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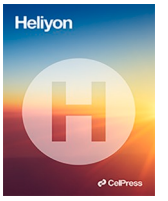

Research article

Global research trends in precision-targeted therapies for systemic lupus erythematosus (2003–2023): A bibliographic study

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a persistent inflammatory disease caused by an autoimmune response that predominantly affects multiple organs and systems. Growing evidence highlights the critical role of precision-targeted therapies in the management of SLE. Surprisingly, only a handful of bibliometric studies have thoroughly assessed this area. This study attempts to assess the global landscape of literature output and research trends related to precision-targeted therapy for SLE.

Method: Publications related to precision-targeted therapy for SLE from 2003 to 2023 were searched in the Web of Science Core Collection (WoSCC) database. VOSviewers, CiteSpace and the R package "bibliometrix" were used to perform this bibliometric analysis.

Results: A total of 3700 papers were retrieved, showing a steady annual increase in publications from 2003 to 2022. The United States led the field with the highest number of papers (36.1 %) and secured the top position in terms of citation frequency (59,889) and H-index (115). Anhui Medical University System claimed the top spot with an impressive output of 70 papers. Principal investigators Tsokos, George C. C., and Lu, Qianjin led the research effort. Among the journals, Frontiers in Immunology stood out, publishing the highest number of articles with 191. In particular, precision-targeted therapy for SLE has become a major research focus in recent years, covering aspects such as T cells, B cells, oxidative stress, remission, and PHASE-III.

Conclusion: This bibliometric study of ours systematically analyses research trends in precision targeted therapy for systemic lupus erythematosus, and this information identifies the research frontiers and hot directions in recent years and will serve as a reference for scientists working on targeted therapies.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multiorgan and multisystem autoimmune disease characterised by increased B- and T-cell activity and inadequate antibody clearance leading to the accumulation of immune complexes in tissues, resulting in a wide

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variable symptoms - from fatigue, joint soreness and rash to more severe diversity damage to multiple systems and organs [1]. Worldwide, the prevalence of SLE in adults ranges from 0.03 % to 0.15 % [2]. Historically, the 5-year survival rate for SLE patients was only 50 %, but recent advances have increased the 10-year survival rate to over 90 % [3,4]. Traditional treatments include the use of non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants and hormones. However, these approaches are associated with a number of side effects and inherent limitations.

Currently, the main treatments for systemic lupus erythematosus (SLE) include glucocorticoids, nonsteroidal anti-inflammatory drugs, hydroxychloroquine and immunosuppressants [5]. Besides that, these treatments mainly control symptoms and do little to address the underlying problem. In addition, the wide range of non-specific effects of these drugs raises concerns about associated toxicity. Targeted therapies for SLE have been investigated in several areas, including B-cell and T-cell targeted therapies.B-cell targeted therapies have shown significant efficacy by inhibiting or eliminating abnormal B cells. For example, the anti-CD20 monoclonal antibody rituximab (Rituxan) is widely used in the treatment of SLE and has shown significant clinical efficacy [6,7].T-cell-targeted therapies affect the balance of immune responses mainly by modulating T-cell function [8]. In contrast, immunomodulatory therapies treat SLE by modulating the activity and function of the immune system. As our understanding of the pathogenesis of SLE grows, researchers are exploring precision therapeutics that target specific aspects of disease pathogenesis. The search for novel targeted drugs is imminent, with the aim of improving therapeutic efficacy. This quest has long been a central and vibrant area of research in the treatment of SLE.

Bibliometrics serves as a methodological approach to examine the output and standing of publications within a given field, encompassing both quantitative and qualitative dimensions. This includes the study of countries, authors, journals, institutions, references, keywords, and more [9,10]. Bibliometric tools such as CiteSpace [11], VoSviewer [12], and the R package “bibliometrix” [13] are commonly used to visualise the results of literature analysis. While precision-targeted therapy has been bibliometrically explored in diseases such as cancer [14,15] and myasthenia gravis [16], such analyses have not yet emerged in the context of SLE. Furthermore, there are only two bibliometric studies on SLE to date, one of which briefly analyzed 14,053 articles included in PubMed from 2002 to 2011 [17], demonstrating through the gradual increase in the number of articles that SLE has become an area of interest. Another study outlined the current status of global SLE research from 2013 to 2022 using a systematic bibliometric approach [18]; however, no bibliometric studies were identified that explicitly addressed areas related to precision-targeted therapy for SLE. Therefore, to further explore this area, our study aimed to conduct an in-depth bibliometric analysis of publications and relevant information related to precision targeted therapy for SLE over the past two decades. (August 5, 2003–August 5, 2023). Our target is to make the identification of resercher that made the main contribution to relevant research in the field, the current state of research, and to forecast trends and prospects for future research.

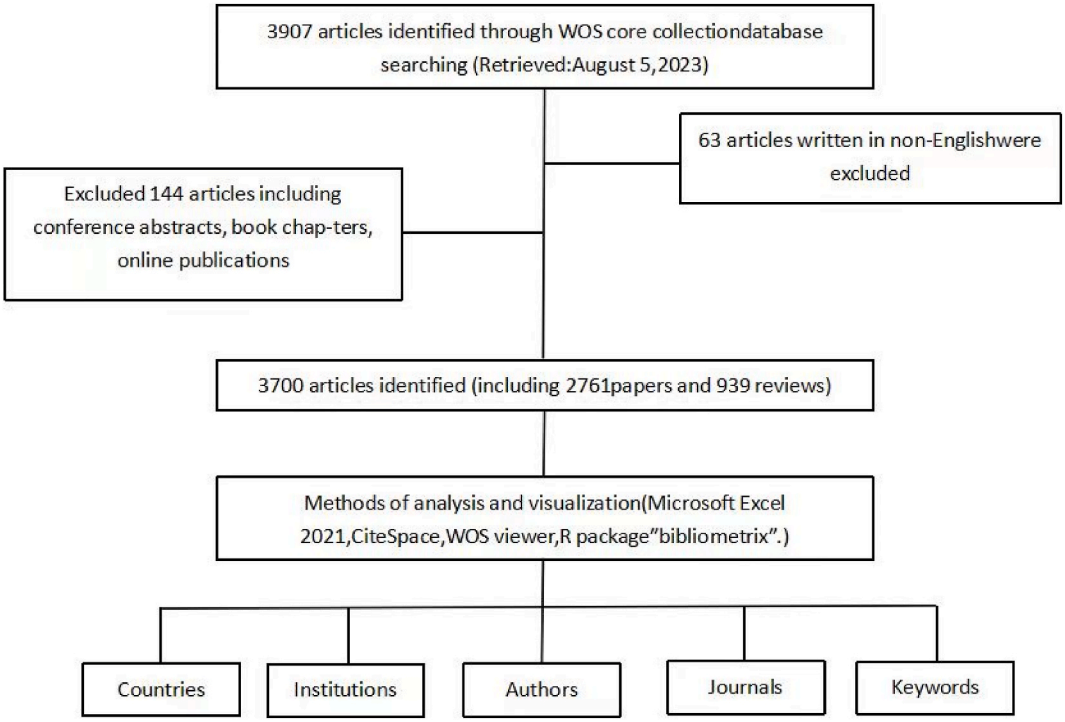

Fig. 1. Flowchart of selected publications for this study.

2. Methods and materials

2.1. Data searching and literature screening

The SCI Extended Citation Index (SCI) of the Web of Science Core Collection (WoSCC) database was chosen as the data source for this research. Employing a precise search strategy, the query included terms such as (((((((TS=(Immunotherapies)) OR TS=(Molecular Targeted Therapies)) OR TS=(Targeted Therapy)) OR TS=(Molecular Targeted)) OR TS=(Targeted Molecular Therapy)) OR TS=(Molecular Therapy)) OR TS=(Targeted)) OR TS=(Targeted Molecular)) AND TS=(SLE).The search spanned from August 2003 to August 2023, the search was conducted on August 5, 2023. All searches and downloads were performed within one day to avoid bias due to daily database updates. A total of 3907 relevant articles were retrieved. We then restricted the language to English, excluding 63 non-English articles, and restricted the article type to papers and reviews, again excluding 144 articles such as conference abstracts, book chapters and online publications. In total 3700 relevant articles (2761 papers and 939 reviews) were included, and the results of the search were exported as "complete records and cited references" and saved as plain text files for further processing. (Fig. 1).

