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*Original Research*

# Bibliometric analysis of the inflammatory mechanism in aortic disease

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**Abstract**

**Background**: In view of the key role of inflammation in the pathogenesis of aortic disease, we visually analyzed the research hotspots of inflammatory mechanism in aortic disease in this work through the method of bibliometrics from the Web of Science (WOS) Core database over the past three decades. **Methods**: A visual bibliometric network of research articles on inflammatory mechanisms in aortic disease was obtained from VOSviewer and Citespace based on the WOS Core Collection. **Results**: A total of 1278 documents from January 1990 to February 2021 were selected for analysis. The United States and China had the highest percentage of articles, comprising 34.01% and 24.92% of articles worldwide, respectively. Harvard University has published the most articles in this field, followed by the University of Michigan and Huazhong University of Science and Technology. The top 3 research hotspots were atherosclerosis, oxidative stress, and macrophages. The journal with the most articles in this area was Arteriosclerosis Thrombosis and Vascular Biology, followed by Atherosclerosis and PLOS One. The research trend on inflammatory mechanisms in the aortic system has 5 distinct directions: (1) atherosclerosis, NF-κB, expression, smooth muscle cell, and oxidative stress; (2) coronary artery disease, C-reactive protein, risk factors, endothelial dysfunction, and aortic stenosis; (3) abdominal aortic aneurysm, matrix metalloproteinases, macrophage, and pathogenesis; (4) cholesterol, metabolism, low-density lipoprotein, gene expression, and a therosclerotic lesions; and (5) calcific aortic valve disease, interstitial cells, calcification, and stenosis. **Conclusions**: Inflammatory mechanism research has shown a tendency to rise gradually in the aortic field. Numerous studies have explored the role of inflammatory responses in aortic disease, which may increase the risk of endothelial dysfunction (aortic fibrosis and stiffness) and induce plaque formation. Among them, NFκB activation, nitric-oxide synthase expression, and oxidative stress are particularly essential.

**Keywords:** aortic disease; inflammation; inflammatory response markers; knowledge mapping analysis; research hotspots

## 1. Introduction

Aortic disease, which mainly includes aortic aneurysm and aortic dissection, is a cardiovascular disease that seriously threatens health. According to the Institute for Health Metrics and Evaluation, the incidence of aortic dissection is approximately 4.7 cases per million annually, while that of aortic aneurysm is approximately 6 cases per 100,000 patient years [1]. With the modernization of lifestyles and high incidences of diseases such as hypertension, arteriosclerosis, and diabetes, the incidence of aortic disease is rising rapidly [2]. Therefore, its pathogenesis needs to be further explored. From a pathological perspective, this disease can be either hereditary or sporadic [3,4]. Among them, aortic aneurysm is the dilatation of the whole aortic wall. Aortic dissection is the formation of a primary rupture in the aortic intima where the blood flow scours into the intima, which makes the aortic wall form true and false cavities and renders the weak outer wall of the blood vessel prone to rupture and bleeding [5]. Currently, few drugs are available to limit the progression of aortic disease, and only surgical treatment can be performed if the indications are met [6].

In recent years, different studies have showcased the existence and mechanisms of the inflammatory response and its relationship with aortic disease progression. Inflammatory cells infiltrate the media and outer wall of the aorta in cases of aneurysms and dissections, including lymphocytes, macrophages and mast cells, which normally participate in tissue damage responses and reconstruction [7]. At different stages of aortic stress, injury, repair, and remodeling, the cellular and extracellular components that make up the aortic wall adapt to the changes of the external environment [8]. However, in the inflammatory state, the imbalance of various components leads to biomechanical dysfunction and decreases wall compliance and mechanical strength, resulting in aortic aneurysm, dissection, and even rupture [9].

Although inflammatory mechanisms in aortic disease have only recently become popular research themes, no published bibliometric reports have analyzed the corresponding scientific data to summarize development processes and research hotspots and identify useful scientific trends in this field.

We used a bibliometric approach to identify and visualize scientific literature on the study of inflammatory

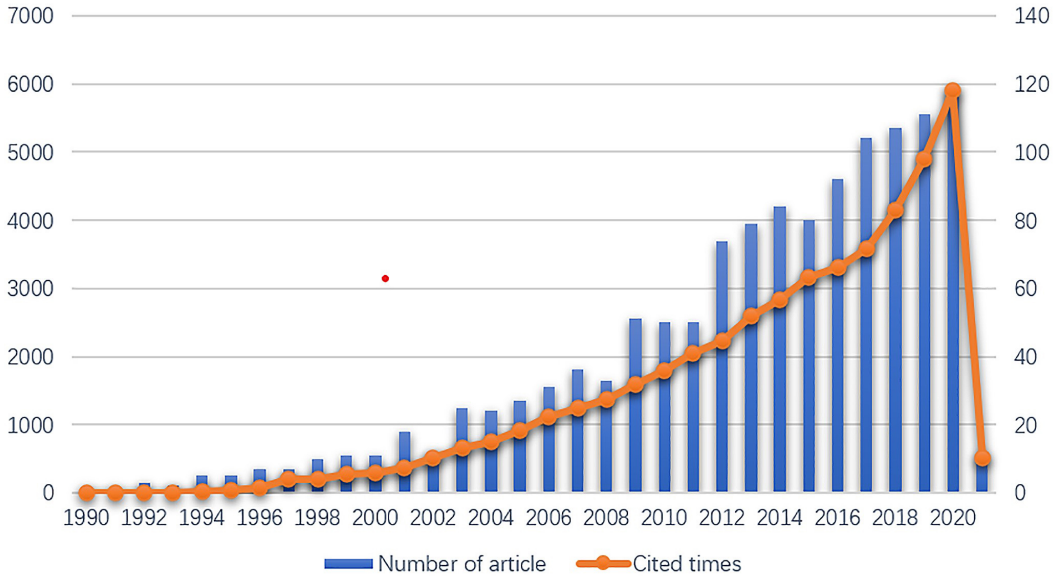


**Fig. 1. Trends in the growth of the publications and numbers of cited articles worldwide from 1990 to 2021.** There is an upward trend in the number of articles on the mechanisms of aortic inflammation from 1990 to 2021, with articles cited more frequently between 2015 and 2020, especially in 2020.

mechanisms in aortic disease. This revealed popular research topics, key authors, scientific institutions, countries, and journals. We further aimed to capture and describe the specific diseases and signaling pathways that are most frequently investigated in studies of inflammatory mechanisms in aortic disease and to provide new insights for future studies.

## 2. Methods

Bibliometric analysis was performed based on the Core Collection of the Web of Science (WOS), which is considered the optimal data source for bibliometrics. The search formula was set to TS = (aortic disease) and TS = (inflammatory mechanism) from January 1, 1990 to February 21, 2021.

This yielded a total of 1278 records (Fig. 1). Only English original articles and reviews were considered in this study. Two authors, WLC and ZSY, separately selected and recorded the data. All disagreements were discussed until reaching a consensus. Related data were collected and recorded in Microsoft Excel (Microsoft, Redmond, WA, USA) for analysis.

