Review

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Research trends and hotspots of the applications of single-cell RNA sequencing in cardiovascular diseases: a bibliometric and visualized study

Yue Yu, MD[a], Juan Ye, MD[a], Rubing Wang[a], JingJing Wang, MD[a], Junnan Wang, MD[a], Qiumeng Xu, MD[b], Pei Wang, MD[a], Bei Wang, PhD, MD[c,*], Yufeng Zhang, PhD, MD[a,*]

Background: Cardiovascular diseases (CVDs) are the leading causes of death globally. The use of single-cell RNA sequencing (scRNA-seq) in CVDs has gained significant attention in recent years, and there is a growing body of literature on the subject. However, a thorough and impartial analysis of the existing state and trends of scRNA-seq in CVDs is lacking. This study aims to examine the development of scRNA-seq in CVDs using bibliometric and visualized analysis.

Methods: Global publications on scRNA-seq and CVDs from 2009 to 2023 were extracted from the Web of Science Core Collection (WoSCC) database. The R package "Bibliometrix", VOSviewer, and CiteSpace were employed to perform a bibliometric study.

Results: After applying the screening criteria and omitting documents that met exclusive criteria, this bibliometric study included 1170 papers. These were authored by 8595 scholars from 1565 organizations in 57 countries or regions and were published in 369 journals, with 51 073 co-cited references included. Publication volume, citations, and relative research interest index focusing on this field have dramatically increased since 2019. The cooperation network showed that the USA, the Chinese Academy of Medical Sciences, and Qingbo Xu were the most active countries, institutes, and authors in this field, respectively. *Circulation Research* was the journal with the most publications, which was confirmed to be the top core source by Bradford's law. The hotspots and emerging direction in the field manifest in (1) three CVDs (atherosclerosis, myocardial infarction, and heart failure) and (2) three cell types (macrophage, fibroblast, and smooth muscle cell).

Conclusions: Our study provides a systematic visualization of the research literature on scRNA-seq in CVDs and provides guidance and reference for understanding the current research status and discovering new research directions.

Keywords: bibliometrics, cardiovascular diseases, CiteSpace, scRNA-seq, VOSviewer

Introduction

Cardiovascular disease (CVDs) stands as a major health concern worldwide, serving as a prime contributor to the global mortality rate[1,2]. The pathogenesis related to the cardiovascular system has not been fully elucidated. Cells are regarded as the fundamental unit of biological structure, process, and function[3]. The cell types that make up the cardiovascular system are highly diverse, and the exact extent of their diversity remains unclear and poorly investigated[4]. The interactions between these different types of cells are also very sophisticated, which significantly enhances the challenge of studying and treating CVDs[5]. Accordingly, to deepen our comprehension of the effects of cell types in this field, we should broaden and enrich our knowledge of CVDs at the cellular level.

Single-cell RNA sequencing (scRNA-seq) technology has revolutionized the way that we explore organs and organisms, enabling an unprecedented level of resolution in the evaluation of cell demographics in both healthy and diseased states. This high-throughput approach facilitates analysis of the genome,

[a]Department of Cardiothoracic Surgery, Changzheng Hospital, Naval Medical University, Shanghai, People's Republic of China, [b]Department of Orthopaedics, Changzheng Hospital, Naval Medical University, Shanghai, People's Republic of China and [c]Department of Nursing, Changzheng Hospital, Naval Medical University, Shanghai, People's Republic of China

Yue Yu, Juan Ye, Rubing Wang, and JingJing Wang contributed equally to this work and share first authorship.

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*Corresponding author. Address: Department of Nursing, Changzheng Hospital, Naval Medical University, No. 415 Fengyang Road, Huangpu District, Shanghai 200003, People's Republic of China. Tel.: +86 139176 705 71. E-mail: wangbeishcz@163.com (B. Wang); Department of Cardiothoracic Surgery, Changzheng Hospital, Naval Medical University, No. 415 Fengyang Road, Huangpu District, Shanghai 200003, People's Republic of China. Tel.: +86 133 719 602 69. E-mail: zyflwj@smmu.edu.cn (Y. Zhang).

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transcriptome, epigenome, and other genetic data at the level of a single cell, providing critical insights into cell type, function, status, and variations[6]. The use of scRNA-seq in CVDs has gained significant attention in recent years, and there is a growing body of literature on the subject. However, this field still lacks a global and comprehensive report to help researchers quickly understand the research trends and hotspots in this area.

Bibliometrics is a field of study that uses quantitative and statistical methods to analyze the production and dissemination of research literature[7]. Bibliometrics has several advantages, including the capability to identify and quantify the impact of research, provide evidence-based evaluations of scientific productivity, and monitor the dissemination and influence of study over time[8]. Additionally, bibliometrics can aid in identifying research trends, emerging fields, and collaborations, which helps to inform strategic planning and resource allocation in research institutions[9]. The purpose of this paper is to comprehensively analyze the relevant literature, systematically demonstrate the research direction evolution, and intuitively reveal research frontiers and hot directions in the field of scRNA-seq and CVDs.

HIGHLIGHTS

- This study is the first bibliometric analysis to explore the emerging topic and provide a comprehensive knowledge map related to scRNA-seq and cardiovascular diseases (CVDs).
- The cooperation network showed that the USA, the Chinese Academy of Medical Sciences, and Qingbo Xu from Zhejiang University in China were the most active countries, institutes, and authors in this field, respectively. The USA maintained the dominant position as a 'Knowledge and Cooperation bridge' in the field of scRNA-seq and CVDs, with China following closely behind.
- *Circulation Research* was the journal with the most publications, which was confirmed to be the top core source by Bradford's law.
- The hotspots and emerging direction in the field manifest in (1) three CVDs (atherosclerosis, myocardial infarction, and heart failure) and (2) three cell types (macrophage, fibroblast, and smooth muscle cell).

Method

Data source and literature search strategy

The selection of Web of Science Core Collection (WoSCC) (all database editions) as the primary database for this research was based on its comprehensive coverage of more than 12 000 scholarly journals. The WoSCC database, known for its rigorous journal selection, has become internationally recognized for evaluating the scientific achievements of scholars and institutions and for assessing the development of disciplines[10]. Searches, data extraction, and download activities were performed within one day on 15 March 2024 to prevent deviation resulting from the database update. All authors participated in the development of the search strategies following consultations with senior literature search experts and based on some relevant references[11–14]. Boolean operators (AND, OR, NOT) were utilized for searching. The search strategy was as follows: TS = ("single-cell RNA sequencing" OR "single-cell RNA-seq" OR "single-cell RNA-sequencing" OR "scRNA-seq" OR "single-cell sequencing" OR "single-cell transcriptomic*" OR "single-cell ATAC" OR "single-cell omics sequencing" OR "Single-cell transcriptome" OR "single-cell multiomics sequencing") AND TS = ("valve disease*" OR "mitral valve" OR "aortic valve" OR "tricuspid valve" OR "ischemic heart" OR "myocardial infarction" OR "angina pectoris" OR "coronary artery" OR "coronary disease*" OR "myocardial ischemia" OR "pericarditis" OR "pericardium" OR "endocarditis" OR "myocarditis" OR "cardiomyopathy" OR "arrhythmias" OR "arrhythmias" OR "atrial fibrillation*" OR "atrial flutter" OR "heart failure*" OR "ventricular failure*" OR "cardiac failure*" OR "heart decompensation*" OR "myocardial failure*" OR "heart aneurysm" OR "atherosclerotic*" OR "atherosclerosis*" OR "congenital heart" OR "heart defect*" OR "congenital heart defect" OR "heart attack" OR "hypertension" OR "blood pressure" OR "heart disease*" OR "heart disorder*" OR "cardiovascular disease*" OR "cardiac*" OR "cardiovascular event*" OR "artery disease*" OR "cardio*").

Inclusion and exclusion criteria

The search period was restricted from 1 January 2009 to 31 December 2023. To facilitate further analysis of literature content, we designated English as the only language. The literature studies were restricted to articles or reviews because these document types typically undergo peer review, ensuring the quality and suitability for bibliometric analysis. Two reviewers (Y.Y. and Y.Z.) independently identified and discussed potential discrepancies in the data search and screening, ultimately reaching a consensus. The detailed information on the literature query equation and screening criteria are shown in Figure 1.