2.2. Data extraction and analysis

Data extraction was performed independently by the first author and included annual studies, countries, institutions, authors, journals, citations, and keywords. Quantitative analyses were performed using Microsoft Excel 2021 to calculate various metrics, including total annual number of publications, average number of citations per publication, annual number of publications by country, cumulative number of publications over the years, and cumulative number of publications by institution, author, and journal. To measure publication quality, we used impact factors (IF) and categorization data from the Journal Citation Reports (JCR) 2022 as evaluative indicators. Additionally, the H-index was employed as a metric to assess the quality of scientific output, academic standing of researchers, and the productivity and impact of countries, institutions and journals. The H-index, defined as the minimum number 'h' where a researcher has published at least 'h' papers, each of which has been cited at least 'h' times, served as a valuable tool in evaluating productivity and academic impact of researchers, countries, institutions, and journals.

In the area of visual analysis, the VOS viewer (5.8 R3 version) is used to conduct co-authorship and co-citation analysis of countries, institutions, authors, and journals, as well as to perform keyword co-occurrence analysis. CiteSpace V (5.8 R3 version) is used to generate dual-map overlays of journals. The R software package "bibliometrix" (3.2.1 version) (https://www.bibliometrix.org) is used for thematic evolution analysis and constructing global distribution networks. Each node in the map represents a unique record, such as a country, organisation, or keyword. The size of the node is determined by the weight of the entry, reflecting metrics such as number of publications, citations or frequency of occurrence. Larger nodes indicate a higher weight. The colour of the nodes and the lines between them is determined by the cluster to which they belong. Nodes and lines are coloured according to their respective clusters, with the lines representing the links between them. The Total Link Strength (TLS) quantifies the overall link strength of co-authorships and co-citations between countries, institutions, and authors.

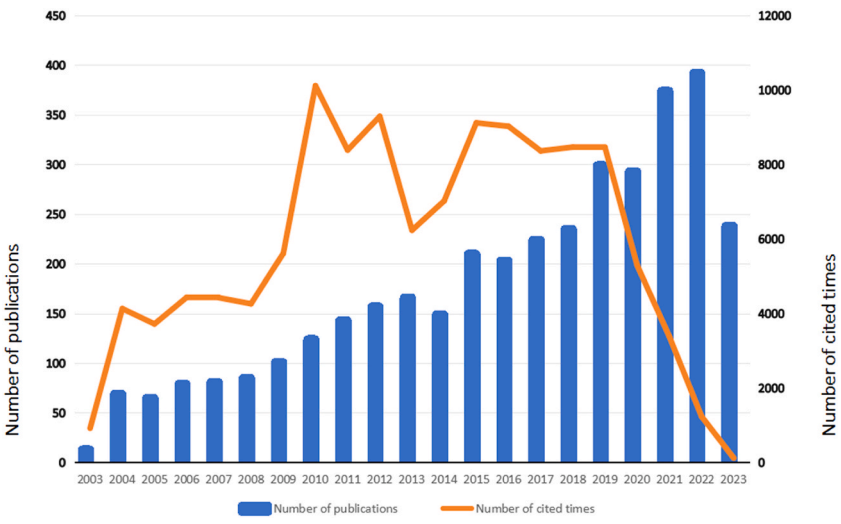

Fig. 2. Trend of the number of articles published annually and the total amount of citations of annual articles.

3. Results

3.1. Publication outputs and citation trend

We included a total of 3700 relevant articles from the WOSCC database from August 5, 2003 to August 5, 2023. As demonstrated in Fig. 2, from 2003 to 2022, there has been a gradual increase in the number of publications, with the most significant increase occurring between 2018 and 2022. Furthermore, the citation frequency of the included articles showed two peaks, notably in 2010–2012 and 2015–2019. However, post-2019, despite a noteworthy increase in the overall article count, the total number of citations showed a decreasing trend year by year, accompanied by a decrease in the H-index.

3.2. Distribution of countries

Table 1 shows the top 10 countries contributing to precision therapy articles in the field of SLE, as well as the developing trend of relevant publications from these countries from 2003 to 2023. The United States led the tally with the highest number of papers, constituting 36.1 % (1336/3700) of the total, trailed by China (25.8 %, 954/3700) and England (8.1 %, 300/3700). Publications originating from the United States garnered the most citations (59,889) and the highest H-index (115). Given collaborative efforts, there was an overlap in the total number of articles. Fig. 3A illustrates the inter-country citation relationships, revealing the United States as having the largest TLS at 491, followed by England (TLS = 243) and China (TLS = 222). Subsequently, utilizing the R package "bibliometrix," we constructed a geographical distribution, as depicted in Fig. 3B, based on the number of publications and collaborative relationships within each country. Notably, active collaboration emerged prominently among various countries.

3.3. Distribution of institutions

As of September 2023, a total of 3652 institutions have contributed to the discourse on the precision treatment of SLE. It is worth noting that five out of the top ten institutions in terms of publication volume are from the United States. Anhui Medical University has emerged as the most prolific contributor in terms of published papers, closely followed by the Karolinska Institute and Johns Hopkins University. Harvard University stands out with the highest H-index and has the distinction of having the highest average number of citations per article among all institutions, as shown in Table 2.

Fig. 4A and B provide a visual representation of inter-institutional collaboration and citations. In Fig. 4A, the graph exhibits 147 entries and 1774 links, with the 147 entries organised into nine clusters distinguished by colour. Institutions within each cluster have close links. The citation analysis network graph in Fig. 4B shows 146 entries and 6394 links. Harvard Medical School emerges as the institution with the highest TLS at 1119, highlighting its significant connectivity within the network.

3.4. Authors and co-cited authors

In the collective effort of 18,171 authors contributing to 3700 articles, Table 3 lists the top 10 authors with the highest number of published papers. Notably, George C. C. Tsokos from the United States emerges as the most prolific author, with 58 articles, boasting the highest H-index of 33. Michelle Petri, also from the United States, stands out with the highest average number of citations per article, reaching an impressive 76.73 per article.

Fig. 5A provides a visual representation of the collaborations and links between authors. Notably, Chaim Putterman, a prolific figure in the field, has a more extensive network of collaborators compared to others. Fig. 5B unveils the authors' co-citation network graph with 146 entries, 12 clusters and 6394 links. Leading authors in terms of TLS include Lu, Qianjin (TLS = 144), Zhao, Ming (TLS = 116), and Doria, Andrea (TLS = 109), highlighting their remarkable connectivity within the authorship network.

3.5. Journals and co-cited journals

A total of 153 journals contributed to the discourse on precision therapy in SLE. Table 4 lists the top 10 journals selected after

Table 1
The 10 most productive countries in terms of publications.

