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Deciphering myocardial fibrosis: a comprehensive bibliometric analysis of mechanism over the period 1992–2023

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Abstract

Background Myocardial fibrosis is a critical link in preventing the progression of heart disease. This study conducted a bibliometric analysis of its mechanism to identify trends and hotspots, aiming to provide valuable references for heart disease prevention and treatment.

Methods This research relies on the Web of Science Core Collection, capturing all related publications on the mechanism of myocardial fibrosis up to November 11, 2023. For the bibliometric analysis, CiteSpace 6.2.R5 (64-bit) and VOSviewer 1.6.19 software tools were utilized.

Results The mechanism of myocardial fibrosis research involves 14,931 authors from 2,370 institutions in 71 countries/regions, resulting in 2,431 published studies. Nattel Stanley is the most prolific author, while Francogianis Ng is noted for the highest co-publication frequency. The United States leads in countries/regions, with the University of California System being the top institution. Cardiovascular Research is a primary outlet for new studies, and Circulation is a key reference in this research community. Current research primarily examines how myocardial fibrosis contributes to heart failure, myocardial infarction, and myocardial hypertrophy. This emerging field also explores the role of fibroblasts in myocardial injury and investigates innovative treatments to reduce myocardial fibrosis.

Conclusions Preventing myocardial fibrosis is a crucial strategy in the fight against heart disease. This study utilises bibliometric analysis to explore the vast array of literature on the mechanism of myocardial fibrosis, mapping the research landscape and provide literature references for potential breakthroughs in heart disease prevention and treatment strategies.

Keywords Myocardial fibrosis, Mechanism, Heart faliure, Preventive cardiology, Bibliometrics

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Introduction

Myocardial fibrosis (MF), which involves the excessive accumulation of scar tissue in the heart, is a common pathophysiologic companion of many different myocardial conditions [1]. MF negatively affects the heart's ability to contract, relax, and conduct electrical signals, leading to serious health issues, including heart failure (HF), irregular heartbeats, and unexpected cardiac mortality, underscoring its prevalence in heart disease pathology [2]. Current research on myocardial fibrosis primarily aims to uncover its underlying mechanisms and develop effective prevention strategies. Prioritizing the prevention of MF can greatly improve the quality of life for patients. Therefore, understanding the mechanisms of myocardial fibrosis (MoMF) is essential for advancing both treatment and prevention strategies for heart disease [3].

"Bibliometrics" refers to the field that employs quantitative techniques, including mathematical and statistical methods, to assess and characterize scientific literature. This area of research encompasses both descriptive statistics and network analysis, which examines connections among authors, institutions, and identifies patterns within literature clusters [4]. Conducting bibliometric analysis on the MoMF is crucial in preventive cardiology. This approach helps identify knowledge gaps and provides literature-based support to guide future research in developing more effective strategies for preventing and treating heart disease.

Our goal was to perform an exhaustive analysis to identify the "research hotspots" and track the evolution of trends in MoMF research. For this purpose, visualization tools such as VOSviewer and CiteSpace were utilized to thoroughly examine the body of literature on this topic spanning from 1992 to 2023.

Methods

Data sources and search strategy

The data analyzed in this study were retrieved on 1 November 2023 from all editions in the Web of Science Core Collection (WoSCC).

Subsequently, a detailed search was conducted using the specified strategy: [TS=("myocardium" OR "cardiac muscle" OR "heart muscle" OR "heart") AND TS=("mechanism") AND TS=("generate" OR "produce" OR "accelerate" OR "promote") AND TS=("fibrosis" OR "fibroses" OR "fibroblast")]. The time span was 1 January 1985 to 1 November 2023.

Inclusion criteria were articles related to MoMF, published as Articles, Reviews, or Early Access, and written in English. Exclusion criteria encompassed literature not pertinent to the cardiovascular system, medicine, or biology, such as Urinary System, Tissue Engineering, Environmental Science, Historical Humanities, or those with themes not concerning MoMF.

Analysis tools

The following tools were used to analyze the literature:

- CiteSpace 6.2.R5 (64-bit) (http://citespace.podia.com), a software that applies set theory for data normalization, evaluating knowledge unit similarities. This approach, developed by Professor Chao-Mei Chen, aids in grasping the field's growth and trends [5]. It was used to analyze and visualize various bibliometric aspects, including countries/regions and institutional collaborations, co-cited references, "reference bursts", and dual-map overlays of journals, providing a comprehensive view of the scholarly landscape. CiteSpace parameters were configured with "Time-slicing" from January 1992 to December 2023, setting each slice to one year.
- VOSviewer 1.6.19 (https://www.vosviewer.com/) is a bibliometric analysis tool created by Nees Jan van Eck and Ludo Waltman, which is used for mapping the intellectual structure of a field and visualizing connections between keywords and authors, aiding in the comprehension of research dynamics and collaborations [6]. In the conducted research, VOSviewer 1.6.19 was utilized for the analysis and visualization of data related to journals, co-citations of journals, authors, co-citations of authors, and keywords.

Data analysis

The Web of Science database's analysis tool compiled key metrics, including the total number of publications and their average citations, providing a quantitative overview of the research impact and productivity in the studied area. Literature records and cited reference data were compiled as "Full Record and Cited References" and downloaded in "Plain Text" format. After cleansing, the data were uploaded into the aforementioned software to conduct an analysis of the internal structure.

Ethical considerations

The study sourced its data from the WoSCC. It did not involve patient or public contributions in any phase of the research process.

Results

The literature screening process, which involves systematically reviewing and selecting relevant studies, and the comprehensive research framework, which outlines the methodology and structure of the study, are detailed in Fig. 1. Additionally, the following text offers a detailed

