Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Global Research Trends in Oxidative Stress and Myocardial Fibrosis: A Dual-Software Bibliometric Study

Sihan Jia[1], Yanjie Lian[1], Xiaolei Lai[1], Sinai Li[1,2], Juju Shang[1], Hongxu Liu[1]

[1]Department of Cardiovascular, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100010, People's Republic of China; [2]Beijing Institute of Traditional Chinese Medicine, Beijing, 100010, People's Republic of China

Correspondence: Hongxu Liu; Juju Shang, Department of Cardiovascular, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100010, People's Republic of China, Email liuhongxu@bjzhongyi.com; shangjuju@bjzhongyi.com

Objective: To conduct a visualization analysis of the literature on the role of oxidative stress in myocardial fibrosis (MF), explore the research progress, frontier hotspots, and development trends in this field, with the aim of providing a reference for the research on the prevention and treatment of MF related to oxidative stress.

Methods: Web of Science was selected as the data source, and the relevant English literature on the role of oxidative stress in MF from the database establishment to December 31, 2024 was collected. Bibliometric methods were used for statistical analysis of the literature that met the research standards, and CiteSpace 6.3.R2 and VOSviewer 1.6.20 software were used for visualization of information such as publishing countries, institutions, authors, and keywords.

Results: A total of 1831 SCI articles were included. The global publication volume showed an upward trend year by year, Publications increased by 16% annually after 2014, with China and the United States leading in publication volume. Keyword and cited literature analysis showed that the research hotspots and frontiers in this field mainly include the phenomenon of extracellular matrix (ECM) cell migration, the activation of the renin-angiotensin-aldosterone system, the regulatory mechanisms of oxidative stress in MF of different etiologies, and the mechanisms of action of oxidative stress in MF.

Conclusion: The field of research into the role of oxidative stress in myocardial fibrosis is currently experiencing a period of rapid expansion. By leveraging the complementary strengths of CiteSpace for analyzing temporal and geographic trends, and VOSviewer for mapping collaboration networks, researchers have gained multidimensional insights into this area. The identification of the NLRP3 inflammasome as the fastest-growing research frontier, highlights its potential as a novel therapeutic target for clinical investigation. The mechanism by which oxidative stress activates the NLRP3 inflammasome signaling pathway to promote myocardial fibrosis is likely to emerge as a significant future research trend and warrants further in-depth exploration and study.

Keywords: oxidative stress, myocardial fibrosis, citespace, bibliometrics, visual analysis

Introduction

MF is a common pathological change in the development of various cardiovascular diseases, characterized by the pathological remodeling of the ECM.[1] Persistent fibrosis can affect myocardial metabolism, reduce tissue compliance, lead to ventricular remodeling, and accelerate the progression to heart failure (HF).[2,3] Globally, the annual incidence rate of MF is approximately 1.7%. Notably, the progression of MF to HF is associated with a significantly elevated mortality risk, with 5-year mortality rates ranging from 40% to 60%.[4] How to effectively prevent and delay fibrosis is a hot and challenging issue in the treatment of HF. Modern medicine posits that the pathogenesis of MF is associated with the continuous activation of the Renin-Angiotensin-Aldosterone System (RAAS), inflammatory responses, and autophagy. Clinically, treatments for MF include RAAS inhibitors, beta-blockers, and statins. These medications can alleviate clinical symptoms in patients but have limited effects in halting or reversing MF. When patients discontinue these medications or develop drug tolerance, their conditions may deteriorate further.[5,6] Multiple studies have shown that

Received: 19 March 2025
Accepted: 27 May 2025
Published: 11 June 2025

oxidative stress is an important factor in promoting the occurrence and development of MF, so how oxidative stress plays a role in the different stages of MF development has increasingly attracted the attention of researchers.

Oxidative stress refers to the abnormal metabolic state caused by an imbalance between the oxidative and antioxidant systems in the body, resulting in the accumulation of large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS) under the stimulation of various harmful factors.[7,8] In a physiological state, low levels of ROS and RNS are necessary signaling molecules for mediating cell signal transduction and maintaining the body's balance. However, the excessive production of ROS and RNS can lead to an oxidative stress response, causing the denaturation of proteins, lipids, DNA, and RNA, thereby damaging myocardial cells.[9] Increasing research has shown that oxidative stress plays an important role in multiple stages of the development of MF, mainly related to the induction of myocardial cell apoptosis, the promotion of inflammatory factor expression, and the abnormal proliferation of cardiac fibroblasts (CFs) leading to ECM remodeling.[9] Therefore, alleviating oxidative stress is an effective strategy to inhibit inflammation and MF.

CiteSpace, developed by Professor Chaomei Chen at Drexel University in the United States, is a widely recognized bibliometric software that has garnered substantial attention from both domestic and international scholars in recent years.[10–12] This software is uniquely equipped to systematically trace hidden patterns and associations within extensive document collections. By analyzing key indicators such as the volume of literature output, author collaboration networks, co-occurrence of keywords, and citation trajectories, CiteSpace not only quantifies the development trends of research topics but also uncovers latent knowledge structures that traditional review methods might overlook.[10–12] However, CiteSpace is not the only tool available in this domain. VOSviewer, developed by Van Eck and Waltman at Leiden University in the Netherlands, is another powerful bibliometric mapping tool.[13] It excels in generating various visualizations based on bibliometric relationships, such as co-citation networks of authors or journals and co-occurrence networks of keywords. Consequently, this tool is particularly useful for revealing the structure, evolution, and collaboration within a knowledge domain. In the early stages of COVID-19 research, bibliometric analysis unexpectedly revealed that the academic attention given to Remdesivir far exceeded the level of clinical evidence supporting its efficacy. This "premature focus" in the academic community not only exposed the collective cognitive bias of the scientific community towards potential therapies during public health crises but also directly propelled discussions on the paradigm of evidence weighting and resource allocation principles in research on emerging infectious diseases. Thus, while CiteSpace and VOSviewer offer valuable insights into research trends and knowledge structures, their findings also highlight the importance of aligning academic attention with robust clinical evidence, particularly in the context of public health emergencies.[14] Therefore, this study used CiteSpace 6.3.R2 and VOSviewer 1.6.20 to visualize the knowledge maps of literature on oxidative stress related to MF in the Web of Science database, and conducted bibliometric analysis, in order to demonstrate the current research status, development trajectory, research hotspots, and potential trends, with the aim of providing reference and inspiration for future related research.

Data and Methods

Data Sources and Search Strategy

The Web of Science Core Collection (WoSSC) provides a comprehensive overview of relevant information, including publications, citations, authors, references, and keywords, making it one of the most widely used databases in bibliometric research.[15] This study used WoSSC as the data source for the basic search, with the search terms TS = ("Oxidative Stress" OR "Antioxidative Stress") AND TS = ("myocardial fibrosis" OR "myocardial interstitial fibrosis" OR "cardiac fibrosis" OR "atrial fibrosis" OR "ventricular fibrosis" OR "heart fibrosis" OR "myocard* fibrosis" OR "myocard* interstitial fibrosis" OR "card* fibrosis"), limiting the publication time from the database inception to December 31, 2024, and the document types to "Article" and "Review", with the language limited to "English". The search was conducted on December 31, 2024, and irrelevant literature was excluded. The full records (including title, author, source, abstract, keywords, cited references, and publication year) were exported in text format for analysis, and named in the format "download_**.txt". Furthermore, to ensure the accuracy and reliability of the research data, two researchers independently completed the data collection and screening tasks, and a third person was involved to make the final decision if there were any disagreements.

Analysis Methods

Using the VOSviewer software, author and institution collaboration network maps were created. Based on CiteSpace 6.3. R2 software, visualization analyses were conducted for countries and keywords, to analyze the current research status, frontiers, and development trends of oxidative stress related to MF.