Data collection and processing

A complete record and cited references (title, country and region, author, publisher, date of publication, total citations, H-index, keywords, etc.) were then extracted from relevant publications and saved in plain text format for further research. Our data cleaning process involved several key steps: (1) Country Consolidation: we merged countries that are geographically or politically part of the same entity. For example, "Scotland", "England", and "Northern Ireland" were combined under the "United Kingdom (UK)"; (2) Synonym merging and abbreviations standardization for countries: we consolidated synonyms for countries, such as replacing "Peoples R China" and "Taiwan" with "China"; (3) Synonym merging and abbreviations standardization for institutions: we consolidated synonyms for institutions, such as replacing "Peking Union Medical College" with "Chinese Academy of Sciences"; (4) Synonym merging and abbreviations standardization for keywords: we consolidated synonyms for keywords, such as replacing "scRNA-seq" with "single-cell RNA sequencing"; (5) Author Identity Verification: we conducted thorough identity verification to eliminate confusion caused by authors with the same name. Besides using ORCID information for identity verification, we also referred to reliable sources such as official institutional websites and ResearchGate (https://www.researchgate.net/).

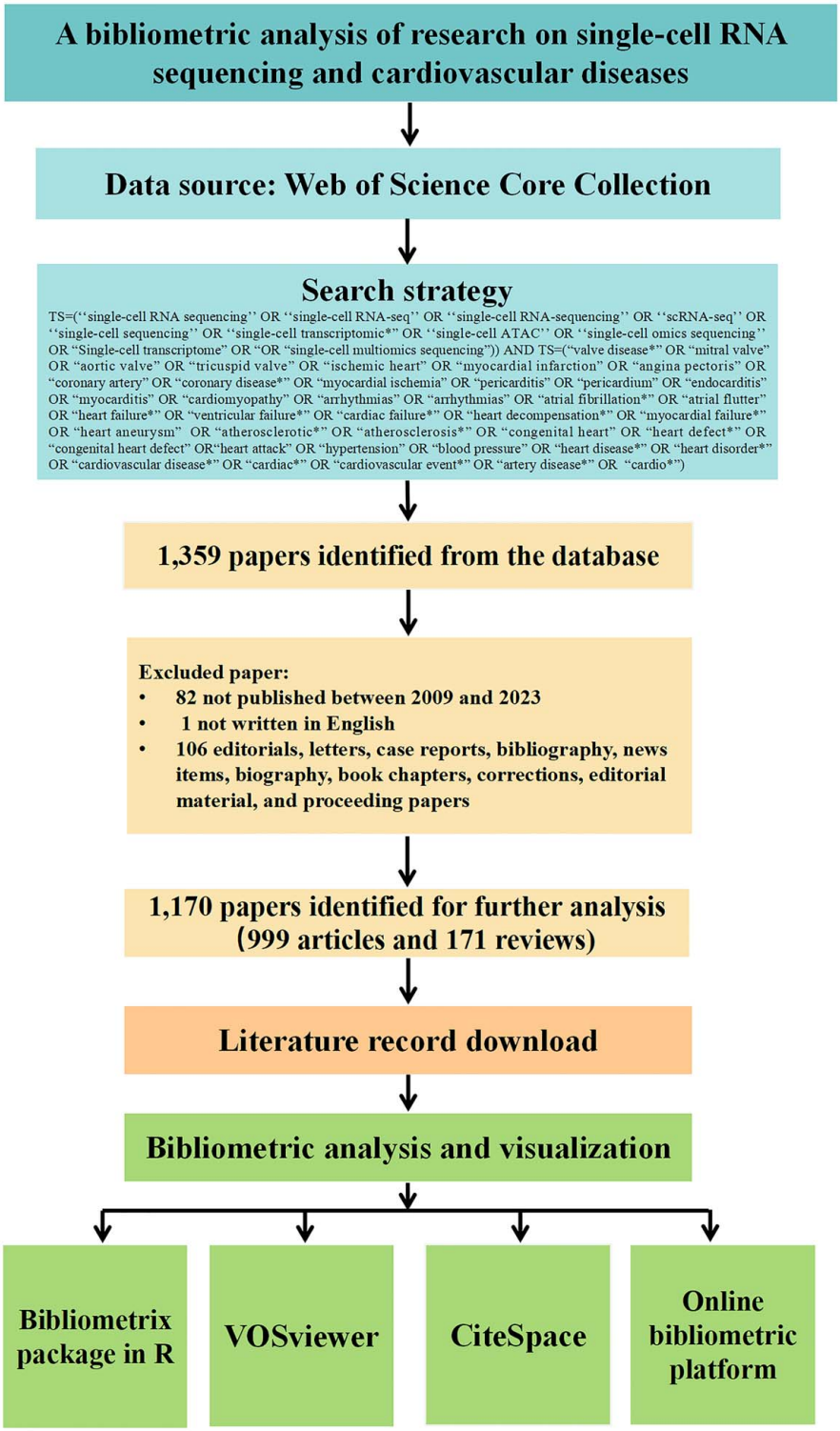

Figure 1. Flowchart of literature screening and bibliometric analysis.

Bibliometric analysis

The data is analyzed and visualized using the following tools: VOSviewer (version 1.6.1)[15], R package "bibliometrix" (version 4.1.3)[16], CiteSpace (version 5.8.R3)[17], an online bibliometrics platform (https://bibliometric.com/), and Microsoft Excel (2019).

VOSviewer is a software tool used for generating, visualizing, and exploring bibliometric maps[15]. VOSviewer was used in this present research for the co-authorship (country, institution, and author) and co-occurrence (keywords) analyses. In this review, co-authorship analysis was constructed to reveal the teamwork relationships among authors, institutions, and countries, while

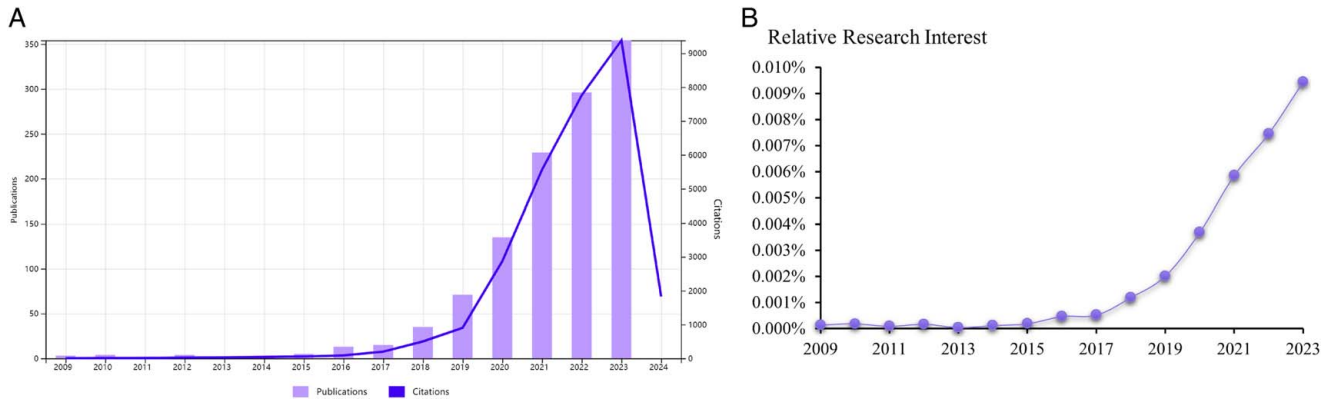

Figure 2. Overview of publication status. (A) Publication counts and citations per year. (B) Relative research interest index per year.

co-occurrence analysis exhibited the association among different keywords. It also advanced the analysis by adding a time-overlaying feature to visualize the network over a time span. Full-counting was selected, with established thresholds as detailed in the corresponding section. The size of the circles in the clustering network and the time-overlapping network represent the number of publications. The link line reflects the co-authorship or co-occurrence relationship, and the thickness of the link line reflects the collaboration strength. In the cluster map, the different colors of the circles represent different clusters. In the time-overlapping network, early-appearing countries, institutions, authors, or keywords are displayed in blue, while a recent appearance is displayed in red. The number of publications, citations, and keyword frequency were calculated using VOSviewer. The following are the specific parameter settings: (1) For the country co-authorship analysis, countries with a minimum of one paper were included in the visualization (Attraction: 4, Repulsion: −1). (2) For the institutional co-authorship analysis, countries with a minimum of 10 papers were included in the visualization (Attraction: 4, Repulsion: −1). (3) For the author co-authorship analysis, authors with a minimum of five papers were included in the visualization (Attraction: 4, Repulsion: −1); (4). Keyword co-occurrence analysis included keywords with a minimum of 20 occurrences (Attraction: 4, Repulsion: 2).

