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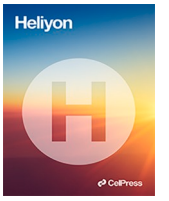

Research article

Knowledge mapping of macrophage and its role in aneurysm from 1999 to 2022: A bibliometric analysis

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A B S T R A C T

Background: Various factors play crucial roles in aneurysm development and prognosis. Macrophages have recently emerged as a major research focus. Despite the numerous studies on the role and function of macrophages in aneurysm pathogenesis, no bibliometric analyses have focused on this topic.
Objective: This study aimed to analyze articles related to macrophages and aneurysms to reveal trends, hotspots, and new frontiers in macrophage-related aneurysm research.
Methods: We retrieved and incorporated 1211 articles from the Science Citation Index Expanded database of the Web of Science Core Collection between 1999 and 2022. The data were analyzed and visualized using CiteSpace and VOSviewer, and Microsoft Excel 2019 was used to plot the data.
Results: The most influential articles were published between 1999 and 2022, with a total citation count of 43870. This study encompassed a comprehensive analysis of 74 research directions. The year with the highest number of publications was 2021 when 109 articles were published. 'ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY' journal has made significant contributions by publishing the highest number of articles (99 articles), while funding support primarily came from the National Institutes of Health and United States Department of Health and Human Services. The United States exerted a substantial influence within this field, with a total publication count of 453 publications and the highest centrality value (0.63). Recent studies have focused on understanding the developmental processes underlying aneurysms and devising preventive measures to effectively impede disease progression.
Conclusions: Our analysis demonstrates the rapid growth in research exploring the relationship between macrophages and aneurysms over the past two decades. Continued exploration and collaboration among different specialties and manufacturers will facilitate innovative approaches for effective management strategies that target patients with diverse forms of aneurysms.

1. Introduction

Aneurysms are pathologically dilated arteries with the potential risk of rupture caused by multiple factors. It is diagnosed when the

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arteries exhibit permanent dilation or bulking with a diameter exceeding 50 % of the normal range. Although most patients with aneurysms remain asymptomatic, certain types of aneurysms, such as intracranial and aortic aneurysms, can have severe consequences. Once ruptured, these aneurysms have high fatality rates [1]. Currently, there are no pharmacological interventions that explicitly halt the growth of aneurysms or prevent their rupture. Hence, it is crucial to prioritize the clinical and fundamental exploration of aneurysms as they play a pivotal role in offering guidance and objectives for future diagnostic and therapeutic approaches. Recently, there has been a noticeable increase in aneurysm research, leading to significant progress. Particularly, investigations into the early development of macrophages in aneurysms have gained increasing attention.

Macrophages are immune cells that perform various functions, including phagocytosis of pathogens, presentation of antigens, and tissue remodeling. They respond to physiological or pathological stimuli by polarizing into distinct phenotypes, each characterized by specific biomarkers [2]. These phenotypes play crucial roles in the pathogenesis of various diseases, including cardiovascular disease [3–5]. Studies have reported that spatiotemporal imaging techniques are imperative for visualizing macrophage phenotypes and polarization. It facilitates the tracking of disease progression and the evaluation of therapeutic responses to drug candidates [2]. Moreover, infiltration and proliferation of tissue macrophages and macrophages derived from circulating monocytes may contribute to vascular injury. Studies have demonstrated that the mobilization of peripheral storage macrophages is the primary mechanism leading to arteritis, and it is speculated that macrophages also play a crucial role in maintaining the integrity of vascular walls in atherosclerosis. Inflammation is a prominent feature of aneurysm pathophysiology, in addition to extracellular matrix degradation and vascular wall remodeling. Macrophages play a crucial role in the production and influence of inflammatory mediators [6,7]. Additionally, various factors other than chemokines and cytokines have been found to regulate macrophage inflammatory activity and affect aneurysm development [8]. Macrophages play a pivotal role in tissue remodeling during the healing response, rendering them of paramount importance. During aneurysm development, macrophages can effectively phagocytose tissue debris and toxic substances, such as extracellular hemoglobin [9] which accumulate in the aortic wall. Certain subgroups of macrophages have been suggested to possess a protective function in aneurysms by facilitating hemoglobin clearance and regulating oxidative stress and inflammatory responses. Therefore, it is imperative to thoroughly investigate the role of macrophages in aneurysm pathophysiology.

Bibliometry is a mathematical statistical tool that provides insight into the current status, trends, and future directions of specific research fields by identifying and evaluating quantitative factors, such as paper quantity and geographical distribution [10]. Additionally, bibliometric analysis can inform government policies, guide funding decisions, and reward scientific researchers. Because of these advantages, bibliometric analyses have been widely conducted on various medical topics, including heart failure [11], coronary heart disease [12], and nervous system disease [13]. To date, no bibliometric study has focused on macrophages and their role in aneurysm research. Given the recent advancements in macrophage-aneurysm research, it is necessary to conduct the first bibliometric analysis on this topic to comprehensively understand its background and development.

In this study, we conducted a systematic bibliometric analysis using CiteSpace, VOSviewer, and bibliometric.com/app to analyze the trends, hotspots, and new frontiers of macrophage-related aneurysm research between 1999 and 2022.

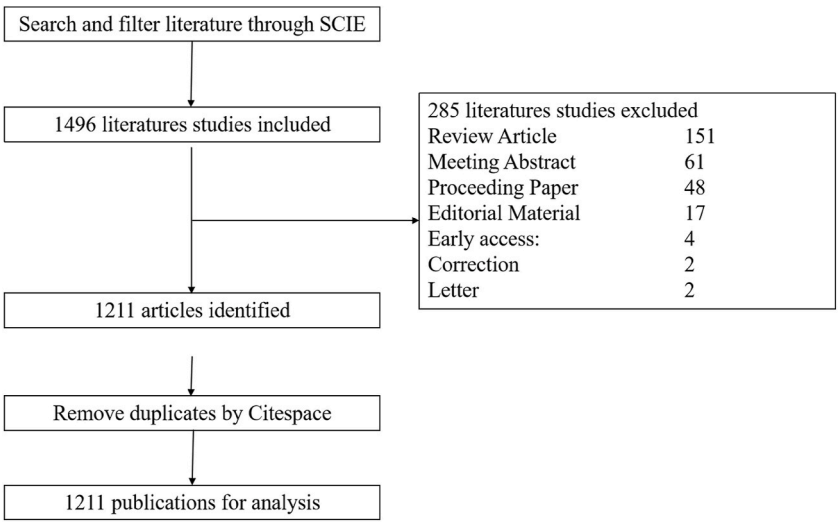

Fig. 1. Flowchart of the literature search and selection process.Data were collected from Web of Science Core Collection (WoSCC) database. The time frame for the search was set from January 1st, 1999, to December 31st, 2022. A total of 1496 records were obtained and 285 review records were excluded.

2. Methods

2.1. Data collection

We conducted a comprehensive literature search of the Science Citation Index Expanded of the Web of Science Core Collection database using the following strategy: (TS=(macrophage*) AND TS=(aneurysm)) AND LA=(English)). The time frame for the search was set from January 1st, 1999 to December 31st, 2022. All searches and data collection were performed on a single day to minimize the bias resulting from database updates. A total of 1496 records were obtained. Subsequently, we excluded 285 records pertaining to reviews, early access articles, editorial materials, proceedings papers, meeting abstracts, letters, corrections, and book chapters. Finally, 1211 original articles were included in the analysis. The collected data were imported into the bibliometric.com/app, CiteSpace (version 6.2. R4), and VOSviewer (version 1.6.19). The dataset contains all the necessary information for bibliometric analysis, including authors, affiliations/institutions/countries to which they belong, and keywords used in the publications. Fig. 1 illustrates the procedure used in the literature search.

2.2. Data analysis

In this study, the CiteSpace parameters were configured as follows: the time span was set from January 1999 to December 2022; each film year was set to 1; and the selection criterion for the g-index was set at k = 25. In the visualized network graph, the nodes represent countries, institutions, authors, or keywords. The sizes of the nodes and distinct colored rings correspond to their respective quantities and years of occurrence. The lines connecting the nodes depict cooperative or co-citation relationships among these factors. Nodes with purple outer circles indicate high centrality (greater than 0.1), signifying research hotspots or significant influences in the field. Keyword co-occurrence maps, keyword cluster timelines, and keyword bursts depict research hotspots and frontiers across different periods. VOSviewer was used to draw a visual network diagram for the keyword co-occurrence analysis. The network graph parameters were set as follows: The minimum number of keyword occurrences was 18. In the network visualization map, the size of each node represents the number of publications associated with it, whereas the color indicates the different clusters identified within the network. Additionally, the line thickness was used to depict the link strength between the nodes. Furthermore, an overlay visualization map was created for the keywords, where distinct colors were assigned based on the average publication years. Keywords that appeared earlier are denoted in blue, whereas recent frequently occurring keywords are highlighted in yellow. Data were plotted using Microsoft Excel 2019.

3. Results

3.1. General information and publication outputs

Between 1999 and 2022, 1496 publications on macrophages and aneurysms were published. After excluding reviews, abstracts from meetings, proceedings papers, editorials, early access publications, corrections, and letters, we identified 1211 articles (Fig. 1). The cumulative citation count without self-citations was 43,870. On average, each article received approximately 40.59 citations (Table 1). As shown in Fig. 2a, prior to 2012, the annual publication rate in this field remained below 50 but experienced rapid growth thereafter, peaking at 109 articles by 2021. These findings indicate that significant progress has been made in this field.

The study encompassed 74 Web of Science categories, with Peripheral Vascular Disease (348, 28.737 %), Cardiac Cardiovascular Systems (246, 20.314 %), and Surgery (165, 13.625 %) being the most extensively explored areas. Table 2 lists the top ten categories identified in the analysis.

