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REVIEW ARTICLE

EXPLORING THE ROLE OF LONG NON-CODING RNAs AS BIOMARKERS IN CARDIOVASCULAR DISEASE: A BIBLIOMETRIC ANALYSISArthisri Anandhi Sekar^{1,2}, Vishnu Priya Veeraraghavan^{1*}, Thirumal Raj A³^{1*} Centre of Molecular Medicine and Diagnostics (COMManD) Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences Saveetha University Chennai 600077 India. Email: drarthisri@gmail.com, drvishnupriyav@gmail.com² Department of Oral Medicine and Radiology Meenakshi Academy of Higher Education and Research (MAHER), Meenakshi Ammal Dental College and Hospital (MADC), Alapakkam main road, Maduravoyal, Chennai 600095 India.³ Department of Oral & Maxillofacial Surgery & Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Najran University, Najran, PO box 1988, Kingdom of Saudi Arabia. Email: thirumalraj666@gmail.com**Corresponding Authors:*****Arthisri Anandhi Sekar** Centre of Molecular Medicine and Diagnostics (COMManD) Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences Saveetha University ,Chennai 600077 India. Email: drarthisri@gmail.com***Vishnu Priya Veeraraghavan** Centre of Molecular Medicine and Diagnostics (COMManD) Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences Saveetha University ,Chennai 600077 India. Email: drvishnupriyav@gmail.com*Received: Feb. 18, 2025; Accepted: Mar . 6, 2025; Published: Mar. 20, 2025***Background:** Cardiovascular diseases (CVDs) are a leading cause of mortality globally, necessitating novel biomarkers for diagnosis and treatment. Long non-coding RNAs (lncRNAs) have emerged as significant regulatory molecules in cardiovascular biology, yet comprehensive bibliometric analyses in this area are lacking.**Objective:** This study aims to conduct a bibliometric analysis of lncRNAs as biomarkers in CVD to identify publication trends, key contributors, and thematic developments from 2008 to 2023.**Methods:** A systematic search was performed across PubMed, Scopus, and Web of Science using the keywords "(Long non-coding RNA) OR (lncRNA) AND (Cardiovascular disease) OR (Cardiovascular disorders) AND (Biomarkers)." A total of 33,805 records were retrieved, with duplicates removed, resulting in 29,545 unique records. After screening, 341 relevant articles were selected for bibliometric analysis using VOSviewer.**Results:** A total of 341 publications were analyzed, involving 54 countries/regions, 548 institutions, and 1744 authors across 177 journals. The United States (84 publications) and China (61 publications) were the leading contributors. Zhengzhou University had the highest publication output, while Guo Wei was the most prolific author. Keyword analysis revealed a focus on lncRNAs' roles in the occurrence, development, diagnosis, treatment, and prognosis of CVD.**Conclusion:** This bibliometric analysis provides insights into the research landscape of lncRNAs as biomarkers in CVD, highlighting significant trends, influential authors, and collaborative networks. The findings underscore the importance of lncRNAs in cardiovascular research and suggest potential areas for future investigation**Keywords:** Biomarker, Long coding RNA, Cardiovascular disease

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, responsible for approximately 17.9 million deaths annually according to the World Health Organization (WHO).^{1,2} The substantial morbidity and mortality associated with CVDs, including heart failure,³ myocardial infarction,⁴ and stroke,⁵ emphasize the urgent need for novel biomarkers to enhance early diagnosis, guide therapeutic interventions, and predict prognosis.⁶ In recent years, long non-coding RNAs (lncRNAs) have emerged as promising molecular entities in this regard.⁷

lncRNAs are a class of RNA molecules longer than 200 nucleotides that, unlike messenger RNAs (mRNAs), do not code for proteins but play crucial roles in regulating gene expression and various cellular processes.⁸ They have been implicated in numerous biological functions, including chromatin remodeling, transcriptional regulation, splicing, and post-transcriptional modification.⁷⁻¹³ In the context of cardiovascular diseases, lncRNAs have been shown to regulate pathways involved in heart development, vascular function, and pathological remodeling following myocardial injury.⁷⁻¹⁰

The unique properties of lncRNAs, such as tissue-specific expression and stability in body fluids, make them attractive candidates for non-invasive biomarkers. These features provide opportunities for their use in diagnostic assays, which could facilitate early detection and personalized treatment strategies for CVD patients.¹⁴⁻¹⁶ Despite the increasing body of research on lncRNAs in cardiovascular biology, a systematic evaluation of the publication trends, key contributors, thematic developments, and collaborative networks in this field has been lacking. Bibliometric analysis offers a powerful tool to analyze the structure and dynamics of scientific literature, providing insights into research progress and guiding future studies.¹⁷

This study aims to conduct a comprehensive bibliometric analysis of research on lncRNAs as biomarkers in cardiovascular diseases from 2008 to 2023. By examining publication trends, co-authorship networks, country collaborations, and keyword co-occurrence patterns, this analysis seeks to identify key contributors, thematic foci, and emerging trends. Ultimately, this analysis will provide a detailed overview of the research landscape, identifying influential authors, journals,

and institutions while highlighting potential areas for future investigation.

Methodology for Bibliometric Analysis

This bibliometric analysis was conducted to investigate the research landscape of long non-coding RNAs (lncRNAs) as biomarkers in cardiovascular disease. The methodology involved several key steps to ensure a comprehensive and systematic approach to data collection and analysis. (Figure 1)

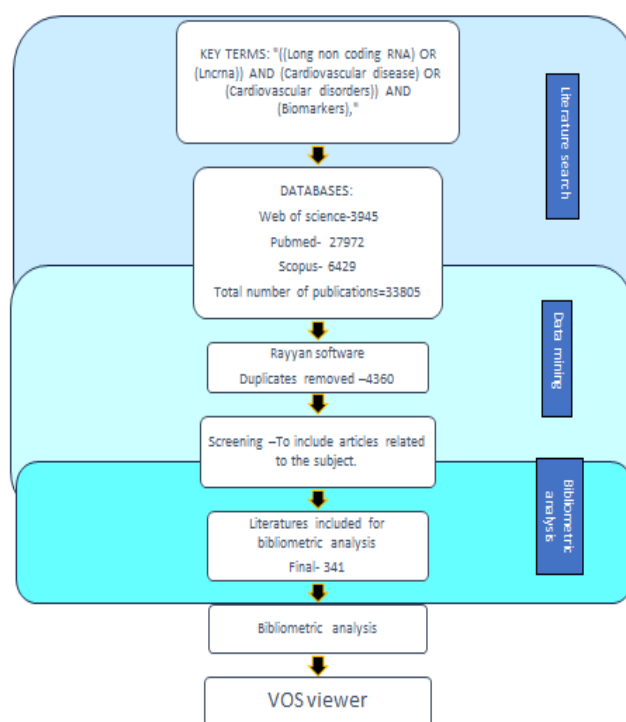


Figure 1. Bibliometric analysis methodology flow chart

Data Sources

To capture the breadth of research on lncRNAs as biomarkers in cardiovascular diseases, data were retrieved from three major academic databases: PubMed (27,972 records), Scopus (6,426 records), and Web of Science (3,945 records). These databases were selected for their comprehensive coverage of biomedical and life sciences research.