CiteSpace is an effective tool for visualizing citations and exploring current collaboration, key points, internal frameworks, potential hotspots, and development trends within a specific field[18]. Hence, we use CiteSpace to analyze the dual map of journals, the timeline view of keywords and citations, and keywords and citation bursts. The following are the specific parameter settings: time span (2009–2023), years per slice, pruning (pathfinder and pruning sliced networks), group labels were identified by light semantic indexing and the log-likelihood ratio algorithm, the minimum length of burstiness (2 years), and other settings remained at their default values. In CiteSpace visualization, the size of nodes indicates frequency, and the connecting line represents the co-occurrence relationship. The nodes and lines are colored according to different years, transitioning from purple to yellow between 2009 and 2023.

"Bibliometrix" is a comprehensive R language package for bibliometric analysis and scientific visualization[19]. In this study, topic trends and thematic mapping analyses were used. The thematic map is a two-dimensional diagram constructed using the Density Index as the *Y*-axis and the Centrality Index as the *X*-axis. The thematic map is divided into four quadrants based on centrality and density rank: the first quadrant (top right) is for motor themes; the second quadrant (top left) is for developed and isolated themes; the third quadrant (left bottom) is for emerging or vanishing themes; the fourth quadrant (right bottom) is for fundamental and transversal themes.

Some indicators are also calculated for bibliometric analysis. Relative research interest (RRI) was defined as the number of publications in a particular research field divided by the total number of publications across all fields per year[20]. The H-index serves as a valuable metric for evaluating scientific accomplishments. This index signifies that a unit has authored a minimum of H papers, and each paper has been cited in other publications at least H times[21]. The latest journal impact factor (IF) and quartiles are provided by Web of Science InCites Journal Citation Reports (JCR)[22].

Results

Literature screening process

We originally screened 1359 articles in the database. As shown in Figure 1, 82 articles were published outside the years 2009–2023 and 1 non-English paper was excluded through manual screening. One hundred six articles were excluded because of irrelevant article categories. Finally, 1170 eligible studies (999 original articles and 171 reviews) were retained for further analysis.

Overview of publication status

It has been recognized that the development landscape in a research field closely correlates with the volume of articles published in each period. These 1170 documents have been cited a total of 29 279 times (25 39 times without self-citations), with an H-index of 84. The trend of annual publications is illustrated in Figure 2A. Analyses revealed that (i) in the initial 7 years (2009–2015), fewer than five articles were published annually; (ii) in the subsequent 3 years (2016–2018), the annual publication rate started to rise steadily; (iii) in the recent 5 years (2019–2023), the publication number has dramatically increased, reaching its peak in 2023 ($n = 354$). The changing trend of the citation number per year was close to that of the annual publication counts. Compared with publications in all fields, global research hotspots measured by the RRI index also rose exponentially after 2018, as shown in Figure 2B. Since data

Table 1

Top 10 productive countries and institutions in the field of scRNA-seq and CVDs.

Rank	Country	Document	Citation	Total link strength	Institution	Document	Citation	Total link strength
1	USA	553	17847	466	Chinese Academy of Medical Sciences	61	863	64
2	China	434	6933	185	Stanford University	58	2084	48
3	Germany	157	6495	248	Harvard University	49	2525	94
4	UK	116	4851	218	Zhejiang University	41	564	32
5	Netherlands	80	3262	167	Karolinska Institutet	36	1319	76
6	Sweden	46	1843	114	University of California, San Diego	36	1715	71
7	Canada	46	2456	106	Shanghai Jiao Tong University	34	1838	30
8	Japan	42	1823	45	University of Virginia	32	1127	73
9	Australia	40	2164	84	University of Cambridge	29	1943	44
10	France	35	1102	71	Huazhong University of Science and Technology	27	457	18

CVDs, cardiovascular diseases; scRNA-seq, single-cell RNA sequencing.

collection was completed in December 2023, we could not infer that the number of publications would keep rising in 2024. However, we can anticipate that the development of research in this field will not stop accelerating in the future.

Contribution of countries to publications

All the documents were published in 57 countries or regions. The United States of America (USA) exhibited the highest contribution to research on scRNA-seq in CVDs ($n = 553$), closely followed by China ($n = 434$) and Germany ($n = 157$), as shown in Figure 3A and Table 1. Meanwhile, the number of citations in the USA ($n = 17\ 847$) far exceeded those of other countries, followed by China ($n = 6933$) and Germany ($n = 6495$). The above results showed that the USA maintained its lead in the number and quality of publications. In Supplementary Figure S1 (Supplemental Digital Content 1, http://links.lww.com/MS9/A632), we summarized the funding data in this field and identified that the United States Department of Health and Human Services funded the highest number of projects ($n = 391$).

As part of our investigation, we visualized the collaborations among countries or regions. In Figure 3B, the most frequent collaborations were between the USA and China (frequency = 77). Additionally, among the top 10 countries with the highest frequency of cooperation, the USA-centered international cooperation held six positions. A country co-authorship analysis of all publications across the 57 countries above was also conducted by VOSviewer. As shown in Figure 3C, the 57 countries formed 15 clusters, and the USA had closer ties to other nations than any

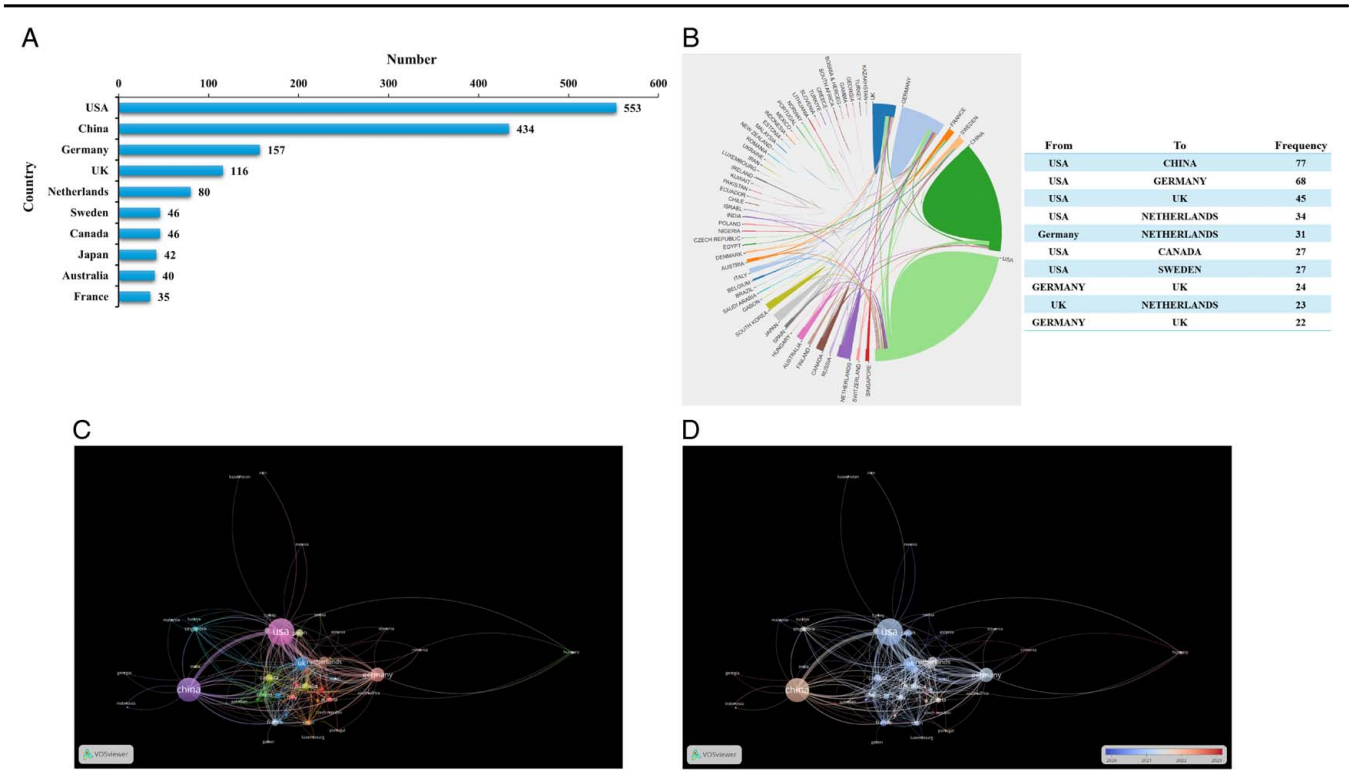

Figure 3. Analysis of publications from different countries or regions. (A) Top 10 productive countries. (B) Global collaborations and the frequency of collaboration among nations. (C) Network clustering of country co-authorship analysis by VOSviewer. (D) Time-overlapping network of country co-authorship analysis by VOSviewer.