Furthermore, the five leading journals with the most publications on macrophages and aneurysms (details in Table 3) included ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY (99, 8.175 %), PLOS ONE (50, 4.129 %), JOURNAL OF VASCULAR SURGERY (44, 3.633 %), Antibiotics Basel (42, 3.468 %), and CIRCULATION (31, 2.56 %). Among them, three were vascular-related journals (14.368 % of the total articles), and one was a comprehensive journal. Most of these studies were funded by the National Institutes of Health and the United States Department of Health and Human Services at an equal rate of support for both institutions, with a total of 311 studies each (25.681 %). In addition, the National Natural Science Foundation of China provided funding for 176 studies (14.533 %), followed by the Ministry of Education, Culture, Sports Science and Technology for 125 studies (10.322 %) [Table 4].

Table 1
Top 5 countries in terms of publications.

	Publications	Times Cited	Average per item	H-index	Centrality
Total	1211	49153	40.59	103	NA
USA	453	26095	57.6	84	0.63
PRC	323	5866	18.16	37	0.06
Japan	249	9174	36.84	52	0.31
Germany	72	3215	44.65	29	0.16
England	65	4306	66.25	32	0.1

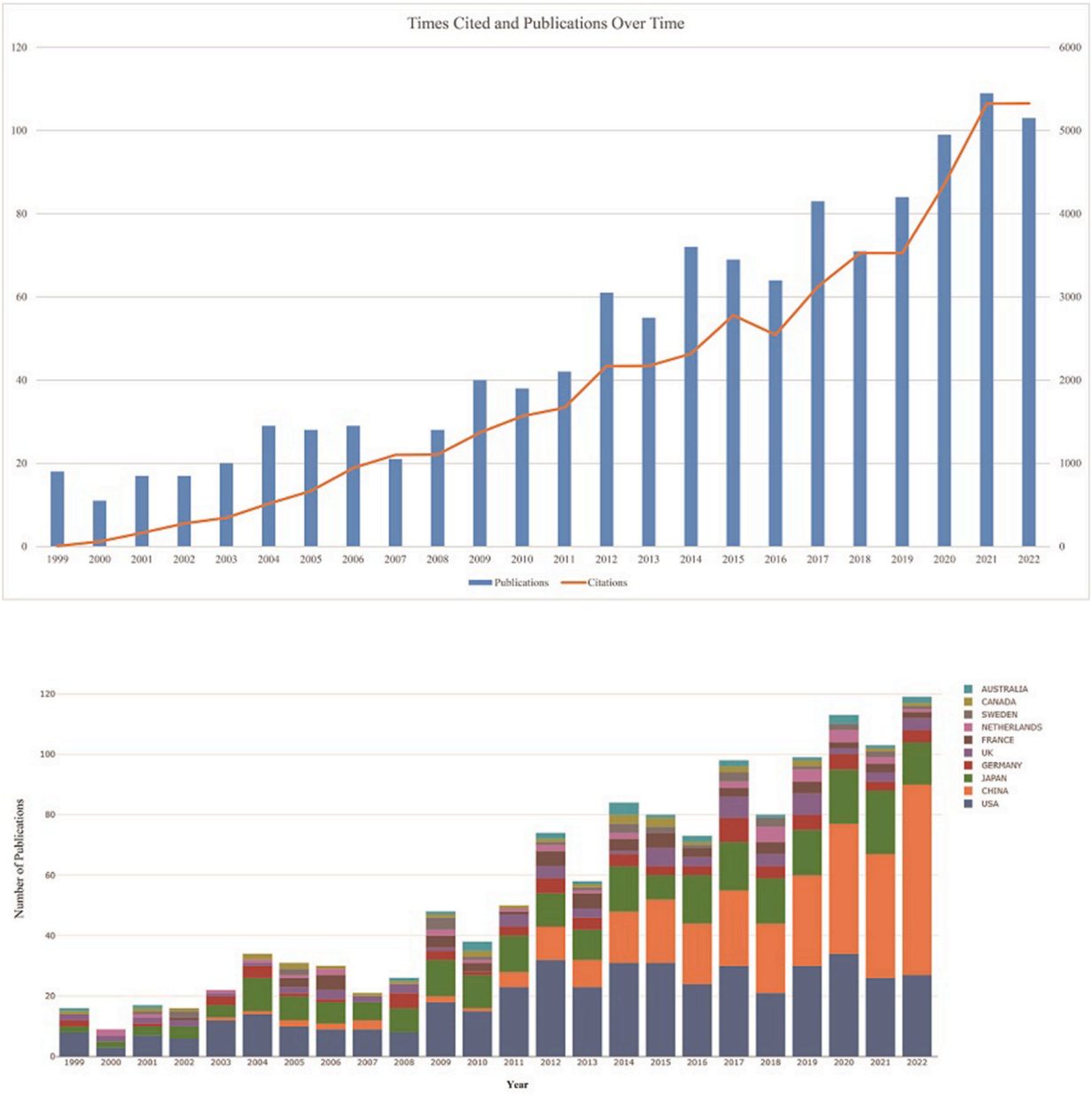

Fig. 2. Information of publication accounts in the field of Marcrophage and Aneurysm.(a) Global trend of annual publications and citations related to Macrophage and Aneurysm from 1999 to 2022. (b) The annual number of publications from the top 10 countries/regions between 1999 and 2022.

3.2. Contribution of countries and institutions

Researchers from 51 countries/regions and 1358 institutions participated in studies focusing on the relationship between macrophages and aneurysms. As shown in Table 1, the United States (453, 37.407 %) made the most significant contribution to publications, followed by China (323, 26.672 %), Japan (249, 20.562 %), Germany (72, 5.945 %), and England (65, 5.367 %). Fig. 3a and b visually represents the collaborations between different countries. Fig. 3a shows these through nodes, indicating the publication numbers and links denoting the degrees of cooperation. The purple outer circle surrounding a node signifies a high centrality (>0.1), highlighting its crucial position within the network structure. Fig. 3b illustrates that the United States exhibited the highest level of global cooperation in this field, closely followed by China. China and the USA have established a particularly robust connection, as depicted by the links representing pathways for international collaboration. Remarkably, despite having a substantial number of publications and strong cooperation, China exhibited a relatively low centrality value (0.06), suggesting fewer pioneering research

Table 2
Top 10 research categories related to macrophage and aneurysm.

Web of Science Categories	Record Count	%
Peripheral Vascular Disease	348	28.737
Cardiac Cardiovascular Systems	246	20.314
Surgery	165	13.625
Hematology	127	10.487
Medicine Research Experimental	119	9.827
Cell Biology	95	7.845
Multidisciplinary Sciences	94	7.762
Biochemistry Molecular Biology	90	7.432
Clinical Neurology	89	7.349
Pharmacology Pharmacy	66	5.450

Table 3
Top 10 journals with most publications in the field of macrophage and aneurysm.

Rank	Journal	Record Count	%
1	ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY	99	8.175
2	PLOS ONE	50	4.129
3	JOURNAL OF VASCULAR SURGERY	44	3.633
4	ATHEROSCLEROSIS	42	3.468
5	CIRCULATION	31	2.560
6	SCIENTIFIC REPORTS	25	2.064
7	CARDIOVASCULAR RESEARCH	21	1.734
8	EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY	21	1.734
9	JOURNAL OF THE AMERICAN HEART ASSOCIATION	21	1.734
10	FRONTIERS IN CARDIOVASCULAR MEDICINE	21	1.734

Table 4
The top 10 funding agencies contributed to research of macrophage and aneurysm.

Rank	Funding Agencies	Record Count	%
1	National Institutes Of Health	311	25.681
2	United States Department Of Health Human Services	311	25.681
3	National Natural Science Foundation Of China	176	14.533
4	Ministry Of Education Culture Sports Science And Technology	125	10.322
5	Japan Society For The Promotion Of Science	120	9.909
6	Grants In Aid For Scientific Research	111	9.166
7	NIH National Heart Lung Blood Institute	109	9.001
8	American Heart Association	73	6.028
9	British Heart Foundation	29	2.395
10	European Union	23	1.899

efforts and lower influence in this field than other nations. Conversely, Japan demonstrated a higher influence with fewer articles but has the second-highest centrality value (0.31). Other countries with significant centrality values included the USA (0.63), Germany (0.16), and England (0.1), as indicated in Table 1.

According to Table 5, the top five institutions/organizations are Harvard University (63, 5.202 %), Harvard Medical School (55, 4.542), Brigham Women's Hospital (46, 3.799 %), University of Kentucky (46, 3.799 %), and University of California System (44, 3.633 %). VOSviewer was used to analyze 108 institutions that contributed with six or more publications in this field. Brigham Women's Hospital has published a considerable number of relevant papers, with an impressive citation count of 1223, and the highest overall link strength value reaching up to 60.

