Observational Study

Medicine

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Dyslipidemia in osteoarthritis

A study combining bibliometric analysis and retrospective data mining

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Abstract

Osteoarthritis (OA) is one of the common chronic arthritis in middle-aged and elderly people, but the effect of lipid metabolism on OA is still unclear. The aim of this study was to explore the value of lipid metabolism markers as emerging biomarkers for assessing OA disease activity. The literature on OA and lipid metabolism indicators was extensively analyzed by bibliometric. Correlation analysis was used to analyze the correlation between lipid profile indicators (total cholesterol; triglycerides [TG]; high density lipoprotein cholesterol [HDL-C]; and low density lipoprotein cholesterol) and immunoinflammatory indicators (high sensitivity C-reactive protein; erythrocyte sedimentation rate [ESR]) in patients with OA as well as the disease activity level (visual analog scale (VAS). Logistic regression modeling was used to calculate univariate and multivariate factors of disease activity. A total of 843 papers were retrieved. China and the United States are the 2 most productive countries in this field, and the United States has the highest H-index. In addition, Osteoarthritis and Cartilage is the most published journal. OA lipid metabolism research has long focused on inflammation, lipid metabolism, and pain. The levels of inflammation (ESR, high sensitivity C-reactive protein) and lipid metabolism indicators (total cholesterol; TG, HDL-C) were significantly increased in OA patients. Inflammation indicators were significantly correlated with lipid metabolism indicators. In addition, HDL-C, ESR, and TG were identified as independent influencing factors for OA-VAS. In summary, the role of lipid metabolism in OA has been a hot topic. Markers of inflammation and lipid metabolism were independent influencing factors of OA-VAS.

Abbreviations: AC = the average citation, ESR = erythrocyte sedimentation rate, FAs = fatty acids, HDL-C = high density lipoprotein cholesterol, hs-CRP = hypersensitive C-reactive protein, IF = influence factor, IL-1β = interleukin-1β, IL-6 = interleukin-6, LDL-C = low density lipoprotein cholesterol, NP = number of publications, OA = osteoarthritis, RA = rheumatoid arthritis, TC = the total citations, TC = total cholesterol, TG = triglycerides, TNF-α = tumor necrosis factor-α, VAS = visual analog scale.

Keywords: bibliometrics, inflammation indicators, lipid metabolism indicators, osteoarthritis

1. Introduction

Osteoarthritis (OA) is a chronic joint disease characterized by joint pain, stiffness, and impaired mobility, involving all joint tissues including the menisci, subchondral bone, synovial membrane, and cartilage.[1] At present, OA has gradually affected more than 250 million people worldwide, becoming one of the main causes of disability in the elderly.[2] Without early intervention, late joint replacement will become the only option, resulting in considerable costs due to revision and complications, placing a heavy financial burden and psychological stress on patients.[3] The prevalence of OA is expected to increase by 48.6% to 95.1% by 2050.[4] Therefore, there is a great incentive to identify the factors that influence OA and find the best ways to reduce these costs.

Inflammation and dyslipidemia are key factors that trigger and amplify OA.[5] Inflammation consists mainly of synovitis and chondritis, and the level of inflammation and the ability of synovitis to proliferate and invade, as well as degenerative damage to cartilage and loss of homeostasis, are associated with disturbances in lipid metabolism.[6,7] Obese people and animals tend to show higher levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL) 1β, and IL-6, produced by adipose tissue-derived macrophages,[5] they

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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can directly induce chondrolysis, but also indirectly cause OA through adiponectin, fatty acids (FAs) or leptin. Studies have shown that the levels of TNF-α, IL-1β, triglyceride [TG], and cholesterol in OA are significantly higher than those in non-OA group.[8] Notably, studies have shown that abnormally low levels of high density lipoprotein (HDL) cholesterol and apolipoprotein A1 can lead to worsening inflammation and OA.[9]

Since immune inflammation and lipid metabolism play an important role in OA, in addition to immune inflammation indicators, the monitoring of lipid profiles is also particularly important. Lipid profile is an emerging indicator of systemic inflammation association in OA patients,[10] easy to detect, low-cost, and available through serum biochemical tests, it has been used by many researchers as a useful tool to predict the occurrence and severity of OA.[11] Lipid profiles include HDL cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), TG, and total cholesterol (TC).[12] Previous studies have established that HDL-C, LDL-C, TG, and TC appear to have an inflammatory driven pleiotropic relationship with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP),[13] although this phenomenon is seen in rheumatoid arthritis (RA), Kasher M et al show that it is not only mediated by RA.[14] They were also able to activate the innate immune response to OA, manifested by increased expression of IL-6 and TNF-α pro-inflammatory cytokines. At the same time, inflammation can also cause changes in the subcomponents and structure of HDL particles, promote the oxidation of LDL and further worsen LDL metabolic abnormalities.[15] While high levels of LDL-C, TC, and TG, low levels of HDL-C are important risk factors for rheumatic diseases such as RA, OA, systemic lupus erythematosus.[16–18]

The visual analog scale (VAS) is often recommended to assess overall pain in patients with OA and is one of the most widely used tools to assess the effectiveness of OA treatment.[19] Tended to vary significantly and be more sensitive to pain subscale than Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[20] there was a negative correlation with pain threshold. This difference can be explained by the fact that the WOMAC subscore and VAS belong to the pain assessment of one-dimensional measurement and the pain intensity in 5 different activities, respectively.[21] Including patient scores, physician scores, and overall scores, clinical improvement was determined if pain reduction on the VAS was >20 mm and the patient improved at least 20 percent from baseline.[22] In addition, there is a strong linear correlation between serum high sensitivity-CRP (hs-CRP) level and VAS score. Therefore, VAS score is usually improved by lowering serum hs-CRP levels, thus relieving pain.[23]

Although predecessors have devoted themselves to studying the relationship between inflammation and lipid metabolism in OA and have made considerable achievements, few studies have systematically combed and analyzed these research results, and there is a lack of understanding of the relationship between countries, sources and authors published in this field, as well as keyword analysis and visualization of hot trends. Bibliometrics is the study of academic publishing,[24] it uses statistical data to describe the national distribution of publications, analyzes the influence of journals and authors, and highlights the research keywords and hot trends of published works. It is one of the important research methods accepted and applied by multiple disciplines.

The purpose of this study is to solve the following problems: (1) to explore the status quo and development trend of lipid metabolism research on OA and realize visualization; (2) retrospective evaluation was conducted to assess whether inflammation and lipid metabolism were associated with OA and whether they could be factors influencing VAS scores. Therefore, this paper takes the relevant research on OA lipid metabolism in the core database of Web of Science as the analysis object, and uses VOSviewer, CiteSpace, and other software. By means of keyword co-occurrence analysis, cluster analysis, burst word analysis, and so on, this paper makes a systematic bibliometric visual analysis of OA lipid metabolism research. In addition, we retrospectively evaluated the relationship between inflammation, lipid profiles, and VAS in patients with OA.

2. Materials and methods

2.1. Bibliometric analysis

2.1.1. Search strategy. Bibliometrics is a scientific discipline that quantitatively studies bibliographic data on specific topics. This study referred to previous published literature. The Web of Science core collection is a database strictly evaluating publications and updating them adequately to provide the most influential and reliable information.[25,26] The Web of Science core collection as literature metrology analysis commonly used at present, is also one of the most authoritative database, can check in at https://www.webofscience.com/wos/woscc/basic-search.[27] To clarify, the following sub-datasets were included in the search: Science Citation Index Expanded (SCI-EXPANDED); Social Sciences Citation Index (SSCI). All searches were conducted under the same December 21, 2023 conditions to reduce bias. All members of our research team unanimously agreed on this search strategy. The advanced search is performed using the following formula: TS = ("Osteoarthritis") AND TS = ("Hyperlipidemia" OR "lipid metabolism" OR "triglyceride" OR "Total cholesterol" OR "Dyslipidemia" OR "Low-Density Lipoprotein Cholesterol" OR "High-Density Lipoprotein Cholesterol" OR "Adiponectin" OR "leptin" OR "resistin" OR "visfatin" OR "lipoprotein" OR "fatty acid" OR "bile acid"), Use "Articles" or "Review Articles" as The document type, The literature was published between 2010 and 2023. Citespace was used to duplicate and refine the search results, resulting in 843 publications. All the obtained data are suitable for bibliometric analysis. The records were exported as plain text files with the content of "Full records and cited references" for subsequent analysis. The detailed search processes and analysis procedures were shown (Fig. 1).

