Original Article

Global research trends in atherosclerosis-related NF-κB: a bibliometric analysis from 2000 to 2021 and suggestions for future research

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Background: Atherosclerosis (AS) is closely related to stroke and cardiovascular diseases. Nuclear factor kappa-B (NF-κB) is the master regulator of inflammation, and thus, modulating the transcription of NF-κB can improve AS.

Methods: In this study, we conducted a bibliometric analysis to identify the frontiers, hotspots, and features of global research output on NF-κB in AS from 2000 to 2021. Papers published from 2000 to 2021 and the recorded information were retrieved from the Science Citation Index-Expanded of the Web of Science Core Collection. Bibliometric analysis and visualization were performed using VOSviewer and CiteSpace, including an analysis of the general distribution of annual output, highly productive countries, active journals, active institutions and authors, keywords, and co-cited references.

Results: A total of 5,439 original articles and reviews were retrieved and analyzed, and the results indicated that the annual number of publications on NF-κB in AS has been increasing in waves over the past 22 years. The majority of papers were published in China, while the USA had the highest number of citations and H-index. The most productive affiliation and journal were the University of California System and Arteriosclerosis Thrombosis and Vascular Biology, respectively. The papers of Chiu JJ. received the highest number of citations globally in 2011. The keywords, "nlrp3 inflammasome" and "microRNA", have recently attracted considerable attention, and very frequently occurring keywords included "NF kappa B", "atherosclerosis", "expression", "activation", "endogenous cell", and "oxidative stress". New keywords in 2021 included "muscle", "attenuates atherosclerosis", "mesenchymal transition", "metabolic disorder", and "palmitic acid".

Conclusions: AS and inflammation have become research hotspots lately. Over the past decade, most studies have focused on basic research, and pathways associated with the regulatory role of NF-κB in AS have become a particular focus in recent studies. Moreover, our study revealed that NF-κB plays a remarkable role in AS and may be a therapeutic target.

Keywords: Bibliometrics; atherosclerosis (AS); nuclear factor kappa-B (NF-κB); CiteSpace; VOSviewer

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Introduction

Atherosclerosis (AS) refers to the formation of fibrofatty lesions in the arterial wall (1) and is characterized by low-grade chronic inflammation (2). AS is a leading cause of myocardial infarctions, strokes, and peripheral artery disease among Westerners (3). In addition, the progression of AS is closely related to an increase in cardiovascular morbidity and mortality rates. Therefore, researchers and healthcare workers should pay more attention to the development and pathogenesis of AS.

AS was previously believed to be a lipid storage disease that is driven by oxidized low-density lipoprotein and protected from high-density lipoprotein cholesterol (4). However, increasing evidence points out that the role of the immune system, including inflammation, has become an emerging risk factor for AS (5). Nuclear factor kappa-B (NF-κB) is a family of transcription factors whose activation process must be tightly regulated. NF-κB induction genes include inflammatory genes, immunomodulatory genes, antiapoptotic genes, and genes that regulate the cell cycle. Furthermore, nuclear NF-κB pathway is involved in the regulation of lipid metabolism, and inhibition of the expression of NF-κB pathway can promote lipid metabolism and reduce lipid deposition.

The activation of NF-κB occurs in normal cells only after the upregulation of its target gene. Some researchers have proposed that NF-κB may be activated by different signaling pathways, such as cytokines, growth factors, and C-reactive proteins (6). The enhanced expression of toll-like receptors, insulin growth factor receptors (7), and tumor necrosis factor receptor family members may be associated with NF-κB activation. In addition, signaling pathways, such as the nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) (8) and toll-like receptor 4 (TLR4) (9) pathways, are also involved in the activation of NF-κB. The NF-kB pathway is involved in the expression of NLRP3 inflammasome during macrophage initiation in AS. Inhibition of NLRP3 inflammasome can be achieved by inhibition of NF-κB pathway (10). Pharmacological inhibition of NLRP3 inflammasome is mediated by inhibition of NF-κB pathway (11). In addition, the process by which lipids deposited in artery walls eventually form local plaques is mediated by inflammation. The cells involved in these inflammatory responses are mononuclear, macrophage or activated T cells. Inflammation is an essential factor leading to the instability of atherosclerotic plaques. Inhibition of inflammatory response in treating AS is an effective treatment method. Anti-inflammatory therapy can prevent vascular inflammation from improving the atherosclerotic plaques, prognosis of patients and related clinical symptoms. Undoubtedly, NF-κB plays an important role in the immune response and regulating the stable state of the cell cycle. NF-κB is considered one of the major pathways for the expression of inflammatory response genes, which has been identified as a primary mechanism that underlies AS. At the same time, NF-κB can be involved in genes that regulate cell apoptosis (12), adhesion, or migration (13). All of these process changes are involved in the advancement and progression of AS, which confirms the clear link between NF-κB and AS.

With the surge in interest in NF-κB and the publication of several related papers in recent years, researchers have experienced difficulty in defining development trends and research hotspots in the field. Numerous scholars have successively conducted research in this field and published several papers. The introduction of new technologies and the emergence of novel concepts pose considerable challenges to both new and existing researchers. Different methods are available for quantitative literature analysis, such as traditional review, main path analysis, and bibliometrics (14). Bibliometrics utilizes mathematical statistics for quantitative analysis and publication evaluation (15) and has been widely applied to the exploration of development trends and research frontiers in various fields (16,17). Through the bibliometric analysis of publications, researchers can focus on current research priorities, follow highly cited publications, and predict future research hotpots.

Highlight box

Key findings

- Hotspots of NF-κB in atherosclerosis included "muscle", "attenuates atherosclerosis", "mesenchymal transition", "metabolic disorder", and "palmitic acid".

What is known and what is new?

- NF-κB plays an important role in the pathogenesis of atherosclerosis.
- The most papers of NF-κB in atherosclerosis were published in China.

What is the implication, and what should change now?

- Bibliometric analysis reveals the research hotspots, current situation and future development trend in the field of NF-κB in atherosclerosis.

CiteSpace (School of Information Science and Technology, Drexel University, Philadelphia, PA, the USA) exhibits a good ability to generate and analyze networks of co-cited references; it can visualize the basic knowledge and hotspots of a research field and predict development trends and research frontiers (18). VOSviewer (Centre for Science and Technology Studies, Leiden University, Leiden, the Netherlands) can be applied to create bibliometric networks by using data acquired from bibliographic sources, such as the Web of Science Core Collection (WoSCC). Our study can assist VOSviewer users in selecting the most appropriate counting technique for their analysis (19). WoSCC is the primary source of input data for the bibliometric analysis of publications. CiteSpace and VOSviewer can categorize research hotspots and development trends that are currently being studied by extracting keywords from titles and abstracts (20). In the present study, we employed CiteSpace and VOSviewer to investigate the research trends, major contributors, research topics, institutions, and hotspots in the field of NF-κB in AS.

Methods

Data source search strategies

Publications on NF-κB in AS were retrieved from the Science Citation Index (SCI)-Expanded of WoSCC. The study period was set from 2000 to 2021. We used the following terms to yield as many results as possible: "atherosclerosis" OR "atherosclerosis" OR "atherogenesis" OR "atherosclerosis" OR "atheromatosis" OR "atherogenesis" OR "arteriosclerosis" AND "NF-kappa B" OR "NF kappaB" OR "NF-κB" OR "Nuclear Factor Kappa b" OR "nuclear transcription factor-κB" OR "NF-κB" OR "Nuclear Factor Kappa b" OR "nuclear transcription factor-κB" OR "nf kappa b" OR "NF-KB". To avoid deviations, the publication retrieval was completed in a single day (August 20, 2022).

We eliminated invalid documents, including proceeding papers [103], meeting abstracts [63], editorial materials [26], book chapters [24], early access documents [7], letters [6], retracted publications [6], corrections [2], reprints [2], and publications with an expression of concern [2]. The language was limited to English. A total of 5,439 papers were acquired, including articles [4,376] and reviews [1,063]. All information, including the numbers of publications (Np) and citations (Nc), titles, authors, institutions, countries, keywords, journals, year of publications, and references were gathered for bibliometric analysis. The data were saved as plain text files (*Figure 1A*).

