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Hypercoagulability in Rheumatoid Arthritis: A Bibliometric Analysis and Retrospective Data Mining Study

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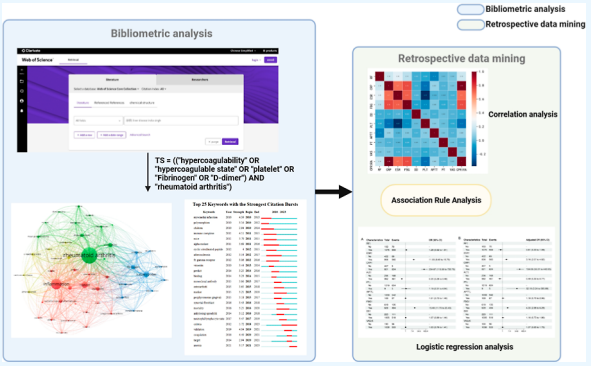
ABSTRACT: Background: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic systemic inflammation, leading to joint deformities and functional loss. RA progression is accompanied by abnormalities in the coagulation−fibrinolysis system, clinically manifested as a hypercoagulable state. However, there are currently no bibliometrics or visualization analysis in this field. Objective: The present study aims to reveal the knowledge structure, research status, and research trends related to hypercoagulability in RA through bibliometric analysis and to evaluate the utility of inflammatory and coagulation markers in RA disease activity through retrospective data mining. Methods: English articles and reviews on RA hypercoagulability published from 2010 to 2023 were extracted from the Web of Science Core Collection (WoSCC) database on March 1, 2023. VOSviewer and CiteSpace software were used for knowledge mapping analysis of the included papers in terms of countries/regions, institutions, journals, authors, keywords, research hotspots, and frontiers. A retrospective analysis was conducted on the general information on RA patients. The demographic and clinical indicators of all participants were collected to determine the correlation of inflammatory and coagulation markers with the Chinese patient-reported activity index for rheumatoid arthritis (CPRI-RA). Results: A total of 957 papers were retrieved. The United States was the most productive country in this field and had the highest h-index, and the most prolific institution was the Karolinska Institute. The Annals of the Rheumatic Diseases was the journal with the most publications, and KLARESKOG L. was the most productive author. From keyword analysis, it could be seen that "inflammation", "activation", "disease-activity", and "risk" had long been the focuses of RA hypercoagulability research. "Criteria", "validation", "coagulation", "target", and "anemia" were the latest popular keywords in the past 5 years. Retrospective data mining revealed that the levels of inflammation (RF, ESR, and CRP) and coagulation (PLT and DD) were significantly increased in RA patients. FBG, CRP, and ESR were significantly correlated with CPRI-RA. Additionally, ESR, CRP, and FBG were identified as independent risk factors for CPRI-RA. Conclusion: The mechanism and application of hypercoagulability in RA have been research hotspots in recent years. Inflammation and coagulation markers are independent risk factors for CPRI-RA.



1. INTRODUCTION

Rheumatoid arthritis (RA) is a prevalent chronic autoimmune disease that can cause joint pain and even functional disability, significantly compromising patients' quality of life.[1] RA mainly affects the synovial membrane, manifested as synovial inflammation (synovitis), vascular pannus formation, synovial hyperplasia, and fibrosis-like changes. Persistent synovitis leads to destruction of the subchondral bone and cartilage, ultimately resulting in joint deformities and functional impairments.[2] The prevalence of RA in China is as high as 0.42%.[3] RA has become the leading cause of physical disability among Chinese women and one of the top 10 most common chronic diseases in China. In terms of the extent of quality of life loss caused by common chronic diseases, RA ranks third, surpassing hypertension and diabetes.[4]

RA disease progression is accompanied by disturbances in coagulation and fibrinolysis systems, leading to a hypercoagulable state clinically.[5] Coagulation and fibrinolysis markers mainly include platelets (PLTs), D-dimers (D−Ds), and fibrinogen (FBG). RA patients commonly present with a significant increase in platelet counts along with immune, inflammatory, and metabolic abnormalities. Platelet activation factor (PAF) is a potent inflammatory mediator involved in many disease processes.[6] In RA, PAF not only exacerbates the local infiltration of inflammatory cells, leading to synovitis and angiogenesis but also induces platelet aggregation, contributing

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to the development of a hypercoagulable state in the body.[7] Prostaglandin I2 (PGI2), also known as prostacyclin, can enhance the activity of adenylate cyclase and cause vessel dilation, thereby protecting blood vessels from the adverse effects of disease progression.[8]

The immune-inflammatory response plays a critical role throughout the development of RA. Chronic inflammation can lead to joint swelling, deformity, and functional impairment.[9] Various immune cells and inflammatory mediators can infiltrate synovial tissue, promoting the degradation of cartilage and bone and contributing to the immune-inflammatory response in RA.[10] The patient-reported outcome (PRO) scale is more advantageous than traditional physician-reported outcome measures in RA medication efficacy evaluation, disease monitoring, and chronic disease management.[11−13] The Chinese patient-reported activity index with rheumatoid arthritis (CPRI-RA) is a RA-PRO scale that presents clinical outcome indicators of Chinese RA patients from the patient's perspective. As an important supplement to existing RA assessment tools, CPRI-RA provides a reliable tool for clinical efficacy evaluation, disease monitoring, clinical medication trials, and chronic disease management, as well as an objective and quantitative basis for the efficacy evaluation system of traditional Chinese medicine in the treatment of RA, thereby improving the recognition and acceptance of the efficacy evaluation of traditional Chinese medicine for RA treatment.[14]

Bibliometrics is a reliable statistical method for evaluating publications related to specific topics, which allows quantitative and qualitative analysis of a vast amount of scientific literature to evaluate the spatiotemporal distribution of research status and reveal research trends and hot topics.[15] This interdisciplinary field has been embraced by researchers and applied in medical domains, such as orthopedics,[16] oncology,[17−19] and rheumatology.[20] To the best of our knowledge, several researchers have already applied it to the field of RA. For example, Zhang et al.[21] conducted a bibliometric study on publications regarding RA-related interstitial lung disease for the first time, identifying the most influential publications and analyzing the research status and trends in this field.

In this study, we employed bibliometrics to gain an understanding of the current status and development trends related to coagulation and hypercoagulability in RA. Then, we explored the bursting keywords related to RA hypercoagulability and visually evaluated and predicted the research status, hot topics, and future development trends. Furthermore, we retrospectively evaluated the correlation of inflammatory and coagulation markers with disease activity in RA patients.

2. MATERIALS AND METHODS

2.1. Literature Data Sources. This bibliometrics analysis was performed by referring to the previous relevant literature.[22,23] The Web of Science Core Collection (WoSCC) database from Clarivate Analytics encompasses over 15,000 peer-reviewed journals from more than 250 disciplines worldwide.[24] WoSCC is recognized as one of the most comprehensive and authoritative databases for accessing global academic information, making it the optimal database for bibliometric analysis.[25] In addition to general literature retrieval, it also offers an important function of citation indexing, which helps to evaluate the academic performance of the literature and journals in specific fields. Therefore, we chose the Science Citation Index Expanded (SCI-Expanded, 1900-present) database within WoSCC to replace other databases (Scopus and PubMed) as our data source for literature retrieval.