WOS-based literature analysis was used to summarize the general information of the distribution of publication years, journals, organizations, authors, and research fields, which was ranked using the Standard Competition Ranking method. Afterwards, the bibliometric analysis and network visualization including the top authors, keywords, research cooperation relationships, and co-citation network analysis of reference were performed with the VOSviewer version 1.6.16 software (Leiden University, Leiden, Netherlands) and Citespace version 5.7.R3 software (Drexel University, Philadelphia, PA, USA) [10,11]. The "citation report" function from WOS was applied to assess citation rates and h-index. Each keyword has its own label and circle. Different colored circles represent different clusters, and the size of the circle is proportional to its frequency of occurrence [12].

## 3. Results

### *3.1 Chronological map of the literature*

The number of research articles on aortic inflammatory mechanisms trended upward from 1990 to 2021 (Fig. 1). From 1990 to 2000, 2003 to 2007, 2012 to 2014, and 2017 to 2020, the number of published articles showed a steady increase. Meanwhile, there were slight declines in 2002, 2008, and 2015, and sharp rises in 2001, 2003, 2009, 2012, 2016, and 2017. The number peaked in 2020 and fell in 2021 due to incomplete trace time. Publications between 2015 and 2020 were cited with higher frequency, and the most cited articles were published in 2020 (Fig. 1).

### *3.2 National and regional distribution of the literature*

Institutions from the United States and China published the most articles, accounting for 34% and 25% of the total number of articles, respectively. Their combined number comprised more than half of all articles, suggesting that these two countries had a high research interest in this field. As for actual citation index (ACI) values, the top three countries are the United States (53.3), Germany (52.6), and Japan (51.2), indicating that they have been working on this field for longer than other countries and have produced more advanced and mature results (Table 1).

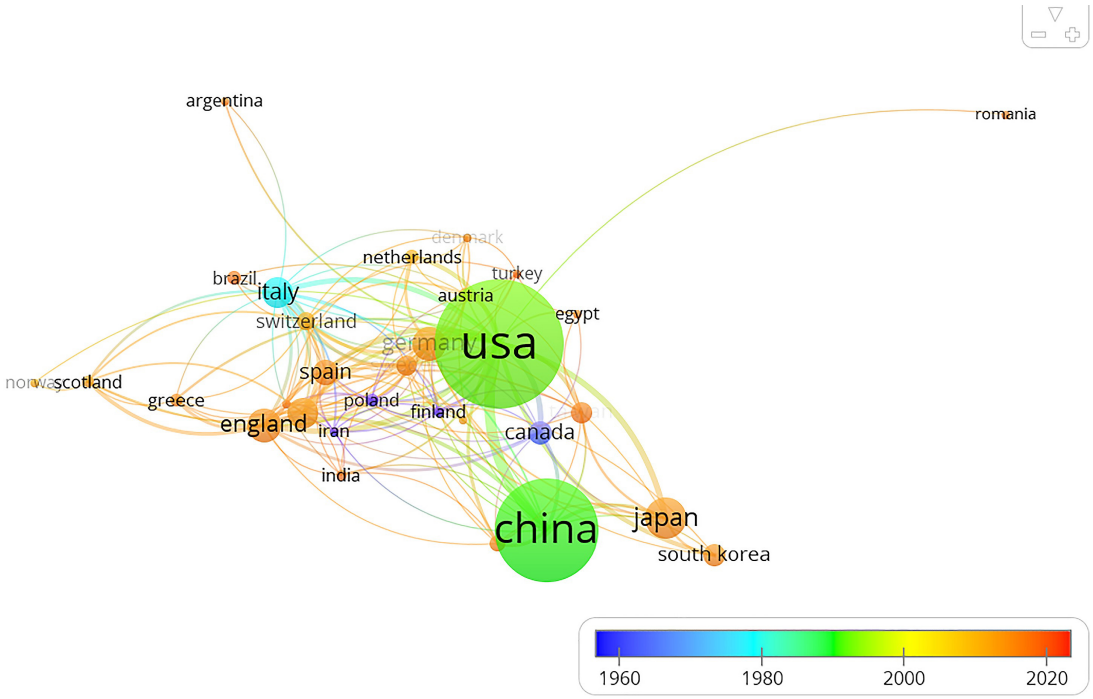


**Fig. 2. Cooperation map of countries of inflammatory mechanism in aortic disease.** Different colors represent different countries that work closely together, the size of the circle is proportional to the total number of articles from that country, and the distance between two countries is inversely proportional to the number of articles from those two countries. Among them, four distinct groups of regions work closely together.

There are four distinct clusters of regional close cooperation (Fig. 2). The United States and China most frequently collaborated with the United Kingdom, Japan, Canada, and Italy; Germany and England with Spain, Switzerland, and India; Japan with South Korea; and Italy with Austria.

As shown in Fig. 3, the average number of citations per publication per country over the entire period of analysis (1990–2021) was approximately 26, with the most cited countries being the US 91 (430), China (316), and Japan (92).

### *3.3 Distributions of authors and institutions*

Xianzhong Meng, David Fullerton and Lihua Ao from the University of Colorado ranked among the top three authors in terms of the number of publications. Among the top 10 authors published, nine are from the United States, including four from the University of Colorado and three from Temple University. The top three authors in citation frequency were Elena Aikawa from Brigham and Women's Hospital of Harvard Medical School, Hong Wang from Temple University, and Xianzhong Meng from the University of Colorado (Table 2).

Fig. 4 shows clusters of authors that collaborated. For example, Masanori Aikawa collaborated closely with Norbert Gerdes, and Haipeng Guo collaborated closely with Yingjie Chen and Yuan Li.

The institution with the largest number of research papers published in this field is Harvard University with 32 papers, followed by Huazhong University with 22 papers, and Shandong University with 19 papers. The institution which had the top ACI value in this field is the University of California in Los Angeles (120.73), followed by Harvard University (85.38) and Brigham and Women's Hospital 105 (60) (Table 3).

The different colors in Fig. 5 show clusters of intimate relationships between different research institutions. For example, Harvard University collaborated closely with the University of Michigan, Huazhong University of Science, Cornell University, and Tokyo Medical and Dental University, and China Medical University collaborated closely with Chang Gung University and Yale University.

### *3.4 Disciplinary distribution of the literature*

The top three disciplines with the most published articles were cardiac cardiovascular systems (20.6%), peripheral vascular disease (19.1%), and biochemistry/molecular biology (13.9%). Other disciplines represented in the literature included pharmacology/pharmacy (13.3%), cell biology (10.3%), experimental medicine research (8.5%), hematology (6.6%), multidisciplinary sciences (5.6%), immunology (5.1%), surgery (5%), and other disciplines. This indicated that the research performed in this field was broad and that the research methods were diverse (Table 4).

