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REVIEW

Bibliometric Analysis of microRNA: A Comprehensive Evaluation of Its Contribution to Acute Coronary Syndromes

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Objective: This study employs bibliometric analysis to map the evolution, identify emerging trends, and evaluate key research themes in microRNA (miRNA) research related to Acute Coronary Syndromes (ACS). By analyzing global publications, we aim to highlight hotspots and translational directions for advancing miRNA applications in ACS diagnosis and therapy.

Materials and Methods: Articles on miRNA and ACS published between 2007 and 2023 were retrieved from the Web of Science Core Collection. Data from 1,244 eligible studies were analyzed using CiteSpace and VOSviewer to assess contributions by countries, institutions, authors, journals, and keywords. Visualization tools mapped collaboration networks, co-citation patterns, and keyword trends.

Results: China contributed 60% of publications, followed by the United States (12.86%). Harbin Medical University was the most productive institution, while Thum Thomas emerged as the leading researcher. Key research areas included miRNA biomarkers for ACS diagnosis, therapeutic targets for ischemia-reperfusion injury, extracellular vesicles in cardiac repair, and mechanistic studies on apoptosis, autophagy, and inflammation. Emerging frontiers encompassed ventricular remodeling post-AMI, oxidative stress, and clinical translation of miRNA-based strategies.

Conclusion: This study provides the first comprehensive bibliometric overview of miRNA research in ACS, revealing sustained growth and interdisciplinary potential. Findings underscore China's dominance in output and the need for enhanced international collaboration to bridge gaps between basic research and clinical applications. Prioritizing extracellular vesicle-mediated therapies, optimizing miRNA delivery systems, and validating biomarkers in multicenter trials are critical for future advancements.

Keywords: microRNAs, acute coronary syndrome, biomarkers, therapeutic targets, bibliometric analysis, translational medicine

Introduction

Acute coronary syndrome (ACS) is a severe and life-threatening condition in medical practice that encompasses unstable angina pectoris (UAP), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).[1] This disorder is highly significant and urgent, being responsible for a significant portion of overall mortality rates, with an incidence of 200–250 cases per 100,000 person-years in high-income countries.[2–5]Although the exact etiology of ACS remains to be fully elucidated, early detection, early treatment, and early preventive measures are crucial to minimize the detrimental impact of ACS and enhance patient outcomes.[2] Recent research has emphasized the pivotal role of microRNAs in ACS, as they actively participate in the genetic regulation of numerous vital proteins involved in essential signaling pathways.[6–8]

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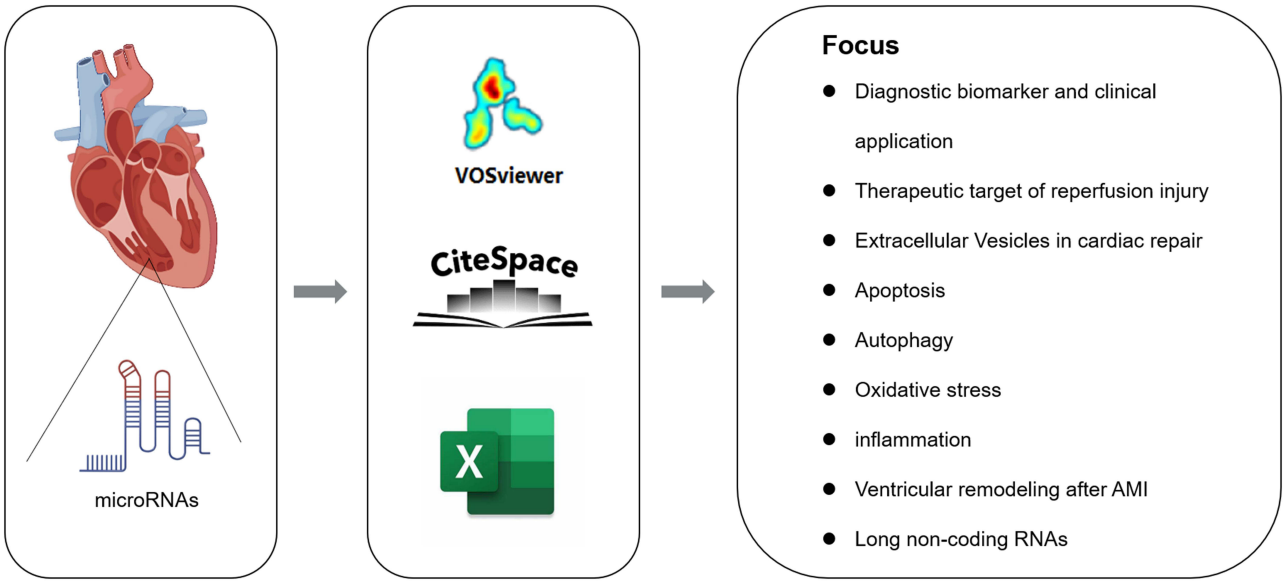
Graphical Abstract



MicroRNAs (miRNAs) are RNA molecules that do not encode proteins. They are approximately 20–24 nucleotides long and are produced by genes within cells. MiRNAs can be found in eukaryotic cells and can bind to messenger RNAs (mRNAs) to hinder subsequent protein synthesis pathways.[9] Research has indicated that approximately 60% of human genes involved in protein production are regulated by miRNAs. These miRNAs play crucial roles in various biological processes, including cell proliferation, differentiation, apoptosis, and the cell cycle.[10] Over the years, researchers have demonstrated that miRNAs are key targets in the regulation of numerous cardiovascular diseases, such as acute coronary syndrome (ACS), heart failure, and atherosclerosis.[11] Although several studies have investigated the role of miRNAs in ACS, there is currently a lack of scientific econometric analysis within this field.[12–14]

Bibliometric analysis is an interdisciplinary subject that involves the use of information visualization methods, such as authors, journals, countries, institutions, references, and keywords, to analyze quantitatively and summarize various indicators in the global literature. This approach allows for a more systematic and intuitive understanding of the knowledge structure, as well as the identification of frontiers or hotspots in specific research fields.[15,16] To conduct bibliometric analysis, researchers often utilize software tools such as VOSviewer and CiteSpace, which enable them to analyze the current status of disciplinary research, identify research hotspots and trends, and determine research directions.[17,18]

Currently, there is no systematic bibliometric study that integrates global research trends in the field of miRNAs in acute coronary syndrome (ACS). This study is the first to reveal research hotspots and potential translational directions through multi-dimensional visual analysis, thereby offering priority references for clinical researchers.

Methods

Data Sources and Search Strategies

To conduct our research, we utilized the Web of Science core collection (WOSCC) database, which encompasses a vast amount of data up until December 31, 2023. Supplementary Data S1 provides a comprehensive overview of our search strategy, delving into the specifics. Our investigation encompassed a timeframe from January 1, 2007, to December 31, 2023. On the aforementioned date, we proceeded to download all available publications, resulting in a total of 3577 records. To ensure the validity of our findings, we meticulously eliminated any documents that were deemed irrelevant,

including meeting abstracts, letters, editorial materials, proceedings papers, corrections, retracted publications, retractions, book chapters, and expressions of concern. After this rigorous process, we included 1244 articles, which were subsequently exported and saved in plain text format. For a visual representation of our selection process, please refer to Figure 1, which displays a flow chart illustrating each step.

The data from the search results were obtained in the "Plain text file" format, including complete records and references from the WOSCC database. To conduct a thorough analysis, the data were carefully reviewed and then imported into Microsoft Excel 2019, VOSviewer 1.6.19, and CiteSpace 5.7.R5. These software tools were selected to further examine the data. Specific data, including the title of the research, the year of publication, the author's name, the country in which the research was conducted, the institution that conducted the research, the number of citations the research received, the journal in which the research was published, the keywords associated with the research, and the references cited within the research, were extracted for analysis. This comprehensive approach ensured that all relevant information was considered for the analysis.