Results

Distribution of Literature

An analysis was conducted on the 1,831 included articles, and a flowchart was created, as shown in Figure 1. The annual publication trend was plotted, as shown in Figure 2. From the figure, it can be seen that research on oxidative stress related to MF first appeared in 1999, and the publication volume has slowly increased since then. 2014 was a turning point, global

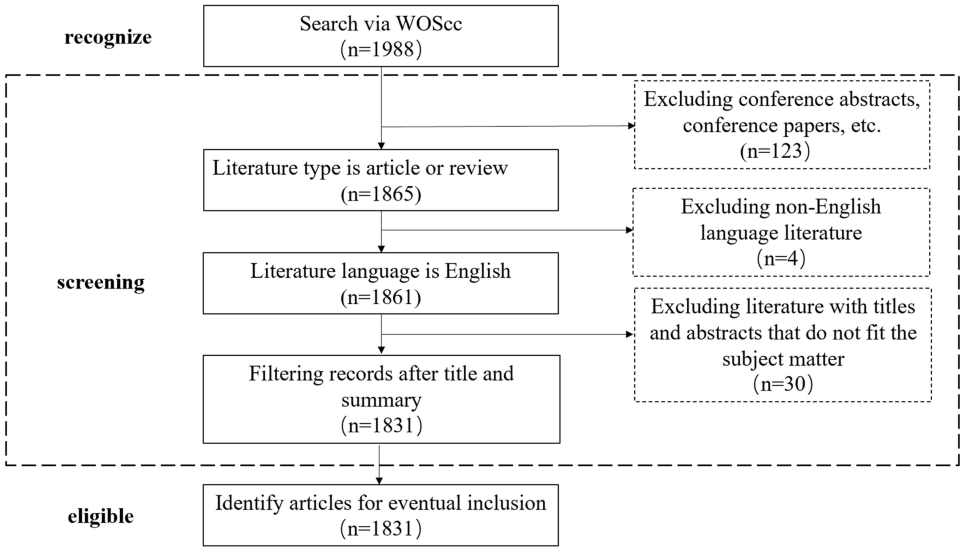

Figure 1 Flowchart for incorporating articles.

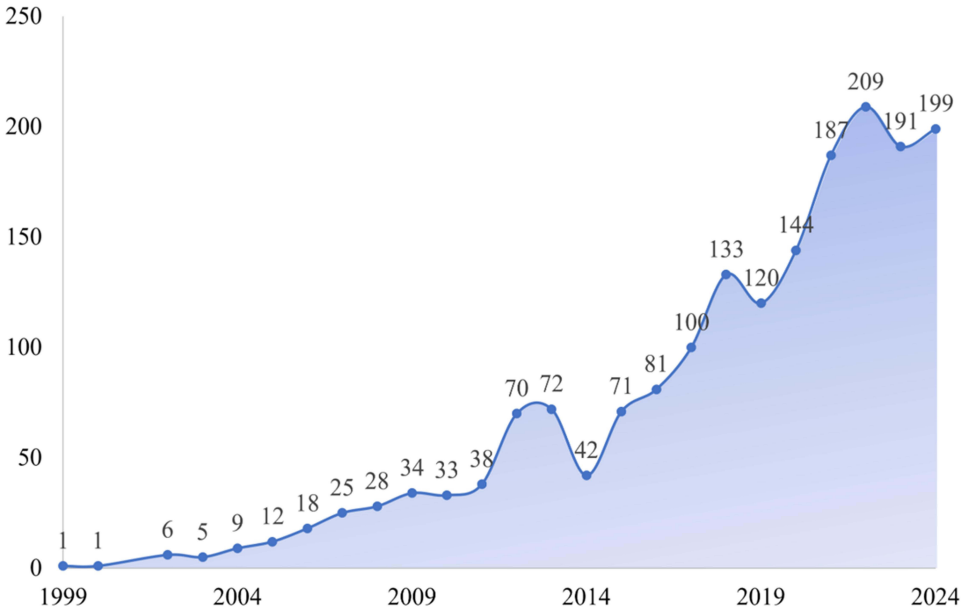

Figure 2 Trend of annual publication volume.

https://doi.org/10.2147/JMDH.S525389

Table 1 Authors with a Publication Frequency of ≥11

Rank	Author	Year	Publications
1	Sowers, James R	2085	19
2	Habibi, Javad	729	13
3	Nagata, Kohzo	365	13
4	Young, Morag J	732	13
5	Demarco, Vincent G	601	12
6	Murohara, Toyoaki	410	12
7	Aroor, Annayya R	729	11
8	Cachofeiro, Victoria	297	11
9	Li, Jun	297	11
10	Wang, Jing	90	11

publications increased at a compound annual growth rate (CAGR) of 16.0%, after which the publication volume began to grow rapidly, reaching a historical high in 2022. Overall, the publication volume on the topic of oxidative stress in MF research has shown a stable growth trend, reflecting the immense development potential and prospect of this research field.

Collaborative Network Analysis

Distribution of Authors

The visualization map can provide information on influential research teams and potential collaborators, and can help researchers establish collaborative relationships.[16] The 1,831 articles involved 215 authors, with the most prolific author being Sowers, James R (19 articles). The top 10 authors by publication volume are shown in Table 1. Using VOSviewer, an author collaboration network map was generated, as shown in Figure 3. Overall, the collaboration relationships among scholars are relatively close. By analyzing the author collaboration relationships, it can be seen that several major research teams have taken shape around Sowers, James R, Young, Morag J, Cachofeiro, Victo, Wang, Jing, and others, indicating that they have made important contributions to the research on the role of oxidative stress in MF.

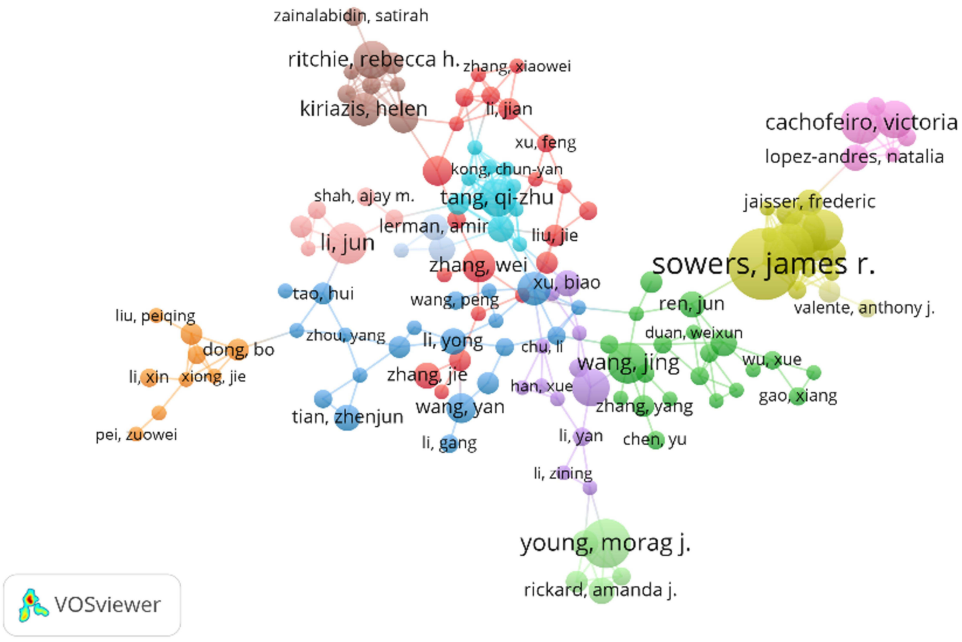

Figure 3 Author collaboration chart.

Table 2 Number of National Publications

Country	Publications	Percentage	Year
Peoples R China	847	0.22	2007
USA	329	0.48	2002
Japan	132	0.11	2003
Canada	68	0.08	2000
Austrilia	59	0.06	2004
Germany	52	0.18	2004
Italy	52	0.13	2002
India	50	0.02	2002
England	45	0.06	2006
Spain	40	0.08	2005

Distribution of Countries/Institutions

Analyzing the distribution of authors' countries/institutions can help understand the research enthusiasm of various countries and institutions in the field of oxidative stress related to MF. CiteSpace software and VOSviewer were used to generate country co-occurrence maps and institution co-occurrence maps, respectively. The results of this study show that 66 countries have participated in the related research on oxidative stress in MF, and the distribution of the top 10 countries/regions by publication volume is shown in Table 2.

The top 10 countries are mainly distributed in North America, Asia, and Europe. The country with the most published papers is China (n = 690, 39.32%), followed by the United States (n = 451, 25.70%). China and the United States account for more than half of the total publications, indicating that these two countries have invested relatively more research funding and personnel in the field of oxidative stress in MF, which also reflects that economic development is the basis for driving disease prevention and health development.