**Table 1. Top 10 productive countries in regard to the research on inflammatory mechanism in aortic disease.**

| Rank | Country | Quantity | Percentage | ACI | H-index | Total link strength |
|---|---|---|---|---|---|---|
| 1 | USA | 434 | 34 | 53.3 | 85 | 536 |
| 2 | China | 320 | 25 | 15.9 | 36 | 353 |
| 3 | Japan | 94 | 7.4 | 51.2 | 30 | 130 |
| 4 | England | 72 | 5.6 | 39.6 | 32 | 109 |
| 5 | Germany | 71 | 5.6 | 52.6 | 32 | 87 |
| 6 | France | 61 | 4.8 | 35.8 | 22 | 88 |
| 7 | Italy | 61 | 4.8 | 29.5 | 22 | 107 |
| 8 | Spain | 46 | 3.6 | 40.8 | 18 | 51 |
| 9 | Canada | 43 | 3.4 | 31.9 | 21 | 32 |
| 10 | South Korea | 42 | 3.3 | 24.5 | 16 | 39 |

ACI, average citations per item.

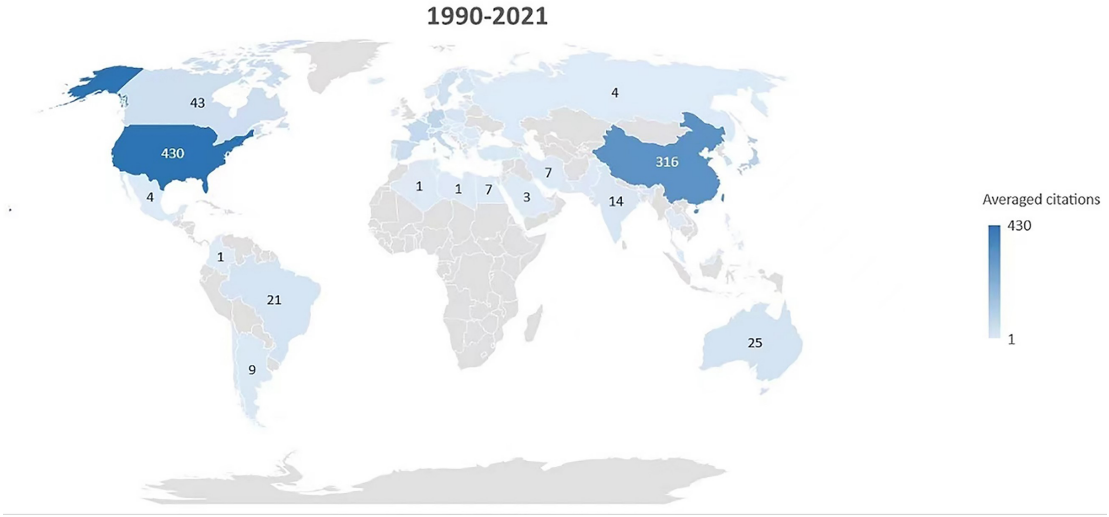


**Fig. 3. World map depicting the average number of citations per paper related to aortic inflammation published from 1990–2021.** The background color of the country is positively correlated with the average citation rate, and countries in the same color may have co-authorship of articles. Of these, the most cited country is the United States.

The journals with the highest number of articles in this field were Arteriosclerosis Thrombosis and Vascular Biology and Atherosclerosis (44 each), followed by PLOS One (41), Circulation (28), Biochemical and Biophysical Research Communications (23), and Circulation Research (22). The magazine with the highest ACI value was Circulation (143.6), followed by Cardiovascular Research (76.1), Arteriosclerosis Thrombosis and Vascular Biology (69.2), Circulation Research (69.1), Atherosclerosis (40), PLOS One (21.7), and Vascular Pharmacology (21.3) (Table 5).

### *3.5 Analysis of highly cited literature*

As shown in Table 6, the most cited article was "Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappa B signaling through a cAMP-dependent pathway," in which Ouchi *et al.* [13] discussed the mechanism of modulation of endothelial function by adiponectin.

The second most cited article was "The role of oxidized lipoproteins in atherogenesis". In this article, Berliner and Heinecke reviewed the understanding as of 1996 of the mechanisms of low-density lipoprotein oxidation and the potential role of oxidized lipoproteins in atherosclerosis [14].

The third most cited article was "Magnetic resonance imaging of atherosclerotic plaque with ultrasmall superparamagnetic particles of iron oxide in hyperlipidemic rabbits". In this article, Ruehm *et al.* [15] confirmed that ultrasmall superparamagnetic particles of iron oxide are phagocytosed by macrophages in atherosclerotic plaques of the aortic wall of hyperlipidemic rabbits in a quantity sufficient to cause susceptibility effects detectable by magnetic resonance imaging.

These papers have presented a crucial theoretical basis as well as clinical evidence for research in this area. Four of the most highly cited articles were reviews, while seven were original articles. The most highly cited articles were published from 2000 to 2007.

This period could be considered to represent the leaping development stage of this field. During this period,

**Table 2. Top 10 authors in the studies of inflammatory mechanism in aortic disease.**

| Rank | Author | Country | Institution | Total publications | Citations | H-index | Total link strength |
|---|---|---|---|---|---|---|---|
| 1 | Xianzhong Meng | USA | University of Colorado System | 12 | 251 | 8 | 157 |
| 2 | David Fullerton | USA | University of Colorado Denver | 10 | 243 | 7 | 148 |
| 3 | Lihua Ao | USA | University of Colorado System | 7 | 196 | 5 | 128 |
| 4 | Dingli Xu | China | Southern Medical University | 5 | 91 | 4 | 91 |
| 5 | Rui Song | USA | Loma Linda University | 6 | 123 | 6 | 90 |
| 6 | Qingchun Zeng | USA & China | University of Colorado Denver & Southern Medical University | 5 | 99 | 5 | 83 |
| 7 | Elena Aikawa | USA | Harvard university & Brigham and Women's Hospital | 7 | 685 | 7 | 31 |
| 8 | Hong Wang | USA | Temple University | 8 | 266 | 10 | 16 |
| 9 | Xiaohua Jiang | USA | Temple University | 5 | 194 | 7 | 14 |
| 10 | Xinyuan Li | USA | Temple University | 5 | 160 | 7 | 14 |