3.3. Analysis of author contribution

Over 7000 authors have contributed to research on macrophages and aneurysms. As shown in Table 6, the five most prolific authors ranked in descending order were Daugherty, Alan (n = 34), Aoki, Tomohiro (n = 33), Libby, Peter (n = 30), Dalman, Ronald L (n = 26), and Shi, Guo-Ping (n = 25). The top five most cited authors were Daugherty, Alan (n = 672), Cassis, Lisa A (n = 581), Baxter, B Timothy (n = 480), Xiong, Wan-fen (n = 384), and Libby, Peter (n = 321). The first authors with the highest productivity were Aoki, Tomohiro (n = 15), Shimizu, Kampei (n = 6), Lai, Chao-Han (n = 5), Liu, Cong-Lin (n = 5), and Kugo, Hirona (n = 5). The corresponding authors who made significant contributions were Shi, Guo-Ping (n = 17), Aoki, Tomohiro (n = 16), Golledge, Jonathan (n = 12), Upchurch, Gilbert R (n = 12), and Daugherty, Alan (n = 10). Fig. 4 presents a visual representation of the top 15 authors who experienced significant increases in citations during specific periods, indicating their notable influence on research. The graph displays

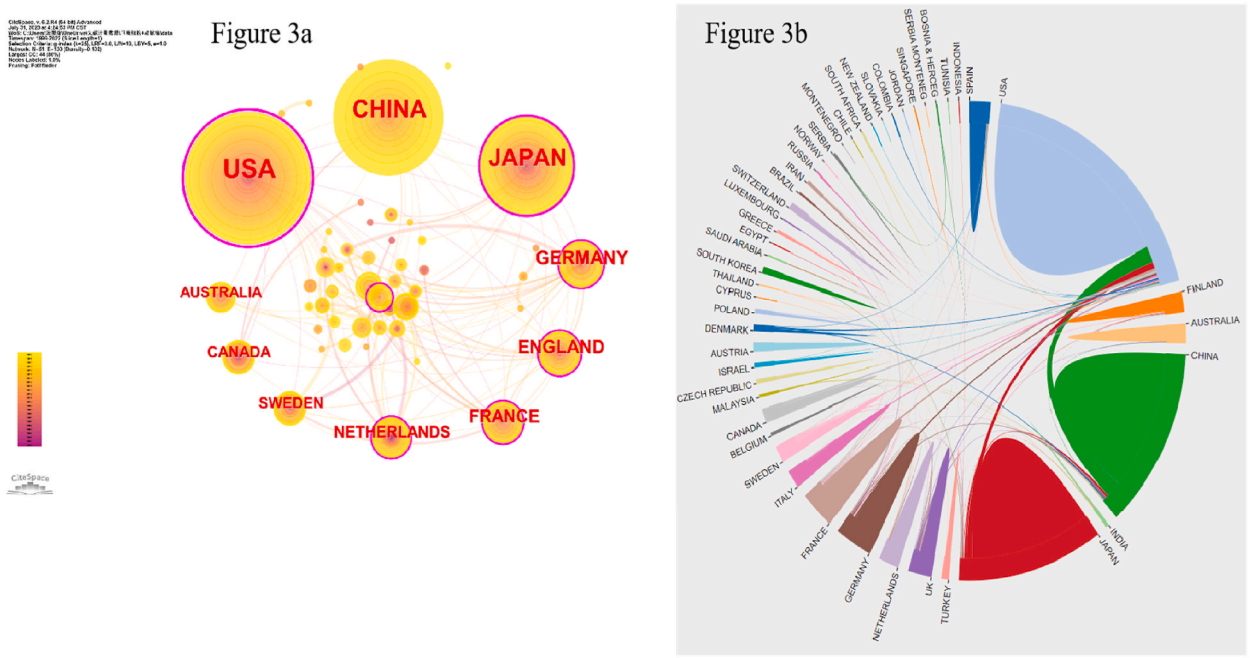

Fig. 3. Visualization of countries.(a) Collaboration network of countries. (b) Distribution and international cooperation of countries/regions that are involved in Macrophage and Aneurysm. The thickness of the line reflects the frequency of the cooperation. The thicker the line, the stronger the cooperation.

Table 5
The top 5 institutions/organizations contributed to macrophage and aneurysm in terms of publications and overall link strength.

Rank	Institutions/Organizations	Total link strength	Citations	Rank	Institutions/Organizations	No. of publications
1	BRIGHAM WOMEN S HOSPITAL	60	1223	1	HARVARD UNIVERSITY	63
2	HARVARD MEDICAL SCHOOL	60	615	2	HARVARD MEDICAL SCHOOL	55
3	KYOTO UNIVERSITY	60	1527	3	BRIGHAM WOMEN S HOSPITAL	46
4	UNIVERSITY OF CALIFORNIA SYSTEM	56	1772	4	UNIVERSITY OF KENTUCKY	46
5	UNIVERSITY OF KENTUCKY	50	4027	5	UNIVERSITY OF CALIFORNIA SYSTEM	44
6	NATIONAL CEREBRAL AND CARDIOVASCULAR CENTER	43	276	6	UDICEFRENCH RESEARCH UNIVERSITIES	43
7	BAYLOR COLLEGE MEDICINE	41	483	7	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM	42
8	HARVARD UNIVERSITY	41	3656	8	STANFORD UNIVERSITY	40
9	SHIGA UNIVERSITY OF MEDICAL SCIENCE	41	433	9	KYOTO UNIVERSITY	39
10	PEKING UNIVERSITY	39	664	10	PEKING UNIVERSITY	31

Table 6
The top 10 authors in terms of publication, citations, 1st author and correspondence.

Rank	Publications		No. of citations		No. of 1st author		No. of correspondence	
1	Daugherty, Alan	34	Daugherty, Alan	672	Aoki, Tomohiro	15	Shi, Guo-Ping	17
2	Aoki, Tomohiro	33	Cassis, Lisa A	581	Shimizu, Kampei	6	Aoki, Tomohiro	16
3	Libby, Peter	30	Baxter, B Timothy	480	Lai, Chao-Han	5	Golledge, Jonathan	12
4	Dalman, Ronald L	26	Xiong, Wan-fen	384	Liu, Cong-Lin	5	Upchurch, Gilbert R	12
5	Shi, Guo-Ping	25	Libby, Peter	321	Kugo, Hirona	5	Daugherty, Alan	10
6	Upchurch, Gilbert R	25	Aoki, Tomohiro	310	Xiong, Wanfen	4	Liu, Bo	10
7	Sukhova, Galina K	23	Manning, Michael W	299	Hasan, David M	4	Baxter, B Timothy	10
8	Kataoka, Hiroharu	19	Zhao, Yunge	260	Miyake, Toshiharu	4	Dalman, Ronald L	10
9	Nozaki, Kazuhiko	18	Greiner, Timothy C	259	Reeps, Christian	4	Zheng, Yue-Hong	9
10	Liu, Bo	17	Nozaki, Kazuhiko	256	Hoh, Brian L	4	Kataoka, Hiroharu	9

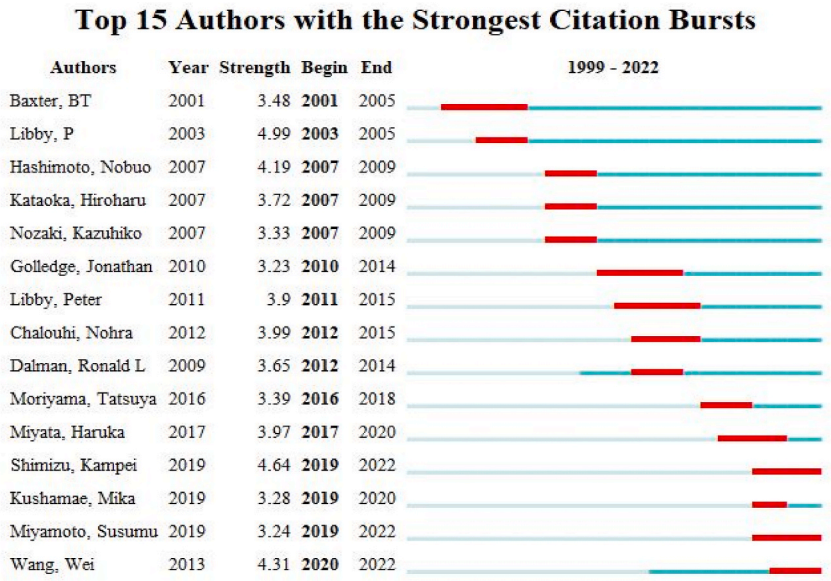

Fig. 4. The top 15 authors with the strongest citation bursts.A visual representation of the top 15 authors who experienced significant increases in citations during specific time periods were conducted, indicating their influence on research. Blue line:the timeframe; Red line: duration of each citation surge. Strength: The higher values, the greater impact.

the blue line representing the timeframe and the red line depicting the duration of each citation surge. The strength metric measures the intensity of these surges, with higher values indicating a greater impact. Peter Libby from Brigham and Women's Hospital ranked first among these authors, specializing in the fields of medicine, cardiology, atherosclerosis, and immunology. Shimizu Kampei from Kyoto University holds second place, while Wang Wei from China holds the third position. Tomohiro achieved an impressive total link strength score of 139, followed by Nozaki Kazuhiko, with a total link strength of up to 87 (data from VOSviewer).

3.4. Research topics

3.4.1. Top 10 highly cited references

Publications that received a high number of citations indicated their significant impact and frequency of reference, reflecting the focus and depth of the research in a specific field. Table 7 displays the top 10 references with high citation counts in the research area from 1999 to 2022. Among these ten papers, Raffort et al.'s article published in NATURE REVIEWS CARDIOLOGY holds the first

Table 7
Top 10 most cited references.

