Original Article

Global trends in research on oxidative stress related to heart failure from 2012 to 2021: a bibliometric analysis and suggestion to researchers

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Background: Oxidative stress leads to an increase in reactive oxygen in the body. During heart failure (HF), when the body's antioxidant defense system fails to remove excessive reactive oxygen species, myocardial cells will be damaged or even die. Over the past ten years, the number of research publications on oxidative stress related to HF has increased.

Methods: We searched publications published in 2012–2021 and the Web of Science Core Collection (WoSCC) recording information. Based on the VOSviewer and CiteSpace, we conducted a bibliometric analysis of the overall distribution of journals, keywords, authors, major countries, annual output, active institutions, and cocited literature. The Global Citation Score (GCS) was used to evaluate the impact and quality of highly cited papers.

Results: We retrieved 5,616 articles and reviews. Over the past ten years, the number of annual publications on oxidative stress related to HF has increased. USA has published the largest number of articles and obtained the highest number of citations (NC) and H-index. The University of California and PLoS One are the most productive affiliations and journals in terms of publications on oxidative stress related to HF. The GCS of articles written by Paulus WJ in 2013 was 1,632, which was the top ranking. The most frequent keywords are "oxidative stress", "heart failure", "inflammation", "dysfunction" and "apoptosis". The top three authors are Kang Yuming, Ren Jun and Okoshi Katashi. "Impact", "induced myocardial infarction", "cardiovascular outcome", "empagliflozin", "sglt2 inhibitor", "protect", and "Na^+/H^+ exchanger" have become popular research topics.

Conclusions: Our research shows the research focus and development trends of oxidative stress related to HF in the past decade. Understanding the most important indicators of oxidative stress related to HF and the hot spots in the field of oxidative stress research related to HF can assist scholars, countries and policy-makers in the field in better understanding oxidative stress related to HF and can also lead to better decisions in oxidative stress treatment.

Keywords: Bibliometrics; oxidative stress; heart failure (HF); CiteSpace; VOSviewer

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Introduction

Heart failure (HF) is a global disease with high incidence. A variety of heart injuries can lead to heart failure, such as myocardial infarction, increased preload or afterload, abnormal valve structure, pericardium, endocardial, cardiac rhythm, or a combination of factors. Cardiac structural changes and neuroendocrine changes lead to abnormal myocardial cell function (1). As a major public health problem, HF causes a high economic burden for patients. Although the incidence rate of HF has declined in recent years, HF is still a serious condition, and its incidence rate, mortality and readmission rate are still high. HF is one of the most common causes of hospitalization, and the risk of HF accounts for approximately 20% of hospitalizations (2). As of 2016, there were at least 26 million patients with HF worldwide, and this number is increasing yearly (3); HF is a clinical syndrome with multiple causes and high hospitalization and mortality rates, which brings considerable and growing burden to medical care (4). The main clinical symptoms and signs of HF include decreased exercise tolerance, increased jugular pressure, fatigue, dyspnea, and tachycardia, among others (5). HF is also a risk factor of cardiac arrest (6). HF clinical subtypes determine shockable rhythm during cardiac arrest (7). Hypothermia is directly associated with mortality in HF patients who have suffered cardiac arrest (8).

The formation of HF is related to inflammatory reactions and oxidative stress (9). Oxidative stress imbalance and cell apoptosis are the main pathological characters of HF. Inhibiting oxidative stress could reduce multi-type of cell death, including necrosis and pyrolysis (10). The accumulation of reactive oxygen species (ROS) is one of the main mechanisms of pathogenesis in HF (11). Oxidative stress could active metallomatrix proteases to induce the myocardium remodeling (12). Oxidative stress occurs when the body produces too many oxidative active substances or the antioxidant capacity of the body is weakened; this occurrence causes some oxygen metabolites and some active oxygens to build up, leading to an increase in active oxygen in the body, destroying the balance of oxidation and reduction in the body, and causing oxidative damage to cells. In the state of HF, excess ROS exceed the scavenging capacity of the antioxidant system, and myocardial cells are damaged or killed (13). Oxidative stress increases in HF and affects the progression of the disease, which is one of the pathogeneses of HF (14).

In recent years, a growing number of studies associated with oxidative stress in HF have been conducted, and new discoveries and papers have been published. The introduction of new technologies and concepts has brought great challenges to new and old researchers. Therefore, it is urgent to summarize this field and predict future development trends. In general, the current state of a research field and research hotspots are summarized through a literature review, which is susceptible to subjective factors and suffers from a number of flaws. At the same time, researchers and health care practitioners must face the challenge of the constant emergence and introduction of new technologies and concepts (15). As a quick and easy method of reviewing the state of a field of study, bibliometrics can assess research trends and clarify important research directions by analyzing the characteristics of databases and publications. In addition, bibliometrics can provide valid evidence for guiding funding decisions and research strategies (16). Over the years, bibliometric

Highlight box

Key findings

- This study clarify the research focus and development trends of oxidative stress related to HF in the past decade.

What is known and what is new?

- Over the past 10 years, publications on oxidative stress related to HF have increased.
- USA is a major producer in the field and has had great influence. Clinical research and basic research vary. SGLT2 inhibitors and Na+/H+ exchangers are a potential research hotspot. Research on the treatment of heart failure with traditional Chinese medicine monomers should be further expanded in this regard.

What is the implication, and what should change now?

- Understanding the most important indicators of oxidative stress related to HF and the hot spots in the field of oxidative stress research related to HF can assist scholars, countries and policy-makers in the field better understand oxidative stress related to HF and make decisions.

Table 1 TS search queries and refinement procedure

Set	Results	Refinement
1	9,200	Topic: (TS=("heart failure") and TS=("oxidative stress")). Database =WoSCC
2	6,080	Refined by publication years: (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021)
3	5,758	Refined by document types: (Articles OR Review Articles)
4	5,616	Refined by languages: (English)

TS, topical subject.

research findings, such as prenatal stress (17), gouty arthritis (18), and macrophages in acute lung injury (19), have been reported. Nevertheless, no bibliometric studies on oxidative stress in HF have been found. Through bibliometric analysis and a comprehensive review of oxidative stress in HF, this study discussed the research trend of HF and made suggestions for future study.

Methods

Retrieval method

The document dataset was compiled using the Web of Science Core Collection (WoSCC). The database provides a set of comprehensive and standardized data for output, which has been widely used in the academic community (20). In consideration of the rapid growth of the database, a literature search was conducted within one day (October 24, 2022) to avoid deviation. Here are the search terms: [TS = ("heart failure") and TS = ("oxidative stress")]. In various studies, only English articles and reviews are included. From 2012 to 2021, a total of 5616 articles were analyzed. The results of the screening are shown in *Table 1*.

Data download

Data of all confirmed publications were downloaded from the WoSCC database, including year of publication, countries/regions, journals, authors, affiliations, number of papers (NP) and number of citations (NC), H-index, references and keywords. Then, based on the online program (http://www.bioinformatics.com.cn/), CiteSpace (version 5.8. R3) and VOSviewer v1.6.10.0, the data were further analyzed.

