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Rheumatoid Arthritis and Fibromyalgia Syndrome: A Bibliometric and Bioinformatics Perspective on Comorbidity Research

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Objective: Rheumatoid arthritis (RA) and fibromyalgia syndrome (FMS) are two common chronic pain disorders which complicate diagnosis and treatment. However, the pathological mechanisms, epidemiological characteristics, and research trends in comorbidities have not yet been systematically reviewed.

Methods: Literature related to RA and FMS published between January 2015 and December 2024 was retrieved from the Web of Science (WOS) database. VOSviewer, CiteSpace, Scimago Graphica, and Excel were used to conduct co-occurrence and clustering analyses of countries, institutions, authors, journals, and keywords to evaluate research dynamics and knowledge structures. GeneCards was used to identify shared gene targets between RA and FMS, whereas Protein-Protein Interaction (PPI) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to explore potential comorbidity mechanisms.

Results: In total, 760 articles were included in the study, with annual publication counts showing periodic fluctuations. The United States consistently ranked first in publication output and formed a highly influential collaborative network. Among the institutions, the *University of Michigan* and *Karolinska Institute* tied for first place, but the *University of Michigan* demonstrated a greater influence. *Clinical and Experimental Rheumatology* published the highest number of articles, whereas *Journal of Rheumatology* received the most citations. Author analysis revealed that Daniel J. Clauw published the most articles, received the most citations, and had the highest total link strength. Keyword analysis indicated that the research primarily focused on clinical studies with limited exploration of comorbidity mechanisms. GeneCards identified 216 RA and FMS overlapping genes. PPI and KEGG analyses suggested that inflammatory reactions and neuroactive ligand-receptor interactions play key roles in the mechanisms of comorbidity.

Conclusion: Current research on RA-FMS comorbidity lacks depth and mechanistic insight. Future studies should explore neuroimmune regulation, central sensitization, and inflammation-pain pathways through interdisciplinary collaboration across rheumatology, neuroscience, pain medicine, and bioinformatics to establish a unified comorbidity framework.

Keywords: rheumatoid arthritis, fibromyalgia syndrome, bibliometric analysis, research trends

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by systemic symmetrical polyarticular swelling, pain, and stiffness.[1] Fibromyalgia syndrome (FMS) is a chronic rheumatic disorder that manifests as widespread musculoskeletal pain, fatigue, cognitive impairment, depression, and sleep disturbances.[2] FMS is diagnosed more frequently in women.[3] Accumulated evidence from epidemiological studies, clinical observational research, and biological mechanisms has demonstrated a close association between FMS and RA.[4,5] Epidemiological studies indicate that the prevalence of FMS in the general population is approximately 2%, whereas it increases significantly to 18–24% among patients with RA, highlighting a marked comorbidity burden.[6,7] Multiple studies have demonstrated that FMS can lead to erroneous overestimation of disease activity in patients with RA, resulting in excessive testing and treatment.[8,9] From a health

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perspective, the presence of FMS in RA patients reduce the quality of life, increases functional impairment and health assessment scores.[10,11] Socioeconomically, the increased demand for multidisciplinary care, polypharmacy, more frequent healthcare visits, and diagnostic procedures, coupled with significant productivity losses, imposes a substantial burden on patients, healthcare systems, and society as a whole.

There is an increasing prospect that the development of fibromyalgia may be secondary to inflammatory arthritis.[12] Factors such as depression, sleep disturbance, and pro-inflammatory cytokines may contribute to the development of fibromyalgia in RA.[13] However, the precise etiological mechanisms and pathways underlying RA-FMS comorbidity remain unclear and require further investigation. Emerging evidence suggests potential links between chronic inflammation-mediated transitions from peripheral to centralized pain, and central sensitization.[14] Over the past two decades, advances in immunology, genetics, and pain neuroscience have improved our understanding of these disorders. However, challenges persist in delineating the pathophysiological boundaries and optimizing therapeutic strategies. Meanwhile, systematic synthesis and interdisciplinary exploration of their intersection remain scarce. Bibliometrics, a critical methodology for mapping research landscapes, enables the systematic organization and quantitative analysis of literature to visualize influential authors, institutions, and nations while identifying research hotspots, trends, and emerging directions.[15,16] Bioinformatic analysis offers a powerful tool for identifying disease correlations and molecular mechanisms. By integrating bibliometric and bioinformatic methods, research hotspots and key information derived from bibliometric analysis can be further investigated through bioinformatic approaches. This combination effectively bridges macro-level research trends with micro-level biological mechanisms, significantly enhancing the interpretation and contextualization of scientific findings. This combined approach has already been adopted in recent study, demonstrating its value in uncovering novel insights into complex research landscapes.[17] This study employed bibliometric and bioinformatics approaches to analyze the RA-FMS literature, aiming to uncover research trajectories, provide novel insights into their comorbidity mechanisms, and ultimately guide improved diagnosis and management.

Materials and Methods

Data Collection and Search Strategy

The data collection for this study was conducted on 11th April, 2025, using the Web of Science (WOS) Core Collection (https://www.webofscience.com/wos/woscc/), utilizing both the Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) databases. The search encompassed publications from 1st January, 2015, to 31st December, 2024, employing a combination of subject-specific search terms (Table 1). This was followed by a rigorous screening process that excluded irrelevant document types, including conference abstracts, conference papers, editorials, and book chapters. To ensure compatibility with the analytical tools, the final dataset was exported in two formats: plain text for CiteSpace analysis and tab-delimited for VOSviewer processing.

Analytical Tools

This study employed a multi-tool collaborative analytical framework, including CiteSpace 6.4. R1 for constructing document co-citation networks and keyword evolution analysis, VOSviewer 1.6.19 for processing collaboration networks and co-occurrence analysis, Scimago Graphica 1.0.25 for visualizing country/region collaboration networks, WPS Excel 2023 for Bar Chart Generation.

Table 1 The Topic Search Query

Set	Search Query
#1	TS=("Rheumatoid Arthritis" OR "Juvenile Rheumatoid Arthritis" OR "Juvenile Idiopathic Arthritis" OR "Seropositive Rheumatoid Arthritis")
#2	TS=("Fibromyalgia Syndrome" OR "Fibromyalgia"OR "Primary Fibromyalgia Syndrome")
#3	#1 AND #2

Bibliometric Parameter Settings

After importing the data into CiteSpace, the WOS core collection database was selected as the data source. Duplicate publications were identified and removed using CiteSpace's built-in duplication check function. The CiteSpace analysis parameters were configured as follows: (1) time slicing: 2015–2024 (annual slices); (2) threshold selection: g-index (K=10); (3) network optimization: Pathfinder algorithm for slice network simplification, with secondary simplification after network merging; and (4) visualization metrics: node diameter proportional to the occurrence frequency and link width reflecting co-occurrence strength.

VOSviewer Analysis Workflow

The VOSviewer analysis process included: (1) data preprocessing: Converting Web of Science export files to UTF-8 encoding, (2) network construction: layout optimization based on the Linlog modularity algorithm, and (3) weight calculation, which is proportional to the document count or citation frequency.

Scimago Graphica

Scimago Graphica was primarily used to analyze country collaboration networks. The GML-format country collaboration table obtained from VOSviewer was imported into Scimago Graphica with the following parameters: (1) label selection: country, and (2) cluster selection: string. The country collaboration network map was generated with node diameter mapped to publication volume per country and link thickness determined by the intercountry collaboration frequency.

