Am J Transl Res 2023;15(12):6867-6877
www.ajtr.org /ISSN:1943-8141/AJTR0149752

Brief Communication

A bibliometric analysis of studies of exosomes in ischemic stroke published from 2002 to 2021

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Received February 19, 2023; Accepted December 1, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Recently, research on exosomes in ischemic stroke has become an attractive field worldwide, and therefore the number of relevant publications has increased. The objective of the present study is to visualize the current research status and hotspots in this area by performing bibliometric analysis and helping researchers predict future research trends. Studies regarding exosomes in ischemic stroke were retrieved from the Science Citation Index-Expanded and Social Sciences Citation Index databases of the Web of Science. Knowledge maps were constructed and visualization analysis was performed using VOSviewer and CiteSpace software. In total, 504 publications (336 articles and 168 reviews) published from 2002 to 2021 were identified in this bibliometric analysis. The leading publishing countries were China and the USA, and the top collaborating institutions were Henry Ford Hospital and Oakland University. Analyses of keywords and co-cited references revealed that microRNA, biomarkers, stem cells, therapeutic effects, neurogenesis, and neurovascular plasticity were significant hotspots and emerging trends. According to the bibliometric analysis results, our study identified the research hotspots and emerging trends relevant to exosome involvement in ischemic stroke.

Keywords: Ischemic stroke, exosomes, bibliometrics, VOSviewer, CiteSpace

Introduction

Stroke is reported to be the second leading cause of death and disability worldwide, and ischemic stroke accounts for 87% of all stroke cases [1]. Ischemic stroke continues to be an intractable human health concern and results in long-term neurological deficits and death. Currently, the general therapeutic principles for ischemic stroke mainly focus on revascularization and neuroprotection. However, most neuroprotective agents have difficulty crossing the blood-brain barrier (BBB), even in the context of BBB damage and increased permeability [2]. Recognized effective treatments, including intravenous administration of recombinant tissue plasminogen activator and endovascular interventions, can only benefit a minority of patients given their narrow therapeutic window, poor revascularization ratio, and risk of hemorrhagic transformation [3]. Therefore, it is necessary to explore innovative therapeutic strategies to improve the prognosis of ischemic stroke.

Exosomes are nano-sized lipid bilayer particles generated by various cell types. Because of the biological characteristics of exosomes, they can freely cross the intact BBB. Functionally, exosomes can affect a variety of biological processes, such as RNA transfer, intercellular communication, and immunomodulatory activity, because they are loaded with an abundance of biofunctional molecules, including microRNAs, mRNAs, proteins, lipids, and nucleic acids [4]. Exosomes can effectively protect the bioactive components that they are carrying from degradation via proteases and nucleases. After they are released into the extracellular matrix, exosomes can reach and affect target cells via three possible mechanisms, including direct membrane fusion, internalization, and receptor-ligand interactions [5]. Recently, exosome-based therapies have been widely demonstrat-

ed to exert neuroprotective and neurological recovery effects in ischemic stroke and may be a novel alternative strategy for ischemic stroke treatment [6, 7]. In addition, studies related to the use of exosomes as diagnostic biomarkers and the use of engineered exosomes as drug-delivery vehicles for clinical translation have recently emerged.

As a comprehensive literature analysis methodology, bibliometric analysis provides qualitative and visual analyses of the available existing publications. Using CiteSpace and VOSviewer software, the knowledge network of annual publications, leading authors and institutions, and burst analysis of keywords can be determined to reveal research hotspots and predict future research trends in a certain field [8, 9]. Exosomes exhibit considerable potential for both diagnosis and treatment of ischemic stroke. Therefore, it is worthwhile to examine this field. Bibliometric analysis can be used to provide an intuitive and comprehensive visual description of this important topic. This method can not only provide a reference for future scholars, but also inspire innovative approaches for diagnosis and therapies for stroke in the future.

Data and methods

Data collection and analysis

All articles included in this study were retrieved from the Science Citation Index-Expanded and Social Sciences Citation Index of the Web of Science (WoS). The retrieval time spanned from June 5, 2002, to June 5, 2022, and all the data were collected from articles within one day (April 30, 2022) to avoid database update bias. The search themes were as follows: "TS=(exosomes) OR TS=(extracellular vesicles) OR TS=(exovesicles)", AND "TS=(stroke) OR TS=(CVA) OR TS=(cerebrovascular accident)", AND Language: English. A total of 504 documents were searched, excluding those not published in English, meeting abstracts, proceedings papers, editorial materials, letters, corrections, early access articles, and book chapters. The document types were original articles and reviews. The flow diagram of the elaborated data retrieval strategy and inclusion criteria for this study is shown in **Figure 1A**. Data analysis was performed using CiteSpace and VOSviewer software.