2.2. Data Collection and Retrieval Strategy. To prevent redundancy from frequent updates to the database, we completed the literature retrieval within 1 day, with the date of the last search being March 1, 2023. To comprehensively and accurately search for all of the literature related to RA coagulation, we employed a combination of subject terms and titles. The search strategy was as follows: TS = ("hypercoagulability" OR "hypercoagulable state" OR "platelet" OR "Fibrinogen" OR "D-dimer") AND "rheumatoid arthritis", with the search year limited to January 1, 2010, to March 1, 2023. Only English-language articles and reviews were considered. Conference abstracts, letters, brief reports, editorial materials, news, revisions, reprints, retractions, and other types of publications were excluded from this study. A total of 1236 articles and reviews were retrieved, and after removing 279 irrelevant publications, we finally obtained a data set of 957 valid publications.

2.3. Synonym Replacement. Since some synonyms in the country, journal, author, and keywords may lead to biased results, we replaced some of the synonyms, especially those closely related to the topic. For example, we categorized publications from Taiwan under China before data analysis, and publications from England, Northern Ireland, Scotland, and Wales were combined under the United Kingdom.

2.4. Research Software/Tools. 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 three types of visual maps—label view, overlay view, and density view—with notable features of user-friendliness and aesthetically pleasing graphics.[26] 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.[27]

2.5. Bibliometric Analysis. Bibliometric analysis and visualization were mainly conducted using VOSviewer, CiteSpace, Microbial Informatics Platform (http://www.bioinformatics.com.cn/), and Microsoft Excel software. All relevant data collected from the WoSCC database were imported into CiteSpace (version 6.1) and VOSviewer (version 1.6.18). Notably, the files were renamed with the prefix "download" to enable the identification and processing by the CiteSpace software, thus obtaining duplicates and global annual publication volume.

Microsoft Excel 2019 was used to conduct annual publishing trend analysis and create global annual publication volume and citation statistics graphs. VOSviewer software was primarily selected to construct and visualize the bibliometric network of the collected publications, including the analysis of contributions from different countries, institutions, journals, and authors. The distribution of publications by different countries was visualized in conjunction with a world map. Co-occurrence and clustering analyses were performed on keyword clusters with a threshold of 20. Additionally, CiteSpace was used for keyword citation burst analysis, thereby visually evaluating and predicting the research status, hot topics, and future development trends.

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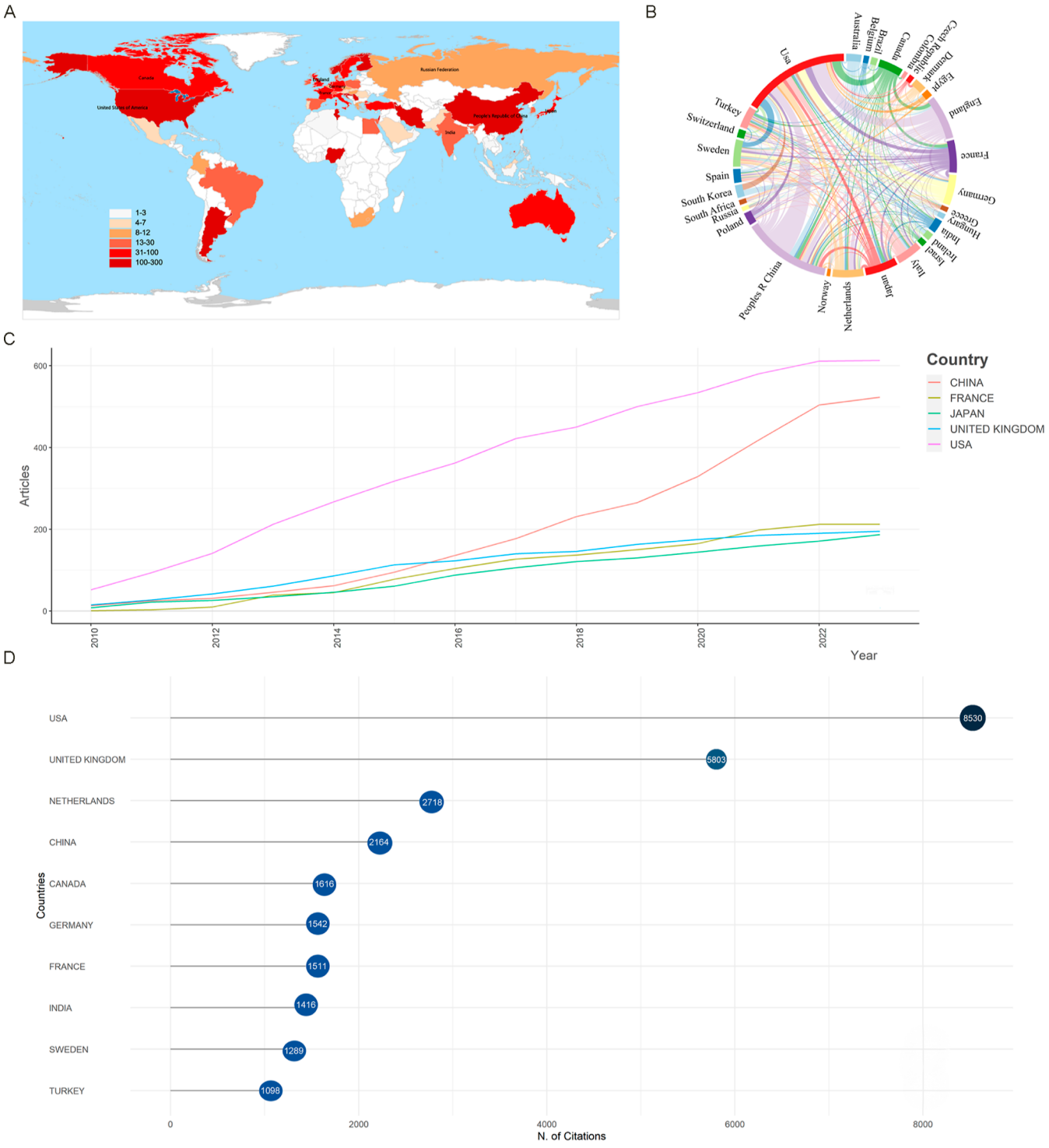

Figure 1. (A) Geographical distribution of publications on RA coagulation; (B) chord chart of cooperation among the top 30 countries in terms of publication volume; (C) publication volume of top 5 countries over time; and (D) top 10 most cited countries.

2.6. Patient Clinical Information. This study collected clinical data from RA patients admitted to the Rheumatology and Immunology Department of the First Affiliated Hospital of Anhui University of Chinese Medicine. The hospital's Health Information System (HIS) records patient's basic information, such as age, gender, height, weight, and disease duration. Patients with severe infections, severe cardiovascular, respiratory, and hematopoietic diseases, as well as other autoimmune diseases were excluded. Ultimately, a total of 1228 RA patients were eligible to participate in this study. Subsequently, laboratory examination indicators were obtained for these 1228 patients including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), platelet (PLT) count, fibrinogen (FBG), D-dimer (DD), prothrombin time (PT), and activated partial thromboplastin time (APTT). The study protocol was approved by the ethics committee of the hospital, and all procedures were in accordance with the ethical standards outlined in the *Declaration of Helsinki*.