Bibliometric Analysis

Microsoft Excel was used to analyze the trend of annual publications, whereas VOS viewer and Citespace were used to construct visualization maps. For bibliometric analysis, VOS viewer was used to create visual maps of countries, institutions, authors, keywords co-occurrence, co-cited authors, co-cited journals and reference networks for general information in this field. Additionally, a keyword density visualization map via VOS viewer and keyword clustering, keyword timeline view, keyword burst detection, reference clustering and reference burst

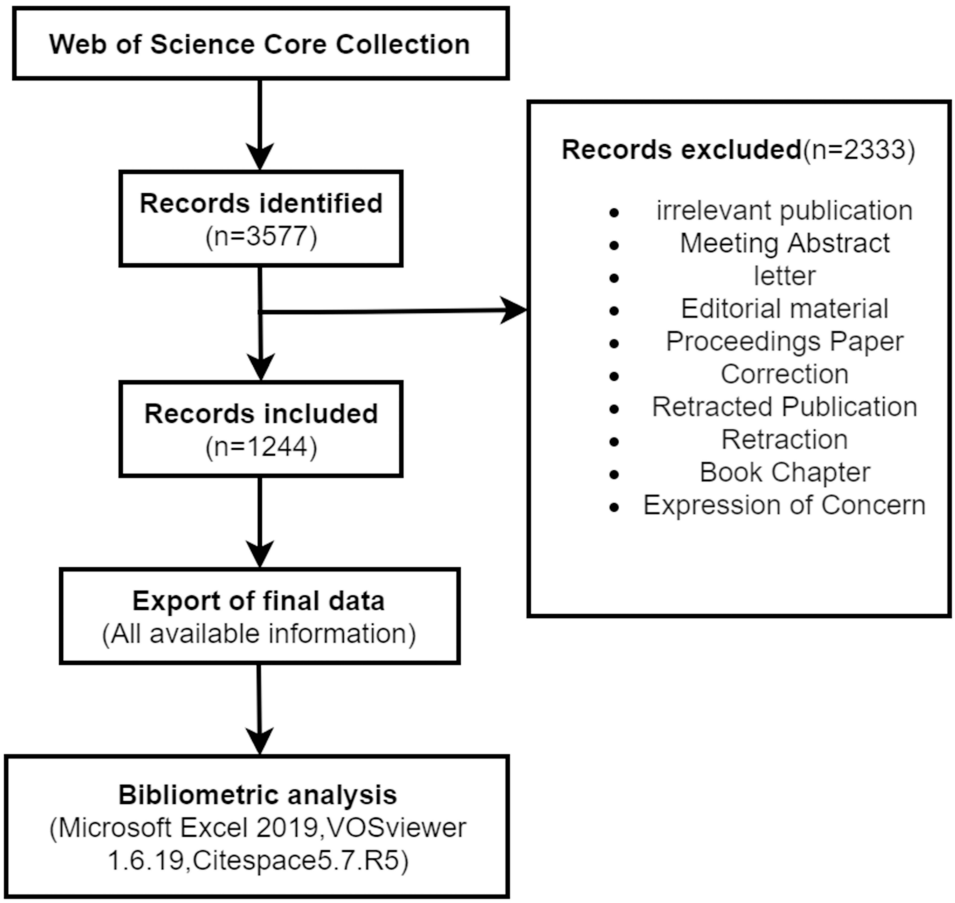


Figure 1 Flowchart of literature selection.

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detection via CiteSpace were constructed to understand the research hotspots and development trends in the field of miRNAs in ACS.

Results

Annual Publications

We ultimately included 1244 articles in this study. As depicted in Figure 2, since 2007, publications on this topic have been published, and the number of published articles has been increasing steadily every year, indicating that miRNAs in ACS have gradually received attention. Of these, 85.20% (1,060) were original articles.

Co-Authorship: Countries, Institutions, and Authors

Countries

The literature in this field was analyzed from 57 countries/regions, with over 60% of the articles being from China. The United States accounted for 12.86% of the articles, whereas other countries made up the remaining quarter of publications. The network analysis depicted in Figure 3A highlights extensive collaborations among various countries in studies related to miRNAs in ACS. The United States has emerged as the country with the most collaborations, particularly with China. Additionally, Table 1 reveals that the countries/regions closely cooperating with China were primarily the USA, Japan, and Germany. The distribution of published articles by country is further visualized in Figure 3B via VOS viewer.

Institutions

In this field, a total of 1370 institutions have contributed to the published literature. Notably, the leading 20 institutions, hailing from China, Singapore, and Germany, have been highly prolific. An analysis of the collaboration and co-authorship patterns depicted in Figure 3C clearly reveals that Harbin Medical University has the highest number of published papers. On the other hand, Shanghai Jiao Tong University has emerged as a prominent collaborator with authors from various institutions, especially within Shanghai, and has garnered the highest citation count.

Authors

A total of 6999 authors were involved in 1244 research studies. As depicted in Table 2, three authors clearly contributed to the publication of more than 10 articles. Among the top 10 prolific authors, two are from Germany, and eight are from China. The diverse color clustering in the network diagram signifies the collaborative associations among these authors. The interconnecting lines between the nodes represent the cooperative relationships established between them. The

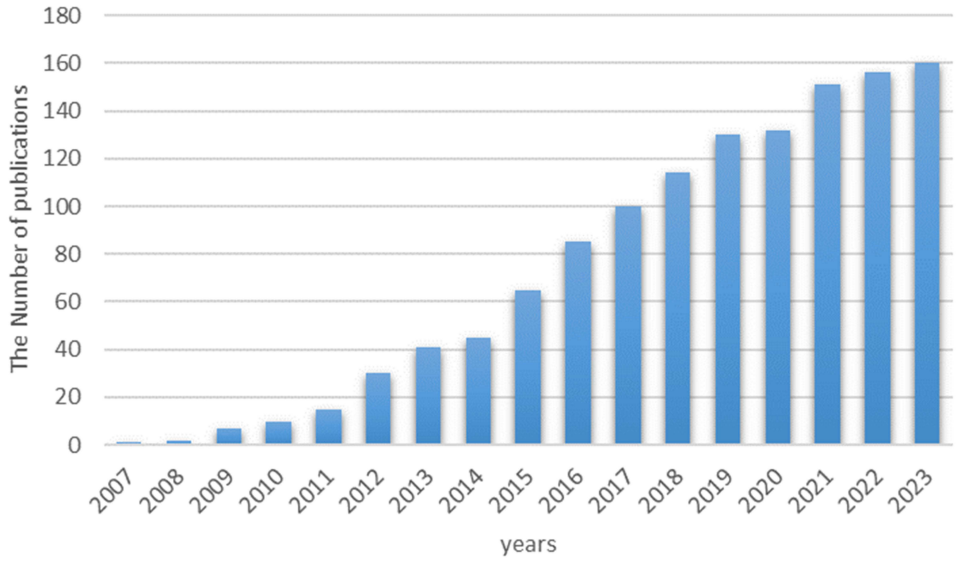

Figure 2 Trends in the growth of publications.