2.1.2. Research software/tools. An online analytic platform (https://bibliometric.com/) is a free, public platform for analyzing the influence of countries, affiliations, journals, and authors.[28]

VOSviewer (Nees Jan van Eck and Ludo Waltman, Leiden University, Netherlands), a bibliometric software that can extract important parameters from a large number of scientific publications, is broadly used to generate collaboration networks, cocitation relationships, and co-occurrence of keyword clusters among countries, institutions, and authors. Additionally, VOSviewer provides 3 types of visual maps-label view, overlay view, and density view-with notable features of user-friendliness and aesthetically pleasing graphics.

CiteSpace (Chaomei Chen, Drexel University, USA) is a Java-based free software for scientific literature visualization and bibliometric analysis. It is suitable for constructing dual-map overlays of journals, analyzing knowledge map landscapes, conducting burst detection, and investigating research status, hot topics, and temporal trend distribution. The parameters used with CiteSpace were set as follows: time slice (2010–2023 by year), text processing (term source: keywords), term type (burst terms), node type (set based on the item), links (strength: cosine; scope: within slices), selection criteria (top 50 objects), and pruning (pathfinder and pruning sliced networks).

RStudio Desktop Software, version:2022.07.01 (© Posit Software, Massachusetts, United States, 2022), linked to R Software, version:4.2.1 (The R Foundation, Vienna, Austria, 2022). For analysis, the following were used: the Bibliometrix R package (© K-Synth Srl, Academic Spin-Off of the University of

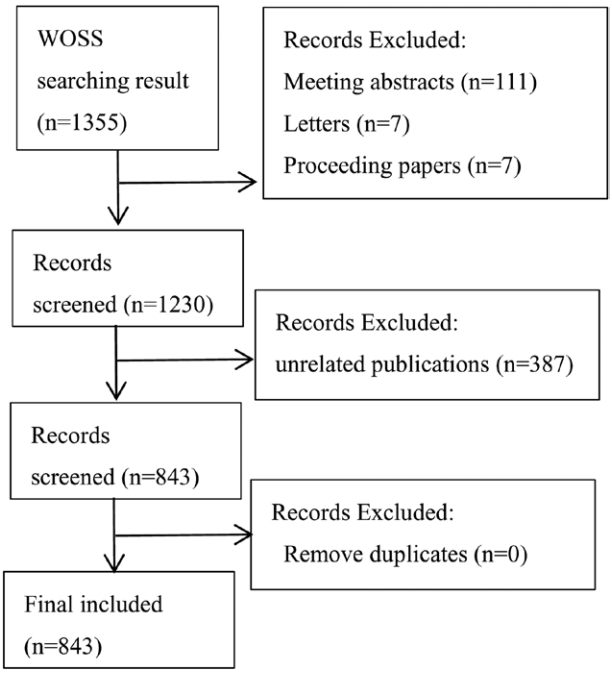

Figure 1. Summary of data source and selection.

Naples Federico II, Naples, Italy, 2022), its graphical web interface, Biblioshiny, and VOSviewer Software, version:1.6.18 (© Centre for Science and Technology Studies, Leiden University, Leiden, The Netherlands, 2022).

Origin 2021 was used to assess the correlation between keywords and the mathematical model of publication output. The linear forecasting model can be described as f(x) = ax + b, where x is the publication year and f(x) is the number of publications.

2.2. Data mining

2.2.1. Collection of patient clinical information. The clinical data of OA patients admitted to the Department of Rheumatology and Immunology of the First Affiliated Hospital of Anhui University of Chinese Medicine were collected through the Health Information System. The system records basic information about patients, such as age, gender, number of hospitalizations and duration of illness. Exclude patients with severe organic diseases (including cardiac, cerebral, pulmonary, hepatic, renal, hematopoietic, or psychiatric disorders), severe joint deformities, complete loss of joint function, those who received immunosuppressive agents or biological therapies within the past 3 months, and those with incomplete clinical laboratory data. A total of 2437 OA patients were ultimately eligible for participation in this study. Subsequently, we obtained complete laboratory indicators and joint pain assessment scales for all 2437 included patients. Laboratory measures include ESR, hypersensitive C-reactive protein (hs-CRP), TC, TG, HDL-C, LDL-C, the joint pain scale uses the VAS. This research was ratified by the Ethical Committee of Scientific Research in the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine (2023AH-52) and we conducted anonymous retrospective data mining, which is a secondary use of data and does not require patients' informed consent. Conformed to pertinent Declaration of Helsinki rules.[29]

2.2.2. VAS scoring principles. VAS is a scale used to assess joint pain. It is widely used in clinical practice in China.[30] The basic method is to use a walking scale about 10 cm long, marked with 10 scales on 1 side, and the 2 ends are respectively "0" and "10." 0 indicates no pain, and 10 indicates the most unbearable pain. When used, the graduated side is turned back to the patient, so that the patient can mark the corresponding position on the ruler that can represent their pain degree, the doctor will evaluate the score according to the position marked by the patient, and the clinical evaluation is divided into "0 to 2" into "excellent," "3 to 5" into "good," "6 to 8" into "tolerable," and > "8" into "intolerable."

2.2.3. Association rules. The apriori module in IBM SPSS Modeler 18.0 software was used to assess the association between blood lipid profile and inflammation indicators. The minimum support was defined as 60%, and the minimum confidence as 50%.

$$\text{support}\,(X \to Y) = \sigma\frac{(X \bigcup Y)}{N},$$

$$\text{confidence}\,(X \to Y) = \sigma\frac{(X \bigcup Y)}{\sigma\,(X)},$$

$$\text{lift}\,(X \to Y) = \text{confidence}\frac{(X \to Y)}{\sigma\,(Y)}$$

2.3. Statistical analysis

Microsoft Excel 2016 and Microsoft Word 2016 were used for statistical description and to draw the flowchart of literature screening. Literature was imported to VOSviewer, CiteSpace, bibliometric, and RStudio to draw national geographic visualization, national cooperative relationship, number of national publications, number of institutional publications, keyword co-occurrence map, and quantitative indicators such as country, institution, magazine, author citations, and H-index.

SPSS 24.0 software was used for statistical analysis and graph drawing. Data on sex, age, and smoking and drinking are expressed as figures or percentages. Other continuous variable data are expressed in median and quartile ranges (IQR). SPSS Modeler 18.0 was used for association rule analysis to analyze the correlation coefficient between lipid metabolism indicators and inflammatory indicators. For specific methods, refer to previous studies.[31] Spearman correlation analysis was used to evaluate the correlation between the indicators in the data. Logistic regression model was used to evaluate the statistical correlation between each indicator and VAS score.

3. Results

3.1. General statistics

From 2010 to 2023, WOSCC database yielded 843 research publications on the topic of OA. According to the results after removing duplicates, these 843 papers came from 48 nations, 1205 institutions, 4070 authors, and 335 journals. The average number of citations per paper is 28.1, there were 6.85 coauthors per paper. They contain 26,046 reference and 1975 keywords. The types of literature were separated into 2 categories: research-based literature (98.69%) and review-based literature (1.31%). This shows that the range of OA-related studies mapped (countries, institutions, authors, etc) is wide and the depth of research is deep.