We have constructed a time zone map according to the publication time order of the 66 countries, as shown in Figure 4. From Figure 4, we can see that China started relatively late in this field, but with the rapid economic

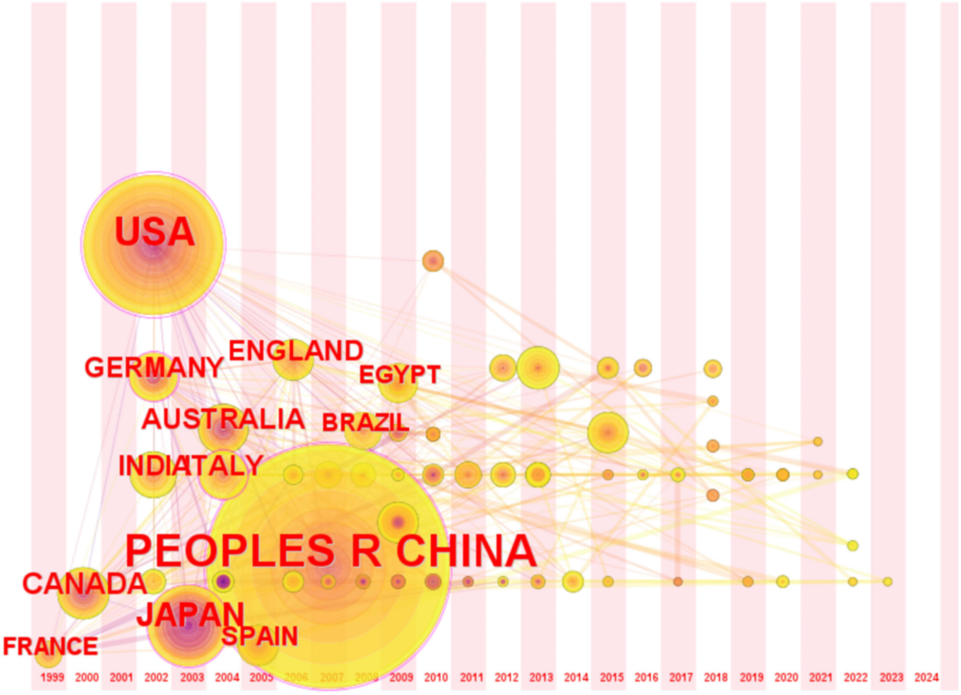

Figure 4 Research country co-occurrence map.

https://doi.org/10.2147/JMDH.S525389

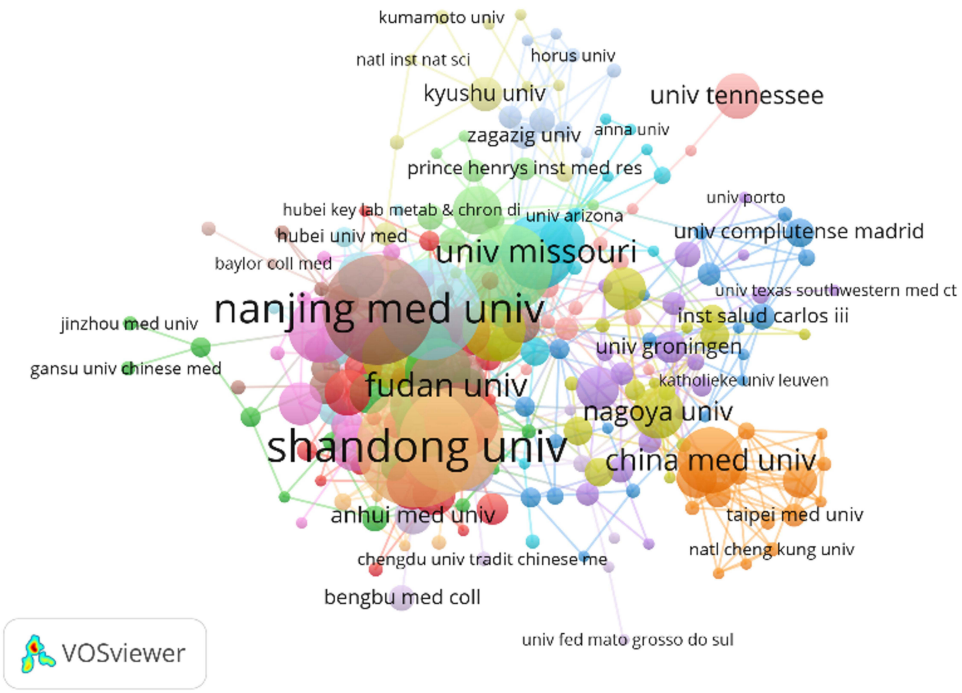

Figure 5 Mapping of institutional cooperation.

development and the continuous increase in research investment, China's academic contribution in this field has made significant progress and has become one of the countries with the most publications in this field. In addition, the cooperation among countries is quite close. For example, the United States cooperates closely with Australia and Canada; China cooperates more with the United States and the United Kingdom.

The institution collaboration map is shown in Figure 5, and the top 10 institutions by publication volume are shown in Table 3, which are Shandong University (China; n = 42), Nanjing Medical University (China; n = 38), Shanghai Jiao Tong University (China; n = 36), Wuhan University (China; n = 35), Monash University (Australia; n = 30), Fudan University (China; n = 27), Capital Medical University (China; n = 26), University of Missouri (USA; n = 26), China Medical University (China; n = 23), and China Academy of Chinese Medical Sciences (China; n = 23). Among them, Chinese institutions occupy 8 places, suggesting that China is active in the research on oxidative stress in MF, indicating that Chinese researchers have invested a great

Table 3 Top 10 Research Institutions in Terms of the Number of Publications and Centrality

Rank	Research institutions	Frequency	Quote
1	Shandong University	42	1034
2	Nanjing Medical University	38	645
3	Shanghai Jiao Tong University	36	702
4	Wuhan University	35	934
5	Monash University	30	1872
6	Fudan University	27	931
7	Capital Medical University	26	766
8	University of Missouri	26	2217
9	China Medical University	23	454
10	Chinese Academy of Medical Sciences	23	588
11	Shandong University	42	1034
12	Nanjing Medical University	38	645

deal of effort and resources in this field, and have played an important role in the construction of the global scientific knowledge system in this field.

Number of Journal Publications

Through the analysis of the published journals, the important journal sources and characteristics of the literature on oxidative stress related to MF can be revealed. There are a total of 13 journals with more than 20 publications, as shown in Table 4. Among them, "INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES" reported the most in this field, with 42 papers. "CARDIOVASCULAR RESEARCH" has the highest impact factor (IF = 10.9), indicating that the quality and academic impact of research papers in this field have received attention and recognition from authoritative international journals.

Keyword Analysis

Keyword Co-Occurrence Analysis

Co-occurrence keywords can reflect the core research content of the research field of oxidative stress related to MF, that is, the research hotspots. As shown in Figure 6, the co-occurrence keyword map was obtained, and combined with the analysis of Table 5, the top 20 keywords with the highest frequency in this field are oxidative stress, MF, heart failure, cardiac hypertrophy, dysfunction, expression, activation, etc. A comprehensive analysis of the above keywords reveals that the research hotspots in the field of oxidative stress-related MF research are mainly focused on: The regulatory mechanisms of oxidative stress in MF caused by different etiologies (heart failure, myocardial infarction, diabetic cardiomyopathy, cardiomyopathy, atrial fibrillation); The biological processes that coexist in MF oxidative stress, such as inflammation, apoptosis, injury, and dysfunction; The substances involved in regulating the oxidative stress process in MF, such as angiotensin II, NADPH oxidase, NF-κB, etc.

Keyword Clustering Analysis

After running Citespace for keyword clustering analysis, a keyword clustering peak-valley map was obtained, as shown in Figure 7. Based on the keyword clustering map, the research on oxidative stress related to MF can be divided into nine major clusters: glucocorticoid receptor, reperfusion injury, diabetic cardiomyopathy, MF, atrial fibrillation, cardiovascular disease, protein kinase C (PKC), dilated cardiomyopathy, and ECM. The nine major research directions of oxidative stress related MF research are summarized based on the keywords in each cluster, as shown in Table 6.