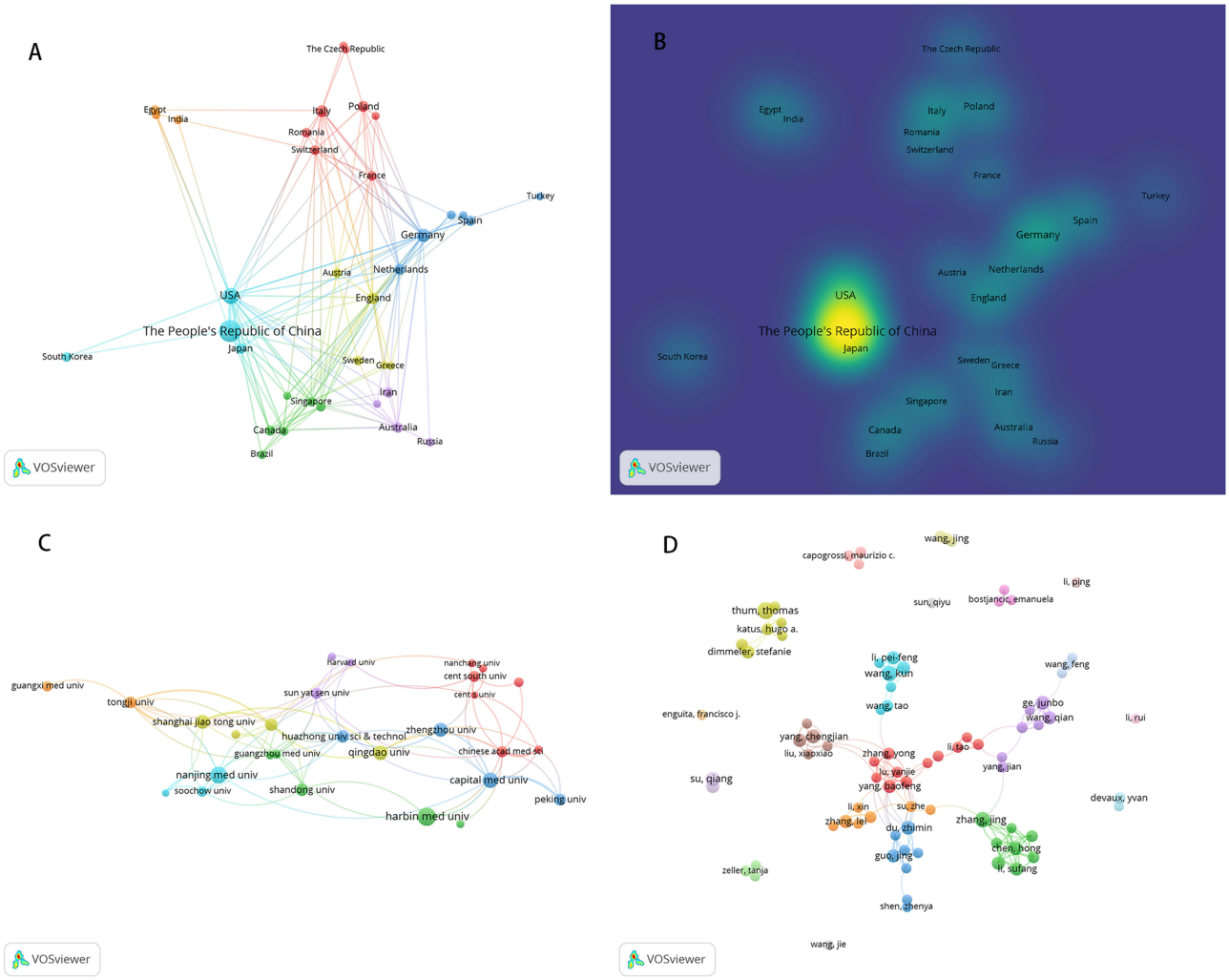

Figure 3 Analysis of co-authorship (**A**) Countries co-authorship map. (**B**) Countries density visualization. The greater the number of items near a node is, the higher the weight of adjacent items, and the closer the color of this point is too yellow. (**C**) Institutions co-authorship map. (**D**) Authors co-authorship map. In networks (**A, C** and **D**) the larger the node is, the greater the contribution of the country, institution or authors to that field. The link strength between two nodes represents their collaboration, and the wider the link is, the greater the degree of cooperation between them.

graphical representation in Figure 3D illustrates the presence of distinct research groups, characterized by various colors, within this specific domain of study.

Co-Citation: Journals, Authors and References

Journals

A comprehensive analysis of scientific journals revealed prominent journals focused on miRNAs in ACS. An examination of a sample of 3318 co-cited journals revealed that ten journals were cited more than 1,000 times, as shown in Table 3. The journal with the highest number of citations among the top 10 co-cited journals was Circulation Research (3039 citations), followed by Circulation (3039 citations), PLOS One (1648 citations), European Heart Journal (1477 citations), and PNAS (1413 citations). To visualize the journal network in miRNA ACS publications via VOS viewer, a minimum publication requirement of at least 2 publications per journal was set. Consequently, a total of 394 journals were included in the visualization, with the top 191 journals meeting the threshold (Figure 4).

Authors

References in the 1244 articles were from a total of 22140 authors. The top 10 authors with the highest total number of citations of papers published between 2007 and 2023 are shown in Table 3. Moreover, the top 10 productive authors were

Table 1 Top 10 Productive Countries in the Field of microRNAs in ACS

Rank	Country	Count	TLS*
1	China	779	79
2	USA	160	120
3	Germany	73	76
4	Italy	43	31
5	England	42	66
6	Netherlands	30	35
7	Poland	26	13
8	Australia	21	24
9	Spain	21	8
10	Canada	19	25

Notes: *Total link strength (TLS) refers to the total number of co-occurrences of a country and other countries.

Table 2 Top 10 Productive Authors in the Field of microRNAs in ACS

Author	Count	TLS*
Thum, Thomas	14	6
Wang, Kun	11	34
Zhang, Jing	11	18
Su, Qiang	10	5
Chen, Hong	9	45
Du, Zhi-min	9	20
Ge, Jun-bo	9	19
Yang, Cheng-jian	9	18
Stefanie Dimmeler	8	44
Guo, Jing	8	44

Notes: *Total link strength (TLS) refers to the total number of co-occurrences of country and other countries.

mostly not consistent with the authors of the most highly cited articles. Among these top 10 researchers, only Thum, Thomas's and Wang, Kun's articles were 2 of the top 10 most highly cited articles.

References

According to the total citation map, a thorough analysis reveals that a considerable number of articles, specifically 1,244, have made reference to a total of 32,382 sources. Among all these articles, those with the highest number of citations range from 115–248. Furthermore, delving into the references exhibiting the most pronounced citation bursts and conducting reference clustering analysis can assist researchers in identifying prevailing themes that occur unusually frequently or that experience sudden popularity spikes within a specific field. To redirect their searches effectively, researchers should closely scrutinize the references that exhibit the most overwhelming citation bursts and undergo reference clustering analysis. As demonstrated in Figure 5, CiteSpace has successfully identified the top 25 documents that have witnessed tremendous citation explosions. Notably, the earliest occurrence of reference with such citation bursts can be traced back to 2007. The title "MicroRNA-133 controls cardiac hypertrophy" was authored by Alessandra Carè et al. The article was published in Nature Medicine.[19]

The analysis of co-cited references via cluster methodology can provide valuable insights into the prevalent research themes found in related references. Over the course of the past 15 years, a total of 15 prominent subjects have emerged, as depicted in Figure 6. These subjects have been concentrated within this particular area of study. The resulting cluster

Table 3 Top 10 Journals and Authors with the Highest Number of Citations

Rank	Journals	IF*	JCR*	Citations*	Authors	Citations*
1	Circulation Research	16.5	Q1	3039	Eva van Rooij	547
2	Circulation	35.5	Q1	2638	David P Bartel	290
3	PLOS One	2.9	Q2	1648	Cheng, Yun-hui	282
4	European heart journal	37.6	Q1	1477	Thum, Thomas	269
5	Proceedings of the National Academy of Sciences of the United States of America (PNAS)	9.4	Q1	1413	D'Alessandra, Yuri	248
6	Nature	50.5	Q1	1391	Wang, Guo-Kun	248
7	Cardiovascular Research	10.2	Q1	1372	Devaux, Yvan	246
8	Cell	45.5	Q1	1125	Wang, Kun	240
9	Journal of the American College of Cardiology (JACC)	21.7	Q1	1081	Thygesen, Kristian	178
10	Journal of Molecular and Cellular Cardiology	5.0	Q2	1057	Zhang, Yong	174