WPS Excel

WPS Excel was mainly used for descriptive statistical analysis, creating bar charts from the obtained data.

Bioinformatics Analysis of RA and FMS Comorbidity

A comprehensive bioinformatic approach was employed to investigate the molecular basis of RA-FMS comorbidity. Target genes for each condition were first retrieved from the GeneCards database using disease-specific queries, followed by identification of their intersection as RA-FMS comorbidity targets.[18] Protein-protein interaction (PPI) analysis was conducted using the STRING database (v11.5) with high-confidence parameters (interaction score $\geq$0.700; Homo sapiens), and the resulting network was visualized and analyzed in Cytoscape to identify hub genes and key interactions.[19–21] Parallel Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed using clusterProfiler in R, applying rigorous statistical thresholds ($p<0.05$, with FDR correction) while excluding disease-specific pathways to focus on fundamental shared mechanisms, after which a target pathway regulatory network was constructed and visualized using Cytoscape.[22–24]

Results

Annual Publication Volume and Citation Frequency

A search of the WOS database revealed 760 research articles on FMS and RA, published between January 2015 and December 2024. The annual publication volume and frequency are shown in Figure 1. From 2015 to 2018, the number of publications gradually increased, peaking at 86 articles in 2018. A slight decline was observed in 2019, which was followed by a further decrease to 64 by 2020. The publication count reached a secondary peak of 83 articles in 2022 but subsequently dropped to 73 and 64 articles in 2023 and 2024, respectively, indicating an overall cyclical fluctuation trend in annual publications. A consistent upward trend was observed in terms of citation frequency, although the growth rate notably slowed down between 2021 and 2023.

National Contributions and Cross-Border Research Networks

The collaborative networks and country clusters were visualized using the Scimago Graphica software (Figure 2A), revealing five distinct clusters: Cluster 1, Denmark, France, Italy, Netherlands, Norway and Sweden; Cluster 2, Australia, Belgium, Brazil, Germany, Israel and Turkey; Cluster 3, Canada, China, South korea and USA; Cluster 4, Scotland and UK; and Cluster 5, Mexico and Spain. During the study period (2015–2024), the United States consistently maintained its position as the most productive country in this field, with an annual publication output ranging between 16–27 papers

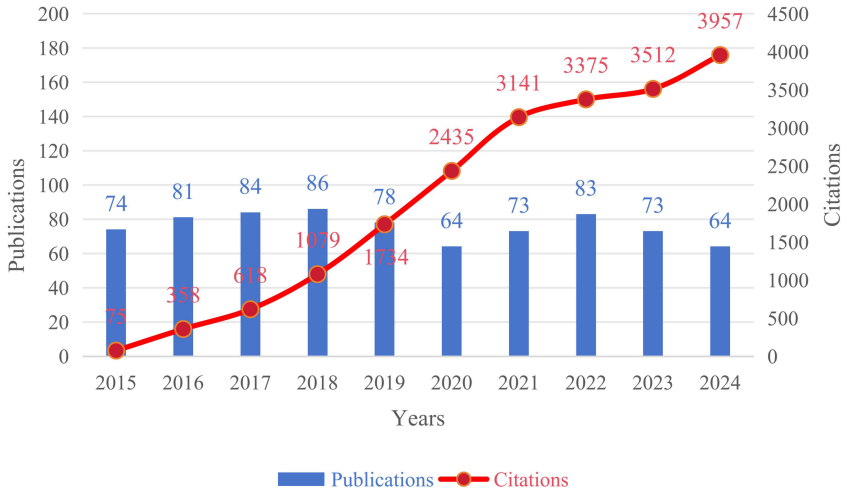

Figure 1 Annual publication volume and citation frequency from 2015 to 2024. The blue bars represent the annual number of publications, and the red line indicates the citation count of related articles.

(Figure 2B). The chord diagram analysis demonstrated the strength and structure of international collaborations, with the United States occupying the central position and exhibiting the most frequent cooperative relationships, particularly with the United Kingdom, Germany, and Canada, as evidenced by the thickest connecting lines. European countries have close interconnections and form concentrated regional collaborative networks. The overall network architecture exhibited a polycentric pattern, with the United States, United Kingdom, and several European nations serving as the primary hubs of scientific collaboration (Figure 2C).

Inter-Institutional Publication and Collaboration Networks

Collaborative network analysis of RA and FMS-related publications from 2015 to 2024 was performed using VOSviewer, resulting in the identification of seven distinct institutional clusters (Figure 3A). Cluster 1, represented by the University of Michigan, predominantly comprised institutions from the United States, including Boston University, Brigham & Women's Hospital, Cardiff University, Harvard Medical School, Johns Hopkins University, King's College London, Massachusetts General Hospital, Mayo Clinic, Northwestern University, Stanford University, University of Alabama at Birmingham, University of Florida, University of Glasgow, University of Washington and Vanderbilt University. Cluster 2, centered around Tel Aviv University, included institutions from both the United States and Europe, such as Diakonhjemmet Hospital, Klinikum Saarbrücken, the National Data Bank for Rheumatic Diseases, Paris Descartes University, Rush University, Sheba Medical Center, Technical University of Munich, the University of Pennsylvania, and the University of Twente. Cluster 3, represented by the University of Jaén, consisted of institutions from Spain, the Netherlands, and the United Kingdom, including the University of Cádiz, the University of Granada, the University of Groningen, the University of Manchester, and the Vrije Universiteit Amsterdam. Cluster 4, led by Lund University, encompasses institutions from Denmark and Sweden, namely the Copenhagen University Hospital, Spenshult Research & Development Centre, University of Gothenburg, and University of Southern Denmark. Cluster 5, represented by the University of Milan, was exclusively composed of Italian institutions, including Sapienza University of Rome, University of Messina, University of Pisa, and Polytechnic University of Marche. Cluster 6, centered on the Karolinska Institute, included institutions from Sweden and Canada, specifically the Karolinska University Hospital, McGill University, and the University of Toronto. Finally, Cluster 7, represented by Ghent University, comprised institutions from the Netherlands, Belgium, and Australia, including Maastricht University, University Hospital Brussels, and the University of Sydney. Notably, the Karolinska Institute, University of Michigan, and University of Washington occupied central positions within the network, exhibiting dense connectivity and demonstrating a strong collaborative influence. The analysis revealed particularly robust connections between Nordic and North American institutions, while certain