Data analysis

CiteSpace is a pivotal citation visualization software program developed by Chaomei Chen [8]. It can not only provide general information about studies including annual publications and various contributions of different countries/regions, organizations, journals, and authors, but it can also reveal research hotspots and predict research frontiers by detecting keyword bursts and producing a timeline view of co-cited references.

The VOSviewer was initially developed by Nees Jan van Eck and Ludo Waltman [9]. It has been frequently adopted to conduct visual analysis of high-frequency co-cited references and keywords using three visualization maps (network, overlay, and density visualizations). This study primarily used these two software programs to visually analyze data from the literature.

Results

Basic overview of the publications

A total of 504 publications consisting of 336 articles (66.7%) and 168 reviews (33.3%) published from 2002 to 2021 were included in the study (**Figure 1A**). The annual publication trend exhibited an overall increase during the last 20 years (**Figure 1B**), especially in the most recent 5 years. Analysis of the cooperation network of different countries/regions (**Figure 1C**) and the top 10 most productive countries/regions showed that China (190, 37.70%) and the USA (161, 31.95%) were the most prolific countries, accounting for more than half of the total publications. Centrality can reveal the cooperation and core roles of the countries/regions and institutions in network maps. Notably, China was the most productive country, but its centrality was far below the average value.

The collaborative relationships between various institutions are depicted in the visualization map (**Figure 1D**). The top 10 collaborating institutions are also listed in **Table 1**, half of which were from the USA. The three most prolific institutions were Henry Ford Hospital (30, USA), Oakland University (25, USA), and the League of European Research Universities (20), while Harvard University (0.15) had the highest centrality value. The dual-map overlay