Notes: *The citations represent citations.
Abbreviations: IF, Impact Factor (2024); JCR, Journal Citation Reports.

map exhibits 15 distinct clusters, each characterized by a unique research theme and corresponding average appearance timeframe. Notably, clusters #0, #5, #6, #7, and #14 represent the most recent areas of focus, as indicated by their respective colors on the map. The silhouette values associated with these clusters range from 0.833 (cluster #3) to 1 (cluster #14), suggesting a high level of consistency among clustered members. Notably, cluster #14 consists of relatively few articles, signifying the nascent stage of research in this domain. Moreover, clusters #13 (termed "Heart

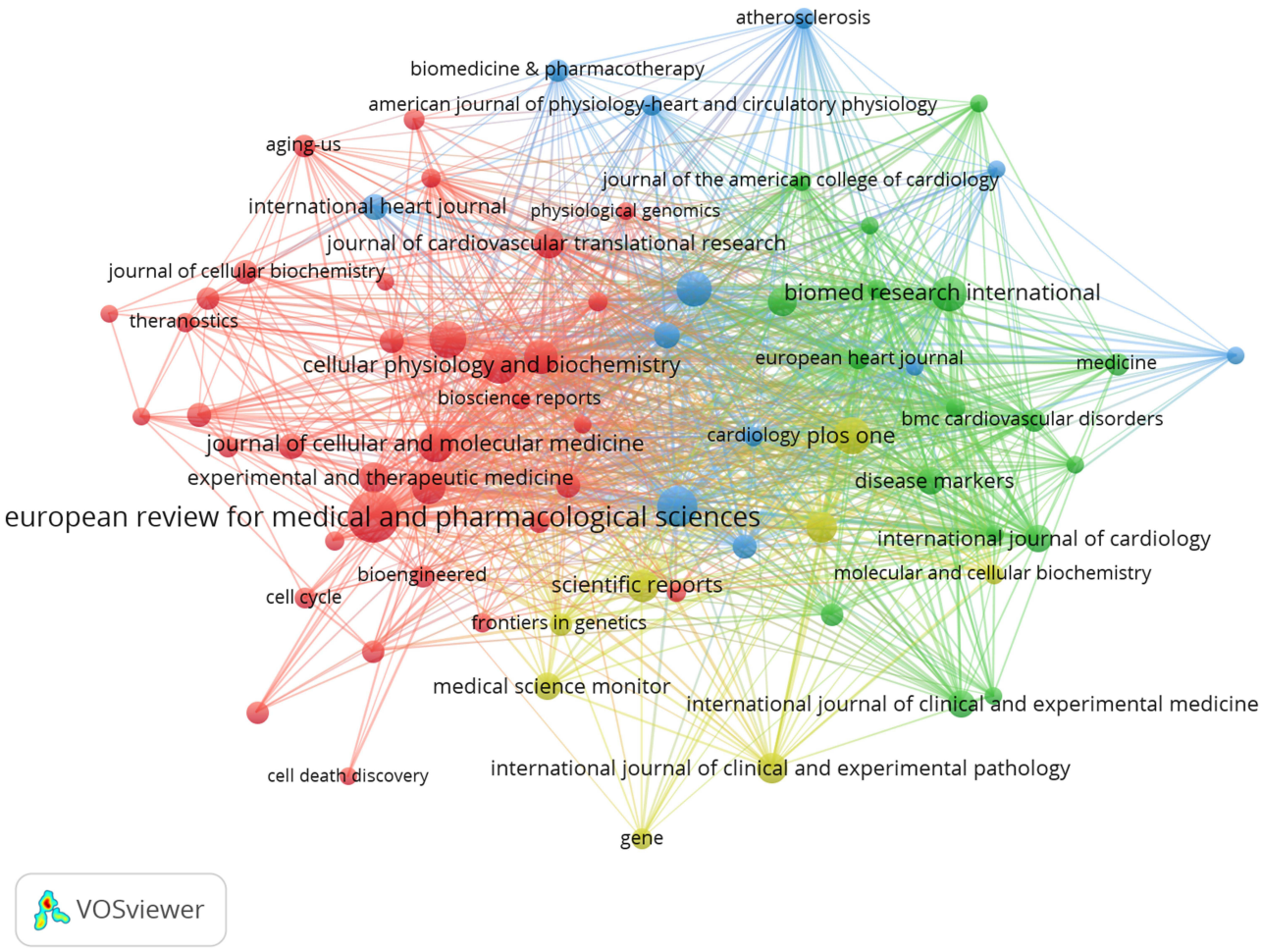

Figure 4 Visualization network map of journal-published articles.

https://doi.org/10.2147/JMDH.S525150

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2007 - 2023
Care A, 2007, NAT MED, V13, P613, DOI 10.1038/nm1582, DOI	2007	15.45	2007	2012	
van Rooij E, 2006, P NATL ACAD SCI USA, V103, P18255, DOI 10.1073/pnas.0608791103, DOI	2006	14.09	2007	2012	
Yang BF, 2007, NAT MED, V13, P486, DOI 10.1038/nm1569, DOI	2007	14	2007	2012	
Thum T, 2007, CIRCULATION, V116, P258, DOI 10.1161/CIRCULATIONAHA.107.687947, DOI	2007	13.12	2007	2012	
van Rooij E, 2008, P NATL ACAD SCI USA, V105, P13027, DOI 10.1073/pnas.0805038105, DOI	2008	22.04	2009	2014	
Thum T, 2008, NATURE, V456, P980, DOI 10.1038/nature07511, DOI	2008	16.29	2009	2014	
Ai J, 2010, BIOCHEM BIOPH RES CO, V391, P73, DOI 10.1016/j.bbrc.2009.11.005, DOI	2010	15.93	2010	2016	
Bonauer A, 2009, SCIENCE, V324, P1710, DOI 10.1126/science.1174381, DOI	2009	15.23	2009	2014	
van Rooij E, 2007, SCIENCE, V316, P575, DOI 10.1126/science.1139089, DOI	2007	14.68	2009	2012	
Mitchell PS, 2008, P NATL ACAD SCI USA, V105, P10513, DOI 10.1073/pnas.0804549105, DOI	2008	13.48	2009	2014	
Dong SM, 2009, J BIOL CHEM, V284, P29514, DOI 10.1074/jbc.M109.027896, DOI	2009	12.99	2009	2014	
Wang GK, 2010, EUR HEART J, V31, P659, DOI 10.1093/eurheartj/ehq013, DOI	2010	26.06	2011	2016	
DAlessandra Y, 2010, EUR HEART J, V31, P2765, DOI 10.1093/eurheartj/ehq167, DOI	2010	24.53	2011	2016	
Fichtlscherer S, 2010, CIRC RES, V107, P677, DOI 10.1161/CIRCRESAHA.109.215566, DOI	2010	19.69	2011	2016	
Corsten MF, 2010, CIRC-CARDIOVASC GENE, V3, P499, DOI 10.1161/CIRCGENETICS.110.957415, DOI	2010	18.64	2011	2016	
Widera C, 2011, J MOL CELL CARDIOL, V51, P872, DOI 10.1016/j.yjmcc.2011.07.011, DOI	2011	17.16	2011	2016	
Kuwabara Y, 2011, CIRC-CARDIOVASC GENE, V4, P446, DOI 10.1161/CIRCGENETICS.110.958975, DOI	2011	14.79	2011	2016	
Cheng YH, 2010, CLIN SCI, V119, P87, DOI 10.1042/CS20090645, DOI	2010	13.38	2011	2016	
Tijsen AJ, 2010, CIRC RES, V106, P1035, DOI 10.1161/CIRCRESAHA.110.218297, DOI	2010	13.08	2011	2016	
Zampetaki A, 2012, J AM COLL CARDIOL, V60, P290, DOI 10.1016/j.jacc.2012.03.056, DOI	2012	13.39	2013	2018	
Devaux Y, 2015, J INTERN MED, V277, P260, DOI 10.1111/joim.12183, DOI	2015	13.24	2015	2020	
Boon RA, 2015, NAT REV CARDIOL, V12, P135, DOI 10.1038/nrcardio.2014.207, DOI	2015	17.03	2017	2020	
Sun T, 2017, INT J MOL SCI, V18, P0	2017	15.16	2017	2022	
Navickas R, 2016, CARDIOVASC RES, V111, P322, DOI 10.1093/cvr/cvw174, DOI	2016	12.64	2017	2020	
Reed GW, 2017, LANCET, V389, P197, DOI 10.1016/S0140-6736(16)30677-8, DOI	2017	16.23	2019	2023	

Figure 5 Top 25 references with the strongest citation bursts. The blue bar indicates that the reference has been published; the red bar indicates that the citation has exploded.