3.2. Publication time statistics

The quantity of literature and its patterns reflect this topic's current study state.[32] Bas, Sylvette et al Published Adipokines correlate with pain in OA in 2010, indicating

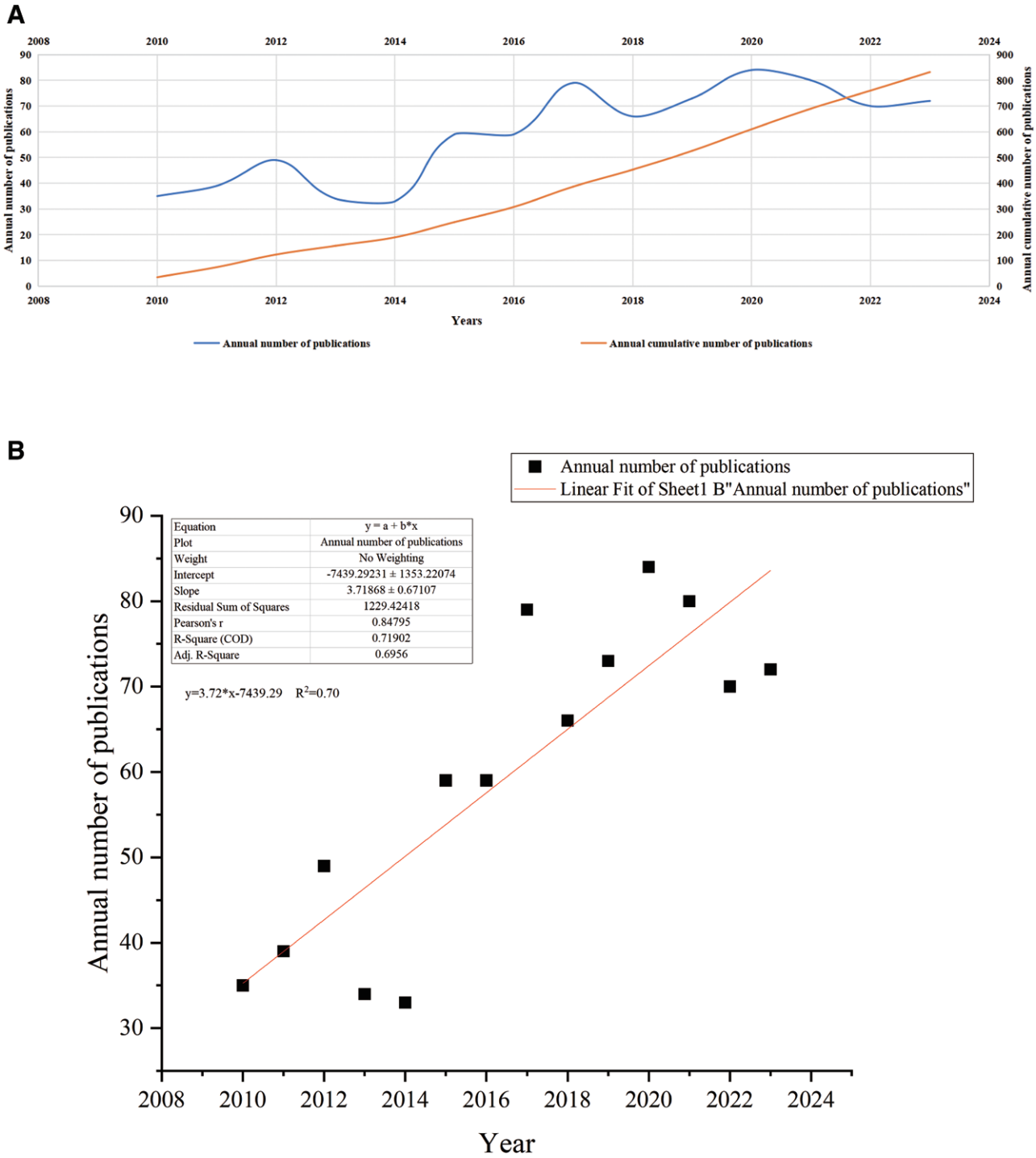

Figure 2. (A) Annual cumulative number of publications and Annual cumulative number of publications; (B) the linear fit between the year and the number of publications on lipid metabolism in OA.

that hyperlipidemia may be a risk factor for pain in OA patients and participate in the occurrence and development of OA. This study shows the annual number of publications and annual cumulative number of publications from 2010 to 2023 in the field of lipid metabolism and OA. In terms of total literature records, the publications increased quickly from 2014 to 2015, 2016 to 2017, and 2018 to 2020, with an average of 64.84 publications per year, and the maximum number was 84 in 2020 (Fig. 2A). According to the linear fit (Fig. 2B) between the year and the number of publications on lipid metabolism in OA was significantly correlated (R^2 = 0.70, y = 3.72*x-7439.29). According to the mathematical model, publication output will reach 90 in 2024.

3.3. Country analysis

Geographic distribution of the top 10 countries or regions for publications on lipid metabolism in OA. The top 10 countries in terms of publication volume accounted for almost 3-quarters of all 843 papers. China is the country with the most papers published, followed by the United States, the United Kingdom, Canada, Korea, Netherlands, Australia, France, Spain, and Italy.

Table 1

Top 5 most productive countries.

Country	NP	% (n = 843)	SCP	MCP	TC	AC	H-index
China	232	27.52	205	27	4290	18.5	38
United States	108	12.81	78	30	3228	29.9	55
United Kingdom	41	4.86	24	17	2100	51.2	33
Canada	40	4.74	31	9	1318	33	28
Korea	36	4.27	32	4	611	17	23

AC = the average citation, MCP = the number of coauthored papers with authors from other countries, NP = number of publications, SCP = the number of papers coauthored by authors of the same nationality, TC = the total citations.

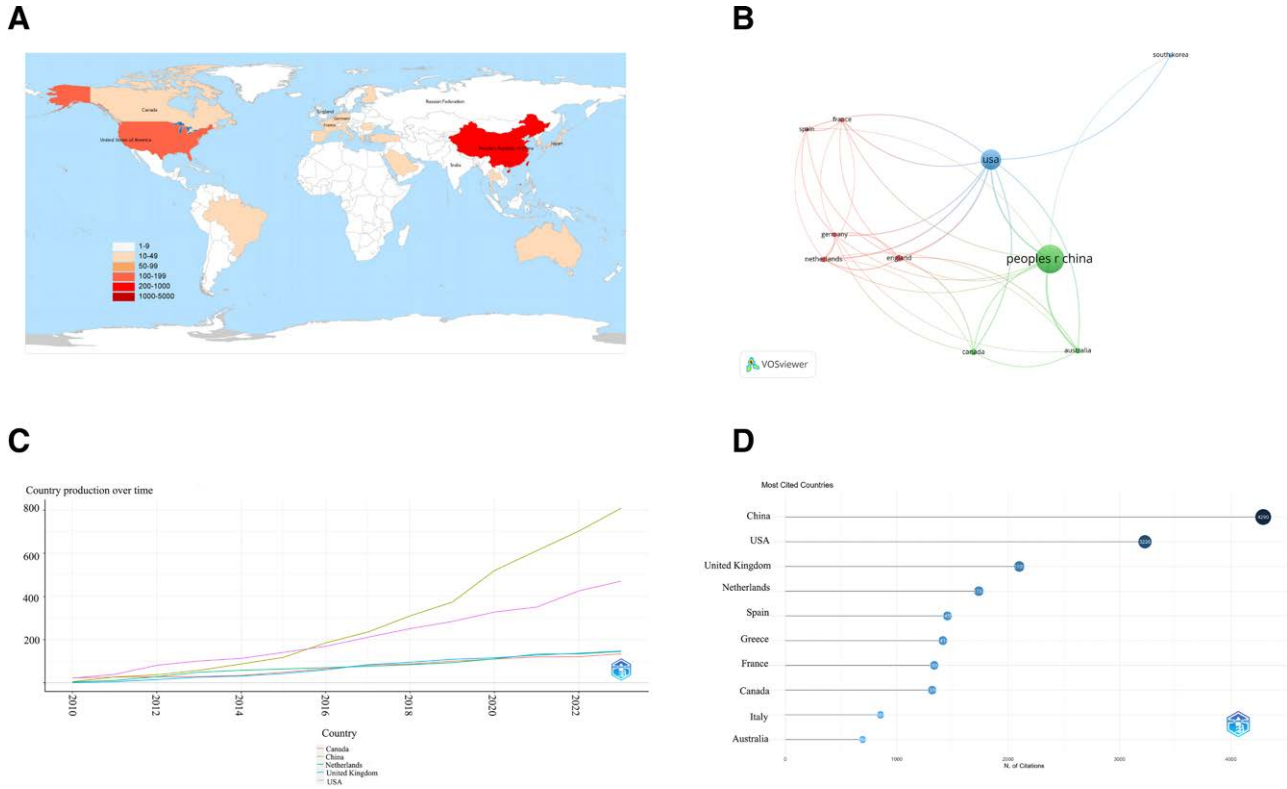

Figure 3. (A) Geographical distribution of publications on lipid metabolism in OA; (B) cooperative network diagram among the top ten countries in terms of publication volume; (C) publication volume of top 5 countries over time; and (D) top 10 most cited countries.