Bibliometric analysis

Bibliometric analysis was performed using CiteSpace (version 5.8. R3), VOSviewer (version 1.6.16) and online tools (http://www.bioinformatics.com.cn/). The NP and citations are used to indicate bibliometric indicators. As two basic viewpoints for measuring research performance, NP is often used to quantify production capacity, and NC can indicate the impact factor of a journal. Using the H-index, the scientific contributions of the researchers were evaluated, and the academic future achievements of the research was predicted. The H-index unifies productivity and influence by determining the threshold for connecting NP and NC (19). If a scholar has published H articles and each article was cited H times at least, then the H-index of the scholar is H. In addition, the H index is designed to assess individual academic performance. In addition, it can define the publishing production of a region/country and the production of a journal or institution (21,22). In addition, the impact factor (IF) calculated according to the newest Journal Citation Report (JCR) is considered the most important indicator for the impact and quality of journals (23). The Global Citation Score (GCS) is considered the global NC of an article. It is an important indicator of the contribution of an article to the field of knowledge. A high GCS indicates that there is high interest amongst scientists around the world (18). By using the fitted polynomial model, the annual publication quantity is predicted, which further explains the change in the annual publication quantity. With VOSviewer v1.6.16.0, a bibliometric network diagram was built and visualized (15). In this study, VOSviewer is used for cocitation and co-occurrence analysis. The size of the nodes represents the number of publications, the thickness of the lines represents the strength of the relationships, and the color of the nodes represents different clusters or periods. Clustering analysis, timeline or time zone view, references and keywords burstness are used in CiteSpace to help visually evaluate knowledge fields and development trends (24). Cluster analysis is able to elucidate references and keywords and find basic study topics of oxidative stress related to HF. A series of references and keywords are often used to predict

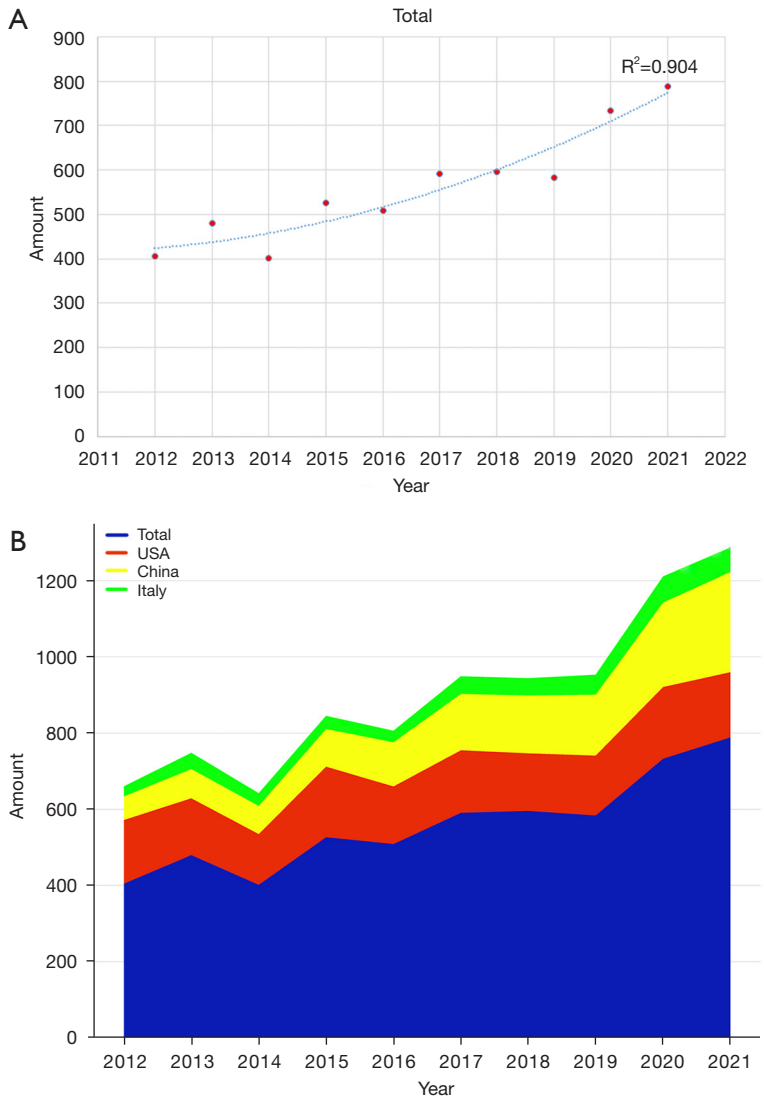


Figure 1 Annual trends of publications. (A) Curve fitting of the total annual growth trend of publications (R^2=0.904). (B) The number of publications published each year in the past 10 years.

research trends.

Results

Literature review on oxidative stress related to HF

According to the search strategy, 5,616 papers published in the past decade were retrieved with an average NC of 29.57 per article. The total H-index is 148.

Annual trends of publications

The polynomial fitting curve of the annual trend of paper publishing volume is shown in *Figure 1A*. The number of publications issued each year is significantly related to the publication year, with the correlation coefficient R^2 reaching 0.904. *Figure 1B* shows annual NP in oxidative stress related to HF. Generally, although there were fluctuations in NP over the last 10 years, NP rose from 402 in 2014 to 789 in 2021, and NP reached its peak in 2021. From 2011, the NP of USA and Italy in each year remained steady, but the Np of China rose rapidly. In general, our findings showed that research on oxidative stress related to HF has attracted the attention of researchers and entered a rapid development period.

Table 2 The top 10 countries/regions with the highest productivity

Rank	Country	NP	NC	H-index
1	USA	1,616	63,001	116
2	China	1,373	29,963	72
3	Italy	440	15,605	62
4	Japan	380	10,103	49
5	Germany	371	17,082	63
6	England	252	10,586	53
7	Brazil	248	4,704	35
8	Canada	229	8,191	49
9	India	171	3,488	30
10	France	164	6,318	41

NP, number of papers; NC, number of citations.

Contribution of countries/regions to global publications

The 10 high-output countries/regions according to NP are ranked in *Table 2*. USA has the largest NP (1,616/28.77%), followed by China (1,373/24.45%) and Italy (440/7.83%). American papers were cited 63,001 times, which accounted for 41.53% of total NC, and nest countries were China (29,963 times) and Germany (17,082 times). In addition, the H index of the United States is the highest [116], more than twice that of Japan [49], the United Kingdom [53], Brazil [35], Canada [49], India [30] and France [41]. Compared with Italy and Japan, Germany's NP is slightly lower, but its H index and NC are significantly higher than those of Italy and Japan. The co-occurrence of countries/regions is shown in *Figure 2A*. Different countries/regions cooperate closely, with USA, China, Italy, Japan, Germany, England and Brazil at the core of the network.