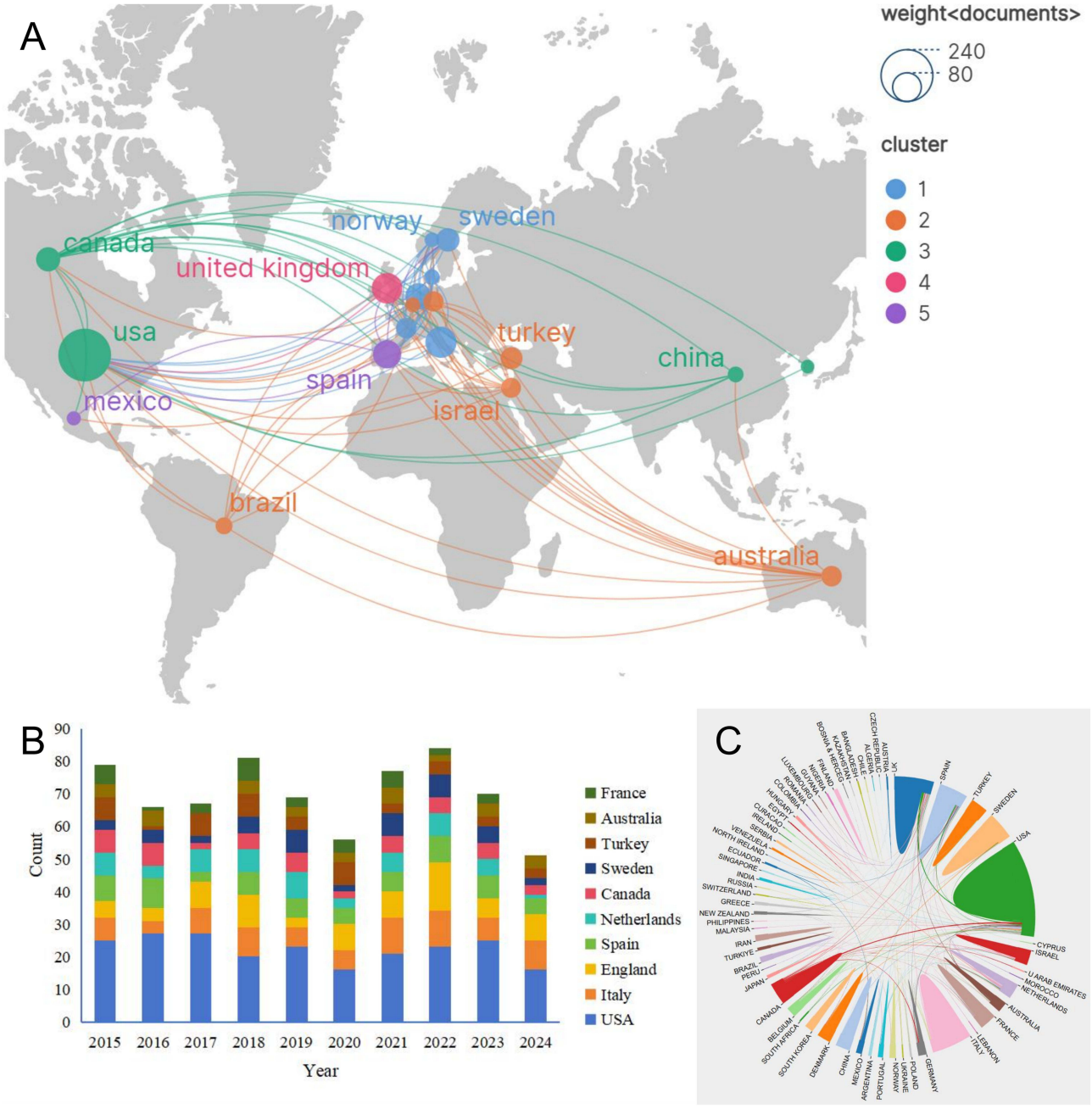

Figure 2 (**A**) Country collaboration network based on co-authorship links. (**B**) Annual publication counts of the top 10 productive countries (2015–2024). (**C**) International collaboration chord diagram illustrating inter-country linkages. In the international collaboration network, the node size corresponds to the publication output, while the connection width reflects the collaboration intensity.

universities, such as Tel Aviv University and Lund University, served as important bridges connecting different collaborative clusters.

The top ten most productive institutions were the University of Michigan (20 publications), Karolinska Institute (20 publications), Tel Aviv University (19 publications), Lund University (17 publications), University of Gothenburg (16 publications), University of Washington (16 publications), University of Jaén (14 publications), University of Manchester (14 publications), University of Twente (14 publications), and King's College London (13 publications) (Table 2). Further visualization of the relationship between publication count and citation frequency (Figure 3B) demonstrated that although the University of Michigan and Karolinska Institutet had identical publication counts, the former significantly

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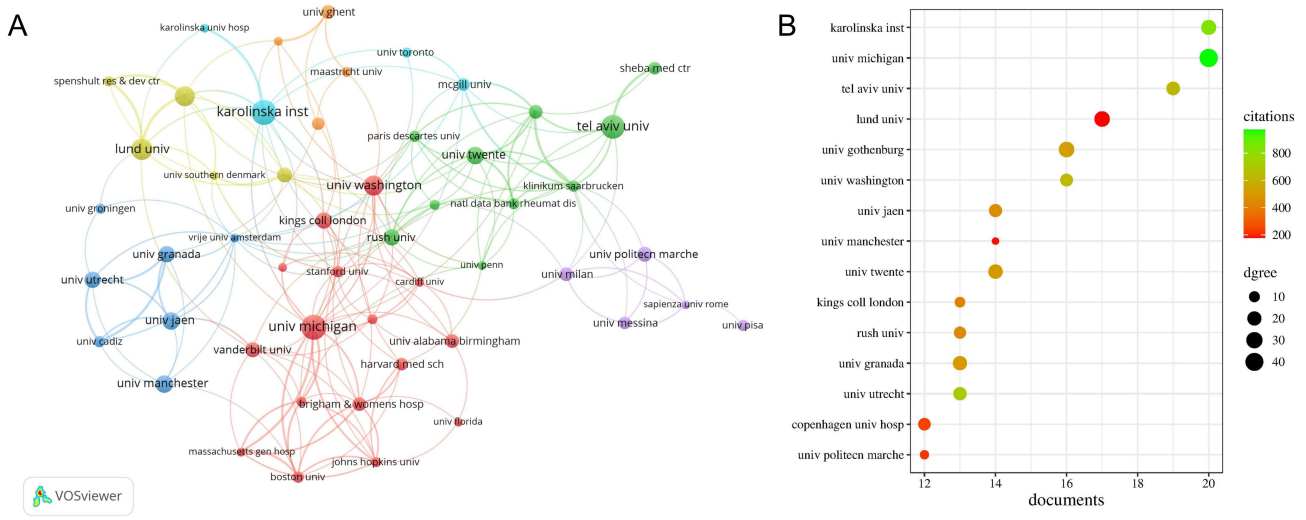

Figure 3 (**A**) Network and clustering patterns among institutions. (**B**) Bubble plot visualizing institutional publications and citations.

outperformed the latter in terms of total citations (972 citations) and network centrality, reflecting its greater scientific impact. Tel Aviv University, despite having slightly fewer publications (19), achieved a substantial citation impact (626 citations), indicating the effective dissemination of its research findings within the field. By contrast, some institutions with relatively high publication outputs, such as the University of Manchester, demonstrated a more limited influence in terms of citation metrics.