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Table 1. Top Five Most Productive Countries

rank	country	NP	% (n = 957)	NC	AC	H-index
1	USA	219	22.88	8530	38.95	62
2	CHINA	178	18.60	2164	12.16	35
3	UNITED KINGDOM	98	10.24	5803	59.21	40
4	FRANCE	66	6.90	1511	22.89	23
5	JAPAN	66	6.90	633	9.59	17

Table 2. Top Five Most Productive Affiliated Institutions

rank	affiliations	country	NP	% (n = 957)	NC	AC	H-index
1	KAROLINSKA INST	Sweden	52	5.43	3616	69.54	27
2	LEIDEN UNIV	Netherlands	41	4.28	2527	61.63	19
3	STANFORD UNIV	USA	40	4.18	3223	80.56	23
4	KAROLINSKA UNIV HOSP	Sweden	33	3.45	1836	55.64	19
5	UNIV AMSTERDAM	Netherlands	31	3.24	1695	54.68	18

2.7. Chinese Patient-Reported Activity Index with Rheumatoid Arthritis (CPRI-RA). All patients were required to complete the CPRI-RA questionnaire simultaneously, including the following 11 items:[14] (1) How severe is your current joint pain? (2) How do you feel the degree of joint swelling? (3) How long does your joint stiffness last in the morning (how long can joint stiffness be alleviated through activity)? (4) Compared with other joints, do your painful joints feel hot to touch? (5) Do you have difficulty with upper limb joint activities (e.g., holding a bowl, lifting objects, combing hair)? (6) Do you have difficulty with lower limb joint activities (e.g., squatting, going up and down the stairs, walking on level ground)? (7) Do you experience fatigue in your daily life and work? (8) Do you feel muscle soreness? (9) How is your appetite? (10) Have you recently felt restless or depressed? (11) Do you have difficulty with daily life, work, or learning?

Each item was scored on a scale of 0 to 3, ranging from asymptomatic to worsening symptoms. The total score was calculated using the following formula: 1.43 × item 1 + 0.93 × item 2 + 0.40 × item 3 + 1.09 × item 4 + 0.11 × item 5 + 0.18 × item 6 + 0.24 × item 7 + 0.04 × item 8 + 1.17 × item 9 + 0.19 × item 10 + 0.02 × item 11.

2.8. Statistical Analysis. Statistical analysis and graph plotting were performed by using SPSS 24.0 software. Count data were represented as numbers or percentages, and comparison between groups was conducted by using the chi-square test. Continuous data were presented as the median and interquartile range (IQR), and comparison was performed by using the Mann−Whitney U test. The specific calculation formula for association rule analysis was referenced from previous studies.[28] Pearson correlation analysis or Spearman correlation analysis was used to assess the correlation between indicators in normally distributed and non-normally distributed data, respectively. Logistic regression models were employed to evaluate the statistical association between the indicators and disease activity in patients.

3. RESULTS

3.1. Country Analysis. We retrieved a total of 957 papers from WoSCC spanning the years 2010 to 2023, including 746 articles and 211 reviews. The total number of citations for the retrieved papers was 34,035, with an average of 24.34 citations per paper.

Figure 1A depicts the geographic distribution of publications regarding RA coagulation from all countries and regions. The top five countries in terms of publication volume produce two-thirds of all 957 papers. The United States is the country with the most papers published, followed by China, the United Kingdom, France, and Japan.

We have rated the top five most productive countries, as shown in Table 1. The United States has the highest total number of publications (NP) (219/22.88%), followed by China (178/18.60%) and the United Kingdom (98/10.24%). We have listed the total number of citations (NC) of the retrieved papers, the average citation (AC) per paper, and the h-index for all publications. Among them, papers from the United States have been cited 8530 times, accounting for 25.06% of the total number of citations, followed by the United Kingdom (5803 times) and China (2164 times) (Figure 1D). In addition, the United States has the highest h-index (62), followed by the United Kingdom (40) and France (35), while the United Kingdom has the highest average citation per paper (59.21). We also examined the publication quantity and collaboration network between the top 30 countries in terms of publication volume (Figure 1B). It can be observed that the United States has the closest collaboration with the United Kingdom and China. Most collaborations occur in European, American, and East Asian countries, while collaboration with underdeveloped countries needs to be further strengthened. Furthermore, Figure 1C shows the publication volume over time for the five aforementioned countries, highlighting a significant increase in publication volume for China and France over time.

3.2. Institution Analysis. Table 2 presents detailed information on the top five most productive institutions, including the country, NP, NC, h-index, and AC. Specifically, Karolinska Institute from Sweden ranks first with 52 publications (5.43%), followed closely by Leiden University from The Netherlands and Stanford University from the United States with 41 and 40 publications, respectively. The next two institutions are Karolinska University Hospital from Sweden (33 publications) and the University of Amsterdam from The Netherlands (31 publications). In terms of quantifiable indicators, Karolinska Institute achieves the highest NC (3616) and the greatest h-index (27), while Stanford University achieves the highest AC (80.56). Figure 2A illustrates the top 10 institutions in terms of publication volume. Figure 2B shows the publication volume trend over time for the top five institutions, indicating a steady increase.

3.3. Author Analysis. Table 3 lists the top 10 most productive authors. They published a total of 169 papers,

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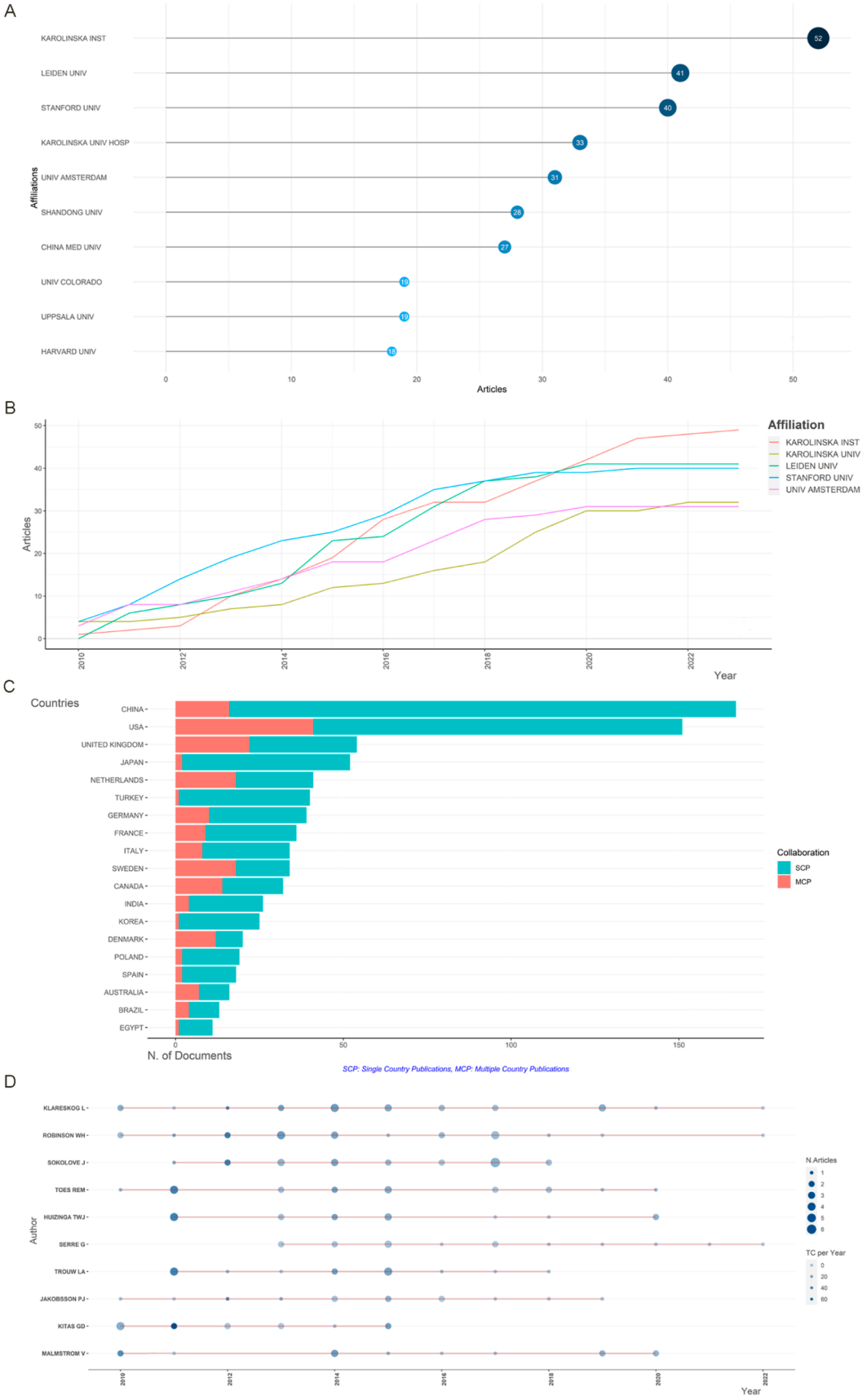