Rank	Countries	Article count	Percentage (n/3700)	H-index	TLS	Total citations	Average citation per article
1	United States	1336	0.3611	115	824	59889	44.83
2	China	954	0.2578	64	303	18955	19.87
3	England	300	0.1111	65	434	14797	49.32
4	Germany	245	0.0662	58	344	11518	47.01
5	Japan	214	0.0578	42	126	6613	30.90
6	Italy	212	0.0573	49	243	7669	36.17
7	France	163	0.0441	44	208	6439	39.50
8	Sweden	132	0.0357	44	240	7223	54.72
9	Spain	125	0.0338	37	237	5661	45.29
10	Australia	115	0.0311	37	190	4902	42.63

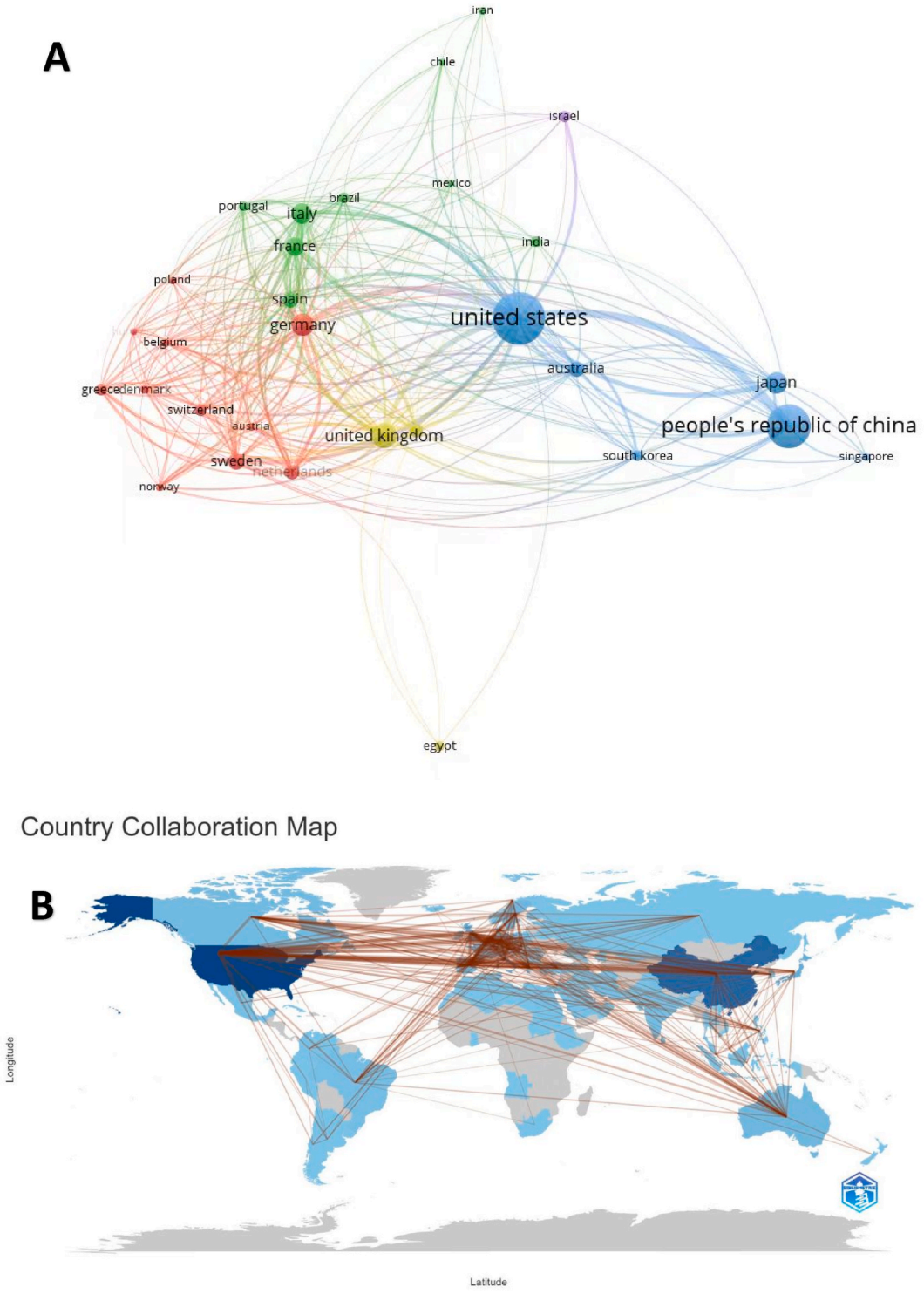

Fig. 3. **(A)** Visualization map of the country citation network produced by the VOS viewer (version 5.8 R3). China, people's republic of china. England, united kingdom.**(B)** The geographical distribution.

comprehensive quality assessment. Together, these elite journals have published 1008 articles up to November 2023, representing 27.2 % of the total articles in the field. Frontiers in Immunology (IF 2022 = 7.3) leads with the highest number of articles (191), followed by Lupus (IF 2022 = 2.6) and Journal of Autoimmunity (IF 2022 = 12.8). Among the top ten, six journals are affiliated with

Table 2
The 10 most productive institutions ranked by the numbers of publications.

Rank	Institutions	Countries	Article count	H-index	Total citations	Average citation per article
1	Anhui Medical University	China	70	24	1864	26.63
2	Karolinska Institute	Sweden	67	30	3504	52.30
3	Johns Hopkins University	United States	66	33	4130	62.58
4	University of California, Los Angeles	United States	65	32	2910	44.77
5	University of London	Englend	65	42	2565	39.46
6	Shanghai Jiao Tong University	China	64	26	2589	40.45
7	Harvard Medical School	United States	60	47	3102	51.70
8	Harvard University	United States	55	48	4779	86.89
9	Central South University	China	55	26	647	11.76
10	Monash University	Australia	52	23	2612	50.23

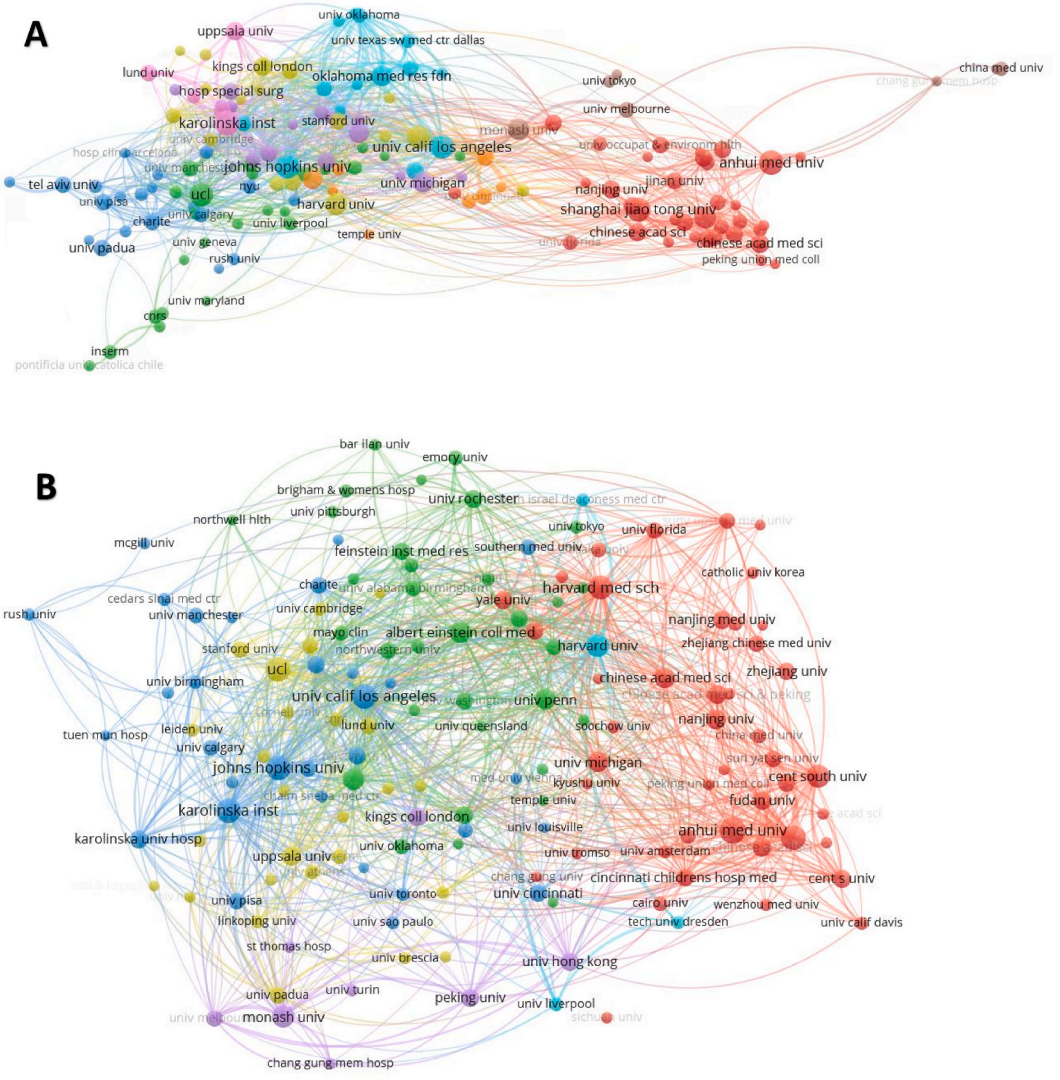

Fig. 4. **(A)** Visualization map of the institutions' collaboration network produced by the VOS viewer (version 5.8 R3) **(B)** The institutions' citation network visualization map generated by VOS viewer (version5.8 R3).

