

# Trends and Evolution in Coronary Microcirculation Research: A Bibliometric Analysis from 2004 to 2023

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## ABSTRACT

**Background:** The coronary microcirculation system, a complex network of small blood vessels, plays a crucial role in regulating the myocardial blood flow to ensure adequate myocardial perfusion. Coronary microcirculation dysfunction has become a significant focus of myocardial ischemia research. This study aimed to review and analyze global research trends and hotspots in coronary microcirculation over the past 20 years through bibliometric analysis and visualization techniques, providing new perspectives for researchers and clinicians.

**Methods:** We systematically searched the Web of Science Core Collection (WoSCC) for literature on coronary microcirculation published between 2004 and 2023. GraphPad Prism v8.0.2 was used to analyze annual publication volume, country distribution, and proportion. Cite Space (version 6.2.4R) and VOS viewer (version 1.6.18) were employed to mine the data and generate scientific knowledge maps to visualize research hotspots.

Results: A total of 2,463 publications were analyzed, including 2,011 research papers and 452 review articles. Global research activity on coronary microcirculation has steadily increased, with a notable increase from 2018 to 2023. The United States produced the most research, with the University of Amsterdam as the most active institution. High-quality research has been published in journals such as the "American Journal of Physiology-Heart and Circulatory Physiology" and "Circulation," the latter being highly cited. The key research theme was coronary microvascular dysfunction. Keyword burst analysis indicates that "microvascular dysfunction," "impact," "outcome," "pathophysiology," "international standardization," "ST-segment elevation myocardial infarction (STEMI)," and "diagnostic criteria" will be future research focuses.

Conclusion: The coronary microcirculation is crucial for cardiovascular disease research. Future studies should focus on identifying therapeutic targets for coronary microvascular dysfunction, developing early prevention strategies, and exploring new research directions. International collaboration is essential to advance this field.

## INTRODUCTION

Coronary microcirculation is part of the cardiac vascular system, referring to the network of small blood vessels branching from the main coronary arteries to the myocardial microvasculature Joerg et al. (2012). These tiny vessels are the primary channels for supplying blood to myocardial cells and are responsible for delivering oxygen and nutrients to the heart muscle and removing metabolic waste products Li et al. (2023).

In 1967, Likoff et al. first reported a group of patients diagnosed with coronary heart disease (CHD) but with normal coronary angiography results Likoff et al. (1967). Subsequently, Cannon RO, and Epstein SE conducted extensive research on patients with angina but normal coronary angiography results, and in 1988, they first proposed the concept of microvascular angina Cannon et al.

(1988). Since then, the concept of coronary microcirculation has gradually gained the vision of many clinicians, leading to decades of research in this field. In 2013, the European Society of Cardiology first recognized coronary microvascular disease (CMVD) as a clinical type of coronary heart disease Filippo et al. (2014). Furthermore, increasing research has found that coronary microcirculation dysfunction is prevalent in clinical cardiovascular events, and in patients without significant coronary artery obstruction (less than 50% stenosis), microcirculation dysfunction can increase the incidence of major adverse cardiovascular events (MACE) Teresa et al. (2020), Sechtem et al. (2020), Del Buono et al. (2021). Therefore, exploring the role and mechanisms of coronary microcirculation in the cardiovascular field can provide new insights and direction for the treatment of microcirculation disorders.

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With widespread and simplified access to literature, a large number of basic and clinical research publications require a simple and efficient statistical method to extract key information. Bibliometrics is a method that studies the quantity and quality of the scientific literature. It evaluates the impact of the literature by analyzing citation, referencing, and download metrics. This method helps to collect and analyze large volumes of publications, providing objective and statistically significant data to explore future research trends. Thus, we applied bibliometrics to review the literature over the past 20 years to construct a framework for coronary microcirculation Ellegaard et al. (2015). By searching the Web of Science for relevant literature, we found that research in this field will continue to increase, peaking in 2023. We used bibliometrics to visualize and analyze relevant literature on coronary microcirculation from the Web of Science Core Collection over the past 20 years (2004-2023) using CiteSpace and VOS viewer, systematically exploring the current status, hotspots, and trends of international research on coronary microcirculation, aiming to provide a basis for subsequent research and practical exploration van Eck et al. (2017), Chaomei et al. (2005).