Rank	Title	No. of citations	Year	Journal	Author
1	Monocytes and macrophages in abdominal aortic aneurysm	86	2017	Nature Reviews Cardiology	Juliette Raffort
2	Abdominal aortic aneurysm: update on pathogenesis and medical treatments	48	2019	Nature Reviews Cardiology	Jonathan Golledge
3	Inflammatory cell phenotypes in AAAs: their role and potential as targets for therapy	35	2015	Arterioscler Thromb Vasc Biol	Matthew A Dale
4	Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms	30	2002	Journal Of Clinical Investigation	G Matthew Longo
5	Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms	26	2000	Journal Of Clinical Investigation	R Pyo
6	TGF-beta activity protects against inflammatory aortic aneurysm progression and complications in angiotensin II-infused mice	26	2010	Journal Of Clinical Investigation	Yu Wang
7	The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm	25	2018	Journal Of Vascular Surgery	Elliot L Chaikof
8	Genetic and pharmacologic disruption of interleukin-1β signaling inhibits experimental aortic aneurysm formation	24	2013	Arterioscler Thromb Vasc Biol	William F Johnston
9	An adventitial IL-6/MCP1 amplification loop accelerates macrophage-mediated vascular inflammation leading to aortic dissection in mice	23	2009	Journal Of Clinical Investigation	Brian C Tieu
10	Elastin-Derived Peptides Promote Abdominal Aortic Aneurysm Formation by Modulating M1/M2 Macrophage Polarization	22	2016	Journal of Immunology	Matthew A Dale

position, with an impressive total of 86 citations [14]. The authors conducted a comprehensive review of potential applications for detecting, assessing, and imaging different subsets of macrophages in abdominal aortic aneurysms while discussing their clinical relevance. Additionally, second- and third-ranked articles consisted of reviews summarizing recent research findings and current theories regarding abdominal aortic aneurysm (AAA) pathogenesis [15,16]. These reviews include discussions on both the advantages and disadvantages associated with existing rodent models used for studying AAA, as well as highlighting potential medical treatments for this condition by summarizing previous, ongoing, and prospective clinical trials involving medical interventions for small AAAs. The authors emphasized that gaining insight into proinflammatory phenotypes and developing innovative strategies to target them could provide valuable therapeutic options for aneurysm management.

The comprehensive guidelines provided by The Clinical Practice Council of the Society for Vascular Surgery, known as the seventh-ranked article, cover various aspects such as patient evaluation (including assessing the risk of aneurysm rupture and associated medical conditions), intervention guidelines, strategies during surgery, care before and after surgery, protocols for long-term follow-up, and approaches to address late complications. These guidelines include specific suggestions derived from three systematic reviews. Two reviews focused on ascertaining the most effective surveillance methods and frequency after endovascular aneurysm repair, whereas the third review aimed to identify evidence-based strategies for diagnosing and managing AAA. The resulting guidelines revised prior recommendations and addressed novel areas of significance. Proposed suggestions include the recommendation of surveillance imaging every 12 months for patients with an AAA measuring 4.0 and 4.9 cm in diameter. To facilitate shared decision-making between physicians and patients when considering aneurysm repair, the Vascular Quality Initiative mortality risk score is recommended. Treatment options for type I and III endoleaks have also been suggested, in addition to addressing type II endoleaks accompanied by aneurysm expansion; however, continued monitoring is advised for type II endoleaks not associated with aneurysm expansion. Antibiotic prophylaxis before dental procedures involving manipulation of the gingival or periapical region or perforation of the oral mucosa in patients with an aortic prosthesis is recommended but not necessary prior to respiratory tract procedures, gastrointestinal or genitourinary procedures, and dermatologic or musculoskeletal procedures, unless there is a potential risk of infection or if the patient has compromised immune function. This guideline offers new recommendations for the care of patients with AAA that aim to improve shared decision-making between healthcare providers and patients/families while enhancing perioperative outcomes in elective and emergent repair cases.

3.5. Keyword co-occurrence

The term 'keyword co-occurrence' refers to the simultaneous appearance of two or more keywords within a single paper. Table 8 and Fig. 6 present keywords that exhibit a high frequency of occurrence; the larger the circle, the more occurrences, and the thicker the connected lines, the more co-occurrences. Among them, the top ten keywords with the highest occurrence frequency are as follows: 'expression' (358), 'abdominal aortic aneurysm' (349), 'inflammation' (247), 'smooth muscle cell' (192), 'atherosclerosis' (190), 'macrophage' (188), 'activation' (151), 'cells' (149), 'matrix metalloproteinases'(146), and 'angiotensin II' (113). We created a network graph (Fig. 6) to visualize the co-occurrence of keywords based on their frequencies. The results obtained were aligned with the keyword networks analyzed using VOSviewer (Fig. 7). We also performed keyword analysis using VOSviewer, and 95 keywords with a frequency of occurrence of more than 18 were identified and categorized into six clusters. The red cluster represents the underlying pathogenesis associated with macrophages and aneurysms, while the green cluster pertains to the investigation of genes and proteins. The blue cluster indicates mechanisms associated with inflammation. Fig. 8 presents a network visualization of keywords. Fig. 8 shows an overlay visualization of Fig. 7, reflecting the trends in this research field. The node color indicates the average publication year, where recent frequently occurring keywords are depicted in yellow. Examples include intracranial aneurysms, oxidative stress, and biomarkers.

3.6. Keyword cluster timeline and burst

Keyword clustering analysis allows the grouping of related points and the identification of clusters that represent distinct research fields. The size of each cluster indicates the number of terms it encompasses. In CiteSpace, cluster #0 was the largest, followed by clusters such as cluster #1. Our keyword clustering analysis revealed 14 keyword clusters in the research domains of macrophages and

Table 8
The top 10 keywords in terms of frequency and centrality.

Rank	Frequency	Keywords	Rank	Centrality	Keywords
1	358	expression	1	0.11	aortic aneurysm
2	349	abdominal aortic aneurysm	2	0.09	cells
3	247	inflammation	3	0.09	disease
4	192	smooth muscle cell	4	0.09	aneurysm
5	190	atherosclerosis	5	0.08	macrophage
6	188	macrophage	6	0.08	angiotensin II
7	151	activation	7	0.08	atherosclerotic lesions
8	149	cells	8	0.07	abdominal aortic aneurysm
9	146	matrix metalloproteinases	9	0.07	inflammation
10	113	angiotensin II	10	0.07	activation

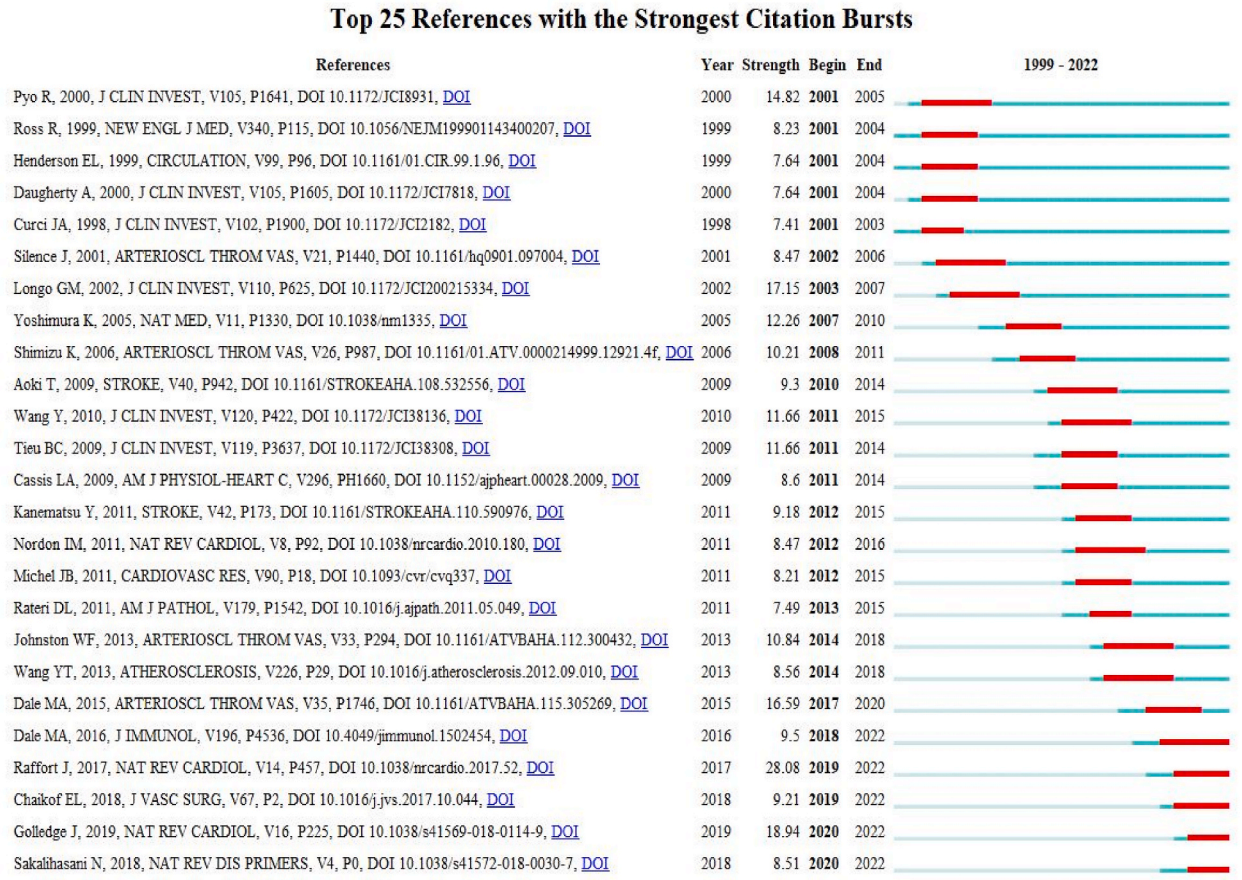

Fig. 5. The top 25 references with the strongest citation bursts.Citation bursts represent a current focus and trends. While the majority of reference bursts have concluded, a few are still ongoing. The red segment represents the begin and end year of the burst duration.

aneurysms. These clusters cover various topics, including 'e-deficient mice,' 'elevated fasting plasma,' 'ascending aortic dissection,' 'focal adhesion kinase,' 'flow-induced outward vascular remodeling,' 'phenotypic change,' 'arterial bifurcation,' 'versican concentration,' 'acute coronary syndrome,' 'pilot study,' 'kidney-specific klotho gene deletion,' 'complex aortic surgery,' 'n-terminal function,' and 'kawasaki disease (Fig. 9). From a timeline perspective, keywords are distributed within their respective clusters based on their year of appearance. This approach facilitates the tracking of research progression and the identification of hotspots across different periods.