Figure 2. (A) Most relevant affiliations; (B) affiliations' production over time; (C) corresponding author's countries; and (D) authors' production over time.

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Table 3. Top Ten Most Productive Authors

rank	author	country	affiliations	NP	% (n = 957)	NC	AC	H-index
1	KLARESKOG L	Sweden	KAROLINSKA INST	23	2.40	319	13.87	9
2	ROBINSON WH	USA	STANFORD UNIV	22	2.30	1953	88.77	18
3	SOKOLOVE J	USA	STANFORD UNIV	21	2.19	1469	69.95	16
4	TOES REM	Netherlands	Leiden University	18	1.88	1941	107.83	16
5	SERRE G	Sweden	KAROLINSKA INST	16	1.67	183	11.44	8
6	HUIZINGA TWJ	Netherlands	Leiden University	15	1.57	1158	77.20	12
7	TROUW LA	Netherlands	Leiden University	15	1.57	1244	82.93	13
8	HANSSON M	Sweden	KAROLINSKA UNIV HOSP	13	1.36	448	34.46	9
9	HOLMDAHL R	Sweden	KAROLINSKA UNIV HOSP	13	1.36	716	55.08	9
10	JAKOBSSON PJ	Sweden	KAROLINSKA INST	13	1.36	928	71.38	9

Table 4. Top Ten Most Influential Journals

rank	source	country	NP	% (n = 957)	NC	AC	H-index	IF (2021)	quartile in category (2021)
1	ANNALS OF THE RHEUMATIC DISEASES	England	47	4.91	1944	41.36	26	27.97	Q1
2	ARTHRITIS RESEARCH & THERAPY	England	37	3.87	1483	40.08	23	5.61	Q1
3	ARTHRITIS & RHEUMATOLOGY	USA	33	3.45	1485	45	19	15.48	Q1
4	FRONTIERS IN IMMUNOLOGY	Switzerland	33	3.45	838	25.39	15	8.79	Q1
5	PLOS ONE	USA	31	3.24	1277	41.19	18	3.75	Q2
6	ARTHRITIS AND RHEUMATISM	USA	29	3.03	2442	84.21	23	15.48	Q1
7	RHEUMATOLOGY INTERNATIONAL	Germany	22	2.30	645	29.32	11	3.58	Q3
8	CLINICAL RHEUMATOLOGY	England	19	1.99	306	16.11	10	3.65	Q3
9	CLINICAL AND EXPERIMENTAL RHEUMATOLOGY	England	17	1.78	164	9.65	7	4.86	Q2
10	JOURNAL OF RHEUMATOLOGY	Canada	17	1.78	515	30.29	13	5.35	Q2

accounting for 17.66% of all submissions. L. KLARESKOG from Karolinska Institute in Sweden takes first place with 23 publications in RA research, followed by W.H. ROBINSON and J. SOKOLOVE from Stanford University in the USA with 22 and 21 publications, respectively. W.H. ROBINSON and R.E.M. TOES have higher NC values (1953, 1941), while W.H. ROBINSON has the highest h-index, and R.E.M. TOES has the highest AC, indicating that their research has attracted more attention from scholars. Additionally, all of the top ten authors are from the USA, Sweden, and The Netherlands, suggesting that there are more outstanding researchers focusing on RA research in these countries. Furthermore, we have also analyzed the countries where the corresponding authors are located, as well as single-country and multiple-country publications (Figure 2C). The publication volume over time of the top 10 authors is depicted in Figure 2D.

3.4. Journal Analysis. Table 4 summarizes the country of publication, NP, NC, h-index, and impact factors (IFs) of the top 10 most productive journals. As shown in Table 4, the Annals of the Rheumatic Diseases (47 publications, IF: 27.97) publishes the most studies on RA hypercoagulability (Figure 3). The Annals of the Rheumatic Diseases aims to cover all current clinical and experimental research trends, including inflammation, metabolism, immune, and degenerative soft and hard connective tissue diseases. The next two most productive journals are Arthritis Research & Therapy (37 publications, IF: 5.61) and Arthritis & Rheumatology (33 publications, IF: 15.48). Among them, Arthritis & Rheumatology has the highest NC (2442) and AC (84.21). Approximately 30% of the publications are published in the top 10 academic journals (285/29.78%). Furthermore, all the top 10 most productive journals have a high IF (defined as >3.000).

3.5. Analysis of Research Hotspots. Keyword co-occurrence and burst analysis help to discover the research themes and hot trends of publications. As shown in Table 5, the top 20 high-frequency keywords are "rheumatoid arthritis" (309), "disease" (122), "inflammation" (115), "autoantibodies" (98), "association" (87), "expression" (77), "activation" (75), "disease-activity" (72), "fibrinogen" (72), "systemic lupus erythematosus" (68), "risk" (66), "antibodies" (55), "classification" (49), "synovial fluid" (49), "criteria" (45), "c-reactive protein" (39), "identification" (37), "pathogenesis" (34), and "collagen-induced arthritis" (33).As shown in Figure 4, we categorize the colors of all keywords based on their frequency of occurrence. We also analyze the keywords' frequency over time and trend topics of the top 10 high-frequency keywords and note that "inflammation", "activation", and "risk" have been long-standing focuses of RA research (Figure 4D).

In VOSviewer, by counting the frequency of keyword occurrence in publications and simplifying the co-occurrence network, we select keywords with a co-occurrence count greater than 20, ultimately obtaining a co-occurrence network consisting of 4 clusters and 586 connections (Figure 5). Cluster 1 (green) focuses on research related to the diagnosis of RA, as shown in Figure 5A. Cluster 2 (red) focuses on RA inflammation. Cluster 3 (blue) emphasizes research on RA indicators. Cluster 4 (yellow) mainly deals with clinical research on RA. Additionally, we find that "criteria", "validation", "coagulation", "target", and "anemia" are the most recent hot keywords in the past 5 years.

3.6. Clinical Characteristics of RA Patients. The baseline characteristics of the study population are summarized in Table 6. A total of 1228 patients were recruited, with a median age of 56.00 years old (IQR: 50.00−67.00). Most of the recruited patients are female (82.00%) and nonsmokers (90.15%), while 7.88% of patients report a history of alcohol consumption. The median duration of illness is 8.50 months (IQR: 3.00−15.00). The examination of laboratory indicators shows median values

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Figure 3. (A) Most relevant sources; (B) most local cited sources; (C) sources' local impact; (D) collaboration network between sources with a publication volume of ≥5; and (E) sources' production over time.

of 89.70 for RF, 40.00 for ESR, 12.41 for CRP, 3.92 for PLT, 16.70 for TT, 10.60 for PT, 27.40 for APTT, 4.00 for FBG, and 100.00 for DD. The median visual analogue scale (VAS) score and disease activity score are 6.00 (IQR: 5.00−7.00) and 9.84 (IQR: 8.24−11.43), respectively. The detected inflammatory levels (RF, ESR, and CRP) and coagulation levels (PLT and DD) of RA patients all exceed the reference values.