Performance of affiliations

Table 3 shows the top 10 affiliations with high NP on oxidative stress related to HF. The University of California has the highest NP [125], followed by the National Medical School [118] and the Department of Veterans Affairs [108]. The United States Department of Veterans Affairs ranks first in NC [5,558]. The Veterans Health Administration VHA and the Department of Veterans Affairs ranked first for the H-index [43]. The NP of the National Veterans Institute is high, but its H-index is behind that of the VHA of the Department of Veterans Affairs and Veterans Health Administration of USA. *Figure 2B* shows the affiliation of association relationships. It can be seen from the figure that the affiliations of different countries/regions is closely linked, indicating that the affiliations of different countries/regions is closely cooperative.

Performance of authors

The top 10 authors published 224 articles, accounting for 3.99% of the total articles published (*Table 4*). Kang Yuming from Xi'an Jiaotong University was tied for the first place, followed by Ren Jun from the University of Wyoming in USA and Okoshi Katashi from University of Paulista in Brazil. As shown in *Table 4*, Ren Jun has very high NC. In addition, half of the top 10 authors are in Brazil. Co-occurrence among authors is shown in *Figure 2C*. It can be seen from the figure that the relationship between different authors is not close, indicating that there is less cooperation among different authors.

Performance of journals

As shown in *Table 5*, PLOS ONE published the largest number of publications on oxidative stress related to HF, while *International Journal of Molecular Sciences* (127 publications, IF: 6.208) and *Oxidative Medicine and Cellular Longevity* (109 publications, IF: 7.31) ranked second and third, respectively. The top 10 academic journals published approximately 20% of all articles (976/17.38%). *The International Journal of Molecular Sciences*, *Oxidative Medicine and Cellular Longevity*, *American Journal of Physiology Heart and Circulatory Physiology*, *Journal of Molecular and Cellular Cardiology* and *Free Radical Biology and Medicine* journal have high IF values (more than 5.000). It is worth noting that *PLoS One* (IF=3.752) has the highest citation volume and H-index.

Global citations (GCS) analysis

The number of GCSs of the top 10 articles in each year is shown in *Figure 3*. The GCS of an article written by WJ Paulus in 2013 is 1,632, which was the highest. In their article, WJ Paulus mentioned that in speech-sensitive hypertensive patients, excessive salt intake can cause systemic oxidative stress, which may be due to the proinflammatory cytokines produced by the kidney. In patients with HF, with anemia or without, iron deficiency leads to oxidative stress and immune response. Recently, a study has shown

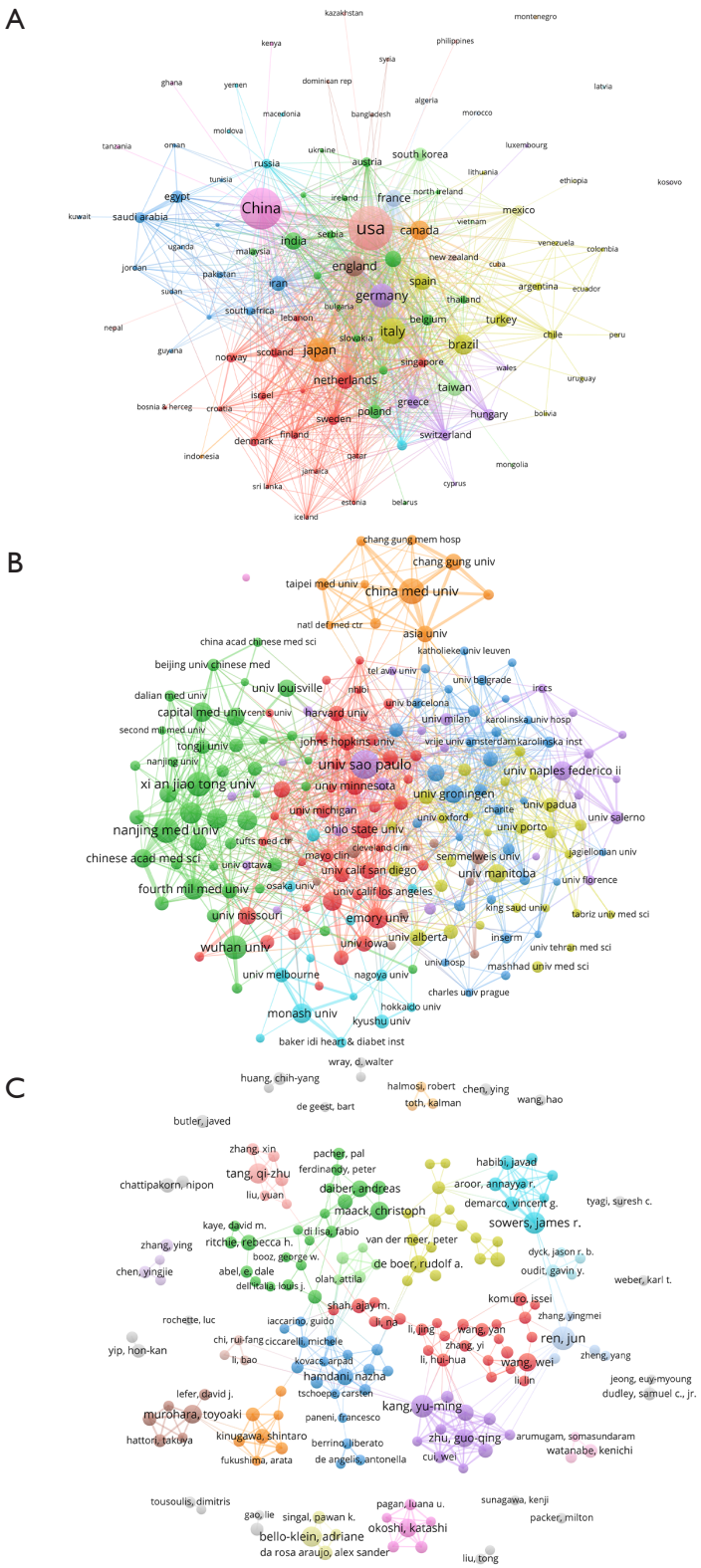


Figure 2 Co-occurrence network. (A) Co-occurrence network of countries/regions. (B) Co-occurrence network of affiliations. (C) Co-occurrence network of authors.

Table 3 The top 10 most productive affiliations

Rank	Affiliation	NP	NC	H-index	Country
1	University of California System	125	4,871	41	USA
2	National Institute of Health and Medical Research	118	4,561	39	France
3	US Department of Veterans Affairs	108	5,558	43	USA
4	Veterans Health Administration (VHA)	103	5,517	43	USA
5	Harvard University	99	4,341	34	USA
6	University of Sao Paulo	91	2,062	28	Brazil
7	Udice French Research Universities	80	3,515	30	France
8	University of Texas System	79	3,682	37	USA
9	Egyptian Knowledge Bank (EKB)	77	1,205	19	Egypt
10	Harvard Medical School	73	2,729	28	USA

NP, number of papers; NC, number of citations.