Bibliometric analysis

We used CiteSpace (version 5.8.R3) and VOSviewer (version 1.6.16) for the bibliometric analysis (*Figure 1B*). In general, Np represented productivity, while Nc was used to indicate impact; these two were the primary indexes used to evaluate the level of research (21). Recently, the *H*-index has been widely employed to assess a researcher's academic contribution and forecast his/her future achievements (22). The H-index combines productivity and quality by determining the threshold related to Np and Nc. Furthermore, the impact factor (IF), which is calculated using the most recent edition of Journal Citation Reports (JCR), is widely regarded as one of the most important indicators of a journal's quality and influence. Co-occurrence, co-citation, and co-authorship are the most common types of bibliometric analysis (23). A co-occurrence analysis examines the relationship between items based on how frequently they occur together. According to co-citation analysis, the number of cited items determines the strength of the relationship between them. In co-authorship analysis, the number of publications between countries, institutions, or authors is regarded as evidence of a relationship between them (24).

Results

Overview of the publications on NF-κB in AS

Based on our search strategy, 5,439 articles and reviews published from 2000 to 2021 were retrieved. The total Nc of all the publications was 296,11 5, while the average Nc for each paper was 57.68. The overall *H*-index of the included articles was 217.

Annual trends in paper publication quantity

As presented in *Figure 2*, although fluctuations occurred in the research trends regarding NF-κB in AS, an overall growth trend was observed over the past 22 years. According to the fitting curve, the correlation between year and output was clear, i.e., the correlation coefficient (R^2) was 0.9599. Furthermore, the annual Np fluctuated from 2000 to 2009 but increased sharply in 2010. One possible reason for this is that people's dietary structure has changed with the improvement of living standards in recent decades, and the

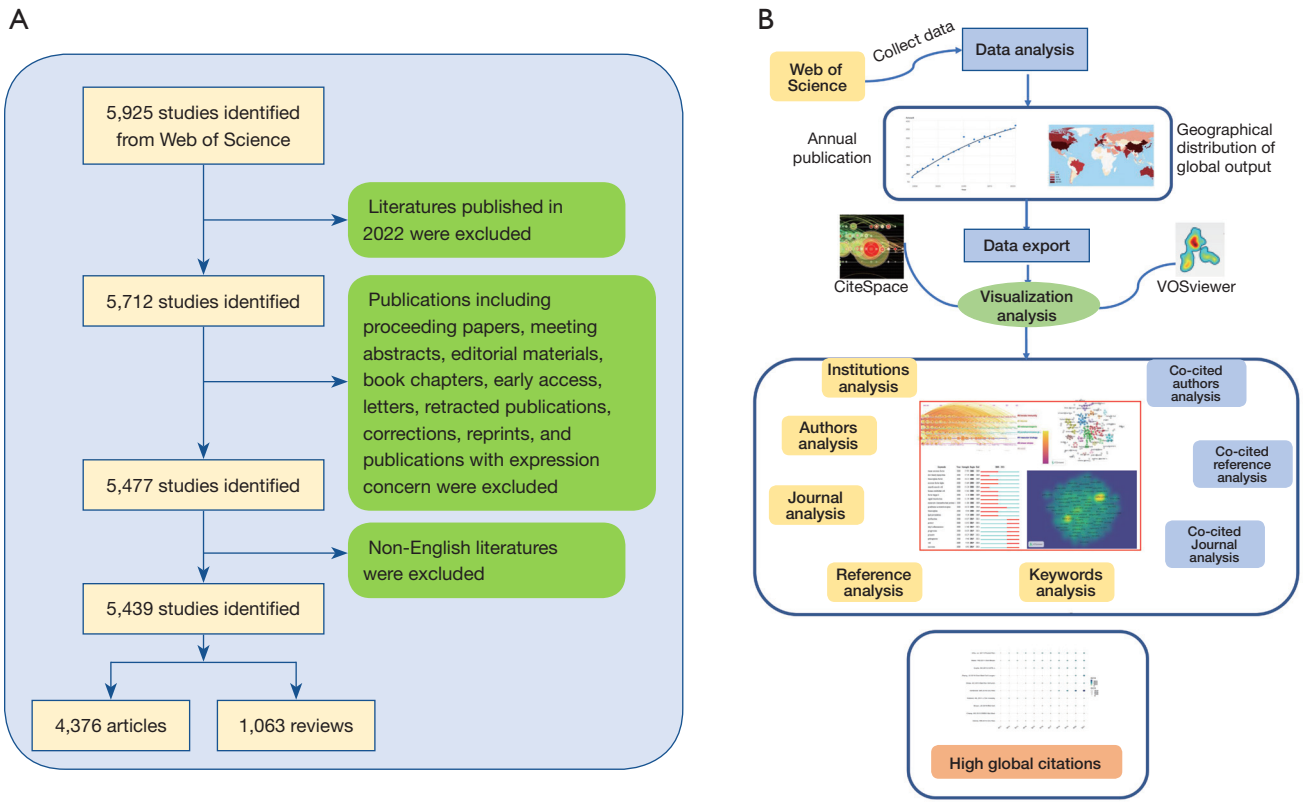

Figure 1 The entire study framework based on bibliometrics. (A) Flowchart of the document retrieval process; (B) main research methods and research content map.

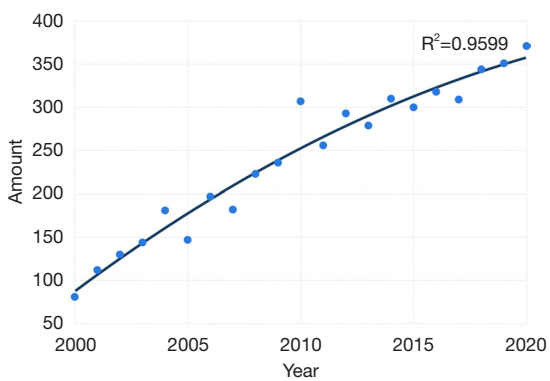

Figure 2 The amount of annual publications over the past 22 years, curve fitting of annual growth trend of publications (R^2=0.9599).

incidence of AS has also increased significantly, leading to the increase of the overall onset time. Accordingly, research on the disease has also expanded. In the period from 2010 to 2021, Np increased rapidly, with the number of papers published peaking at 371 in 2020.

Contributions of countries/regions to global publications

A total of 85 countries have published papers related to NF-κB in AS. *Figure 3A* shows the geographical distribution of global output. *Table 1* lists the top 10 high-output countries/regions ranked according to the Np. A total of 1,922 articles were published in China, achieving the highest output, followed by the USA (Np=1,452) and South Korea (Np=427). Apart from the USA, the Np in China was more than four times higher than those in other countries. In terms of Nc, the USA ranked first [141,821], followed by China [48,745] and Germany [39,141]. Moreover, the USA had the highest *H*-index [173]. England had the highest average number of citations [117.34], followed by Germany [117.1] and the USA [99.62]. The annual Np of the top 10 countries is presented in *Figure 3B*. Before 2010, papers published in the USA ranked first. Since 2010; however, China's Np has gradually taken the lead.