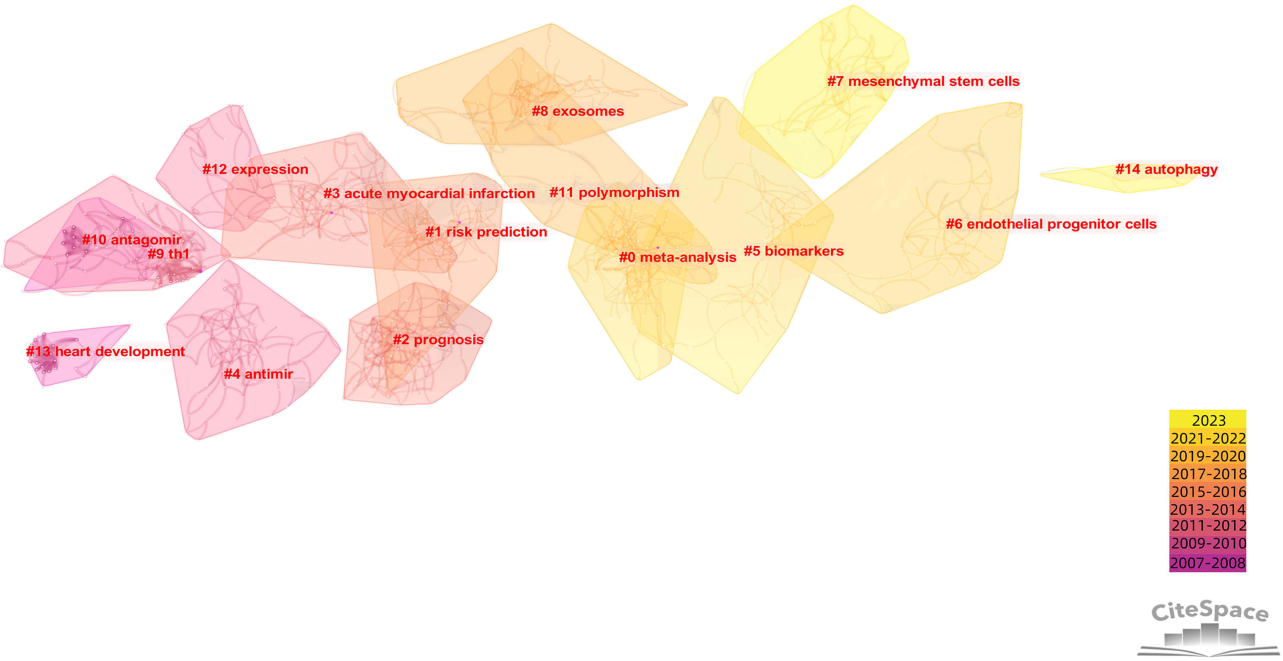

Figure 6 Analysis of co-citation references in the field of miRNAs in ACS. The network map of co-citation clusters. Fifteen clusters with different research topics and average times to appear were formed, reflected in different colors on the map. The redder the color is closer to 2007, and the more yellow the color is closer to 2023.

development"), #10 (referred to as "Antagomir"), and #9 (identified as "Th1") present the earliest average publication years among their constituent studies (2005, 2006, and 2007, respectively), thus indicating their status as early research subjects within this field.

Keywords Co-Occurrence and Burst Detection

Keywords Co-Occurrence

We created a keyword density visualization map (Figure 7). The keywords with high occurrence frequency are Acute Coronary Syndrome (889), microRNAs (595), expression (370), biomarker (304), apoptosis (276), and circulating microRNAs (234).

Keywords Timeline Viewer Analysis of Clustering

Using keyword clustering as our basis, we devised a visualization known as the keyword timeline (Figure 8) to enhance the extraction of research themes within the domain in a more efficient and comprehensible manner. The timeline view effectively shows the prominent keywords within each cluster throughout time. Assessing the scale of the cluster, indicated by a numerical value, provides insight into the extent of keyword involvement within it. Consequently, eleven out of the fifteen clusters persist. Notably, cluster #0 (clopidogrel) was the most substantial cluster, followed by cluster #2 (myocardial fibrosis), cluster #3 (angiogenesis), cluster #4 (biomarker), and cluster #5 (mechanism).

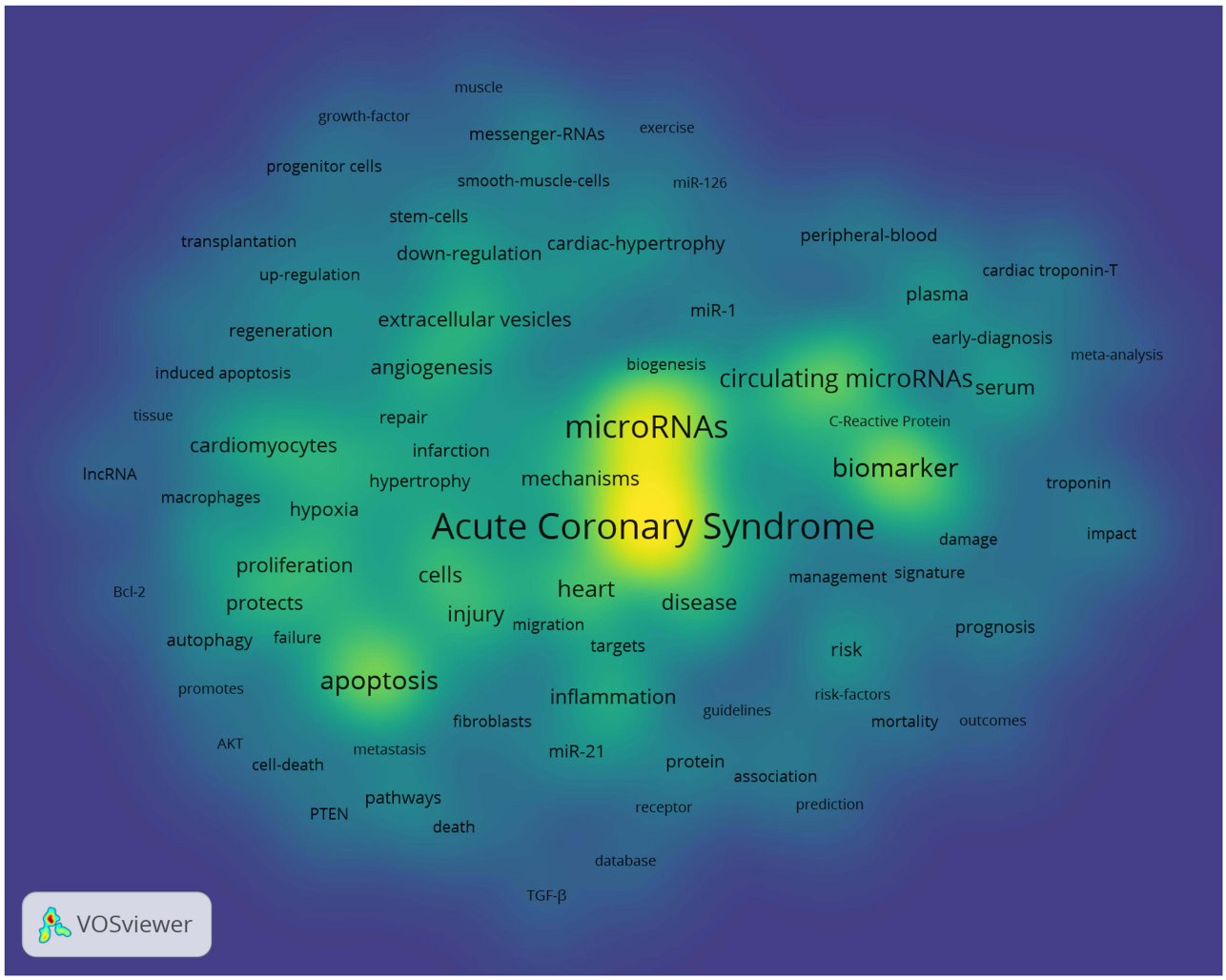

Figure 7 Keywords density visualization. The greater the number of items near a node is, the higher the weight of adjacent items, and the closer the color of this point is too yellow.

