization option on VOSviewer showed that articles around the world on SCT and CVA shifted around 2012 from focusing on stem cells and SCT, moving to proliferation and neurogenesis in 2014, with more patient-oriented research. This was followed by studies on various diseases and stem cell therapy in 2016, with more focus on efficacy and safety. In 2018, different types of stem cell therapy (mesenchymal for example) were introduced, along with meta-analyses and reviews (Figure 7).

DISCUSSION

The potential of stem cells to repair damaged tissue and improve neurological function has provided an impetus for researchers to investigate this emerging field. On this basis, we examined the state of the literature on SCT for patients with CVA over the past two decades. The increasing popularity of this field was particularly noted in developed countries such as the United States, China, and Japan, consistent with the leading countries in life sciences research worldwide[22]. The number of papers produced from the United States and China is nearly three times higher compared to Japan. Approximately 68% of the research was done in high-income countries, with mesenchymal stem cells being the most extensively studied. Research focus shifted from *in vitro* studies, assessing stem cell proliferation and neurogenesis, to *in vivo* studies, targeting efficacy and safety, and the number of reviews increased.

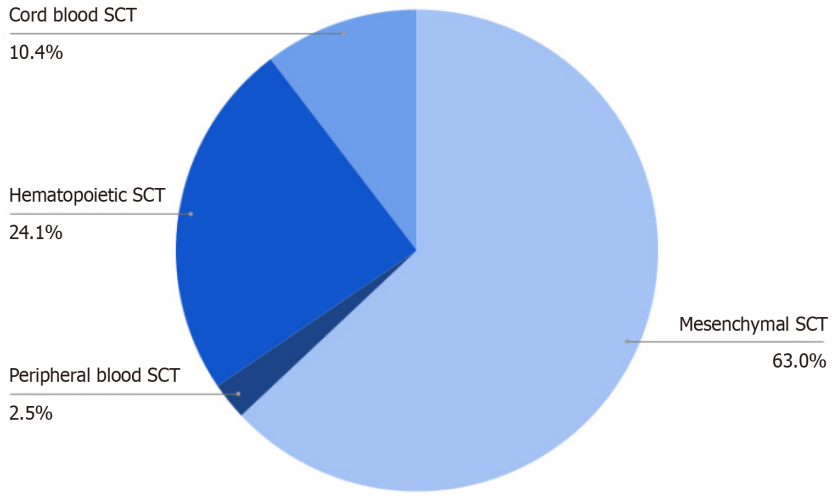

Figure 4 Percentage of articles mentioning each type of stem cell transplantation in patients with cerebrovascular accident. SCT: Stem cell transplantation.

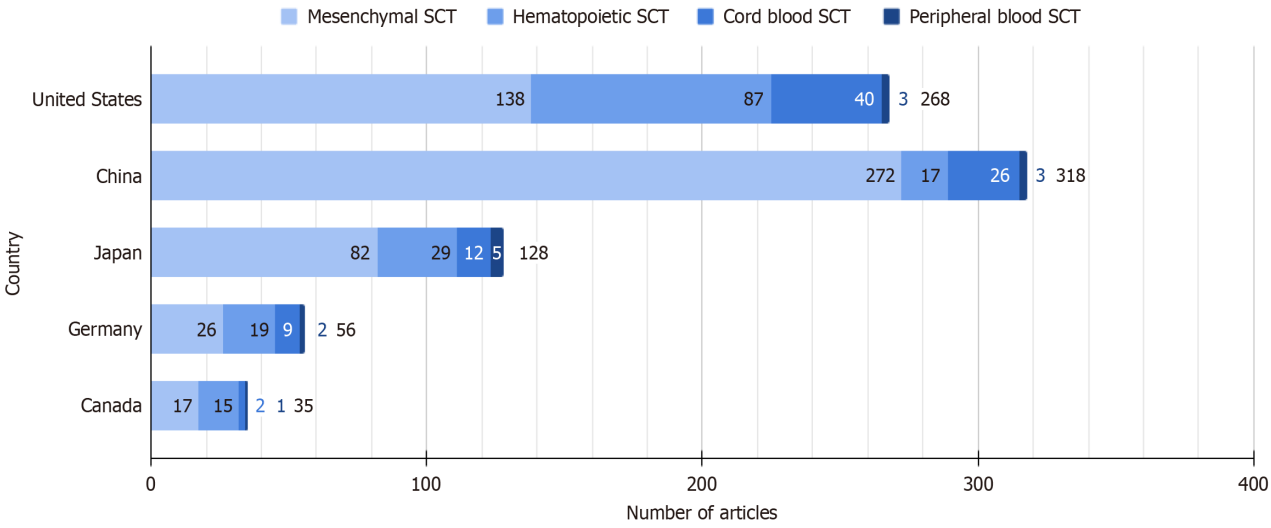

Figure 5 Contribution of the top five active countries for each type of stem cell transplantation in patients with cerebrovascular accident. SCT: Stem cell transplantation.