We conducted further analysis of the burst of keyword citations using CiteSpace (Fig. 10). A sudden surge in the number of citations of specific keywords within a particular research area and timeframe is referred to as a keyword burst, and the red line indicates its duration. Fig. 10 reveals that 'matrix metalloproteinases' (19.51) exhibit the highest strength, signifying their significance in recent years. There are several keywords that have experienced prolonged bursts lasting over four years: 'localization' (1999–2005), 'gelatinase' (1999–2009), 'tissue inhibitor' (2000–2005), 'iv collagenase' (2000–2004), 'matrix metalloproteinases' (2001–2011), 'atherosclerotic plaque' (2001–2012), 'lesions' (2001–2006), 'nitric oxide synthase' (2005–2009), 'matrix metalloproteinase' (2006–2010),'e-deficient mice' (2008–2015), 'deficient mice' (2012–2017). These findings suggest that these research directions have enjoyed sustained popularity over an extended period. The most recent burst keywords include 'aortic dissection' (2020–2022), 'thoracic aortic aneurysm' (2020–2022), 'growth' (2020–2022), and 'oxidative stress' (2020–2022), which may be linked to the emergence of the Coronavirus disease 2019 pandemic. These results represent the current frontiers of research.

4. Discussion

4.1. General information

To the best of our knowledge, the present study is the first bibliometric analysis on the area of macrophages and aneurysms from 1999 to 2022. In contrast to systematic and scoping reviews, bibliometric analysis has emerged as a potent tool for summarizing the current state of knowledge and predicting future directions [17,18]. Drawing on information science, computer science, scientometrics, and applied mathematics, the visualization map depicts specific domains of knowledge and structural relationships using

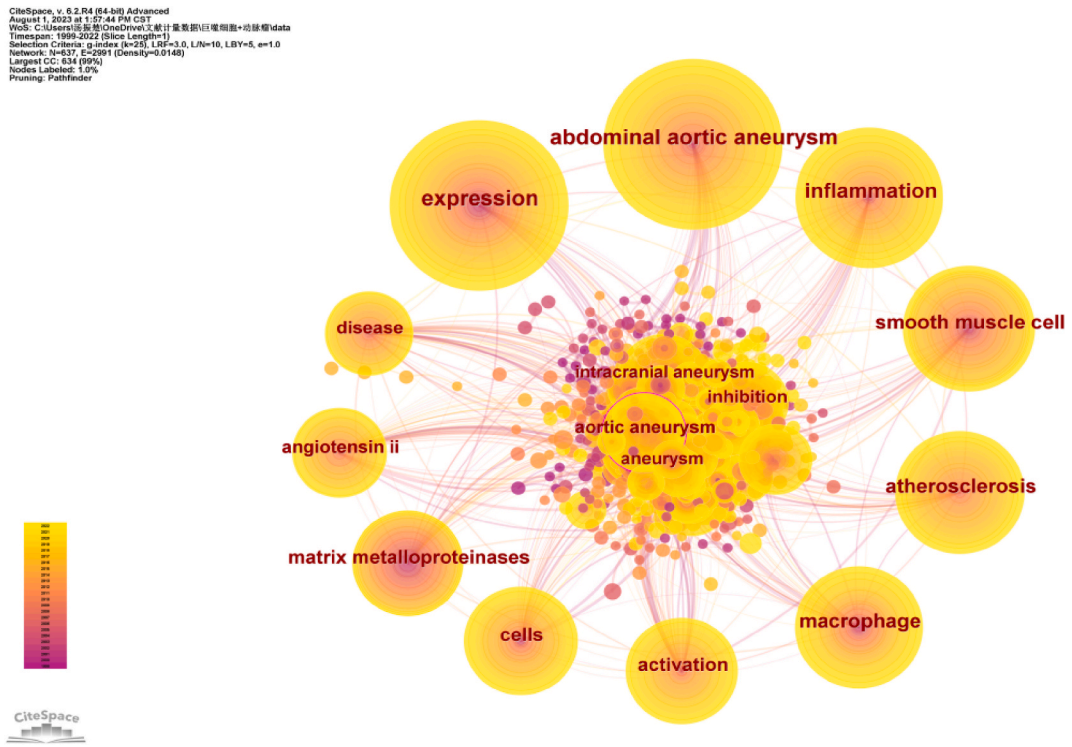

Fig. 6. Co-occurring keywords map.The frequency of keywords occurrence were shown. The larger the circle, the more occurrences. The thicker the connected lines, the more co-occurrences.

VOSviewer and CiteSpace [19,20]. After excluding 285 studies that did not meet the inclusion criteria, 1211 publications in 371 journals with references co-cited by 27843 sources from institutions across 51 countries/regions were eligible for analysis. Subsequently, bibliometric tools and visualization analyses were employed to identify key publications and citations, contributing nations/regions, institutions involved in the research output, authors' contributions, and funding agencies supporting the studies conducted in this field. Furthermore, the study explored the knowledge base encompassing research hotspots and emerging topics. Between 1999 and 2022, over ten thousand research papers were dedicated to the study of aneurysms. Of these, 1496 Science Citation Index Expanded publications were related to the correlation between macrophages and aneurysms, accounting for approximately 12.14 % of the total publications. Fig. 2a shows a consistent increase in the number of publications on macrophages and aneurysms since 1999, reaching a peak in 2021 with an annual publication count of 109. However, the annual number of publications was below 50 before 2012, exhibiting a substantial surge thereafter. This was probably because there were influential manuscripts published in 2011, including one entitled 'Critical roles of macrophages in the formation of intracranial aneurysm' [21]. This paper illustrated the critical roles of macrophages and proper macrophage functions in the formation of aneurysms, and it started a strong citation burst between 2012 and 2015, which is also demonstrated in Fig. 5. These important papers, published in 2011, drew considerable attention from scientists in this field, thus producing more publications. Moreover, the total number of publications declined by 2022. Possible factors contributing to this decrease include: (1) researchers shifting their attention toward coronavirus disease 2019 research, (2) normal fluctuations in article publication numbers while maintaining an overall upward trend, and (3) insufficient efforts made to collect relevant literature. The yellow line in Fig. 2a represents the yearly citation frequency of the publications included in this study, which gradually increased after 1999. This indicates the growing interest in understanding the role and function of macrophages in aneurysms. The only reduction observed occurred in 2016, with a yearly citation count of 2544 citations per year – a decrease of 235 compared with that in 2015. This phenomenon may be attributed to scientists redirecting their focus toward other subjects, as evidenced by the decline in the number of publications from 2014 to 2016. For example, gene editing using the clustered regularly interspaced short palindromic repeats-Cas9 system emerged as a prominent area for investigation during those years [22,23].

There has been a noticeable increase in the number of studies on macrophages and aneurysms in recent years, indicating the need for active exploration in this field. The analysis revealed two distinct phases: a period of gradual growth from 1999 to 2008 and a rapid expansion phase from 2009 to 2022. Although there was a steady rise in publications from 1999 to 2008, it went unnoticed because the average annual publication volume was fewer than 30 articles. However, after 2008, there was a significant surge in yearly publication output, peaking in 2021 and accounting for approximately 73.5 % of all publications. The citation patterns mirrored those of the publications, suggesting that these findings can be attributed to notable scientific advancements in this field. These remarkable advancements include the discovery by Wang et al. [24] that the deletion of microsomal prostaglandin E synthase-1 can protect hyperlipidemic mice against AAA formation induced by angiotensin II (Ang II) by reducing oxidative stress. Potential therapeutic