3.7. Correlation Analysis. The correlation of inflammation markers (RF, ESR, and CRP) and coagulation indicators (PLT, PT, APTT, FBG, and DD) with disease activity (VAS and CPRI-RA) is analyzed (Table 7 and Figure 6). RF, ESR, CRP, FBG, and APTT are positively correlated with CPRI-RA. In particular, CRP shows a strong correlation with CPRI-RA (rho = 0.99, $p < 0.0001$). ESR and FBG are also strongly correlated with CPRI-RA (rho = 0.70, 0.76, $p < 0.0001$, Table 8).

3.8. Association Rules. According to the average CPRI-RA score, RA patients are divided into two groups: the low-moderate disease activity group (CPRI-RA ≤ 9.8) and the high disease activity group (CPRI-RA > 9.8). Based on the VAS score, they are also assigned to two groups: the mild-moderate RA group (VAS ≤ 5) and the severe RA group (VAS > 5). We further analyze the correlation of inflammatory and coagulation markers with disease activity, with the minimum support set at 40%, the minimum confidence set at 60%, the lift set at >1, and the p-value set at <0.01. The results are sorted based on the highest confidence. There exists a significant association between abnormal increases in DD, CRP, and RF and VAS > 5. Additionally, an abnormal increase in FBG, CRP, and ESR is significantly correlated with CPRI-RA ≥ 9.8 (Table 9).

3.9. Logistic Regression Analysis. The logistic regression analysis determines the correlation between inflammation, coagulation markers, VAS, and CPRI-RA to further identify RA-related factors and high-risk populations. In the univariate regression analysis, ESR (OR = 11.6, $p < 0.001$), CRP (OR = 255, $p < 0.001$), and FBG (OR = 15.4, $p < 0.001$) are found to be independent risk factors for CPRI-RA. When all variables are included in the multivariate logistic regression analysis, a stronger correlation is revealed (Table 10). ESR (OR = 3.16, $p < 0.001$), CRP (OR = 134, $p < 0.001$), and FBG (OR = 4.33, $p < 0.001$) remain independent predictors of RA disease activity. Additionally, PT (OR = 62.2, $p < 0.001$) is also identified as one of the risk factors for RA disease activity (Table 10, Figure 7).

4. DISCUSSION

Recently, bibliometrics has emerged as a standout method for studying medical academic publishing compared to traditional system evaluation,[29] which can sort out research hotspots and trends from the perspective of time and clustering[30] and thereby provide an in-depth understanding of significant achievements and advancements. In this study, a total of 957 articles and reviews published between 2010 and 2023 articles were retrieved and analyzed. According to our statistics and fitting analysis, despite slight fluctuations in the number of publications over the past 20 years, both the publication volume and citation volume have shown an overall increasing trend. It is suggested that an increasing number of researchers are becoming interested in the field of RA hypercoagulability. To begin, we present an overview of the distribution of research status among countries, institutions, journals, and authors. Overall, the United States ranks first in terms of the total number of publications, total number of citations, and h-index. Two scholars from the United States have entered the top ten most productive authors list. These data indicate that there are more experts and scholars in the United States focusing on RA-hypercoagulability research and also explain the leading position of the United States in this research field.

Keyword co-occurrence and burst analysis also help to identify research topics and hot trends in publications. The top

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Table 5. Top 20 High-Frequency Keywords

rank	keyword	occurrences	strength	rank	keyword	occurrences	strength
1	rheumatoid arthritis	309	1832	11	risk	66	419
2	disease	122	769	12	antibodies	55	431
3	inflammation	115	1454	13	cells	55	357
4	autoantibodies	98	822	14	classification	49	367
5	association	87	681	15	synovial fluid	49	370
6	expression	77	484	16	criteria	45	317
7	activation	75	478	17	c-reactive protein	39	347
8	disease activity	72	513	18	identification	37	262
9	fibrinogen	72	701	19	pathogenesis	34	255
10	systemic lupus erythematosus	68	471	20	collagen-induced arthritis	33	229

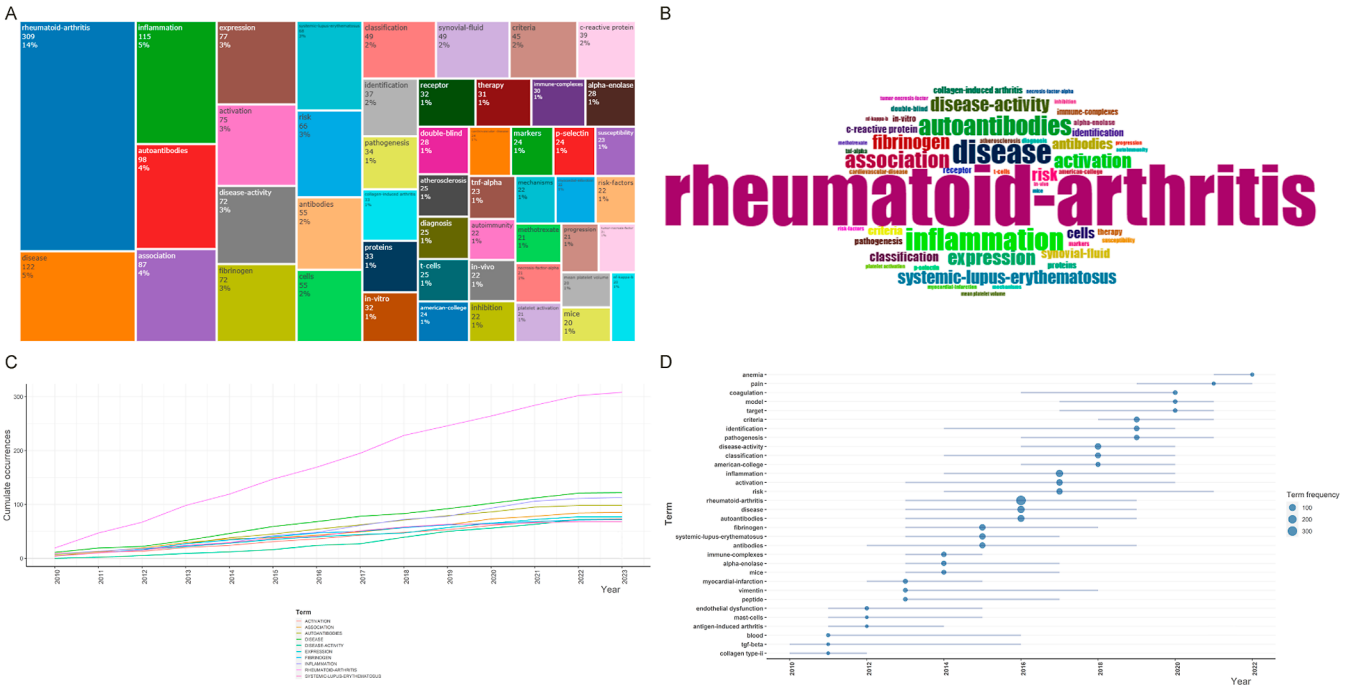

Figure 4. Analysis of research hotspots. (A) Dendrogram of keyword frequency; (B) keyword cloud; (C) keywords' frequency over time; and (D) trend topics.