Table 4 The top 10 authors with the most publications

Rank	Author	NP	NC	H-index	Affiliation	Country
1	Yu-Ming Kang	28	730	18	Xi'an Jiaotong University	China
2	Jun Ren	27	1,234	18	University of Wyoming	USA
3	Okoshi Katashi	26	491	15	Paulista State University	Brazil
4	Toyoaki Murohara	22	785	16	Nagoya University	Japan
5	Guo-Qing Zhu	21	524	15	Nanjing Medical University	China
6	Patricia C. Brum	21	571	13	University of Sao Paulo	Brazil
7	Adriane Bello-Klein	21	229	10	Federal University of Southern University	Brazil
8	Alex Sander Da Rosa Araujo	20	242	11	Federal University of Southern University	Brazil
9	Leonardo Zornoff	20	305	12	Paulista State University	Brazil
10	Xiaojing Yu	18	447	14	Xi'an Jiaotong University	China

NP, number of papers; NC, number of citations.

Table 5 The top 10 journals with the most publications

Rank	Journal	NP	NC	H-index	IF (2021)
1	*PLoS One*	153	4,480	40	3.752
2	*International Journal of Molecular Sciences*	127	3,302	31	6.208
3	*Oxidative Medicine and Cellular Longevity*	109	2,924	31	7.31
4	*American Journal of Physiology Heart and Circulatory Physiology*	101	2,942	34	5.125
5	*Journal of Molecular and Cellular Cardiology*	92	4,391	36	5.763
6	*International Journal of Cardiology*	91	2,654	30	4.039
7	*Scientific Reports*	82	1,575	23	4.997
8	*Frontiers in Physiology*	77	1,838	24	4.755
9	*Free Radical Biology and Medicine*	74	2,523	28	8.101
10	*Heart Failure Reviews*	70	2,068	24	4.654

NP, number of papers; NC, number of citations; IF, impact factor.