Table 2

Top 5 most productive affiliations.

Affiliation	Country	NP	% (n = 843)	TC	AC	H-index
China Medical University	China	53	6.29	325	5.60	5
Leiden University Medical Center	Netherlands	37	4.39	99	8.25	14
Duke University	United States	33	4.15	599	14.26	12
Leiden University	Netherlands	33	4.15	287	13.67	15
Erasmus Medisch Centrum	Netherlands	31	3.68	125	6.25	11

AC = average citation, NP = number of publications, TC = total citations.

We have rated the top 5 most productive countries (Table 1). China has the highest total number of publications (NP) (232/27.52%), followed by United States (108/12.81%) and the United Kingdom (41/4.86%). We have listed the total citations of countries, and the average citation (AC) per paper and H-index for all publications, the United Kingdom has the highest average citation per paper (51.2), followed by the United States (29.9), China (18.5). Among them, papers from China have been cited 4290 times, accounting for 18.14% of the total number of citations(n = 23,649), followed by the United States (3228 times) and United Kingdom (2100 times) (Fig. 3D). We also examined the publication quantity and collaboration network between the top 10 countries in terms of publication volume (Fig. 3A and B). It can be observed that China has the closest collaboration with the United States and Canada. Most collaborations occur in East Asian countries, American, and European, while collaboration with underdeveloped countries needs to be further strengthened. Furthermore, the publication

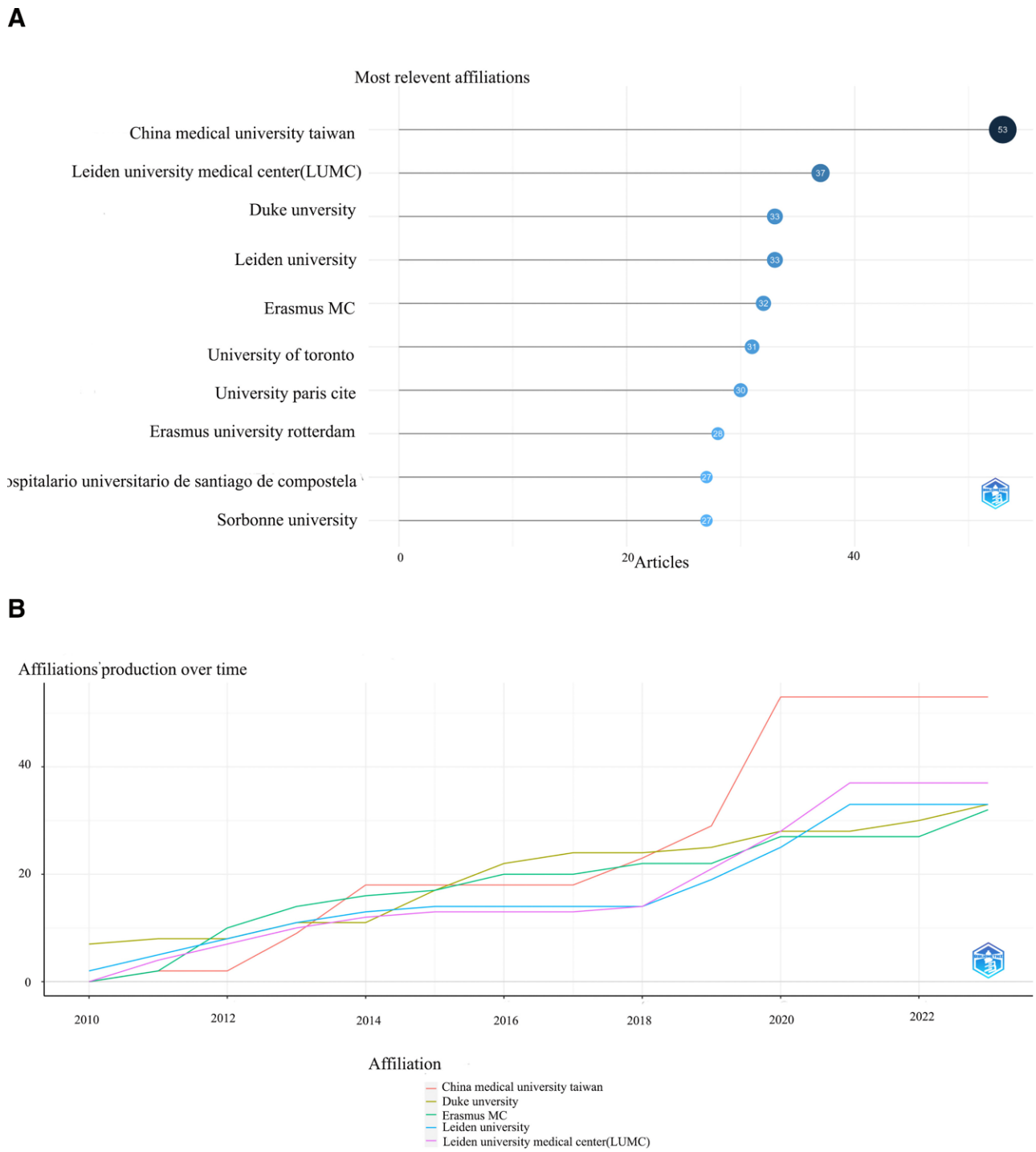

Figure 4. (A) The top 10 affiliations in terms of publication volume; (B) the publication volume trend over time for the top 5 affiliations.

Table 3

Top 5 most productive authors.

Authors	Country	Affiliation	NP	% (n = 843)	TC	AC	H-index
Ding CH	China	Anhui Medical University	16	8.19	87	5.44	10
Jones G	Australia	University of Tasmania	14	1.66	85	6.07	10
Gualillo O	Spain	Inst Invest Sanitaria Santiago de Compostela Santiago University Clinical Hospital	13	1.54	157	12.08	12
Guilak F	United States	Washington University	13	1.54	193	14.85	11
Kloppenburg M	Netherlands	Leiden University Medical Center	13	1.54	232	17.85	11

AC = the average citation, NP = number of publications, TC = the total citations.

Table 4

Top 5 most productive journals.

Journal	Country	NP	% (n = 843)	TC	AC	H-index	IF (2022)	Quartile in category (2022)
Osteoarthritis and Cartilage	United Kingdom	59	7.00	515	8.73	27	7	Q1
Arthritis Research & Therapy	United Kingdom	34	4.03	406	11.94	25	5.6	Q1
International Journal Of Molecular Sciences	United States	24	2.85	96	4	11	5.6	Q1
Scientific Reports	United Kingdom	23	2.73	67	2.91	12	4.6	Q2
Plos One	United States	19	2.25	122	6.42	12	3.7	Q2

AC = the average citation, IF = Influence factor, NP = number of publications, TC = the total citations.