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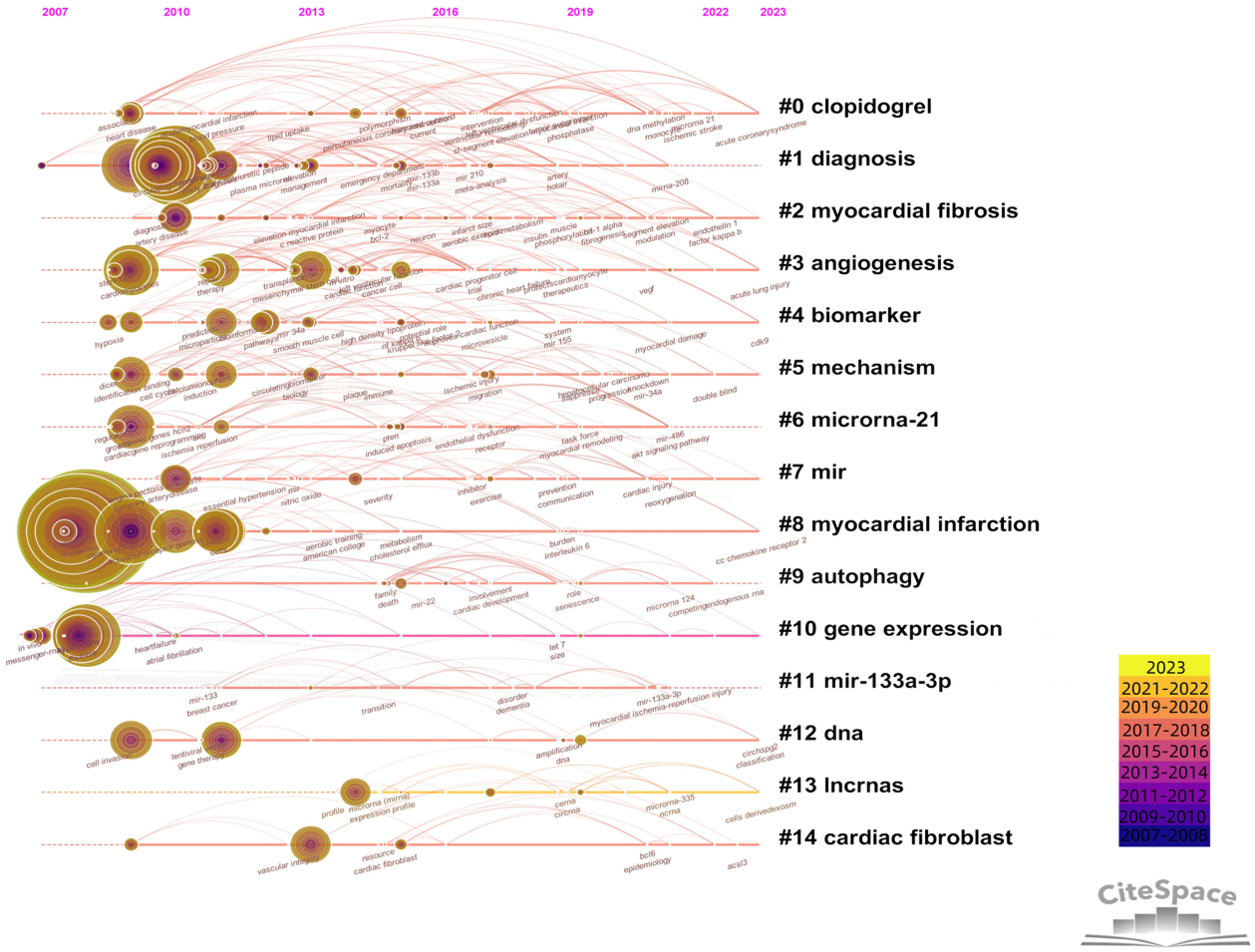

Figure 8 Timeline distribution of keyword cluster analysis. Each horizontal line represents a cluster; the time is at the top, and keywords are located at their first co-occurrence time in the cluster. The cluster labels were extracted from the title and abstract information via LLR.
Abbreviation: LLR, log-likelihood ratio.

Keywords Burst Detection

Keyword bursts refer to those keywords that have been frequently cited over a specific timeframe. As illustrated in Figure 9, the initial keyword displaying citation bursts was muscle-specific microRNA, which presented the highest burst strength (9.76). Moreover, within this selection of the top 25 keywords, six experienced bursts in the preceding three years that persisted until either 2022 or 2023. These keywords encompass oxidative stress, protection, extracellular vesicles, cardiac repair, improvement and reperfusion injury.

Discussion

General Trends

In the era of information explosion, grasping the key points of a specific field, keeping up with the latest information, and identifying research trends and popular areas can be quite challenging. Scholars often turn to knowledge management and bibliographic analysis as common approaches to address these concerns.[20–22] The objective of this study was to employ innovative techniques, specifically bibliometric tools such as CiteSpace and VOSviewer, to examine and visualize the knowledge structure within the realm of miRNAs and Acute Coronary Syndrome. By searching the WOSCC database as of December 31, 2023, we discovered that 1244 studies on this subject had been published by 6999 authors affiliated with 1370 institutions across 57 countries/regions. The overall trend in the number of publications in this field has steadily increased, particularly since 2015, with significant and rapid growth representing 89.4% of the