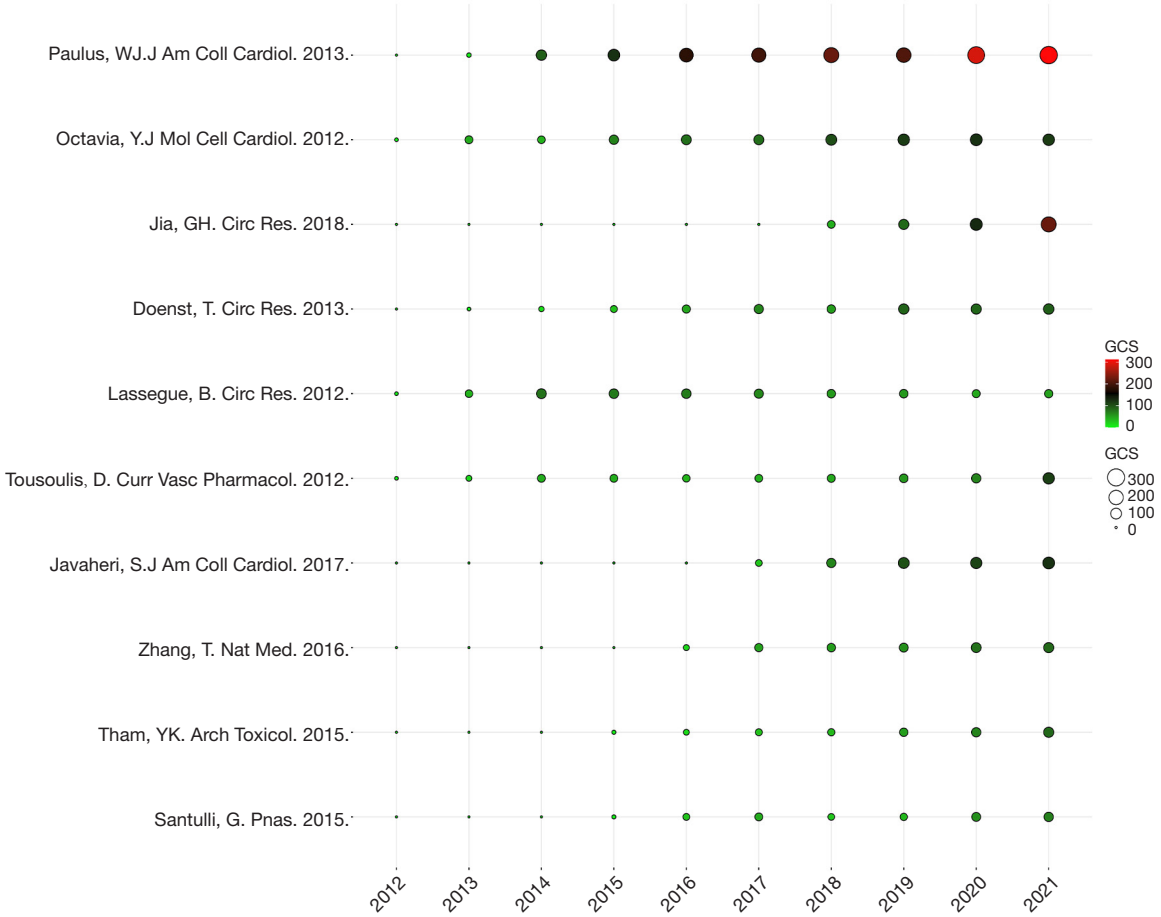


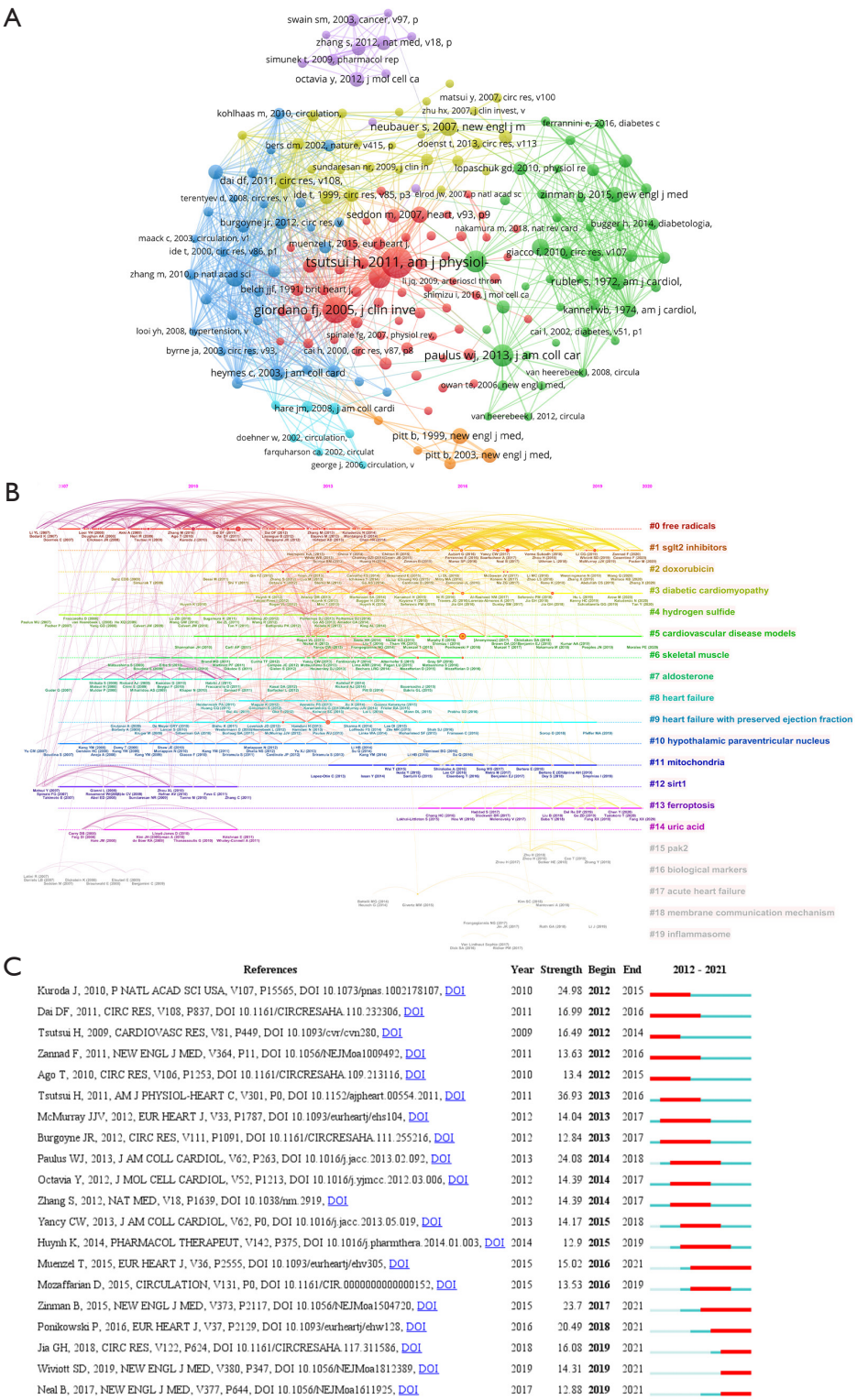
Figure 3 Annual global citations of papers with high GCS. GCS, Global Citation Score.

that HF patients with preserved ejection fraction have more severe deterioration of cardiac structure and function than patients with arterial hypertension (25). Additional mechanisms involved in HF also clarified why HFPEF has a worse prognosis than concomitant diseases (25). In Yanti Octavia's paper, the production of induced free radicals was the main mechanism of adriamycin-induced myocardial injury. The unique vulnerability of the heart to oxidative stress makes cardiomyopathy induced by adriamycin an important focus of this article (26). Guanghong Jia summarized that HF and incidence rate as well as mortality were increasing, which is largely due to the increase in diabetes, aging and obesity. Clinical symptoms related to HF were much more serious in diabetes patients than in patients without diabetes. In diabetes patients, there is myocardial dysfunction, valve disease and other risk factors, which leads to the descriptive term diabetes cardiomyopathy. With the increase in diabetes, the prevalence of diabetic cardiomyopathy is also increasing (27). Torsten Doenst highlighted that metabolic remodeling in HF not only leads to damage to heart energy but also leads to other processes related to the pathogenesis of HF, such as oxidative stress (28). Bernard Lassegue noted that excessive NOX2 can lead to the development of oxidative stress, HF and other diseases (29). Dimitris Tousoulis clarified that nitric oxide produced by endothelial injury has an important function in oxidative stress. The occurrence and development of HF is closely related to this process (30). Shahrokh Javaheri summarized that respiratory disorder events are related to a series of disorders, including oxidative stress, and have a causal relationship with HF (31). Ting Zhang identified CaMKII as a new RIP3 substrate and described a mechanism of myocardial necrotic ptosis of RIP3 CaMKII MPTP, which is expected to become a target for treating HF and myocardial injury induced by oxidative stress and ischemia (32). Keat Tham discussed

cardiac hypertrophy as a reaction of the heart to an increase in load and cardiac injury such as heart attack or gene mutation. The main characteristics of pathological myocardial hypertrophy and many mediators involved in the pathogenesis of oxidative stress or inflammation are typical precursors of HF (33). Gaetano Santulli noted that oxidative stress can cause HF, but the function of mitochondrial calcium in HF is still unclear. SR calcium leakage during diastole leads to mitochondrial calcium supercharge load and function disorder in mice with HF after myocardial infarction. There are two calcium release channels on myocardial SR: type 2 ranidine receptor (RyR2) and type 2 inositol 1,4,5-triphosphate receptor (IP3R2). In a mouse model with RyR2 mutation, we found that leakage of the RyR2 channel led to mitochondrial calcium overload, morphological abnormalities and dysfunction. In contrast, the deletion of heart-specific IP3R2 has no significant impact on the suitability of mitochondria in HF. In addition, the enhancement of mitochondrial antioxidant activity can improve its function and improve the posttranslational modification of the RyR2 macromolecular complex. The data of this study show that leaking RyR2 channels, rather than IP3R2 channels, will lead to mitochondrial calcium overload and dysfunction in patients with HF (34). In conclusion, these studies have played a role in the research of oxidative stress related to HF, which can be said to be groundbreaking, and they will increase the amount of follow-up publications in the field.