Search Strategy

A comprehensive search was performed using the following keywords:

"((Long non-coding RNA) OR (lncRNA)) AND (Cardiovascular disease) OR (Cardiovascular disorders) AND (Biomarkers)"

This search yielded a total of 38,346 records from the three databases mentioned above.

Data Cleaning and selection

After the initial search, the records were screened for duplicates, resulting in the removal of 4,360 duplicate entries, leaving 33,986 unique records. The remaining records were then manually screened for relevance. Only articles directly addressing lncRNAs as biomarkers in cardiovascular diseases were included in the final dataset. This process narrowed the focus to 341 publications, which formed the basis for the bibliometric analysis.

Analysis Tools

The bibliometric analysis was performed using VOSviewer (Version 1.6.20), a software tool specifically designed for constructing and visualizing bibliometric networks. VOSviewer was used to analyze co-authorship networks, citation networks, and keyword co-occurrence patterns. These analyses allowed for the identification of key authors, institutions, journals, and thematic clusters within the research domain.

Metrics and Network Construction

In the analysis, several key metrics were utilized:

- **Degree Centrality:** This metric was used to measure the influence of individual authors and institutions within the research network. Degree centrality refers to the number of direct connections an entity has within the network, indicating its centrality and influence.
- **Cluster Analysis:** To identify thematic clusters within the research landscape, VOSviewer’s clustering algorithm was applied to the co-authorship and keyword networks. Each cluster represents a group of related studies, often centered around a specific subtopic within the field.
- **Citation Analysis:** Citation networks were constructed to identify the most influential articles, authors and journals. The strength of the links between nodes in these networks reflects the frequency with which articles are co-cited, providing insight into the most impactful research within the field.
- **Keyword Co-occurrence Analysis:** This analysis was used to identify key themes and emerging trends in the field of lncRNAs and cardiovascular diseases by examining the frequency and co-occurrence of specific keywords within the literature.

- **Bibliometric coupling:** Bibliometric coupling is a method used to measure the similarity between two documents based on the number of references they share.

RESULTS

Yearly trends publications

The graph depicts yearly publication trends related to long non-coding RNAs and cardiovascular disease. Research activity saw a sharp rise, peaking in 2021 with 64 publications, followed by sustained high output in 2022 and 2020.

(Figure 2) Early years, such as 2013 to 2016, had minimal publications, indicating that the research area was emerging. However, starting from 2017, there was a marked increase in interest. Recent years show a decline, with 12 publications in 2024, likely reflecting the year’s incomplete status or shifting research priorities. Overall, the field experienced rapid growth but fluctuated in recent years.

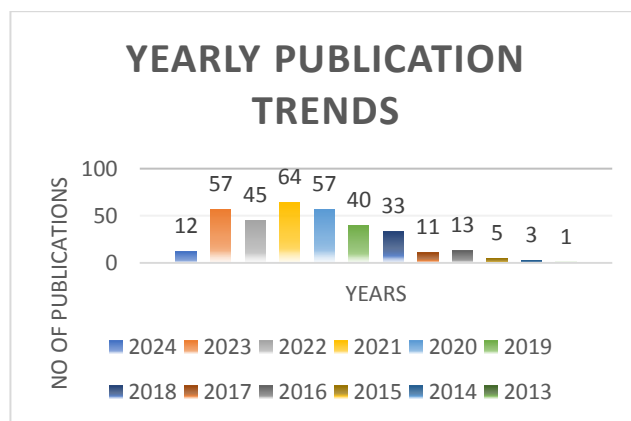


Figure 2. Yearly trend of publications

Analysis of Journals Having Maximum Publications: The Journal of Cardiovascular Research leads with 17 publications in the field of long non-coding RNAs and cardiovascular disease, followed by Frontiers in Cardiovascular Medicine with 11 publications and the International Journal of Genetics with 8 publications. (Figure 3) Other journals like the Journal of Cellular and Molecular Medicine and Advances in Experimental Medicine and Biology also contribute significantly. Overall, cardiovascular-specific journals dominate the publication landscape, while genetics and molecular biology journals also play important roles.

Analysis of Publications by Country

The graph highlights the global distribution of research publications on long non-coding RNAs and cardiovascular disease, with the United States leading the way at 84 publications, followed by China and England, each contributing 61 publications. (Figure 4) The United Arab Emirates makes a significant showing with 48 publications, reflecting its growing investment in scientific research and innovation. Switzerland follows with 18 publications, showcasing its strong tradition in life sciences and biotechnology. Countries like Brazil and Australia, with 13 and 8 publications respectively, also contribute meaningfully to the field, despite facing different levels of research funding and resources. Smaller contributors such as India, Turkey, Serbia, Luxembourg, Iran, Singapore, South Korea, and Poland have published between 1 to 6 papers, indicating a global interest in this emerging area of study. Overall, the distribution reflects both the dominance of a few key nations and the broad international engagement in understanding the role of long non-coding RNAs as biomarkers in cardiovascular disease.

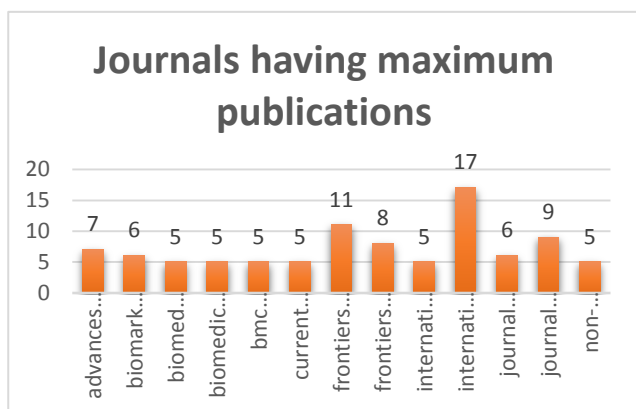


Figure 3. Analysis of journals having maximum publications

Co-Author Network Analysis:

Co-Author Network Analysis: Specific Authors in Key Domains

The image provided is a co-authorship network analysis visualized using VOSviewer, depicting the collaborative relationships between authors within a specific research domain.