## **METHODS AND MATERIALS**

## **Data Retrieval and Collection**

Bibliometric analysis was based on the Core Collection of the Web of Science (WOSCC), which is considered the best data source for bibliometrics. On February 24, 2024, we searched the WOS for all articles related to coronary microcirculation published between January 1, 2004, and December 31, 2023. The search formula was as follows: (coronary microcirculation))/TS= microvascular circulation). The inclusion criteria were as follow: (1) full-text publications related to coronary microcirculation. (2) Articles and review manuscripts written in English. (3) Articles published between January 1, 2004, and December 31, 2023. The exclusion criteria were as follow: (1) topics unrelated to coronary microcirculation. (2) Articles that were conference abstracts, news items, and briefings. The search process (Figure 1).

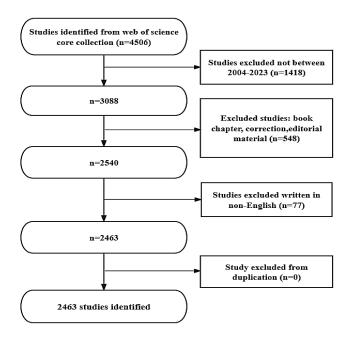
## **Data Analysis**

Graphpad Prism v8.0.2 was used to analyze and plot the annual publication trends and proportions of papers by country.

VOS viewer v.1.6.17, was employed to identify productive journals, clarify author collaboration relationships, and create keyword co-occurrence maps to identify research trends and hotspots. The authors were divided into different clusters represented by different colors, with

connecting lines representing their collaborative relationships and node sizes indicating their influence.

Figure 1: Flowchart of Literature Retrieval Process



The CiteSpace (6.1.4R) software was used to plot citation bursts, co-cited journal analysis, reference, and keyword analysis by authors, journals, countries, and institutions. The node size is related to citation frequency, and the links represent co-occurrence relationships.

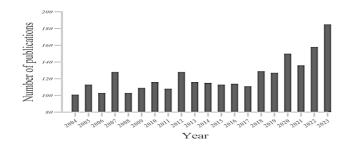
## **RESULTS**

From January 1, 2004, to December 31, 2023, a total of 2,463 documents related to coronary microcirculation were found in the WOSCC database, including 2,011 articles (81.65%) and 452 reviews (18.35%). The literature includes 81 countries and regions, 2,409 institutions, and 11,879 authors.

## Trends in Annual Growth

Since 2004, the number of published papers has slowly increased each year (Figure 2a). We divided this into two phases: from 2004 to 2017, the growth was slow and stable, whereas from 2018 to 2023, the number of publications gradually increased, reaching a peak in 2023.

Figure 2(a): Annual Publication Volume.



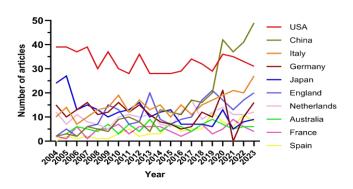


This indicates that the field has gradually entered the research community's vision and has gained attention, with the expected continued growth in coronary microcirculation research in the near future.

#### **Countries and Institutions**

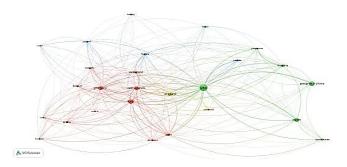
Research on coronary microcirculation was conducted in 81 countries. In the past decade, the top 10 countries in annual publication volume were the United States, followed by China, Italy, Germany, and Japan (Figure 2b). The United States accounted for 26.72% of the total publications, followed by China (311: 12.63%). The United States has the highest citation frequency (31,607) and the highest average citation rate (48.3).

Figure 2(b): Annual Publication Volume by Country.