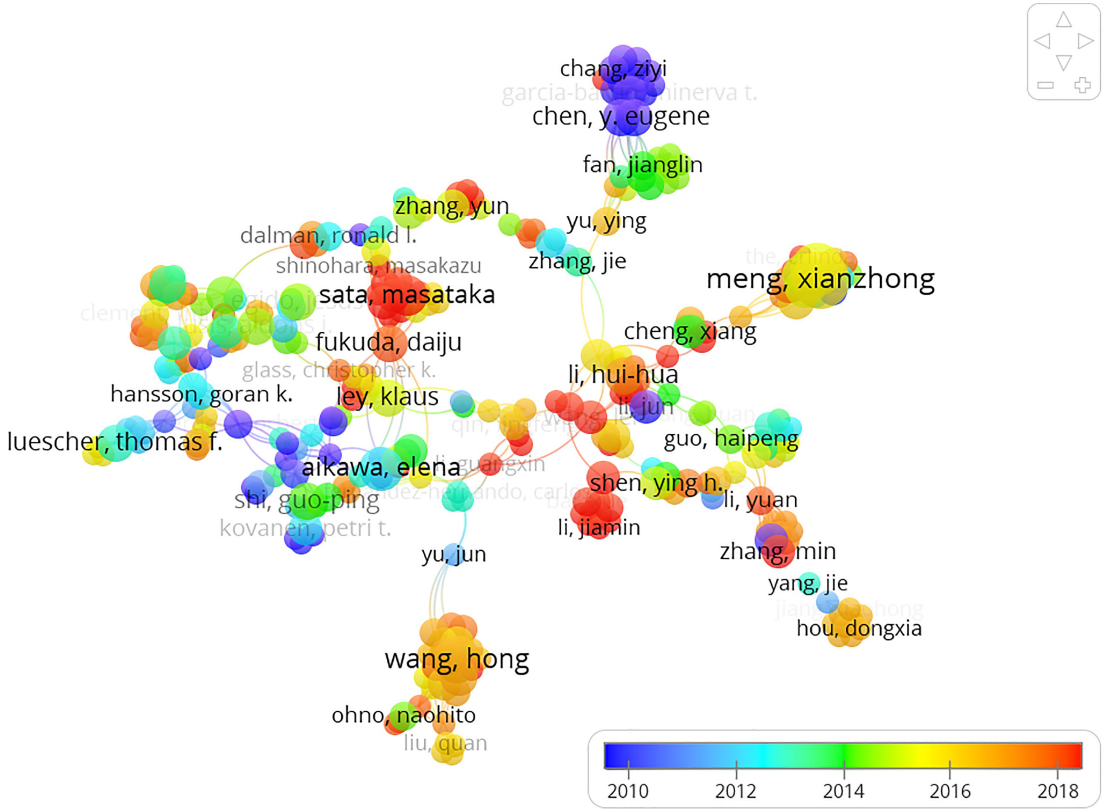


**Fig. 4. Cooperation map of authors in the studies of inflammatory mechanism in aortic disease.** Different colors represent different authors who work closely together, the size of the circle is proportional to the total number of articles by that author, and the distance between the two authors is inversely proportional to the degree of cooperation between them.

there were eight papers with at least two institutions but only one article with more than one country.

### *3.6 Hotspots and future directions*

#### 3.6.1 Analysis of research hotspots

Keywords represent the intrinsic content of the paper and thus are used to find the evolution of related research frontiers [16]. As illustrated in Table 7, besides "inflammation" and "atherosclerosis", the keywords that appeared most frequently were "oxidative stress" (71), "macrophage" (57), "abdominal aortic aneurysm" (43), "cardiovascular disease" (33), "endothelial cells" (34), and "endothelial dysfunction" (30).

Fig. 6 presents the keywords co-occurrence network map; the thicker the connection between the nodes is, the more frequently the two keywords appear together. The keywords formed 5 clusters, representing five major research directions in the field.

**Table 3. Top 10 institutions in the studies of inflammatory mechanism in aortic disease.**

| | Institution | Country | Quantity | ACI | STC | Total link strength |
|---|---|---|---|---|---|---|
| 1 | HARVARD UNIV | USA | 32 | 85.38 | 2732 | 15 |
| 2 | HUAZHONG UNIV SCI TECHNOL | China | 22 | 19.59 | 431 | 13 |
| 3 | SHANDONG UNIV | China | 19 | 14.42 | 274 | 12 |
| 4 | CHINA MED UNIV | China | 18 | 11.61 | 209 | 12 |
| 5 | UNIV MICHIGAN | USA | 17 | 46.59 | 792 | 10 |
| 6 | CAPITAL MED UNIV | China | 16 | 21.56 | 345 | 8 |
| 7 | KAROLINSKA INST | Sweden | 16 | 47.88 | 766 | 8 |
| 8 | SOUTHERN MED UNIV | China | 16 | 9.94 | 159 | 6 |
| 9 | BRIGHAM WOMENS HOSP | USA | 15 | 60 | 900 | 6 |
| 10 | UNIV CALIF LOS ANGELES | USA | 15 | 120.73 | 1811 | 5 |

ACI, average citations per item; STC, sum of the times cited.

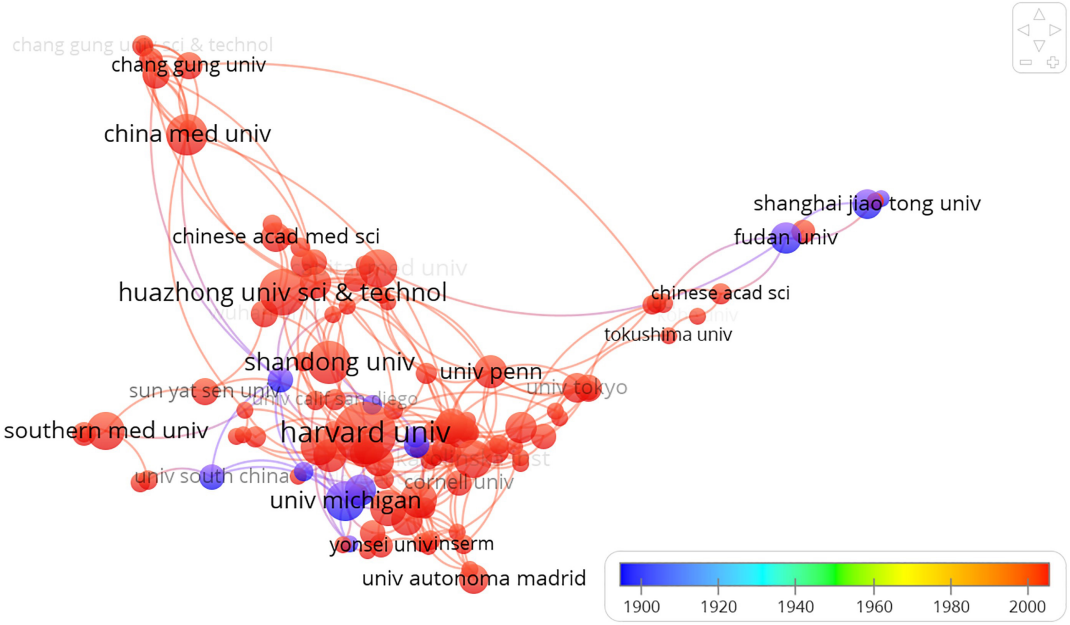


**Fig. 5. Cooperation map of institutions in the studies of inflammatory mechanism in aortic disease.** Different colors represent different institutions that cooperate closely, the size of the circle is proportional to the total number of articles in that institution, and the distance between two institutions is inversely proportional to the degree of cooperation between them.