Journal Publication and Citation Analysis

In terms of the number of published articles, the top 10 journals were *Clinical and Experimental Rheumatology* (44 articles), *Clinical Rheumatology* (33), *Arthritis Care & Research* (31), *Rheumatology* (24), *Rheumatology International* (21), *Journal of Rheumatology* (20), *Arthritis Research & Therapy* (16), *International Journal of Rheumatic Diseases* (14), *PLOS ONE* (13), and *Seminars in Arthritis and Rheumatism* (12). The publication counts, citation frequencies, impact factors, and JCR quartiles for the journals are presented in Table 3. Among the top ten journals, the impact factors were generally low (range: 2.4–4.7), with JCR partitions predominantly in Q2 and Q3; only *Rheumatology* ranked in Q1. However, the average citation counts of these articles significantly exceeded the journals' impact factors, suggesting that research on RA and FMS substantially enhanced journal influence. VOSviewer-based co-citation analysis revealed that *Clinical and Experimental Rheumatology, Arthritis Care & Research, Journal of Rheumatology*, and *Rheumatology International* occupied central positions in the network, exhibiting high node density and robust connectivity, underscoring their pivotal roles in disseminating research on this topic (Figure 4A).

Table 2 Top 10 Institution with the Highest Number of Publications

Rank	Institution	Documents	Citations	Total Link Strength
1	University of Michigan	20	972	41
2	Karolinska Institute	20	838	23
3	Tel Aviv University	19	626	18
4	Lund University	17	177	26
5	University of Washington	16	637	15
6	University of Gothenburg	16	522	26
7	University of Twente	14	505	21
8	University of Jaén	14	458	16
9	University of Manchester	14	182	6
10	King's College London	13	406	9

Table 3 Top 10 Journals by Publication Volume

Source	Documents	citations	Citations/Documents	IF(2024)	JCR Partition(2024)
Clinical and Experimental Rheumatology	44	557	12.7	3.4	Q3
Clinical Rheumatology	33	744	22.5	2.9	Q3
Arthritis Care & Research	31	837	27	3.7	Q2
Rheumatology	24	682	28.4	4.7	Q1
Rheumatology International	21	463	22	3.2	Q2
Journal of Rheumatology	20	508	25.4	3.6	Q2
Arthritis Research & Therapy	16	640	40	4.4	Q2
International Journal of Rheumatic Diseases	14	330	23.6	2.4	Q3
PLOS ONE	13	725	55.8	2.9	Q2
Seminars in Arthritis and Rheumatism	12	393	32.8	4.6	Q2

Further analysis of the cited journals revealed that the top 10 most frequently cited journals were *The Journal of Rheumatology* (n=1,970), *Pain* (n=1,837), *Annals of the Rheumatic Diseases* (n=1,645), *Arthritis Care & Research* (n=1,233), *Arthritis & Rheumatology* (n=1,076), *Rheumatology* (n=1,075), *Clinical and Experimental Rheumatology* (n=826), *Arthritis Research & Therapy* (n=657), *Rheumatology International* (n=622), and *Clinical Rheumatology* (n=595) (Table 4, Figure 4B).

Scholarly Influence of High-Productivity Authors

Using VOSviewer software, we conducted a collaborative network and academic influence analysis of leading authors in this research field (Figure 5A). The top 10 most productive authors are presented in Table 5 and Figures 5B and C, showing their publication counts, citation frequencies, and Total Link Strength. The most prolific author was Daniel J. Clauw, with 16 publications receiving 873 citations, and a Total Link Strength of 43, occupying a central position in the author collaboration network. The ranking second was Yvonne C. Lee, with 12 publications cited 295 times and collaboration strength of 38. These two authors formed a high-density collaborative network core. Other notable contributors included Eva Kosek (10 publications, 649 citations), whose collaborative cluster primarily comprised Nordic scholars, and Winfried Haeuser (7 publications, 463 citations), who demonstrated distinct cross-group collaboration patterns by establishing connections with authors from multiple regions. Jo Nijs (seven publications, 502 citations) and Stefan Duschek (seven publications, 317 citations) also achieved a significant research impact despite moderate publication output. Sarzi-Puttini and Atzeni formed collaborative clusters. Notably, Frederick Wolfe showed the highest average citation count (79.6 citations per publication), followed by Brian Walitt (72.9), and Jo Nijs (71.7).

Keyword Clustering and Emerging Research Hotspots

From 2015 to 2024, keyword co-occurrence analysis revealed that this research field has a relatively clear thematic structure and evolutionary trajectory. The cluster network and timeline diagrams constructed using CiteSpace identified 12 clusters (Figure 6A) representing different research subdirections. Among them, Cluster #0 “rheumatic diseases” was the largest cluster, encompassing keywords such as symptoms, population, rheumatic diseases, and questionnaire, forming the core foundation of this field; Cluster #1 “copcord” included keywords: classification, arthritis, criteria, risk; Cluster #2 “systematic review” was associated with keywords including fibromyalgia syndrome, musculoskeletal pain, clinical trials, stress, and low back pain; Cluster #3 “chronic pain” contained keywords chronic widespread pain, women, chronic pain; Cluster #4 “ultrasound” featured keywords inflammation, impact, association, health, concomitant fibromyalgia; Cluster #5 “neuropathic pain” related to keywords neuropathic pain, knee osteoarthritis, central sensitization; Cluster #6 “quality of life” emphasized health-related quality of life assessment, containing keywords quality of life, fibromyalgia, fatigue, rheumatoid arthritis; Cluster #7 “country” mainly addressed geographical and population-level aspects, including keywords meta-analysis, back pain, management; Cluster #8 “psoriatic arthritis” included psoriatic arthritis, ankylosing spondylitis, disease activity, depression; Cluster #9 “reliability” contained keywords validity,