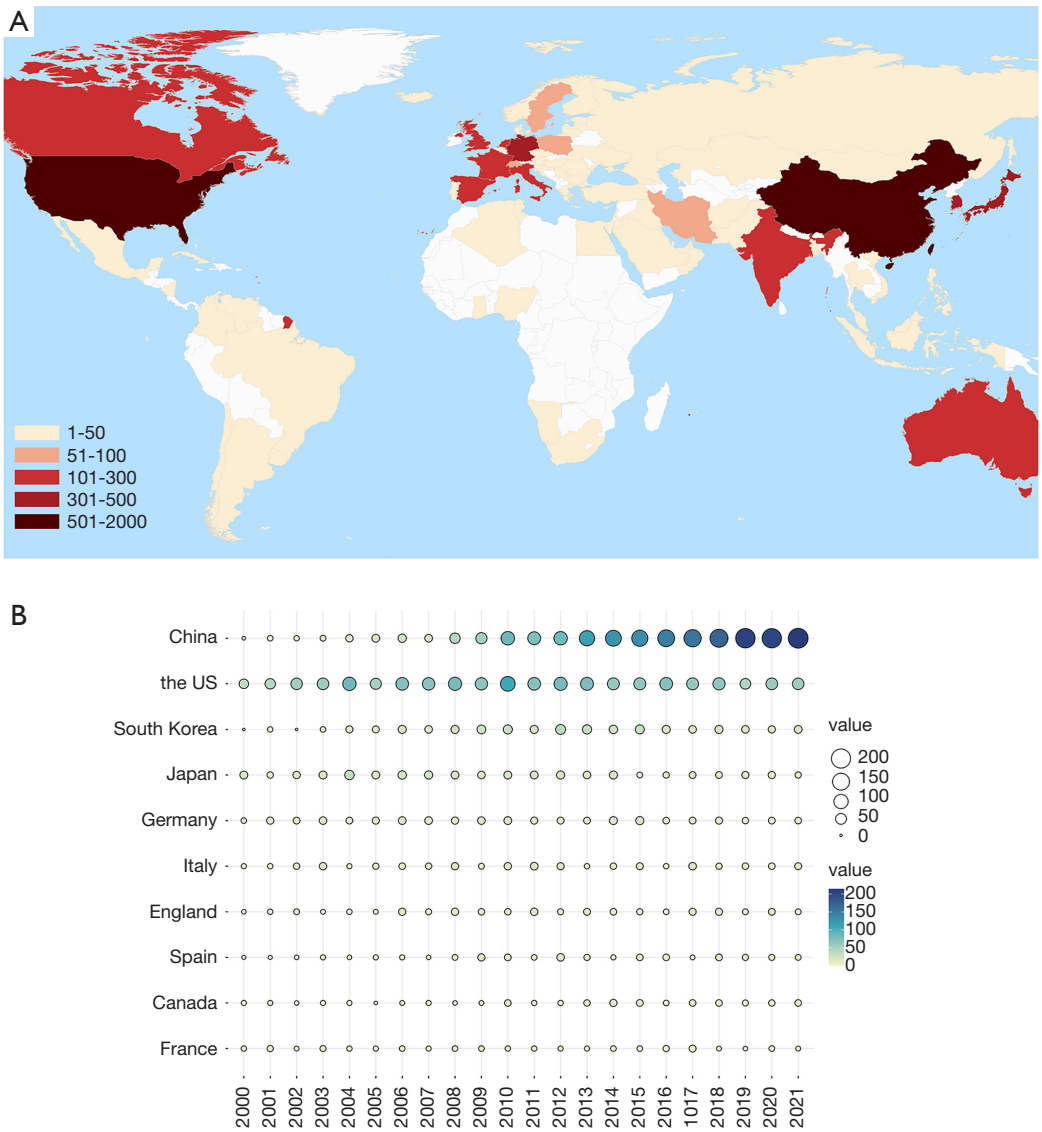

Figure 3 Leading countries in terms of published research on NF-κB. (A) Geographical distribution of global output; (B) annual output trend of the top 10 most productive countries.

Analysis of authors and affiliations

Among the 26,441 authors, the minimum number of documents by an author was set as 8; thus, 145 authors were included in the network. The cooperative relationship among authors was not extremely strong (*Figure 4A*). The top 10 most productive authors who were first authors, corresponding authors, or co-authors of these articles are listed in *Table 2*. Nearly one-third of the top 10 authors were from the USA. Egido J from Spain ranked first in terms of Np, followed by Hennig B from the USA. Libby P had the highest Nc [9,605], achieving the highest average per item [437.36]. Among the top 10 authors, 40% were from China and South Korea, indicating that research in this field is relatively advanced in Asia. *Figure 4B* shows the top 20 most representative authors in terms of burst strength, time, and duration. Lerman A and Toborek M began research on AS earlier and had higher burst strengths. In addition, owing to a strong citation burst during the past few years, Xu SW achieved the highest burst strength. Zhang L and Zhang J are new researchers in this study field, and thus, more attention should be given to the publications of these researchers.

Table 1 Contributions of the 10 most productive countries/regions

Rank	Country	Np	Nc	Average per item	H-index
1	China	1,922	48,745	26.7	89
2	USA	1,452	141,821	99.62	173
3	South Korea	427	17,572	41.95	64
4	Japan	399	20,977	53.06	74
5	Germany	336	39,141	117.1	80
6	Italy	255	17,356	68.8	65
7	England	222	25,888	117.34	73
8	Spain	173	8,768	51.36	52
9	Canada	172	10,511	61.71	53
10	France	144	140,442	97.93	54

Np, the numbers of publications; Nc, the numbers of citations.

A total of 3,901 institutions published articles on NF-κB in AS, and the minimum number of documents for an institution was set as 13. So, 198 institutions were included in the network (*Figure 4C*). Harvard University, Shanghai Jiao Tong University, China Medical University, and Shandong University, which belonged to different clusters, had larger nodes and were in the core position. Institutions with blue nodes conducted research on NF-κB in AS earlier than those with yellow nodes. The top 10 institutions with the highest productivity on NF-κB in AS research are listed in *Table 3*. In terms of output, the University of California System in the USA (Np=168) was the leading institution, followed by Harvard University in the USA (Np=135) and Institut National De La Sante Et De La Recherche Medicale Inserm in France (Np=111). Harvard University did not rank first in terms of Np, but its Nc and average per item were the highest, indicating that the research conducted by Harvard University was in-depth. The Np of Shanghai Jiao Tong University was high but its Nc (average per item) and *H*-index were not, indicating that its research might not be in-depth. In addition, the top 20 most active institutions varied in different periods, as shown in *Figure 4D*. Before 2010, Harvard University, the University of Texas, and Osaka University exhibited high influence. After 2014, Nanjing Medical University, Southern Medical University, Peking Union Medicine University, Capital Medical University, and Zhengzhou University, which are all in China, demonstrated high influence, indicating that the regional advantages of the research in this area have shifted from European and American countries to Asian countries.

Analysis of publications and journals

Figure 5A shows the publication co-occurrence network. Given the large number of publications, the minimum citation number of papers was set as 216. Only 221 of the 5,439 publications were selected for analysis. *Figure 5B* shows the journal co-occurrence network. *Arterioscler Thromb Vasc Biol*, *Atherosclerosis*, *Biochem Biophys Res Commun*, *PLoS One*, *Circ Res*, and *Cardiovasc Res* had relatively large nodes, and these nodes were at the core of the network, suggesting that these journals published numerous papers and exhibited high influence in this field. The top 10 most active journals are listed in *Table 4*. Among these journals, *Arterioscler Thromb Vasc Biol* had the highest Np [186] and *H*-index [71]. *Circ Res* had the highest Nc [14,680] and IF [23.213], and a high *H*-index [65]. The *Free Radic Biol Med* and *Cardiovasc Res* journals also had high Np, Nc, and IF, suggesting that they are highly valuable for research in the field of NF-κB in AS. Except for those of *Biochem Biophys Res Commun*, *PLoS One*, and *Mol Med Rep*, the IFs of the remaining journals were high (IF >5), indicating that the research on NF-κB in AS published in these journals was relatively in-depth.

Co-citation analysis

Analysis of the co-cited references

Two nodes connected by a line were referenced in the same publication, and the size of the node represented the total link strength and the total number of references to