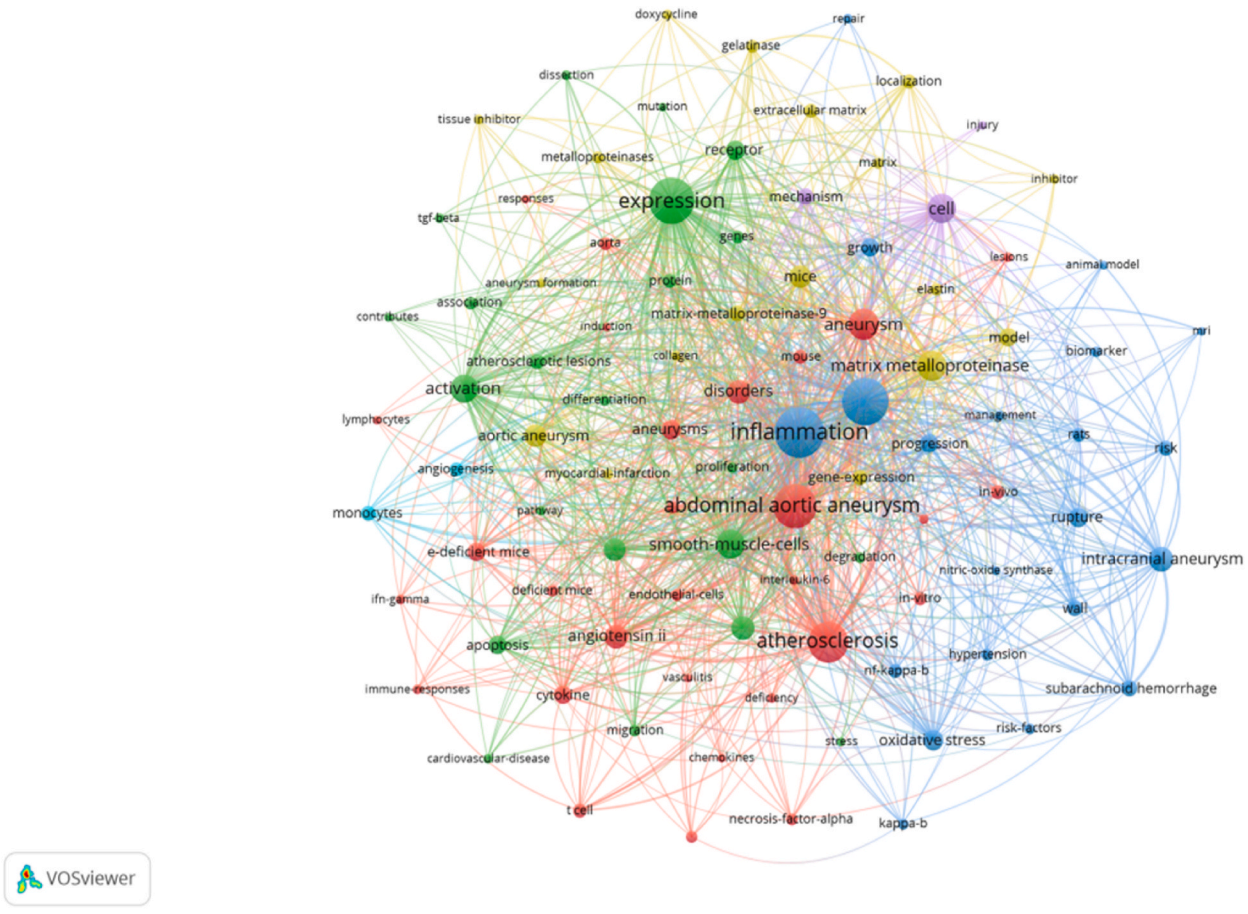

Fig. 7. Network visualization of keywords based on VOSviewer.Network visualization of keywords based on VOSviewer. In this network map, keywords with close relationships are assigned to one cluster with the same color. All the keywords could be divided into five clusters: cluster 1 (red nodes), cluster 2 (green nodes), cluster 3 (blue nodes), cluster 4 (yellow nodes), and cluster 5 (purple nodes).

strategies or diagnostic markers that target or exploit macrophage migration inhibitory factors to manage cardiovascular diseases or disorders have been reported [25]. Furthermore, scientists have advised the utilization of microphysiological models that closely resemble human physiology in the examination of individualized disease traits and advancement of drug discovery for thoracic aortic aneurysms [26]. These studies have paved the way for innovative research focusing on preventing or delaying the formation of aneurysms.

4.2. The most contributing countries and institutions

The distribution of countries/regions and institutions contributing to this field exhibits certain characteristics. As shown in Table 1 and Fig. 2b, the United States emerged as the leader in terms of publication count, citations, and the h-index. The United States has established a strong foundation for medical scientific research over an extended period. It has received substantial financial support and boasts of a significant pool of researchers and institutions based on funding and institutional analyses. The primary funding agencies were the National Institutes of Health and the United States Department of Health and Human Services, closely followed by China's National Natural Science Foundation (NSFC). Among the top 10 institutions with the highest number of publications, six were affiliated with organizations from the United States. This observation underscores the fact that the United States has an unparalleled influence in this domain compared with other nations. In addition to America's dominance, China has witnessed notable progress in this area in recent years, owing to the increased attention devoted to research endeavors. Due to the rapid growth of the Chinese economy, there is an increasing need for healthcare services for the general population. Consequently, financial support for medical and health research has gradually increased, with a specific focus on treatment options in molecular biology. Despite China having more publications than Japan, it falls behind in terms of citations and h-index. Additionally, while there has been a notable rise in Chinese publications in international journals, top-tier journals rarely feature high-quality research papers [27,28]. This could be attributed to the fact that Chinese researchers prioritize quantity over quality when producing articles. However, policymakers have acknowledged this issue and are actively encouraging researchers to prioritize research quality over quantity [29]. Other factors that

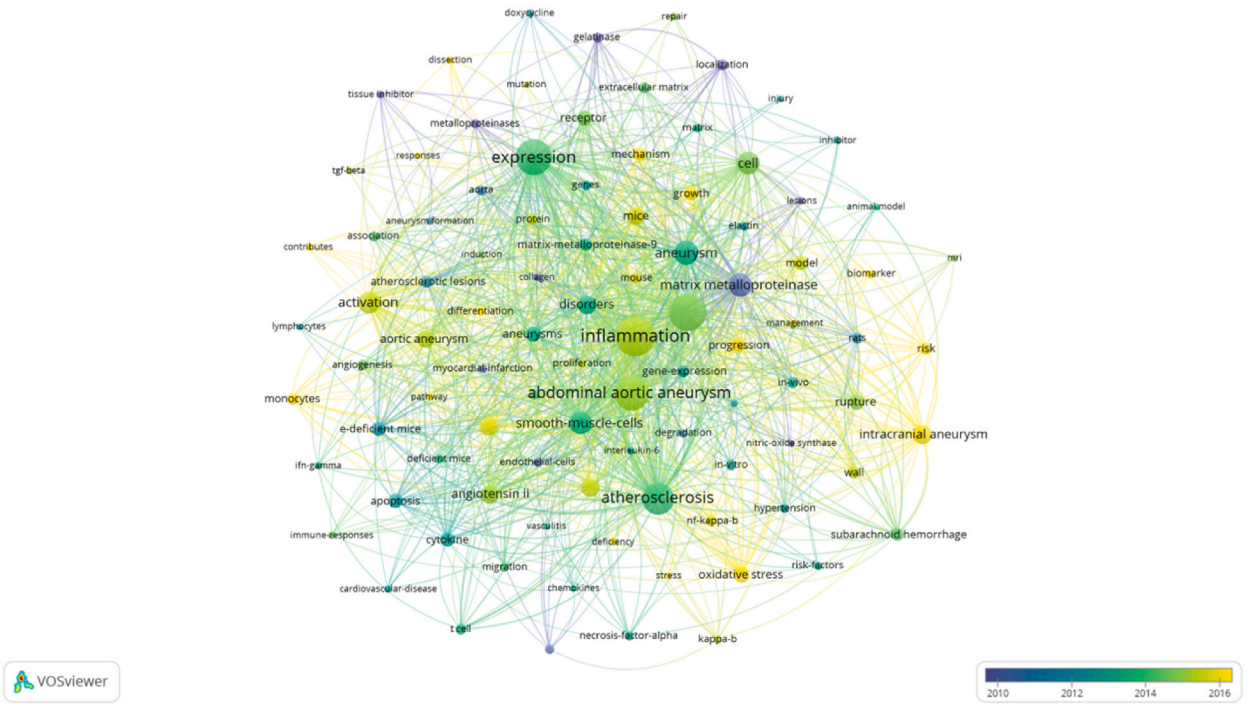

Fig. 8. Overlay visualization of keywords based on VOSviewer.The nodes marked with purple or blue color represent the keywords that appeared relatively earlier, whereas keywords coded with yellow color represent the current research focuses.

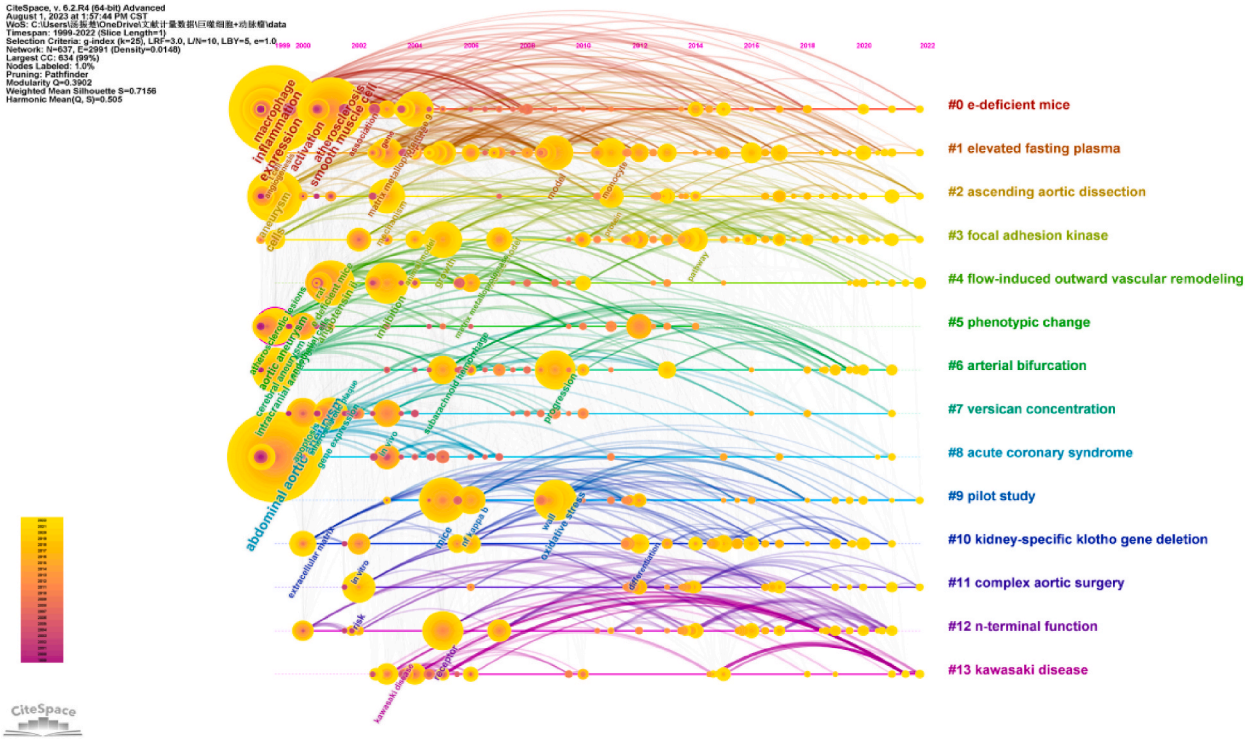

Fig. 9. Fourteen keyword clusters in Macrophage and Aneurysm research domain.The application of keyword clustering analysis enables the systematic grouping of interconnected concepts and facilitates the identification of distinct research domains. The relative size of each cluster serves as an indicator for the number of terms encompassed within.