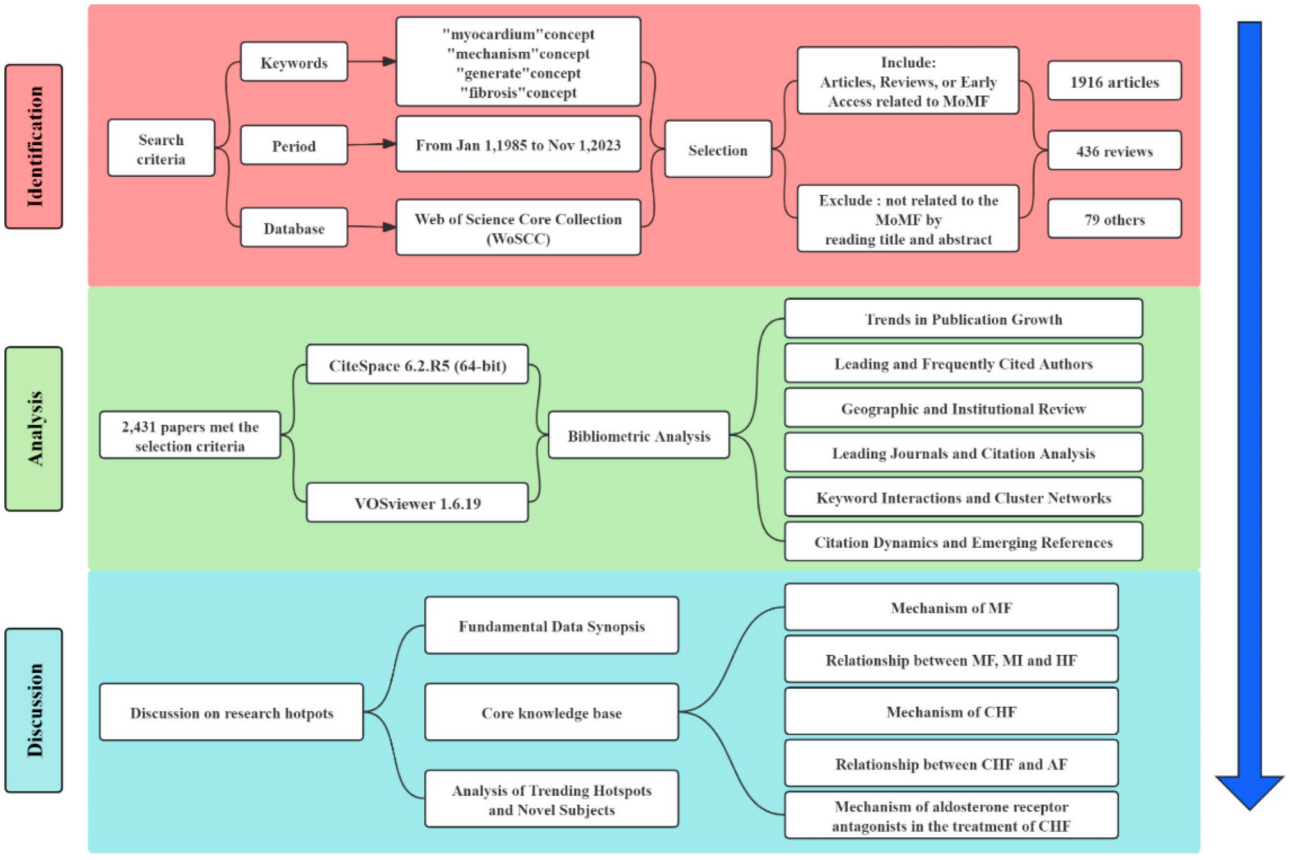

Fig. 1 Flowchart of the literature-screening process and research framework

explanation and an in-depth discussion of the survey results.

Trends in publication growth

Based on the data selection criteria, 2,431 studies concerning the MoMF spanning 1985 to 2023 were sourced from WoSCC: 1,916 original articles (78.8%), 436 reviews (17.9%), and 79 others (3.3%). Articles on the MoMF displayed a generally rising trend with intermittent fluctuations (Fig. 2). A peak in article publication occurred in 2022 (263), while 1992(4) saw the fewest releases. The annual citation count for articles shows a consistent upward trajectory (Fig. 2). This observation may be due to the fact that WoSCC currently holds records from 1985 to the present. Based on our search strategy, the initial articles on MoMF surfaced in the WoSCC in 1992. For earlier studies, it may be necessary to consult additional databases to capture the earliest contributions to the field.

Leading and frequently cited authors

Bibliometric analyses revealed that 14,931 authors penned 2,431 articles, with Nattel, Stanley leading in publication count ($n = 16$), closely trailed by Ge, Junbo ($n = 15$), Du, Jie and Li, Jun ($n = 12$), Komuro, Issei and Zhang, Yan ($n = 11$), and other four authours ($n = 10$) (Table 1). Price's Law stipulates that the threshold number of publications by core authors (m) is calculated using $m = 0.749 \times \sqrt{n_{max}}$, approximating to 3, where n denotes the maximum papers by the most prolific authors. Consequently, core authors in this study were required to author at least 3 papers. A density map was drawn using VOSviewer to identify 632 core authors, and the map only showed the largest connected cluster of 472 items among them. As Fig. 3a shows, the color of each point on the density map reflects the item density at that point, going from blue to yellow. A point is yellow if it has a high item density, and blue if it has a low item density.

Within our study, "co-cited authors"—defined as two or more authors cited together in one or more subsequent articles—were identified. A search yielded 65,730 co-authors, with Frangogiannis, Ng ($n = 372$) emerging as the most frequently co-cited, followed by Weber, Kt ($n = 280$), Zhang, Y ($n = 183$), Brilla, Cg ($n = 176$), and Pitt, B ($n = 154$) (Table 1). Additionally, 620 authors with twenty or more co-citations were pinpointed, enabling the creation of a cooperative network map that highlights the key co-cited contributors in MoMF (Fig. 3b).

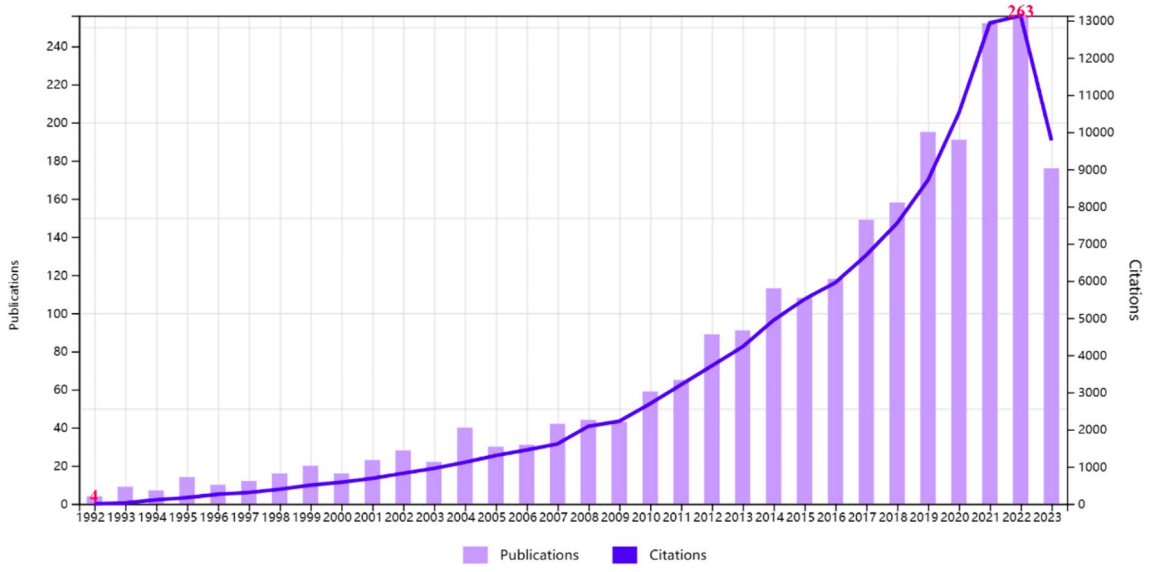

Fig. 2 Chronological trend of publications and citations on the mechanism of myocardial fibrosis

Table 1 Top 10 authors and co-cited authors related to the study of the MoMF[a]