England, three with the United States, and one with Switzerland. Annals of the Rheumatic Diseases claims the highest H-index (44), while Arthritis and Rheumatism has the highest total citations (6,182) and Annals of the Rheumatic Diseases has the highest Impact Factor (IF 2022 = 27.4).

Table 3
The top 10 most productive authors in publications.

Rank	Author	Article count	H-index	Countries	Total citations	Average citation per article	Institutions
1	Tsokos, George C. C.	58	33	United States	4067	70.12	Harvard Medical School
2	Lu, Qianjin	55	22	China	1878	34.15	Central South University
3	Putterman, Chaim	35	24	Israel	1671	47.74	Galilee Medical Center, Nahariya
4	Petri, Michelle	33	23	United States	2532	76.73	Johns Hopkins University
5	Pan, Hai-Feng	33	17	China	949	28.76	Anhui Medical University
6	Wu, Haijing	32	18	China	838	26.19	Central South University
7	Shen, Nan	30	19	China	1849	61.64	Shanghai Jiao Tong University
8	Ye, Dong-Qing	27	17	China	828	30.67	Anhui Medical University
9	Tanaka, Yoshiya	25	16	Japan	520	20.80	University of Occupational & Environmental Health
10	Doerner, Thomas	25	17	Germany	1854	74.16	Charite Universitatsmedizin Berlin

This study delves into the intricate web of citation relationships between journals spanning multiple domains, and visualises these connections through a dual map overlay. And by overlaying two graphs, these connections are visualized. The left side of Fig. 6 displays the references cited by the research, the right side shows the references that cited the research - the citing literature (on the left side of the map) can be considered applied research, while the cited literature (on the right side of the map) can be considered basic research. Within this visualization, all identifiable citation paths are exposed, with different colours indicating causality. Three main reference paths are identified in the figure: one orange path and two green paths. The orange path indicates that research published in Molecular, Biology and Genetics journals is commonly cited by studies published in Molecular, Biology and Immunology journals; the green paths indicate that research published in Molecular, Biology, Genetics and Health, Nursing and Medicine journals is commonly cited by studies published in Medicine, Medical and Clinical journals. In addition, the elliptical curves at the periphery visualise the extent to which the cited literature has spread its influence in the field.

3.6. Citations and co-cited citations

Table 5 presents the top 10 most cited articles in the field. Notably, ARTHRITIS AND RHEUMATISM emerges as a key source contributing significantly to the landscape, with 20 % of the top 10 most cited articles originating from this journal. All references within the top 10 have received over 490 co-citations, underlining their profound impact. The study by Hakkim, A et al. (2010), published in PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, stands out as the most cited article, with an impressive 996 citations. Using CiteSpace V (version 5.8 R3), we searched for citation bursts and identified a total of 25 references, encompassing the most pronounced bursts, as depicted in Fig. 7. The onset of citation bursts dates back to 2003, originating from two papers in that year. In particular, 64 % of the references experienced citation bursts between 2010 and 2020. The most recent reference to experience a citation burst appeared in 2021, and this burst is currently ongoing.

3.7. Keywords analysis of research hotspots

We systematically extracted keywords from the titles and abstracts of the 3700 included articles. We then used the VOS browser (version 5.8 R3) for visualization and analysis, focusing on keywords with more than 100 occurrences. A subsequent layer of in-depth cluster analysis was performed, resulting in the identification of 46 high-frequency keywords. These keywords were then organised into three different clusters, each represented by a different colour (clusters 1–3 are labelled red, green and blue). The connections between these keywords resulted in a network of 1001 links, as illustrated in Fig. 8A.

We filtered out keywords that appeared more than 30 times in order to refine the focus, and then conducted comprehensive thematic analysis of the keyword trends using the R package “bibliometrix”. The results, shown in Fig. 8B, revealed clear thematic shifts over the years. Between 2006 and 2016, the dominant keywords in research included anticardiolipin antibodies, B-cell depletion, Epstein-Barr-virus, INF-α, T-cells, lymphocytes, among others. From 2016 to 2018, there was a shift in the research landscape towards monoclonal-antibody, nephritis, double-blind, disease-activity, and related themes. After 2018, there was a notable increase in the scientific exploration of oxidative stress, autoimmune phenomena, RISK, and associated topics. Moreover, three keywords - REMISSION, PHASE-III and VALIDATION - showed a significant increase in frequency over the last two years. This increase suggests that these keywords are probably to represent the present research hotspots in the field of precision-targeted therapy for SLE.

4. Discussion

In this study, we employed bibliometric analysis to quantify the global scientific output related to precision treatment of SLE from August 2003 to August 2023. From 2003 to 2022, the number of relevant articles published globally has shown a gradual increasing trend, with a significant surge from 2018 to 2022 (Fig. 2). This surge suggests a continued high level of enthusiasm for the field in the coming years. However, recent trends indicate a decline in the total number of citations and H-index of articles in the field. Even