Analysis of cocited references

Different from local citation analysis, cocitation networks focus on study topics closely associated with specific fields (35). Due to the large number of cited references, we set 42 as the minimum NC per reference. There were 226,831 references cited by all papers, and we selected 180 for cocitation analysis (*Figure 4A*). There were 55 references in Cluster 1 (in red), which mainly focused on important molecules in the pathogenesis of HF, myocardial hypertrophy and other diseases. Cluster 2 (in green) mainly focused on the treatment of heart disease. Cluster 3 (in blue) centered on the redox process in myocardial activity. The theme of Cluster 4 (in yellow) is the critical role of energy change in the mechanism of HF. Cluster 5 (in purple) focused on the cardiotoxicity of some drugs. Cluster 6 (in light blue) and Cluster 7 (in orange) were mostly about the effects of gout drugs and aldosterone on patients with HF. The most typical references in terms of burst time, length and strength are described in *Figure 4B*, and the top 20 clusters of cocited references were "free radicals", "sglt2 inhibitors", "doxorubicin", "diabetic cardiomyopathy", "hydrogen sulfides", "cardiovascular disease models", "skeletal muscle", "aldosterone", and "heart failure", among others. The top 20 references are shown in *Figure 4C*. The paper of Tsutsui *et al*. has the highest strength (36). His paper revealed that oxidative stress had an important function in the pathophysiology of HF and cardiac remodeling. At a lower level, oxidative stress causes subtle changes in intracellular redox signals. ROS come from a variety of intracellular sources. ROS production in the mitochondria of HF increased, while normal antioxidant enzyme activity remained unchanged. The chronic increase in ROS production in mitochondria leads to a disastrous cycle of mitochondrial DNA (MtDNA) damage, as well as functional decline, further ROS production, and cell damage. ROS directly damage contractile function by changing the protein of the excitation contraction coupling center. In addition, ROS can also activate a variety of hypertrophy signaling pathways and transcription factors and mediate apoptosis. They also stimulate the proliferation of cardiac fibroblasts, activate matrix metalloproteinases, and lead to extracellular matrix remodeling. These cellular events are involved in the occurrence and development of inadaptable myocardial remodeling and failure. Oxidative stress also participates in skeletal muscle dysfunction, which may be related to exercise tolerance and insulin resistance. Therefore, oxidative stress is involved in the pathophysiology of heart and skeletal muscle central failure. A better understanding of these mechanisms may contribute to the development of new and effective anti-HF treatment strategies (36). We also discovered that the study of Kuroda *et al*. possess higher burst strength (37). In his paper, he noted that NAD P H oxidase (NOX) produces O_2^- and plays an important role in cardiovascular pathophysiology. NOX4 isoforms are mainly expressed in the mitochondria of myocardial cells. To clarify the role of endogenous NOX4 in the heart, he bred heart-specific NOX4 (–/–) [c-NOX4 (–/–)] mice. In c-NOX4 (–/–) mice, the expression of NOX4 was inhibited in a heart-specific manner, while no compensatory upregulation was observed in other NOx enzymes. The decrease in O_2^- levels in the hearts of these mice suggests that NOX4 is an important source of O_2^- in cardiomyocytes. The basic cardiac phenotype of young c-NOX4 (–/–) mice was normal. In the c-NOX4 (–/–) group, myocardial hypertrophy, interstitial fibrosis and apoptosis were significantly reduced,



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References	Year	Strength	Begin	End	2012 - 2021
Kuroda J, 2010, P NATL ACAD SCI USA, V107, P15565, DOI 10.1073/pnas.1002178107, DOI	2010	24.98	2012	2015	
Dai DF, 2011, CIRC RES, V108, P837, DOI 10.1161/CIRCRESAHA.110.232306, DOI	2011	16.99	2012	2016	
Tsutsui H, 2009, CARDIOVASC RES, V81, P449, DOI 10.1093/cvr/cvn280, DOI	2009	16.49	2012	2014	
Zannad F, 2011, NEW ENGL J MED, V364, P11, DOI 10.1056/NEJMoa1009492, DOI	2011	13.63	2012	2016	
Ago T, 2010, CIRC RES, V106, P1253, DOI 10.1161/CIRCRESAHA.109.213116, DOI	2010	13.4	2012	2015	
Tsutsui H, 2011, AM J PHYSIOL-HEART C, V301, P0, DOI 10.1152/ajpheart.00554.2011, DOI	2011	36.93	2013	2016	
McMurray JJV, 2012, EUR HEART J, V33, P1787, DOI 10.1093/eurheartj/ehs104, DOI	2012	14.04	2013	2017	
Burgoyne JR, 2012, CIRC RES, V111, P1091, DOI 10.1161/CIRCRESAHA.111.255216, DOI	2012	12.84	2013	2017	
Paulus WJ, 2013, J AM COLL CARDIOL, V62, P263, DOI 10.1016/j.jacc.2013.02.092, DOI	2013	24.08	2014	2018	
Octavia Y, 2012, J MOL CELL CARDIOL, V52, P1213, DOI 10.1016/j.yjmcc.2012.03.006, DOI	2012	14.39	2014	2017	
Zhang S, 2012, NAT MED, V18, P1639, DOI 10.1038/nm.2919, DOI	2012	14.39	2014	2017	
Yancy CW, 2013, J AM COLL CARDIOL, V62, P0, DOI 10.1016/j.jacc.2013.05.019, DOI	2013	14.17	2015	2018	
Huynh K, 2014, PHARMACOL THERAPEUT, V142, P375, DOI 10.1016/j.pharmthera.2014.01.003, DOI	2014	12.9	2015	2019	
Muenzel T, 2015, EUR HEART J, V36, P2555, DOI 10.1093/eurheartj/ehv305, DOI	2015	15.02	2016	2021	
Mozaffarian D, 2015, CIRCULATION, V131, P0, DOI 10.1161/CIR.0000000000000152, DOI	2015	13.53	2016	2019	
Zinman B, 2015, NEW ENGL J MED, V373, P2117, DOI 10.1056/NEJMoa1504720, DOI	2015	23.7	2017	2021	
Ponikowski P, 2016, EUR HEART J, V37, P2129, DOI 10.1093/eurheartj/ehw128, DOI	2016	20.49	2018	2021	
Jia GH, 2018, CIRC RES, V122, P624, DOI 10.1161/CIRCRESAHA.117.311586, DOI	2018	16.08	2019	2021	
Wiviott SD, 2019, NEW ENGL J MED, V380, P347, DOI 10.1056/NEJMoa1812389, DOI	2019	14.31	2019	2021	
Neal B, 2017, NEW ENGL J MED, V377, P644, DOI 10.1056/NEJMoa1611925, DOI	2017	12.88	2019	2021	

Figure 4 (A) Network diagram of cocited literature. Among 226,831 references, at least 42 were cited (divided into 7 categories). (B) Timeline distribution of the first 20 clusters. (C) The first 20 cocited articles with the highest citation burst. HF, heart failure.

myocardial cell apoptosis was significantly reduced, and cardiac function was significantly improved. The swelling of mitochondria and the decrease in mitochondrial DNA and aconitase activity in C-NOX4 (–/–) mice were all decreased. NOX4 overexpression in mouse hearts aggravates PO-induced cardiac dysfunction, fibrosis and apoptosis. These results indicate that NOX4 in myocardial cells is the main source of mitochondrial oxidative stress. The high-intensity literature has conducted relevant research on oxidative stress related to HF from multiple perspectives, including epidemiological studies on HF-related oxidative stress and studies on the inflammatory mechanism of HF-related oxidative stress.