Rank	Author	Document	Citation	Average C/P[b]	Co-cited author	Citation
1	Nattel, Stanley	16	3057	191.06	Frangogiannis, Ng	372
2	Ge, Junbo	15	335	22.33	Weber, Kt	280
3	Du, Jie	12	879	73.25	Zhang, Y	183
4	Li, Jun	12	409	34.08	Brilla, Cg	176
5	Komuro, Issei	11	479	43.55	Pitt, B	154
6	Zhang, Yan	11	246	22.36	Sun, Y	151
7	Blyszczuk, Przemyslaw	10	385	38.50	Wang, Y	141
8	Liu, Xin	10	135	13.50	Wang, J	139
9	Packer, Milton	10	461	46.10	Packer, M	136
10	Pan, Zhenwei	10	622	62.20	Wynn, Ta	136

[a]MoMF: mechanism of myocardial fibrosis

[b]C/P: Citation/Publication

Geographic and institutional review

From 2,370 institutions across 71 countries/regions, 2,431 articles on MoMF were authored. China ($n = 912$, 37.52%) ranked first in publication volume, with the subsequent rank held by the United States ($n = 832$, 34.22%), Germany ($n = 169$, 6.95%), Japan ($n = 154$, 6.33%), and Canada ($n = 139$, 5.72%) (Table 2). China and the United States accounted for 71.74% of the total publications, significantly surpassing others. The United States, boasting foremost centrality was pivotal in the network graph, indicating its central role in research. France (0.21), England (0.18), Germany (0.17), Canada (0.12), Australia (0.11) and Italy (0.11) also emerged as a key player, with a centrality greater than 0.1. (In CiteSpace, nodes exceeding a 0.1 centrality value are deemed critical). Average citation (citation: publication) refers to the average number of citations within a certain period, the higher this indicator, the higher its academic level and contribution, and the more it is valued and recognized by the international academic community. Within the top 10 countries/regions for MoMF article publication, the United States led with 54,878 citations, significantly outpacing others, and demonstrated a high ratio of citation: publication (65.96), reflecting a substantial output of quality research. While the publication volume of Netherlands is only 82 articles, the average citation is the highest (78.09). Despite leading in publication count among the top 10, China has the lowest average citation (22.39) and centrality (0.04).

As far as institutional contributions, the University of California System ($n = 72$, 2.96%) holds the premier position in the publish volume, followed by Harvard University ($n = 65$, 2.67%), Shanghai Jiao Tong University ($n = 64$, 2.63%), Inerm ($n = 59$, 2.43%), and UDICE-French Research University ($n = 51$, 2.1%) (Table 2). Nevertheless, the University of California System (0.15) and Harvard University (0.16) were the only institution with a centrality exceeding 0.1. Additionally, publications from

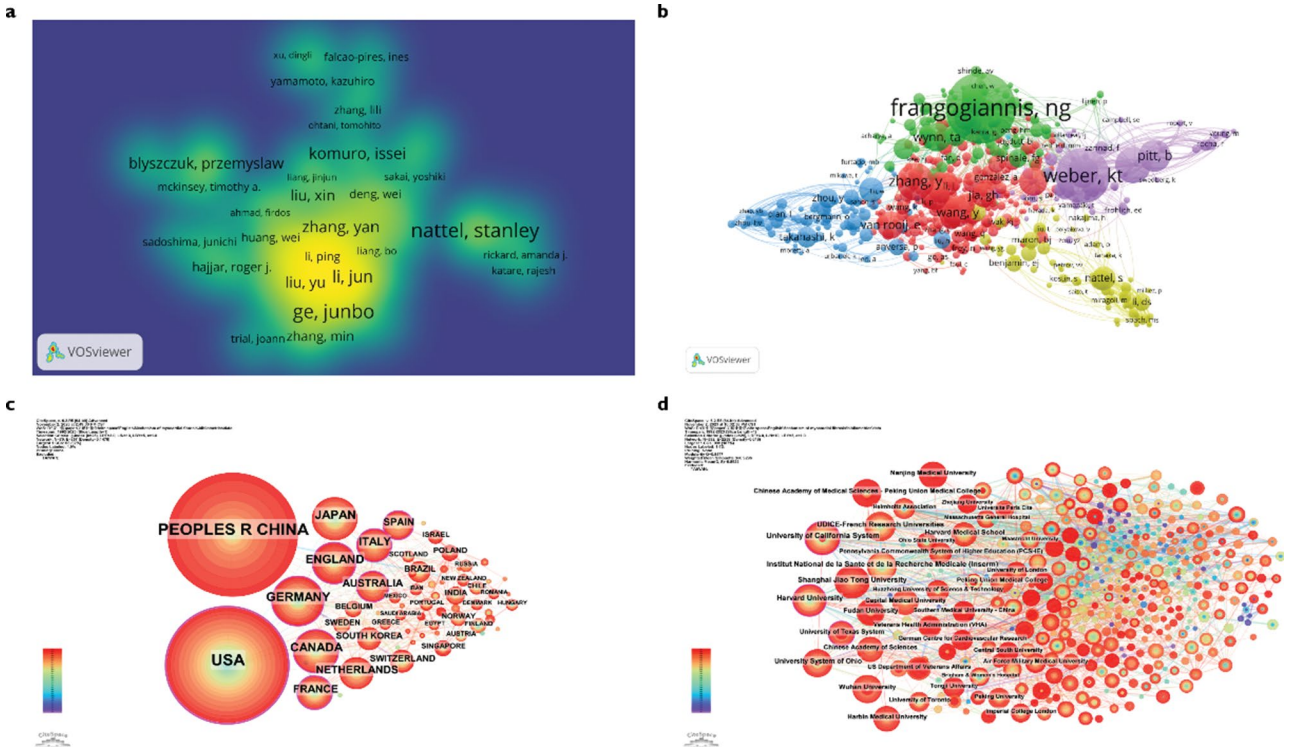

Fig. 3 Co-occurrence maps for the mechanism of myocardial fibrosis. (**a**) Authors. The size of the world and circle and the opacity of yellow are positively associated with the co-citation frequency. (**b**) Co-authors. The size of the node indicates the co-occurrence frequency for the author. The different colors reflect different clusters. The links reflect the co-occurrence relationship between authors. (**c**) Countries/Regions. (**d**) Institutions. The size of each node represents the co-occurrence frequency and the links reflect the co-occurrence relationships. The color of each node and line indicate different years

Harvard University have the highest average citation (86.80) among all institutions.

Beyond merely noting the quantity of articles through node sizes or identifying significant centrality (above 0.1), indicated by purple nodes (Fig. 3c, d), this analysis extends to uncovering collaborations between countries/regions or institutions through the connections between nodes.

Leading journals and citation analysis

Statistical analyses indicate that 2,431 studies were disseminated through 507 academic journals. Table 3 enumerates ten leading journals, ranked by publication frequency and co-citation metrics, in the MoMF domain. Cardiovascular Research ($n = 77$, 3.17%) published the highest number of studies, with the subsequent rank held by Circulation Research ($n = 77$, 3.17%), Journal of Molecular and Cellular Cardiology ($n = 72$, 2.96%), and American Journal of Physiology-Heart and Circulatory Physiology ($n = 65$, 2.67%). In addition, half of the journals ranked in the Q1 division of the Journal Citation Report (JCR), outperforming at least 75% of their category peers by impact factor (IF), with "Circulation" boasting the highest IF at 37.8. Regarding the co-cited journals in Table 3, Circulation ($n = 7,820$) secured the top spot, succeeded by Circulation Research ($n = 7,035$), Journal of Biological Chemistry ($n = 3,571$), Cardiovascular Research ($n = 3,443$), and Journal of Molecular and Cellular Cardiology ($n = 3,094$). Additionally, seven journals fell within the Q1 JCR category, with "Nature" achieving the highest impact factor at 64.8. Figure 4a, b present density views of journals, highlighting the map's structure and emphasizing key areas. Word size and yellow intensity directly reflect frequency.