20 high-frequency keywords in research over the past 10 years are "rheumatoid arthritis" (309), "disease" (122), "inflammation" (115), "autonomy" (98), "association" (87), "expression" (77), "activation" (75), "disease activity" (72), "fibrinogen" (72), "systemic lupus erythematosus" (68), "risk" (66), "antibiotics" (55), "classification" (49), "synovial fluid" (49), "criteria" (45), "c-reactive protein" (39), "identification" (37), "pathogenesis" (34), and "collagen-induced arthritis" (33). At the same time, "criteria", "validation", "coordination", "target", and "anima" are the latest popular keywords in the past 5 years. "Inflammation", "activation", "disease activity", and "risk" have long been the focus of RA-hypercoagulability research.

Inflammatory response is a key event in the pathogenesis of RA, involving interactions between various immune and nonimmune cells, cytokines, and inflammatory mediators. Fibroblast-like synoviocytes (FLSs) are the central effector cells contributing to RA synovitis and joint destruction.[31] The stimulation from inflammatory signals can lead to the abnormal proliferation of RA-FLSs, resulting in the production of various inflammatory cytokines. The two factors mutually promote each other, forming a vicious cycle.[32] IL-6 is a pleiotropic pro-inflammatory cytokine with significant functions in the immune system.[33] On the contrary, IL-10 is a well-established anti-inflammatory cytokine that can inhibit the synthesis and activity of pro-inflammatory mediators. Moreover, IL-10 can exhibit synergistic effects with various anti-inflammatory mediators.[34]

RA is characterized by the activation of the coagulation and fibrinolysis system, which clinically manifests as a hypercoagulable state of blood.[35−37] The coagulation and fibrinolysis markers primarily include platelet count (PLT), D-dimer (D−D), and fibrinogen (FBG). RA patients demonstrate that the significant increase in PLT in RA patients, along with abnormalities in immune, inflammatory, and metabolic indicators, jointly indicates the pathogenesis of RA.[38] Abnormal platelet parameters are related to clinical indicators such as ESR, CRP, IgA, and rheumatoid factors. Notably, platelet parameters in RA patients during active stages are significantly correlated with symptoms such as joint swelling, skin−nail matrix dystrophy, and tongue petechiae.[39] Platelet-activating factor (PAF), a potent inflammatory mediator, is a product of platelet activation and plays a crucial role in various disease processes.[40] In RA, PAF not only causes local infiltration of inflammatory cells in joints, leading to synovitis and angiogenesis but also induces platelet aggregation, leading to the occurrence of a

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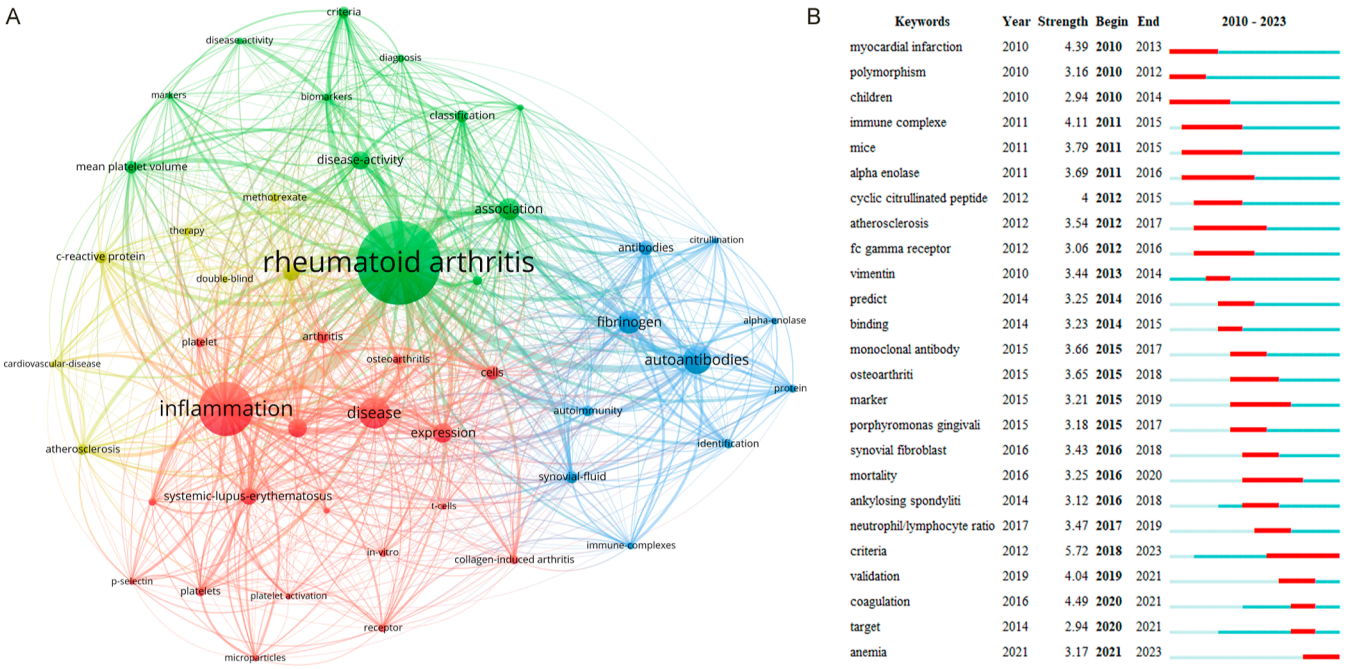

Figure 5. RA keyword mapping. (A) 168 terms that appear more than 20 times are divided into four clusters by different colors. Cluster 1 (green): diagnostic research on RA. Cluster 2 (red): inflammation research on RA. Cluster 3 (blue): indicator research on RA. Cluster 4 (yellow): clinical research on RA. The size of the node represents the frequency of occurrence. (B) Top 25 keywords with the highest number of bursts. The year between "start" and "end" represents the period when the keyword is more influential. The year in light green means that the keyword has not yet appeared; the year in dark green means that the keyword has less influence; and the year in red means that the keyword has more influence.

Table 6. Baseline Characteristics of RA Patients

variables	characteristics	levels	stats	normal reference range
	gender	female	1007 (82.00%)	
		male	221 (18.00%)	
	age	median (IQR)	56.00 (50.00 to 67.00)	
	height	median (IQR)	162.00 (159.00 to 170.00)	
	weight	median (IQR)	60.00 (53.00 to 69.00)	
	Course of disease	median (IQR)	8.50 (3.00 to 15.00)	
baseline characteristics	IF_SMOKE	no	1053 (90.15%)	
		yes	115 (9.85%)	
	SMOKE_YEAR	median (IQR)	20.00 (10.00 to 30.00)	
	IF_DRINK	no	1075 (92.12%)	
		yes	92 (7.88%)	
	DRINK_YEAR	median (IQR)	20.00 (18.50 to 30.00)	
	RF (U/mL)	median (IQR)	89.70 (32.30 to 239.75)	≤14
	ESR (mm/h)	median (IQR)	40.00 (23.00 to 65.00)	2−12
	CRP (mg/L)	median (IQR)	12.41 (3.14 to 35.94)	<5
laboratory indicators	PLT ($\times 10^9$/L)	median (IQR)	3.92 (3.60 to 4.24)	1.25−3.50
	PT (sec)	median (IQR)	10.60 (10.10 to 11.20)	9−13
	APTT (sec)	median (IQR)	27.40 (25.90 to 29.30)	25−33.8
	FBG (g/L)	median (IQR)	4.00 (3.23 to 4.98)	2−4
	DD (mg/L)	median (IQR)	100.00 (0.95 to 983.00)	0−0.55
score	VAS	median (IQR)	6.00 (5.00 to 7.00)	
	disease activity	median (IQR)	9.84 (8.24 to 11.43)	

hypercoagulable state.[7] The deposition of immune complexes and elevation of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-1, and IL-6, can activate endothelial cells, enhance tissue factor expression, and trigger the activation of coagulation and fibrinolysis systems, leading to the formation of microthrombosis associated with vasculitis in RA.[41] Lu et al. have found that the serum levels of D−D and FBG are significantly higher in the high activity group of RA patients compared to the normal group, which may be attributed to the pronounced inflammatory response within the joints of high activity RA patients. Inflammation within the joint induces the entry of plasma components, such as prothrombin and FBG into the joint cavity. Subsequently, these components are activated under the induction of inflammatory factors in the joint cavity, triggering a coagulation reaction.[42]