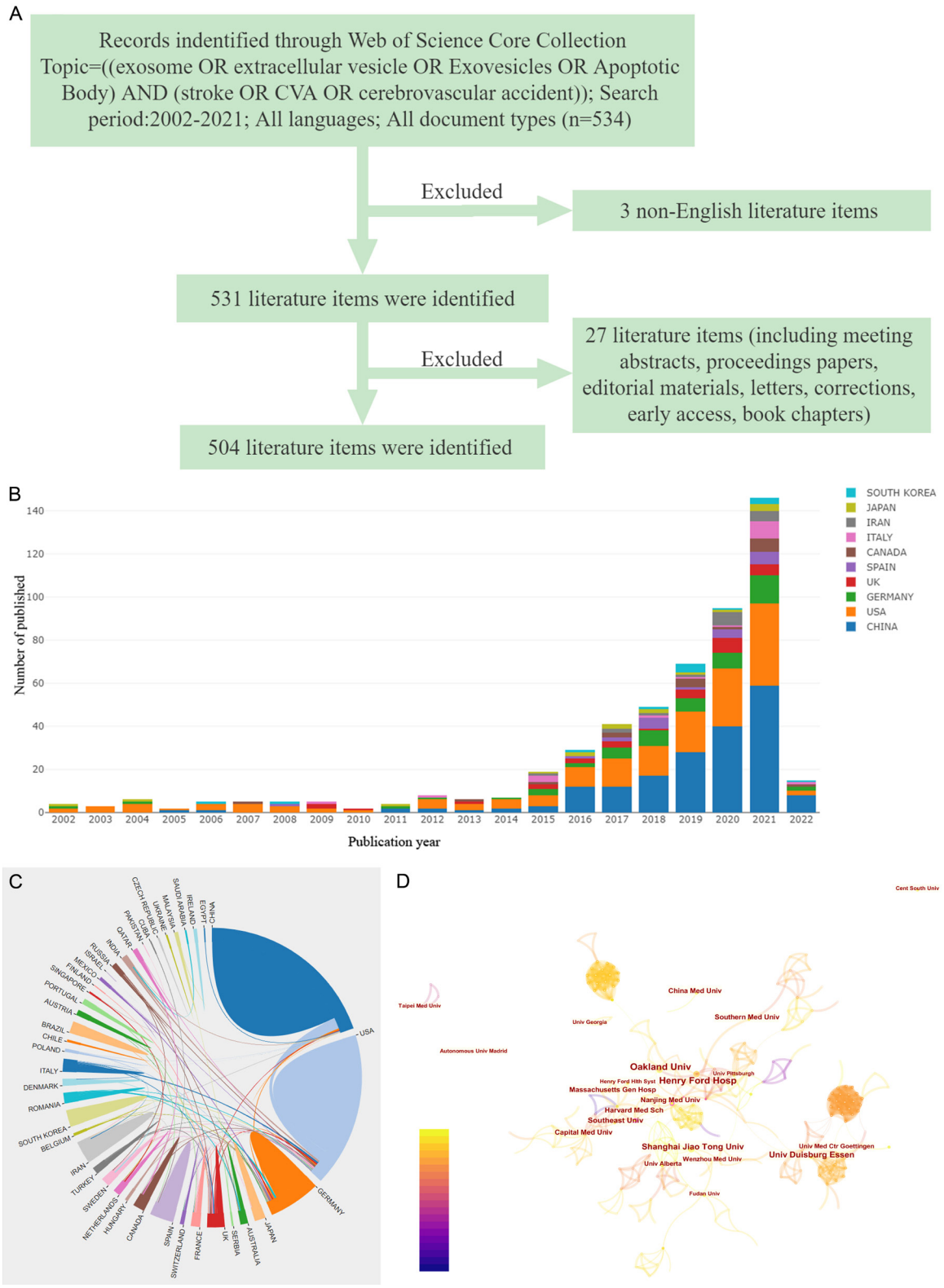


Figure 1. The overview of the publications on exosomes in ischemic stroke over the past 20 years. A. Flowchart of literature selection. B. Trends of publications. C. Co-operation of countries/regions. D. Co-operation of institutions.

of journals represents the citation relationships between various journals. The most obvious citation path is shown in orange in **Figure 2A**, with citations by molecular/biology/immunolo-

Table 1. The top 10 countries/regions, institutions and journals

Rank	Country			Institutions			Author				
	Country	Articles Counts	Centrality	Institutions	Articles Counts	Centrality	Author	Articles Counts	Centrality	Total Citations	H-index
1	China	190	0.00	Henry Ford Hospital	30	0.00	Chopp M	26	0.06	3177	18
2	USA	161	0.28	Oakland University	25	0.00	Hermann DM	17	0.04	709	10
3	Germany	50	0.00	League of European Research Universities	20	0.00	Zhang ZG	17	0.01	2504	13
4	UK	24	0.59	University of Duisburg-Essen	19	0.08	Doeppner TR	15	0.02	631	8
5	Spain	20	0.09	Harvard University	16	0.15	Zhang Y	14	0.00	1122	10
6	Canada	17	0.04	Shanghai Jiao Tong University	15	0.01	Li Y	12	0.00	1849	7
7	Italy	17	0.45	University of Göttingen	15	0.00	Bahr M	10	0.01	264	7
8	Iran	16	0.13	University of California System	12	0.00	Buller B	9	0.00	1094	7
9	Japan	15	0.00	Massachusetts General Hospital	11	0.02	Wang Y	9	0.00	205	6
10	South Korea	13	0.00	Southeastern University	11	0.00	Giebel B	8	0.00	561	7

gy journals on the left and citations by molecular/biology/genetics journals on the right.

A total of 2924 authors contributed to this research area, and a list of the top 10 most prolific authors is presented in **Table 1**. These top authors published 137 documents, contributing 27.18% of the total documents. Chopp M ranked first with 26 publications and also had the highest H-index (18) and the most total citations (3177), followed by Hermann DM, Zhang ZG, and Doeppner TR. Chopp M is obviously the most influential and central scholar in this field. The network of author cooperation (**Figure 2B**) indicated that Chopp M and Zhang ZG were the most active and cooperative authors.