Keyword Mutation Analysis

Burst keywords are words whose frequency change rate is relatively high during a certain period, which can reflect the research frontiers and the evolution of research topics over the years. Using the Burstness function in CiteSpace, it can be seen from Figure 8 that the early and long-lasting burst keywords were found to be "tumor necrosis factor α", "angiotensin converting enzyme", "nitric oxide synthase", and "gene expression". The longest-lasting burst was "gene expression" at 15

Table 4 Number of Journal Articles

Rank	Journal	Number	IF
1	International Journal of Molecular Sciences	42	5.6
2	Oxidative Medicine and Cellular Longevity	41	7.31
3	Frontiers in Pharmacology	42	5.6
4	Biomedicine & Pharmacotherapy	34	7.5
5	PLos One	32	3.7
6	Hypertension	30	8.3
7	American Journal of Physiology-Heart and Circulatory Physiology	28	4.8
8	Life Sciences	26	6.1
9	European Journal of Pharmacology	25	5
10	Frontiers in Cardiovascular Medicine	22	3.6
11	Cardiovascular Research	21	10.9
12	Scientific Reports	20	4.6

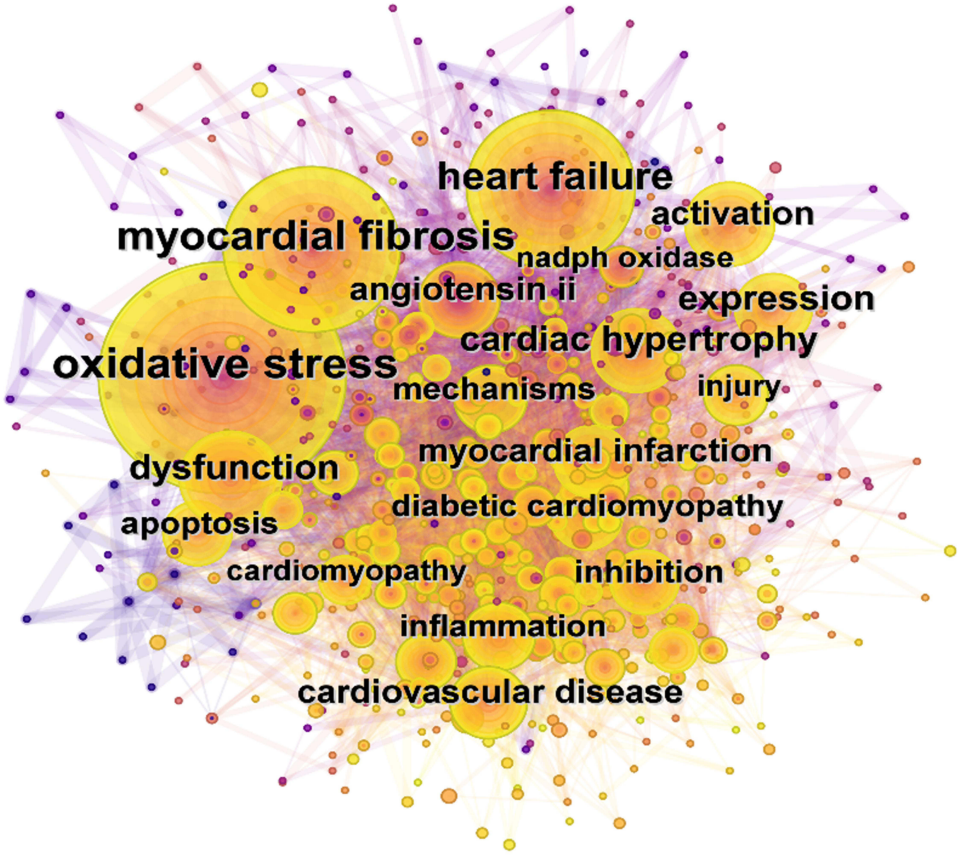

Figure 6 Keyword co-occurrence mapping.

years. Keywords with burst strength greater than 10 include "angiotensin II", "glucocorticoid receptor", "NADPH oxidase", and "blood pressure", with "angiotensin II" having the highest burst strength of 19.43 and lasting for 10 years. A recent burst keyword is "NLRP3 inflammasome", which suggests that researchers in this field believe oxidative stress can activate the NLRP3 inflammasome signaling pathway to promote the development of MF. This indicates that research on inflammation-related signaling pathways will be a key focus in the future of oxidative stress in MF.

Co-Citation Analysis of Journals

The knowledge flow analysis method was used to explore the evolution of journal citations and co-citations.[16] The journal's dual-map overlay shows the distribution of academic journal topics, changes in citation trajectories, and the transfer of research

Table 5 High-Frequency Keywords

Rank	Keyword	Frequency	Centrality	Rank	Keyword	Frequency	Centrality
1	Oxidative stress	1200	0.04	11	mechanisms	168	0.02
2	Myocardial fibrosis	724	0.02	12	apoptosis	164	0.03
3	Heart failure	653	0.02	13	diabetic cardiomyopathy	164	0.01
4	Cardiac hypertrophy	300	0.06	14	inflammation	157	0.02
5	Dysfunction	291	0.06	15	inhibition	133	0.02
6	Expression	260	0.07	16	injury	114	0.02
7	Activation	238	0.05	17	cardiomyopathy	111	0.02
8	Cardiovascular disease	207	0.05	18	NADPH oxidase	107	0.04
9	Angiotensin II	187	0.04	19	atrial fibrillation	99	0.03
10	Myocardial infarction	183	0.03	20	nf kappa b	92	0.03

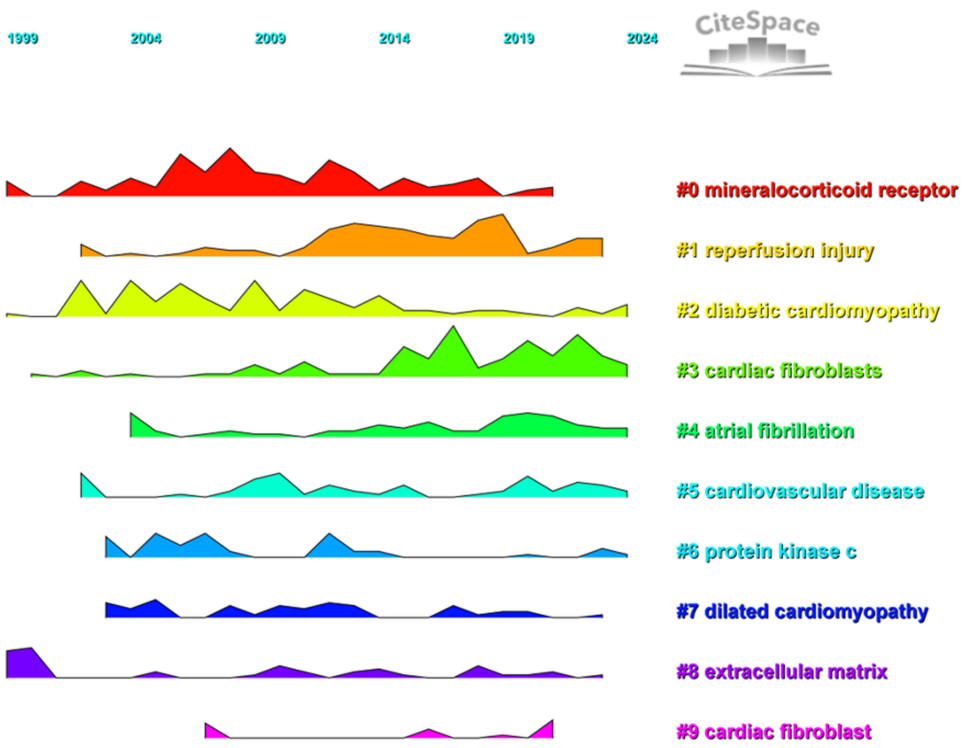

Figure 7 Keyword clustering.

centers. The left-hand labels of the dual-map represent the citing fields, and the right-hand labels represent the cited fields.[17] The Z-score function is used to merge the citation lines. The colored connection curves originating from the citation map and pointing to the cited map show the context of the citations, called citation paths. As shown in Figure 9, there are mainly 3 citation paths: The green citation line indicates that research from medical and clinical journals is often cited by molecular, biological, and genetic journals. The two orange citation lines indicate that research from molecular, biological, and immunological journals is often cited by molecular, biological, genetic, nursing, and medical journals. In summary, the dual-map overlay analysis reveals the disciplinary connections and knowledge flows between different academic journals in this research field.