Although China ranks second in publication volume (311 articles), its average citation rate is much lower than that of the other top ten countries, indicating that the quality of articles published in the field of coronary microcirculation in China needs improvement. VOS viewer analysis shows that China and the United States collaborate closely, which may be related to the recent sharp increase in China's publication volume (Figure 2c).

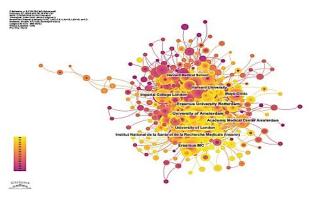
Figure 2(c): National Collaboration Network.



According to the CiteSpace analysis, a total of 2,409 institutions have published articles on coronary microcirculation. The three institutions with the highest number of publications were the University of Amsterdam, Erasmus University Rotterdam, and Erasmus MC, with 83, 69, and 69 publications, respectively. Among the top the research institutions, four were from the Netherlands,

three from the United States, two from the United Kingdom, and one from France (Figure 2d). Erasmus University Rotterdam had the highest total citations, followed by Imperial College London and Erasmus MC, indicating that Dutch institutions contribute the most to research on coronary microcirculation. The Mayo Clinic in the United States had the highest average number of citations per publication.

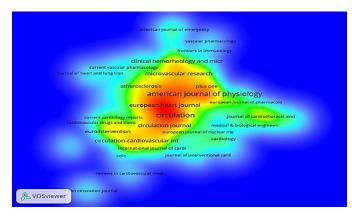
Figure 2(d): Institutional Collaboration Network.



# **Journal Analysis**

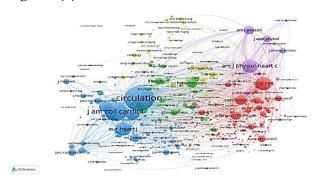
The journal output density map for coronary microcirculation (Figure 3a) shows that "Circulation" and the "European Heart Journal," as leading journals in cardiovascular medicine, have published the most articles on microcirculation research. This indicates a growing interest in this field within the medical community.

Figure 3(a): Institutional Collaboration Network.



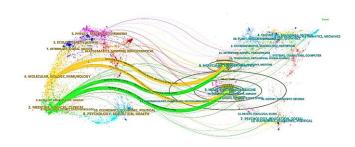
The visualization of the cited journals demonstrates that "Circulation" and the "Journal of the American College of Cardiology" are the most frequently cited journals, signifying their leading position in this research area (Figure 3b). According to the journal's dual-map overlay results (Figure 3c), we identified four main colored citation paths. Research published in the journals molecular/biology/genetics and health/nursing/medicine mainly cited by research molecular/biology/immunology field, while studies in the molecular/biology/genetics and health/nursing/medicine fields are primarily cited by research in the medicine/

Figure 3(b): Institutional Collaboration Network.



medical/clinical field. This may reflect that the current coronary microcirculation research is mainly focused on clinical applications, pathogenesis, and health care. Crosscitation among journals in these fields highlights the close connection and mutual influence between different disciplines, underscoring the importance of interdisciplinary research.

Figure 3(c): Journal Dual-Map Overlay.



# Author and Reference Analysis

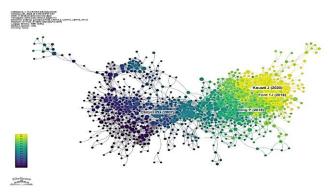
Analyzing author and cited author data helps to identify core authors and major collaborations in the field (Table 1). Table 1 summarizes the most prolific and highly cited authors. Based on the publication volume in this area, the results indicate that Duncker and Escaned are the most authoritative authors, whereas PG Camici is the most cited author.