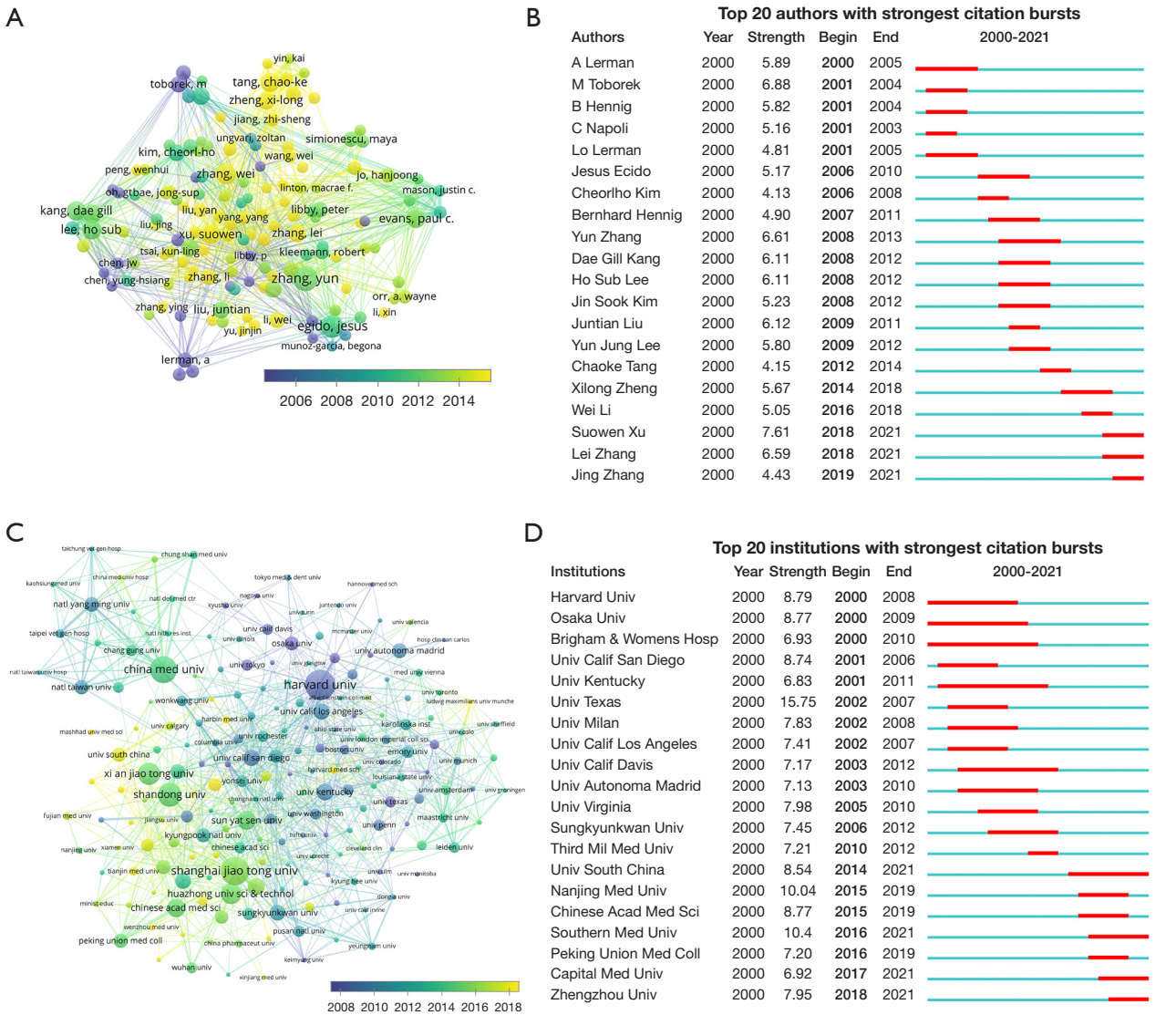

Figure 4 Visualization of the active institutions and authors. (A) Co-occurrence network of the authors; (B) the top 20 authors with the strongest bursts; (C) co-occurrence network of the institutions; (D) the top 20 institutions with the strongest bursts.

the document (25). Considering the large number of co-cited references, the minimum number of citations of a cited reference was set as 41. Among the 205,342 cited references in the papers, 203 references were selected for co-citation analysis (*Figure 6A*). The different clusters of references were colored differently; Cluster 1 (in red) included 59 references and Cluster 2 (in green) included 49 references. The latter mostly addressed the remarkable role of inflammation in the pathogenesis of AS cardiovascular disease. Cluster 3 (in blue) concentrated on the relationship between TLR4 and AS, while Cluster 4 (in yellow) focused on the important role of peroxisome proliferator-activated receptor gamma (PPARγ) in AS. The theme of Cluster 5 (in purple) was the critical role of shear stress in plaque formation, and Cluster 6 (in cyan) mostly elucidated the inflammatory responses in endothelial cells and AS. *Figure 6B* presents the density map of these co-cited references.

In terms of burst strength, duration, and time, *Figure 6C* provides the most representative co-cited references. The work of Ross *et al.* [1999], which discussed the association between AS and inflammation, exhibited the strongest

Table 2 The top 10 most productive authors

Rank	Author	Country	Institution	Np	Nc	Average per item	H-index
1	Egido J	Spain	Autonomous University of Madrid	30	1,514	51.83	23
2	Hennig B	USA	University of Kentucky	29	1,547	55.03	24
3	Mehta JL	USA	University of Arkansas Medical Sciences	24	1,802	76.54	22
4	Kang DG	South Korea	Wonkwang University	23	565	25.3	14
5	Lee HS	South Korea	Wonkwang University	22	553	25.91	14
6	Libby P	USA	Brigham & Women's Hospital	22	9,605	437.36	19
7	Tang CK	China	University of South China	22	767	36.32	18
8	Toborek M	USA	University of Kentucky	26	1,494	59.35	23
9	Liu J	China	Xi'an Jiaotong University	20	610	32.3	15
10	Martin-ventura JL	Spain	Autonomous University of Madrid	19	1,163	62.84	18

Np, the numbers of publications; Nc, the numbers of citations.

Table 3 The top 10 productive affiliations

Rank	Affiliations	Country	Np	Nc	Average per item	H-index
1	University of California System	USA	168	18,138	108.73	67
2	Harvard University	USA	135	25,282	188.31	62
3	Institut National De La Sante Et De La Recherche Medicale Inserm	France	111	11,955	108.15	51
4	Shanghai Jiao Tong University	China	99	2,837	28.91	29
5	Veterans Health Administration Vha	USA	91	5,584	61.69	40
6	U.S. Department of Veterans Affairs	USA	91	5,580	61.65	40
7	University of Texas System	USA	90	11,488	128.1	43
8	Chinese Academy of Medical Sciences Peking Union Medical College	China	82	1,782	21.96	25
9	Udice French Research Universities	France	79	7,812	99.16	36
10	Shandong University	China	78	2,145	27.67	22

Np, the numbers of publications; Nc, the numbers of citations.

bursts (26). Gimbrone concluded that endothelial cell dysfunction is an important contributor to AS cardiovascular disease. This finding has important implications for the regulation of hemostasis and thrombosis, local vascular tone, redox homeostasis, and the coordination of responses that are chronic and acute in the arterial wall (27). The article by Ridker, which introduced anti-inflammatory therapy with canakinumab for atherosclerotic disease, exhibited a high influence in the last 4 years, indicating that this research had attracted the attention of a number of researchers over this period (28).

Analysis of co-cited journals

The minimum number of citations for a journal was set as 304 due to the large number of co-cited journals. Co-citation analysis was performed on 198 journals among the 10,248 co-cited journals. The co-occurrence network of co-cited journals is shown in *Figure 7A*. The large nodes represented frequently cited journals, most of which were top journals, such as *Nature*, *Circulation*, and *Atherosclerosis*. *Figure 7B* shows the most representative journals in terms of burst time, duration, and strength. *Arterioscler Thromb*, *Lab Invest*, and *Am J Pathol* published research articles on

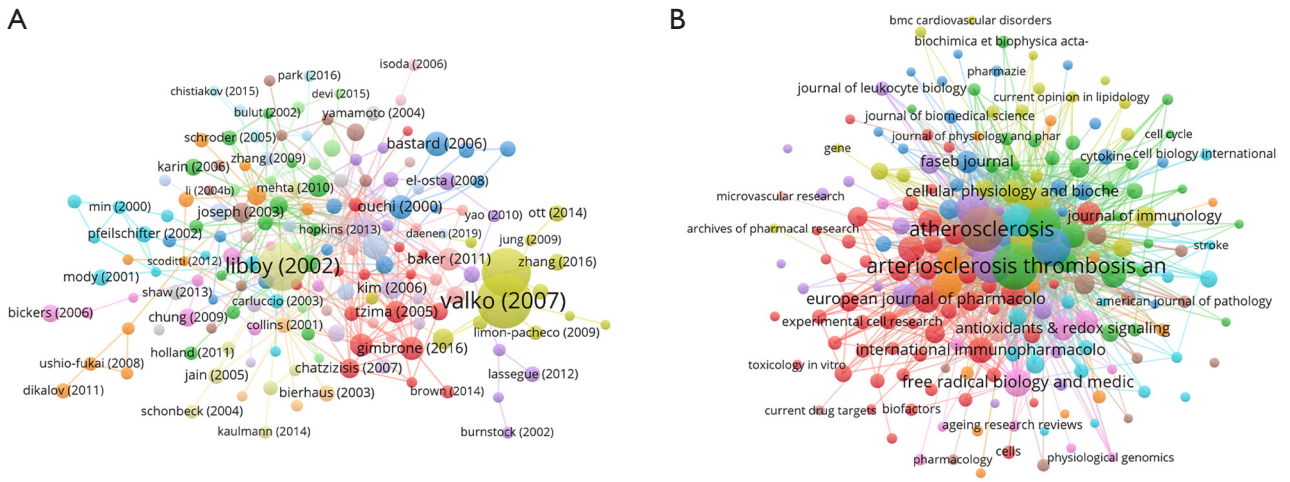

Figure 5 Visualization of the papers and journals. (A) Co-occurrence network of the papers; (B) co-occurrence network of the journals.