Table 6 Clustering Labels

Number	Frequency	Centrality	Keyword
0	124	0.583	mineralocorticoid receptor; aldosterone; cardiac remodeling; left ventricular dysfunction; smooth muscle cells
1	110	0.536	reperfusion injury; myocardial ischemia; metabolism; mesenchymal stem cells; left ventricular function
2	107	0.579	diabetic cardiomyopathy; myocardial fibrosis; oxidative stress; reactive oxygen species; inhibition
3	105	0.555	cardiac fibroblasts; renal fibrosis; endoplasmic reticulum stress; organ fibrosis; doxorubicin-induced cardiomyopathy
4	67	0.683	atrial fibrillation; atrial fibrosis; atrial remodeling; diabetes mellitus; cardiac fibrosis
5	60	0.666	cardiovascular disease; chronic kidney disease; uremic cardiomyopathy; left ventricular hypertrophy; fine particulate matter
6	46	0.775	protein kinase c; diabetic nephropathy; pioglitazone; advanced glycation end products; inflammation
7	45	0.812	dilated cardiomyopathy; experimental autoimmune myocarditis; c-reactive protein; myocardium; receptor
8	43	0.781	extracellular matrix; endothelial cells; down regulation; microvascular dysfunction; muscle cell migration

https://doi.org/10.2147/JMDH.S525389

Top 20 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1999 - 2024
necrosis factor alpha	1999	8.07	1999	2012	
angiotensin converting enzyme	1999	7.87	1999	2013	
smooth muscle cells	1999	7.59	1999	2012	
gene expression	1999	6.25	1999	2014	
nitric oxide synthase	1999	6.1	1999	2011	
congestive heart failure	2003	7.43	2003	2014	
angiotensin ii	2002	19.43	2004	2014	
aldosterone	2004	9.09	2004	2010	
spironolactone	2004	7.48	2004	2012	
hypertension	2004	5.24	2004	2013	
matrix metalloproteinases	2005	4.96	2005	2009	
mineralocorticoid receptor	2006	10.47	2006	2013	
left ventricular dysfunction	2002	6.38	2006	2014	
nadph oxidase	2005	18.19	2008	2016	
blood pressure	2004	11.12	2008	2013	
left ventricular hypertrophy	2005	6.76	2009	2017	
dilated cardiomyopathy	2003	6.12	2010	2013	
metabolic syndrome	2008	5.88	2011	2018	
diastolic dysfunction	2006	7.2	2014	2017	
nlrp3 inflammasome	2017	7.42	2021	2024	

Figure 8 Keyword burst.

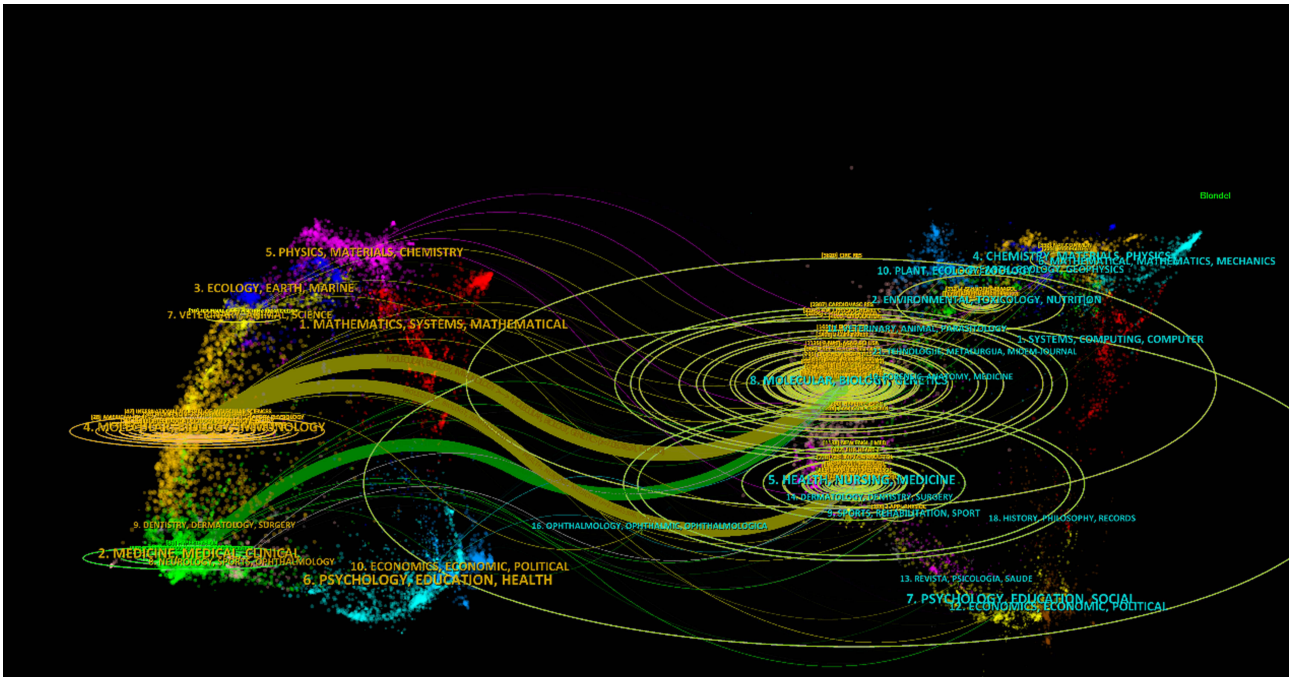

Figure 9 Clustering relationship of journal analysis.

Discussion

MF is a reactive remodeling process in response to myocardial injury, mainly manifested by the proliferation of myocardial fibroblasts and the excessive production and deposition of ECM proteins to replace the damaged tissue. However, the excessive generation and deposition of ECM, along with the increased ratio of type I and III collagen, lead to pathological fibrotic remodeling, which promotes the development of cardiac dysfunction and ultimately progresses to

HF. This study applied CiteSpace 6.3.R2 and VOSviewer 1.6.20 literature analysis software to analyze the research hotspots and trends of oxidative stress in the field of MF from aspects of publication volume, authors, countries, institutional collaboration networks, as well as keyword co-occurrence, clustering, and burst words.

Publications on Oxidative Stress in MF

The overall publication volume of literature on oxidative stress-related MF has shown an upward trend, indicating that the research on oxidative stress in the field of MF is receiving increasing attention. It is predicted that the research hotspot will continue to increase, and the publication output is expected to maintain a growth trend in the coming years.

China ranks first in the world in terms of publication volume in the field of oxidative stress-related MF research. The intertwined and complex co-occurrence network map suggests that preliminary collaborative relationships have been established among institutions in different countries, but the in-depth cooperation between countries is currently mainly limited to some economically and technologically more developed nations. This indicates that although preliminary cooperation exists, international collaborative research still needs to be strengthened. It is recommended to establish national academic exchange programs to promote exchange and cooperation among different institutions internationally, which can leverage complementary strengths to produce more fruitful research results and provide more effective methods for the prevention and treatment of MF.

The publishing institutions are mainly concentrated in medical universities and some comprehensive universities, with Shandong University having the highest publication volume. However, there is not yet a globally comprehensive collaborative network among different institutions, which is not conducive to the long-term stable development of this field. Therefore, we suggest that research institutions in different countries should carry out more comprehensive and in-depth collaborative research to promote the development of the global research network on oxidative stress in MF.

In terms of the authors, Sowers, James R, Habibi, Javad, Nagata, Kohzo, and Young, Morag J have had a significant impact in this field, and following the achievements of these authors will help better understand the frontier dynamics and development trends in this field.

Most of the research on oxidative stress in MF is published in the journal "International Journal of Molecular Sciences" (n = 42), which has an impact factor of 4.9, is in the Q1 quartile, and publishes articles related to biochemistry, molecular and cellular biology, molecular biophysics, and molecular medicine, among others. In addition, the overlaid journal map (Figure 9) shows that "medicine, clinical, molecular" is frequently cited in "molecular, biology, genetics", indicating that the current research on oxidative stress in the field of MF is increasingly focused on basic research.