Table-1: Author Publications and Co-Citations

Rank	Author	Count	Rank	Co-cited author	Citation
1	duncker, dirk j.	34	1	CAMICI PG	315
2	escaned, javier	34	2	FEARON WF	261
3	piek, jan j.	30	3	GIBSON CM	217
4	sellke, frank w.	29	4	PIJLS NHJ	181
5	camici, paolo g.	27	5	CHILIAN WM	173
6	feng, jun	27	6	GOULD KL	170
7	gutterman, david d.	27	7	DE BRUYNEB	167
8	crea, filippo	25	8	NICCOLI G	162
9	fearon, william f.	22	9	HEUSCH G	156
10	van royen, niels	21	10	KLONER RA	142

The most cited coronary microcirculation studies (Figure 4). The most notable citations in coronary microcirculation research are the two seminal papers by Knuuti and Camici. Among them, the "2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes" authored by Knuuti J et al., received the highest number of citations due to its authoritative and systematic summary of the diagnosis, treatment, and risk management of coronary microvascular angina Knuuti et al. (2020). The article "Coronary Microvascular Dysfunction" by Camici PG et al. is highly cited for its detailed review of the assessment of coronary microvascular function, the pathogenesis, classification, and specific characteristics of microvascular dysfunction with and without coronary disease/myocardial disease. This highlights that functional abnormalities in structural the coronary microcirculation are significant mechanisms leading to myocardial ischemia Camici et al. (2007).

Figure 4: Co-Cited Literature Network Map

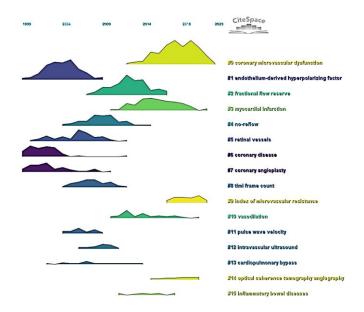


A ridge Line Plot of Clustering Research Hotspots in Cited Literature Over Time (Figure 5). The ridge-line plot illustrates 16 evolving research hotspots in the cited literature over time. Among these, "coronary microvascular dysfunction" (#0) is the largest cluster, with "endothelium-derived hyperpolarizing factor" (#2), "coronary disease" (#6), and "coronary angioplasty" being the key topics in the initial research on coronary microcirculation.



Current hotspot research areas include "coronary microvascular dysfunction" (#0) and "index of microvascular resistance" (#9). Additionally, "index of microvascular resistance" (#9) has emerged as a recent focus of interest.

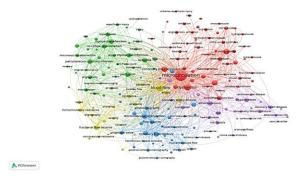
Figure 5: Co-Cited Literature Volcano Map



# Keyword Analysis: Hotspots and Emerging Topics

A total of 7,940 keywords were extracted from the titles and abstracts. Based on keyword co-occurrence in VOS viewer, the most frequent keywords are "microcirculation," followed by "blood-flow," "dysfunction," and "coronary microcirculation" (Figure 6). We removed irrelevant keywords and constructed a network of 188 keywords that appeared at least 27 times, resulting in five distinct clusters.

Figure 6: High-Frequency Keyword Network Map

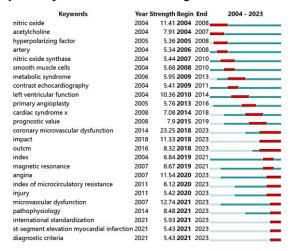


Keyword co-occurrence highlights scientific interests and future research directions, establishing a framework, and defining useful concepts (Figure 7). In this study, the top 183 keywords were divided into five clusters, represented by different colors (red, green, blue, yellow, and purple). The most frequently used keywords include "microcirculation," "blood-flow," "dysfunction," "coronary microcirculation," "nitric oxide," "endothelial dysfunction," "microvascular dysfunction" and "coronary flow reserve."

Moreover, the time-based keyword burst visualization analysis clearly shows that since 2021, the research focus has significantly shifted towards cutting-edge topics such as "microvascular dysfunction," "impact," "outcome," "pathophysiology," "international standardization," "ST-segment elevation myocardial infarction (STEMI)" and "diagnostic criteria," This trend not only underscores coronary microcirculation dysfunction as a current hotspot in medical research but also reflects the growing attention and refinement of detection techniques in this area.

**Figure 7:** Top 25 Most Cited Keywords. Keyword bursts identify indicators of new trends in the field of coronary microcirculation.