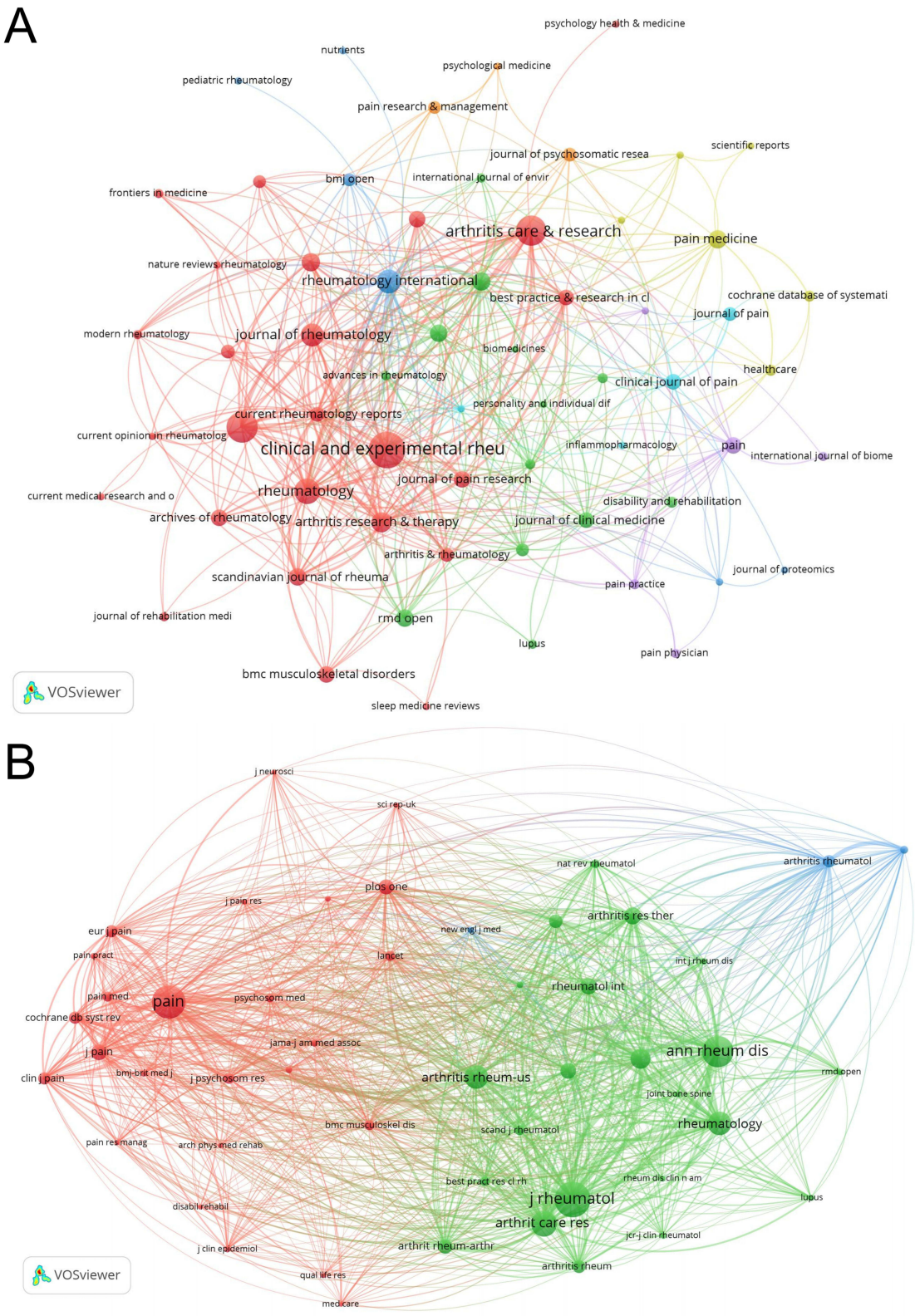

Figure 4 (**A**) Journal co-occurrence network analysis of FMS and RA publications. (**B**) Journal co-citation network analysis of FMS and RA publications.

Table 4 Top 10 Most Frequently Cited Journals

Source	Citations	IF(2024)	JCR Partition(2024)
The Journal of Rheumatology	1970	3.6	Q2
Pain	1837	5.9	Q1
Annals of the Rheumatic Diseases	1645	20.3	Q1
Arthritis Care & Research	1233	3.7	Q2
Arthritis & Rheumatology	1076	11.4	Q1
Rheumatology	1075	4.7	Q1
Clinical and Experimental Rheumatology	826	3.4	Q3
Arthritis Research & Therapy	657	4.4	Q2
Rheumatology International	622	3.2	Q2
Clinical Rheumatology	595	2.9	Q3

disability, american college; Cluster #10 "disease" focused on comprehensive clinical indicator research with disease, efficacy, prevalence; Cluster #11 "polysymptomatic distress" included the keyword validation (Figure 6B).

The keyword co-occurrence network (Figure 6C) displays a dense co-occurrence pattern. High-frequency keywords including "rheumatoid arthritis", "fibromyalgia", "pain", "quality of life", "chronic pain", "prevalence", "depression", and "disease activity" were all located in central or semi-central positions of the map, with larger node sizes indicating their higher frequency in research. The "rheumatoid arthritis" node was the largest, with extensive radiating connections, surrounded by related keywords such as "prevalence", "pain", "quality of life", "systemic lupus erythematosus", and "chronic pain", forming a core semantic cluster. Keywords "classification", "criteria", "health", "epidemiology", and "population" were distributed in the left region with high aggregation density, where some nodes like "classification" and "criteria" showed tight connections, forming independent local sub-networks. "Depression" and "disease activity" were located at the edges of the map but with significant node rings, indicating their high usage frequency in literature but fewer co-occurrence connections. Keywords like "central sensitization" and "symptoms" maintained stable co-occurrence relationships with the core area of the map, serving as bridging connections. The node ring colors represented the year of first appearance, with red-orange nodes mainly concentrated from 2022 to 2024, representing active keywords in recent three years, such as "rheumatoid arthritis", "fibromyalgia", "pain", and "quality of life". Most high-frequency keywords in the diagram show multilayered rings, indicating persistent co-occurrence across multiple years.

Combined with burst term analysis, this study further revealed the phased evolutionary characteristics of research themes. The figure lists the top 25 keywords by burst strength for 2015–2024 and their corresponding time intervals. Among them, keywords that began bursting from 2015 included: "united states" (3.5), "population" (2.89), "reliability" (2.85), "scale" (2.6), "impact questionnaire" (2.6), and "risk" (3.09), most of which ended their burst periods before 2016 with relatively short durations. In 2016, a "randomized controlled trial" (RCT) (2.51) was added, which continued to burst until 2019. Keywords entering the burst phase in 2017 included: "clinical trials" (4.83), "disease activity score" (4.03), "general population" (3.68), "28 joints" (2.75) and "systemic lupus erythematosus" (2.68). Keywords starting to burst in 2018 were "posttraumatic stress disorder" (3.39); in 2019 they were "chronic musculoskeletal pain" (3.03) and "risk factors" (2.51), with relatively longer durations. Burst keywords in 2020 included "impact" (4.04), "care" (2.73), "meta analysis"(3.38) and "axial spondyloarthritis" (2.64). Keywords entering the burst phase after 2022 included: "management" (3.38), "remission" (3.34), "stress" (2.96), "multiple sclerosis" (2.92), and "irritable bowel syndrome" (2.63), mostly remaining as hot terms still in burst status in 2024 (Figure 6D).

Bioinformatics Analysis of RA and FMS Comorbidity

A total of 302 FMS-related genes and 6,704 RA-associated genes were identified in the GeneCards database, with 216 RA-FMS comorbidity targets obtained through intersection analysis. The protein-protein interaction (PPI) network constructed from these comorbidities (Figure 7A) revealed the top 20 hub genes: IL6 (degree=55), IL1B (52), TNF (52), INS (42), IFNG (41), IL10 (40), CXCL8 (37), CCL2 (35), IL2 (34), TLR4 (34), ALB (33), IL4 (31), CRP (29), POMC (29), IL17A (28), BDNF (27), ICAM1 (27), IGF1 (27), IL18 (27), and CXCL10 (26)