(Figure5A) Each node in the network represents an author, while the edges (links) between them represent co-authorship relationships. The size of the nodes typically indicates the number of publications or the impact of the author, while the thickness of the edges reflects the strength of the collaboration (e.g., how often authors have co-published). The color gradient from blue to yellow shows the temporal evolution, with blue indicating earlier collaborations and yellow indicating more recent collaborations.

Network Metrics

Degree Centrality:

- Thomas Thum, Stefanie Dimmeler, and Lars Maegdefessel have high degree centrality, reflecting their extensive collaboration networks. These authors are likely key influencers or leaders in the research domain.

Cluster Analysis:

In this co-author network, several distinct clusters represent different research domains within the broader study of long non-coding RNAs (lncRNAs) and their role as biomarkers in cardiovascular disease (CVD). Below is an interpretation of the authors within each domain, grouped by their clusters.

A. Largest Cluster - Cardiovascular Biomarkers and Therapeutics

This cluster likely centers on translational research related to the therapeutic application of lncRNAs in cardiovascular disease. Authors like Thomas Thum and Stefanie Dimmeler are recognized leaders in this space, contributing to studies on lncRNAs as biomarkers for heart failure, myocardial infarction, and other cardiovascular conditions.

B. Yellow Cluster - Molecular Mechanisms and Regulatory Pathways

This cluster appears to focus on the molecular biology of lncRNAs, particularly their regulatory roles in cellular pathways involved in cardiovascular diseases. Yunzhu Peng and Luqiao Wang are likely conducting research on how lncRNAs influence gene expression and cardiovascular pathology.

C. Blue Cluster - Fundamental Research in lncRNA and Cardiovascular Disease

The blue cluster seems to be involved in foundational research regarding the molecular and genetic mechanisms of

lncRNAs in cardiovascular health. Authors like **Zhiguo Wang** and **Yong Zhang** are likely contributing to key insights in gene regulation and the basic biology of lncRNAs.

D.Green Cluster - Emerging Research on lncRNAs and CVD

The green cluster represents emerging researchers in the field. **Guoping Li** and **Ying Liu** are likely newer contributors focusing on the identification and functional analysis of lncRNAs in cardiovascular diseases. This cluster may be exploring newer aspects of how lncRNAs function as biomarkers or contribute to disease mechanisms.

E. Purple Cluster - Genetic and Cellular Research

This cluster seems to focus on genetic and cellular studies related to lncRNAs, possibly involving animal models and gene expression experiments. Researchers like **Chunyu Zeng** and **Yujia Wang** may be investigating how lncRNAs interact with various cellular processes in the context of cardiovascular conditions.

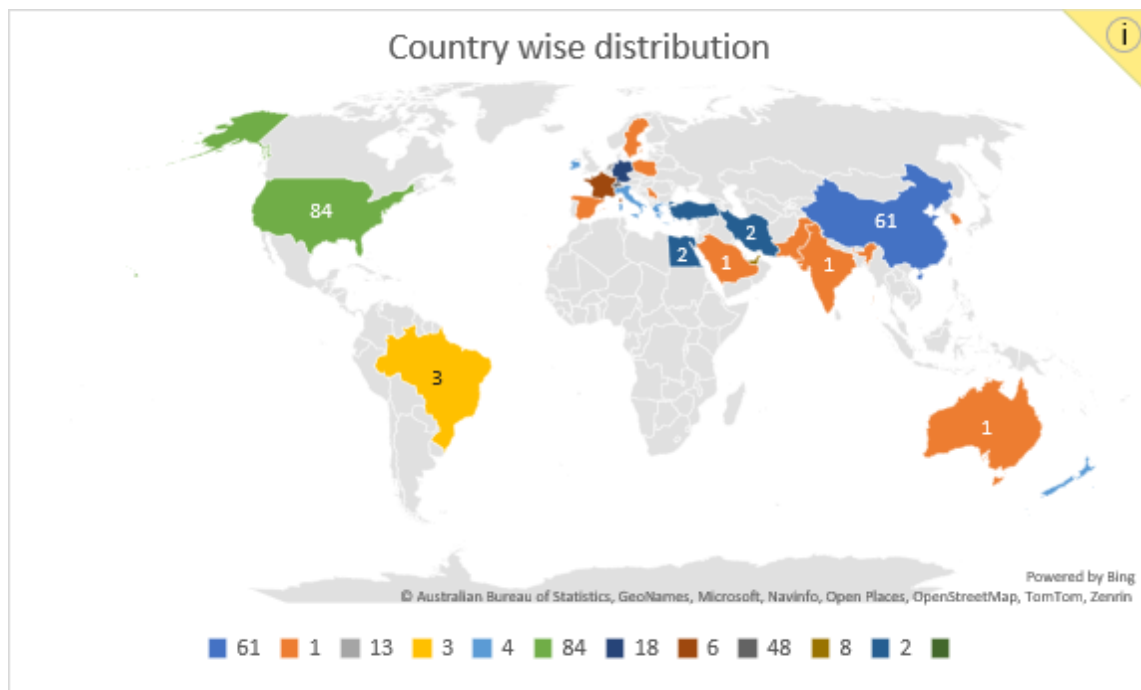


Figure 4. Analysis of Publications by Country

Co-Authorship Network of Organizations

Each domain identified in the network visualization represents a group of organizations that collaborate closely in the study of long non-coding RNAs (lncRNAs) and their role as biomarkers in cardiovascular disease.(Figure 5B) Below is a detailed explanation of how these organizations contribute to this specific area of research.

Cluster 1 - Leading Biomedical and Cardiovascular Research Institutions(Green)

This cluster is composed of some of the world's leading biomedical and cardiovascular research institutions. **Harvard University** and **Massachusetts General Hospital** are at the forefront of clinical and translational research, particularly in developing novel biomarkers for heart disease, including the investigation of lncRNAs. **Chinese institutions** like the **Chinese Academy of Medical Sciences** and **Nanjing Medical University** have rapidly expanded their research capacity, focusing on the molecular mechanisms by which lncRNAs regulate cardiovascular diseases.