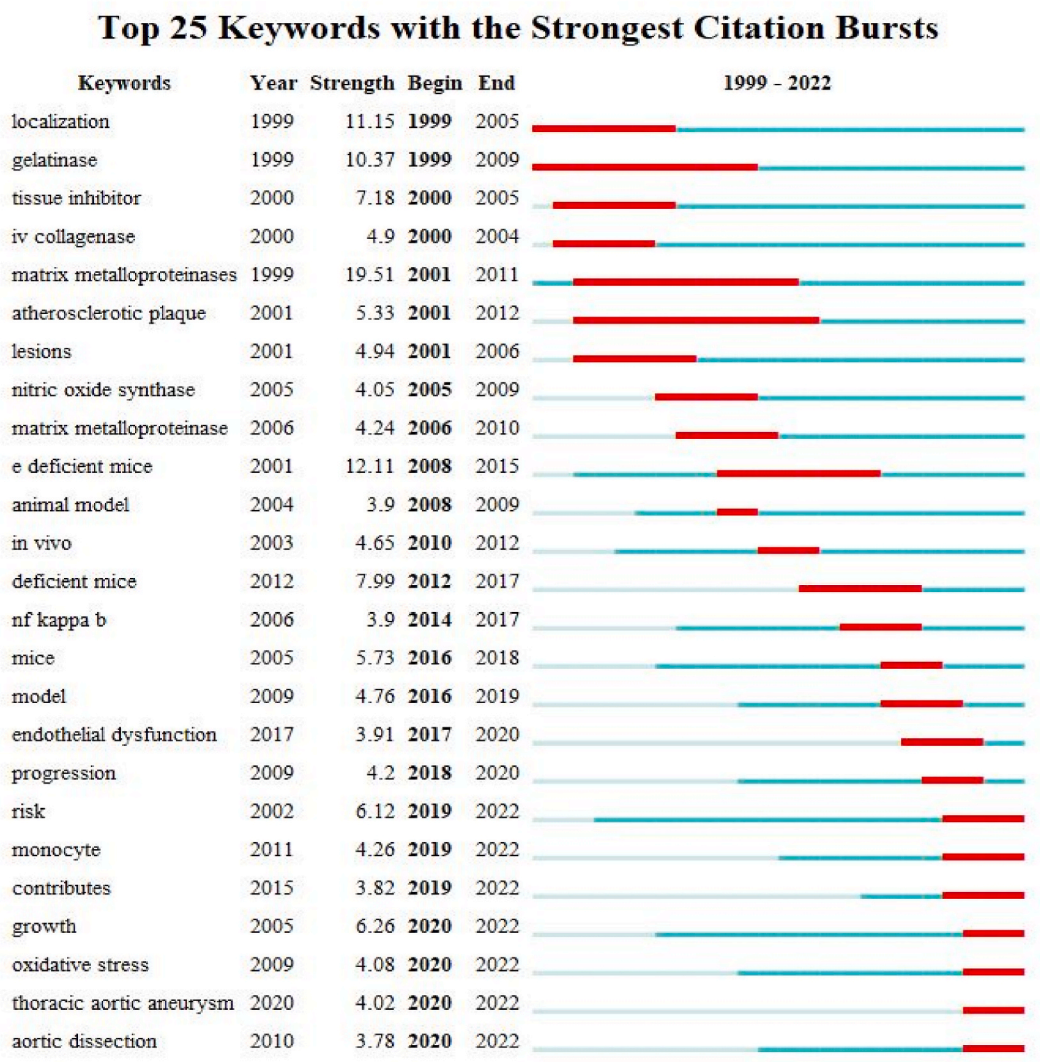

Fig. 10. The top 25 keywords with the strong citation bursts in articles related to Macrophage and Aneurysm.The burst of keywords represents research hotspots and trends. Recent bursts of keywords indicate a significant emphasis on "risk","monocyte","contributes","growth","oxidative stress","thoracic aortic aneurysm" and "aortic dissection" in the field of macrophage and aneurysm.

may contribute to the high research output in China include the necessity for Chinese researchers to secure additional financial support and publications as part of their promotion system. Consequently, they are compelled to diversify their research areas, which can make it challenging to specialize in a specific field of study. In terms of international collaboration in this domain, the United States demonstrated the highest level of engagement, followed by China and Japan (Fig. 3b). However, collaborations between China and other countries are not as strong as those with the USA. Therefore, developing nations must actively encourage their institutions to be involved in research activities, foster robust partnerships with other countries, facilitate advancements in relevant fields, and promote the dissemination of high-quality scholarly articles.

4.3. The most influencing journals and authors

Examining academic publications and co-cited articles can offer researchers valuable insights when choosing the most appropriate journal for submitting their manuscripts [13]. Approximately 30.8 % of the papers were published in the top ten journals (Table 3). ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY (IF = 8.7) emerged as the most productive publication in this field, followed by PLOS ONE (IF = 3.7) and JOURNAL OF VASCULAR SURGERY (IF = 4.3). Renowned journals such as Cell, Nature, Science, and PNAS possess high-impact factors despite not being included in this list. ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY holds a prestigious position among academic professionals specializing in cardiology, vascular biology, physiology, pharmacology, and hematology. Researchers can focus on these journals to stay up-to-date with research trends and advancements related

to aneurysms. Additionally, identifying the most suitable journals for timely manuscript submission can help avoid unnecessary delays in study completion.

According to our analysis, Daugherty Alan from the University of Kentucky has an impressive publication record and a significant number of citations, making him the most productive author. Daugherty Alan holds prestigious positions, including the Gill Foundation Chair of Preventive Cardiology, directorship of the Saha Cardiovascular Research Center, chairmanship of the Department of Physiology, and senior associate dean for research at the College of Medicine. Furthermore, he serves as the editor-in-chief for Atherosclerosis, Thrombosis, and Vascular Biology, a well-known journal associated with the American Heart Association. His pioneering research primarily focused on unraveling the molecular mechanisms underlying vascular diseases such as atherosclerosis and aortic aneurysms [30].

4.4. The most cited articles

The frequency of citations directly correlates with the perceived significance of an article in a specific field, thereby establishing the most frequently referenced publications or influential literature as the fundamental knowledge base within that particular domain. As shown in Table 7, there were three comprehensive evaluations, six randomized controlled trials (RCTs), and one guideline document. Analysis of the publication timeline revealed that four articles were published during the initial phase (2000–2010), all of which were RCTs; three articles were published during the intermediate phase (2011–2016), including two RCTs and one evaluation; and three articles were published from 2017 onward until the present time (recent phase), consisting of two evaluations and one guideline.

The three most frequently mentioned reviews have focused on the development of macrophages in aneurysms and their potential medical applications in clinical settings. These reviews play a significant role in understanding the underlying mechanisms of aneurysm pathogenesis and exploring ways to detect, evaluate, and visualize the different types of macrophages involved. Among these reviews, the article titled 'Monocytes and macrophages in abdominal aortic aneurysm' received the highest number of citations [14]. Raffort et al. identified key pathological features of AAA, including changes in extracellular matrix composition, loss of vascular smooth muscle cells, and accumulation and activation of inflammatory cells. Inflammation plays a critical role in AAA development and significantly affects various aspects of aortic wall remodeling. The authors specifically examined the roles, origins, and functions of monocytes and macrophages during this process while summarizing current knowledge. Additionally, they proposed that distinct subsets of monocytes and macrophages have unique roles at different stages (initiation, progression, and healing) of the aneurysmal process. Based on the experimental findings and clinical studies discussed in this review, potential translational applications for the detection of specific macrophage subsets associated with abdominal have been explored. The relevance of these applications in clinical practice has also been emphasized. The second co-cited paper, titled 'Advancements in the understanding and treatment of abdominal aortic aneurysm,' was authored by Jonathan Golledge [15] and published in Nature Reviews Cardiology (IF = 49.421) in 2019. This comprehensive review provides a detailed examination of the most recent research discoveries and current theories regarding AAA pathogenesis. It provides a critical assessment of the strengths and limitations associated with existing rodent models used for studying AAA while also highlighting potential medical interventions through a summary of past, ongoing, and prospective clinical trials targeting small AAAs. As an exemplary high-quality review article, it serves as an essential point of reference for investigating the role of macrophages in the development and progression of aneurysms. Moreover, it is anticipated that future advancements in this field will lead to innovative approaches to medical intervention within the next decade. A paper titled 'Exploring the potential of targeting inflammatory cell phenotypes in AAAs for therapeutic purposes' was written by Dale [16]. The authors emphasize the importance of understanding and developing innovative approaches to address the proinflammatory phenotype, which could potentially lead to valuable treatment options for diseases that currently lack pharmaceutical interventions.