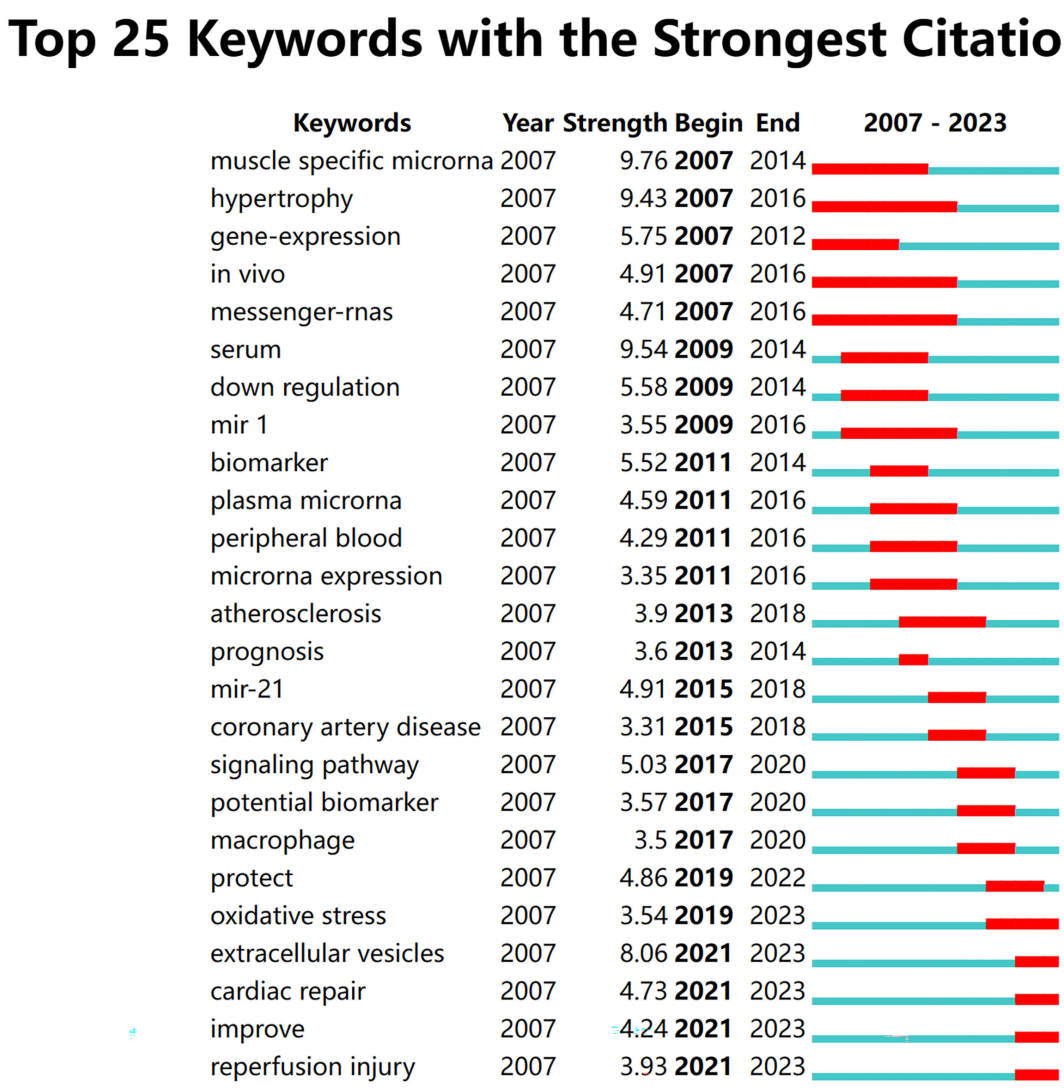

Figure 9 Top 25 keywords with the strongest citation bursts. The red bar represents the time period when the keyword bursts.

included publications. The annual publication count reflects the developmental trajectory of research in this field, with over 100 articles published every year from 2017–2023. This trend signifies sustained interest among academics and suggests a promising future for the field.

In the realm of national and institutional studies, China possesses an undeniable advantage in terms of the quantity of published articles. On the other hand, the United States presents greater total link strength (120), with China (79) and Germany (76) following suit. These observations indicate that China and the USA stand as the predominant nations in miRNA and ACS research. In terms of international collaboration, the United States takes the lead, leaving China lacking in comparison. Among the top 20 institutions in terms of publication count, the overwhelming majority, namely, 18, hail from China. This occurrence exemplifies the flourishing development of this particular field within China. Overall, most collaborative institutions confine their efforts to internal connections, whereas interborder cooperation and result sharing remain scarce. As a result, the long-term progress of this research field has been hindered. Consequently, countries are highly encouraged to intensify efforts to eliminate academic barriers and foster collaboration, sharing, and communication among their respective research institutions.

The hottest publishing centers in terms of co-cited journals for the study of miRNAs in ACS include Circulation Research, Circulation, PLOS One, and the European Heart Journal. These journals have strong theoretical support and

are closely related to other journals in the field. The majority of research in this area is currently focused on molecular biology and physiology, with a focus on basic medical research. To promote the practical application of related disciplines, it is important to actively convert research outcomes into clinical practice.

Highlighting prominent researchers, such as coauthors or co-cited authors in a specific field, can offer additional research pathways and academic guidance for scholars in that domain.[23] Thomas from Hannover Medical School and Wang Kun from Qingdao University claimed the top two positions in terms of publications as key authors in the field. These authors also ranked fourth and eighth, respectively, among co-citation authors, highlighting their significant contributions to miRNAs in ACS. Professor Thum Thomas's team suggested that miRNAs serve as vital regulators of gene expression and play a fundamental role in cardiovascular function, both in health and disease. Maintaining tight control over miRNA expression is critical for the preservation of tissue homeostasis.[24] He and his team are dedicated to the study of miRNAs and the diagnosis, prognosis, treatment and pathogenesis of cardiovascular diseases, in which acute coronary syndrome accounts for a certain proportion, particularly the exploration of miRNAs as novel biomarkers for Acute Coronary Syndrome and its and their involvement in pathological mechanisms and prognosis.[25–28] Professor Wang, Kun, as an up-and-coming younger, compared with Thum, Thomas, investigated the role of the miR-34 family, miR-188-3p, miR-421 and miR-762 in the pathological mechanisms of ACS and sought translation from experiments to the clinic.[29–33]

Research Hotspots and Trend Analysis

Keyword analysis is a valuable tool for understanding the core themes and frontiers of a research field. By examining clusters and timeline views, researchers can gain insight into hot topics and emerging trends within the field. Burst terms serve as indicators of frontier topics.[34] Furthermore, analyzing clusters in the reference co-citation network can provide a deeper understanding of the knowledge base and evolution of research fronts.[35] On the basis of these analyses, six hotspots and frontiers can be summarized in the following prospects.

Diagnostic Biomarker and Clinical Application

Combined with keyword frequency, co-occurrence, bursts, and clusters of co-cited references, we found that one of the current hotspots in this field is the exploration of miRNAs as biomarkers for Acute Coronary Syndrome. Currently, a variety of scientists have shown that miRNAs play key roles in the development and progression of ACS, such as evaluating the severity of coronary artery lesions (miR-221, miR-222, miR-143 and miR-145),[36,37] predicting the risk of ACS (miR-4286),[38] modeling ACS risk (miR-142-3p),[12] early diagnosis of MI (miR-22 and miR-499),[39] ischemic risk stratification after AMI (miR-126-3p and miR-223-3p),[40] and predicting AMI and UA (miR-21 and miR-126).[41] Circulating miRNAs have proven to be reliable methods for diagnosing diseases. These small RNA molecules remain stable in plasma or serum, making them easily detectable Quantitative reverse transcription–polymerase chain reaction (qRT–PCR) is a common technique used to accurately measure the expression of these miRNAs. Therefore, the use of this method to identify early changes in the levels of circulating miRNAs could be highly beneficial in the diagnosis of ACS at the onset of symptoms. This early detection could lead to quicker and more effective treatment strategies for ACS.[42] In addition, compared with troponin, which is an emerging biomarker, whether microRNAs are more specific for the diagnosis of ACS is currently a hot topic and remains to be further studied.[43]

The primary basis for diagnosing AMI involves clinical symptoms, abnormalities in ECG, and specific biomarkers such as cTnT and cTnI. Nonetheless, delayed troponin release hinders timely detection of myocardial infarction. To facilitate early diagnosis of AMI, exploration of novel biomarkers is imperative. Numerous clinical trials indicate the heightened expression of specific miRNAs in the plasma of AMI patients, enabling more sensitive and prompt detection. Consequently, miRNAs have potential as early diagnostic markers.[44–47] Therefore, the translation of miRNAs from clinical trials to clinical applications is currently a priority. Research on the potential of miRNAs as diagnostic markers for UA is limited, and more similar studies are needed in the future. Although the potential of miRNAs as biomarkers has garnered widespread attention, their specificity and the need for standardized detection methods remain subjects of debate (eg, there is a lack of sufficient comparative studies with troponin), highlighting the necessity for further multicenter clinical validation in the future.