Top 25 Keywords with the Strongest Citation Bursts



#### **DISCUSSION**

In the rapidly evolving contemporary information society, swiftly acquiring and summarizing the latest scientific research hotspots is crucial for understanding development trends and planning future directions in various research fields. Unlike traditional methods of literature review and identifying research hotspots, bibliometric analysis systematically processes the original literature across various fields, tracks current research hotspots, reveals landmark papers and research trends, and presents trends in a clearer and more intuitive graphical format. This study employed bibliometric methods to collect literature information, construct a knowledge base, and delineate the structure of research in coronary microcirculation. As of December 31, 2023, the WoSCC database retrieved 2,463 articles representing the work of 12,644 authors from 81 countries and 2,409 institutions across 810 journals, with 7,940 co-occurring keywords.

Our study indicates that research on coronary microcirculation experienced a prolonged stable period (2004-2017) before entering a rapid development phase (2018-2023). According to the trends shown in Figure 2, 885 articles were published between January 1, 2018, and



December 31, 2023, highlighting the growing interest among scholars in the role of coronary microcirculation in cardiovascular science. Additionally, with the increase in publication volume, citation frequency has also increased. The number of publications on coronary microcirculation peaked in 2023 (n=185), indicating a high point in publishing activity that had not yet declined as of December 2023. These data suggest that the "burst" period has not yet arrived; thus, further research on this topic is required.

Subsequently, based on the analysis of publication volume and citation strength by country (Figures 2b and 2c), the United States remains the country with the highest publication volume, citation count, and average citations. This indicates that research in this field is still dominated by the United States. This may be due to the pioneering work of renowned American cardiologists, such as Likoff W. and colleagues, who first reported cases of angina without detectable coronary artery stenosis on angiography14. This groundbreaking research drew attention to the field and led to substantial investment in this area in the U.S. Interestingly, while China initially had a low publication volume, research in this field has seen explosive growth since 2019, surpassing the U.S. in 2020. This growth could be attributed to China's increasing research funding in this field and its growing collaborations with countries like the U.S. However, it is worth noting that despite ranking second in publication volume, China's citation count and average citation rate remain low, indicating that China has not yet secured a leading position in this field and must focus more on improving the quality of its publications. Based on the analysis of institutional collaboration networks (Figure 2d), the University of Amsterdam's extensive collaborations with various international organizations and research centers may explain its position as the leading institution in terms of publication volume.

A subsequent detailed analysis of journal publication volumes (Figure 3a) revealed that the field of coronary microcirculation has garnered significant attention from the academic community. The top five journals in this field are the American Journal of Physiology-Heart and Circulatory Physiology, Circulation, Microcirculation, the International Journal of Cardiology, and the European Heart Journal. Notably, the Circulation and European Heart Journal, as flagship journals in cardiovascular medicine, are highly focused on research trends in coronary microcirculation, possibly signaling a new wave of interest and focus in cardiovascular research. Furthermore, an in-depth analysis of co-cited journals (Figure 3b) shows that Circulation, J Am Coll Cardiol, New Engl J Med, Eur Heart J, and Am J Cardiol occupy the top positions. In particular, Circulation and Eur Heart J not only have a significant publication volume, but also high citation frequencies, strongly indicating their core status and profound influence in

coronary microcirculation research, leading and advancing the field's research directions and academic discussions.

In the field of coronary microcirculation, the dual-map overlay analysis of journals revealed that research focuses on basic science and clinical medicine (Figure 3c). The figure clearly shows four dominant and colorfully distinct citation paths integrating rich research results from molecular biology, immunology, genetics, nursing, and medicine. Notably, journals in these fields not only publish a large number of high-quality papers on coronary microcirculation independently, but also frequently appear as co-cited journals, demonstrating a complex network of cross-disciplinary citations. This phenomenon reflects multidisciplinary integration in coronary microcirculation research and highlights the crucial role of interdisciplinary collaboration in advancing the field. The close interaction and mutual influence among different disciplines not only broadens research perspectives, but also provides diverse viewpoints and innovative solutions for addressing complex issues in coronary microcirculation. Therefore, strengthening interdisciplinary research and collaboration is vital for advancing both the field of coronary microcirculation and the broader cardiovascular sciences.