Mechanisms of Oxidative Stress in MF

①Cell Injury and Cell Death: Oxidative stress can lead to excessive production of ROS, which can directly damage the DNA, proteins, and lipids of cardiomyocytes, causing impaired cell function. Persistent oxidative stress can also trigger cell apoptosis pathways, leading to cardiomyocyte death, which is one of the important causes of MF.②Activation of Signaling Pathways: ROS can act as signaling molecules, activating multiple signaling pathways related to fibrosis. ROS can activate the TGF-β signaling pathway, inducing the proliferation and differentiation of CFs into myofibroblasts, which then secrete large amounts of collagen and other ECM components, leading to MF.[18] Empagliflozin can inhibit oxidative stress and fibrosis by suppressing the TGF-β/Smad pathway and activating the Nrf2/ARE signaling transduction.[19] ROS can also promote CF proliferation and accelerate the development of MF by activating the MAPK-ERK/JNK pathway.[20] ③Mitochondrial Dysfunction: Oxidative stress can damage mitochondria, leading to mitochondrial dysfunction. Mitochondria are the "power plants" of the cell, and their impaired function can further exacerbate the energy metabolism disorder of cardiomyocytes, thereby promoting the occurrence of fibrosis. Related studies have shown that 2-APQC, a SIRT3 activator, can alleviate myocardial hypertrophy and fibrosis by regulating mitochondrial homeostasis, which may provide a new clue for the development of future heart failure treatments.[21] ④Aggravation of Inflammatory Response: Oxidative stress can activate signaling pathways such as nuclear factor-κB (NF-κB), thereby upregulating the expression of various inflammatory factors, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These inflammatory factors not only exacerbate the injury to cardiomyocytes but also promote the activation and proliferation of fibroblasts, accelerating the progression of MF.[22,23] ⑤Regulation of Matrix Metalloproteinases (MMPs):

MMPs can participate in the degradation and deposition of collagen in the myocardial interstitium, and tissue inhibitors of metalloproteinases (TIMPs) can inhibit the activity of MMPs. The TIMPs/MMPs system is the main target for maintaining the dynamic balance between collagen synthesis and metabolism, playing a role in maintaining the normal structure and function of the myocardium.[24] ROS can activate MMPs, inducing cardiomyocyte hypertrophy, apoptosis, and interstitial fibrosis,[25] thereby promoting the formation of MF.

Research Focus Evolution of Oxidative Stress Related Studies in MF

Based on the analysis of keyword co-occurrence networks and clustering, this paper summarizes the evolving research focuses on the role of oxidative stress in MF, which mainly includes the following aspects:

Activation of the Renin-Angiotensin-Aldosterone (RAAS) System

The widespread activation of the RAAS system accompanies the entire process of the occurrence and development of MF, which can promote oxidative stress and lead to cardiac hypertrophy, fibrosis, arterial stiffness, and inflammatory response.[26] Angiotensin II (Ang II) mediates multiple effects, including cell proliferation, migration, and ECM protein synthesis, through its Angiotensin II Type 1 Receptor (AT1R) in CFs.[27] Wang et al[28] confirmed that Ang II activates AT1R to induce the expression of transforming growth factor-β (TGF-β), promoting the activation of CFs and stimulating collagen synthesis and deposition. Ang II can also promote CFs to secrete interleukin-6, which upregulates TGF-β and phosphorylates Smad3 protein, thereby promoting MF.[29] Aldosterone can directly induce inflammation and oxidative stress responses by activating NADPH oxidase and mitochondria to generate reactive oxygen species, upregulating TGF-β, and promoting the development of MF.[30] Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II Type 1 Receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) have been proven to reduce the occurrence of MF, induce cardiac reverse remodeling, and alleviate cardiac diastolic dysfunction.[31–34]

Mechanisms Regulating Oxidative Stress in MF Due to Different Etiologies

According to the etiology and anatomy, MF can be divided into reactive interstitial fibrosis and replacement fibrosis.[35] Diffuse fibrosis refers to the increased deposition of ECM caused by increased myocardial pressure load, with diffuse deposition of fibrous tissue in the interstitium and around blood vessels, which is often found in non-ischemic cardiomyopathy, valvular heart disease, and normal aging of the heart.[36,37] The release of inflammatory cytokines and chemokines, as well as changes in cell signaling caused by persistent oxidative stress, may promote the MF process.[38] Replacement fibrosis is more common after acute myocardial infarction (AMI) and hypertrophic cardiomyopathy, forming localized fibrotic scars in the infarcted myocardium, which are mainly composed of type I collagen. This type of fibrosis is part of the repair process and helps maintain the integrity of the ventricular structure and prevent ventricular wall rupture.[39,40] During the cardiac repair process, excessive ROS are produced, which promote the transformation of CFs into myofibroblasts and increase the deposition of ECM.[41,42]

Understanding the different types of MF is crucial for developing appropriate treatment strategies and improving patient prognosis. Treatment strategies should be customized based on the specific nature and exact timing of the adverse myocardial remodeling events.

New Advances in Controlling Oxidative Stress as a Strategy Against MF

① CAR-T cell therapy: CAR T cells can target specific fibrosis-related proteins to reduce fibrosis.[43] The team led by Joel G. Rurik1 used modified messenger RNA (mRNA) to deliver CAR to mouse T cells, reprogramming T cells in vivo to reverse MF and restore cardiac function in HF mice.[44] ② Gene regulation: Bromodomain and extraterminal (BET) proteins are a highly conserved and widely expressed acetyl-lysine reading protein family that can collectively activate transcription. Their small molecule inhibitors have become an effective tool for reversibly interfering with the signaling transduction from enhancers to promoters in vivo.[45] Systemic administration of BET inhibitors can improve HF in mice.[46] BET inhibitors may regulate MF through the transcription factor MEOX1 in CFs, as the MEOX1-dependent transcriptional switch can control the state of CFs in HF, making MEOX1 a potential new therapeutic target for MF.[47]③ Exosome therapy from different stem cell sources: Exosomes are 30–200 nm extracellular vesicles secreted by various cell types, carrying specific proteins, lipids, nucleic acids, and glycoconjugates, and participating in intercellular communication.[48] Studies have shown that exosomes

from different stem cell sources can significantly reduce or inhibit MF in vivo and in vitro during pathological pro-fibrotic changes in the myocardium, replacing stem cell-based cardiac repair.[49] This therapy regulates the pathological formation of MF by transmitting information through internal miRNAs and regulating target cells, and has the potential to guide disease diagnosis and treatment. ④ Gut microbiota and their metabolites: Based on the gut microbiota and their metabolites, multiple new strategies for the treatment and prevention of MF have emerged, including dietary interventions, antibiotics, probiotics, and fecal microbiota transplantation.[50] These methods influence the progress of MF by regulating the systemic and local inflammatory response and oxidative stress of the host.[51,52]

Trends in Oxidative Stress in MF-Related Research

The NLRP3 inflammasome is a multi-protein complex composed of the nucleotide-binding oligomerization domain-like receptor (NLR) family member NLRP3, the adaptor protein apoptosis-associated speck-like protein (ASC), and the effector caspase-1 (caspase-1).[53] The NLRP3 inflammasome is expressed at a low basal level in the healthy heart to maintain the structural integrity of the cardiac ECM. In the early stage of the post-AMI response, the NLRP3 inflammasome is activated in the inflammatory response secondary to myocardial injury, which can promote wound healing, tissue repair, and induce myofibroblast formation after AMI.[54] In diabetic cardiomyopathy, the NLRP3 inflammasome induces an increase in TGF-β and IL-1β, activating the pro-fibrotic mediators TGF-β receptor, AT1R, and IL-1R in the myocardium to induce ROS generation and promote myofibroblast formation.[55] The mechanism by which the NLRP3 inflammasome expression leads to myofibroblast formation is complex, involving multiple pathways, including the TGF/Smads signaling pathway,[56] the TLR-4/NF-κβ signaling pathway,[57] and the cGMP-PKG signaling pathway,[58] but the specific intracellular signaling pathways and biological mechanisms are still unclear. Potential therapeutic strategies targeting the NLRP3 inflammasome may help alleviate myofibroblast formation and improve cardiac function, providing a direction for the development of new treatments. Some potential therapeutic strategies are under investigation, such as NLRP3 inhibitors that have shown inhibitory effects on NLRP3 activity in various animal models,[59–61] and IL-1β receptor antagonists that can indirectly inhibit its inflammatory effects,[62–64] although they have not yet been applied to myofibroblast-related diseases and require further basic and clinical studies to verify their safety and efficacy. Recent studies have demonstrated that certain pharmacological agents can modulate the NLRP3 inflammasome and its upstream and downstream targets. However, the mechanisms linking different pathways and their resultant effects remain unclear, necessitating further investigation into the hierarchical relationships between these pathways. Future research should focus on extensive docking studies between various compounds and targets to identify drugs that can sustainably and efficiently inhibit NLRP3 inflammasome activation. Additionally, elucidating the precise mechanisms of action will be crucial for mitigating MF and improving cardiac dysfunction.