Despite the positive correlation between stroke and low sociodemographic status, as well as the increase in cases in low-income countries compared to a decrease in high-income countries, the majority of research was done in high and middle high-income countries[23]. Stem cell therapy is an expensive protocol that requires extensive research to reach the targeted therapeutic stage, thus requiring a large amount of funding[24-26]. This might explain our findings, as higher-income countries typically have larger budgets, better infrastructure with more advanced technology, and can afford to invest more in research on SCT, as well as to support expensive therapy protocols once approved[27,28].

When following the trends in research on stem cell therapies in CVA, a decline can be noticed around 2020. This decline could be linked with the coronavirus disease 2019 pandemic, which had a major impact on research productivity worldwide[29]. The pandemic also led to an overall shift or decrease in research productivity, as many researchers have been forced to work from home or had their research projects delayed or canceled[30]. Despite the increase in stroke cases due to the potential of the virus to cause blood clots in the brain's vasculature in around 2% of coronavirus disease 2019-infected patients, research efforts shifted towards more prevalent complications, leading to this decrease in research productivity concerning SCT[31,32]. Moreover, *Stroke* was found to be the leading journal in the field of stem cell therapy for stroke. The countries with the highest number of publications in this journal are United States, Japan, and Germany, which is consistent with our findings[33].

Main keywords that have received extensive attention in this field during the past 5 years included "mesenchymal stem cell therapy," "clinical target," and "therapeutic target." When compared to an earlier era, "hypoxia-ischemia" and "adult rat" were the main keywords. This shift reflects the ongoing transformation from preclinical findings to clinical trials. Stem cell research has shifted to concentrating on "human pluripotent stem cells," "mesenchymal stem cell therapy," and "neural stem cell (NSC)." Since stroke recovery relies heavily on the regeneration of nerves and blood vessels, the formation of the neurosphere from NSCs opened up new possibilities for the regenerative treatment in CVA

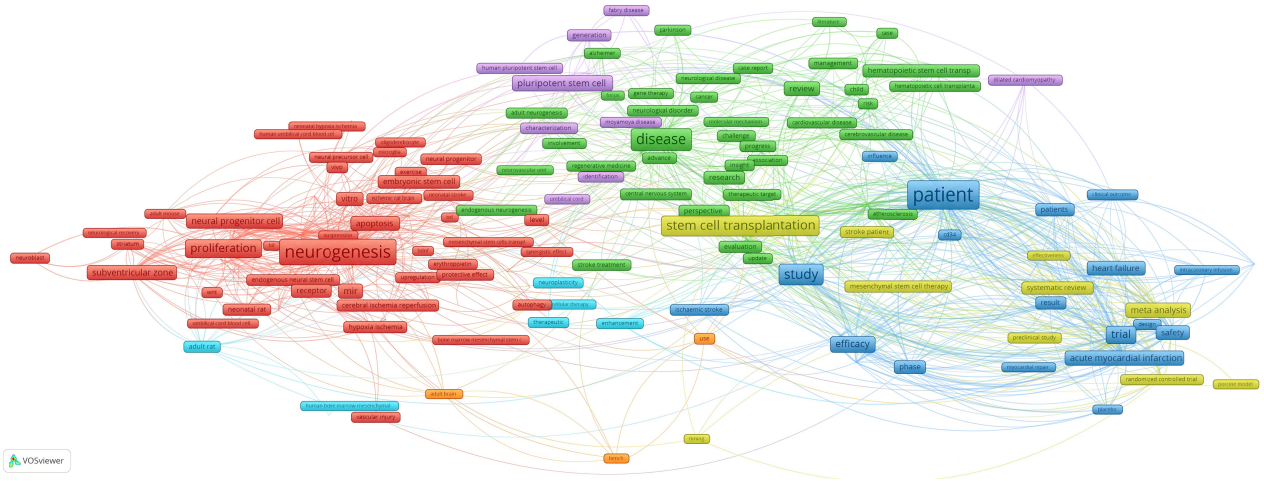

Figure 6 VOSview of the main occurrences of stem cell transplantation in patients with cerebrovascular accident in articles between 2000 and 2023.