Analysis of keywords

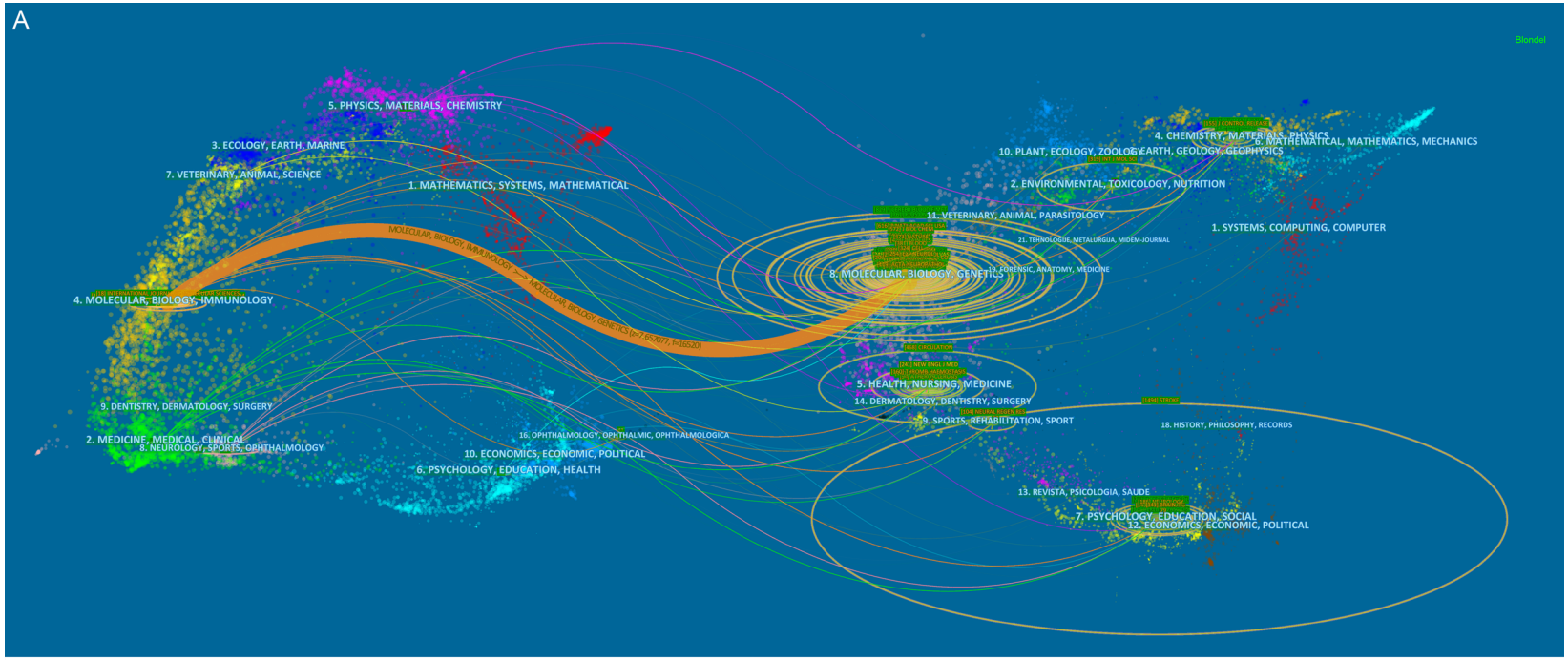
Analysis of keywords extracted from titles and abstracts can help predict the hotspots and frontiers of related fields. The keywords appearing with high frequency were classified into six main clusters, and each differently colored cluster shown in **Figure 2D** represents a different research direction. Cluster 1 (red) primarily consists of extracellular vesicles, exosomes, acute ischemic stroke, biomarkers, and microRNA, thus mainly concentrating on the role of exosomes as diagnostic biomarkers in acute ischemic stroke. Cluster 2 (purple) mainly explores the relationship between exosomes and other central nervous system diseases. Cluster 3 (green) contains stem cells, mesenchymal stem cells, transplantation, cell therapy, and repair, demonstrating the therapeutic effects of exosomes on stroke. Cluster 4 (yellow) is focused on neurogenesis and neurovascular plasticity. Cluster 5 (blue) mainly includes apoptosis, reperfusion, brain, pathway, and inhibition, mainly elucidating the molecular mechanisms of exosome function in stroke. Furthermore, the VOSviewer color-coded all of the selected keywords according to the average publication year, as shown in **Figure 2E**. Warmer colors represent more recently appearing keywords and imply potential research hotspots. The emerging keywords in recent years mainly included biomarkers, cell therapy, neurogenesis, neurovascular plasticity, and microRNAs. Burst detection of the keywords can reflect the research hotspots of a certain time period. The red line denotes an explosive period. **Figure 2C** shows the top 10 keywords with the strongest citation bursts, which focused on the aspects of "functional recovery", "therapy", "mechanism", and "stromal cell".

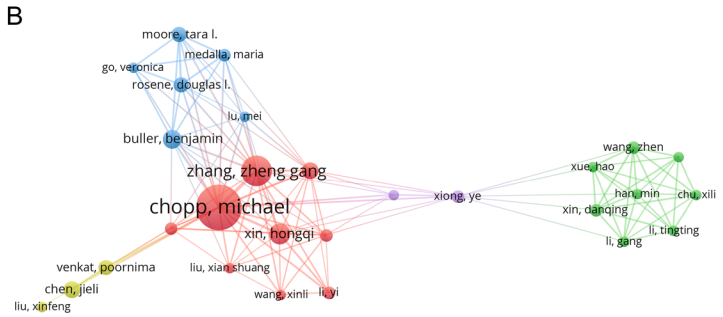
Analysis of co-cited references

Frequently cited studies are generally considered to be highly influential and widely accepted in particular research areas. As shown in **Figure 3A**, Xin HQ had the most co-cited references, which were closely related to the co-citations of Doeppner TR and Zhang ZG. The cluster network (**Figure 3B**) identified seven main categories of co-cited references: cluster #0 ("neural plasticity"), cluster #1 ("multipotent mesenchymal stromal cells"), cluster #2 ("clinical translation"), cluster #3 ("apoptosis"), cluster #4 ("biomarker"), cluster #5 ("mesenchymal stromal cell"), and cluster #6 ("tumor microenvironment"). The timeline view of the clusters is shown in **Figure 3C** and intuitively reflects the stage hotspots and development in the temporal dimension. Before 2007, this research area was in a very early stage. The results indicate that the use of exosomes as biomarkers for early identification of stroke and their neuroprotective role in stroke is a recent vital focus. The use of engineered exosomes for clinical translation is also an important potential research direction.