In summary, based on bibliometric analysis, this study summarized the current status, evolutionary process, and latest progress of oxidative stress research in the field of myofibroblasts from the establishment of the database to December 31, 2024, and analyzed its prospects and development trends. Currently, the study of oxidative stress in myofibroblast-related diseases is in a period of rapid development. The pathological mechanism of myofibroblast formation is complex, and we need to conduct more in-depth research on the oxidative stress-related mechanisms of myofibroblast formation from the perspective of precision treatment, in order to develop new drugs, explore new therapeutic targets and strategies, and provide more options for the prevention and treatment of myofibroblast-related diseases. The activation of the NLRP3 inflammasome signaling pathway by oxidative stress to promote myofibroblast formation may be a future research trend and deserves further exploration and study.

Data Sharing Statement

Data will be made available on request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Supported by Beijing Municipal Key and Difficult Disease Collaborative Research Project (No. 2023BJSZDYNJBXTGG-011); Science and Technology Development Fund of Beijing Hospital of Traditional Chinese Medicine (No. LYYB202303).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Czubryt MP, Hale TM. Cardiac fibrosis: pathobiology and therapeutic targets. *Cell Signal*. 2021;85:110066. doi:10.1016/j.cellsig.2021.110066
2. Wilhelmi T, Xu X, Tan X, et al. Serelaxin alleviates cardiac fibrosis through inhibiting endothelial-to-mesenchymal transition via RXFP1. *Theranostics*. 2020;10(9):3905–3924. doi:10.7150/thno.38640
3. González A, Schelbert EB, Díez J, Butler J. Myocardial Interstitial Fibrosis in Heart Failure. *J Am Coll Cardiol*. 2018;71(15):1696–1706. doi:10.1016/j.jacc.2018.02.021
4. Zhao X, Kwan JYY, Yip K, Liu P, Liu FF. Targeting metabolic dysregulation for fibrosis therapy. *Nat Rev Drug Discov*. 2020;19(1):57–75. doi:10.1038/s41573-019-0040-5
5. Zhang M, Sui W, Xing Y, et al. Angiotensin IV attenuates diabetic cardiomyopathy *via* suppressing FoxO1-induced excessive autophagy, apoptosis and fibrosis. *Theranostics*. 2021;11(18):8624–8639. doi:10.7150/thno.48561
6. Fang Z, Raza U, Song J, et al. Systemic aging fuels heart failure: molecular mechanisms and therapeutic avenues. *ESC Heart Fail*. 2025;12 (2):1059–1080. doi:10.1002/ehf2.14947
7. Kang Q, Yang C. Oxidative stress and diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications. *Redox Biol*. 2020;37:101799. doi:10.1016/j.redox.2020.101799
8. Lin J, Xiong Z, Gu J, et al. Sirtuins: potential therapeutic targets for defense against oxidative stress in spinal cord injury. *Oxid Med Cell Longev*. 2021;2021:7207692. doi:10.1155/2021/7207692
9. Zhu K, Cai H. Research progress on ventricular remodeling induced by oxidative stress. *Anhui Med Pharm J*. 2015;19(9):1633–1636. doi:10.3969/j.issn.10096469.2015.09.001
10. Chen C, Song M. Visualizing a field of research: a methodology of systematic scientometric reviews. *PLoS One*. 2019;14(10):e0223994. doi:10.1371/journal.pone.0223994
11. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci USA*. 2004;101(Suppl 1):5303–5310. doi:10.1073/pnas.0307513100
12. Chen Y, Chen C, Liu Z, Hu Z, Wang X. The methodology function of CiteSpace mapping knowledge domains. *Stud Sci Sci*. 2015;33(2):242–253. doi:10.16192/j.cnki.1003-2053.2015.02.009
13. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
14. Ogunsakin RE, Ebenezer O, Jordaan MA, Shapi M, Ginindza TG. Mapping scientific productivity trends and hotspots in remdesivir research publications: a bibliometric study from 2016 to 2021. *Int J Environ Res Public Health*. 2022;19(14):8845. doi:10.3390/ijerph19148845
15. López-Belmonte J, Parra-González ME, Segura-Robles A, Pozo-Sánchez S. Scientific mapping of gamification in web of science. *Eur J Investig Health Psychol Educ*. 2020;10(3):832–847. doi:10.3390/ejihpe10030060
16. Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. *AMIA Annu Symp Proc*. 2005;2005:724–728.
17. Zhang J, Song L, Xu L, et al. Knowledge domain and emerging trends in ferroptosis research: a bibliometric and knowledge-map analysis. *Front Oncol*. 2021;11:686726. doi:10.3389/fonc.2021.686726
18. Ren B, Feng J, Yang N, Guo Y, Chen C, Qin Q. Ginsenoside Rg3 attenuates angiotensin II-induced myocardial hypertrophy through repressing NLRP3 inflammasome and oxidative stress via modulating SIRT1/NF-κB pathway. *Int Immunopharmacol*. 2021;98:107841. doi:10.1016/j.intimp.2021.107841
19. Li C, Zhang J, Xue M, et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. *Cardiovasc Diabetol*. 2019;18(1). doi:10.1186/s12933-019-0816-2
20. Zhang Z, Yang Z, Wang S, Wang X, Mao J. Targeting MAPK-ERK/JNK pathway: a potential intervention mechanism of myocardial fibrosis in heart failure. *Biomed Pharmacother*. 2024;173:116413. doi:10.1016/j.biopha.2024.116413
21. Peng F, Liao M, Jin W, et al. 2-APQC, a small-molecule activator of Sirtuin-3 (SIRT3), alleviates myocardial hypertrophy and fibrosis by regulating mitochondrial homeostasis. *Signal Transduct Target Ther*. 2024;9(1):133. doi:10.1038/s41392-024-01816-1
22. Zhuang L, Zong X, Yang Q, Fan Q, Tao R. Interleukin-34-NF-κB signaling aggravates myocardial ischemic/reperfusion injury by facilitating macrophage recruitment and polarization. *EBioMedicine*. 2023;95:104744. doi:10.1016/j.ebiom.2023.104744
23. Zhang X, Qu H, Yang T, Liu Q, Zhou H. Astragaloside IV attenuate MI-induced myocardial fibrosis and cardiac remodeling by inhibiting ROS/caspase-1/GSDMD signaling pathway. *Cell Cycle*. 2022;21(21):2309–2322. doi:10.1080/15384101.2022.2093598
24. Russo I, Cavalera M, Huang S, et al. Protective effects of activated myofibroblasts in the pressure-overloaded myocardium are mediated through smad-dependent activation of a matrix-preserving program. *Circ Res*. 2019;124(8):1214–1227. doi:10.1161/CIRCRESAHA.118.314438
25. Tsutsui H, Kinugawa S, Matsushima S. Mitochondrial oxidative stress and dysfunction in myocardial remodelling. *Cardiovasc Res*. 2009;81 (3):449–456. doi:10.1093/cvr/cvn280
26. Schnee JM, Hsueh WA. Angiotensin II, adhesion, and cardiac fibrosis. *Cardiovasc Res*. 2000;46(2):264–268. doi:10.1016/s0008-6363(00)00044-4
27. Brilla CG, Rupp H, Funck R, Maisch B. The renin-angiotensin-aldosterone system and myocardial collagen matrix remodelling in congestive heart failure. *Eur Heart J*. 1995;16(Suppl O):107–109. doi:10.1093/eurheartj/16.suppl_o.107
28. Wang L, Zhang Y, Lin Q, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. *Eur Heart J*. 2018;39(20):1818–1831. doi:10.1093/eurheartj/ehy085