other country, highlighting that the USA acted as a 'bridge' node, particularly with certain European countries, China, and Canada. In Figure 3D, the time-overlapping network showed that the UK and the USA were early pioneers in this field, while there has been a rapid progression in Chinese research outputs recently.

Contribution of institutions to publications

All the documents were conducted at 1565 academic institutions worldwide. Chinese Academy of Medical Sciences in China ($n = 61$), Stanford University in the USA ($n = 58$), Harvard University in the USA ($n = 49$), Zhejiang University in China ($n = 41$), and Karolinska Institutet in Sweden ($n = 36$) are the top five institutions in terms of publication number respectively (Table 1 and Supplementary Fig. S2, Supplemental Digital Content 1, http://links.lww.com/MS9/A632). To further investigate collaboration between institutions, we performed an institutional co-authorship analysis. Using VOSviewer with a threshold of a minimum of 10 publications per institution, we identified 75 nodes and 5 clusters. As shown in Supplementary Figure S2B (Supplemental Digital Content 1, http://links.lww.com/MS9/A632), the Chinese Academy of Medical Sciences was located at the center of the yellow cluster and cooperated closely internally, but further collaboration with other clusters was needed. Harvard University had the highest total link strength ($n = 94$) and occupied a core position in the blue group. In Supplementary Figure S2C (Supplemental Digital Content 1, http://links.lww.com/MS9/A632), the time-overlapping network showed that several American research institutions (for example, Massachusetts General Hospital and Brigham and Women's Hospital) contributed significantly to early development. In contrast, multiple Chinese research institutions (for example, Zhejiang University) have become more involved in this field in recent years.

Contribution of authors to publications

A total of 8595 authors participated in research on scRNA-seq and CVDs in the present study. As shown in Supplementary Figure S3A (Supplemental Digital Content 1, http://links.lww.com/MS9/A632) and Table 2, Qingbo Xu from Zhejiang University in China was the most productive scholar, with 17 articles published. Following closely behind were Klaus Ley ($n = 16$, La Jolla Institute for Immunology, USA) and Joseph C. Wu ($n = 15$, Stanford University, USA). More than half of the top 10 most prolific scholars were from China. Klaus Ley had the highest value in the citation ($n = 1188$), followed by Joseph C. Wu ($n = 1145$) and Holger Winkels ($n = 1116$, La Jolla Institute for Immunology, USA).

Researchers' collaborative relationships are shown in Supplementary Figure S3B (Supplemental Digital Content 1, http://links.lww.com/MS9/A632). One hundred authors with five or more articles were grouped into 21 clusters. By analyzing the clustering network of co-authors, we found that the cooperative relationship among these authors presented a dispersive distribution, indicating that most of the cooperated authors were from the same units and that geographical factors influenced collaboration between authors. The time-overlapping network results are shown in Supplementary Figure S3C (Supplemental Digital Content 1, http://links.lww.com/MS9/A632). We observed that researchers from China were forming a new research network in this field. National and institutional collaborations are one of the future directions due to the inadequate collaboration between different research groups.

Contribution of journals to publications

Table 3 and Figure 4A lists the top 10 journals ranked by publication quantity. The top five prolific journals were *Circulation Research* (count: 52, IF: 20.1, H-index: 25), *Circulation* (count: 45, IF: 37.8, H-index: 25), *Frontiers in Immunology* (count: 44, IF: 7.3, H-index: 10), *Frontiers in Cardiovascular Medicine* (count: 43, IF: 3.6, H-index: 9), and *Nature Communications* (count: 42, IF: 16.6, H-index: 23), respectively. Among these 10 academic journals, 6 journals belonged to the Q1 category of JCR quartiles. There were 4 journals from the USA, and 3 from Switzerland and the UK, respectively. According to Bradford's law, the grey box refers to core journals in this field, as shown in Figure 4C. Figure 4D is the journal's dual-map overlay analysis, which revealed the distribution of journal topics. The map's left section illustrates the citing journals, while the right section represents the cited journals. The labels of various color clusters suggest the discipline of the corresponding journals. The thickest path from left to right is the citation trajectory, reflecting the flow of citations. The horizontal axis of the ellipse is positively correlated with the number of contributing authors, while the longitudinal axis is positively correlated with the journal's output. As shown in Figure 4D, there were three main citation paths, containing two yellow paths and one green path, respectively. Two yellow path suggested studies published in Molecular/Biology/Genetics journals, and Health/Nursing/Medicine

Table 2

Top 10 productive authors in the field of scRNA-seq and CVDs.

Rank	Author	Institution	Country	Document	Citation	Total link strength
1	Qingbo Xu	Zhejiang University	China	17	274	58
2	Klaus Ley	La Jolla Institute for Immunology	USA	16	1188	51
3	Joseph C. Wu	Stanford University	USA	15	1145	28
4	Li Wang	Xingtai People's Hospital	China	14	378	12
5	Jiangping Song	Chinese Academy of Medical Sciences	China	13	213	31
6	Gerard Pasterkamp	Utrecht University	Netherlands	13	535	46
7	Stefanie Dimmeler	Goethe University Frankfurt	Germany	12	496	24
8	Holger Winkels	La Jolla Institute for Immunology	USA	11	1116	37
9	Xiao Chen	Chinese Academy of Medical Sciences	China	10	202	28
10	Yanhua Hu	Zhejiang University	China	10	251	44

CVDs, cardiovascular diseases; scRNA-seq, single-cell RNA sequencing.

Table 3

Top 10 productive journals in the field of scRNA-seq and CVDs.

Rank	Journal	Country	Count	Citation	IF	H-index	JCR quartile
1	*Circulation Research*	USA	52	3261	20.1	25	Q1
2	*Circulation*	USA	45	2282	37.8	25	Q1
3	*Frontiers in Immunology*	Switzerland	44	508	7.3	10	Q1
4	*Frontiers in Cardiovascular Medicine*	Switzerland	43	290	3.6	9	Q2
5	*Nature Communications*	UK	42	1589	16.6	23	Q1
6	*Cardiovascular Research*	UK	35	727	10.9	15	Q1
7	*Arteriosclerosis Thrombosis and Vascular Biology*	USA	33	856	8.7	14	Q1
8	*Scientific Reports*	UK	28	287	4.6	10	Q2
9	*Frontiers in Cell and Developmental Biology*	Switzerland	26	151	5.5	7	Q2
10	*Cell Reports*	USA	19	1323	8.8	13	Q2

CVDs, cardiovascular diseases; IF, impact factor; JCR, Journal Citation Report; scRNA-seq, single-cell RNA sequencing.

journals, were generally cited by studies in Molecular/Biology/Immunology journals.

High-cited publications and co-cited references

In Table 4, we list the top 10 high-cited publications, with all articles cited over 320 times. There was one article entitled 'Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection' received the most citations ($n = 1426$) by the primary author of Xin Zou in 2020[23]. This study provided an overview of 2019-nCoV infection-related vulnerable organs according to ACE2 expression using state-of-the-art single-cell techniques[23]. The article that ranked second was 'Cells of the adult human heart' with 659 citations by the primary author Monika Litviňuková in 2020[24]. They characterized six anatomical adult heart regions and provided a human cardiac cell atlas by combining single-cell and single-nuclear RNA-seq data with machine learning and in situ imaging techniques[24].