Table 4 The top 10 most active journals

Rank	Journal	Np	Nc	H-index	Average per item	IF (2021)	JCR
1	Arterioscler Thromb Vasc Biol	186	14,849	71	80.17	10.514	Q1
2	Atherosclerosis	178	8,239	52	46.48	6.847	Q1
3	Biochem Biophys Res Commun	131	4,835	39	37.04	3.322	Q3
4	PLoS One	129	3,740	36	29.09	3.752	Q2
5	Circ Res	101	14,680	65	145.69	23.213	Q1
6	J Biol Chem	88	9,340	51	106.27	5.486	Q2
7	Cardiovasc Res	85	6,579	44	77.68	13.081	Q1
8	Int J Mol Sci	76	2,470	25	32.61	6.208	Q2
9	Mol Med Rep	63	709	16	11.29	3.423	Q3
10	Free Radic Biol Med	60	4,171	33	69.92	8.101	Q1

Np, the numbers of publications; Nc, the numbers of citations; IF, the impact factor; JCR, Journal Citation Reports.

NF-κB in AS earlier and had higher burst strengths. The clustering timeline showed that the top seven clusters were "innate immunity", "Long non-coding RNA (lncRNA)", "osteoprotegerin, "porphyromonas gingivalis", "vascular biology", "shear stress", and "ezh2". In recent years, "innate immunity", "lncRNA", "shear stress", and "osteoprotegerin" demonstrated high influence (*Figure 7C*). Innate immune inflammation is related to the development of local AS, and shear stress plays an important role in the AS process.

Analysis of co-cited authors

Given the enormous number of co-cited authors, the minimum number of citations for co-cited authors was set as 82. Among the 113,931 co-cited authors in the retrieved publications, 220 were chosen for co-citation analysis. Libby P was the most frequently cited author (n=1,760), followed by Ross R (n=1,418), Hansson GK (n=823), Ridker PM (n=681), and Collins T (n=531). Libby P (n=16,980) ranked first in terms of total link strength, followed by Ross R (n=13,434), Hansson GK (n=8,196), Ridker PM (n=8,028), and Tabas I (n=5,136).

Figure 8A shows the co-occurrence network of co-cited authors. *Figure 8B* presents the most representative co-cited authors in terms of burst time, duration, and burst strength. Baeuerle PA, Marx N, and Collins T published a research paper on NF-κB in AS early and achieved a high burst

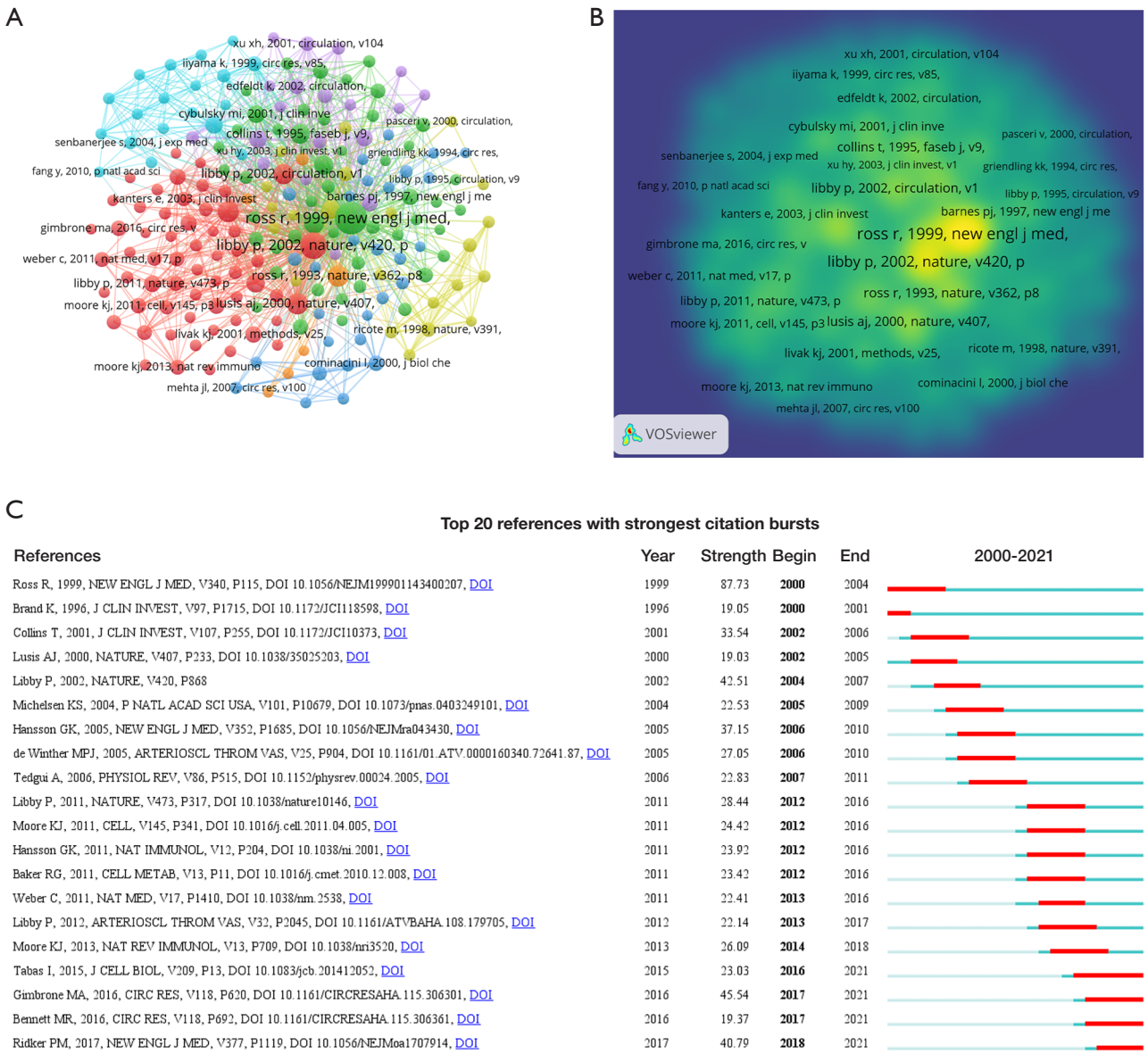

Figure 6 Visualization of the co-cited references analysis. (A) The network of co-cited references; (B) density visualization for co-cited references; (C) the top 20 co-cited references with the strongest citation bursts.

strength. From 2017 to 2021, Chistiakov, D.A. exhibited a strong citation burst and the highest burst strength. In the last 3 years, Gimbrone MA, Zhang L, Liu T, and Kattor AJ exerted high influence, and thus, greater attention should be paid to the publications of these co-cited authors. The clustering timeline showed that the top 11 clusters were "network pharmacology", "toll-like receptor", "nuclear factor-kappa b", "C-reactive protein", "angiotensin II", "shear stress", "lox-1", "inflammasome", "migration", "high glucose", and "osteoprotegerin". "Network pharmacology" and "inflammasome" exhibited a high influence in recent years (*Figure 8C*); network pharmacology provides a novel approach to analyzing the mechanisms of AS drug treatments.

Analysis of global citations (GCS)

Figure 9 shows the annual number of GCS of the top 10 articles. The paper by Chiu published in 2011 had a