The dual-map overlay illustrates the journal landscape, mapping the connections with citing sources on the left and those cited on the right. Each point on the map signifies a journal, with the left side depicting the citation landscape and the right side the referenced landscape, while the connecting curves detail the citation relationships. The colored trajectory in the dual-map denotes the bibliographic connections, and the strength and smoothness of the trajectories are shown by the Z-Scores function, with higher scores having thicker lines. The ellipse represents each journal's metrics, with its length corresponding to author count and width to publication volume. A journal with a longer vertical axis has more publications, and a journal with a longer horizontal axis has more authors. As shown in Fig. 4c, the map highlights 2 distinct primary citation trajectories, yellow trajectory implies that scholarly articles featured in journals in the domain of Molecular/Biology/ Immunology were

Table 2 Top 10 C/R[a] and institutions involved studies on the MoMF[b]

Rank	C/R[a]	Article count (%)	Citation	Average citation	Centrality	Institution	Article count (%)	Citation	Average citation	Centrality
1	China	912 (37.52%)	20,417	22.39	0.04	U[c]. of California System	72 (2.96%)	4865	67.57	0.15
2	United States	832 (34.22%)	54,878	65.96	0.43	Harvard U[c].	65 (2.67%)	5642	86.80	0.16
3	Germany	169 (6.95%)	11,249	66.56	0.17	Shanghai Jiao Tong U[c].	64 (2.63%)	1774	27.72	0.04
4	Japan	154 (6.33%)	9039	58.69	0.05	Inserm[d]	59 (2.43%)	3586	60.78	0.08
5	Canada	139 (5.72%)	9461	68.06	0.12	UDICE-French Research U[c].	51 (2.1%)	3106	60.90	0.09
6	England	122 (5.02%)	6347	52.02	0.18	U[c]. System of Ohio	49 (2.02%)	2759	56.31	0.09
7	Italy	93 (3.83%)	4409	47.41	0.11	Harvard Medical School	46 (1.89%)	3784	82.26	0.09
8	France	86 (3.54%)	5145	59.83	0.21	Wuhan U[c].	44 (1.81%)	835	18.98	0
9	Netherlands	82 (3.37%)	6403	78.09	0.09	Chinese Academy of Medical Sciences - Peking Union Medical College	42 (1.73%)	1089	25.93	0.04
10	Australia	74 (3.04%)	3610	48.78	0.11	Fudan U[c].	42 (1.73%)	982	23.38	0.01

[a]C/R: Countries/Regions

[b]MoMF: mechanism of myocardial fibrosis

[c]U: University

[d]Inserm: Institut National de la Santé et de la Recherche Médicale

Table 3 Top 10 journals and co-cited journals associated with the study of the MoMF[a]

Journal	Count	Citation	IF[b]	JCR[c]	Co-cited journal	Citation	IF[b]	JCR[c]
Cardiovasc Res	77	7545	10.8	Q1	Circulation	7820	37.8	Q1
Circ Res	77	7378	20.1	Q1	Circ Res	7035	20.1	Q1
J Mol Cell Cardiol	72	3368	5	Q2	J Biol Chem	3571	4.8	Q2
Am J Physiol-Heart C	65	3259	4.8	Q2	Cardiovasc Res	3443	10.8	Q1
Circulation	61	8210	37.8	Q1	J Mol Cell Cardiol	3094	5	Q2
Plos One	59	2089	3.7	Q2	P Natl Acad Sci Usa	2946	11.1	Q1
Frontiers in Cardiovascular Medicine	47	352	3.6	Q2	J Clin Invest	2811	15.9	Q1
Frontiers in Pharmacology	46	514	5.6	Q1	J Am Coll Cardiol	2722	24	Q1
Scientific Reports	46	1188	4.6	Q2	Am J Physiol-Heart C	2694	4.8	Q2
Int J Mol Sci	41	609	5.6	Q1	Nature	2620	64.8	Q1

[a]MoMF: mechanism of myocardial fibrosis

[b]IF: impact factor (Journal Citation Reports 2023)

[c]JCR: Journal Citation Reports 2023

predominantly referenced by research studies published in Molecular/Biology/ Genetics and Health/ Nursing/ Medicine journals. Green trajectory shows that studies published in Medicine/ Medical/ Clinical journals were cited by research published in Molecular/Biology/ Genetics journals research citations.

Keyword interactions and cluster networks

VOSviewer analysis extracted 9,732 keywords from 2,431 studies, with "fibrosis" being the most frequent, followed by "expression" ($n = 493$), "heart-failure" ($n = 469$), "mechanisms" ($n = 423$), "heart" ($n = 404$), "inflammation" ($n = 314$), "activation" ($n = 305$), "oxidative stress" ($n = 264$), "cardiac fibrosis" ($n = 251$), and "hypertrophy" ($n = 247$) (Table 4), which highlighted the research focal points of the MoMF. A map illustrating the frequency of