Analysis of hotspots in research

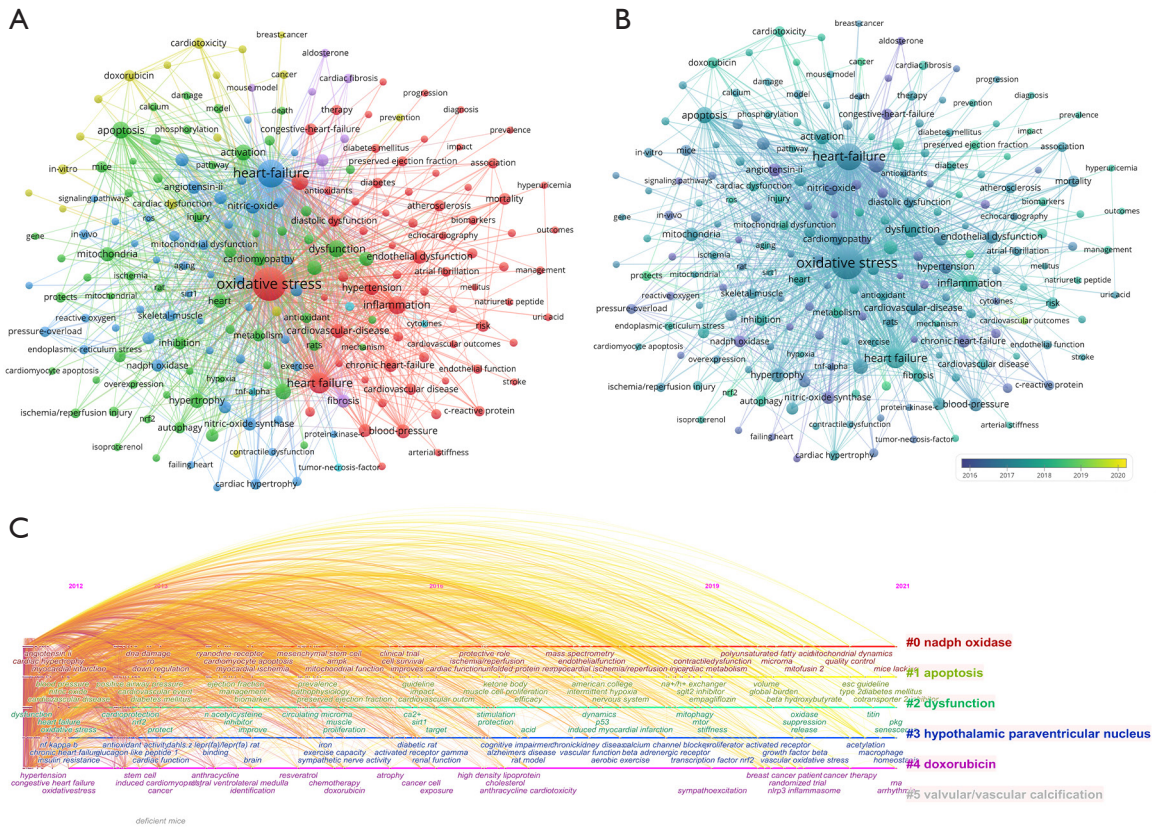
In addition to search terms, VOSviewer and CiteSpace also evaluated keywords collected from 5616 publication titles and abstracts. Cluster 1 (red) primarily focused on clinical research, discussing the pathogenesis of HF caused by oxidative stress and research on the comorbidity of HF, as shown in *Figure 5A*. Cluster 2 (green) mainly focused on basic research and explored various related pathways and mechanisms in the pathogenesis of HF caused by oxidative stress. Cluster 3 (blue) mainly focused on the role of nitric oxide and reactive oxygen species in HF caused by oxidative stress. Cluster 4 (yellow) focused on research on the treatment of HF and drug toxicology. Cluster 5 (purple) and Cluster 6 (light blue) described cardiac fibrosis and cytokines. *Figure 5B* shows that the latest keyword was "cardiovascular outcomes" (Cluster 1, APY:2019.14), followed by "protects" (Cluster 1, APY: 2018.43) and "cardiovascular diseases" (Cluster 1, APY: 2018.43), both of which are closely associated with HF. In addition, "biomarker" (Cluster 1, APY:2018.02) and "preserved ejection fraction" (Cluster 1, APY: 2018.13), as well as "cardiovascular diseases" (Cluster 1, APY: 2018.43), were the most recent hot topics in the field. Additionally, "nadph oxidase", "apoptosis", "dysfunction", "hypothalamic paraventricular nucleus", and "doxorubicin" were a focus in oxidative stress related to HF, as shown in *Figure 5C*. At the same time, the terms "impact", "induced myocardial infarction", "cardiovascular outcome", "empagliflozin", "sglt2 inhibitor", "protect", and "na^+/h^+ exchanger" were the most recent hotspots over the previous 4 years, as shown in *Figure 5D*.

Analysis of research on oxidative stress related to HF Caused by COVID-19

COVID-19 patients will have respiratory distress and dyspnea when their symptoms worsen, which will lead to HF. Some patients may even have metabolic acidosis and coagulation dysfunction. From the 5,616 articles we searched, 26 papers about oxidative stress related to HF associated with COVID-19 were screened and analyzed to further understand the trends and hotpots of this area of study (*Figure 6*). As shown in *Figure 6*, except for COVID-19, oxidative stress, HF, cardiovascular disease, endothelial dysfunction, inflammation, SARS-CoV-2, coronavirus, HF, disease, cytokine storm, expression, and injury appeared most frequently. Additionally, *Figure 6* shows the involvement of oxidative stress related to HF induced by COVID-19. Moreover, the mechanism by which anti-inflammatory treatment of HF induced by COVID-19 inhibits oxidative stress was revealed (*Figure 6*).

Discussion

This is the first bibliometric study of oxidative stress related to HF worldwide. Our study analyzed the research hotspots and trends in this field using WoSCC, VOSviewer and CitesSpace. We searched 5,616 papers between 2012 and 2021. With the polynomial fitting curve, although NP publishing has fluctuated slightly in this decade, there is a general trend to publish more papers. This increasing trend also indicates that an increasing number of researchers are interested in this topic. USA (n=1,616) produced the largest number of publications, followed by China (n=1,373), Italy (n=440) and Japan (n=380). USA was in first place in the top 10 countries/regions, which indicates that USA is a very productive country. Six universities in USA and five scholars from Brazil rank in the top 10, indicating that USA possesses the best affiliations and Brazil has trained the best experts and scholars. In addition, compared to China, the NC and H-index of USA are higher. In addition, USA has conducted more in-depth research on the subject than other countries. It is suggested that Chinese researchers and academic affiliations improve the quality of their research. Similarly, there are differences in the quantity and quality of publications between Italy and Japan. As far as subordination is concerned, more than half of the top 10 universities are from USA, showing that USA has good academic ability in this field. Kang Yuming,



Keywords	Year	Strength	Begin	End	2012 - 2021
left ventricular dysfunction	2012	9.04	2012	2015	
nadph oxidase	2012	8.88	2012	2014	
nad(p)h oxidase	2012	8.85	2012	2014	
angiotensin ii	2012	7.85	2012	2013	
necrosis factor alpha	2012	5.68	2012	2013	
ventricular myocyte	2012	5.15	2012	2015	
hypertensive rat	2012	7.8	2013	2015	
nitric oxide synthase	2012	6.86	2013	2015	
transgenic mice	2012	5.46	2013	2015	
european society	2012	7.28	2014	2017	
sympathetic nerve activity	2012	6.3	2015	2018	
metaanalysis	2012	7.07	2016	2017	
impact	2012	6.51	2018	2021	
induced myocardial infarction	2012	5.67	2018	2021	
p53	2012	5.23	2018	2019	
cardiovascular outcm	2012	8.01	2019	2021	
empagliflozin	2012	7.99	2019	2021	
sglt2 inhibitor	2012	6.25	2019	2021	
protect	2012	5.71	2019	2021	
na+/h+ exchanger	2012	5.21	2019	2021	

Figure 5 Keyword map of oxidative stress related to HF. (A) Using different colors, 204 terms that appear more than 50 times are divided into 6 categories. (B) Visualization of keywords according to APY. The different colors indicate the relevant year of publication. (C) Timeline distribution of keyword cluster analysis. (D) The top 20 keywords with the highest number of bursts. APY, average publication year; HF, heart failure.