In Table 5, we list the top 10 co-cited references. We found that the majority of these co-cited references focused on continuous technological advances and data analysis of scRNA-seq itself. As shown in Supplementary Figure S4 (Supplemental Digital Content 1, http://links.lww.com/MS9/A632), Cluster '#0 Congenital Heart diseases', Cluster '#1 vascular smooth muscle cell (SMC)', and Cluster '#7 myocardial infarction' were still hotspots in this field. Based on references cited frequency in a certain period, we set at least 2 years of burst duration in CiteSpace and detected the top 50 references with the strongest citation bursts, as shown in Supplementary Figure S5 (Supplemental Digital Content 1, http://links.lww.com/MS9/A632). The article with the strongest burstiness (strength = 21.94) was entitled 'Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets'[25]. This paper described Drop-seq, a strategy for quickly profiling thousands of individual cells by separating them into nanoliter-sized aqueous droplets, associating a different barcode with each cell's RNAs, and sequencing them all together[25]. "Wang Y, 2019, ARTERIOSCL THROM VAS, V39, P876"[26], "Pedroza AJ, 2020, ARTERIO SCL THROM VAS, V40, P2195"[27], and "Miao YF, 2020, CELL STEM CELL, V27, P574"[28] were the recent high-citation references. We found that two out of the three articles focused on the exploration of SMC.

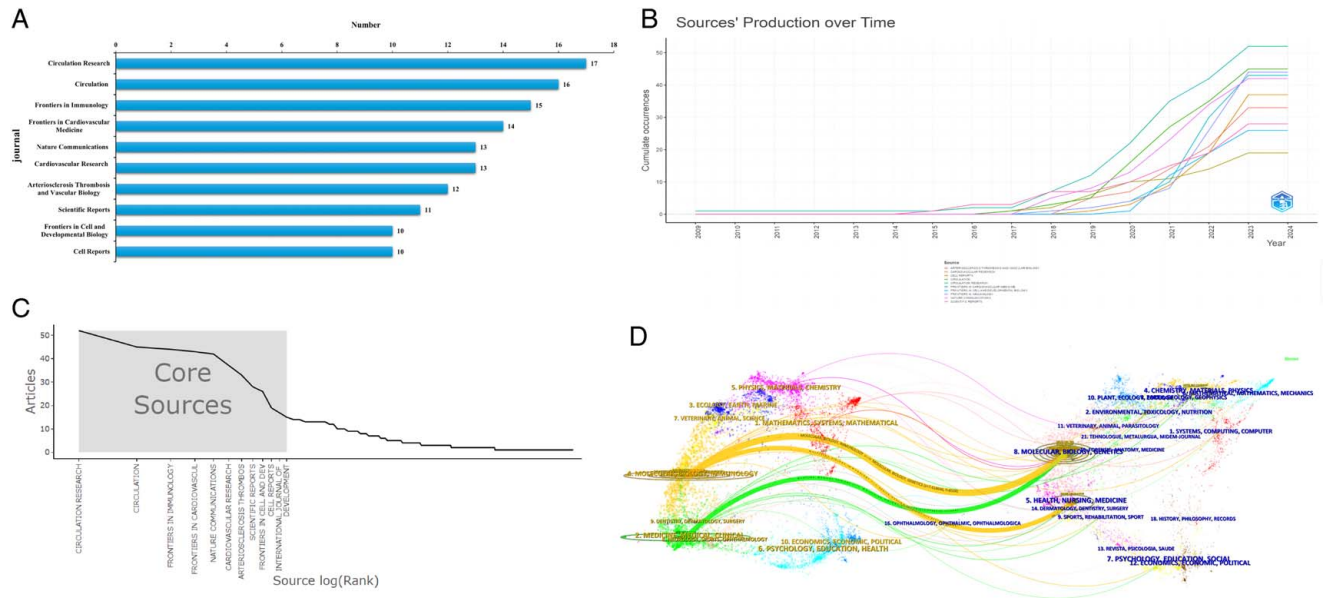

Figure 4. Analysis of publications from different journals. (A) Top 10 productive journals. (B) Journals' production over time. (C) Core journals by Bradford's law by R tool. (D) A dual-map overlap of journals by CiteSpace.

Table 4

Top 10 high-cited articles in the field of scRNA-seq and CVDs.

Rank	Title	Publication year	Journal	First author	Affiliation	Citation	Type
1	Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection	2020	*Frontiers of Medicine*	Xin Zou	Shanghai Jiao Tong University	1462	Article
2	Cells of the adult human heart	2020	*Nature*	Monika Litviňuková	Wellcome Genome Campus	659	Article
3	Single-cell RNA-seq reveals the transcriptional landscape and heterogeneity of aortic macrophages in murine atherosclerosis	2018	*Circulation Research*	Clément Cochain	University Hospital Würzburg	493	Article
4	Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis	2019	*Nature Medicine*	Robert C. Wirka	Stanford University	390	Article
5	scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, Leydig and Sertoli cells	2020	*Cells*	Zhengpin Wang	National Institutes of Health, USA	389	Article
6	Endometrial stem/progenitor cells: the first 10 years	2016	*Human Reproduction Update*	Caroline E. Gargett	Hudson Institute of Medical Research	368	Review
7	Tissue resident CCR2^{-} and CCR2^{+} cardiac macrophages differentially orchestrate monocyte recruitment and fate specification following myocardial injury	2019	*Circulation Research*	Geetika Bajpai	Washington University	353	Article
8	Single-cell transcriptional profiling reveals cellular diversity and intercommunication in the mouse heart	2018	*Cell Reports*	Daniel A. Skelly	The Jackson Laboratory	329	Article
9	Single-cell expression profiling reveals dynamic flux of cardiac stromal, vascular and immune cells in health and injury	2019	*Elife*	Nona Farbehi	Victor Chang Cardiac Research Institute	328	Article
10	A spatiotemporal organ-wide gene expression and cell atlas of the developing human heart	2019	*Cell*	Michaela Asp	KTH Royal Institute of Technology	322	Article

CVDs, cardiovascular diseases; scRNA-seq, single-cell RNA sequencing.

Frequency and clustering analysis of keyword

A total of 4751 keywords were identified by VOSviewer. If these keywords had similar meanings, they were merged for subsequent analysis. Supplementary Table S1 (Supplemental Digital Content 2, http://links.lww.com/MS9/A633) lists the top 20 keywords by frequency of occurrence. The high frequency of keywords can be classified: mechanism-related keywords (expression [$n = 470$], inflammation [$n = 183$], differentiation [$n = 110$], activation [$n = 109$], proliferation [$n = 80$], mechanisms [$n = 66$], heterogeneity [$n = 54$]), three cardiovascular diseases (atherosclerosis [$n = 200$], myocardial infarction [$n = 55$], and heart failure [$n = 54$], three cell types (macrophages [$n = 102$], fibroblasts [$n = 59$], SMC [$n = 55$]), and scRNA-seq ($n = 174$). Among these keywords, 70 met the threshold of 20 occurrences and were grouped into four groups (Fig. 5). Group 1, represented in green, focused on the exploration of the mechanism of atherosclerosis, especially the immune system, and was composed of the following keywords: atherosclerosis, dendritic cell, macrophage, monocytes, t-cell, apoptosis, inflammation, mechanism, and vascular SMC. Group 2, represented in red, focused on cell behavior and molecular biology in CVDs and was composed of the following keywords: activation, angiogenesis, dysfunction, proliferation expression, inhibition, growth, identification, receptor, gene, protein, and cell. Group 3, represented in blue, focused on the application of scRNA-seq in CVDs and was composed of the following keywords: cardiomyocyte, atlas, differentiation, heterogeneity, mutation, phenotype, pluripotent stem cell, progenitor cell, and reconstruction. Group 4, represented in yellow, focused on heart failure and myocardial infarction and was composed of the following keywords: heart failure, myocardial infarction, repair, fibroblast, fibrosis, injury, extracellular matrix, repair, and regeneration. Figure 5B shows the visualization of the time-overlapping of keywords. Immune cells (macrophages, monocytes, and t-cells), heart failure, and inflammation have been emerging topics recently.