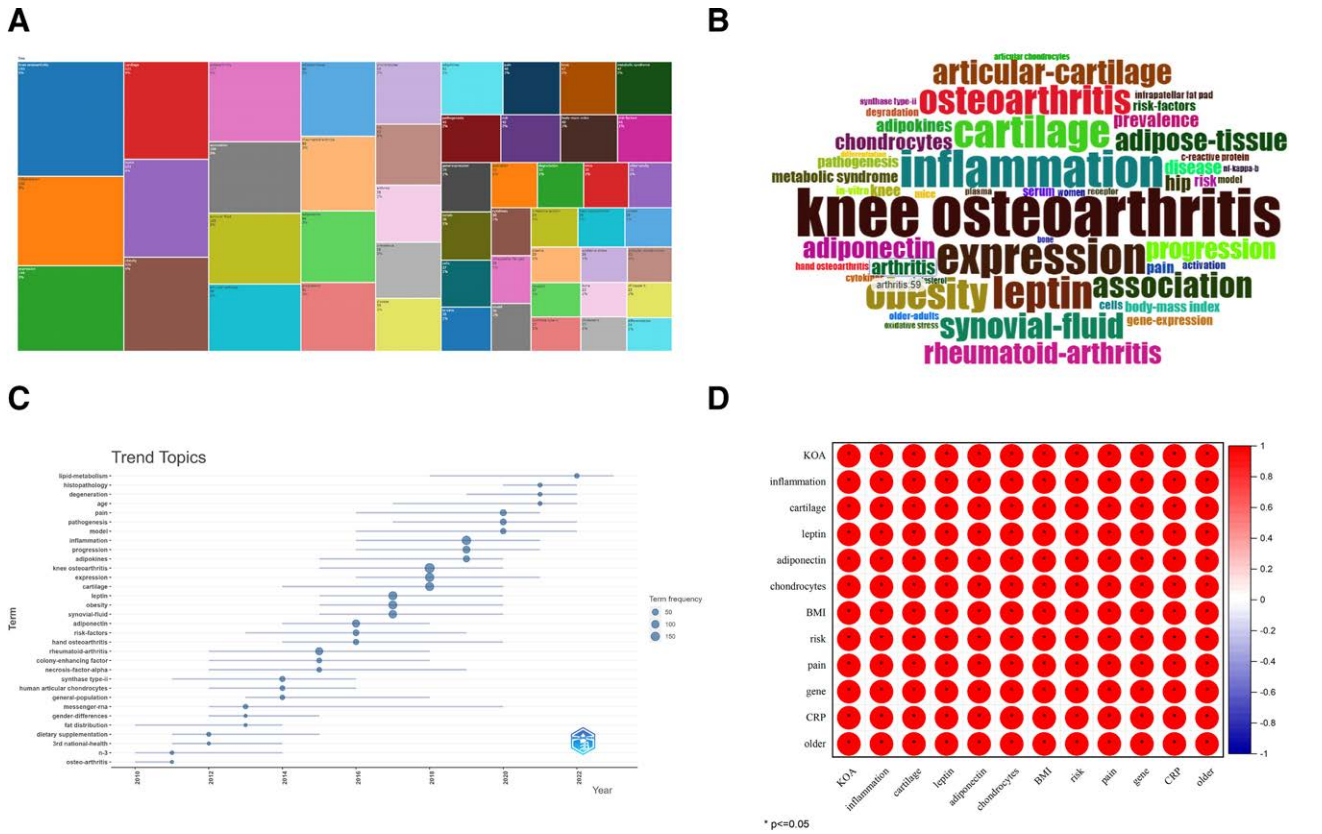

Figure 5. (A) The tree map of the top 50 most frequent keywords; (B) keywords cloud; (C) trend topics; (D) correlation analysis among keywords.

volume over time for the 5 aforementioned countries were showed (Fig. 3C), highlighting a significant increase in publication volume for China and United States over time.

3.4. Affiliation analysis

Detailed information on the top 5 most productive affiliations are presented in Table 2, including the country, NP, total citations, H-index, and AC. Specifically, China medical university ranks first with 53 publications (6.29%), followed by Leiden university medical center from the Netherlands and Duke university from the United States with 37 and 33 publications, respectively. The next 2 affiliations are Leiden university from the Netherlands (33 publications) and the Erasmus Medisch Centrum from the Netherlands (31 publications). In terms of quantifiable indicators, China medical university achieves the highest NC (53 publications), Leiden university achieves the greatest H-index (15), and Duke university achieves the highest AC (14.26). Figure 4A illustrates the top 10 affiliations in terms of publication volume. Figure 4B shows the publication volume trend over time for the top 5 affiliations, indicating a steady increase.

3.5. Author analysis

The top 5 most productive authors published a total of 69 papers, accounting for 8.19% of all the literatures (Table 3). Ding CH from Anhui Medical University in China, takes first place with 16 publications on lipid metabolism in OA research, followed closely by JONES G from University of Tasmania in the Australia with 14 publications. In terms of quantifiable indicators, Ding CH from China achieves the highest NC (16 publications), GUALILLO O from Inst Invest Sanitaria Santiago de Compostela Santiago University Clinical Hospital in Spain achieves the most H-index (12), and KLOPPENBURG M from Netherlands achieves the highest AC (17.85). indicating that their research has attracted more attention from scholars. Additionally, all of the top 5 authors are from China, USA, Europe, and The Netherlands, suggesting that there are more outstanding researchers focusing on lipid metabolism in OA research in these countries.

3.6. Journal analysis

The country of publication, NP, total citations, H-index, and impact factors (IFs) of the top 5 most productive journals are

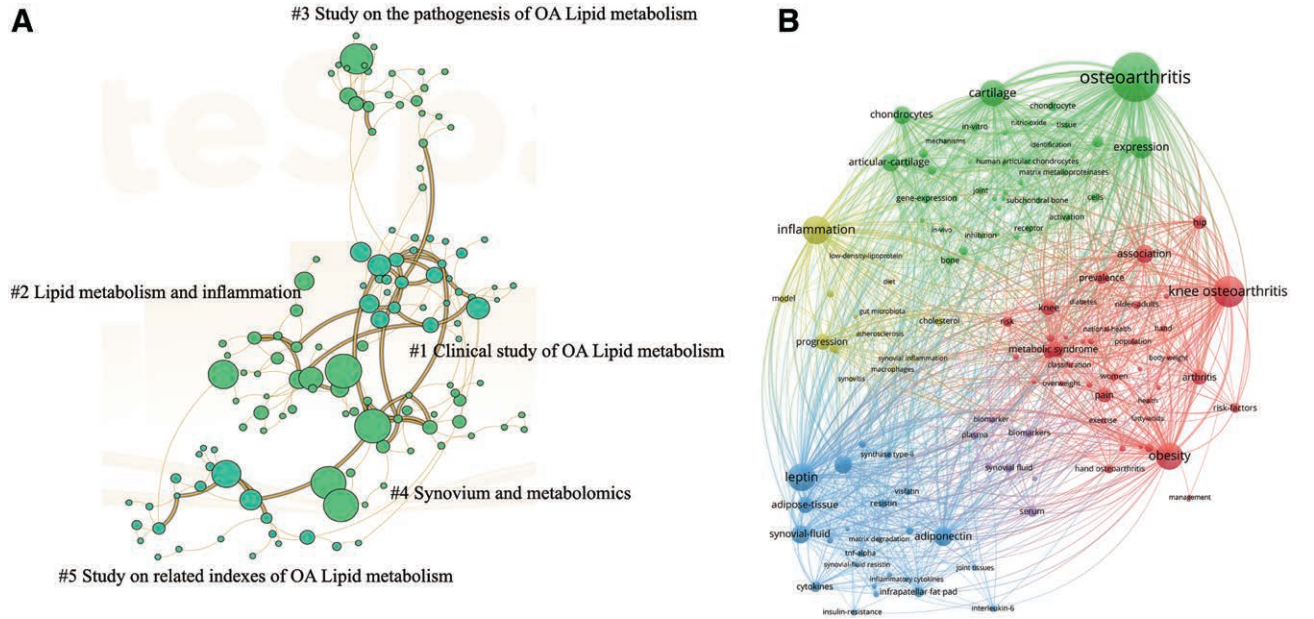

Figure 6. (A) Keywords clustering; (B) the co-occurrence network of keywords.

listed in Table 4. Osteoarthritis and Cartilage (59 publications, IF: 7) publishes the most studies on lipid metabolism in OA. Osteoarthritis and Cartilage aims to promote the cross-merger of clinical and basic science research results from different disciplines, including OA, cartilage, molecular biology, clinical pharmacology, orthopedics, rheumatology, physical medicine, biochemistry, epidemiology, and collagen. The next 2 most productive journals are Arthritis Research & Therapy (34 publications, IF: 5.6) and International Journal of Molecular Sciences (24 publications, IF: 5.6). Among them, Osteoarthritis and Cartilage has the highest total citations (515) and H-index(27); Arthritis Research & Therapy has the highest AC (11.94). Furthermore, all the top 5 most productive journals have a high IF (defined as > 3.000).