In the citation ranking of coronary microcirculation research presented in Figure 4, two original articles by Knuuti and Camici stand out prominently. First, the 2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes compiled by Knuuti J and his team are highly authoritative and systematic. This guideline provides a comprehensive and in-depth summary of the diagnostic processes, treatment strategies, and risk assessment of coronary microvascular angina, earning widespread recognition and numerous citations in the field. This guideline not only offers valuable references for clinicians but also significantly advances research on coronary microvascular diseases Knuuti et al. (2020). On the other hand, the work by Camici PG et al., titled Coronary Microvascular Dysfunction, is equally impressive. This article is the first to provide a detailed review of the assessment techniques for coronary microvascular function and the complex pathophysiological mechanisms of microvascular dysfunction. It also proposes a classification system for this condition Camici et al. (2007). Notably, this article analyzes the unique characteristics of microvascular dysfunction, both in the context of coronary heart disease/myocardial disease and in its absence, offering new insights into understanding this disease state. Additionally, this paper highlights the crucial role of abnormalities in coronary microcirculation function and structure in the occurrence of myocardial ischemia. This perspective is of significant importance for elucidating the pathogenesis of myocardial ischemia, contributing to its high academic impact and recognition.



The ridge-line chart (Figure 5) vividly illustrates 16 research hotspot clusters evolving over time, focusing on dynamic changes in the field of coronary microcirculation based on the cited literature. Among these, "coronary microvascular dysfunction" (#0) stands out as the most significant cluster, highlighting its central role in the field's research agenda. Within this large cluster, "endotheliumderived hyperpolarizing factor" (#2), "coronary disease" (#6), and "coronary angioplasty" have laid a solid early exploration foundation for of microcirculation research. As research progresses, current hotspots are increasingly concentrated in more refined and cutting-edge areas. Notably, "coronary microvascular dysfunction" (#0) remains a focal point, indicating a sustained interest in this complex pathological process. At the same time, the "index of microvascular resistance" (#9), emerging as a new research tool, is gaining increasing attention. As a novel method for assessing coronary microcirculation function, this tool offers valuable support for elucidating disease mechanisms and guiding clinical treatment. It is particularly noteworthy that the "index of microvascular resistance" (#9) as a newly emerging research topic not only shows the rapid evolution of research directions but also suggests potential new breakthroughs in coronary microcirculation research. This trend reflects the scientific community's proactive response to the need for precision medicine and personalized treatment as well as a profound recognition of the pivotal role of technological innovation in advancing medical progress.

Notably, the temporal keyword burst visualization clearly demonstrates that since 2021, research focus has significantly shifted towards cutting-edge topics such as "microvascular dysfunction," "impact," "outcome," "pathophysiology," "international standardization," "STEMI," and "diagnostic criteria." This trend not only highlights coronary microvascular dysfunction (CMD) as a current hotspot in medical research but also reflects the growing attention and advancements in CMD diagnostic techniques within the scientific community. Specifically, some STEMI patients continue to experience chest discomfort after PCI, despite angiographic results showing unobstructed blood flow in the major coronary arteries. Further evaluation using coronary microcirculation detection techniques revealed inadequate myocardial perfusion, indicating CMD. A one-year follow-up found that the number of major adverse cardiovascular events (MACE) was significantly higher in patients with CMD compared to those without Jeremias et al. (2019), Patel et al. (2022). At the 2013 European Cardiovascular Congress, CMD was officially classified as a type of chronic coronary artery disease Filippo et al. (2014). Subsequent research using Myocardial Blush Grade (MBG) technology showed coronary microvascular perfusion after mitral valve replacement were more prone to developing postoperative atrial fibrillation Çiçek et al. (2023). However, there were no available techniques in the past to directly observe coronary microcirculation in the human body. Specifically, in the past, there were no relevant technologies to directly observe coronary microcirculation within the human body. Measurements relying on quantifying coronary blood flow have typically been used to describe the function of the coronary microvascular system. Diagnostic methods for this condition mainly include invasive and non-invasive examinations Chen et al. transthoracic Doppler echocardiography Milasinovic et al. (2024), cardiac magnetic resonance imaging Tian et al. (2020), Liu et al. (2020) computed tomography coronary angiography Taqueti et al. (2024), positron emission tomography (PET) Zhang et al. (2022), MBG17, coronary flow reserve (CFR) and microvascular resistance index (IMR) De Bruyne et al. (2021), Konst et al. (2021), and intracoronary acetylcholine stimulation tests (ACh-test) Ong et al. (2020).