29. Ma F, Li Y, Jia L, et al. Macrophage-stimulated cardiac fibroblast production of IL-6 is essential for TGF β/Smad activation and cardiac fibrosis induced by angiotensin II. *PLoS One*. 2012;7(5):e35144. doi:10.1371/journal.pone.0035144
30. Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat Rev Nephrol*. 2013;9(8):459–469. doi:10.1038/nrneph.2013.110
31. Ciampi CM, Sultana A, Ossola P, Farina A, Fragasso G, Spoladore R. Current experimental and early investigational agents for cardiac fibrosis: where are we at? *Expert Opin Investig Drugs*. 2024;33(4):389–404. doi:10.1080/13543784.2024.2326024
32. Jin T, Fu X, Liu M, An F. Finerenone attenuates myocardial apoptosis, metabolic disturbance and myocardial fibrosis in type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2023;15(1). doi:10.1186/s13098-023-01064-3
33. Rodriguez-Gonzalez M, Lubian-Gutierrez M, Cascales-Poyatos HM, Perez-Reviriego AA, Castellano-Martinez A. Role of the renin-angiotensin-aldosterone system in dystrophin-deficient cardiomyopathy. *Int J Mol Sci*. 2020;22(1):356. doi:10.3390/ijms22010356
34. Hayashi M, Tsutamoto T, Wada A, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation*. 2003;107(20):2559–2565. doi:10.1161/01.CIR.0000068340.96506.0F
35. Li X, Yang Y, Chen S, Zhou J, Li J, Cheng Y. Epigenetics-based therapeutics for myocardial fibrosis. *Life Sci*. 2021;271:119186. doi:10.1016/j.lfs.2021.119186
36. Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. *J Am Coll Cardiol*. 2010;56(2):89–97. doi:10.1016/j.jacc.2010.02.047
37. Nakayama H, Nishida K, Otsu K. Macromolecular degradation systems and cardiovascular aging. *Circ Res*. 2016;118(10):1577–1592. doi:10.1161/CIRCRESAHA.115.307495
38. Pang X, Lin X, Du J, Zeng D. LTBP2 knockdown by siRNA reverses myocardial oxidative stress injury, fibrosis and remodelling during dilated cardiomyopathy. *Acta Physiol*. 2020;228(3):e13377. doi:10.1111/apha.13377
39. Liu J, Zhao S, Yu S, et al. Patterns of replacement fibrosis in hypertrophic cardiomyopathy. *Radiology*. 2022;302(2):298–306. doi:10.1148/radiol.2021210914
40. Qiao P, Wang Y, Zhu K, et al. Noninvasive monitoring of reparative fibrosis after myocardial infarction in rats using ^{68}Ga-FAPI-04 PET/CT. *Mol Pharm*. 2022;19(11):4171–4178. doi:10.1021/acs.molpharmaceut.2c00551
41. Wang Q, Liu A, Li T, Tang Q, Wang X, Chen X. Ghrelin ameliorates cardiac fibrosis after myocardial infarction by regulating the Nrf2/NADPH/ROS pathway. *Peptides*. 2021;144:170613. doi:10.1016/j.peptides.2021.170613
42. Hao S, Sui X, Wang J, et al. Secretory products from epicardial adipose tissue induce adverse myocardial remodeling after myocardial infarction by promoting reactive oxygen species accumulation. *Cell Death Dis*. 2021;12(9):848. doi:10.1038/s41419-021-04111-x
43. Baker DJ, Arany Z, Baur JA, Epstein JA, June CH. CAR T therapy beyond cancer: the evolution of a living drug. *Nature*. 2023;619(7971):707–715. doi:10.1038/s41586-023-06243-w
44. Rurik JG, Tombácz I, Yadegari A, et al. CAR T cells produced in vivo to treat cardiac injury. *Science*. 2022;375(6576):91–96. doi:10.1126/science.abm0594
45. Filippakopoulos P, Qi J, Picaud S, et al. Selective inhibition of BET bromodomains. *Nature*. 2010;468(7327):1067–1073. doi:10.1038/nature09504
46. Anand P, Brown JD, Lin CY, et al. BET bromodomains mediate transcriptional pause release in heart failure. *Cell*. 2013;154(3):569–582. doi:10.1016/j.cell.2013.07.013
47. Alexanian M, Przytycki PF, Micheletti R, et al. A transcriptional switch governs fibroblast activation in heart disease. *Nature*. 2021;595(7867):438–443. doi:10.1038/s41586-021-03674-1
48. Hohn J, Tan W, Carver A, Barrett H, Carver W. Roles of exosomes in cardiac fibroblast activation and fibrosis. *Cells*. 2021;10(11):2933. doi:10.3390/cells10112933
49. Tang X, Leng M, Tang W, et al. The roles of exosome-derived microRNAs in cardiac fibrosis. *Molecules*. 2024;29(6):1199. doi:10.3390/molecules29061199
50. Xu H, Yang F, Bao Z. Gut microbiota and myocardial fibrosis. *Eur J Pharmacol*. 2023;940:175355. doi:10.1016/j.ejphar.2022.175355
51. Pitt B, Diez J. Possible role of gut microbiota alterations in myocardial fibrosis and burden of heart failure in hypertensive heart disease. *Hypertension*. 2024;81(7):1467–1476. doi:10.1161/HYPERTENSIONAHA.124.23089
52. Russo M, Guida F, Paparo L, et al. The novel butyrate derivative phenylalanine-butyramide protects from doxorubicin-induced cardiotoxicity. *Eur J Heart Fail*. 2019;21(4):519–528. doi:10.1002/ejhf.1439
53. Deng Y, Liu X, Xie M, et al. Obesity enables NLRP3 activation and induces myocardial fibrosis via hyperacetylation of HADHa. *Diabetes*. 2023;72(11):1597–1608. doi:10.2337/db23-0264
54. Lénárt N, Brough D, Dénes Á. Inflammasomes link vascular disease with neuroinflammation and brain disorders. *J Cereb Blood Flow Metab*. 2016;36(10):1668–1685. doi:10.1177/0271678X16662043
55. Yue Y, Meng K, Pu Y, Zhang X. Transforming growth factor beta (TGF-β) mediates cardiac fibrosis and induces diabetic cardiomyopathy. *Diabet Res Clin Pract*. 2017;133:124–130. doi:10.1016/j.diabres.2017.08.018
56. Tian J, Zhang M, Suo M, et al. Dapagliflozin alleviates cardiac fibrosis through suppressing EndMT and fibroblast activation via AMPKα/TGF-β/Smad signalling in type 2 diabetic rats. *J Cell Mol Med*. 2021;25(16):7642–7659. doi:10.1111/jcmm.16601
57. Gyöngyösi M, Winkler J, Ramos I, et al. Myocardial fibrosis: biomedical research from bench to bedside. *Eur J Heart Fail*. 2017;19(2):177–191. doi:10.1002/ejhf.696
58. Mezzasoma L, Antognelli C, Talesa VN. Atrial natriuretic peptide down-regulates LPS/ATP-mediated IL-1β release by inhibiting NF-kB, NLRP3 inflammasome and caspase-1 activation in THP-1 cells. *Immunol Res*. 2016;64(1):303–312. doi:10.1007/s12026-015-8751-0
59. Grant AJ, Yang N, Moore MJ, et al. Selective NLRP3 inflammasome inhibitor MCC950 suppresses inflammation and facilitates healing in vascular materials. *Adv Sci*. 2023;10(20):e2300521. doi:10.1002/advs.202300521
60. Ismailani AB, MacMullin N, Abdirahman F, Adi M, Rotstein BH, U.S. Synthesis and evaluation of [^{11}C]MCC950 for imaging NLRP3-mediated inflammation in atherosclerosis. *Mol Pharm*. 2023;20(3):1709–1716. doi:10.1021/acs.molpharmaceut.2c00915
61. Shao B, Xu Z, Han B, Su D, Liu C. NLRP3 inflammasome and its inhibitors: a review. *Front Pharmacol*. 2015;6:262. doi:10.3389/fphar.2015.00262

62. Hurtado-Navarro L, Cuenca-Zamora EJ, Zamora L, et al. NLRP3 inflammasome activation and symptom burden in KRAS-mutated CMML patients is reverted by IL-1 blocking therapy. *Cell Rep Med*. 2023;4(12):101329. doi:10.1016/j.xcrm.2023.101329
63. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ Res*. 2020;126(9):1260–1280. doi:10.1161/CIRCRESAHA.120.315937
64. Potere N, Garrad E, Kanthi Y, et al. NLRP3 inflammasome and interleukin-1 contributions to COVID-19-associated coagulopathy and immunothrombosis. *Cardiovasc Res*. 2023;119(11):2046–2060. doi:10.1093/cvr/cvad084