3.7. Analysis of keywords hotspots

High-frequency keywords could reflect research hotspots. A total of 3149 keywords were extracted from the 843 publications. Ultimately, 97 keywords with more than 15 occurrences were identified. The top 50 high-frequency keywords are listed (Fig. 5A and B) and the top 5 keywords ranked by number of occurrences were as following: knee OA (n = 193), inflammation (n = 150), expression (n = 144), cartilage (n = 131), and leptin (n = 131). We also analyze the keywords' frequency over time and trend topics of the top 10 high-frequency keywords and note that "inflammation," "Lipid metabolism," and "pain" have been long-standing focuses on OA research (Fig. 5C). Additionally, we also manually de-duplicated the keywords with the top 50 frequencies (synonymous keywords with similar meanings), and then imported the names and frequency of the de-duplicated keywords into the R Studio for correlation analysis. The results showed that KOA, inflammation, adiponectin, BMI, CRP and pain were all statistically significantly correlated with each other (Fig. 5D).

Vosviewer was used to analyze the co-occurrence network of keywords, and citespace was used to analyze the keyword clustering (Fig. 6A and B), the keywords were grouped into 5 clusters. Notably, the primary keywords for cluster 1 (red) referred to Clinical study of OA. Cluster 2 (yellow) referred to Lipid metabolism and inflammation. Cluster 3 (green) referred to Study on the pathogenesis of OA, cluster 4 (purple) referred to Synovium and metabolomics, and cluster 5 (blue) referred to Study on related indicators of OA.

Burst terms were identified with CiteSpace to indicate new research trends and frontier topics.[33] The node type was set as "Keyword," and other parameters were set in accordance with the description in Section 2. The minimum duration was set to the default value of 2. Thirty-one keywords with strong citation bursts were found (Fig. 7). Among the top keywords, lipid metabolism had the highest burst strength (6.63). Other keywords with high burst strengths from 2013 to 2023 include Chondrocytes, fatty acids, adiponectin, TNF-α, IL-6, IL-1β, Degenerative joint disease, and Pain.

3.8. Clinical characteristics of OA patients

Table 5 summarizes the baseline characteristics of the study population. A total of 2437 patients were enrolled with a median age of 58.00 years (IQR: 51.00, 69.00). The majority of recruited patients were female (77.26%), and nonsmokers and nondrinkers accounted for 92.99% and 91.63% of all study populations, respectively. The median course of disease was 10 years (IQR: 5.00, 15.00). Laboratory indicators showed a median ESR of 15.00, hs-CRP of 1.92, TC of 5.50, TG of 2.33, HDL-C of 1.25, LDL-C of 2.87. The median VAS was 6.00 (IQR: 5.00, 7.00). The inflammatory markers (ESR, hs-CRP) and some of lipid metabolism markers (TC, TG) detected in OA patients exceeded the reference values.

3.9. Correlation analysis

Analysis of the correlation between inflammatory markers (ESR and hs-CRP) and lipid metabolism indicators (TC, TG, HDL-C, and LDL-C) showed (Table 6 and Fig. 8) that HDL-C and ESR (Correlation coefficient = –0.124, $P < .001$), both hs-CRP (correlation coefficient = –0.120, $P < .001$) were strongly negatively correlated, while TC was only strongly positively correlated with hs-CRP (correlation coefficient = 0.126, $P < .001$). In addition, analysis results of correlation between them and VAS showed (Table 6 and Fig. 8) that ESR, TC, TG, LDL-C, and hs-CRP were positively correlated with VAS, among which hs-CRP was the strongest positively correlated with VAS (correlation coefficient = 0.054, $P = .008$). HDL-C showed a strong negative correlation with VAS (correlation coefficient = –0.045, $P = .026$).

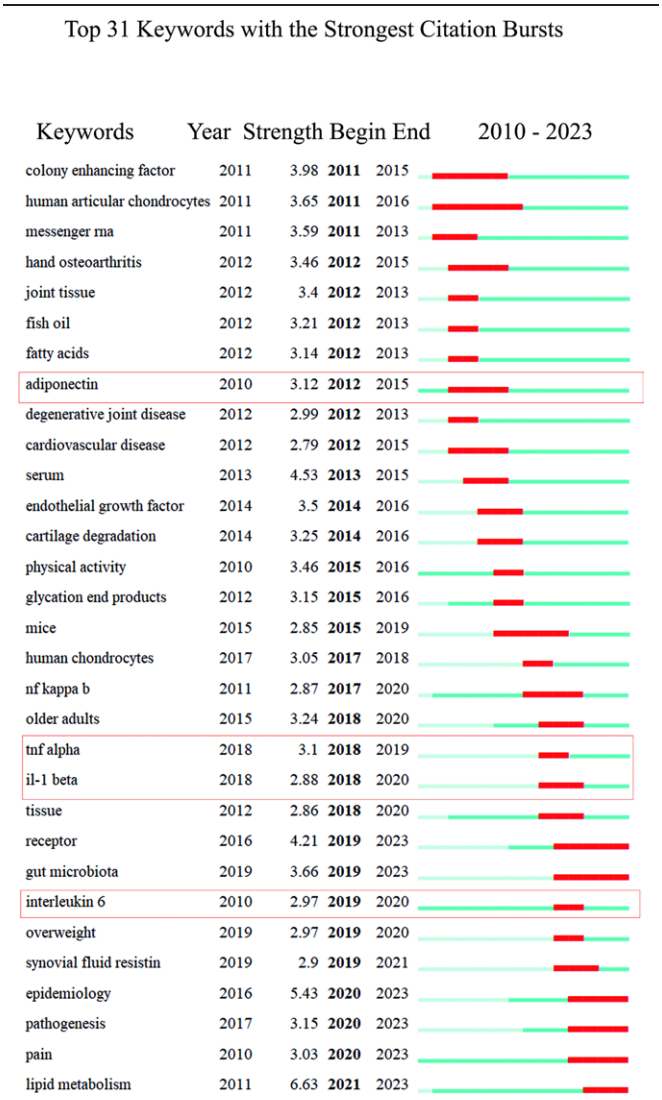

Figure 7. Top 31 keywords with the strongest citation bursts.

3.10. Association rule analysis

We have found that HDL-C was strongly negatively correlated with ESR and hs-CRP; TC was strong positive correlation between hs-CRP. Therefore, we further conducted association rule analysis on blood lipid profile and inflammation indicators (Table 7), and set the minimum support value as 65%, the minimum confidence value as 50%, the boost value as > 1, and the *P* value as < 0.01. Finally, we found that HDL-C < 1 mmol/L, LDL-C ≥ 3.4 mmol/L, TG ≥ 1.7 mmol/L, TC ≥ 5.2 mmol/L were significantly correlated with hs-CRP ≥ 1 mg/L and ESR > 12 mm/h.

3.11. Univariate and multivariate regression analysis

Logistic regression analysis determined the correlation between inflammatory markers, lipid profiles, and VAS to further identify the influencing factors for OA (Table 8 and Fig. 9). In univariate regression analysis, we found that HDL-C (OR = 0.698, *P* = .003) was an independent protective factor for OA-VAS. When all variables were included in regression analysis, HDL-C was still an independent protective factor for OA-VAS, and was more significant. In addition, TG (OR = 1.269, *P* = .018) and ESR (OR = 1.214, *P* = .041) also showed dangerous properties for OA-VAS and became risk factors for OA-VAS.

4. Discussion

Current bibliometrics is a brief review of impact factors, the source standardization impact of each paper, the H-index, and alternative indicators.[34] A total of 843 articles and reviews published between 2010 and 2023 were searched and analyzed. Firstly, based on the statistics of the annual number of publications and the annual cumulative number of publications (Fig. 2A), it is observed that while the annual number of publications has shown slight fluctuations over the past 2 decades, the annual cumulative number of publications has exhibited a general increasing trend. The increasing number of publications on OA lipid metabolism suggests a growing interest from researchers in this area. Based on the linear correlation between the number of literature and the years (Fig. 2B), it is evident that studies related to OA lipid metabolism have entered a phase of rapid development after long-term knowledge accumulation. It is anticipated that the output will reach 90 publications by 2024. Secondly, we present an overview of research status across various countries, institutions, journals, and authors. Generally, China, the United Kingdom and the United States ranked first in terms of total number of published papers, average number of citations, and H-index respectively. Additionally, 1 institution and 1 scholar from China as well as the United States have made it to the top 5 most effective institutions and authors list. This indicates a growing attention to OA lipid metabolism among scholars in these 2 countries. However, all top 5 journals are based in the United Kingdom and the United States, suggesting that these nations lead in both generating and disseminating relevant ideas in this field.