Discussion

Ischemic stroke is a major disease with high mortality and morbidity rates worldwide. After ischemic stroke, brain tissue will suffer primary damage due to ischemia and hypoxia. Subsequently, the ischemia-reperfusion phase is accompanied by a series of complex pathophysiological changes, including cellular energy depletion, intracellular calcium overload, excess glutamate-mediated excitatory neurotoxicity, and oxidative stress, which cause more severe secondary injury [10]. Ischemic stroke remains an enormous challenge for effective treatment despite decades of relentless research, primarily because of the obstruction of the BBB and the limited time window for treatment. Exosomes are currently a research focus in ischemic stroke because of their neuroprotective effects, ability to permeate the BBB, and low immunogenicity [11]. Therefore, it is important to provide comprehensive insights





C

Top 10 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2002 - 2021
focal cerebral ischemia	2002	4.23	**2015**	2017	
extracellular vesicle	2002	28.97	**2016**	2021	
mechanism	2002	6.83	**2016**	2017	
therapy	2002	8.57	**2018**	2021	
ischemic stroke	2002	7.02	**2018**	2018	
functional recovery	2002	22.31	**2019**	2021	
stroke	2002	21.88	**2019**	2021	
stromal cell	2002	6.31	**2019**	2019	
brain	2002	4.48	**2019**	2019	
exosm	2002	19.51	**2020**	2021	

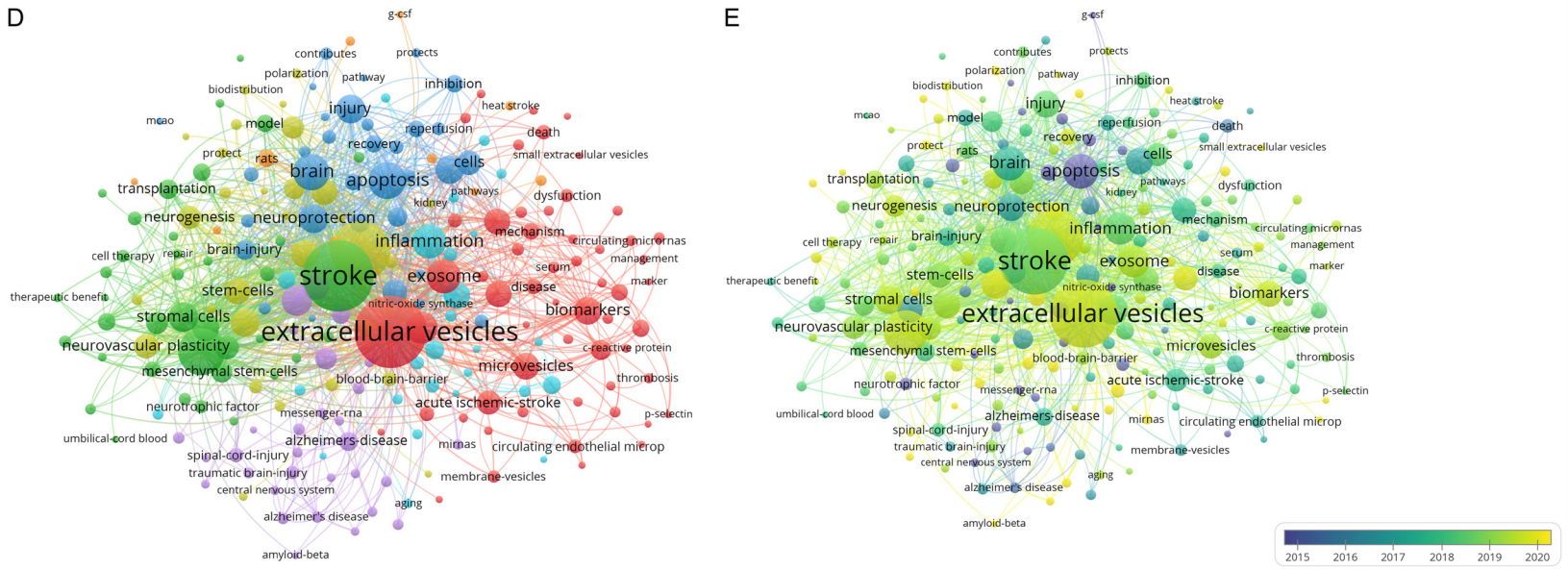


Figure 2. A. The dual-map overlay of journals related to exosomes ischemic stroke research. B. Cooperation between different authors in this research field. C. Keywords with the strongest citation bursts in this research field of exosomes in ischemic stroke from 2002 to 2021. D. Clusters map of keywords in this research field. E. Distribution of keywords according to average publication year (blue: earlier, yellow: later).