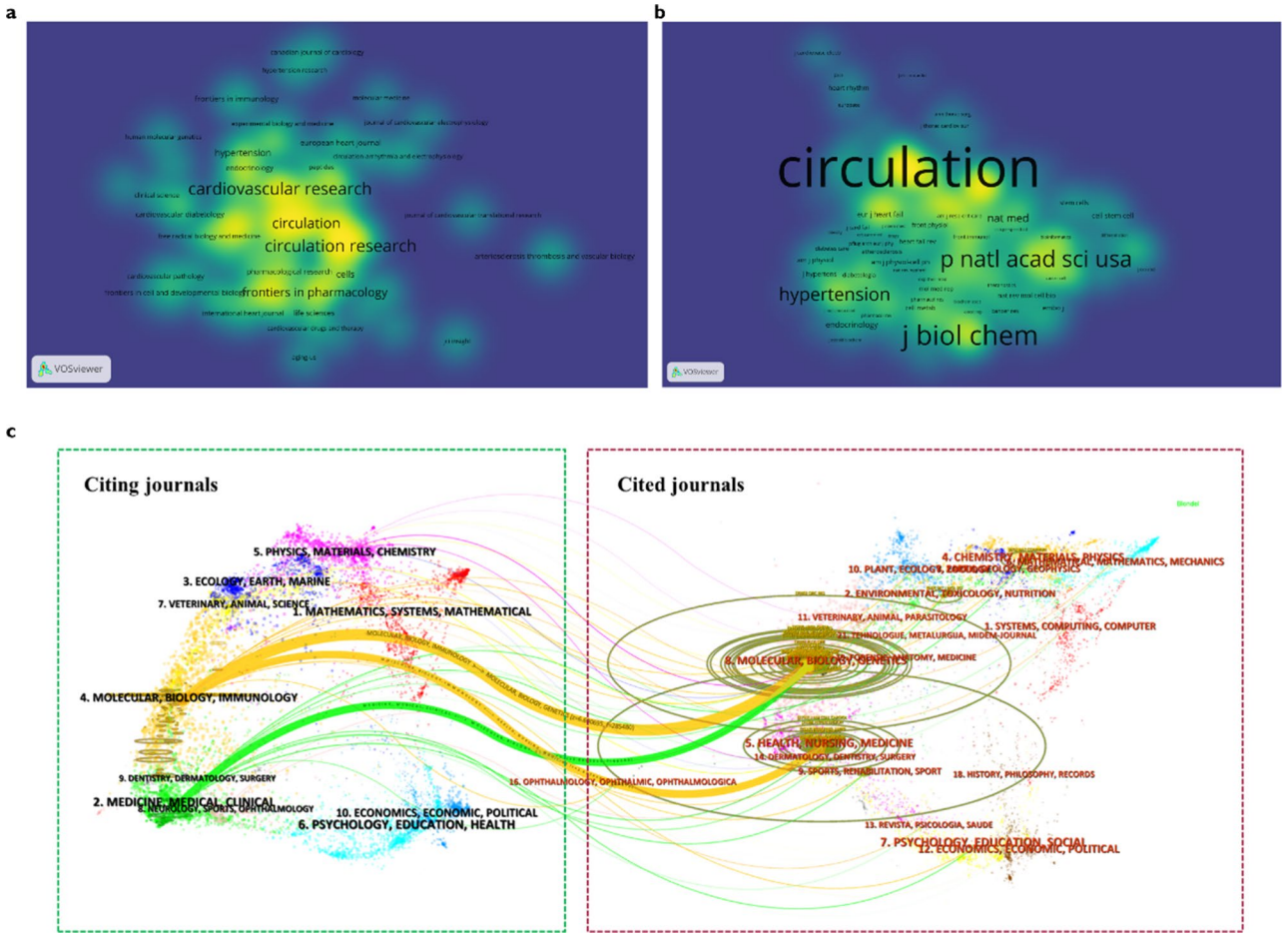

Fig. 4 Maps for leading journals and citation analysis. Density maps of (**a**) journals and (**b**) co-cited journals. The size of the world and circle and the opacity and yellow are positively associated with the frequency of co-citation. (**c**) Dual-map overlay of journals associated with the mechanism of myocardial fibrosis. Left: citingjournals. Right: cited journals

Table 4 Top 20 keywords associated with the MoMF[a]

Rank	Keyword	Count	Rank	Keyword	Count
1	Fibrosis	548	11	Heart Failure	236
2	Expression	493	12	Myocardial-Infarction	228
3	Heart-Failure	469	13	Apoptosis	209
4	Mechanisms	423	14	Myocardial Infarction	195
5	Heart	404	15	Fibroblasts	169
6	Inflammation	314	16	Disease	164
7	Activation	305	17	Inhibition	162
8	Oxidative Stress	264	18	Dysfunction	161
9	Cardiac Fibrosis	251	19	Angiogenesis	152
10	Hypertrophy	247	20	Myocardial Fibrosis	149

[a]MoMF: mechanism of myocardial fibrosis

keyword pairings was generated (Fig. 5a), featuring 209 key terms selected based on specific criteria of "minimum number of occurrences of a keyword ≥ 20."

The diagram of keyword network clustering analysis delineates five distinct clusters (Fig. 5a). Each is color-coded to represent a separate research field and its breadth. Notably, a smaller cluster number signifies greater impact. Cluster 1 encompasses 61 elements, notably "heart", "myocardial infarction", and "fibroblasts". Cluster 2 consists of 51 elements, featuring "inflammation", "oxidative stress", and "heart failure". Cluster 3 encompasses 41 elements, featuring "expression", "hypertrophy", and "cardiac fibrosis". Cluster 4 comprises 36 elements, featuring "activation", "mechanisms", and "heart-failure". Cluster 5 containes 20 elements, featuring "apoptosis", "dysfunction", and "cardiac hypertrophy".

Citation dynamics and emerging references

Using VOSviewer, the co-cited references related to the MoMF were analyzed. The co-occurrence analysis examines "co-cited literature", where two works are jointly cited in a third publication which identified 104,843 co-cited references on the MoMF from 1992. Based on the top 10 recurrently co-cited articles (Table 5), "Cardiac fibrosis: the fibroblast awakens." by Travers Jg et al. (2016) (79 co-citations) published in Circulation Research (IF = 20.1) held the title of the most "co-cited article". Furthermore, CiteSpace was used to conduct cluster analysis on the