Cluster 2 - European Cardiovascular and Genomic Research Leaders(Blue)

This cluster represents European and transatlantic leaders in cardiovascular genomics and translational medicine. **Goethe University Frankfurt**, **Medizinische Hochschule Hannover**, and the **German Centre for Cardiovascular Research** are major players in studying lncRNAs, with a focus on how these molecules can serve as predictive biomarkers for cardiovascular events, such as myocardial infarction or heart failure. **Imperial College London** and **Karolinska Institutet** contribute by integrating genomics with clinical data to improve personalized medicine approaches for CVD. Their collaborations with **British Heart Foundation** and the **Icahn School of Medicine at Mount Sinai** highlight a strong emphasis on applying findings to clinical practice, particularly in cardiovascular health.

Cluster 3 - Asian Academic Institutions Focused on Molecular Biology and Cardiovascular Health(Yellow)

This cluster includes several of Asia's top academic and medical institutions. **Shanghai Jiao Tong University** and **Sun Yat-sen University** are recognized for their contributions to molecular biology, especially in understanding the regulatory roles of lncRNAs in cardiovascular disease

progression. These institutions, along with **Zhejiang University** and **National University of Singapore**, are advancing research on how lncRNAs influence gene expression in cardiovascular health and disease.

Cluster 4 - Emerging Research Organizations in Cardiovascular Science(Purple)

This cluster consists of institutions that are emerging as influential players in cardiovascular research. **The University of Melbourne** and **University of Leicester** are contributing significantly to the field by exploring the genetic and epigenetic roles of lncRNAs in cardiovascular disease. **University Hospital of Basel** and **Centro de Investigación en Red** focus on translational research, bridging the gap between basic molecular findings and their application in clinical environments. **Stanford University** and **Technical University of Munich** add strength in bioinformatics and systems biology, which are critical for analyzing large datasets related to lncRNAs and cardiovascular outcomes, thus facilitating the discovery of novel biomarkers.

Cluster 5 - Specialized Medical and Research Centers(Light green)

This cluster includes specialized medical centers and universities that contribute to niche areas within the broader field of cardiovascular lncRNA research. **Affiliated Hospital of Qingdao University** and **First Affiliated Hospital of Kunming Medical University** focus on integrating clinical observations with molecular research, specifically examining how lncRNAs can be used as non-invasive biomarkers in patient care. **Universidade de Sao Paulo** and **Emory University** contribute to global research efforts by combining epidemiological data with molecular studies to explore the role of lncRNAs in diverse populations.

A .Co-Author analysis

Authorship Network of Organizations

C. Co-Authorship Network of Countries

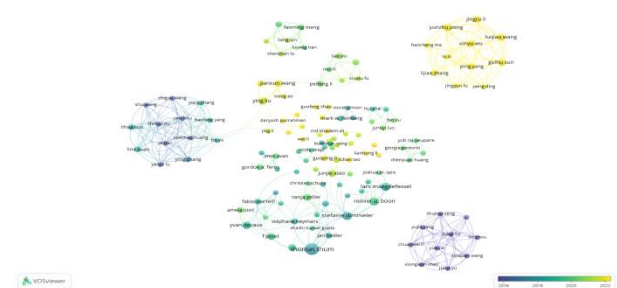


Figure 5. Co- author analysis

Co-Authorship Network of Countries

The image provided is a co-authorship network analysis visualized using VOSviewer, depicting the collaborative relationships between countries within a specific research domain. (Figure 5C) Each node represents a country, and the edges (links) between them represent co-authorship relationships across their research outputs. The size of the nodes typically reflects the volume of research output or the impact of the country in the field, while the thickness and color gradient of the edges indicate the strength of the collaboration and the temporal evolution of these collaborations.

Network Metrics

Degree Centrality:

- **China and the United States** have high degree centrality, reflecting their extensive collaboration networks and central roles in global research. These countries are crucial for fostering international research partnerships.

Cluster Analysis:

- **China-Centered Cluster (Green-Blue):**
 - China has strong connections with countries like the United States, Australia, and several European countries. This indicates that China is a hub for international collaboration, particularly with both Western countries and its regional neighbors.
- **United States-Centered Cluster (Blue-Green):**
 - The United States is connected with numerous countries across Europe, Asia, and the Middle East, highlighting its role as a central node in global research networks. Key collaborators include the United Kingdom, Germany, and Japan.
- **European Cluster (Blue-Purple):**
 - European countries such as **Germany, United Kingdom, Netherlands, and France** form a tightly connected group, with strong collaborative ties within the continent. These countries are pivotal in European research networks and frequently collaborate

with other global research leaders like the United States and China.

- **Emerging Collaborations (Yellow-Green Cluster):**
 - Countries like **India, Iran, and Saudi Arabia** show emerging collaborative activities, indicated by the green-yellow color scheme. These nations are increasing their presence in the global research landscape, particularly through collaborations with established countries like the United States and China.

Co-occurrence - keywords

Through a network visualization of keyword co-occurrence, 11 distinct clusters were identified, reflecting various research themes within this domain. (Figure 6)

Green Cluster - Central Focus on Biology and Long Non-Coding RNAs

- **Domain: Biology, Biochemistry, and Molecular Biology**
- **Keywords:** Long non-coding RNA, biology, computational biology, biochemistry, cancer research.
- This cluster represents the largest body of literature focusing on the fundamental biological processes involving lncRNAs. Specifically, lncRNAs are being studied for their roles in gene regulation, cellular mechanisms, and their potential as biomarkers in various diseases, including cardiovascular conditions

Blue Cluster - Cardiovascular Disease and Clinical Implications

- **Domain: Cardiology and Cardiovascular Health**
- **Keywords:** Coronary artery disease, diagnostic accuracy, clinical practice, biomarkers.
- This cluster is primarily focused on cardiovascular disease (CVD), with a significant emphasis on clinical applications. Research within this cluster examines how lncRNAs can be used as biomarkers for diagnosing and predicting the progression of coronary artery disease and other CVDs. The

focus on diagnostic accuracy and clinical practice suggests that lncRNAs are being evaluated for their translational potential in medical settings.

These studies are essential for understanding the functional roles of lncRNAs in cardiovascular diseases and their potential as biomarkers for early detection.