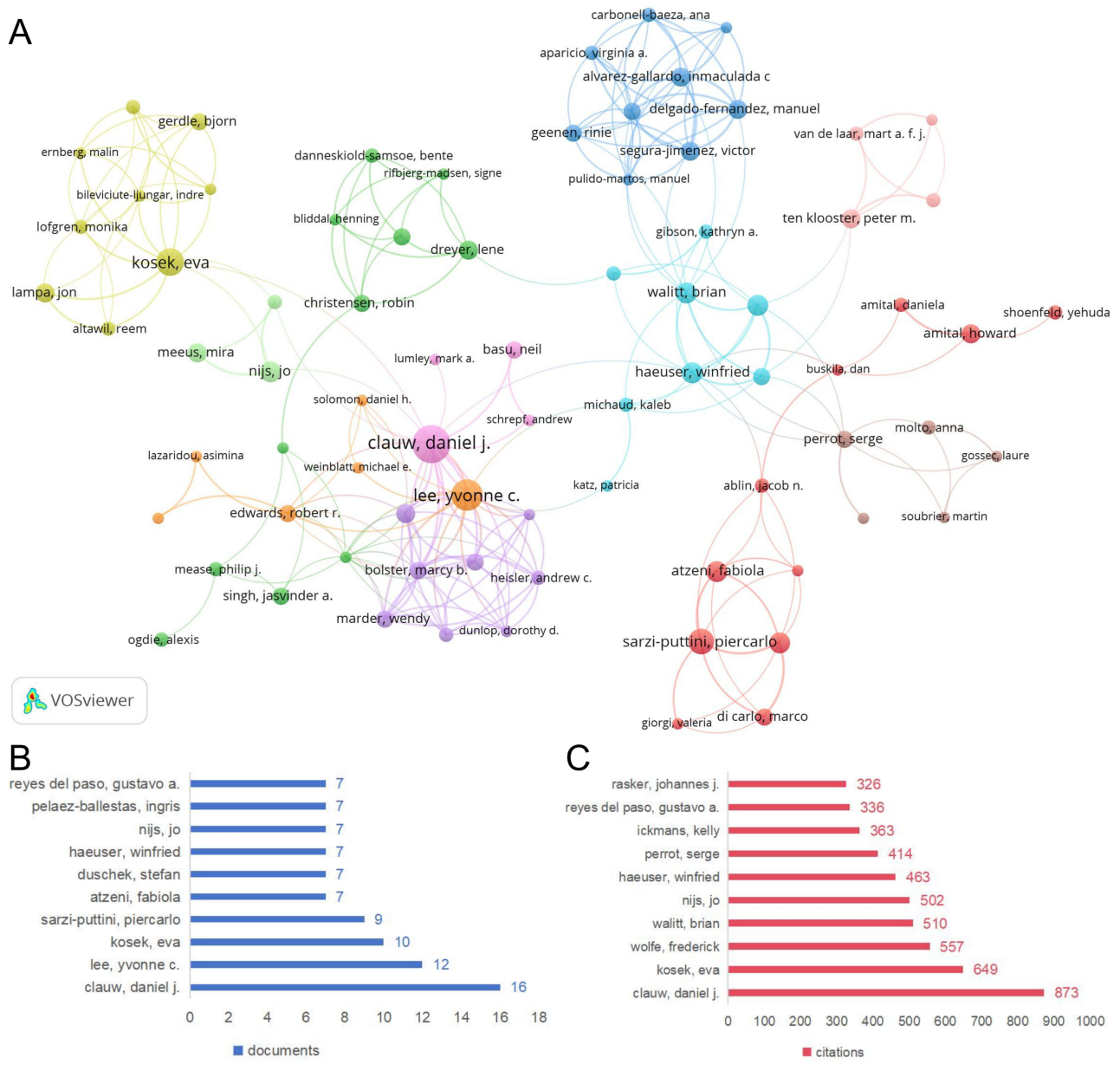

Figure 5 (**A**) Author collaboration network in the research field based on co-authorship links. (**B**) Top 10 authors by publication volume. (**C**) Top 10 authors by citation count.

(Figure 7B). KEGG pathway enrichment analysis of the RA-FMS comorbidity targets identified 67 signaling pathways, including 35 non-disease-related pathways after exclusion. The most significantly enriched pathways (ranked by ascending p-values) were neuroactive ligand-receptor interactions, cytokine-cytokine receptor interactions, viral protein interactions with cytokines and cytokine receptors, IL-17 signaling pathway, hematopoietic cell lineage, calcium signaling pathway, inflammatory mediator regulation of TRP channels, cytosolic DNA-sensing pathway, cAMP signaling pathway, HIF-1 signaling pathway, serotonergic synapse, TNF signaling pathway, JAK-STAT signaling pathway, NF-kappa B signaling pathway, Th17 cell differentiation, NOD-like receptor signaling pathway, intestinal immune network for IgA production, and the PI3K-Akt signaling pathway (Figures 7C and D).

Table 5 Top 10 Most Productive Authors by Publication Count

Author	Documents	Citations	Total link strength	Avg.Citition
Clauw, daniel j.	16	873	43	54.6
Lee, yvonne c.	12	295	38	24.6
Kosek, eva	10	649	18	64.9
Sarzi-puttini, piercarlo	9	152	13	16.9
Wolfe, frederick	7	557	19	79.6
Walitt, brian	7	510	17	72.9
Nijs, jo	7	502	11	71.7
Haeuser, winfried	7	463	18	66.1
Reyes del paso, gustavo a.	7	336	11	48.0
Duschek, stefan	7	317	12	45.3

Discussion

Synovial tissue serves as the primary target organ in rheumatoid arthritis; however, this systemic autoimmune disease often involves multiple extra-articular manifestations and psychological alterations.[25,26] Following treatment, while inflammatory states become effectively controlled in some patients with RA, residual pain persists and continues to impact the quality of life.[27–29] This phenomenon is closely associated with RA-induced damage to cartilage, tendons, and ligaments, and non-inflammatory central sensitization mechanisms may also play significant roles, as observed in RA patients with fibromyalgia syndrome. FMS may complicate the overall health scores and tender joint count assessments in patients with RA, potentially leading to unnecessary clinical interventions[8,30.] It is also a challenging diagnosis in the late pediatric age and poses significant diagnostic issues with other less defined disorders, such as somatoform disorders and pseudo-neurological conditions, which may represent undiagnosed FM and are often overlooked.[31,32] The anatomical overlap between RA-swollen joints and FMS tender points creates diagnostic challenges for early FMS identification in patients with RA.

Bibliometric research demonstrates that from 2015 to 2024, publication volumes in RA and FMS-related fields maintained overall cyclical fluctuation trends with steadily increasing citation counts, indicating the formation of sustained research hotspots and knowledge accumulation effects, with gradually strengthening academic influence. At the national level, the United States consistently ranked first in publication output throughout the decade, reflecting its central position in research, whereas Italy and the United Kingdom showed rapid development in this field. Close international collaborations among the United States, Italy, the United Kingdom, and Spain demonstrate the important role of transnational cooperation in advancing scientific progress. Institutionally, Sweden's Karolinska Institute and the University of Michigan in the United States were tied for the first publication volume, with the University of Michigan ranking first in influence, demonstrating significant research capabilities and international collaboration potential.

Among these journals, *Clinical and Experimental Rheumatology* have published the most research papers. Regarding cited papers, the *Journal of Rheumatology* ranked first in both citation counts and co-citation frequency, indicating its key role in constructing the RA and FMS knowledge system. At the author level, Clauw published the most research papers, whereas Wolfe's work received the most average citations, demonstrating their notable activity and influence in the field. A co-cited reference analysis revealed that highly cited papers mainly focused on FMS guidelines and reviews, with the top ten co-cited publications covering multiple research directions, including meta-analyses of FMS and RA, pain studies in RA patients, the impact of fibromyalgia on disease activity and functional measurements in RA patients, cross-sectional studies of fibromyalgia status in RA, and refractory RA.