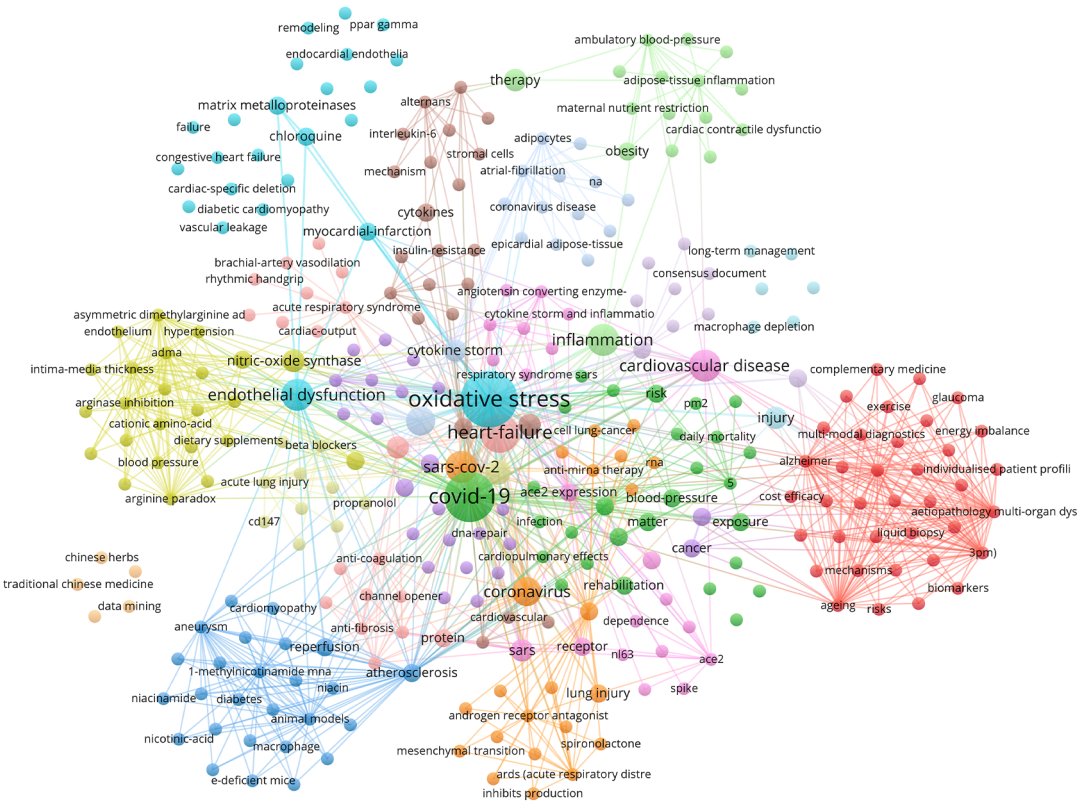


Figure 6 Network mapping of key words of oxidative stress-related heart failure caused by COVID-19.

Ren Jun, and Okoshi Katashi are the top three scholars in this study. The University of California (125 papers published, 4,871 cited) is the most productive institution. It is followed by the Institute National DE LA Sante et DE LA recherche Medical INSERT (118 articles published and 4,561 citations). Five of the top 10 journals have high IF values. This occurrence means that it is not easy to publish research in high-quality publications. The *PLoS One*, *International Journal of Molecular Sciences*, *Oxidative Medicine and Cellular Longevity*, *American Journal of Physiology Heart and Circulatory Physiology* made significant contributions.

Figure 5C shows that "nadph oxidase", "apoptosis", "dysfunction", "hypothalamic paraventricular nucleus", and "doxorubicin" have always been research hotspots. HF is an important cause of death in patients with heart disease, and myocardial tissue damage is an important mechanism of HF (38). Myocardial cell apoptosis is an important pathological change in HF and a turning point from compensatory to decompensated HF. Excessive apoptosis of cardiomyocytes is an important cause of HF, and excessive apoptosis of cardiomyocytes is related to oxidative stress (39). Lipids in cells are oxidized by excessive oxygen free radicals to produce MDA. The reduction in the activity of intracellular antioxidant enzymes leads to the accumulation of excessive oxygen free radicals in cells. SOD and GSH-PX are antioxidant enzymes that widely exist in cells, and their activity is directly related to the accumulation of oxygen free radicals in cells (40). The excessive accumulation of oxygen free radicals under oxidative stress can stimulate mitochondria, reduce mitochondrial membrane potential, release cyt-c and activate caspase-9, thus inducing the activation of caspase-3, the downstream apoptosis executive factor, and inducing apoptosis (41). Several signaling pathways has been proved to regulate oxidative stress in HF, like Nrf2/HO-1/$Ca2^{+}$-SERCA2a axis (42), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway (43), and IL-6/STAT3 (44). Mesenchymal stem cell derived exosomes could inhibit oxidative stress, inflammation and cell apoptosis via inhibiting inflammatory related NF-κB pathway in HF (45). In chronic HF, the level of inflammation is associated with oxidative stress. The serum concentrations of tumor

necrosis factor-alpha, C-reactive protein, white blood cell, neutrophil and monocyte are evidently increased (46). With the development of HF treatment, novel treatment strategies and personalized treatment plans are the hotspots of future researches. Because of individual differences, a one-size-fits-all approach to treatment is not appropriate. Developments in remote monitoring, home care and telemedicine offer hope for personalized treatment (47).

Through literature visualization and bibliometric analysis, hotspots and trends in research on oxidative stress related to HF were better understood. However, our study has some limitations. First, only articles and reviews in English from WoSCC were included in our research. Second, some information may have been overlooked because Citespace and VOSviewer cannot analyze the complete text of publications. Finally, because of the exclusion of literature from 2022, this study has a certain degree of lag.

Conclusions

The bibliometric analysis indicates that the number of articles published on oxidative stress research related to HF has fluctuated slightly in the past decade. Nevertheless, the publishing of an increasing NP is the general trend. Research on oxidative stress related to HF has good prospects. USA is a major producer in the field and has great influence. Clinical research and basic research are widely concerned. The role of SGLT2 inhibitors and Na^+/H^+ exchangers is a potential research hotspot. Research on the treatment of HF with traditional Chinese medicine monomers should be further expanded in the future. Our research will help scholars better understand the current situation of this research from a macro perspective.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6573/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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