### 3.6.2 Red cluster (Part 1)

Papers with the keyword "atherosclerosis" researched the pyrin domain 3 inflammasomes [17], toll- like receptor 4 [18], high low-density lipoprotein (LDL) cholesterol [19], and high lipoprotein(a) [20] to elucidate the inflammatory mechanism in aortic diseases. Papers with the keyword "NF$\kappa$B" studied the TLR3-TRIF-NF$\kappa$B pathway [21] regulated by polyinosinic-polycytidylic acid [22] in aortic valve interstitial cells and its activity in both valve endothelial and interstitial cells in calcific aortic valve disease models [23]. Papers with the keyword "smooth muscle cells" discussed rat aortic [24] and vascular smooth muscle cells [25] that served as the cell model in aortic disease experiments. Papers with the keyword "oxidative stress" investigated its contribution in abdominal aortic aneurysm (AAA) [26] and the effect of mediator myeloperoxidase (MPO) [27] in thoracic aortic aneurysm (TAA) [28], which showed that the Janus kinase/STAT pathway inhibited by S1 peptide [29] slowed the progression of AAA. Furthermore, commonly prescribed medications such as methotrexate and doxycycline alleviated and prevented cardiovascular diseases [30].

### 3.6.3 Purple cluster (Part 2)

Papers with the keyword "coronary artery diseases" (CAD) researched regulators in patients with Kawasaki disease [31] and rheumatoid arthritis [32]. In addition, they studied the use of 18F- fluorodeoxyglucose positron emission tomography imaging [33] for identifying CAD and biomarker proprotein convertase subtilisin/kexin type-9 [34] for predicting CAD. Papers with the keyword "C- reactive protein" (CRP) discussed a positive correlation with arterial stiffness [35] and acute aortic syndromes [36]. Risk factors included age, gender, obesity, smoking, hyperlipi-

**Table 4. Top 10 subject categories in the studies of inflammatory mechanism in aortic disease.**

| Rank | Quantity | WOS categories | Percentage |
|---|---|---|---|
| 1 | 261 | CARDIAC CARDIOVASCULAR SYSTEMS | 20.6 |
| 2 | 241 | PERIPHERAL VASCULAR DISEASE | 19.1 |
| 3 | 176 | BIOCHEMISTRY MOLECULAR BIOLOGY | 13.9 |
| 4 | 168 | PHARMACOLOGY PHARMACY | 13.3 |
| 5 | 130 | CELL BIOLOGY | 10.3 |
| 6 | 108 | MEDICINE RESEARCH EXPERIMENTAL | 8.5 |
| 7 | 84 | HEMATOLOGY | 6.6 |
| 8 | 71 | MULTIDISCIPLINARY SCIENCES | 5.6 |
| 9 | 65 | IMMUNOLOGY | 5.1 |
| 10 | 63 | SURGERY | 5 |

**Table 5. Top 10 journals in the studies of inflammatory mechanism in aortic disease.**

| Rank | Journal | Quantity | ACI |
|---|---|---|---|
| 1 | ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY | 44 | 69.2 |
| 2 | ATHEROSCLEROSIS | 44 | 40 |
| 3 | PLOS ONE | 41 | 21.7 |
| 4 | CIRCULATION | 28 | 143.6 |
| 5 | BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS | 23 | 19.7 |
| 6 | CIRCULATION RESEARCH | 22 | 69.1 |
| 7 | CARDIOVASCULAR RESEARCH | 19 | 76.1 |
| 8 | INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES | 15 | 10.1 |
| 9 | SCIENTIFIC REPORTS | 15 | 16 |
| 10 | VASCULAR PHARMACOLOGY | 15 | 21.3 |

ACI, average citations per item.

demia, hypertension, and type II diabetes mellitus in aortic diseases [37]. Papers with the keyword "endothelial dysfunction" evaluated berberine for treatment [38], $\mu$-calpain isoform [39], and microparticles [40] as part of the signaling pathway.

#### 3.6.4 Yellow cluster (Part 3)

Papers with the keyword "abdominal aortic aneurysm" researched the mechanistic target of the rapamycin (mTOR) pathway [41], roles of interleukin (IL)-1$\beta$ [42] and tumor necrosis factor $\alpha$ (TNF$\alpha$) [43], and the use of spermidine [44] for treatment. Papers with the keyword "matrix metalloproteinases" (MMP) studied the mechanisms of aortic diseases induced by MPO-derived oxidative species [45] and inhibited by doxycycline [46] and hydroxymethylglutaryl-coenzyme A reductase [47]. Papers with the keyword "macrophages" discussed the major role of TNF$\alpha$ inhibition [43] in macrophages in AAA. Also, IL-3 [48] activated macrophages secreted MMP12 [49] in TAA and dissection (TAAD) through mitogen-activated protein kinases pathways [50]. Papers with the keyword "pathogenesis" investigated mechanisms of AAA, TAA, and TAAD [51].

#### 3.6.5 Blue cluster (Part 4)

Papers with the keyword "cholesterol" researched its accumulation leading to atherosclerosis [52]. Papers with the keywords "cholesterol" and "low-density lipoprotein" both investigated the role of LDL cholesterol [53] in diseases related to bicuspid aortic valve [54] and proprotein convertase subtilisin/kexin type 9 [55], which decreased the removal of LDL cholesterol leading to a high risk of atherosclerosis. Papers with the keyword "metabolism" discussed arachidonic acid metabolism [56], nicotinamide adenine dinucleotide metabolism [57], lipid metabolism [58], and secreted phospholipase A2-driven phospholipid metabolism [59]. Papers with the keyword "gene expression" investigated gene expression profiling [60] and approaches for detecting inflammation factors [61] and extracellular matrix (ECM) proteins including MMP [62].

#### 3.6.6 Green cluster (Part 5)

Papers with the keyword "calcific aortic valve diseases" (CAVD) researched its markers, treatment targets such as cadherin-11 [63], and surgical aortic valve replacement [64]. Papers with the keyword "interstitial cells" studied aortic valve interstitial cells (AVICs) [65], interstitial cell phenotypes [66], and their role in CAVD [67]. Papers with the keyword "calcification" discussed apatite [68], non- canonical Wnt signaling [69], microRNA-214 via MyD88/NF-$\kappa$B signaling pathway in AVICs [70], and iron that could be taken up by VIC [71] and subsequently contribute to proliferation [72]. Papers with the keyword "stenosis" investigated aortic stenosis in terms of early diagnosis [73], risk factors [74], and association with CAVD [75].