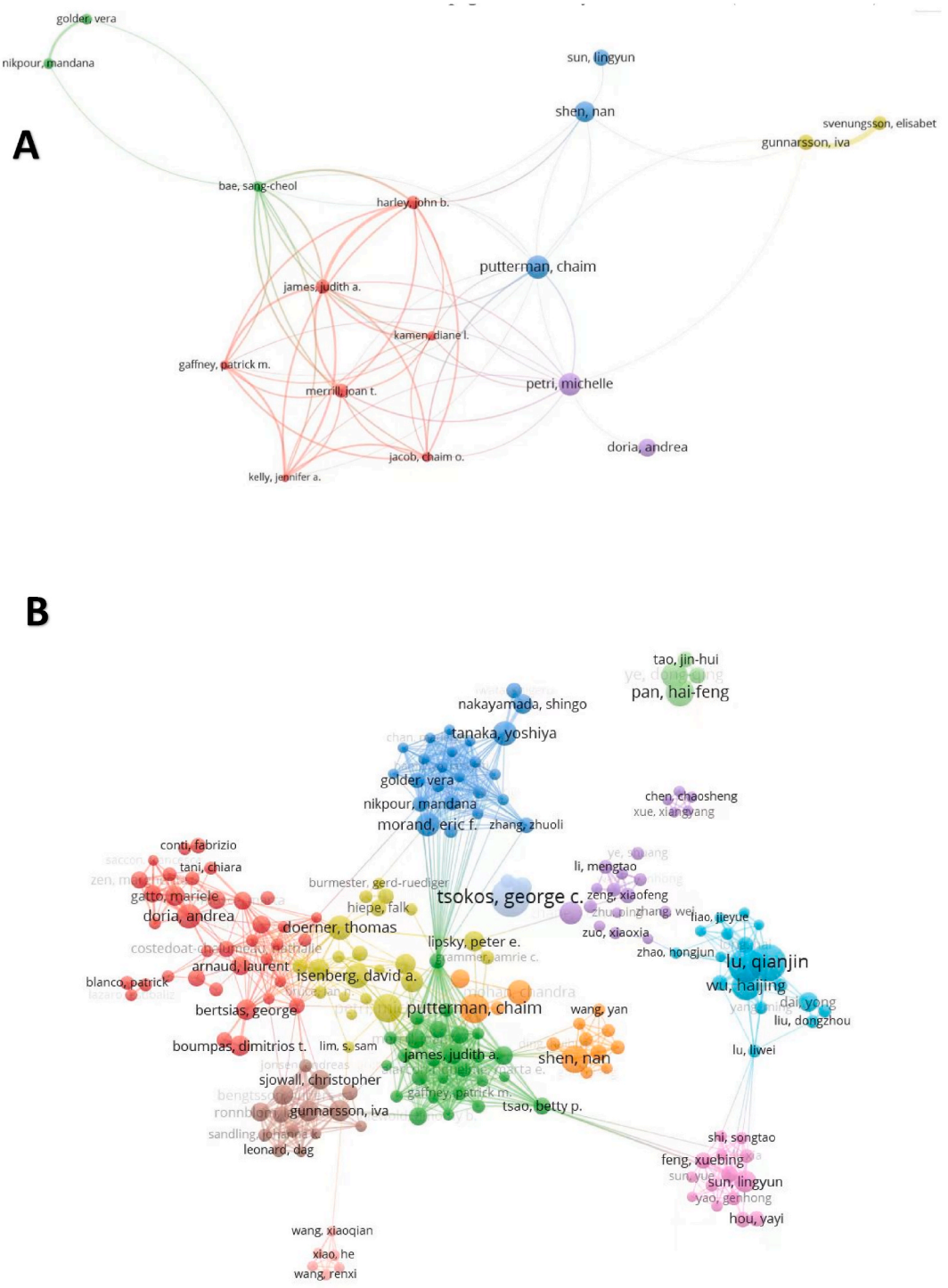

Fig. 5. **(A)** The authors' collaboration network visualization map generated by VOS viewer (version5.8 R3). **(B)** The authors' co-citation network visualization map generated by VOS viewer (version5.8 R3).

allowing for a possible lag in article citations, it is undeniable that the overall quality of articles in the field has recently declined. This underlines the urgent need for the emergence of new research hotspots to reinvigorate and enhance the quality of research output in the related areas.

Upon scrutinizing the countries of publication, it becomes evident that the United States stands out as the leading contributor in this area, with more publications by significant. Meanwhile, the United States has the highest H-index, the highest average number of

Table 4
The top 10 journals of research ranked by publication number.

Rank	Journal Tital	Country	Count	IF(2022)	Quartile in category (2022)	H-index	Total citations
1	Frontiers in Immunology	Switzerland	191	7.3	Q2	34	4493
2	Lupus	England	173	2.6	Q4	29	3435
3	Journal Of Autoimmunity	England	95	12.8	Q1	39	4226
4	Arthritis Research & Therapy	England	94	4.9	Q2	37	3798
5	Rheumatology	England	88	5.5	Q1/2	27	2434
6	Autoimmunity Reviews	United States	85	13.6	Q1	37	4038
7	Arthritis & Rheumatology	United States	79	13.3	Q1	35	2868
8	Annals Of The Rheumatic Diseases	England	75	27.4	Q1	44	5868
9	Arthritis and Rheumatism	United States	64	/	/	41	6182
10	Autoimmunity	England	64	3.5	Q4	28	2450

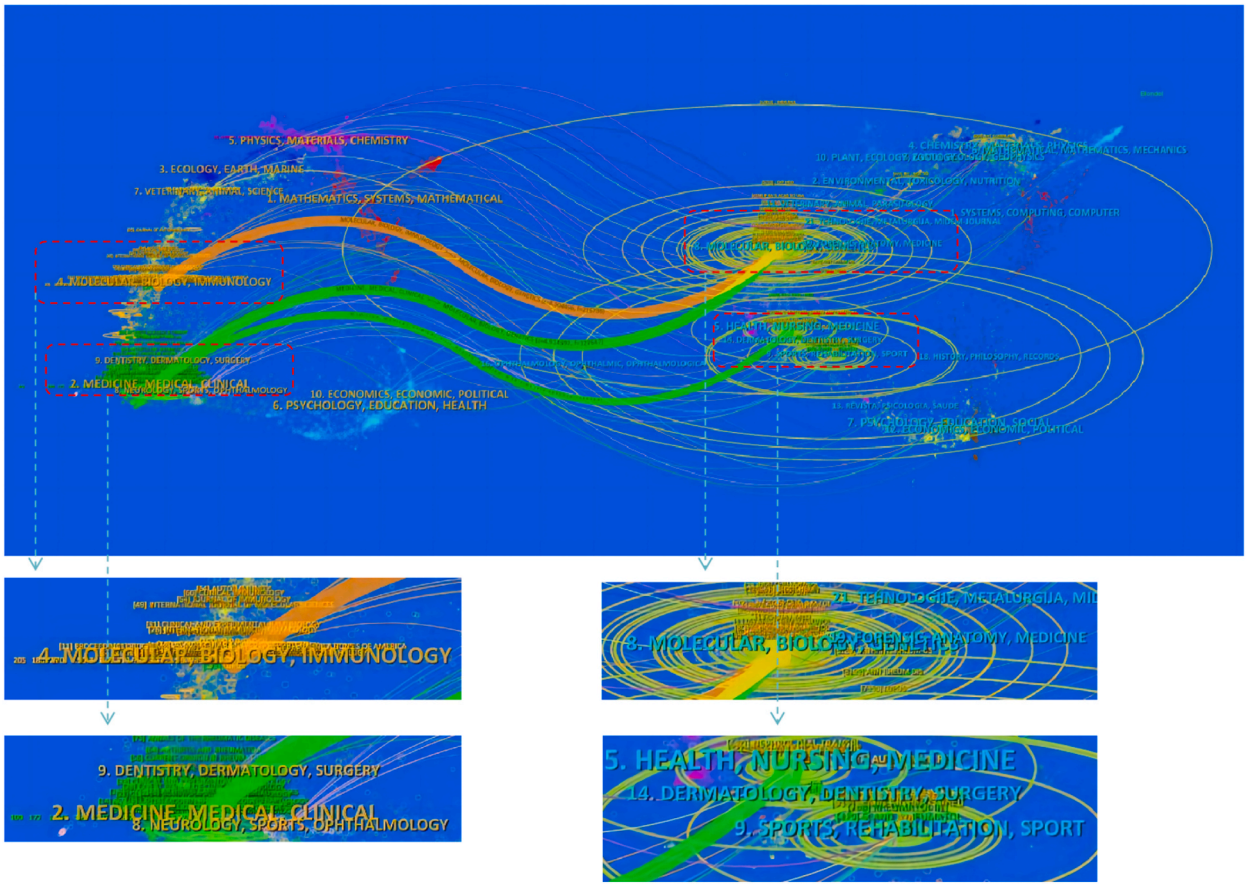

Fig. 6. A dual-map overlay of the relevant journals generated by CiteSpace V (version5.8 R3).

citations and the highest TLS, indicating its superior quality and profound influence in this field. The United States plays a preeminent role in this field, followed by the United Kingdom and Germany. It is noteworthy that while China secures second place in terms of publication volume, its H-index is relatively modest, and both its average number of citations and TLS lag behind, suggesting a need for greater emphasis on the quality of academic publications among Chinese scholars.

Within the roster of top 10 institutions, the United States and China together contribute 40 % and 30 % respectively of the total publications, which is an important explanation for the dominance of these two countries in relevant research output. At the same time, the achievements and standing of other emerging research institutions should not be overlooked, as they play a crucial role in strengthening the academic standing of their respective countries. Recognizing the contributions of these nascent institutions is crucial to providing a sound basis for enhancing the academic status of their countries.

In the correlation analysis of publishing scholars, among the top ten high producers, China accounts for five scholars, two from the United States and the remaining three from Israel, Japan, and Germany, respectively. In particular, US scholars have the highest H-index, total number of citations and average number of citations in their articles. Prolific authors such as Tsokos, George C. C. from

Table 5
The top 10 related articles with the most citations.