Yellow Cluster - Computational Approaches in LncRNA Research

- **Domain: Genomics and Computational Biology**
- **Keywords:** Computational biology, gene expression profiling, RNA splicing, competing endogenous RNA.
- Computational biology plays a key role in identifying and characterizing lncRNAs. This cluster emphasizes the integration of bioinformatics tools to analyze lncRNA expression profiles and their interactions with other RNA species (e.g., miRNAs, mRNAs). Such approaches are crucial for understanding the regulatory roles of lncRNAs in CVD and their potential as therapeutic targets.

Red Cluster - Heart Failure and LncRNA Pathophysiology

- **Domain: Cardiology and Pathophysiology**
- **Keywords:** Heart failure, ischemia, pathogenesis, fibrosis, mechanical engineering.
- This cluster investigates the role of lncRNAs in the pathogenesis of heart failure and related conditions such as ischemia and fibrosis. Research here explores how specific lncRNAs contribute to the molecular mechanisms underlying heart failure, providing insights into their use as biomarkers for disease progression and therapeutic targets.

Purple Cluster - Molecular Techniques in LncRNA Research

- **Domain: Molecular Biology and Genetics**
- **Keywords:** Apoptosis, gene knockdown, autophagy, molecular biology, reperfusion injury.
- This cluster explores the molecular biology techniques used to study lncRNAs, particularly through gene knockdown experiments and their effects on cellular processes like apoptosis and autophagy.

Cyan Cluster - Epidemiology and Public Health Implications of LncRNAs

- **Domain: Public Health and Epidemiology**
- **Keywords:** Population, stroke, public health.
- This cluster highlights the epidemiological aspects of CVD research, particularly in how population studies are being used to identify lncRNA biomarkers for conditions like stroke. The role of lncRNAs in population health research underscores their potential for large-scale diagnostic applications in public health interventions.

Light Green Cluster - LncRNAs in Disease and Inflammatory Pathways

- **Domain: Immunology and Disease Mechanisms**
- **Keywords:** Inflammation, coronary syndrome, disease, biomarkers.
- Inflammation is a critical factor in the pathogenesis of CVD, and this cluster focuses on how lncRNAs are involved in inflammatory processes. The identification of lncRNAs as biomarkers in inflammatory pathways provides valuable insights into their role in the development and progression of CVD, particularly in acute coronary syndromes.

Pink Cluster - Metabolic Health and LncRNA Biomarkers

- **Domain: Endocrinology and Metabolism**
- **Keywords:** Diabetes mellitus, metabolic health, insulin resistance.
- This cluster investigates the intersection between metabolic disorders and CVD, with a focus on how lncRNAs may serve as biomarkers for conditions like diabetes and metabolic syndrome. Given the strong link between metabolic health and cardiovascular risk, this research is critical for developing integrated approaches to managing CVD through the use of lncRNA biomarkers.

Orange Cluster - LncRNAs and Cancer Biology

- **Domain: Cancer Biology**
- **Keywords:** Cancer research, cell biology, gene knockdown, RNA splicing.
- While this cluster focuses on cancer biology, there is significant overlap with cardiovascular research, particularly in how lncRNAs are studied for their regulatory roles in cell biology. The insights gained from cancer research are often applicable to CVD, as many lncRNAs are implicated in both cancer and cardiovascular conditions.

Brown Cluster - Epigenetics and LncRNAs in CVD

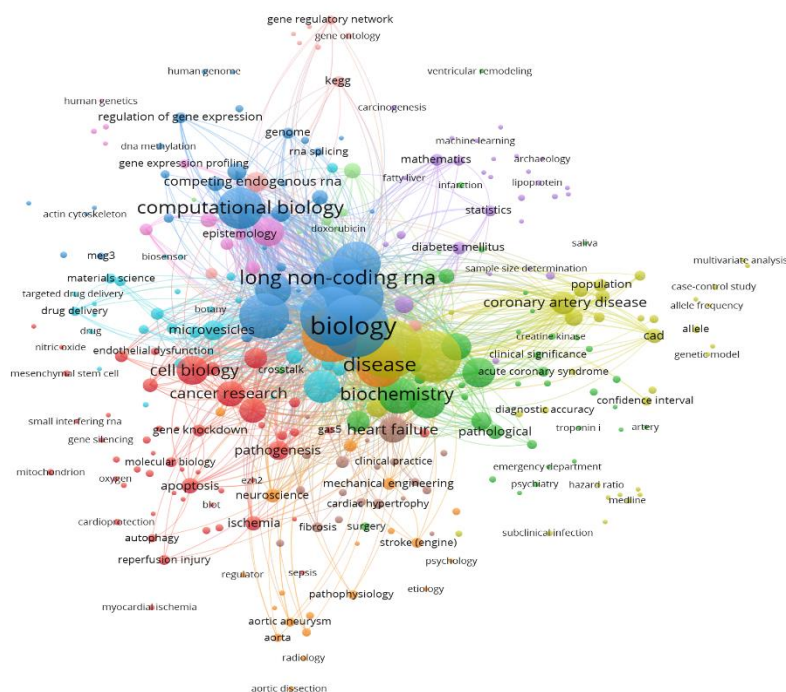
- **Domain: Genetics and Epigenetics**
- **Keywords:** Human genetics, epigenomics, DNA methylation.
- Epigenetic modifications such as DNA methylation play a crucial role in the regulation of lncRNAs. This cluster examines how epigenetic changes influence lncRNA expression and function in CVD, offering potential biomarkers for early

diagnosis and therapeutic interventions.

Dark Blue Cluster - Biomedical Engineering and LncRNA Applications

- **Domain: Biomedical Engineering and Cardiovascular Devices**
- **Keywords:** Mechanical engineering, cardiovascular devices, clinical significance.
- This cluster explores the application of biomedical engineering in the development of cardiovascular devices, with a focus on how lncRNA research can inform the design of new diagnostic and therapeutic tools. The integration of lncRNA biomarkers with biomedical devices represents an innovative approach to improving patient outcomes in cardiovascular care.