Keyword analysis is important for effectively grasping hot topics. Our study found that the top 10 high-frequency keywords related to OA lipid metabolism were knee OA (KOA) (n = 193), inflammation (n = 150), expression (n = 144), cartilage (n = 131), leptin (n = 131), obesity (n = 126), OA (n = 117), association (n = 104), synovial-fluid (n = 103), and articular-cartilage (n = 98). association (n = 104), synovial-fluid (n = 103), and articular-cartilage (n = 98). "inflammation," "Lipid metabolism," and "pain" have been long-standing focuses on OA research. Moreover, we manually deleted the synonyms in the first 50 high-frequency keywords, and after importing them into R Studio for correlation analysis, we found that the correlation between the 2 factors, such as KOA, inflammation, adiponectin, BMI, CRP, and pain, was statistically significant (Fig. 5D). The co-occurrence analysis of keywords facilitated the categorization of major knowledge structures and hotspots, revealing the academic frontiers. Cluster analysis showed that 5 major research clusters existed in OA lipid metabolism related research from 2010 to 2023 (Fig. 6A and B). They are: Clinical study of OA Lipid metabolism; Lipid metabolism and inflammation; The pathogenesis of OA Lipid metabolism; Synovium and metabolomics; related indicators of OA Lipid metabolism. These results suggest that markers of OA lipid metabolism may be involved in inflammatory responses and may be associated with joint pain.

CiteSpace's "burst detection" method identifies keywords over time.[35] Researchers can use keywords with burst characteristics to explore research hotspots. In this study, in addition to lipid metabolism, "chondrocytes," "FAs," "adiponectin," "TNF-α," "IL-6," "IL-1β," "degenerative joint disease," and "pain" were the keywords that continued to break out through 2023. This suggests that focusing on lipid metabolism and pro-inflammatory cytokines in OA may be a potential research hotspot in the future. OA is the most common degenerative joint disease in the elderly, and pain and poor joint mobility often occur. Various immune cells such as T cells and B cell populations are involved in joint pathology,[36] different inflammatory markers are associated with pain, such as IL-6, IL-1β, and TNF-α, which are considered to be the predominant pro-inflammatory factors in OA, increase serum levels of CRP and promote pain.[37] In addition, chronic inflammation is

Table 5

Baseline characteristics of OA patients.

Variables	Characteristics	Status	Statistical description	Normal range
Baseline characteristics	Gender	Female	1883 (77.26%)	
	Gender	Male	554 (22.74%)	
	Age	Median (IQR)	58.00 (51.00, 69.00)	
	Number of hospitalizations	Median (IQR)	1.00 (1.00, 1.00)	
	Course of disease	Median (IQR)	10.00 (5.00, 15.00)	
	If smoke	Yes	173 (7.01%)	
		No	2264 (92.99%)	
	Smoke Year	Median (IQR)	20.00 (10.00, 20.00)	
	If drink	Yes	204 (8.37%)	
		No	2233 (91.63%)	
	Drink Year	Median (IQR)	20.00 (10.00, 20.00)	
Laboratory indicators	ESR	Median (IQR)	15.00 (7.00, 20.00)	2–12 mm/h
	hs-CRP	Median (IQR)	1.92 (0.36, 3.16)	<1 mg/L
	TC	Median (IQR)	5.50 (4.07, 6.36)	<5.2 mmol/L
	TG	Median (IQR)	2.33 (1.14, 2.91)	<1.7 mmol/L
	HDL-C	Median (IQR)	1.25 (1.05, 1.49)	≥1 mmol/L
	LDL-C	Median (IQR)	2.87 (2.34, 3.43)	<3.4 mmol/L
Score	VAS	Median (IQR)	6.00 (5.00, 7.00)	<5

ESR = erythrocyte sedimentation rate, HDL-C = high density lipoprotein cholesterol, hs-CRP = hypersensitive C-reactive protein, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, VAS = visual analogue scale.

Table 6

Correlation between inflammation, blood lipid profile, and VAS score.

Variables	TC	ESR	HDL-C	TG	LDL-C	hs-CRP	VAS
TC	1	-0.027	-0.026	0.267**	0.882**	0.126**	0.006
P value		.177	.060	<.001	<.001	<.001	.769
ESR	-0.027	1	-0.124**	-0.025	0.013	0.619**	0.003
P value	.177		<.001	.218	.514	<.001	.863
HDL-C	-0.026	-0.124**	1	-0.291**	0.187**	-0.120**	-0.045*
P value	.060	<.001		<.001	<.001	<.001	.026
TG	0.267**	-0.025	-0.291**	1	0.149**	0.017	0.031
P value	<.001	.218	<.001		<.001	.057	.052
LDL-C	0.882**	0.013	-0.187**	0.149**	1	0.013	0.008
P value	<.001	.514	<.001	<.001		.320	.701
hs-CRP	0.126**	0.619**	-0.120**	0.017	0.013	1	0.054**
P value	<.001	<.001	<.001	.057	.32		.008
VAS	0.006	0.003	-0.045*	0.031	0.008	0.054**	1
P value	.769	.863	.026	.052	.701	.008	

ESR = erythrocyte sedimentation rate, HDL-C = high density lipoprotein cholesterol, hs-CRP = hypersensitive C-reactive protein, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, VAS = visual analogue scale.

* $P < .05$.

** $P < .01$.

associated with abnormalities in lipid metabolism, such as FAs and TGs, and adiponectin promotes the metabolism of FA and TGs and regulates chronic inflammation.[38] However, some studies have suggested that adiponectin, like leptin, promotes macrophage polarization, tilts toward a pro-inflammatory M1 phenotype, induces obesity inflammation, inhibits autophagy and promotes cartilage degradation senescence to promote OA progression.[39,40] Although scholars have disagreed on the role of adiponectin in OA, there is no doubt that inflammation and lipid metabolism play an important role in the development of OA and are worthy of further study.

OA is characterized by abnormal lipid metabolism and its clinical manifestation is hyperlipidemia.[41] The main markers of the lipid profile include TC, TG, HDL-C, and LDL-C, of which hypercholesterolemia and hypertriglyceridemia have been associated with the development of cardiovascular disease in OA, in addition to being risk factors for OA.[42] TC and LDL-C levels were higher and HDL-C and ApoA1 levels were lower in OA patients compared with non-OA patients,[9] in addition, there is evidence from inverse variance weighted, MR-Egger regression, and weighted median estimator that the risk of OA increases with increasing levels of TC, TG, and LDL.[43] TC refers to the total amount of cholesterol contained in all lipoproteins in the blood. The TC level of the population is mainly determined by genetic factors and lifestyle; HDL-C can transport cholesterol from the extra-hepatic tissues to the liver for metabolism and excretion by bile.[44] Statins and aerobic exercise were able to reduce the concentration of relevant TC in OA and increase the concentration of HDL-C, which was associated with reduced cardiovascular events and all-cause mortality,[45,46] the important mediator for this effect is LDL-C, because when LDL-C is excluded, there is no correlation between any exposure factor and the outcome.[47] Genetically determined LDL-C increments resulted in a reduced risk of both KOA and hip OA, independent of HDL-C, TG, and BMI.[48] TG is the most abundant and productive energy substance in the body, but the research on the relationship between TG and OA is not clear. A quantitative study has shown that every 1 unit increase in TG increases the risk of clinical OA by 5%, and also increases the risk of joint pain in the elderly.[49]

Our retrospective data mining analysis found that the levels of inflammatory indicators (ESR and hs-CRP) and lipid metabolism indicators (TC, TG, and HDL-C) in OA patients were significantly elevated, suggesting that they may be involved in the occurrence of OA. Correlation analysis was used to verify the association of inflammatory markers (ESR and hs-CRP) and lipid metabolism markers (TC, TG, LDL-C, and HDL-C) with disease activity (VAS). HDL-C had a strong negative correlation with ESR (correlation coefficient = –0.124, $P < .001$), hs-CRP (correlation coefficient = –0.120, $P < .001$), and VAS (correlation coefficient = –0.045, $P = .026$), respectively. TC was only strongly positively correlated with hs-CRP (correlation coefficient = 0.126, $P < .001$). In addition, hs-CRP was the strongest positively correlated with VAS (correlation coefficient = 0.054, $P = .008$). These results suggest that inflammation in OA patients is indeed associated with hyperlipidemia, and suggest that TC, TG, LDL-C, and HDL-C have similar effects on inflammatory markers. It can be associated with disease activity (VAS) of OA. Apriori is an algorithm belonging to association rule mining technology. It works by detecting the existence of item sets in a large number of databases, and then formulates corresponding association rules by using indicators such as support, promotion and confidence.[50] Similarly, our association rule results further support previous findings of a high correlation between inflammatory markers (ESR and hs-CRP) and lipid metabolism markers (TC, TG, LDL-C, and HDL-C). In addition, we identified factors associated with VAS and found that HDL-C (OR = 0.698, $P = .003$) was an independent protective factor for OA disease activity. TG (OR = 1.269, $P = .018$) and ESR (OR = 1.214, $P = .041$) were independent risk factors for OA disease activity.