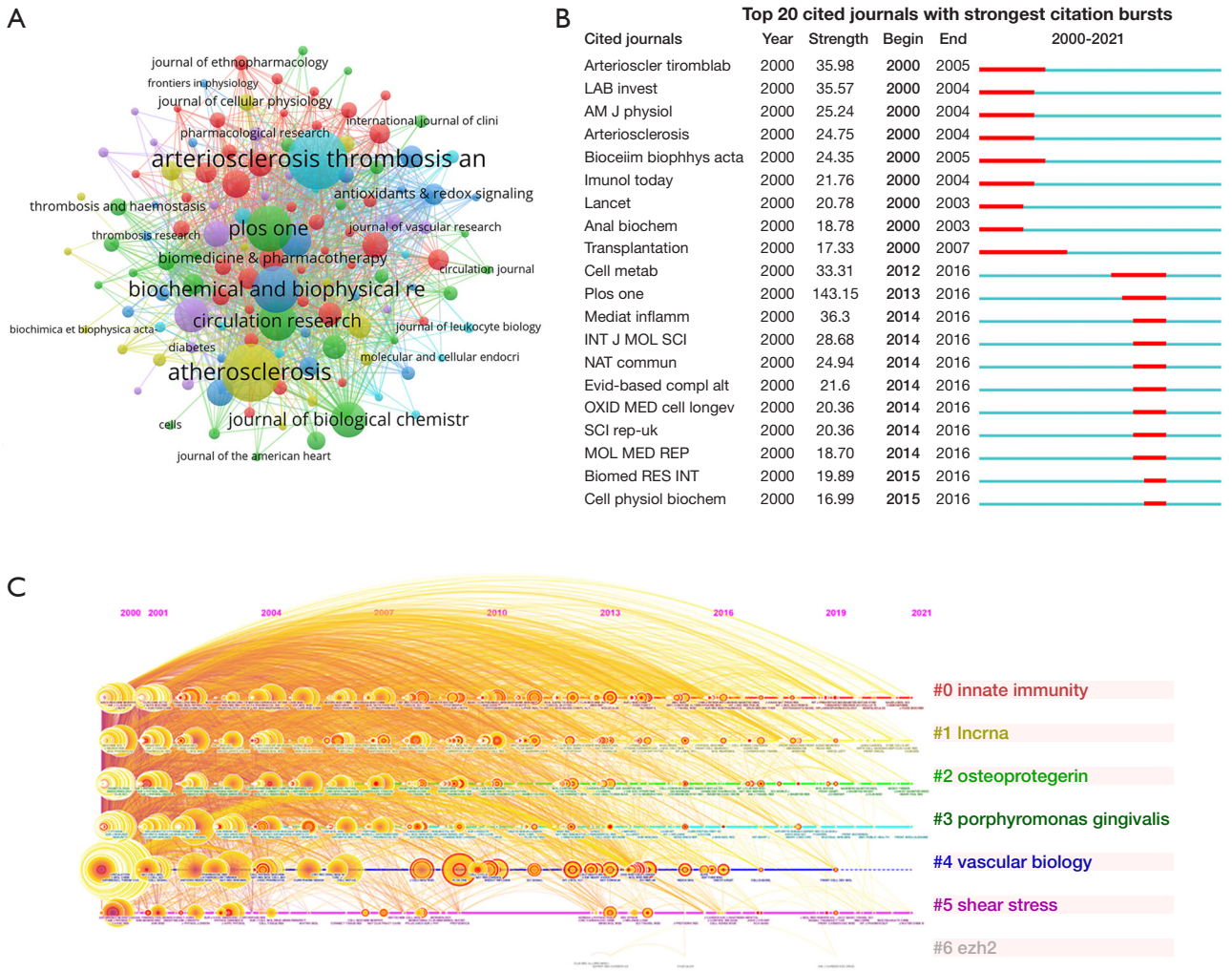

Figure 7 Visualization of co-cited journals analysis. (A) The network of co-cited journals; (B) the top 20 co-cited journals with the strongest citation bursts; (C) timeline distribution of the top seven clusters.

GCS of 1,168, which ranked first. This study proposed that hemodynamics, including fluid shear stress, will affect the structure and function of Endothelial cells (EC), and the resulting endothelial dysfunction will further lead to the occurrence and development of cardiovascular diseases (29). Based on the research of Baker *et al.*, NF-κB plays an important role in the initiation, propagation, and progression of obesity, type 2 diabetes, and AS (30). Moreover, Gupta *et al.* summarized the therapeutic effect of curcumin on AS (31), while Shaw *et al.* pointed out that aging contributes to the development of AS, which is considered related to the TLR and NLRP3 signaling pathways (32). Although the research content of the top 10 most cited articles varied, they collectively promoted the development of this field.

Research hotspots analysis

The minimum number of occurrences of a keyword was set as 45. So, 213 of the 14,598 keywords in the retrieved publications were selected for keyword analysis. These keywords were divided into six clusters based on the network (*Figure 10A*). Cluster 1 (in red) focused on the pathogenesis of AS. Cluster 2 (in green) clarified the important role of NF-κB in cardiovascular diseases. Cluster 3 (in blue) illustrated that AS and NF-κB are closely associated with inflammation. Cluster 4 (in yellow) focused on the etiology of cardiovascular diseases. Cluster 5 (in purple) mostly investigated vascular inflammation associated

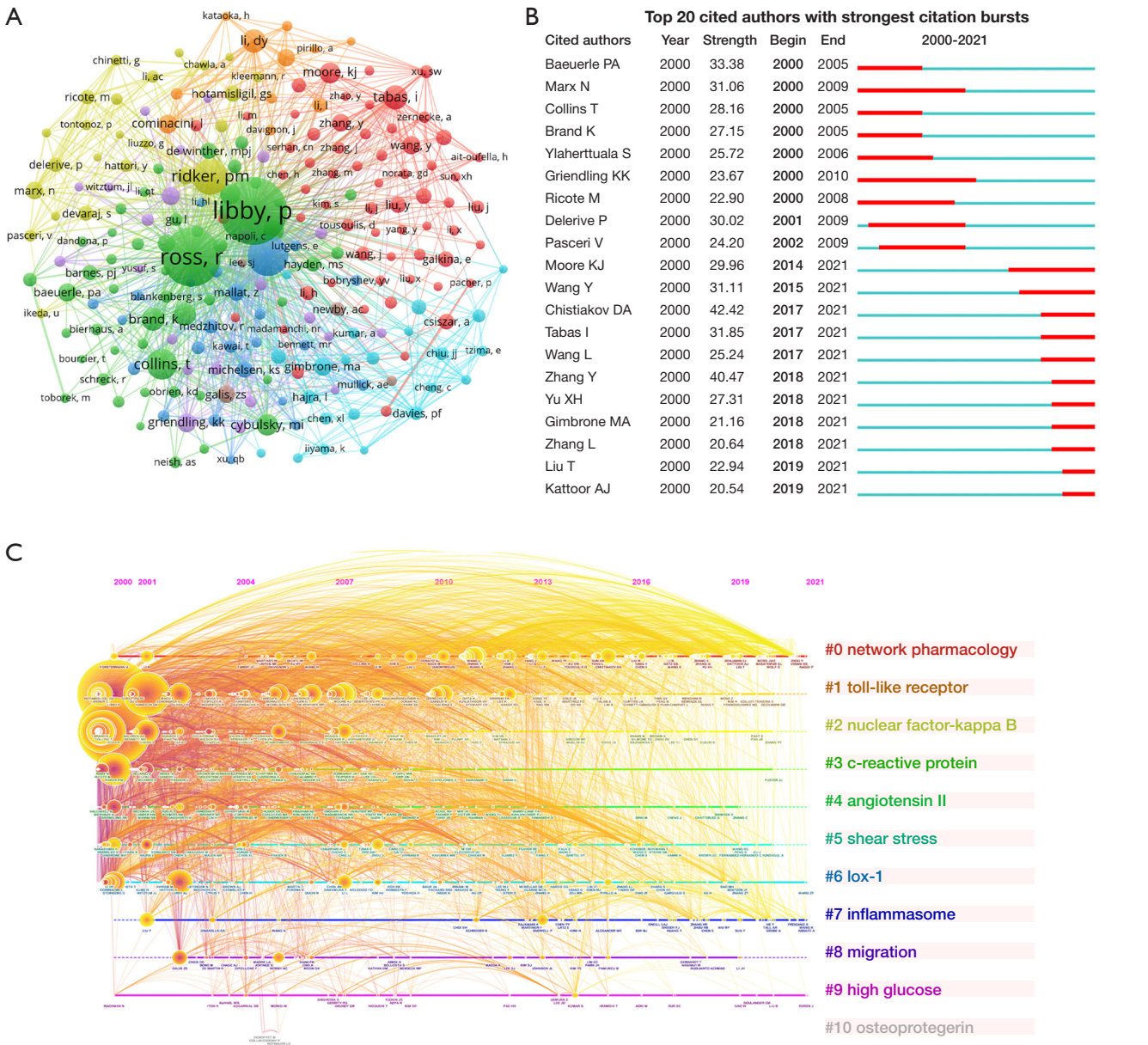

Figure 8 Visualization of the co-cited authors analysis. (A) The network of co-cited authors; (B) the top 20 co-cited authors with the strongest citation bursts; (C) timeline distribution of the top 11 clusters.

with monocyte chemo-attractant protein-1. Cluster 6 (in cyan) had only one keyword, i.e., cyclooxygenase. As shown in *Figure 10B*, the colors of all keywords were separated using VOSviewer according to the average publication year (APY). Over the last 5 years, the keywords included "autophagy" (APY:2017,94), "microRNA" (APY:2017,85), "protects" (APY:2017,75), and "nlrp3 inflammasome" (APY:2018,51). As shown in *Figure 10C*, keywords, such as "tumor necrosis factor", "smooth muscle cell", "human endothelial cell", "intercellular adhesion molecule 1", "growth factor", and "factor kappa B", exhibited high influence before 2014, indicating that research in this field focused on the pathogenesis of AS before 2014.