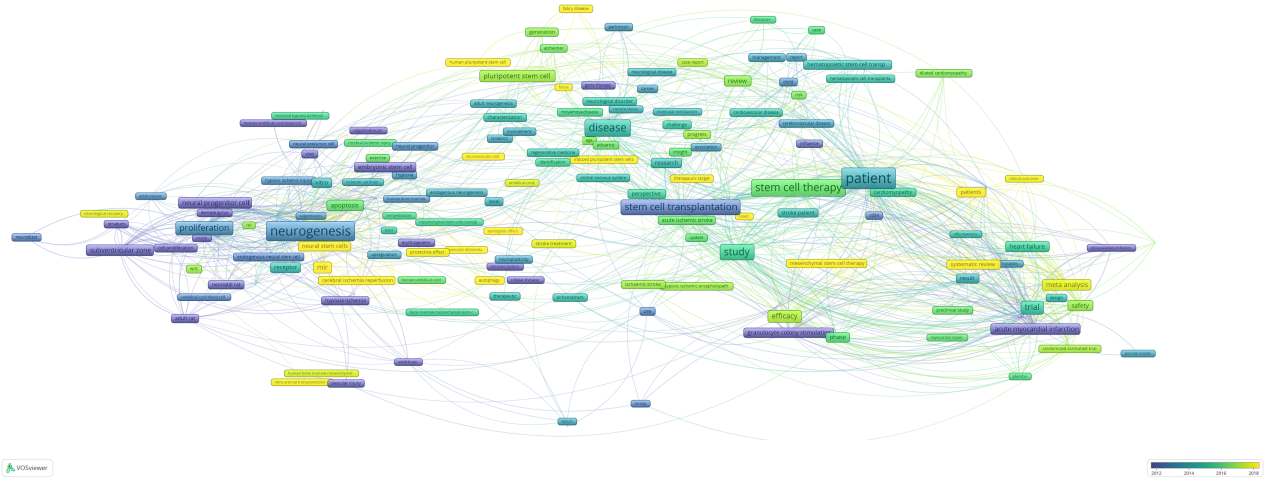

Figure 7 VOSview of the main occurrences of stem cell transplantation in patients with cerebrovascular accident concerning articles between 2000 and 2023.

patients[34].

Regarding mechanistic and molecular factors in stem cell therapy, the results presented highlight a wide gap in this field. For example, cell microenvironment, immunity, genetic and epigenetic stability, scaffolding methods, and regulatory and signaling pathways were minimally targeted, as shown in Figures 6 and 7[35-37]. Even in regard to the few molecular and mechanistic factors that were mentioned, such as Wnt, MIR, brain-derived neurotrophic factor, tumor necrosis factor and cluster of differentiation 34, their discussion was to a lesser extent compared to other clinical and epidemiological factors that were highly tackled. Playing a major role in the effectiveness of stem cell therapy, these factors need to be more studied and targeted in future studies, aiming to reach better outcomes in CVA cases.

In recent years, research on "case reports" has steadily gained popularity, indicating that researchers have been delving further into implementing stem cell therapy. For instance, a phase 1 clinical trial observed neurological improvement after the delivery of single intracerebral doses of the NSC line CTX0E03, with no adverse events. However, only 11 men were recruited in this study[38]. This suggests that further investigation with a larger patient population is needed.

To the best of our knowledge, this study is the first bibliometric analysis to assess research trends regarding stem cell therapy in stroke. However, several limitations should be noted. For instance, only a single database (PubMed) was searched. Despite being one of the largest databases, PubMed does not index all journals, which may have led to the omission of some articles. Furthermore, only papers written in English were included, excluding the very few published in other languages[5]. Finally, while this bibliometric analysis describes research trends on this topic, the content of each paper was not critically analyzed.

CONCLUSION

This article assessed global research trends and activity regarding literature on SCT in CVA. It provides a comprehensive guide for physicians and researchers in the field through an objective overview of research activity. This bibliometric analysis highlights both current trends and gaps, offering a roadmap for guiding future research efforts to ultimately achieve the most beneficial clinical outcomes. Having a potential therapeutic role in CVA, more research is needed in the future to focus on different aspects of SCT, aiming to reach a better treatment strategy and improve life quality in patients.

FOOTNOTES

Author contributions: Masri JE and Ghazi M conceptualized the study; Masri JE, Afyouni A, Hamideh K, and Hosseini H extracted and organized the data; Masri JE, Afyouni A, Hamideh K, and Jurjus A performed the data analyses; Masri JE, Afyouni A, Hamideh K, and Petrosyan R designed the methodology; Salameh P and Hosseini H supervised the study; Masri JE, Afyouni A, Ghazi M, Moubayed I, and Jurjus A wrote the original draft of the manuscript; Jurjus A, Haidar H, and Hosseini H reviewed and edited the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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Country of origin: Lebanon

ORCID number: Abdo Jurjus 0000-0002-5955-656X; Pascale Salameh 0000-0002-4780-0772.

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