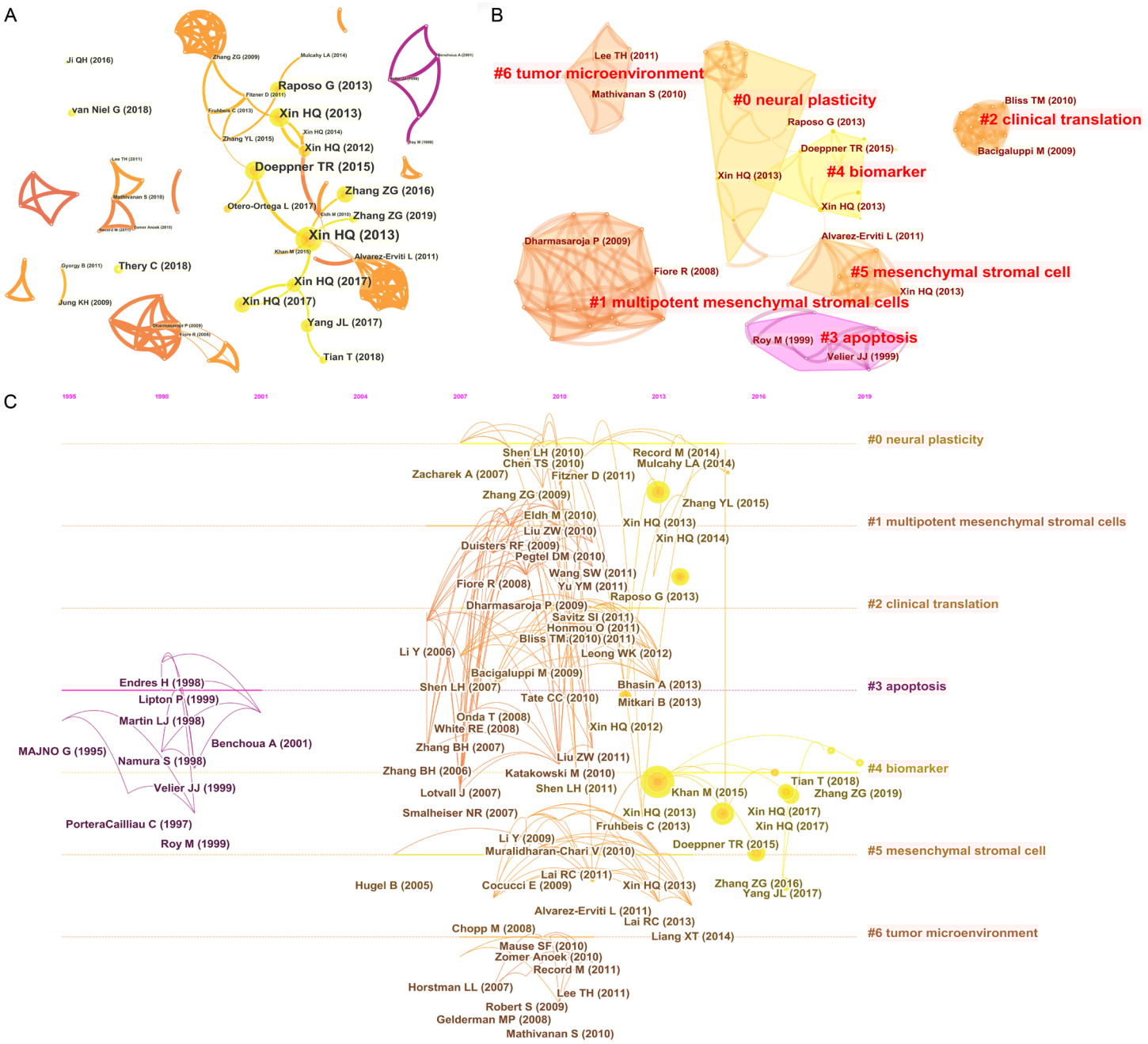

A
Ji QH (2016)
van Niel G (2018)
Zhang ZG (2009)
Mulcahy LA (2014)
Raposo G (2013)
Fitzner D (2011)
Frühbeis C (2013)
Xin HQ (2013)
Zhang YL (2015)
Xin HQ (2014)
Xin HQ (2012)
Doeppner TR (2015)
Zhang ZG (2016)
Otero-Ortega L (2017)
Zhang ZG (2019)
Xin HQ (2013)
Alvarez-Erviti L (2011)
Thery C (2018)
Xin HQ (2017)
Xin HQ (2017)
Yang JL (2017)
Jung KH (2009)
Tian T (2018)
B
Lee TH (2011)
#6 tumor microenvironment
Mathivanan S (2010)
#0 neural plasticity
Raposo G (2013)
Doeppner TR (2015)
#4 biomarker
Xin HQ (2013)
Xin HQ (2013)
Bliss TM (2010)
#2 clinical translation
Bacigaluppi M (2009)
Alvarez-Erviti L (2011)
Dharmasaroja P (2009)
Fiore R (2008)
#5 mesenchymal stromal cell
Xin HQ (2013)
#1 multipotent mesenchymal stromal cells
Roy M (1999)
#3 apoptosis
Velier JJ (1999)
C
1995
1998
2001
2004
2007
2010
2013
2016
2019
#0 neural plasticity
#1 multipotent mesenchymal stromal cells
#2 clinical translation
#3 apoptosis
#4 biomarker
#5 mesenchymal stromal cell
#6 tumor microenvironment
Shen LH (2010)
Chen TS (2010)
Record M (2014)
Mulcahy LA (2014)
Zacharek A (2007)
Fitzner D (2011)
Zhang ZG (2009)
Zhang YL (2015)
Eldh M (2010)
Xin HQ (2013)
Liu ZW (2010)
Xin HQ (2014)
Duisters RF (2009)
Pegtel DM (2010)
Wang SW (2011)
Fiore R (2008)
Yu YM (2011)
Raposo G (2013)
Dharmasaroja P (2009)
Savitz SI (2011)
Honmou O (2011)
Bliss TM (2010) (2011)
Li Y (2006)
Leong WK (2012)
Bacigaluppi M (2009)
Endres H (1998)
Shen LH (2007)
Bhasin A (2013)
Lipton P (1999)
Tate CC (2010)
Mitkari B (2013)
Martin LJ (1998)
Onda T (2008)
White RE (2008)
Xin HQ (2012)
Benchoua A (2001)
MAJNO G (1995)
Zhang BH (2007)
Liu ZW (2011)
Namura S (1998)
Zhang BH (2006)
Katakowski M (2010)
Tian T (2018)
Velier JJ (1999)
Lotvall J (2007)
Shen LH (2011)
Khan M (2015)
Zhang ZG (2019)
PorteraCailliau C (1997)
Smalheiser NR (2007)
Xin HQ (2013)
Xin HQ (2017)
Roy M (1999)
Frühbeis C (2013)
Xin HQ (2017)
Li Y (2009)
Muralidharan-Chari V (2010)
Doeppner TR (2015)
Lai RC (2011)
Hugel B (2005)
Cocucci E (2009)
Xin HQ (2013)
Zhang ZG (2016)
Yang JL (2017)
Alvarez-Erviti L (2011)
Lai RC (2013)
Chopp M (2008)
Liang XT (2014)
Mause SF (2010)
Zomer Anoek (2010)
Record M (2011)
Horstman LL (2007)
Lee TH (2011)
Robert S (2009)