Title	First author	Journal	Year	Citations	Main conclusion
Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis	Hakkim, A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	2010	996	They concluded that timely clearance of neutrophil extracellular traps (NETs) may be essential for tissue homeostasis to avoid autoantigen presentation and demonstrated the pathogenesis of lupus nephritis in patients with systemic lupus erythematosus (SLE) due to the inability to clear NETs. They found that the serum endonuclease DNase1 is essential for NET catabolism. impaired DNase1 function and the inability to catabolize NET are associated with renal involvement. Recognizing SLE patients who are unable to break down NETs may be a useful indicator of renal involvement. Demonstrates that NETs may be a therapeutic target for SLE [53].
Neutrophils Activate Plasmacytoid Dendritic Cells by Releasing Self-DNA-Peptide Complexes in Systemic Lupus Erythematosus	Lande, R	SCIENCE TRANSLATIONAL MEDICINE	2011	901	They demonstrated that the auto-DNA in the immune complexes of SLE patients contains the neutrophil antimicrobial peptides LL37 and HNP. these antimicrobial peptides are required for the ability of auto-DNA to trigger TLR9 in the pDC, and they form a complex with the DNA that protects the DNA from extracellular degradation. the auto-DNA is also required to activate IFN-alpha in the pDC. Neutrophils from SLE patients release large numbers of neutrophil extracellular traps (NETs) and were found to directly activate the pDC to produce IFN-α. SLE patients develop autoantibodies to the DNA and antimicrobial peptides in the NETs, which suggests that the NETs can also trigger the activation of autoreactive B cells. Thus, they identified the ability of neutrophils to activate pDCs through the release of NETs and concluded that dysregulation of this pathway leads to chronic activation of pDCs and autoimmunity in SLE [54].
New insights into the immunopathogenesis of systemic lupus erythematosus	Tsokos, GC	NATURE REVIEWS RHEUMATOLOGY	2016	676	They summarize the progress made in the last decade in the development of targeted therapeutics and drug repurposing for the treatment of SLE. Cytokines, tolerance pathways, local tissue mediators, and epigenetic mechanisms were identified as promising new targets in the treatment of SLE [55].
A ChIP-seq defined genome-wide map of vitamin D receptor binding: Associations with disease and evolution	Ramagopalan, SV	GENOME RESEARCH	2010	633	They used chromatin immunoprecipitation and massively parallel DNA sequencing (ChIP-seq) techniques to determine vitamin D receptor (VDR) binding throughout the human genome. They found that the VDR binds to many genes associated with autoimmune diseases and cancer, and that VDR binding is significantly enriched in patients with systemic lupus erythematosus [56].
Targeting Toll-like receptors: emerging therapeutics?	Hennessy, EJ	NATURE REVIEWS DRUG DISCOVERY	2010	615	They concluded that Toll-like receptors (TLRs) and their signaling pathways have therapeutic potential for the treatment of inflammation, cancer, infection, allergy and autoimmunity. The elucidation of the structures of several TLRs contributes to the rational design of small molecule agonists and antagonists in medicinal

(*continued on next page*)

Table 5 (*continued*)

Title	First author	Journal	Year	Citations	Main conclusion
					chemistry. In the area of TLR antagonists for the treatment of inflammatory diseases, the results of research related to the inhibition of TLR7 and TLR9 for the treatment of systemic lupus erythematosus are noted [57].
MicroRNA-146a Contributes to Abnormal Activation of the Type I Interferon Pathway in Human Lupus by Targeting the Key Signaling Proteins	Tang, YJ	ARTHRITIS AND RHEUMATISM	2009	583	They analyzed 156 miRNAs from SLE patients and demonstrated differential expression of multiple microRNAs, including miR-146a, a negative regulator of innate immunity. miR-146a under-expression was demonstrated to be negatively correlated with clinical disease activity and interferon (IFN) scores in SLE patients. And overexpression of miR-146a decreased type I interferon induction in peripheral blood mononuclear cells (PBMCs), whereas inhibition of endogenous miR-146a increased type I interferon induction. Furthermore, miR-146a directly inhibited transcriptional activation downstream of type I IFN. At the molecular level, miR-146a targets IFN regulatory factor 5 and STAT-1. More importantly, introduction of miR-146a into patient PBMCs alleviated the coordinated activation of the type I IFN pathway. They demonstrated that the microRNA miR-146a is a negative regulator of the IFN pathway. By targeting key signaling proteins, under-expression of miR-146a leads to alterations in the type I IFN pathway in lupus patients. These findings provide potential new strategies for therapeutic intervention [58].
Systemic lupus erythematosus	Kaul, A	NATURE REVIEWS DISEASE PRIMERS	2016	580	They systematically evaluated the diagnosis, treatment, and patient management of systemic lupus erythematosus. Guidance is provided for the selection of biologics for SLE [1].
Autoimmune diseases induced by TNF-targeted therapies - Analysis of 233 cases	Ramos-Casals, M	MEDICINE	2007	525	They analyzed the clinical characteristics, outcomes, and association patterns of the different anti-tumor necrosis factor drugs used in all reports of autoimmune disease following tumor necrosis factor (TNF)-targeted therapies searched through MEDLINE between January 1990 and December 2006. Ninety-two patients were identified who developed systemic lupus erythematosus (SLE)/lupus-like disease after initiation of anti-TNF therapy, of whom infliximab was used in 47 (44 %) cases, etanercept in 37 (40 %) cases, and adalimumab in 15 (16 %) cases [59].
Expansion of Circulating T Cells Resembling Follicular Helper T Cells Is a Fixed Phenotype That Identifies a Subset of Severe Systemic Lupus Erythematosus	Simpson, N	ARTHRITIS AND RHEUMATISM	2010	514	They demonstrated the existence of a unique GC pathway in a subpopulation of SLE patients that can be recognized by a surrogate marker of high levels of circulating $CD4^+$ T cells, which are similar to and possibly derived from Tfh cells, and identified Tfh effector molecules as a possible therapeutic target for an identifiable subpopulation of SLE patients [30].
Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 are	Lee-Kirsch, MA	NATURE GENETICS	2007	493	They demonstrated that mutations in the gene encoding DNase I, the most abundant extracellular DNase, cause

(*continued on next page*)

Table 5 (*continued*)

Title	First author	Journal	Year	Citations	Main conclusion
associated with systemic lupus erythematosus					systemic lupus erythematosus in humans and mice, and that TREX1 acts as both a DNA degrading enzyme and a possible cell membrane DNA sensor during granzyme A-mediated apoptosis, a dual role that may explain why impaired TREX1 function induces a persistent autoimmune response [60].