As we can see in Figure 5C, 7 of 10 clusters (Cluster #0 atherosclerosis, Cluster #1 differentiation, Cluster #2 precision medicine, Cluster #3 myocardial infarction, Cluster #4 sars-cov-2, Cluster #6 oxidative stress, Cluster #8 association) were still ongoing. In the keyword burst analysis (Fig. 5D), we detected 'gene expression' with the most vigorous citation burst (strength = 7.37), which had its citation burstiness from 2014 to 2019. Notably, three keywords (low-density lipoprotein, neural crest, and macrophage-like cells) were still in burstiness until 2023. Figure 5E shows the trend topics and their prevailing year; we can see that 'Macrophage', 'Fibroblast', and 'Aging' were still hot topics in this field. Additionally, the thematic map of keywords (Fig. 5F) showed that heart development and smooth muscle cells were motor themes, signifying these topics were well-developed and crucial for structuring a research subject.

Discussion

Table 5

Top 10 co-cited references in the field of scRNA-seq and CVDs.

Rank	Title	Publication year	Journal	First author	Affiliation	Citation	Type
1	Integrating single-cell transcriptomic data across different conditions, technologies, and species	2018	*Nature Biotechnology*	Andrew Butler	New York Genome Center	208	Article
2	Comprehensive integration of single-cell data	2019	*Cell*	Tim Stuart	New York Genome Center	198	Article
3	Single-cell RNA-seq reveals the transcriptional landscape and heterogeneity of aortic macrophages in murine atherosclerosis	2018	*Circulation Research*	Clément Cochain	University Hospital Würzburg	124	Article
4	Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis	2019	*Nature Medicine*	Robert C. Wirka	Stanford University	120	Article
5	Single-cell expression profiling reveals dynamic flux of cardiac stromal, vascular and immune cells in health and injury	2019	*Elife*	Nona Farbehi	Victor Chang Cardiac Research Institute	110	Article
6	The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells	2014	*Nature Biotechnology*	Cole Trapnell	Harvard University	108	Article
7	Cells of the adult human heart	2020	*Nature*	Monika Litviňuková	Wellcome Genome Campus	105	Article
8	clusterProfiler: an R package for comparing biological themes among gene clusters	2012	*OMICS: A Journal of Integrative Biology*	Guangchuang Yu	Jinan University	98	Article
9	STAR: ultrafast universal RNA-seq aligner	2013	*Bioinformatics*	Alexander Dobin	Cold Spring Harbor Laboratory	94	Article
10	Single-cell immune landscape of human atherosclerotic plaques	2019	*Nature Medicine*	Dawn M. Fernandez	Icahn School of Medicine at Mount Sinai	92	Article

CVDs, cardiovascular diseases; scRNA-seq, single-cell RNA sequencing.

Main information

It is well known that the number of articles published within a certain period is directly correlated with the state of development in that scientific subject. After 2019, the number of publications started to increase significantly each year, reaching its peak in 2023. This phenomenon indicates that research on scRNA-seq in CVDs has entered a stage of rapid development but remains in its preliminary phase. Among the top 10 co-cited referenced publications, several articles were published before 2019 and focused on improvements in single-cell sequencing technology itself, which may lead to a dramatic increase in the number of articles after 2019. The RRI index is an indicator utilized within the domain of bibliometrics to gauge the evolution and relative intensity of research enthusiasm within a designated time frame and field[29]. The increasing RRI index suggests that scRNA-seq in CVDs is gaining interest from researchers and has a promising development landscape in the future.

Are there disparities in the distribution of research on scRNA-seq in CVDs among different countries or institutions? Our findings validated the USA's significant contributions and prominent position in CVD research utilizing scRNA-seq. Despite a delayed beginning, China has quickly ascended to become the second most productive nation and has forged strong partnerships with the USA. Research institutions from these two countries also dominated among the top 10 prolific academic organizations. However, in terms of the number of citations, the USA far exceeded China and other countries. Due to a delayed start, China lacks relevant article publications and has no solid research foundation compared to other countries at the initial stage, leading to a long time needed for China's citation frequency to catch up. These findings above may be linked to these countries' socioeconomic development, financial prosperity, healthcare policymaking, and the COVID-19 outbreak. For example, on 20 January 2015, U.S. President Obama announced an ambitious plan called the 'Precision Medicine Initiative', aiming to deliver genetics-based medical treatments[30]. Chinese government instructed the Ministry of Science and Technology and the National Health and Family Planning Commission to establish a national expert group on China's precision medicine strategy, and China will invest 60 billion RMB in precision medicine by 2030. scRNA-seq technology is an important representative of precision medicine, which amplifies and sequences the genome, transcriptome, and epigenome at the single-cell level in the processes of disease occurrence, development, and treatment, bringing hope for achieving precise diagnosis and treatment of diseases[31]. In addition, the top three countries in terms of publishing papers (the USA, China, and Germany) are also the top three countries in terms of gross domestic product in 2023 (https://statisticstimes.com/index.php). Furthermore, the 2019 coronavirus disease outbreak, which emerged at the end of December 2019, also propelled the use of advanced biotechnologies in the research of the coronavirus disease[32].

The experts who made significant contributions in a specific area, serving as a 'weather vane', may offer numerous directions and guidelines. The top 10 productive scholars each published a minimum of 10 papers, which highlighted the significant contribution of these researchers to this field. Qingbo Xu, a researcher at the Department of Cardiology of the First Affiliated Hospital of Zhejiang University in China, has published the highest number of academic articles and is a pioneer and expert in the field of cardiology and bioinformatics. This reflects that single-cell sequencing technology has started to filter into clinical departments. Klaus Ley, a researcher at La Jolla Institute for Immunology in the USA, has the highest citation times and is a pioneer in the fields of immunology, molecular biology, and cardiology. By examining the connections between co-authors, it