Gelderman MP (2008)
Mathivanan S (2010)

Figure 3. Analysis of Co-cited References on exosomes in ischemic stroke in the past two decades. A. Co-cited references map of publications on exosomes. B. Cluster Analysis of Co-cited References in ischemic stroke. C. CiteSpace visualization map of timeline view.

into the role of exosomes in ischemic stroke. Thus, we conducted a bibliometric analysis to provide a visual overview of relevant global articles published in the past two decades.

In this study, 504 articles were retrieved using a topic term search. The annual publication trend showed overall growth over the previous 20 years, while a sharp increase was observed in the last 5 years. The results showed that an increasing number of studies are being carried out on the involvement of exosomes in ischemic stroke. The visualization map of country/region collaborations implied that China and the USA were the most productive countries. The highest centrality value of the USA reveals its high quality of publications. However, the centrality value of China was extremely low, implying an urgent need for Chinese scholars to improve the quality of publications and to enhance cooperation and communication with other countries to increase their influence and authority in this field. The most productive institutions were from the USA. Harvard University (0.15) had the highest centrality by a value greater than 0.1, indicating its relatively extensive relationships with other institutions. However, most institutions had a low centrality value, which suggest the need to strengthen mutual cooperation to promote the development of this field. The most prolific journals were mainly located in the USA and Europe, and few were located in Asia. However, some Asian countries such as China are very active contributors to this field; therefore, it is necessary to establish authoritative journals in Asia. The dual-map overlay of journals illustrated that the study of exosomes in ischemic stroke has evolved into an interdisciplinary field. The visualization network of authors conducted by the VOSviewer demonstrated that Chopp M was the central scholar in this field, in addition to holding the highest centrality value and H-index.