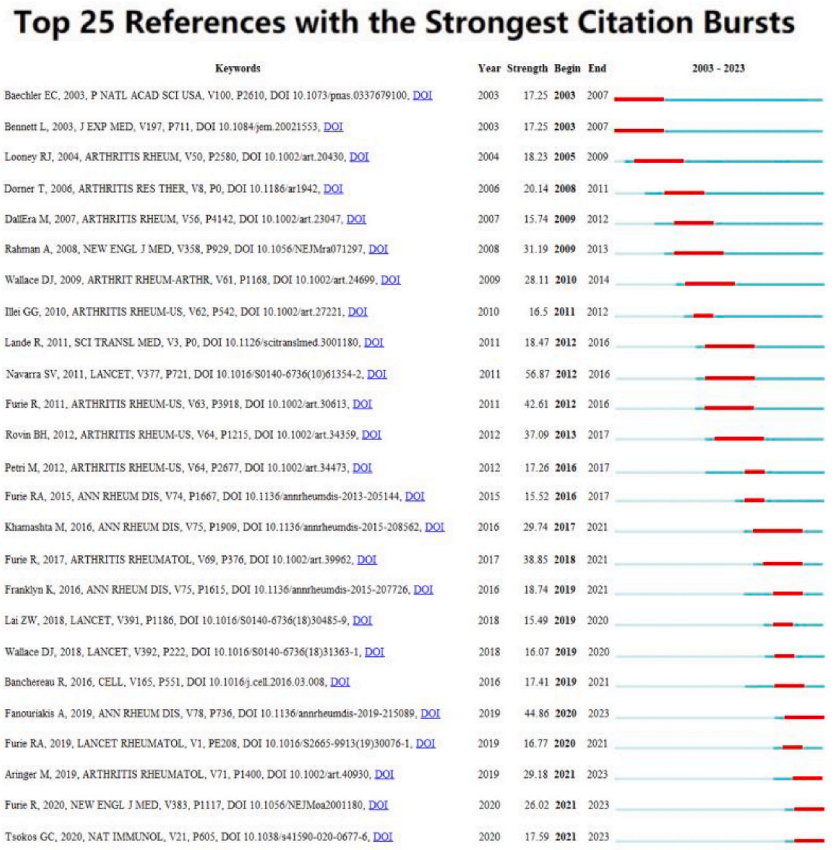

Fig. 7. The top 25 references with the strongest citation. (The green line segment represents the time interval, and the red line segment represents the active time). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Harvard Medical School, Lu, Qianjin from Central South University and Putterman, Chaim from Galilee Medical Center in Nahariya have emerged as the most prolific contributors. Fig. 5A provides a visual representation of the number of co-authored papers by authors versus collaborations, facilitating a deeper understanding of existing collaborations and helping to identify important or potential collaborators in the field. Authors marked with the same colour indicate close collaborations with each other. Fig. 5B shows the co-citation relationships among authors. Authors of the same color share similar research areas. The size of the node corresponds to the influence and strength of the scientists in the field. Notably, Lu, Qianjin, and Putterman, Chaim exhibit vibrant collaborator networks, with Lu, Qianjin having the highest strength of co-citation links. These authors play a pivotal role in the field, and their teams are likely to contribute significantly to the publication of influential papers related to Precision Therapeutics for Systemic Lupus Erythematosus.

Among the top journals, Frontiers in Immunology, Lupus, Journal of Autoimmunity, Arthritis Research & Therapy and Rheumatology emerge as notable authorities in the field of precision therapy for SLE. These findings provide valuable guidance to researchers and encourage increased submissions to these prestigious journals. Notably, four of the top ten journals have an Impact Factor (IF) above 10.0: Journal of Autoimmunity (IF2021, 12.8), Autoimmunity Reviews (IF2021, 13.6), Arthritis & Rheumatology (IF2021, 13.3) and Annals of the Rheumatic Diseases (IF2021, 27.4). In addition, two journals in the top ten fall within the IF range of 5.0–10.0, including Frontiers in Immunology (IF2021, 7.3) and Rheumatology (IF2021, 5.5). Overall, the effort to publish in high IF journals in

the field of precision therapy for SLE still facing some notable challenges.

"References with citation bursts" encompass studies that have been cited frequently within a specific time period. This metric signifies that these papers encapsulate the hotspots and dynamic changes within the field of precision-targeted therapy for SLE, attracting widespread attention from the scientific community during this period. The first citation burst occurred in 2003, originating from a paper by Cunningham D et al., in 2003 [19]. The study involved the collection of PBMCs from both SLE patients and healthy controls and, conducting genome-wide gene expression profiling using microarrays. The results revealed dysregulated expression of IFN pathway genes in approximately half of the patients, with this IFN gene expression "signature" correlating with severe complications in the kidney, hematopoietic cells and/or central nervous system. This surge in citations has increasingly focused scientific attention on the need for precision targeting in SLE, particularly within the IFN pathway.

The relevant summary for keywords can help us quickly grasp the precision-targeted therapy for SLE. Based on the keyword clustering analysis and trend theme analysis (Fig. 8B), we conclude that the research on precision-targeted therapy for SLE is mainly focused on the following aspects:

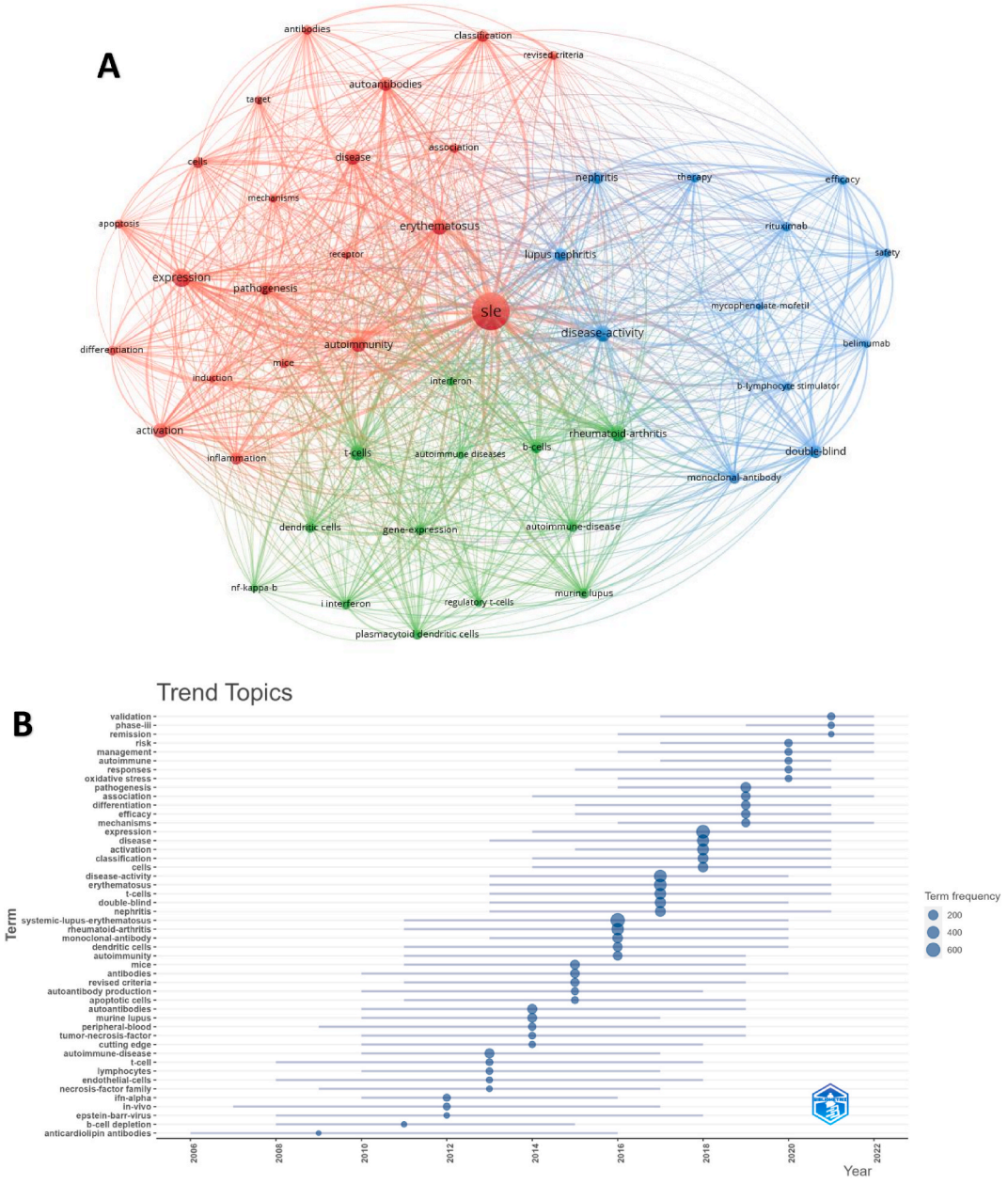

Fig. 8. **(A)** The network visualization map of keywords produced by VOS viewer (version5.8 R3). **(B)** Trend topic analysis.