Among these, invasive tests (i.e., CFR, IMR, and ACh tests) are the most accurate but are limited by their invasive nature and high-cost Tu et al. (2020). With the advent of non-invasive QFR technology, its effectiveness in CMD diagnosis, treatment guidance, and prognosis prediction has been validated in top medical journals such as The Lancet and J Am Coll Cardiol and included in international guidelines in 2023 Song et al. (2022), Xu et al. (2021), Jin et al. (2022), Escaned et al. (2023). This marks a new era in CMD diagnosis and treatment. The acceleration of international standardization further promotes circulation and comparison of global research findings, establishing a unified benchmark for precise CMD diagnosis and treatment. In the treatment field, the use of medications such as SGLT2 inhibitors Capece et al. (2024), Shenxiong Baoyuan pills Ge et al. (2021), ACE inhibitors Handberg et al. (2021), and nicorandil Chen et al. (2024) has been shown to effectively improve patients' microcirculation status. Additionally, in-depth exploration of "impact" and "outcome" reveals the complexity of its pathogenesis and the importance of early intervention, providing scientific evidence for developing individualized and precise treatment plans. Current research has confirmed that atrial fibrillation, metabolic diseases, and inflammation are associated with the occurrence of coronary microcirculation disorders, emphasizing the importance of comprehensive management of underlying conditions and implementing intensive treatment strategies for high-risk groups Mohammed et al. (2024), Huang et al. (2022), Salvatore et al. (2022), Marco et al. (2021), Weber et al. (2024), Zhang et al. (2022). Furthermore, early exercise training programs have been



found to positively promote the recovery of microvascular function, further broadening the perspectives on CMD treatment and rehabilitation Rafique et al. (2021), Roysland et al. (2023). In the future, in-depth exploration of CMD treatment targets and development of early prevention strategies are expected to become new research hotspots. By continuously optimizing CMD diagnosis and treatment systems, we hope to create more effective and safer treatment pathways, bringing new hope to patients with CMD and significantly improving their quality of life and long-term survival rates. This effort not only represents a proactive response to current medical challenges, but also profoundly contributes to the health and well-being of humanity.

This study also has certain limitations. Firstly, although Web of Science is the most suitable database for bibliometric analysis Singh et al. (2021), it does not cover all scientific publications. Additionally, differences in search algorithms and inclusion criteria across various databases may lead to biases in research findings. Therefore, future studies should consider conducting bibliometric analyses across multiple databases to obtain a more comprehensive research perspective. Secondly, analyzing non-English literature may also be important, as it may contain region- or culture-specific research findings that contribute to a more complete understanding of the global distribution and influencing factors of postoperative delirium.

## **CONCLUSION**

In recent years, research on coronary microcirculation has rapidly increased worldwide. Our study reveals research hotspots, key research directions, prolific authors, countries, regions, and institutions in this field. Future research on coronary microcirculation should focus on exploring CMD treatment targets and developing early prevention strategies. International collaboration and the exploration of new research directions are essential for advancing this field.

#### **DECLARATIONS**

## **Author Contributions**

KML and JW: Conception and design; KML and CMQ—administrative support; KML and CMQ—provision of study materials; JW and CMQ—collection and assembly of data; KML and JW—data analysis and interpretation. All authors have written and approved the final manuscript.

## Ethics Approval and Consent to Participate

Ethical approval was unnecessary because the data in this study were retrieved from open sources and no animal experiments or human tissues were used in our research.

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#### **Conflict of Interest**

The authors declare no conflict of interest.

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