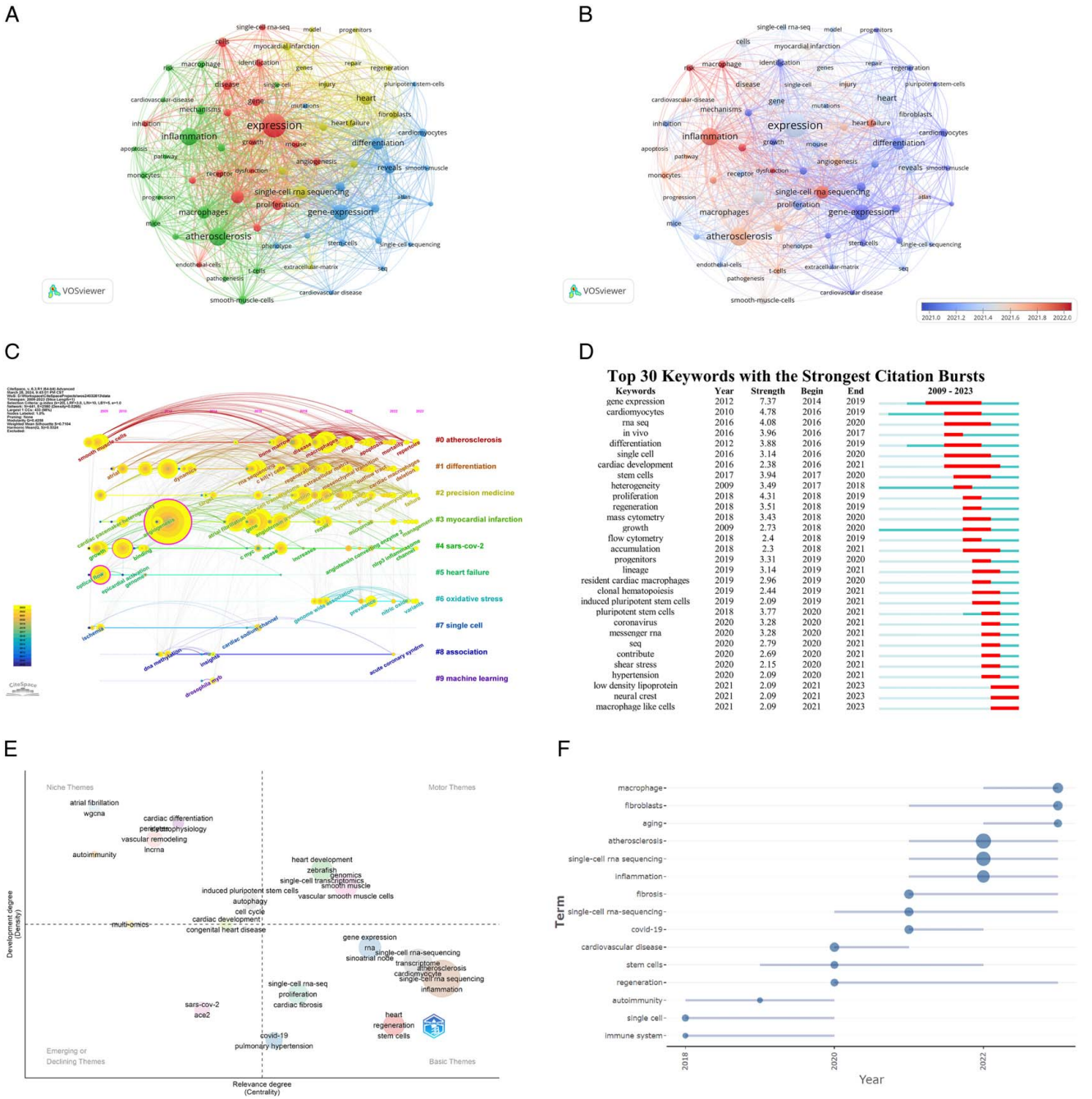

Figure 5. Analysis of keywords. (A) Network clustering of keyword co-occurrence analysis by VOSviewer. (B) Time-overlapping network of keyword co-occurrence analysis by VOSviewer. (C) A timeline view of keywords by CiteSpace. (D) Top 30 keywords with the strongest citation bursts by CiteSpace. (E) A thematic map by R tool. (F) Topic trends by R tool.

became apparent that their collaborative relationships presented a dispersive distribution. This pattern suggests that the majority of these authors collaborating are affiliated with the same institutions. Hence, we recommend encouraging the authors to break academic obstacles, cooperate, and communicate with other countries to facilitate the development of scRNA-seq in CVDs.

Academic publishing cannot exist without a peer-reviewed journal. This study listed the journals with the highest number of publications in this field and identified the core journals using Bradford's laws. Reading their publications would be beneficial for comprehending the knowledge structure in this field. *Circulation Research* was the periodical with the most publications on scRNA-seq and CVDs. Among the top 10 prolific periodicals, the four journals' IF is greater than 10, and 60% of periodicals were classified as Q1 category of JCR quartiles, indicating that scRNA-seq studies are generally of high quality, and researchers pay sufficient attention to the establishment of periodicals. Despite making substantial research contributions,

Asian publishers remain disproportionately low in representation within the leading 10 journals. It is necessary to establish and enhance globally influential academic journals in Asia.

Hotspots and future perspectives of scRNA-seq in CVDs

scRNA-seq: development and challenges

Traditional sequencing methods are based on cell populations, providing an average value that represents a steady state of thousands of cells[33]. These methods overlook the heterogeneity of individual cells (the unique characteristics of each cell) and the significant functions of small cell subpopulations. Consequently, scRNA-seq technology has emerged, promising to address core questions in human biology and medicine that remain unsolved. These questions pertain to the structure, dynamics, and variability of human cells during development, growth, renewal, aging, and disease[6]. In the past decade, significant progress has been achieved in the field of scRNA-seq technology, advancing our comprehension of cellular interactions in both health and disease. Among the top 10 co-cited references, five articles were related to the advancement of single-cell sequencing technology and data analysis. 'Gene expression' had the highest frequency of keyword occurrence, with the most vigorous citation burst from 2014 to 2019. These results indicate that the progress of technology is a prerequisite for the development of the field. Notably, in 2009, Tang F published a study on single-cell mRNA sequencing, which pioneered single-cell sequencing research[34]. In 2015, Harvard University's research groups innovatively merged micro-low fluid technology with scRNA-seq to create two distinct methodologies, known as drop-seq[25] and in-drop[35]. These two techniques can perform comprehensive sequencing of the entire gene expression within a cell while also identifying the specific cell of origin for each gene. Their emergence made it possible to analyze the gene expression of thousands of individual cells rapidly and economically. In 2018, single-cell sequencing was recognized as one of the top 10 scientific breakthrough technologies by *Science*.

The emergence and rapid advancement of single-cell technologies and omics analyses have facilitated a major leap in cardiovascular medicine because this technology is conducive to research in cardiovascular systems characterized by low cell numbers, rare cell types, extensive cell heterogeneity, and scarce samples. With the development of scRNA-seq, it has become possible to reveal new cell types and cell subpopulation heterogeneity in the cardiovascular system and understand the dynamics of cardiovascular cells in pathology[36]. Despite the advancements in scRNA-seq techniques, there is still a long way for further enhancements. Indeed, challenges persist that need addressing. Cell isolation from cardiac tissue, particularly enzymatic breakdown of highly fibrotic tissue, remains difficult and could introduce bias in the isolated cells and changes in their transcriptional profiles. To address this, several papers have compared various digestion protocols for murine and human hearts, and research has shown that nuclear RNA isolation and profiling, rather than cytoplasmic or whole-cell, may help alleviate some of these biases[37]. In addition, most existing platforms face limitations in terms of capture efficiency. Under such circumstances, rare cell populations are likely to be lost. The amount of DNA/RNA contained in a single cell is small, and existing gene sequencing requires initial amplification. However, errors in replication can easily occur during the amplification and copying process. In addition to the technical hurdles, the financial burden of scRNA-Seq analysis, particularly when compared with alternative analytical techniques, serves as a substantial impediment to its wider adoption as a standard tool. In 2018, the market value of single-cell sequencing was $1.83 billion, with a compound annual growth rate of ~16.5%. However, in any region with substantial market potential, intellectual property can lead to conflicts, which may hurt the development of new technologies.

Immune cells and CVDs

Previous studies have shown that the cardiovascular system of healthy adult humans and mice contains major populations of immune cells, including both lymphocytes and myeloid cells[24,38]. In the healthy adult human heart, myeloid cells consist of monocytes, dendritic cells, and several subpopulations of macrophages, such as LYVE1^{+} macrophages (which include MHC-II^{high} and MHC-II^{low}), fibroblast-interacting macrophages and monocyte-derived macrophages[39]. Our analyses showed that the exploration of the immune system of CVDs was both a hot topic and a future research direction. The journal's dual-map overlay analysis showed that immunology was a hot topic in citing journals. The time-overlapping of keywords by VOSviewer and Topic trends by R tool revealed that 'Macrophage' is an emerging research trend. A putative self-renewing subset of tissue-resident macrophages (MHC-II^{low}Lyve1^{+}) was found to contribute to regulating the cardiac lymphatic network during pathological hypertrophy in mice induced by transverse aortic constriction, which constitutes an important mechanism underlying the progression of heart failure[40]. Atherosclerosis, a chronic inflammatory disease distinguished by the accumulation of atheroma within the arterial wall's intima, is a life-threatening manifestation of CVDs due to chronic luminal narrowing, thrombosis, and atheroma rupture[41]. 'Atherosclerosis' ranked second in the top 20 keywords and occupied a prominent position in the green group in the clustering network by VOSviewer. One study reported that among the myeloid cell populations, resident-like macrophages with a gene expression profile similar to aortic resident macrophages were found in healthy and diseased aortas, whereas monocytes, monocyte-derived dendritic cells, and two populations of macrophages (enrichment in Il1b and Trem2) were almost exclusively detectable in atherosclerotic aortas[42]. Thoracic aortic aneurysm and dissection (TAAD) is a life-threatening condition distinguished by medial layer degeneration in the thoracic aorta[43]. Liu *et al.*[44] performed scRNA-seq of thoracic aortic cells from β-aminopropionitrile-induced TAAD mouse models at three different disease stages. Three subpopulations of aortic macrophages were identified, that is, Lyve1^{+} resident-like, Cd74^{high} antigen-presenting, and Il1rn^{+}/Trem1^{+} pro-inflammatory macrophages. Targeting the Il1rn^{+}/Trem1^{+} macrophage subset via blockade of Trem1 using mLR12 can effectively reduce the incidence of aortic rupture in mice.