After 2015, keywords, such as "microRNA", "mitogen activated protein kinase (MAPK)", "nlrp3 inflammasome", "protect", "NRF2 (nuclear factor E2 related factor 2)",

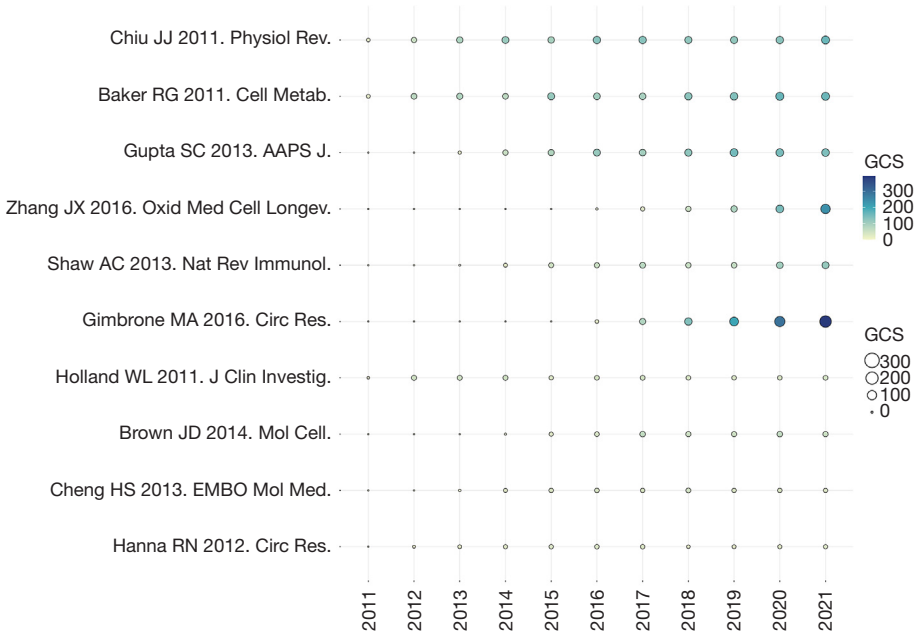

Figure 9 The annual number of global citations of papers with a high number of GCS. The sizes and colors of the nodes represent the GCS of the papers. GCS, global citations.

and "ischemia reperfusion injury", demonstrated high influence, indicating that research in this field focused on the treatment of AS after 2015, along with research on the target and molecular biology. The frequently used and most recent keywords in 2021 are listed in *Table 5*. The most frequent keywords were "NF kappa b", "atherosclerosis", "expression", "activation", "endothelial cell", "oxidative stress", and "smooth muscle cell".

Oxidative stress during the formation and development of an AS plaque and plaque rupture triggers clinical events. The imbalance between oxidation and anti-oxidation leads to the proliferation and migration of smooth muscle cells, and the polarization of macrophages leads to the formation of AS plaques. Therefore, antioxidant therapy has gradually become a new clinical anti-AS target. The treatment of AS should be accompanied by the administration of antioxidants. The new keywords in 2021 included "muscle", "attenuates atherosclerosis", "mesenchymal transition", "metabolic disorder", and "palmitic acid".

The pathological basis of AS is a lipid metabolism disorder; triglyceride metabolism disorder is the sign of AS, and cholesterol metabolism disorder is the basis of AS. The pathological process of AS includes intracellular lipid accumulation, arterial wall inflammatory reaction, extracellular lipid deposition, leukocyte recruitment, AS plaque formation, endothelial cells, and smooth muscle cells. Studies have shown that microRNA (mir) mir-532, mir-18a-5p, mir-20a, mir-200b, mir-29, mir-126, and mir-23 can inhibit endothelial mesenchymal transformation (33-35); while mir-125b, mir-195, and mir-130a can promote endothelial-mesenchymal transformation (36,37). Endothelial-to-mesenchymal transition (ENDMT) plays an increasingly important role in AS cardiovascular disease. Targeting miRNA and endothelial stromal transformation may provide hope for the treatment of cardiovascular diseases.

Discussion

In recent years, more comprehensive research on NF-κB in AS has been carried out, and numerous research results have been published (38-40). In this study, we conducted a bibliometric analysis by using VOSviewer and CiteSpace to analyze the development trends and hotspots of research on NF-κB in AS according to the SCI-Expanded of WoSCC. We collected 5,201 original articles and reviews that were published between 2000 and 2021. The remarkable development of annual Np was primarily due to groundbreaking publications with high GCS. China ranked first in terms of Np among the top countries/

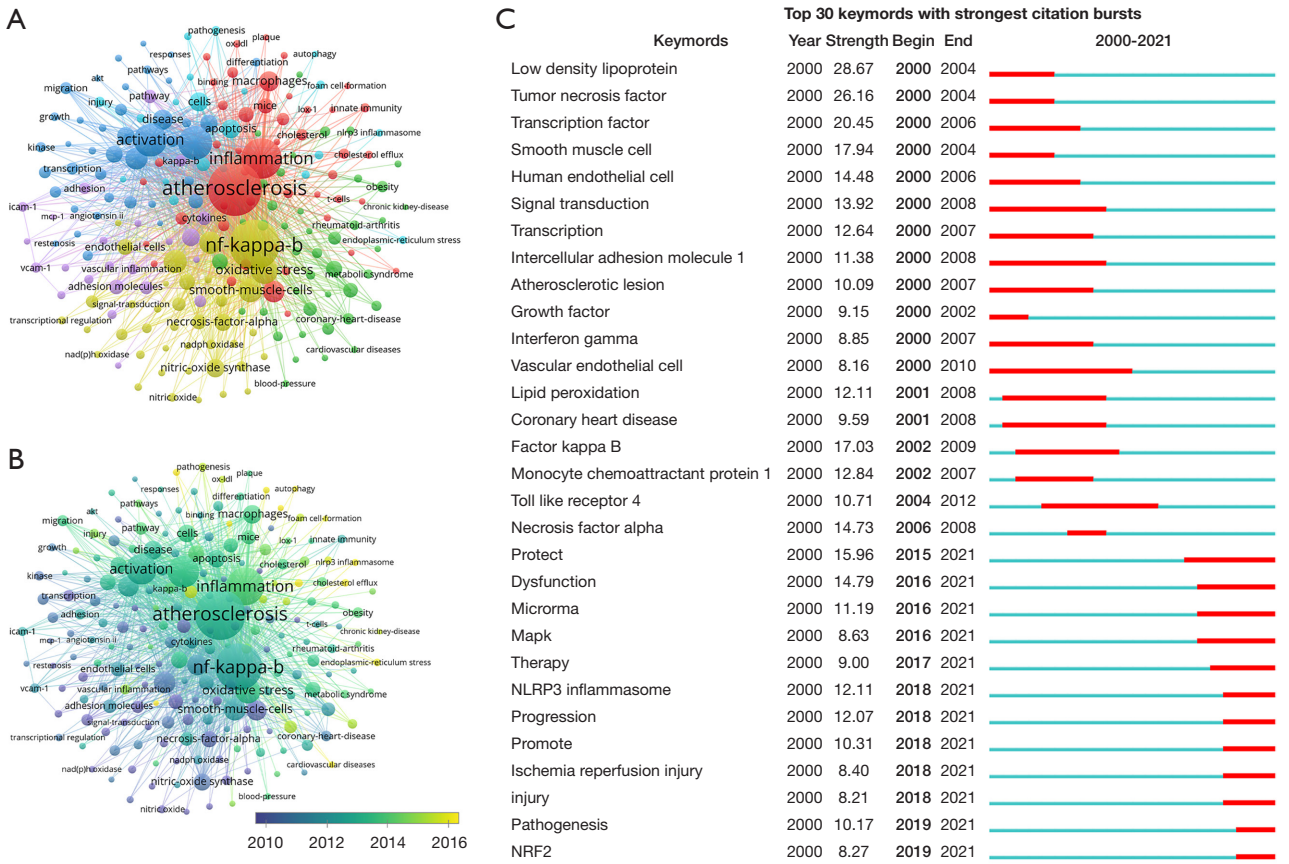

Figure 10 Visualization of the keywords analysis. (A) The co-occurrence of keywords. (B) Visualization of the keywords based on the APY. Keywords in blue appeared earlier than those in yellow. (C) Top 30 keywords with the strongest citation bursts. APY, average publication year.