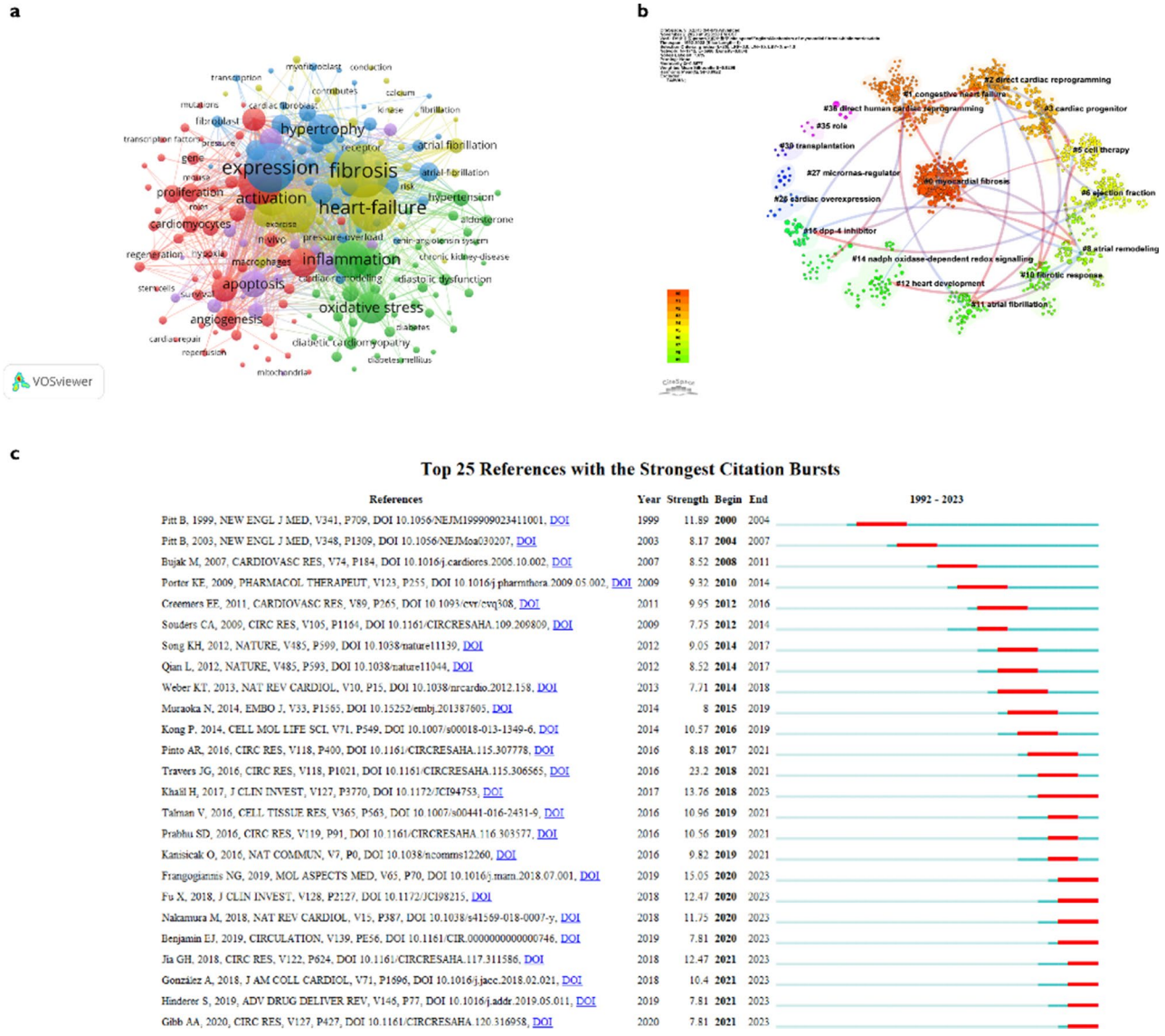

Fig. 5 Maps of keyword interactions, cluster networks and top 25 burst references. (**a**) Maps of keywords and co-occurrence network and clusters. The size of the node and keyword indicates the co-occurrence frequency. The different colors reflect different clusters. The links reflect the co-occurrence relationship. (**b**) Cluster of co-cited references. The colors indicate the different clusters of references, each represented by a point. The number on each point shows the cluster membership. The arrow points to a cluster that evolves into a source cluster overtime. (**c**) Top 25 burst references. The citation bars denote that the reference has been published. Red bars denote the strength of the burst reference

1,712 references based on the cluster analysis of on co-cited works. A summary of the largest 17 clusters is given below Fig. 5b (0 = myocardial fibrosis, 1 = congestive heart failure, 2 = direct cardiac reprogramming, 3 = cardiac progenitor, 5 = cell therapy, 6 = ejection fraction, 8 = atrial remodeling, 10 = fibrotic response, 11 = atrial fibrillation, 12 = heart development, 14 = nadph oxidase-dependent redox signalling, 15 = dpp-4 inhibitor, 26 = cardiac overexpression, 27 = micrornas-regulator, 30 = transplantation, 35 = role, and 36 = direct human cardiac reprogramming). Cluster dependency analysis reveals how different literature clusters are interconnected and how they evolve thematically over time. As illustrated in Fig. 5b, clusters 2 (direct cardiac reprogramming), 3 (cardiac progenitor), and 8 (atrial remodeling) have collectively influenced the development of cluster 0(myocardial fibrosis), indicating a significant collaborative contribution to the field's advancement. Moreover, the lower the number of a cluster, the greater its influence tends to be. The leading two clusters are presented in Table 6.

Reference burst denotes a citation spike for an article post-publication, reflecting heightened scholarly interest. This study identified 120 burst references, adhering to a minimum duration criterion (above 2). The foremost 25 are showcased (Fig. 5c), among which "Cardiac fibrosis: the fibroblast awakens" stands out as the pivotal

Table 5 Top 10 most frequently co-cited references involved studies on the MoMF[a]

Rank	Citation	Title	First author	Year	Journal
1	79	Cardiac fibrosis: the fibroblast awakens.	Travers Jg	2016	Circ Res
2	69	Cardiac fibroblasts: at the heart of myocardial remodeling.	Porter Ke	2009	Pharmacol Therapeut
3	65	Endothelial-to-mesenchymal transition contributes to cardiac fibrosis.	Zeisberg Em	2007	Nat Med
4	64	The pathogenesis of cardiac fibrosis.	Kong P	2014	Cell Mol Life Sci
5	62	The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure.	Pitt B	1999	New Engl J Med
6	58	Cardiac fibroblast: the renaissance cell.	Souders Ca	2009	Circ Res
7	56	The role of TGF-β signaling in myocardial infarction and cardiac remodeling.	Bujak M	2007	Cardiovasc Res
8	56	The Biological Basis for Cardiac Repair After Myocardial Infarction.	Prabhu Sd	2016	Circ Res
9	52	Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation.	Burstein B	2008	J Am Coll Cardiol
10	52	Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors.	Ieda M	2010	Cell

[a]MoMF: mechanism of myocardial fibrosis

sudden reference, boasting a citation strength of 23.2, as published in Circulation Research by Travers JG in 2016. Additionally, 8 references remained as burst references in 2023.

Discussion

Fundamental data synopsis

In this paper, we conduct a detailed bibliometric analysis on global research trends and developments in MoMF from 1992 to 2023 for the first time. Based on the basic information of the research, our analysis led to five principal discoveries. Firstly, the annual publication trend reveals that the research output by MoMF has been on an exponential rise since its inception, marking its growing prominence as a research topic. Secondly, the United States emerged as the leading country in MoMF research, excelling in published papers, centrality, and average citation. Thirdly, prominent figures in this field are Nattel, Stanley and Frangogiannis, Ng, respectively. Fourthly, the institution with the peak value in MoMF is the University of California System, while Cardiovasc Research is the primary publication venue, with Circulation being the journal with the highest citation frequency. Finally, the dual-map overlay of journals analysis indicates that research concerning MoMF predominantly focuses on fundamental studies and the field of translational medicine. Compared to the bibliometric research on MF conducted by Mao Y and colleagues [7], our study provides a more detailed interpretation of MoMF. Additionally, it supplements the analysis with journal dual-mapping overlays, cluster dependency, and burst literature analysis. Based on these enhancements, we further conducted an in-depth discussion on the evolutionary trends of research hotspots in MF.

Core knowledge base

In the study, co-cited literature, indicating two works frequently cited together, forms the foundation of a field's core knowledge. This body of the co-cited literature is divided into 17 main clusters using CiteSpace, with this study focusing on a detailed discussion of the most influential Cluster 0 "myocardial fibrosis" and 1 "congestive heart failure".