**Table 6. Top 10 co-cited articles, cited authors, and cited references in the studies of inflammatory mechanism in aortic disease.**

| Rank | Article title | Journal | Type | Authors | Y | C | IN | CN |
|---|---|---|---|---|---|---|---|---|
| 1 | Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappa B signaling through a cAMP-dependent pathway | CIRCULATION | Original Article | Noriyuki *et al.* | 2000 | 1354 | 2 | 1 |
| 2 | The role of oxidized lipoproteins in atherogenesis | FREE RADICAL BIOLOGY AND MEDICINE | Review | Judith *et al.* | 1996 | 1140 | 4 | 1 |
| 3 | Magnetic resonance imaging of atherosclerotic plaque with ultrasmall superparamagnetic particles of iron oxide in hyperlipidemic rabbits | CIRCULATION | Original Article | Stefan *et al.* | 2001 | 456 | 4 | 3 |
| 4 | Inflammation and cellular immune responses in abdominal aortic aneurysms | ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY | Review | Koichi *et al.* | 2006 | 401 | 2 | 1 |
| 5 | Antagonistic crosstalk between NF-kappa B and SIRT1 in the regulation of inflammation and metabolic disorders | CELLULAR SIGNALLING | Review | Anu *et al.* | 2013 | 397 | 4 | 1 |
| 6 | Host bone-marrow cells are a source of donor intimal smooth-muscle-like cells in murine aortic transplant arteriopathy | NATURE MEDICINE | Original Article | Koichi *et al.* | 2001 | 392 | 1 | 1 |
| 7 | Modified low-density-lipoprotein and its constituents augment cytokine-activated vascular cell-adhesion molecule-1 gene-expression in human vascular endothelial | JOURNAL OF CLINICAL INVESTIGATION | Comparative Study | B V Khan *et al.* | 1995 | 385 | 2 | 1 |
| 8 | Induction of I kappa B alpha expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator-activated receptor-alpha activators | JOURNAL OF BIOLOGICAL CHEMISTRY | Original Article | Philippe *et al.* | 2000 | 362 | 2 | 1 |
| 9 | Induction of inflammation in vascular endothelial cells by metal oxide nanoparticles: Effect of particle composition | ENVIRONMENTAL HEALTH PERSPECTIVES | Original Article | Andrea *et al.* | 2007 | 354 | 2 | 1 |
| 10 | Update on spondyloarthropathies | ANNALS OF INTERNAL MEDICINE | Review | Muhammad *et al.* | 2002 | 324 | 1 | 1 |

Y, year; C, citations; IN, institute number; CN, country number.

### *3.7 Integrated evolutionary path of the literature*

As shown in Fig. 7, the year corresponding to each keyword is the first year in which it appears in the analyzed dataset. The shift between nodes can uncover the development of inflammatory mechanisms in aortic research hotspots. From 2010 to 2012, inflammatory mechanism research began to focus on NF$\kappa$B [76], oxidative stress [77], apoptosis [78], endothelial cells [79], and atherosclerosis [80]. From 2013 to 2015, diabetes mellitus [81], knockout mice [82], LDL cholesterol [83], and macrophages [84] received increased attention. Furthermore, MMPs [85], aortic aneurysm [86], hypertension [87], and dysfunction [88] became the new focus from 2016 to 2018. From 2019 to 2021, the field turned to research on chronic kidney disease [89], oxidative stress, proliferation [90], monocytes [91], and protein [92].

### *3.8 Recognition of research frontiers in the literature*

In Table 8, a blue line is used to mark the timeline. The red segment on top of the blue line represents burst

**Table 7. Top 10 keywords in the studies of inflammatory mechanism in aortic disease.**

| Rank | Keyword | Occurrence | Total link strength |
|---|---|---|---|
| 1 | Inflammation | 306 | 457 |
| 2 | Atherosclerosis | 330 | 380 |
| 3 | Oxidative stress | 71 | 118 |
| 4 | Macrophage | 57 | 104 |
| 5 | Abdominal aortic aneurysm | 43 | 58 |
| 6 | Cardiovascular disease | 33 | 50 |
| 7 | Endothelial cells | 34 | 50 |
| 8 | Endothelial dysfunction | 30 | 45 |
| 9 | Calcification | 27 | 44 |
| 10 | NF-kappa B | 31 | 41 |

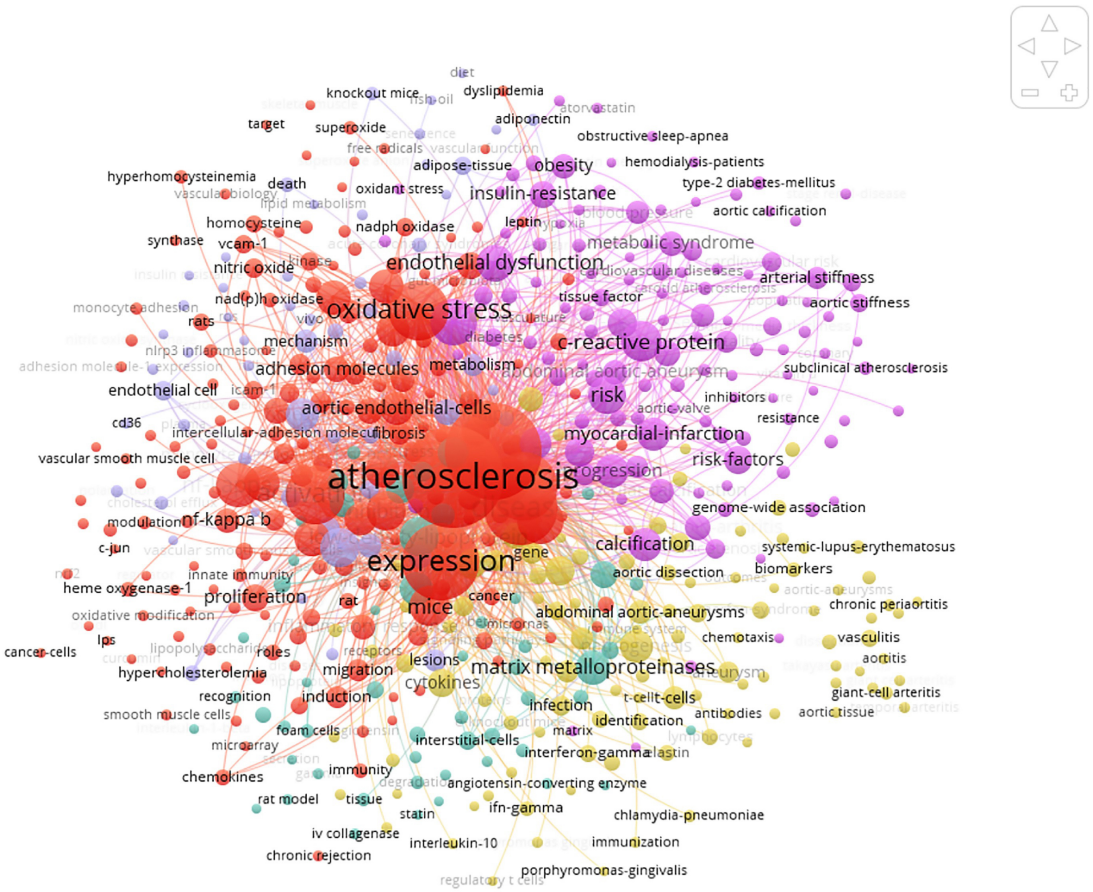


**Fig. 6. Map of keyword clustering in the studies of inflammatory mechanism in aortic disease.** The size of the circles is proportional to the number of occurrences of the keywords. The proximity of the circles indicates the frequency of co-occurrence between the two corresponding terms, and the closer they are, the higher the degree of cooperation between them.

detections by showing the start year, end year, and duration of the burst. We intended to find keywords with research significance to reflect the evolutionary trend of this field. "Dysfunction" showed the strongest burst strength, followed by "gene expression" [93], "low-density lipoprotein" [83] and "insulin resistance" [94]. The terms "nitric oxide" [95] and "insulin resistance" first appeared recently but lasted for a short duration. The burst times of "*in vivo*" [96] and "gene expression" were consistent. "Stenosis", "proliferation" and "pathogenesis" [97] are the current research frontiers in this field and are currently within the burst period.