Table 5 The 20 most frequent keywords and the most recent keywords in 2021

Top 20 keywords
NF kappa b, atherosclerosis, expression, activation, endothelial cell, oxidative stress, smooth muscle cell, inflammation, gene expression, low density lipoprotein, disease, cardiovascular disease, cell, nitric oxide synthase, mechanism, necrosis factor alpha, inhibition, nitric oxide, macrophage
Most recent keywords in 2021
Muscle, attenuates atherosclerosis, mesenchymal transition, metabolic disorder, palmitic acid, non-steroidal anti-inflammatory drug, MAPK, circular RNA, constituent, tumor associated macrophage, endothelial injury, network, bone, calorie restriction, alpha induced apoptosis, aggregation, cardio-cerebrovascular disease, aortic aneurysm formation, ameliorates atherosclerosis, assisted extraction, 3 kinase, cardiac function, aortic aneurysm

MAPK, mitogen activated protein kinase.

regions, indicating that it was a highly productive country in researching NF-κB in AS. Four Chinese authors were included among the top 10 authors, indicating that China has the most qualified researchers in the world, and helps explain why China developed so quickly in this field over the last decade. Compared with China, the USA had a higher Nc and *H*-index. Furthermore, five USA affiliations were in the top 10, indicating that the USA has the most prestigious affiliations. Also, given that the crucial role of inflammation in AS was first hypothesized by American

scholars (26), and considering that the USA developed this subject more than other countries, suggests that Chinese academics and affiliations should focus more on the quality of their articles in this field. In South Korea, a similar disparity was observed between the quantity and quality of publications.

Seven journals with high IFs were included among the top 10 in terms of productivity, indicating that publishing papers on NF-κB in AS in high-quality journals is not difficult. These high IF journals published more potential breakthrough articles in this field because seven out of 10 articles with a high GCS were published in high IF journals, reminding scholars interested in this issue to afford greater attention to these journals. Notably, *Arterioscler Thromb Vasc Biol* had the highest number of articles and *Circ Res* had the largest amount of citations among the top 10 productive journals, suggesting that these two journals are popular in this field. Also, the most cutting-edge studies and key research advances in NF-κB in AS have been published in these two journals.

The majority of research conducted in this field was designed to determine the mechanism of AS, as evidenced by the GCS, co-cited references, and keywords analysis. The study of Chiu *et al.* on the effects of disrupted flow on the AS vascular endothelium received the greatest GCS, indicating that this view was widely accepted by other scholars. Endothelial dysfunction was also found to be a remarkable pathophysiological factor in vascular disorders in this study (29). Moreover, the function of NF-κB in the development of AS was also reported in the article by Baker *et al.*, NF-κB was observed to regulate the expression of genes involved in the initiation and progression of AS, along with various processes involved in plaque formation (30). Furthermore, endothelial cell dysfunction was identified as a common cause of AS; the role of endothelial cell dysfunction in the development of AS and endothelial pro-inflammatory activation in AS was highlighted in this paper. The activation of pleiotropic transcription factors by NF-κB was believed to result in the production of different effector proteins with crucial pathophysiologic implications in the development of AS (27). According to Jonathan DB's research, NF-κB super-enhancers induce pro-inflammatory gene expression in a bromodomain and the extra-terminal domain (BET) bromodomain-dependent manner (41). These studies proposed various research approaches regarding the pathogenesis of endothelial cell dysfunction in AS.

The co-occurrence network of keywords revealed that inflammation in smooth muscle and endothelial cells induced by increased NF-κB activation were popular topics in this research field. The most frequently appearing keywords were "atherosclerosis", "NF-kappa-b", "inflammation", "expression", "activation", "oxidative stress", "smooth-muscle-cells", "gene-expression", "endothelial-cells", and "low-density-lipoprotein", suggesting that research in this field is mostly focused on basic and clinical studies. Shaw *et al.* summarized that aging plays an important role in the pathogenesis of AS, and TLR and NLRP3 signaling are related to the development of AS. Enhanced mitochondrial oxidative stress is related to an elevated inflammatory response (32). Furthermore, Koushki *et al.* found that some statins suppress the inflammasome or TLRs in combination with lowering lipids, helping to alleviate AS by reducing inflammation (42). Coincidentally, Xue *et al.* recently found that hydroxysafflor yellow A can regulate the NLRP3 inflammasome, oxidative stress, and TNFR1/NF-κB signaling pathways (43).

Ross *et al.* first reported that inflammation is necessary for the development of AS (26). Collins *et al.* determined that physiological regulation and pathological activation of the NF-κB system may promote a change in gene expression during AS (44). Libby, found that the major characteristics during the early stage of AS included the high expression of pro-inflammatory cytokines and leukocyte recruitment, and demonstrated that malfunction of the inflammatory pathways is necessary for atheroma formation. Furthermore, thrombosis is promoted by inflammatory pathways (45). The study by Michelsen *et al.* indicated that in a hypercholesterolemic mouse, remarkable pathophysiologic associations were observed between innate immunity, inflammation, and atherogenesis (46).

NF-κB in AS has gradually become the primary topic, eliciting the greatest interest among researchers. Keywords such as "dysfunction", "protect", "nlrp3 inflammasome", "progression", "promote", "pathogenesis", "cell", and "microRNA" had the strongest burst strength from 2015 to 2021. Bennett *et al.* found that vascular smooth muscle cell loss and senescence enhance atherogenesis and plaque instability (47). Although an increasing number of studies have been conducted on the inflammasome, more in-depth studies on the inflammasome are predicted to be undertaken in the future. MicroRNA was another keyword with a strong burst. MicroRNAs can regulate autophagy induction, autophagy nucleation, elongation, maturation, formation and degradation of atherosis-related cells. In addition, microRNA from a variety of sources is involved in the inflammatory process of AS, which leads to a variety of

artery wall lesions by causing inflammatory reactions, thus exacerbating the development of AS. For example, several types of microRNA play essential roles in AS, such as miRNA-223 (48), miRNA-146 (49), and miRNA-150 (50). In summary, microRNA plays an important regulatory role in the occurrence and development of AS. Therefore, regulating the expression of microRNA, or artificially increasing and inhibiting the synthesis of specified microRNA is likely to be one of the key methods to prevent and control AS.

The latest keywords in 2021 involved metabolic disorder, the non-steroidal anti-inflammatory drug, MAPK, circular RNA, endothelial injury, etc. In this field, circular RNA can be used as targets for prevention and treatment of AS. Circular RNAs are the most recent keywords that appear frequently. As regulatory molecules, circular RNAs are involved in releasing inflammatory factors, cell proliferation and migration, apoptosis and senescence in AS (51). With the development of high throughput sequencing technology and bioinformatics, important signal transduction and molecular regulation mechanisms of circular RNA in the occurrence and development of AS have been discovered, providing new ideas for the diagnosis and treatment of AS (52). Circular RNA may be promising targets for AS therapy in the future (53). In addition, non-steroidal anti-inflammatory drugs have more adverse reactions. Therefore, non-steroidal anti-inflammatory drugs should be used cautiously in patients with AS, and the probability of cardiovascular adverse reactions caused by non-steroidal anti-inflammatory drugs should be reduced to the maximum clinically. One of the primary pathological basis of AS is endothelial injury, which leads to the injury of human terminal microvessels. The main mechanism of endothelial injury involves oxidative stress, inflammation, coagulation system, vascular endothelial active substances, etc. The vascular endothelial injury involves functional, structural and other pathological changes throughout the entire process of AS, and the occurrence of vascular endothelial injury will lead to the aggravation of AS. At present, it is necessary to strengthen the research on the mechanism of action of vascular endothelial injury and its relationship with the occurrence and development of AS disease, to clarify the course of AS more clearly, and to obtain the best therapeutic effect while shortening the course of drug therapy.

Several limitations exist in our research that should be noted. Firstly, some of the latest studies in 2022 were excluded, which might lead to a hysteretic quality to a certain degree. In addition, VOSviewer and CiteSpace, which were employed in this study, cannot analyze the full texts of publications.

Conclusions

This bibliometric study suggested that research on NF-κB in AS is currently developing at a rapid pace. The greatest amount of research is published in China, and research published in the USA has provided numerous notable advances in this field. The latest studies and novel advancements in this field have been published in the *Front Physiol*, *Biomed Pharmacother*, *Nat Rev Cardiol*, and *Nutrients* journals. Also, the involvement of the NLRP3 inflammasome in attenuating AS has been a recent research hotspot.

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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-22-6145/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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