Figure 6. Co-occurrence Results Overview



Citation Network Analysis

Sources

1. The image provided is a citation network visualization of journals and sources. (Figure 7A) The nodes represent individual journals, and the connections (edges) represent citation relationships between these journals. The size of the nodes reflects the influence or impact of a journal within the network, often through the number of citations. The color of the nodes reflects the recency of the publications in the journal, with lighter colors indicating more recent activity.
2. **Central Journals and Influential Sources:** Journals like the International Journal of Molecular Sciences, Journal of Cellular and Molecular Medicine, Cells, and Circulation Research are identified as central hubs, frequently cited in the context of lncRNAs and cardiovascular disease.
3. **Specialization and Clustering:** The network reveals clusters of journals that specialize in specific subfields, such as Frontiers in Cardiovascular Medicine and Journal of Molecular and Cellular Cardiology, indicating focused research on the cardiovascular implications of lncRNAs.
4. **Emerging Journals:** Newer journals, including Non-Coding RNA Research and Molecular Diagnosis & Therapy, are gaining traction in the field, likely publishing cutting-edge research on lncRNAs and their applications as biomarkers.
5. **Multidisciplinary Influence:** Journals like Cells and Scientific Reports exhibit broad influence, suggesting that while they publish on cardiovascular lncRNAs, they also engage with a wider range of molecular biology topics, highlighting the interdisciplinary relevance of lncRNA research.
6. **Citation Flow:** The connections between journals illustrate a flow of knowledge from basic science to clinical applications, indicating that foundational research on lncRNAs is being translated into practical medical insights, particularly in cardiovascular contexts.

Co-authorship network with a focus on author citations

The provided image represents a **co-authorship network** with a focus on **author citations**. (Figure

7B) Each node represents an author, and the connections between the nodes represent collaborations (co-authorships). The size of the nodes indicates the relative citation impact of the author, while the color gradient reflects the recency of their publications, ranging from older research (darker colors) to more recent contributions (lighter colors).

Highly Cited Authors

- **Thomas Thum** stands out as the most prominent author in the network, indicated by the large size of his node. This suggests that his work has received a significant number of citations, making him a highly influential figure in the field of lncRNAs and cardiovascular disease.
- **Reinier A. Boon** and **Stefanie Dimmeler** also appear as key contributors with large nodes, indicating their high citation impact. These authors likely publish widely-cited work related to the identification and role of lncRNAs in cardiovascular conditions.
- **Yvan Devaux** and **Lars Maegdefessel** are also notable for their citation impact, connecting widely to both central and peripheral nodes, suggesting their work is both influential and collaborative.

Collaboration and Citation Flow

- Authors like **Jan Fiedler**, **Amelia Jusic**, and **Jingyun Fu** are well-connected to the central figures, implying that their work is frequently co-cited alongside highly influential authors like **Thum**, **Boon**, and **Dimmeler**. This suggests that they are collaborators on key studies or contribute significantly to the same body of work that is heavily cited.
- The dense interconnections among the central nodes suggest that much of the high-impact research in this area is produced through collaborations among these key authors. These collaborations are likely cited together in studies that explore the role of lncRNAs as biomarkers in heart disease.

Emerging Authors with Growing Citation Impact

- Authors such as **Yunzhu Peng**, **Ying Liu**, and **Peifeng Li** appear in lighter colors, indicating more recent contributions to the

field. Though their nodes are smaller compared to the central figures, the fact that they are connected to the network shows they are part of ongoing research that is gaining citations.

- Authors like **Tao Yu** and **Xiuxiu Fu**, located on the periphery with smaller nodes, likely represent newer entrants into the field whose work has not yet amassed a large citation count but may grow as the field evolves.

Peripheral Authors and Niche Research Areas

- Authors such as **Tao Yu** and **Xiuxiu Fu** are located in more isolated clusters, suggesting that they may be working on more specialized or emerging subtopics within the broader field. Their smaller node sizes indicate that their work has fewer citations compared to the central figures but may be highly relevant to niche areas of lncRNA research.

Citation Distribution Across the Field

- The overall network shows a clear distribution of citation influence, with a few key authors receiving the majority of citations (as indicated by their larger nodes) and a broader set of collaborators contributing to the overall growth of the field. The color gradient indicates that the field is still active, with recent publications from newer authors continuing to contribute to the ongoing research.

Citation Network of Organizations

The image provided is a citation network analysis visualized using VOSviewer, depicting the relationships between various organizations based on citation links. (Figure 7C) Each node represents an organization (such as universities, research institutes, or hospitals), and the edges (links) between them represent citations from one organization to another. The size of the nodes reflects the number of citations an organization has received, while the thickness and color gradient of the edges indicate the strength of citation connections and the temporal evolution of these citations.

Citation Patterns:

Dense Citation Network:

- The network is densely interconnected, especially around the central organizations, indicating that the research domain is well-established with a high degree of citation interdependency. This suggests a robust and

A. Citation network visualization of journals and sources

B. Co-authorship network with focus on author citation

C. Citation Network of Organizations

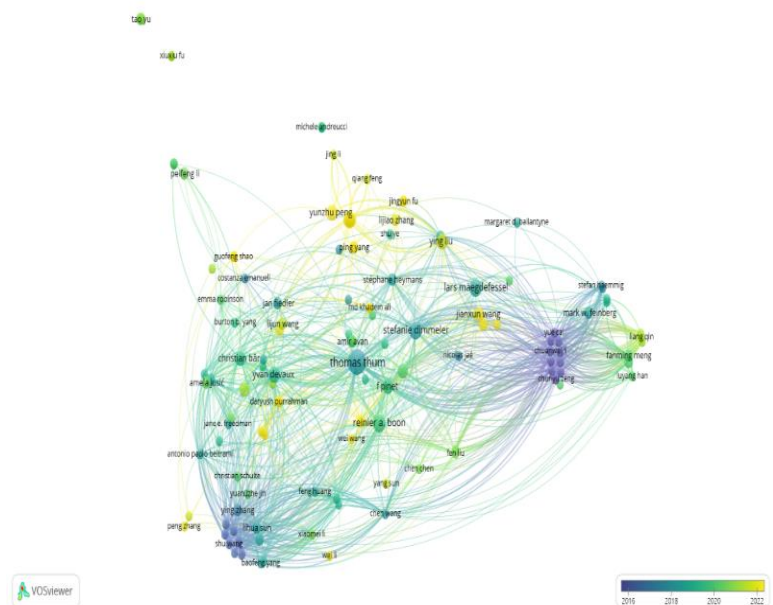


Figure 7. Citation network analysis collaborative research environment where institutions frequently build on each other’s work.

Network Metrics

Degree Centrality

- **Harvard University and Central South University** have high degree centrality, reflecting their broad influence across the research domain. These institutions are central nodes in the citation network, connecting various clusters and serving as major reference points for other organizations.