Through the analysis of the top 10 references in Cluster 0 "Myocardial Fibrosis" (Table 6), it was found that the content primarily focuses on the mechanisms of MF and its relationship with myocardial ischemia (MI) and HF. Specifically, activated fibroblasts (FBs) and myofibroblasts (myoFBs) serve as the pivotal cellular agents of cardiac fibrosis [8], representing the main source of matrix proteins [9, 10], crucial to the development and progression of MF [1, 11]. FBs can be activated by various stimuli, such as inflammation [12], oxidative stress [13] or mechanical stress [14], and transformed into myoFBs, which are more proliferative and fibrotic [15]. Excessive secretion of collagen and other matrix proteins, as well as cytokines and growth factors by myoFBs, can affect the survival and function of myocardial cells [16]. TGF-β upregulation is a hallmark of fibrotic diseases, exerting a pivotal regulatory function in FBs activation and extracellular matrix (ECM) production [17]. Hence, understanding the role and regulation of FBs in MF is vital for devising novel therapeutic strategies to mitigate MF and enhance cardiac function [18]. Meanwhile, following MI, FBs rapidly proliferate and create fibrotic scars, resulting in MF, which exacerbates cardiac remodeling and leads to a decline in cardiac function [19], progressively impairing cardiac function and potentially culminating in HF [20]. Therapeutic strategies aimed at targeting FBs and

Table 6 Top 10 co-cited references involved studies on the MoMF[a]

Rank	Citation	Title	First author	Year	Journal
A. Top 10 references in cluster0 "myocardial fibrosis"					
1	54	Cardiac fibrosis: the fibroblast awakens.	Travers JG	2016	Circ Res
2	48	Cardiac fibrosis: Cell biological mechanisms, molecular pathways and therapeutic opportunities.	Frangogiannis NG	2019	Mol Aspects Med
3	43	Fibroblast-specific TGF-β–Smad2/3 signaling underlies cardiac fibrosis.	Khalil H	2017	J Clin Invest
4	37	Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity.	Jia GH	2018	Circ Res
5	35	Specialized fibroblast differentiated states underlie scar formation in the infarcted mouse heart.	Fu X	2018	J Clin Invest
6	32	Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives.	González A	2018	J Am Coll Cardiol
7	25	Cardiac fibrosis.	Frangogiannis NG	2021	Cardiovasc Res
8	23	Cardiac fibrosis in myocardial infarction—from repair and remodeling to regeneration	Talman V	2016	Cell Tissue Res
9	22	Revisiting Cardiac Cellular Composition	Pinto AR	2016	Circ Res
10	22	Heart Disease and Stroke Statistics— 2019 Update A Report From the American Heart Association	Benjamin EJ	2019	Circulation
B. Top 10 references in cluster 1"congestive heart failure"					
1	19	The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure.	Pitt B	1999	New Engl J Med
2	13	Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction.	Pitt B	2003	New Engl J Med
3	7	Atrial Extracellular Matrix Remodeling and the Maintenance of Atrial Fibrillation.	Xu J	2004	Circulation
4	6	Limitation of Excessive Extracellular Matrix Turnover May Contribute to Survival Benefit of Spironolactone Therapy in Patients With Congestive Heart Failure.	Zannad F	2000	Circulation
5	6	Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease.	Boldt A	2004	Heart
6	6	Aldosterone Production Is Activated in Failing Ventricle in Humans.	Mizuno Y	2001	Circulation
7	6	Aldosterone in congestive heart failure.	Weber KT	2001	New Engl J Med
8	5	Aldosterone induces a vascular inflammatory phenotype in the rat heart.	Rocha R	2002	Am J Physiol-Heart C
9	5	Molecular Mechanisms of Myocardial Remodeling.	Swynghedauw B	1999	Physiol Rev
10	5	Increased Vulnerability to Atrial Fibrillation in Transgenic Mice With Selective Atrial Fibrosis Caused by Overexpression of TGF-β1.	Verheule S	2004	Circ Res

[a]MoMF: mechanism of myocardial fibrosis

the pathological fibrosis they drive promise to mark a significant advancement in the treatment of HF [11]. Recent clinical studies have shown that myocardial fibrosis is a significant contributor to the adverse progression of various heart diseases [21, 22, 23, 24, 25]. Targeted differentiation of cardiac fibroblasts remains a promising approach for treating heart failure [26, 27, 28].

Through the analysis of the top 10 references in Cluster 1 "congestive heart failure" (Table 6), focusing on ventricular remodeling and MF in congestive heart failure (CHF), its connection with atrial fibrillation (AF), and the role of aldosterone receptor antagonists in treatment. CHF is a condition marked by fluid buildup in the lungs and tissues, causing congestion and significantly impacting disability and mortality rates [29]. Deepening our comprehension of the pathophysiological processes that drive congestion and identifying more effective, personalized treatment approaches hold significant clinical importance [30]. Initially, ventricular remodeling serves as an adaptive mechanism to preserve cardiac output and perfusion [31]. However, over time, this adaptation becomes maladaptive, resulting in the progressive decline of heart function and ultimately leading to HF [32]. MF is a critical aspect of cardiac remodeling that can culminate in HF and death [16]. This fibrosis, initially compensatory, can eventually impair tissue stiffness and ventricular function as the disease advances [33]. Additionally, AF is associated with fibrosis, where an elevated concentration of ECM proteins contributes to structural alterations and the development of AF [34]. There is a reciprocal pathophysiological relationship between AF and CHF [35]. AF can precipitate CHF by diminishing cardiac output,

elevating ventricular filling pressures, and triggering tachycardia-mediated cardiomyopathy. Conversely, CHF can incite AF through mechanisms that include atrial dilation, fibrosis, inflammation, and electrical remodeling [36, 37]. In individuals diagnosed with CHF, in addition to standard therapies, spironolactone, through its blockade of aldosterone receptors, can significantly reduce the incidence and mortality risk in patients with severe HF [38], and are pivotal, life-saving treatments for patients with advanced HF [39]. The therapeutic effects of spironolactone correlate with higher baseline levels of collagen synthesis markers, indicating that mitigating excessive ECM turnover may be among the multiple mechanisms by which spironolactone confers benefits in CHF patients [40]. Therefore, the introduction of antifibrotic medications, cellular treatments, and ventricular assist devices has made fibrosis targeting an essential strategy in the treatment of HF [41, 42].

Analysis of trending hotspots and novel subjects

Keywords are concise terms or phrases that summarize the topic, concepts, ideas, and knowledge of an article. Keyword co-occurrence analysis is instrumental in revealing the dominant areas of study and emerging patterns and help researchers navigate and access the vast literature. The analysis of the top 20 high-frequency keywords in the MoMF (Table 4) indicates that the key areas of investigation within MoMF focus on the role of MF in the progression of various conditions, emphasizing inflammation, angiogenesis, oxidative stress, and ventricular remodeling. These interrelated factors underline the intricate pathophysiology of cardiac remodeling and heart failure progression, suggesting that targeting these mechanisms could offer promising prevention and treatment strategies for HF. A recent visualization study of fibroblast-specific networks suggests that targeting fibroblast phenotypic transformation in cardiac remodeling is a promising approach for anti-fibrotic therapy [43].

Keyword clustering analyses offer an insightful perspective on MoMF's research focal points, depicted through five distinct clusters (Fig. 5a). Cluster 1 delves into the cellular and molecular mechanisms of MF, exploring therapeutic avenues and aldosterone's role in CHF treatment. Cluster 2 examines heart repair and regeneration therapies. Cluster 3 addresses the pathological mechanisms behind MF and associated conditions like AF and HF. Cluster 4 investigates factors like STAT3-mediated capillary growth and microRNA's role in dilated cardiomyopathy, alongside issues related to post-transplant hypertrophy and TNF-α. Cluster 5 focuses on the oxygen supply-demand imbalance in HF pathophysiology and innovative cardiac reprogramming strategies for generating new myocardial cells. These results highlight the close integration between basic and clinical research on MoMF. This fusion not only enhances our understanding of MoMF mechanisms at the molecular and cellular levels but also facilitates the rapid translation of these findings into clinical practice, thereby accelerating the development of new diagnostic and therapeutic methods.