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Table 7. Correlation between Inflammation, Coagulation Indicators, and Disease Activity

variables	RF	CRP	ESR	FBG	DD	PLT	APTT	PT	VAS	CPRI-RA
RF	1	0.183	0.246	0.148	−0.021	−0.045	−0.152	0.015	0.042	0.183
CRP	0.183	1	0.699	0.762	−0.03	−0.207	0.092	−0.014	0.041	0.994
ESR	0.246	0.699	1	0.729	−0.01	−0.374	−0.005	−0.003	−0.018	0.701
FBG	0.148	0.762	0.729	1	−0.051	−0.118	0.048	−0.039	−0.009	0.764
DD	−0.021	−0.03	−0.01	−0.051	1	0.014	−0.017	0.024	−0.012	−0.033
PLT	−0.045	−0.207	−0.374	−0.118	0.014	1	0.064	0.021	−0.036	−0.21
APTT	−0.152	0.092	−0.005	0.048	−0.017	0.064	1	0.041	−0.01	0.089
PT	0.015	−0.014	−0.003	−0.039	0.024	0.021	0.041	1	0.032	−0.009
VAS	0.042	0.041	−0.018	−0.009	−0.012	−0.036	−0.01	0.032	1	0.047
CPRI-RA	0.183	0.994	0.701	0.764	−0.033	−0.21	0.089	−0.009	0.047	1

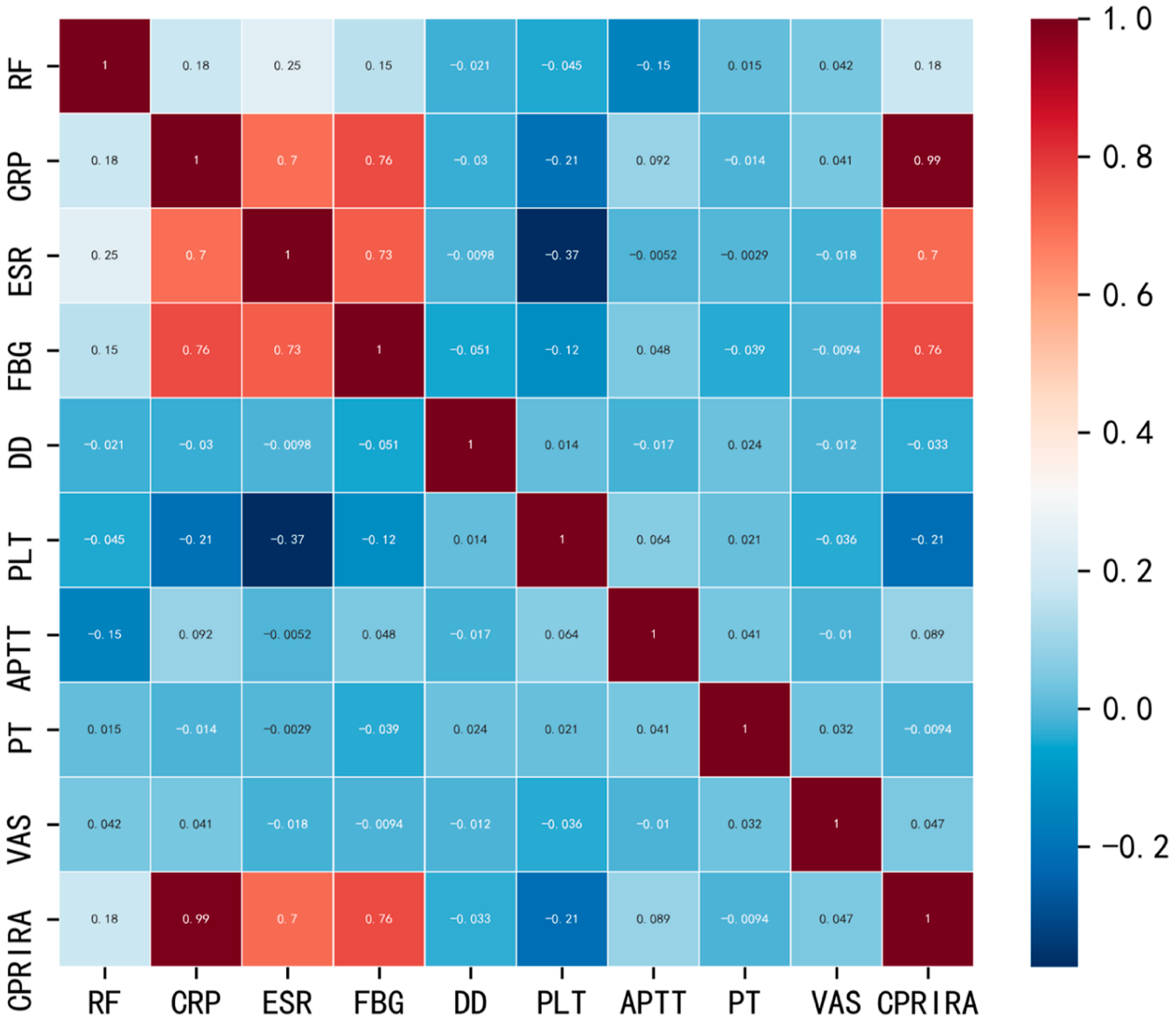

Figure 6. Heat map of correlation analysis. The data represent correlation coefficients with darker shades indicating larger correlations.