Analysis of burst keywords showed that early research focused on methodology and epidemiology, laying the foundations for subsequent clinical practice. As research has deepened, disease assessment tools and comorbidity relationships have been emphasized, with the rise of meta-analyses indicating a growing need for evidence integration. Research perspectives have gradually shifted from biomedical to biopsychosocial models, highlighting psychosocial risk factors and reflecting increased attention to psychological dimensions in patients with chronic pain. Further cluster

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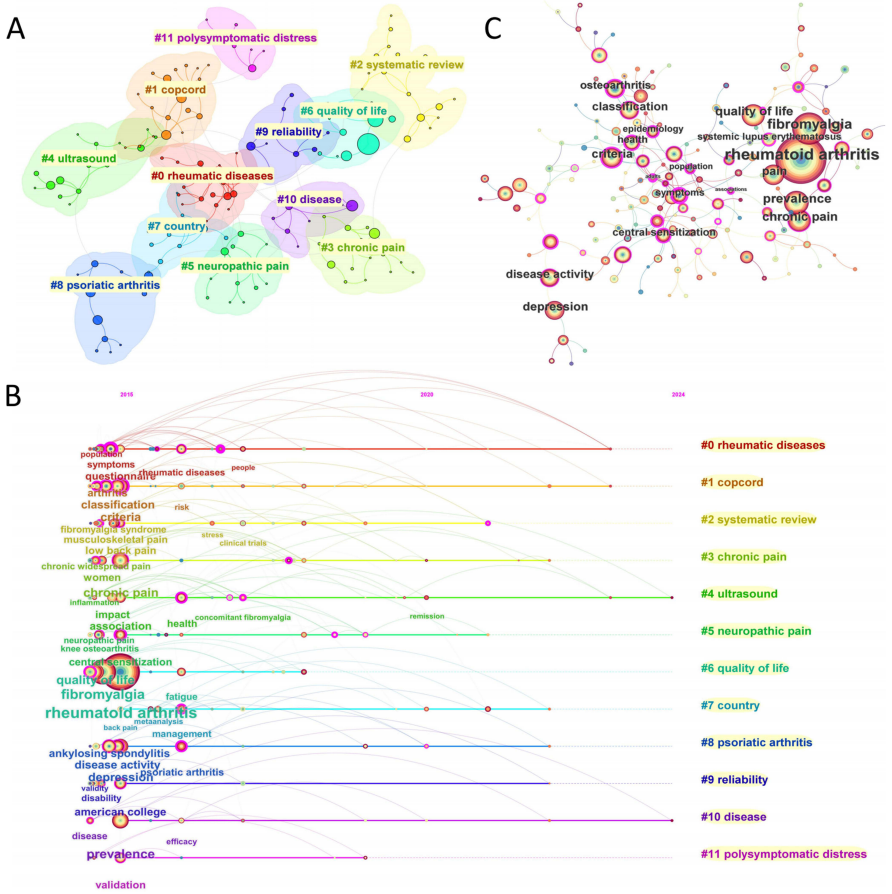

D **Top 25 Keywords with the Strongest Citation Bursts**

Keywords	Year	Strength	Begin	End	2015 - 2024
united states	2015	3.5	**2015**	2018	
population	2015	2.89	**2015**	2016	
reliability	2015	2.85	**2015**	2016	
scale	2015	2.6	**2015**	2016	
impact questionnaire	2015	2.6	**2015**	2016	
risk	2016	3.09	**2016**	2018	
randomized controlled trial	2016	2.51	**2016**	2019	
clinical trials	2017	4.83	**2017**	2018	
disease activity score	2017	4.03	**2017**	2019	
general population	2017	3.68	**2017**	2018	
28 joints	2015	2.75	**2017**	2018	
systemic lupus erythematosus	2015	2.68	**2017**	2018	
posttraumatic stress disorder	2018	3.39	**2018**	2019	
chronic musculoskeletal pain	2019	3.03	**2019**	2021	
risk factors	2015	2.51	**2019**	2021	
impact	2015	4.04	**2020**	2021	
metaanalysis	2016	3.38	**2020**	2024	
care	2020	2.73	**2020**	2024	
axial spondyloarthritis	2020	2.64	**2020**	2021	
patient	2021	2.92	**2021**	2024	
management	2016	3.38	**2022**	2024	
remission	2020	3.34	**2022**	2024	
stress	2017	2.96	**2022**	2024	
multiple sclerosis	2015	2.92	**2022**	2024	
irritable bowel syndrome	2015	2.63	**2022**	2024	

Figure 6 (**A**) Cluster analysis of keywords. (**B**) Temporal evolution of keywords. (**C**) Co-occurrence network of keywords. (**D**) Burst detection of keywords.