Burst references indicate emerging research trends within a field. In this analysis, 120 burst references were identified, with the top 25 presented in Fig. 5c. The analysis ranks 10 references according to the intensity of their citation burst, descending from the highest to the lowest, signifying their importance and impact on the field's development.

The first paper [11] (strength = 23.2) was a review by Travers JG et al., published in Circulation Research, delves into recent advancements in cardiac fibrosis research. It not only covers the latest findings but also outlines prospective research paths and identifies existing challenges in the field. The second paper [44] (strength = 15.05) was by Frangogiannis NG. published in Molecular Aspects of Medicine and provided an overview of cardiac fibrosis, discussing its definition, underlying mechanisms, effects on heart health, and current therapeutic approaches. The third paper [17] (strength = 13.76) was by Khalil H et al., published in The Journal of Clinical Investigation. Their research suggests that TGF-β–Smad2/3 pathways in activated cardiac fibroblasts are key drivers of fibrosis. The fourth paper [15] (strength = 12.47) was by Fu X et al., published in The Journal of Clinical Investigation. The study employed fibroblast lineage tracing specific to developmental stages, mechanistic evaluations in MI models, and mRNA profiling to delineate the varied states and behaviors of cardiac fibroblasts. This approach identified a distinct fibroblast state, termed the "matrifibrocyte", which is characteristic of the mature scar tissue. The fifth paper [45] (strength = 12.74) was by Jia GH et al. and published in Circulation Research. The purpose of this review is to showcase a current perspective on the factors contributing to diabetic cardiomyopathy, alongside mechanistic strategies for its prevention and treatment. The sixth paper [38] (strength = 11.89) was by Pitt B et al., published in The New England Journal of Medicine. The article reports the results of the Randomized Aldactone Evaluation Study (RALES), highlighting that the inclusion of spironolactone, an aldosterone antagonist, in conventional treatment markedly reduces morbidity and mortality risks among those with advanced HF. The seventh paper [46] (strength = 11.75) was by Nakamura M and Sadoshima J and published in Nature Reviews Cardiology. In this Review, the authors delve into the molecular mechanisms behind both physiological and pathological hypertrophy, particularly highlighting the significance of metabolic remodeling in these processes. They also discuss the potential of leveraging current understanding of cardiac hypertrophy to formulate innovative therapeutic

approaches aimed at preventing or reversing pathological hypertrophy. The eighth paper [20] (strength = 10.96) was by TaIman V and Ruskoaho H, published in Cell and Tissue Research. The article provides an overview of the latest insights into the mechanisms and therapeutic approaches for cardiac fibrosis, a disorder marked by the overproduction of cardiac scar tissue following a MI (heart attack). The ninth paper [47] (strength = 10.57) was by Kong P and colleagues and published in Cellular and Molecular Life Sciences. This review shedding light on the complex interplay responsible for cardiac fibrosis. The tenth paper [48] (strength = 10.56) was by Prabhu SD and Frangogiannis NG and published in Circulation Research. This review investigates the cellular components and molecular dynamics contributing to cardiac fibrosis progression, shedding light on the complex interplay responsible for this condition's progression. To sum up, a burgeoning area of interest is the function of FBs post-myocardial injury and novel treatments to mitigate MF. Recent research further elucidates the significant potential of FBs in treating various cardiovascular diseases, including HF, and paves the way for the development of new therapeutic approaches [49, 50, 51, 52, 53].

Limitations

The study identified four primary limitations. Firstly, the literature was sourced exclusively from the WoSCC, which may result in the omission of significant studies from other databases. For instance, databases such as PubMed, Scopus, and Embase also contain a large body of literature on MoMF. The exclusion of these resources could lead to incomplete research findings. Secondly, relying solely on WoSCC may overlook regional studies or literature published in languages other than English, thus failing to fully capture global research trends and progress. Thirdly, the manual deletion of articles not directly related to MoMF could unintentionally exclude studies with potential relevance. Given the complexity and interdisciplinary nature of the research topic, some important studies may not explicitly mention MoMF in their titles or abstracts, yet their content is essential for understanding the mechanisms and applications of MoMF. Additionally, the manual screening process is subject to the researchers'judgment, which may lack uniform standards and objectivity, potentially affecting the completeness of the literature collection and the reliability of the analysis. Finally, the analysis focused primarily on literature from the first two clusters of the core knowledge base, limiting a comprehensive understanding of the entire field. Literature from other clusters may contain emerging research hotspots, cutting-edge theories, and potential development directions. Neglecting these areas may hinder a full understanding of research trends and the overall landscape of MoMF research.

Future directions

An increasing number of studies have demonstrated that early diagnosis of MF is crucial for improving cardiac function, and targeted therapies for MF hold significant potential [54]. However, there is currently a lack of research on early biomarkers for MF [55]. Although various preclinical studies have highlighted the potential effectiveness of new drugs and molecules in treating cardiac fibrosis in animal models, clinical trials investigating these effects remain insufficient [56]. Future research should focus on clinical trials to evaluate the efficacy of fibroblast-targeting therapies in human populations. Additionally, further studies are needed to explore the interaction between myocardial fibrosis and other cardiovascular diseases, which may influence disease progression and treatment outcomes.

Conclusion

The MoMF continues to be a focal point worthy of further exploration. Ongoing research seeks to uncover treatment approaches that are both more specific and effective. Utilizing CiteSpace and VOSviewer, we scrutinized data from the WoSCC, assessing publication volume, citation influence, collaboration trends, key research areas, and emerging themes, thereby delving into the foundational knowledge and prospective research trajectories, and outlining the prevailing challenges in the field. In conclusion, research on the MoMF not only advances the development of targeted therapies and enhances diagnostic tools, thereby effectively preventing HF [2, 57], but also opens new avenues for the application of personalized medicine and regenerative therapies [58, 59]. However, further clinical studies are necessary to validate these emerging approaches.

Abbreviations

MF	Myocardial Fibrosis
HF	Heart Failure
MoMF	Mechanisms of Myocardial Fibrosis
WoSCC	Web of Science Core Collection
JCR	Journal Citation Report
IF	Impact Factor
MI	Myocardial Ischemia
FBs	Fibroblasts
myoFBs	myofibroblasts
ECM	Extracellular Matrix
CHF	Congestive Heart Failure
AF	Atrial Fibrillation

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Author contributions

JZ analyzed the data and wrote the manuscript. WW made revision for the manuscript. ZW acquired the data, which were interpreted by all authors. MZ and SW supervised the study. JZ and WW contributed equally to this work and share first authorship. All authors contributed to the article and approved the submitted version.

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Data availability
The datasets generated and/or analysed during the current study are available in the [The Science Citation Index Expanded (SCI-Expanded 1999- present) of Clarivate Analytics'S Web of Science Core Collection (WoSCC)] repository, https://www.webofscience.com/wos/alldb/basic-search. The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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