Through retrospective data mining and analysis, it is found that the levels of inflammation (RF, ESR, and CRP) and coagulation (PLT and D−D) are significantly elevated in RA patients. Correlation analysis is used to verify the association of inflammation (RF, ESR, and CRP) and coagulation markers (PLT, PT, APTT, FBG, and D−D) with disease activity (VAS and CPRI-RA). RF, ESR, CRP, FBG, and APTT are positively correlated with CPRI-RA, with CRP showing a strong correlation with CPRI-RA (rho = 0.99, $p < 0.0001$). ESR and FBG also have a strong correlation with CPRI-RA (rho = 0.70, 0.76, $p < 0.0001$). Further, we identify the factors and high-risk populations associated with CPRI-RA and find that ESR (OR = 11.6, $p < 0.001$), CRP (OR = 255, $p < 0.001$), and FBG (OR =

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Table 8. *P*-Values of Correlation Coefficients between Inflammation, Coagulation Indicators, and Disease Activity

variables	RF	CRP	ESR	FBG	DD	PLT	APTT	PT	VAS	CPRI-RA
RF	0.000	0.000	0.000	0.000	0.459	0.117	0.000	0.607	0.141	0.000
CRP	0.000	0.000	0.000	0.000	0.294	0.000	0.001	0.630	0.151	0.000
ESR	0.000	0.000	0.000	0.000	0.731	0.000	0.856	0.920	0.538	0.000
FBG	0.000	0.000	0.000	0.000	0.076	0.000	0.097	0.168	0.744	0.000
DD	0.459	0.294	0.731	0.076	0.000	0.613	0.543	0.409	0.672	0.244
PLT	0.117	0.000	0.000	0.000	0.613	0.000	0.026	0.457	0.202	0.000
APTT	0.000	0.001	0.856	0.097	0.543	0.026	0.000	0.153	0.724	0.002
PT	0.607	0.630	0.920	0.168	0.409	0.457	0.153	0.000	0.268	0.742
VAS	0.141	0.151	0.538	0.744	0.672	0.202	0.724	0.268	0.000	0.101
CPRI-RA	0.000	0.000	0.000	0.000	0.244	0.000	0.002	0.742	0.101	0.000

Table 9. Association Rules for Inflammation, Coagulation Indicators, and Disease Activity

items (LHS ⇒ RHS)	support (%)	confidence (%)	lift (%)
disease activity > 9.8 ⇒ CRP↑	0.508	0.992	1.483
ESR↑ ⇒ RF↑	0.598	0.912	1.042
CRP↑ ⇒ RF↑	0.596	0.891	1.018
VAS > 5 ⇒ RF↑	0.742	0.878	1.004
DD↑ ⇒ RF↑	0.717	0.877	1.002
DD↑ ⇒ VAS > 5↑	0.696	0.851	1.007

Table 10. Univariate and Multivariate Analysis of Included Factors

	Univariable					multivariable				
characteristic	*N*	event *N*	OR1	95% CI	*P*-value	*N*	event *N*	OR1	95% CI	*P*-value
RF↑										
no	153	70				153	70			
yes	1075	559	1.28	0.92, 1.81	0.15	1075	559	0.61	0.33, 1.09	0.1
ESR↑										
no	422	69				422	69			
yes	806	560	11.6	8.69, 15.8	<0.001	806	560	3.16	2.07, 4.82	<0.001
CRP↑										
no	407	5				407	5			
yes	821	624	255	116, 721	<0.001	821	624	134	55.3, 442	<0.001
PLT↑										
no	236	168				236	168			
yes	992	461	0.35	0.26, 0.48	<0.001	992	461	0.49	0.30, 0.77	0.002
PT↓										
no	1219	624				1219	624			
yes	9	5	1.19	0.31, 4.84	0.79	9	5	62.2	3.24, 586	<0.001
APTT↓										
no	1059	542				1059	542			
yes	169	87	1.01	0.73, 1.40	0.94	169	87	1.18	0.70, 2.06	0.54
FBG↑										
no	619	135				619	135			
yes	609	494	15.4	11.7, 20.4	<0.001	609	494	4.33	2.98, 6.29	<0.001
DD↑										
no	223	111				223	111			
yes	1005	518	1.07	0.80, 1.44	0.63	1005	518	1.16	0.73, 1.80	0.52
VAS ≥ 5										
no	190	96				190	96			
yes	1038	533	1.03	0.76, 1.41	0.83	1038	533	1.07	0.65, 1.75	0.78

15.4, $p < 0.001$) are independent risk factors for RA disease activity.

This study has several strengths. First, it is a literature-based study with a large sample size, making the results quite reliable. Second, we further confirm the correlation of inflammation and coagulation markers with disease activity in RA patients based on the current research hotspots, achieving mutual verification between literature and clinical research. However, our study also has some limitations. First, it is a retrospective study and lacks longitudinal observation, which may result in selection bias. Second, our study is limited to patients in real-life settings and cannot explore or exclude the impact of treatment on RA, which may lead to confounding bias. Therefore, future multicenter prospective studies are warranted to confirm our findings.

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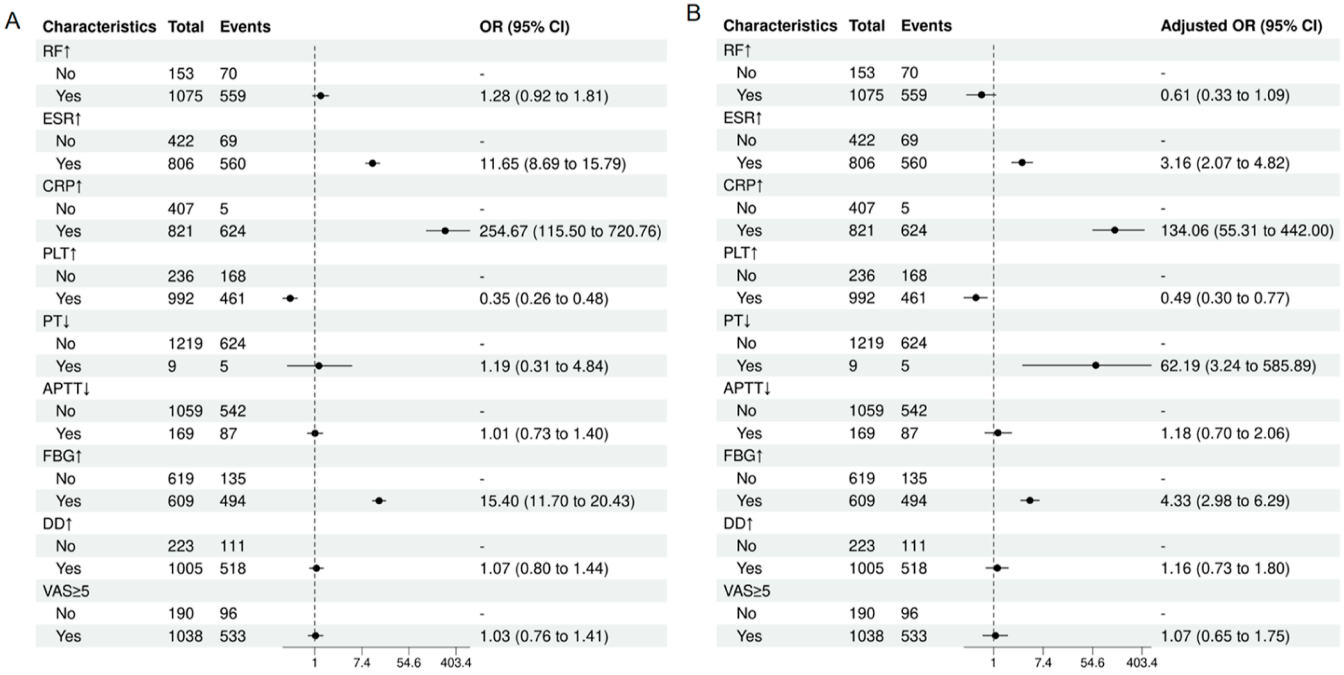

Figure 7. (A) Forest map for univariate regression analysis; and (B) forest map for multivariate regression analysis.

■ ASSOCIATED CONTENT

Data Availability Statement

The data sets in the present study can be obtained from the corresponding author on request. Data are available upon reasonable request.

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Author Contributions

F.W.: methodology, data curation, writing, editing. J.L.: design of research ideas, writing, reviewing, editing. Y.F.: project administration. J.W.: investigation, formal analysis. M.H.: software, validation. Q.H.: software, validation. X.L.: software, validation.

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Notes

The authors declare no competing financial interest.

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