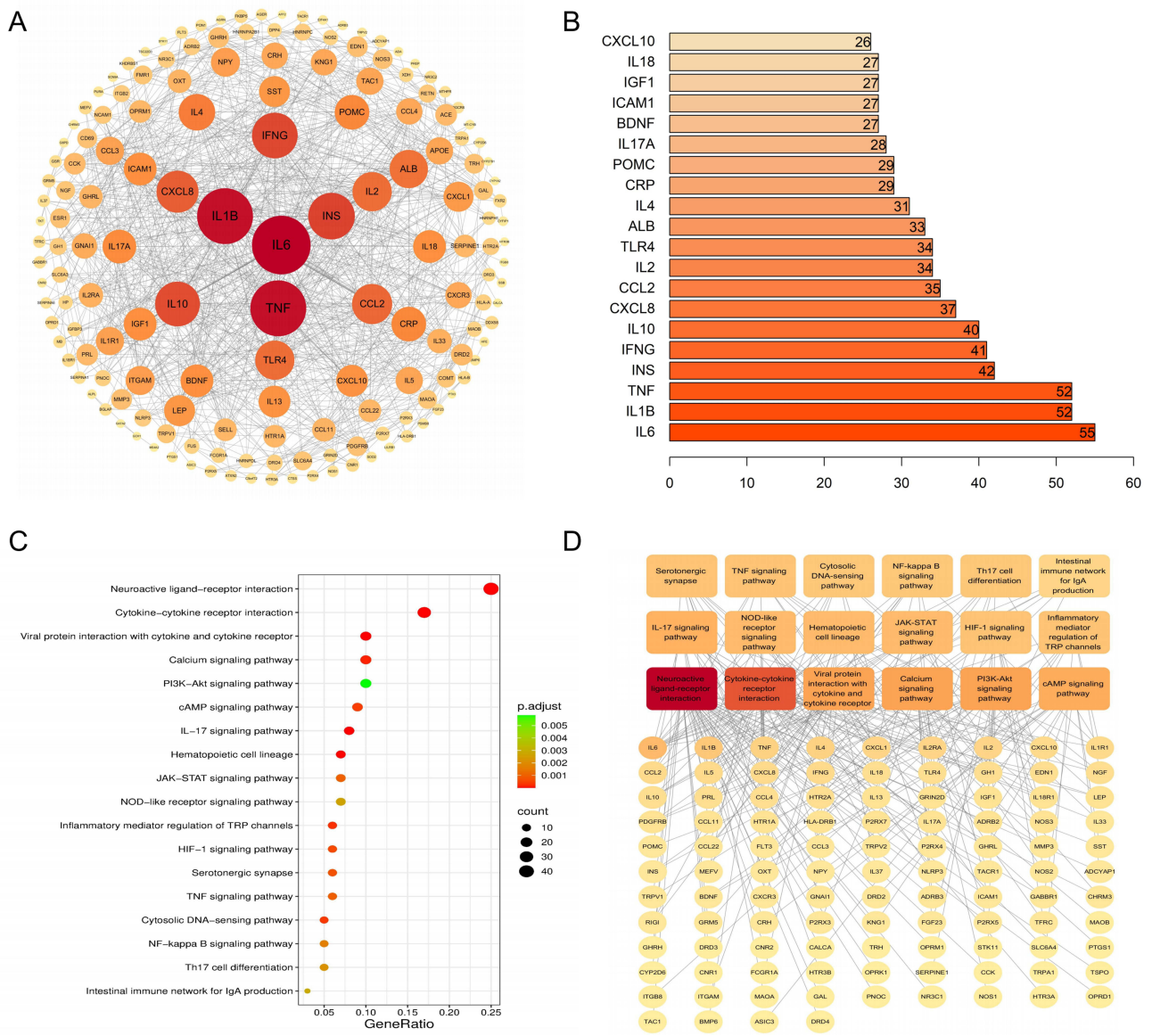

Figure 7 (**A**) Visualization of PPI network for RA-FMS comorbidity targets using Cytoscape. (**B**) Bar graph of top 20 hub gene targets. (**C**) Top 18 significantly enriched signaling pathways from KEGG analysis. (**D**) Target-pathway interaction network.

analysis of keywords revealed themes including rheumatic diseases and chronic pain describing symptom patterns and population characteristics, neuropathic pain exploring central sensitization mechanisms, research methods and evidence integration through systematic reviews and meta-analyses, comorbidity studies through conditions such as psoriatic arthritis, and diagnostic standard optimization through reliability measures. At the management level, quality of life and community programs have explored collaborative models from the perspectives of individual patients and public health. Future research should integrate technologies for mechanistic exploration and emphasize comprehensive disease management to address the challenges in comorbidity complexity, personalized treatment, and psychosocial support for chronic rheumatic diseases.

Given the widely recognized but mechanistically insufficiently studied correlation between FMS and RA, we conducted further bioinformatics exploration. Through GeneCards database analysis, we obtained RA- and FMS-related gene targets, identifying intersection genes as RA-FMS association targets for subsequent PPI and KEGG pathway enrichment analyses. The PPI results identified the top 20 key targets, including IL6, IL1B, TNF, INS, IFNG, IL10, CXCL8, CCL2, IL2, TLR4, ALB, IL4, CRP, POMC, IL17A, BDNF, ICAM1, IGF1, IL18, and CXCL10. Among

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these, IL2, IL6, IL1B, TNF, IFNG, IL17A, and IL18 are proinflammatory cytokines that play crucial roles in RA joint inflammation and FMS pathogenesis.[33–36] IL10 and IL4 are anti-inflammatory cytokines that are potentially important in regulating excessive inflammation, with some studies suggesting that reduced anti-inflammatory cytokine levels may represent potential peripheral sensitization factors.[37] CXCL8, CCL2, and CXCL10 function as chemokines involved in recruiting immune cells to inflammatory sites, and CXCL10 is considered a sensitive marker of disease activity in patients.[38,39] TLR4 acts as a pattern recognition receptor that participates in innate immune responses and its over-activation can trigger various inflammatory factors.[40] ICAM1 mediates T cell activation and cellular adhesion, and plays important roles in promoting inflammatory site adhesion and regulating immune responses. CRP is an acute-phase protein related to inflammation and tissue damage, and serves as a marker for assessing systemic inflammatory responses.[41–44] While RA represents an autoimmune-related systemic inflammatory disease and FMS has traditionally been viewed as non-inflammatory, recent research increasingly highlights the crucial role of low-intensity inflammatory responses in FMS. Therefore, PPI analysis results suggest that the comorbidity mechanisms between the two conditions are closely related to inflammatory factors.

KEGG analysis identified key signaling pathways in RA-FMS comorbidity, with the serotonergic synapse pathway mainly mediating serotonin-regulated neurotransmission processes through synthesis, release, receptor subtype-specific binding, SERT transporter reuptake, dynamic regulation of mood, pain perception, and cognitive function.[45–47] This imbalance is closely correlated with central sensitization and neuroinflammation in conditions, such as depression and fibromyalgia. Through receptor subtype specificity, neuron-glia interactions, and regulation of the inflammatory micro-environment, this pathway serves as a molecular bridge that connects inflammation with central sensitization. Other significant pathways, including the TNF signaling pathway, JAK-STAT signaling pathway, NF-kappa B signaling pathway, Th17 cell differentiation pathway, NOD-like receptor signaling pathway, intestinal immune network for IgA production, and PI3K-Akt signaling pathway, involve various inflammatory processes.[48–52] The JAK-STAT, NOD-like receptor, and PI3K-Akt pathways serve as upstream regulators of NF-kappa B signaling, controlling its activation.[53,54] NF-κB pathway activation subsequently promotes the transcription of various inflammatory factors and chemokines including IL6, IL1B, TNF, IL18, CXCL8, CCL2 and CXCL10.[55]

In summary, the comorbidity mechanisms of FMS and RA are closely associated with inflammatory responses. FMS has traditionally been viewed as a central sensitization-dominated condition. For example, duloxetine, which is approved by the US Food and Drug Administration for treating this condition, exerts its analgesic effect by inhibiting the inhibit reuptake of norepinephrine and serotonin in the descending inhibitory pathways of the brainstem.[56] Recent research has increasingly highlighted the role of immune inflammation in its pathogenesis. The inflammatory microenvironment created by RA may enhance pain perception through two mechanisms: direct induction of peripheral nociceptor sensitization, and synergistic strengthening of abnormal excitability in the central nervous system. Neuroinflammatory processes featuring abnormal neuroimmune cell interactions may be the key factors that exacerbate FMS symptoms. These mechanistic insights open new avenues for developing targeted therapies, such as combining anti-inflammatory agents with neuromodulatory drugs to concurrently address peripheral and central mechanisms of pain. Additionally, identifying key neuroimmune biomarkers may not only improve early diagnosis of FMS in RA patients but also facilitate personalized treatment strategies aimed at specific inflammatory and neural pathways. This study has several limitations that should be acknowledged. First, it relied solely on English language publications from the Web of Science database, which may lead to the omission of some important non-English research outputs and limit the comprehensiveness of the findings. Second, although bibliometrics provide valuable quantitative insights, it does not fully capture the depth or quality of individual studies. Future research should address these constraints by incorporating additional data sources and employing complementary analytical methods to achieve a more comprehensive evaluation of research progress and emerging trends in RA and FMS studies.

Conclusions

This study employed bibliometric and bioinformatics approaches to analyze the research landscape and emerging frontiers of RA and FMS over the past decade while investigating their potential shared targets and pathways. These findings may contribute to improved disease management and therapeutic strategies while providing mechanistic

directions for future research. Our analysis demonstrates that RA-FMS research gained increasing academic influence during this period, with major research foci encompassing disease symptomatology, methodological approaches, comorbid associations with other conditions, quality of life, and psychological dimensions. Bioinformatics investigations further suggest that the "peripheral inflammation-central sensitization" axis may represent the core mechanistic link between FMS and RA, suggesting that clinical management should integrate anti-inflammatory and central analgesic strategies, promote the establishment and development of interdisciplinary collaborative diagnosis and treatment models.

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Disclosure

The authors report no conflicts of interest in this work.

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