An analysis of keywords and references indicated that current research hotspots concentrated on the aspects of therapeutic effects and the role of biomarkers, while future research trends will probably focus primarily on clinical translation based on neural plasticity and anti-inflammatory effects. The keyword clusters and strongest citation burst analysis showed that therapy and functional recovery using exosomes are hotspots. In the early stages, exosomes derived from various stem cells including bone marrow mesenchymal stem cells, adipose stem cells, and umbilical cord stem cells, were extensively studied for their protective effects against stroke. Stem cell-derived exosomes have widely been shown to engage in anti-inflammatory, neuroregenerative, and angiogenesis effects in ischemic stroke through the bioactive molecules that they carry. Studies have shown that exosomes secreted by human neural stem cells can enhance cell viability and resist oxidative stress via microRNAs (hsa-miR-206, hsa-miR-133a-3p, and hsa-miR-3656) in ischemic stroke models [12]. In addition, exosomes released from reactive astrocytes were shown to promote oligodendrogenesis, remyelination, angiogenesis, and reconstruction of endogenous neuronal synaptic circuits [13]. Proteins or microRNAs carried by exosomes can promote the proliferation and migration of neural stem/progenitor cells in the subventricular zone and the dentate gyrus of the hippocampus [14].

The timeline view of the cited references and the cluster analysis of co-cited references reflected that the use of exosomes as biomarkers is a focus and a frontier topic in this research field. Within the ultra-early period after stroke onset, the foremost task is to rapidly restore reperfusion from the occluded vessel, which generally exhibits a heightened time dependence; therefore, earlier treatment initiation improves the functional prognosis [15]. However, early diagnosis of acute ischemic stroke remains challenging due to the lack of effective early molecular markers. Therefore, there is an urgent need for sensitive and reliable hematology biomarkers for the timely diagnosis of stroke. Exosomes can cross the intact BBB and release their contents before they are degraded at the tight junctions of the BBB. Moreover, their substantial stability in circulation and their unique surface biomarkers make exosomes promising biomarkers for early stroke diagnosis and prognosis. Studies have

shown that exosomes derived from different neuronal cells are characterized by unique surface markers, such as the cell adhesion molecules L1CAM and NCAM, GPI-anchored prion protein, GluR2/3, and synaptosome-associated protein 25. The expression profile of exosomes, including proteins, cytokines, microRNAs, circRNAs, and lincRNAs, changes instantly and dynamically with the pathophysiological state of the parent cells; therefore, they are promising candidates for ultra-early diagnostic biomarkers of acute ischemic stroke [16]. Serum exosomal miRNA-126, miR-134, miRNA-223, miR-9, and miR-124 have also shown potential as promising biomarkers for early detection, evaluation of the degree of severity, and prognosis prediction of acute ischemic stroke [17].

The co-cited references cluster map and the timeline view network showed the clinical translational potential of exosomes, although many challenges presently remain, such as low yields, isolation and purification methods, short half-lives, and poor brain targeting capabilities. Excitingly, researchers are now increasingly focusing on bioengineered exosomes to provide increased content yields and enhanced central targeting ability [18]. Scientists have used modified exosomes to load natural compounds such as glycosides and flavonoids and more efficiently deliver these therapeutic agents to ischemic areas with enhanced solubility [19]. Yang's team modified the surface of exosomes with RVG-Lamp2b fusion protein and effectively encapsulated microRNA-124 [20], and the resulting exosomes exhibited enhanced neuronal targeting and therapeutic efficacy.

Limitations and perspectives

This study has some limitations. First, per capita analysis was not conducted when comparing countries with different sizes and populations. Second, some newly published studies may not have received extensive attention and therefore may not be discussed in detail in our study. Data updating and the uneven quality of papers also affected the retrieval results. Moreover, the WoS cannot completely represent all articles in the field, and omissions likely generated research bias. Nevertheless, the WoS is recognized as an authoritative, comprehensive, and reliable literature database, and it is the most frequently used database for bibliometric analyses. Therefore, we suggest that this research represents the overall situation and general trends in the field.

Conclusion

This bibliometric analysis revealed that the field of exosome involvement in ischemic stroke is in a rapid development phase and is increasingly attracting the focus of researchers. China and the USA are the most productive countries in this field. However, most countries lack communication and cooperation. Numerous papers have been published in high-quality international core journals. However, researchers need to strengthen the sharing of results and academic exchange. "Functional recovery", "neuroprotection", "therapy", "mechanism", "stromal cell", "biomarkers", and "clinical translation" are the top keywords. Exploration of the relevant hotspots should be enhanced in the future, especially for clinical translation of engineered exosomes, which would provide tremendous potential candidates for the treatment of ischemic stroke.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (NNSFC) (No. 81960231), and Science and Technology Fund Project of Guizhou Health Commission (gzwkj2022-010).

Disclosure of conflict of interest

None.

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Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundstrom J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C and Fuster V; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol 2020; 76: 2982-3021.

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