## 4. Discussion

This work conducted a bibliometric analysis of literature published from 1990 to 2021 on inflammatory mechanisms in aortic disease using CiteSpace (Drexel University, Philadelphia, PA, USA) and VOSviewer (Leiden University, Leiden, Netherlands) software. The analysis focused

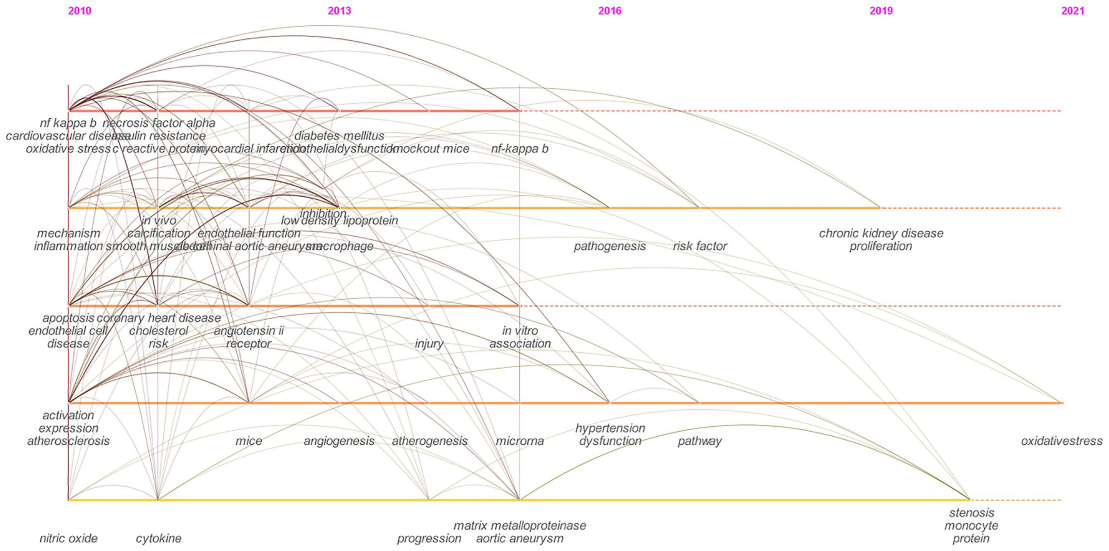


**Fig. 7. Evolutionary path in the studies of inflammatory mechanism in aortic disease.** The keywords were clustered and arranged by the year of first appearance to form a timeline chart. Variations between nodes can reveal the evolution of inflammatory response in the aortic research hotspot.

**Table 8. Top 20 keywords with the strongest citation bursts in the studies of inflammatory mechanism in aortic disease.**

**Top 20 Keywords with the Strongest Citation Bursts**

| Keywords | Year | Strength | Begin | End | 2010 - 2021 |
|---|---|---|---|---|---|
| coronary artery disease | 2010 | 4.1108 | **2010** | 2013 | |
| necrosis factor alpha | 2010 | 2.9527 | **2010** | 2011 | |
| c reactive protein | 2010 | 3.0417 | **2010** | 2012 | |
| nitric oxide synthase | 2010 | 3.1585 | **2010** | 2012 | |
| aortic endothelial cell | 2010 | 4.157 | **2010** | 2012 | |
| cholesterol | 2010 | 2.3643 | **2011** | 2012 | |
| tnf alpha | 2010 | 3.1361 | **2012** | 2015 | |
| gene expression | 2010 | 5.2781 | **2014** | 2015 | |
| in vivo | 2010 | 3.5717 | **2014** | 2015 | |
| apoptosis | 2010 | 2.0481 | **2014** | 2017 | |
| low density lipoprotein | 2010 | 5.1642 | **2015** | 2016 | |
| cytokine | 2010 | 2.6311 | **2015** | 2016 | |
| dysfunction | 2010 | 5.3077 | **2016** | 2019 | |
| hypertension | 2010 | 3.282 | **2016** | 2017 | |
| insulin resistance | 2010 | 5.1224 | **2017** | 2018 | |
| nitric oxide | 2010 | 4.8421 | **2017** | 2018 | |
| macrophage | 2010 | 3.9611 | **2018** | 2019 | |
| stenosis | 2010 | 3.662 | **2019** | 2021 | |
| pathogenesis | 2010 | 3.6359 | **2019** | 2021 | |
| proliferation | 2010 | 4.53 | **2019** | 2021 | |

on the spatial and temporal allocation, author contribution, core literature, heated topics, and research frontier analysis. Using keyword co-occurrence analysis, we were able to identify heated research topics from each period and unveil the evolutionary path of this research area. Afterwards, we identified the current research frontiers of research of inflammatory mechanisms in aortic disease. The main conclusions are as follows.

### *4.1 Research of inflammatory mechanisms in aortic disease shows an upward zigzag trend*

In recent years, people have given more attention to the role of the inflammatory response in the occurrence and development of aortic disease. Aortic wall media degeneration is an important cause of aortic disease formation while the inflammatory response participates in the process of aortic wall remodeling [98]. Some inflammatory cells and factors, such as macrophages, mast cells, and CRP, have been found to change with time in the process of dissection and prognosis, suggesting the possible value of the inflammatory response in the diagnosis and prognosis of aortic disease [99]. Choke *et al.* [100] found that inflammation regulates endothelial cells to induce intimal neovascularization, which accelerates the degradation of media ECM and the migration of aortic endothelial cells, resulting in decreased aortic strength. Inflammation is closely related to the clinical outcome of aortic disease. However, the clinical application of aortic disease treatment through the intervention of inflammation is still in its infancy, and related research and practice still needs to be continuously promoted [101].

### *4.2 Studies on the inflammatory response in the aorta first began in the United States and China, followed by increasing attention in Japan and the United Kingdom*

Research in the United States and China started earlier and has had more time to develop. For example, Harvard University, the University of California in Los Angeles, and Huazhong University of Science and Technology have published a large quantity of high-quality studies. Harvard University mainly studied Th1/Th2 cytokine balance in modulating matrix remodeling [102] and pathological smooth

muscle cells derivation in graft arterial disease [103]. The University of California in Los Angeles explored the effect of NF$\kappa$B signaling on inflammatory gene expression [104] and oxidized LDL cholesterol in aortic stenosis [14]. Huazhong University of Science and Technology explored the effect of drugs on inhibiting oxidative stress and inflammation via the NF$\kappa$B signaling pathway [105], such as metformin [106], Tanshinone IIA [107], and anthraquinone emodin [108].