Therapeutic Target of Reperfusion Injury

Decreased blood flow to the coronary arteries leads to cardiomyocyte death, a defining characteristic of acute myocardial infarction (MI). Early and rapid reperfusion of the myocardium is the most efficient treatment strategy for MI. However, restoring blood flow to the ischemic myocardium can result in additional harm, referred to as ischemia-reperfusion (IR) injury. Novel therapeutic strategies are critical for limiting myocardial IR injury and improving patient outcomes following reperfusion intervention.[48] As depicted in the keyword frequency and burst maps, reperfusion injury during ACS has also attracted much attention in the field of miRNAs. The latest research published in Circulation illustrated that microRNA-210, which targets glycerol-3-phosphate dehydrogenase, controlled mitochondrial bioenergetics and ROS flux and improved cardiac function in a murine model of myocardial infarction in the context of IR injury.[49] In a myocardial ischemia–reperfusion (IR) model, researchers reported that reducing the expression of miR-15b-5p had a positive effect on key factors related to heart injury.[50] Additionally, Jayawardena E et al examined the impact of miR-1 and miR-21 on the regulation of myocardial apoptosis in ischemia–reperfusion injury.[48]

Extracellular Vesicles in Cardiac Repair

Cardiac repair following myocardial infarction has long been a primary focus of cardiovascular research. Studies conducted on MSCs in preclinical and clinical settings have shown substantial potential for the restoration and rejuvenation of cardiac tissues.[51] Nevertheless, the utilization of stem cell transplantation for cardiac repair faces numerous challenges, including inadequate cell retention, a limited survival rate, and incomplete differentiation subsequent to transplantation.[52] In recent years, researchers have shifted their attention from stem cell transplantation, particularly mesenchymal stem cell transplantation, to EVs originating from mesenchymal cells. Mesenchymal stem cell-derived EVs possess therapeutic factors from MSCs, including miRNAs, and overcome the limitations of stem cell transplantation.[53,54] These vesicles exhibit great potential for repairing damaged heart tissue, making them a popular subject of research in the field of myocardial infarction treatment.

Furthermore, the intricate network of intersecting inflammatory pathways and immune cell types orchestrates the pathology of myocardial injury and subsequent repair. Immune-modulating extracellular vesicles and miRNAs hold potential for enhancing repair following cardiac injury, which has aroused great interest among scientists in recent years.[55] For example, Li, L et al found that M2 macrophage-derived EVs inhibited CCR2(+) macrophage numbers, reduced monocyte-derived CCR2(+) macrophage recruitment to infarct sites, induced M1-to-M2 macrophage switching and promoted neovascularization.[56] Analysis of M2 (EV) microRNA content revealed abundant miR-181b-5p, which regulated macrophage glucose uptake and glycolysis and mitigated mitochondrial reactive oxygen species generation. Moreover, multiple miRNAs, including miR-155, miR-146a, miR-208, and miR-29b, are under investigation for promoting heart repair through immune modulation, with several in current clinical trials.[57] However, not all miRNAs in EVs are beneficial. A study conducted by Park et al demonstrated that the therapeutic efficacy of EVs in vitro and cardiac ischemia–reperfusion in a rat model in vivo is augmented by the suppression of miR-192-5p and miR-432-5p within cardiac c-kit+ cell (CPC)-derived extracellular vesicles.[58]

Cardiovascular scientists have long aimed to overcome the limited regenerative capacity of the adult mammalian heart to repair myocardial infarction-induced damage.[59] Thus, targeting extracellular vesicles and miRNAs for cardiac repair is worthy of attention.

Mechanisms: Apoptosis, Autophagy, Oxidative Stress, Inflammation

In recent years, many new studies have focused on the mechanisms of miRNAs in ACS. First, apoptosis and autophagy generally cooccur and are closely related to each other in signaling pathways. Autophagy helps safeguard cells, whereas apoptosis functions to eliminate aging, impaired, or mutated cells, thereby safeguarding overall bodily well-being. However, proper regulation of miRNAs is necessary for cardio protection in regard to autophagy. For example, by inhibiting the Akt/mTOR pathway, miR-223 exerts a protective effect on myocardial tissue against both ischemic damage and hypoxia-induced damage to myocardial cells. This protective role involves the inhibition of apoptosis and autophagy.[60] The inhibition of miR-92a improved the function of endothelial cells and mitigated damage caused by myocardial infarction (MI). This is achieved through the enhancement of autophagy in endothelial cells, which is

mediated by ATG4a, and the regulation of energy metabolism in cardiac cells via CD36 and Abca8b.[61] Second, oxidative stress is one of the main causes of myocardial infarction. Hypoxia-induced oxidative stress and the inflammatory response are significantly inhibited by miR-126-5p knockdown.[62] miR-124-3p can protect and repair myocardial tissues through targeting PTEN.[63] Finally, inflammation has both positive and negative effects. In the initial period after an injury, proinflammatory cytokines are synthesized and released in the ischemic zone, leading to a significant production of inflammatory factors that can impact the survival of cardiomyocytes in the infarct area. To mitigate the negative effects of inflammation after MI, certain miRNAs can negatively regulate the expression of inflammation-related factors, such as NF-κB, MAPK, IL-22, MAP3K2, and CHI3L1, control inflammation, reduce the apoptosis of myocytes, and alleviate cardiac remodeling.[64–67] Hence, exploring the mechanisms underlying the regulation of the inflammatory response by these miRNAs is highly important.

Recent keyword bursts (such as "oxidative stress" and "extracellular vesicles") indicate a transition from basic research to translational medicine, suggesting that future research should focus on optimizing miRNA delivery systems and designing clinical trials.

Ventricular Remodeling after AMI

Ventricular remodeling is a crucial pathological mechanism that underlies the progression of heart failure following AMI. In patients after AMI, the incidence of left ventricular systolic dysfunction is estimated to be approximately 30%-60%.[68] Moreover, studies have shown that miRNAs may contribute to the attenuation of myocardial fibrosis and ventricular hypertrophy, which are important pathological steps in ventricular remodeling.[69–71] In the future, more prospective clinical studies are needed to provide additional evidence.

Long Non-Coding RNAs

Long non-coding RNAs (LncRNAs), known as long noncoding RNAs, have garnered significant attention in the field of noncoding RNA research in recent years. A newly discovered triple network involving lncRNAs, miRNAs, and mRNAs highlights the importance of the lncRNA XIST as a potential biomarker for acute myocardial infarction.[72] In addition, miRNAs are also molecular targets of long noncoding RNAs. Studies have shown that the lncRNA MALAT1 plays a role in hypoxia-induced cardiomyocyte injury, cell autophagy after MI and myocardial IR by targeting miR-5b-5p, miR-217 and miR-30a/beclin-1.[73–75] Another study indicated that MALAT1 could function as an effective biomarker of the no-reflow phenomenon in STEMI patients receiving primary percutaneous coronary intervention.[76]

Limitations

This study has limitations that should be acknowledged. The data sources of this study are limited to WOSCC and English literature, which may overlook significant findings in other languages or non-indexed databases. Future research could incorporate multiple platforms such as Scopus and PubMed to enhance comprehensiveness. To analyze co-authorship, we made an effort to replace the authors' full names. However, when co-referencing is analyzed, bibliometric software faces difficulty in identifying authors with the same name because the abbreviations of certain names in the references are similar. This may have led to a loss of accuracy in the co-reference analysis.

Conclusions

In our study, we found that research on miRNAs in ACS has shown a variable growth tendency over the previous fifteen years. Our purpose was to review previous studies in this field, understand the context of miRNA research, and recommend new directions for future studies. The hotspots identified in this study, such as extracellular vesicle-mediated cardiac repair, may facilitate the development of novel therapeutic strategies. Additionally, the research bottlenecks in diagnostic markers underscore the necessity for strengthened interdisciplinary collaboration to accelerate translation.

Abbreviations

ACS, Acute coronary syndrome; UAP, unstable angina pectoris; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; miRNAs, microRNAs; mRNAs, messenger RNAs; WOSCC, the Web of Science core collection.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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