Cluster Analysis:

- The map reveals distinct clusters that represent different thematic areas or geographical regions:
- **Cluster 1 (Green-Blue):**
 - Harvard University, Central South University, and Massachusetts General Hospital: This cluster is densely connected, indicating strong citation relationships among these institutions. It suggests a core area of research that is highly collaborative and influential.
- **Cluster 2 (Blue-Purple):**
 - Medizinische Hochschule Hannover, German Centre for Cardiovascular Research, and Imperial College London: This cluster is composed of European institutions that are heavily interlinked, indicating strong regional collaboration and citation networks within Europe.
- **Cluster 3 (Green-Yellow):**
 - Zhejiang University, Harbin Medical University, and Sun Yat-Sen University: This cluster represents institutions that are gaining prominence, particularly in Asia. The green-yellow color indicates more recent contributions to the field, highlighting their emerging influence.

Bibliometric coupling - Source Analysis

In the provided bibliometric coupling network, key journals such as the International Journal of Molecular Sciences and Frontiers in Cardiovascular Medicine have a strong presence, indicating their influence and interconnectedness with other sources through shared citations. (Figure 8) These journals are crucial in advancing research on long non-coding RNAs (lncRNAs) as biomarkers in cardiovascular diseases. The network also highlights thematic clusters of journals focused on different areas, such as molecular biology and cardiovascular research, which are frequently co-cited, underscoring the interdisciplinary nature of this field. Furthermore, emerging sources like Biomarkers in Medicine and Human Genomics show increasing relevance, reflecting new directions in research. The interconnected structure of the network demonstrates

a cohesive research community, where shared foundational literature forms the basis for a broad spectrum of studies. This analysis not only showcases the most influential journals but also provides insights into the evolving research trends within this specialized area of cardiovascular medicine.

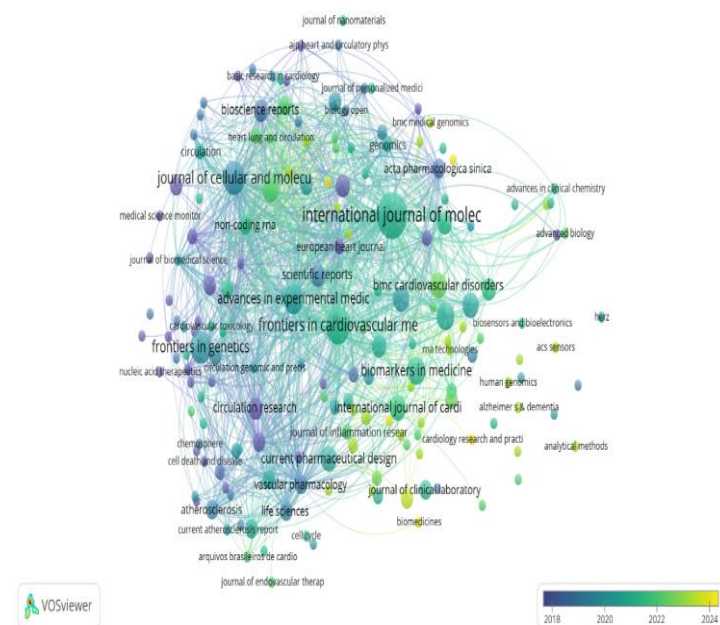


Figure 8. Bibliometric coupling - Source Analysis

DISCUSSION

This bibliometric analysis serves as a critical tool in mapping the trajectory of research activities, illustrating not only the growth of interest in lncRNAs but also the collaborative networks that underpin this field. By synthesizing data from multiple sources, the study provides a comprehensive overview of the current landscape, identifying key contributors and thematic areas that may shape future investigations into the application of lncRNAs in cardiovascular medicine. This study aligns with other bibliometric analyses in the field of cardiovascular biomarkers, such as those focusing on circular RNAs and microRNA. For instance, studies by Zehui et al.¹⁸ and Sun et al.¹⁹ have similarly identified key contributors and trends in cardiovascular research. However, this analysis distinguishes itself through its specific focus on lncRNAs, a relatively underexplored area, and its comprehensive multi-database approach, which enhances the robustness of the findings.

Yearly Trends in Publication Output

The analysis shows a notable increase in research activity on lncRNAs and cardiovascular diseases over the past 15 years, with a sharp rise in publications beginning around 2017 and peaking in 2021.^{20–24} This surge can be attributed to the growing recognition of lncRNAs as critical regulators of gene expression and cellular processes involved in cardiovascular pathology. The decline in publications in 2024 likely reflects the incomplete nature of the data for that year and does not necessarily indicate waning interest in the field.

Leading Contributors: Authors, Journals, and Institutions

The analysis identifies several key authors and institutions that have significantly shaped the research landscape. Guo Wei and Thomas Thum are among the most prolific authors, contributing a substantial number of high-impact publications on lncRNAs in cardiovascular contexts.^{8,25–27}

Journals such as *Journal of Cardiovascular Research* and *Frontiers in Cardiovascular Medicine* have emerged as central venues for disseminating research in this area, highlighting the importance of specialized journals in advancing the field.^{24,28}

Zhengzhou University stands out as the institution with the highest publication output, reflecting its active role in cardiovascular and molecular biology research.²⁹ The prominence of Chinese and American institutions underscores the global nature of this research domain, with these two countries leading in both the volume and impact of publications.

The global distribution of research on lncRNAs as biomarkers in cardiovascular diseases is dominated by the United States and China, which together account for a significant proportion of the publications in this field. The strong presence of these countries in the research landscape is reflective of their advanced biomedical research infrastructures and the substantial funding available for cardiovascular research.

Co-Authorship and collaborative network

The co-authorship network shows that Thomas Thum, Reinier A. Boon, Stefanie Dimmeler, and Yvan Devaux are central and highly cited figures in the field of lncRNAs and cardiovascular disease.^{30,31} These authors' work has significantly influenced the direction of research, as seen by their large node

sizes and extensive collaborations. The network also reveals the importance of collaboration in driving citation impact, with newer authors like Yunzhu Peng and Peifeng Li emerging as contributors to the field. The distribution of citations across both central and peripheral authors demonstrates the dynamic and evolving nature of lncRNA research, with a mix of established leaders and emerging researchers driving forward the exploration of lncRNAs as biomarkers in cardiovascular disease.^{32,33}

The co-authorship network analysis of organizations highlights the key institutions contributing to the research within this domain, emphasizing the global and collaborative nature of the work. Prominent institutions like Harvard University, Imperial College London, and Goethe University Frankfurt play central roles in the network, driving forward key research initiatives. Emerging hubs in Asia, such as Zhejiang University and Shanghai Jiao Tong University, indicate a shift towards new and potentially groundbreaking research. Future research efforts could benefit from fostering these emerging collaborations and integrating insights from the established global network.