### *4.3 Inflammatory response markers are research hotspot in this field*

Inflammatory markers refer to indices that can indicate the existence and progression of inflammatory reactions in clinical diagnosis. After the occurrence of aortic disease, the injury site induces local and systemic inflammatory responses by releasing chemokines, and the changes of related inflammatory markers can also indicate the process of occurrence and development of aortic disease [109]. It is essential to determine diagnostic and predictive factors with high sensitivity and specificity by studying biomarkers related to peripheral circulatory inflammation.

In the process of AAA, many inflammatory cells, including macrophages, mast cells, and neutrophils, infiltrate from the adventitia of the aorta to the intima layer by layer, causing a series of inflammatory reactions. Inflammatory cells and their secreted cytokines, such as IL-1$\beta$, IL-6, and IL- 33, stimulate vascular smooth muscle cells to secrete MMPs, which are directly related to the formation and progression of AAA [110]. Through the degradation of elastin and collagen, these enzymes lead to vascular smooth muscle cell apoptosis and ECM degradation, thus destroying the stability of the aortic wall. Therefore, inflammation has a profound effect on the occurrence and progression of AAA.

IL-6 is a multifunctional circulating cytokine and is related to inflammation, host resistance, and tissue injury. IL-6 is secreted by a variety of different cells, including activated macrophages and lymphocytes, and binds to high-affinity receptor complexes. As a classical inflammatory factor, IL-6 plays an important role in the development and progression of aortic disease and is gradually becoming a reliable biomarker for its diagnosis and the assessment of therapeutic effects and prognosis of patients with aortic disease. Wen *et al*. [99] found that serum IL-6 levels in patients with aortic disease increased in the acute phase and gradually decreased to normal levels in the chronic phase. Ju *et al*. [111] discovered that aortic disease is triggered by the IL-6 signaling pathway and transcription-3 activator through the Th17 lymphocyte-IL-17 axis. Tieu *et al*. [112] found that IL-6 is predominantly located in the tunica adventitia, where monocytes are recruited and activated, leading to promotion of monocyte chemoattractant protein-1 secretion, vascular inflammation, ECM degradation, and aortic instability. It has been recently reported that reducing IL-6 levels by some therapeutic interventions (e.g., antithrombin, dexmedetomidine, ulinastatin) can effectively delay or even reverse progression of aortic disease [113].

CRP is a cyclic pentamer protein found in plasma, which originates from the liver and increases after IL-6 secretion from macrophages and T cells. CRP binds to lysophosphatidylcholine expressed on the surface of dead or dying cells to activate the complement system through C1q. As one of the major and most sensitive markers of non-specific acute phase inflammation in humans, CRP is widely used to predict adverse events in cardiovascular disease. Sbarouni *et al*. [114] found that CRP values were more than five times higher in patients with acute aortic disease than in healthy people. Sakakura *et al*. [115] found that the peak value of CRP in patients with aortic disease during the perioperative period was strongly associated with medium- and long-term adverse events. CRP has been demonstrated to promote expression of MMP-1, an enzyme that plays an important role in plaque fragility and is primarily responsible for cleavage of type I and type III fibrillar collagen, which is a key matrix component of atherosclerotic plaques. CRP increases MMP-1 expression through the extracellular signal-regulated kinase (ERK) pathway. Following elevated CRP levels, the phosphorylation of ERK1/2 reaches a maximum and then decreases. In addition, it has been demonstrated that CRP promotes the expression of AT1-R, a receptor that mediates the proinflammatory effects of angiotensin II, thus promoting the migration and proliferation of vascular smooth muscle *in vitro* and *in vivo*, making it one of the most important bioactive factors involved in the development and progression of atherosclerosis.

TNF$\alpha$, a 17-kDa protein consisting of 157 amino acids, is mainly produced by activated macrophages, T lymphocytes, and natural killer cells. TNF$\alpha$ plays multiple roles in inducing inflammation and is involved in the regulation of cellular transport and activation, pathogen resistance, and immune inflammatory responses. Wen *et al*. [116] reported that TNF$\alpha$ levels were higher in patients with acute aortic disease than in healthy people. Enhancing vascular TNF$\alpha$ by SM22-TNF$\alpha$ transgenes in mice upregulates the aortic Msx2-Wnt3a/Wnt7a axis, leading to increased aortic calcium accumulation. Therapy with infliximab, a TNF$\alpha$-neutralizing antibody, abolishes aortic BMP-2-Msx2- Wnt3a and Wnt7a signaling and significantly alleviates aortic calcium accumulation. In addition, it has also been shown that TNF$\alpha$ can upregulate adhesion molecule expression, leading to formation of fatty streaks and the initiation of atherosclerosis, and is involved in inflammation that leads to plaque rupture.

MMPs are a family of zinc-dependent endopeptidases that target proteins of the ECM. Alterations in specific MMPs could influence arterial remodeling and lead to various pathological disorders such as hypertension, preeclampsia, atherosclerosis, aneurysm formation, excessive venous dilation, and lower extremity venous disease.

Accumulating evidence suggests that increased expression and activity of MMPs in the aortic wall are associated with alterations in histology [117]. In particular, the imbalance between MMPs and tissue inhibitors of MMPs (TIMPs) predisposes ECM degeneration, which induces aortic dilatation and dissection. Factors affecting the regulation of MMPs (e.g., cytokines, plasma systems) seem likely to play a synergistic role in AAA development. It has also been confirmed that the main reason for increased genetic susceptibility to AAA is variation in MMPs, TIMPs, and their mediating genes. Guo *et al*. [118] found that inhibition of MMP-9 expression with IL-1$\beta$ antibodies effectively mitigated the progression of aortic disease.

## 5. Conclusions

The present study is the first bibliometric analysis of research publications on inflammatory mechanisms in aortic disease worldwide. Using information visualization technology, we have assessed the progression and evolution of research in this field, research hot spots, and future study directions into research on inflammatory responses in aortic disease using literature from the past 30 years. The inflammatory response has a crucial role in both research progression and broad application prospects in cardiovascular diseases. This research area is characterized as a multinational cooperation with multidisciplinary intersections, and inflammatory response markers and therapeutic anti- inflammation options will be the focus of future studies.

Based on our discussion and analysis above, we are currently considering several further analyses: (1) more in-depth analysis of specific inflammatory response pathways in specific aortic diseases, such as the TLR3-TRIF-NF$\kappa$B pathway in aortic dissection; (2) comparison of research output trends in other disease areas where a combination of bibliometric and medical skills is useful; and (3) periodically repeating such analyses to observe temporal trends in research results, improve the accuracy of research hotspots, and encourage close collaboration among relevant countries and scholars to ultimately facilitate the diagnosis, treatment, and prevention of aortic disease.

## Author contributions

LCW and XGS—conception and design; YXL and YFL—administrative support; LCW and SYZ—provision of study materials or patients; LCW—collection and assembly of data; LCW—data analysis and interpretation. All authors write and approved the final manuscript.

## Ethics approval and consent to participate

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol was approved by the Institutional Ethics Committee of Fuwai Hospital (No. 2018-1069).

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## Conflict of interest

The authors declare no conflict of interest.

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