SMC and CVDs

SMCs are the predominant cellular component in vessels that not only regulate vascular physiological function but also contribute to CVDs in different ways[45]. The thematic map in our study showed that SMCs were motor themes, signifying this topic was well-developed and crucial for structuring a research subject. Arterial diseases are the underlying causes of the majority of clinical cardiovascular events. scRNA-seq analysis of vascular

SMCs identified a synthetic state enriched in coronary artery SMCs compared with those in pulmonary and aorta artery SMCs, suggesting a specific adaptation of coronary arteries that are constantly exposed to local pressure variations due to cardiac contraction and relaxation[46]. The keywords ('Macrophage-like cells' and 'Neural crest cells') were still in burstiness until 2023 and revealed that they had attracted significant attention from peer researchers recently. Macrophage-like SMCs demonstrate low expression of contractile markers and possess functions similar to macrophages such as innate immune signaling, phagocytosis, and efferocytosis. Neural crest cells (NCCs), characterized by their ability to differentiate and migrate, delaminate from the dorsal region of the neural tube through epithelial-to-mesenchymal transition[47]. The integration of fate mapping with *Wnt1*–Cre and scRNA-seq helped establish the heterogeneity of 34 131 cardiac neural crest cell (CNCC)-derived cardiac cell populations in mouse hearts covering eight developmental stages between embryonic day 10.5 and postnatal day 7[48]. As expected, on postnatal day 7, most of the CNCCs localized to the aorta, pulmonary arteries, and coronary vasculature[48].

Fibroblast and CVDs

In our study, trend topic analysis by R tool showed that 'fibroblast' might be the future research direction. In adult hearts, fibroblasts are continuously modifying the microenvironment by degrading and depositing extracellular matrix (ECM) components[49]. Fibroblasts are also responsible for cardiac fibrosis, which is a common feature of many acute and progressive CVDs. Upon injury or inflammation, activated fibroblasts demonstrate increased collagen production, initially aiding in stabilizing the heart. While the accumulation of ECM can enhance tissue integrity in the beginning, excessive fibrosis may hinder cardiac function[50]. Persistent fibrosis may ultimately result in heart failure. Research utilizing single-cell and single-nucleus transcriptomics studies in developing, healthy, diseased, and partially recovered (unloaded) adult human hearts has verified cell state heterogeneity within fibroblast populations and highlighted additional regulators of fibroblast differentiation. In the human donor heart cell atlas, five distinct fibroblast populations were classified. This includes chamber-specific ECM-producing fibroblasts and fibroblasts enriched for cytokine receptor genes, which might modulate immune responses[24]. As a further improvement, scRNA-seq protocols have allowed researchers to reevaluate markers of activated fibroblasts that arise after injury. Using a microfluidic platform to sort single cells from adherent cells of digested mouse ventricles, investigators were able to use quantitative reverse transcriptase–polymerase chain reaction to quantify transcripts of several candidate markers of activated cardiac fibroblasts and found that Postn may be a better marker than Acta2 for activated fibroblasts in mice subjected to either angiotensin II infusion or myocardial infarction[51].

ScRNA-seq and CVDs

Several similar bibliometric analyses have been reported on the application of single-cell sequencing in various diseases, including different cancers[52–55] and neurodegenerative diseases[11,12,56,57]. One recent research focused on 9929 publications related to single-cell sequencing in the WoSCC, spanning 1 January 2010 until 3 December 2022[11]. Their findings showed that current hot topics in single-cell sequencing research include COVID-19, tumor microenvironment, scRNA-seq, and neuroscience[11]. Before our research, the application of single-cell sequencing in the cardiovascular field had not been reported. ScRNA-seq still has limitations in cardiology applications, from laboratory and clinical patient sample extraction to computer visualization analysis algorithms. Tissue samples for scRNA-seq are more often derived from experimental animals (e.g. mice, rats, chickens). The process of obtaining idealized human heart tissue in healthy or diseased states is restricted due to the specificity of the samples and the ethical principles of clinical medical research. However, with the improvement of bioinformatics technologies and databases, it is foreseen that single-cell sequencing will provide a more comprehensive understanding and advanced microscopic definitions of cardiac physiological and pathological processes. Meanwhile, combining single-cell transcriptome technology with machine learning, clinical trials, and cohort studies in hospitals enables the exploration of novel diagnostic and therapeutic approaches to hereditary diseases and rare diseases, advancing the development of precision medicine.

Strengths and limitations

In the era of Big Data, facing massive amounts of data, researchers may need to spend a considerable amount of time and effort to understand the current state of research areas. When the number of literature search results is large, bibliometrics will continue to play a significant role in evaluating and assessing research. Until now, there has been no bibliometric analysis of this topic. We aimed to fill this gap by conducting the first bibliometric analysis, drawing insights from the most influential papers, current hotspots, and potential research directions related to scRNA-seq in CVDs. Inevitably, some limitations exist in our study. First, only articles written in English from the WoSCC database were collected in this study, which means some valuable studies may be missed. Since WoSCC has a high coverage rate for the large majority of studies, it is considered that such an overlook would not significantly influence the general trends. Second, all literature included was published before 2024. Therefore, the currently collected data failed to completely reflect the condition in 2024 in addition to providing a reference. Third, a variety of innovative single-cell sequencing technologies have been developed, including single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq), single-cell proteomics sequencing, and single-cell methylation sequencing. This study only focused on single-cell transcriptome sequencing. Finally, bibliometrics cannot evaluate individual literature. Newer published literature may have a lower citation rate than earlier published literature. These limitations will slightly affect the results of the bibliometric analysis but will not have a significant impact on the study as a whole.

Conclusion

CVDs are the leading cause of death globally. Single-cell transcriptomics facilitates the exploration of the cardiac cellular landscape at an unprecedented level, beyond its descriptive features, and can further our understanding of the mechanisms of disease and guide functional studies. This study comprehensively evaluated global research trends and hotspots in the field of scRNA-seq and CVDs through bibliometric and visual analysis. Future research directions were also predicted. The increased number of publications

makes it highly significant to review the history, understand the major research achievements, and identify research hotspots and future directions in this field. Our study uncovered a rapidly growing interest in this area, demonstrated by the dramatic rise in related publications and RRI from 2019 to 2023. The majority of these publications are from the USA and China, with the Chinese Academy of Medical Sciences standing out as the most active institution. *Circulation Research* is the most active journal, and Qingbo Xu from Zhejiang University in China is the most productive author. Three hotspots in this field were identified (continuous optimization of scRNA-seq technology itself; three cardiovascular diseases (atherosclerosis, myocardial infarction, and heart failure; three cell types (macrophages, fibroblasts, smooth muscle cells). In summary, our study provides a systematic visualization of the research literature on scRNA-seq in CVDs and provides guidance and reference for understanding the current research status of scRNA-seq in CVDs and discovering new research directions.

Ethical approval

No ethical approval and patient consent were required for all analyses based on literature research.

Consent

All the data were anonymized and downloaded from the Web of Science Core Collection (WoSCC) database, and hence, the requirement for informed consent was waived.

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Author contribution

Y.Y., Y.Z., and B.W.: conceived the analysis; Y.Z. and Y.Y.: extracted all the data; Y.Y., J.Y., R.W., and J.W.: undertook and refined the inclusion process; Y.Y., J.Y., R.W., J.W., and J.W.: co-wrote the paper; Y.Y., Q.X., and P.W.: undertook the statistical analyses. All authors contributed to and revised the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

Our research does not involve human subjects.

Guarantor

Bei Wang, MD, PhD; Department of Nursing, Changzheng Hospital, Naval Medical University, Shanghai 200003, China. Address: No. 415 Fengyang Road, Huangpu District, Shanghai 200003, People's Republic of China. Tel.: 86 13917670571, E-mail: wangbeishcz@163.com. Yufeng Zhang, MD, PhD; Department of Cardiothoracic Surgery, Changzheng Hospital, Naval Medical University, Shanghai, China. Address: No. 415 Fengyang Road, Huangpu District, Shanghai 200003, People's Republic of China. Tel.: 86 13371960269, E-mail: zyflwj@smmu.edu.cn.

Data availability statement

The data in this study is not sensitive in nature and is accessible in the public domain. The data is, therefore, available and not of a confidential nature. All the data used in the study have been included in the article/Supplementary Material.

Provenance and peer review

Our paper is not invited.

Presentation

None.

Assistance with the study

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