The co-authorship network analysis reveals well-established collaborative groups, particularly between institutions in the United States, Europe, and China. These collaborations have facilitated the rapid exchange of knowledge and methodologies, enabling the field to advance at a remarkable pace. However, the emergence of research hubs in countries such as the United Arab Emirates and Switzerland suggests that other regions are increasingly investing in cardiovascular research, contributing to a more globally distributed research effort. European countries form a cohesive cluster with strong internal and external links, while emerging research nations like India and Iran are increasingly integrating into the global research landscape. Future research efforts could benefit from fostering these emerging collaborations and leveraging the established networks of leading countries to address global research challenges.

Thematic Developments and Emerging Trends

Keyword co-occurrence analysis has identified several thematic clusters within the literature, each reflecting different aspects of lncRNA research in cardiovascular disease. The largest cluster focuses on the biological roles of lncRNAs in gene regulation and disease mechanisms, emphasizing the importance of fundamental molecular biology

research in this area. Another prominent cluster is centered around the clinical applications of lncRNAs, particularly their potential as non-invasive biomarkers for the diagnosis and prognosis of cardiovascular conditions.^{3,34,35}

Emerging research themes include the integration of lncRNAs into precision medicine frameworks and the use of computational biology tools to further explore their regulatory functions.^{36,37} These trends suggest that future research will likely focus on developing targeted therapies and diagnostic tools based on lncRNA signatures, potentially transforming the management of cardiovascular diseases.

The common cardiovascular disease and long non-coding RNAs (lncRNAs) expressed can be identified based on the clustering and proximity of keywords. Frequently associated with lncRNAs involved in gene regulation, "coronary artery disease" appears in the network near terms like "biochemistry" and "clinical significance," suggesting that several lncRNAs play a role in this condition.³⁸⁻⁴³ lncRNAs related to "heart failure" are prominent and closely linked to "biochemistry" and "pathogenesis." Specific lncRNAs such as H19 and MIAT have been studied extensively in the context of heart failure.^{44,45} Terms like "ischemia," "myocardial ischemia," and "reperfusion injury" are associated with lncRNAs. Examples include lncRNA MALAT1, which has been studied for its protective roles in ischemic injury and infarction. Cardiac hypertrophy" and "cardiomyopathy" are linked to various lncRNAs such as lncRNA ANRIL and lncRNA KCNQ1OT1, which have been shown to regulate cardiac remodeling and hypertrophic responses.⁴⁶⁻⁵⁰ The term "acute coronary syndrome" is linked with lncRNAs involved in plaque stability and inflammation, like lncRNA MIAT and ANRIL.^{51,52} Involved in cardiac hypertrophy and heart failure, KCNQ1OT1 influences myocardial remodeling and cellular growth, making it a critical target in hypertrophic heart disease.⁵³⁻⁵⁶

From the bibliometric analysis and the terms highlighted in the network, it is evident that lncRNAs such as MIAT, H19, MALAT1, ANRIL, and KCNQ1OT1 are commonly expressed and studied in different cardiovascular diseases, including coronary artery disease, heart failure, myocardial infarction, and cardiac hypertrophy.^{23,57-59} These lncRNAs are central to the regulation of gene expression and play key roles in the pathophysiology of cardiovascular diseases, making them crucial targets for research

and potential clinical applications in diagnostics and therapeutics.

Strength and limitations

While many bibliometric studies rely on a single database, such as Web of Science or Scopus, this analysis utilizes data from three major databases (PubMed, Scopus, and Web of Science). This multi-database approach ensures a more comprehensive coverage of relevant literature. The identification of thematic clusters provides insight into current research focuses and potential future directions in the field of lncRNAs and CVDs. The analysis is limited to published literature, which may overlook significant findings in unpublished studies or those not indexed in the selected databases. The bibliometric approach provides a quantitative overview, but lacks the depth of qualitative analysis that could be obtained through expert interviews or systematic literature reviews.

Future Directions and Implications

The analysis of long non-coding RNAs (lncRNAs) in cardiovascular disease highlights several key future implications for research and clinical applications. First, targeted research should focus on specific lncRNAs, such as MIAT, H19, MALAT1, ANRIL, and KCNQ1OT1, to better understand their roles in disease mechanisms and explore their potential as therapeutic targets. Additionally, the clinical translation of lncRNAs as biomarkers for diagnosis and prognosis should be prioritized, with efforts to validate their utility in clinical settings to improve diagnostic accuracy and inform treatment strategies. Leveraging advancements in genomics and computational biology will be essential for identifying novel lncRNA biomarkers and elucidating their interactions in cardiovascular health. Expanding research to include diverse populations is crucial for understanding variability in lncRNA expression, facilitating personalized medicine approaches. Furthermore, fostering interdisciplinary collaborations among researchers in molecular biology, cardiology, and public health will enhance the understanding of lncRNAs' implications in cardiovascular disease. Lastly, future studies should focus on emerging themes, such as the roles of lncRNAs in inflammation and metabolic health, to provide deeper insights into their multifaceted functions in cardiovascular pathology. Overall, these implications pave the way for innovative research and clinical applications that could significantly improve patient outcomes in cardiovascular disease management.

CONCLUSION

This bibliometric analysis provides a comprehensive insight into the research landscape of long non-coding RNAs (lncRNAs) as biomarkers in cardiovascular disease. It highlights the crucial roles of lncRNAs such as MIAT, H19, MALAT1, ANRIL, and KCNQ1OT1 in various cardiovascular conditions, showcasing their involvement in gene regulation and disease mechanisms. The analysis also reveals significant publication trends, influential contributors, and emerging areas of focus in the field. The growing interest in lncRNA research reflects their promising potential in cardiovascular diagnostics and treatment. Moving forward, future research should aim to capitalize on the existing collaborations and explore the identified emerging themes to enhance the translation of these findings into clinical practice, ultimately improving outcomes for patients with cardiovascular diseases.

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