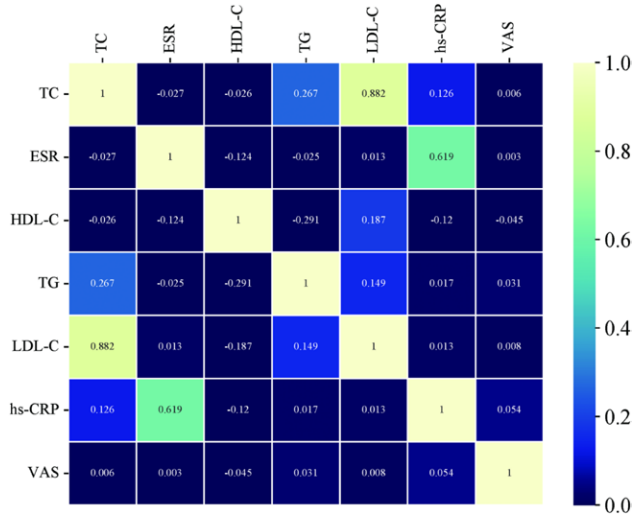

Figure 8. Correlation coefficient between inflammation, blood lipid profile, and VAS score. ESR = erythrocyte sedimentation rate; HDL-C = high density lipoprotein cholesterol; hs-CRP = hypersensitive C-reactive protein; LDL-C: low density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VAS = visual analogue scale.

Our current study has several advantages. First of all, this is a study based on a large number of literature references, and the results are highly reliable. Second, we not only explore the hot trends in OA lipid metabolism research to date, but also further confirm the correlation between inflammation, lipid metabolism markers, and disease activity in OA patients with the advantage of our internal database, achieving cross-validation of the data with the real world. However, our study is merely a single-center retrospective study, and its reproducibility cannot be guaranteed. Moreover, due to the lack of longitudinal comparison, we cannot rule out the existence of bias. In addition, our study is based on real-world data, and the influencing factors are complex, so it cannot be ruled out that our study has no confounding bias. Therefore, it is necessary to design multi-center prospective studies in the future to support our findings.

Table 7

Association rules between inflammation, and blood lipid profile.

Preceding paragraph	Consequent	Support (%)	Confidence (%)	Lift degree
HDL-C < 1 mmol/L	hs-CRP ≥ 1 mg/L	81.74	55.924	1.06
TC ≥ 5.2 mmol/L	ESR > 12 mm/h	69.183	55.042	1.062
LDL-C ≥ 3.4 mmol/L	ESR > 12 mm/h	73.615	54.849	1.058
LDL-C ≥ 3.4 mmol/L	hs-CRP ≥ 1 mg/L	73.615	54.682	1.036
TG ≥ 1.7 mmol/L	hs-CRP ≥ 1 mg/L	67.378	54.507	1.033
TC ≥ 5.2 mmol/L	hs-CRP ≥ 1 mg/L	69.183	54.27	1.028
TG ≥ 1.7 mmol/L	ESR > 12 mm/h	67.378	53.837	1.039
HDL-C < 1 mmol/L	ESR > 12 mm/h	81.74	52.811	1.019

ESR = erythrocyte sedimentation rate, HDL-C = high density lipoprotein cholesterol, hs-CRP = hypersensitive C-reactive protein, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, VAS = visual analogue scale.

Table 8

Univariate and multivariate analysis of OA-VAS score.

	Univariable			Multivariable		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* value
HDL-C > 1 mmol/L	0.698	0.550, 0.886	0.003	0.624	0.485, 0.804	<0.001
TC ≥ 5.2 mmol/L	0.914	0.756, 1.105	0.353	0.962	0.731, 1.265	0.78
LDL-C ≥ 3.4 mmol/L	0.839	0.686, 1.026	0.088	0.768	0.576, 1.024	0.073
TG ≥ 1.7 mmol/L	1.117	0.929, 1.344	0.239	1.269	1.042, 1.544	0.018
ESR > 12 mm/h	1.154	0.969, 1.374	0.108	1.214	1.008, 1.462	0.041
hs-CRP ≥ 1 mg/L	0.945	0.793, 1.125	0.523	0.934	0.775, 1.126	0.476

ESR = erythrocyte sedimentation rate, HDL-C = high density lipoprotein cholesterol, hs-CRP = hypersensitive C-reactive protein, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, VAS = visual analogue scale.

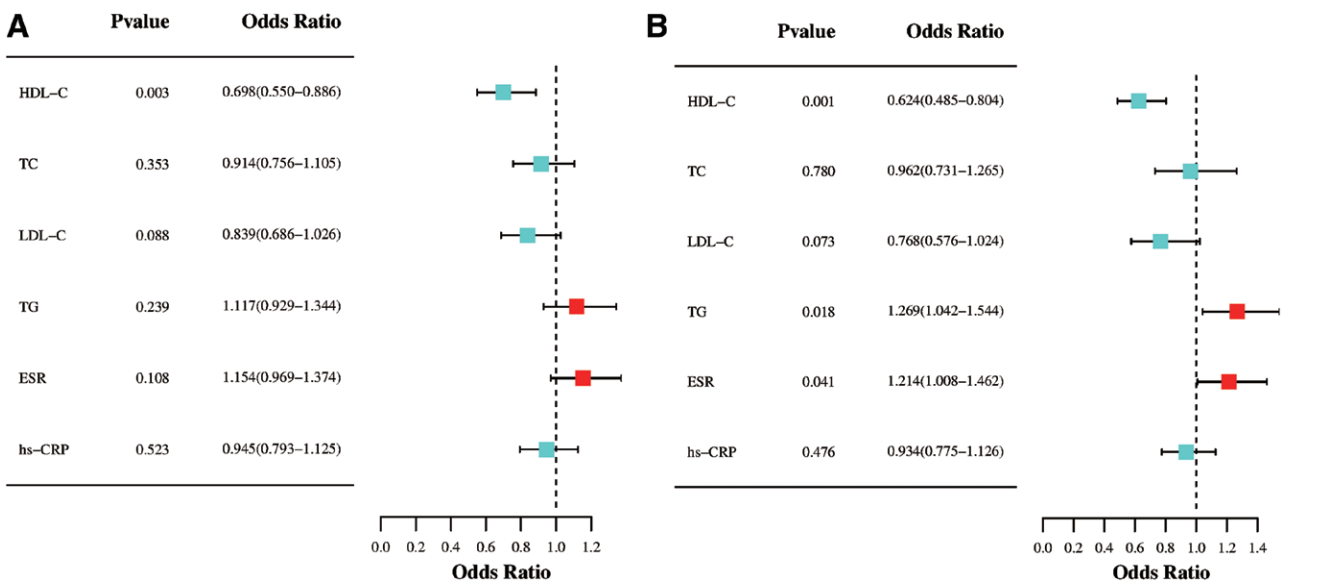

Figure 9. (A) Forest map for univariate regression analysis; and (B) forest map for multivariate regression analysis. ESR = erythrocyte sedimentation rate; HDL-C = high density lipoprotein cholesterol; hs-CRP = hypersensitive C-reactive protein; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

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