In 2009, a study titled 'An amplification loop of IL-6/MCP1 in the adventitia accelerated vascular inflammation caused by macrophages and led to aortic dissection in mice' was published by Tieu [31]. Unlike previous research that mainly focused on AAA, this study provided a comprehensive analysis of both the AAA and the ascending aorta. The results revealed that the infusion of Ang II, a well-known vasopressor that promotes vascular inflammation, induced the production of interleukin (IL)-6, a proinflammatory cytokine, and monocyte chemoattractant protein-1 (MCP-1), which primarily occurs within the tunica adventitia. This was accompanied by the recruitment of macrophages, expansion of the outer layer of the aorta, and development of dissections in the thoracic and suprarenal regions. When Ang II was infused into mice lacking either IL-6 or the MCP-1 receptor C–C chemokine receptor type 2 (CCR2), the occurrence of dissection decreased. Further analysis revealed that Ang II specifically caused the accumulation of macrophages expressing CCR2+CD14hiCD11bhiF4/80- in areas with increased oxidative stress within aortic dissections but not in Il6−/− mouse aortas. The transfer of Ccr2+/+ monocytes into Ccr2−/− mice resulted in the selective uptake of monocytes into the ascending and suprarenal parts of the aorta, where there was an elevated secretion level of IL-6, along with an increased incidence rate for dissection. In vitro experiments demonstrated that when monocytes were co-cultured with fibroblasts from the outer layer of the aorta, conditioned medium enriched with MCP-1 and IL-6 was produced, which promoted the differentiation of monocytes into macrophages while inducing the upregulation of CD14 and CD11b as well as the expression levels of MCP-1 and matrix metallopeptidase 9. These findings suggest that interactions between leukocytes and fibroblasts within the outer layer contribute to IL-6 production, thereby leading to local recruitment and activation of monocytes, which subsequently promotes the secretion of MCP-1, resulting in vascular inflammation, remodeling of the extracellular matrix, and destabilization.

Among the top 10 highly referenced sources in this field, most focus on RCTs with research objectives that include investigating IL-1β and its receptor (IL-1R), expression of IL-6/MCP1 in the adventitia layer, ratio of macrophage polarization (M1/M2), involvement of the tumor growth factor β signaling pathway, and activity levels of matrix metalloproteinases 2 and 9. In addition, five RCTs focused on abdominal aortic aneurysms, while only one addressed tests related to the ascending aorta. These extensively cited references from

the past decade reveal a significant interest among researchers in understanding the development process of aneurysms and devising preventive measures to hinder disease progression. Furthermore, the publication date showed that previous articles mainly consisted of RCTs, whereas recent publications included reviews and guidelines. This implies that research on macrophages and aneurysms has evolved over time. Moreover, the increasing number of citations in recent literature suggests that this area remains a current focus, with ongoing discoveries and reporting of significant findings. This is further supported by the citation burst depicted in Fig. 5, where although most reference bursts have been concluded, several are still ongoing, primarily focusing on assessing the rupture risk of AAA [32] and investigating the role of the M1/M2 imbalance in aneurysm formation [33]. Additionally, potential translational applications are being explored for detecting, assessing, and imaging different subsets of macrophages in aneurysms, along with their potential clinical implications [33].

4.5. Research hotspots and trends

The frequency of keywords reflects research hotspots and frontiers in a specific field. The top 10 most frequently occurring keywords are presented in Table 8; however, the centrality of these three keywords was relatively low. Centrality is an important indicator that reveals the significance of a keyword within a table; a higher centrality suggests a greater impact on the area of macrophages and aneurysms. Table 8 demonstrates that 'aortic aneurysm' holds the highest centrality value at 0.11, followed by 'cells' (0.09) and 'disease' (0.09). Nevertheless, despite their importance, none of the top ten keywords exhibited high centrality values; nine out of ten had values below 0.1, indicating limited associations between different keywords within this research field.

Table 8 and Fig. 8 show that 'inflammation' is a hot topic, indicating that researchers are attempting to elucidate the role of inflammation in macrophages and aneurysms. Recent studies have focused on [(18)F]fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) to detect infection and inflammation in vascular graft [34] and artery aneurysms [35]. 18F-FDG PET/CT is a mature method based on increased glucose utilization by activated macrophages and granulocytes [36].

In addition, CiteSpace was used to analyze the burst of keywords, which helped identify current research trends and frontiers (Fig. 10). Recent bursts of keywords indicate a significant emphasis on comprehending the underlying mechanisms responsible for the development and progression of aneurysms, leading to a significant increase in the number of studies on the mechanisms related to macrophages and aneurysms from 2019. In addition, there is currently a burst of attention toward 'aortic dissection,' highlighting the growing interest in this highly fatal disease. For example, a study published in the 'European Heart Journal' demonstrated that succinic acid plays a crucial role in the pathogenesis of aortic aneurysm and dissection (AAD) and has potential as a novel diagnostic biomarker [37]. Their results indicated that macrophages accumulate in AAD tissues and may release succinic acid into the bloodstream during AAD, resulting in elevated levels of plasma succinic acid, which further exacerbates AAD progression. Moreover, the P38A-CREB-OGDH axis regulates the succinic acid production in macrophages, and the knockout of p38a inhibits the advancement of AAD (Fig. 11). This report serves as a compelling illustration of how scientists investigate the mechanisms underlying aneurysm and aortic dissection formation while also utilizing their discoveries to identify promising therapeutic targets for managing AAD. Therefore, it is crucial to conduct further research in this field to improve treatment options and facilitate personalized precision

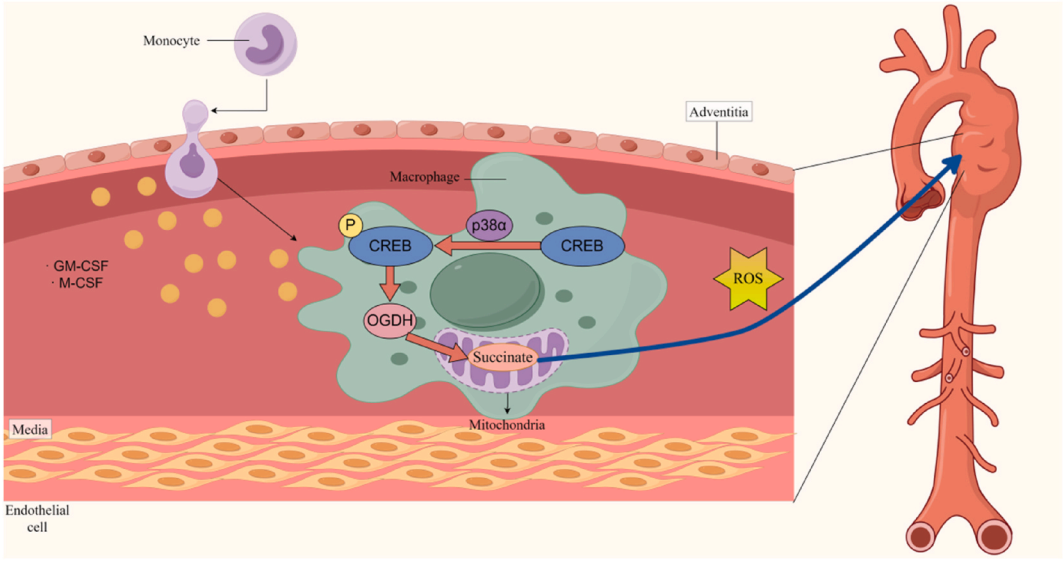

Fig. 11. Structure of macrophage and aneurysm wall layers, along with a representative theory on the role of macrophages in aneurysms.A study published in the European Heart Journal reveals that succinic acid plays a pivotal role in the pathogenesis of AAD. Macrophages accumulate within AAD tissue, potentially releasing succinic acid into the bloodstream during AAD, thereby leading to elevated levels of plasma succinic acid that further exacerbate AAD progression. The P38A-CREB-OGDH axis regulates succinic acid production in macrophages, with knockout of p38a inhibiting AAD advancement.

therapy.

4.6. Strengths and limitations

As far as we know, this study represents the first use of bibliometric analysis to summarize the connections between macrophages and aneurysms. To ensure a comprehensive evaluation of the existing literature, we employed two bibliometric tools (CiteSpace and VOSviewer) in addition to an online platform. Despite these strengths, this study had several limitations. First, owing to language constraints, the scope of this study was confined solely to articles written in English, potentially excluding noteworthy research conducted in other languages. Second, to minimize the bias resulting from recent publications, our database search was conducted within a single day. As a result, there may be a discrepancy between the number of articles included in this study and the total available literature owing to ongoing updates in the databases. Third, only articles were considered for inclusion in this study. Therefore, it is crucial to note that variations in quality among the collected literature might have affected the accuracy of our bibliometric analysis.

5. Conclusions

This study presents a comprehensive overview of global research trends related to macrophages and their roles in aneurysm pathogenesis. The results indicate that the United States, China, and Japan are the leading countries in this field in terms of publication output, citation frequency, and H-index. In addition to preventing aneurysm rupture and investigating the gene and protein expression associated with macrophages in aneurysms, current researchers primarily focus on exploring the therapeutic potential of macrophages in aneurysmal development. Future investigations on aneurysm management are encouraged for its rapid translation into clinical practice. In addition, current trends in this area reflect the fact that researchers are paying more attention to diseases with severe outcomes, such as aortic dissection. Therefore, questions have been raised, such as whether macrophages are related to the pathogenesis and progression of aortic dissection. Can macrophage-related proteins or cytokines be used as targets to prevent aortic dissection? Can therapy-targeted macrophages influence the outcome of patients with aortic dissection? To answer such questions, novel findings and viewpoints may appear, and significant advancements are expected in this field with a surge in future studies. However, several challenges exist in aneurysm research, such as tailoring treatments based on the different types of aneurysms and understanding the potential variations in macrophage involvement across these subtypes. Nevertheless, promoting communication and collaboration among diverse groups of researchers could facilitate the development of innovative and effective management strategies for patients with various types of aneurysms.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Zhenchu Tang: Writing – original draft. **Shan Gao:** Investigation, Formal analysis, Data curation. **Xiangyu Shi:** Validation, Supervision, Project administration. **Lile He:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AAA	abdominal aortic aneurysm
AAD	aortic aneurysm and dissection
RCT	randomized controlled trial
NIH	National Institutes of Health

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35212.

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