B-cell depletion emerged as a research hotspot in the field around 2008, with the chimeric anti-CD20 monoclonal antibody rituximab being the first drug approved by the Federal Drug Administration (FDA) for the treatment of SLE. Early uncontrolled studies suggested some potential benefit, butsubsequent phase III randomised controlled trials, including the EXPLORER trial for non-renal SLE and the LUNAR trial for lupus nephritis (LN), failed to show promising efficacy and did not meet their primary endpoints [20–22]. More recent studies, in particular the BLISS Long-Term Extension Study, have shown favourable results with belimumab, an alternative treatment. Compared with patients receiving standard therapy, those treated with belimumab had significantly lower rates of disease progression and increases in the SLE International Cooperative Group Damage Index [22]. In addition, the BLISS-LN study showed that belimumab, when added to standard therapy, significantly increased the number of patients achieving a primary renal response at 2 years compared to placebo in adult patients with active LN [23]. It's worth noting that the use of rituximab has been associated with several adverse effects, including delayed neutropenia, hypogammaglobulinemia and adverse infusion reactions [24–26].

T cells play a pivotal role in the progression and pathology of SLE patients, with observed defects or alterations in T cell signalling, that belimumab, when added to standard therapy, significantly increased the number of patients achieving a primary renal response at 2 years compared to placebo in adult patients with active LN [23]. It's worth noting that the use of rituximab has been associated with several adverse effects, including delayed neutropenia, hypogammaglobulinemia and adverse infusion reactions [24–26].

T cells play a pivotal role in the progression and pathology of SLE patients, with observed defects or alterations in T cell signalling, cytokine production, proliferation, and regulatory functions [27]. Extensive evidence has shown that T cells contribute to the activation and differentiation of B cells, leading to the production of various pathogenic autoantibodies. In particular, $CD4^+$ T cells are recognized as the primary drivers of B cell differentiation [28]. T cells from SLE patients exhibit increased expression of the CD40 ligand (CD40L) upon activation, and the expression of this co-stimulatory molecule persists for a longer period of time compared to healthy controls [29]. In addition, specific T cell populations, such as follicular helper T (Tfh) cells, demonstrate abnormal expansion in SLE patients. Those with elevated Tfh cell levels tend to have a broader spectrum and higher titers of lupus-associated autoantibodies, an increased number of $CD4^+$ T-cell lymphocytes, and manifestations of end-organ involvement, including glomerulonephritis and haemocytosis [30]. Regulatory T (Treg) cells, known for their immunosuppressive capacity, are found to be relatively low in SLE patients. Conversely, T helper 17 (TH17) cells, which promote inflammatory responses by producing IL-17, are increased. Increased levels of IL-17 have been observed in patients with SLE [31]. These findings have stimulated further research into targeting T-cell--related pathways for the treatment of SLE.

In recent years, research has revealed the involvement of oxidative stress in the pathogenesis of SLE, prompting investigations into therapeutic approaches targeting oxidative stress. In the context of SLE, mitochondrial hyperpolarisation leads to the overproduction of oxygen radicals (e.g. superoxide anion, hydroxyl radical, hydroperoxide) and non-radical derivatives (e.g. hydrogen peroxide, H2O2) by T cell mitochondria [32]. Subsequent exposure of large amounts of hydrogen peroxide to transition metals (e.g. ferrous ions) triggers a Fenton reaction in the presence of ultraviolet light, resulting in the formation of hydroxyl radicals [33]. These hydroxyl radicals induce modifications in various cellular biomolecules [34], leading to the formation of new immunogenic epitopes and the production of autoantibodies. This cascade effect leads to tissue damage, inflammation, excessive autoimmunity and increased disease activity in SLE patients [35–37]. Precision-targeted therapeutic approaches that specifically inhibit oxidative stress and mitochondrial oxidative stress have shown promising therapeutic effects in animal studies. Idebenone, a synthetic analogue of ubiquinone (coenzyme Q10), has been shown to regulate mitochondrial function and exert potent antioxidant effects [38,39]. Treatment with idebenone has been shown to reduce mortality, disease activity and the severity of organ damage in MRL/lpr mice [40]. Other studies have demonstrated the efficacy of acetylcysteine (NAC), a precursor of the antioxidant glutathione, in inhibiting the activation of Triticum aestivum (TIA). This inhibition blocks oxidative stress and prevents the formation of neoantigens. In addition, NAC blocks inflammasome activation and prevents TCE-induced inflammasome activation, B-cell activation, NK cell infiltration in the liver, and histological changes in MRL+/+ mice in vivo [41]. Therefore, further in-depth studies of this hotspot are imperative to advancing our understanding and refine therapeutic interventions.

Since 2022, researchers have focused on the juxtaposition of remission and PHASE-III in the field of precision-targeted therapy for SLE. SLE has both periods of relative stability and periods of active disease, with some patients experiencing persistent activity despite rigorous treatment efforts [42]. While a cure remains the ultimate goal in the treatment of any disease, the current state of research suggests that a cure for SLE is an elusive pursuit goal. The concept of remission, which has been progressively defined as an effective criterion for controlling SLE, was introduced in 2012 by an international panel of SLE experts specifically to guide precision-targeted therapy [43]. Variables that indicate less severe disease, such as lower disease activity at diagnosis, a reduced damage index at baseline, or the absence of comorbid lupus nephritis, contribute to the characterisation of remission [44–46]. The concept of remission has been strategically developed to provide validation criteria for the selection of effective therapeutic targets in the precision-targeted treatment landscape for SLE. Conversely, in recent years numerous targeted agents have shown success in phase II clinical trials but fall to meet endpoints in phase III clinical trials. Examples include eptolizumab (anti-CD22) [47], baratinib (Janus kinase inhibitor) [48], Ligmund (P140 peptide) [49], ustekinumab (IL-12 and IL-23 inhibitor) [50], among others. The suboptimal results in phase III clinical trials can be attributed to factors such as low placebo response rates in corresponding phase II trials, short follow-up periods, and small sample sizes [51]. This highlights that research related to phase III clinical trials of precision-targeted drugs in SLE remains an important area of investigation. However, researchers need to carefully consider the feasibility of transferring indicators and designs from phase II to phase III trials. There is an urgent need for research into new targeted drugs to address the evolving landscape of precision-targeted therapy in SLE.

In conclusion, as a highly complex autoimmune disease whose aetiology has not been fully elucidated, it is essential to further investigate the pathogenesis of SLE in the future, and on the basis of the gradually elucidated pathogenesis, new targeted therapies can

be developed according to the results obtained and gradually enter the clinical trial stage. From the root of the pathogenesis of SLE, it is clear that there are a variety of candidate targets for the treatment of SLE, including inflammatory cytokines and their receptors, intracellular signalling, B cells or plasma cells, co-stimulatory molecules, complement components, T cells, plasma dendritic cells and a variety of other related immune targets. Future research trends may include the development of innovative therapeutic targets and moving them into phase III clinical trials as quickly as possible. A recent systematic review found that as of August 2022, there were 92 SLE drugs in clinical development, including 58 biological DMARDs (bDMARDs) and 34 targeted synthetic (ts) DMARDs, evaluated in 203 clinical trials, with 20 candidates advancing to phase I, 6 to phase Ia/IIb, 51 to phase II and 13 to phase III. 51 entered phase II and 13 entered phase III [52]. At the same time, it is also crucial to modify and improve the endpoints of phase III clinical trials, which are the basis for obtaining reliable and differentiated results in clinical trials.

5. Advantages and limitations

Our study pioneered the application of bibliometric methods and visualization to present global research advances in precision-targeted therapies for SLE over the last two decades. It systematically highlights the progress, current status and limitations of research in this area. However, it is imperative to acknowledge certain limitations. Firstly, our review is limited to the English language literature and may omit other important studies written in different languages. Second, our data collection is limited to the WOSCC database, potentially omitting important studies from databases such as PubMed and Embase. Third, only data from the immunological literature in the WOSCC database were included in this study, and thus some important interdisciplinary studies may have been missed. Finally, bibliometrics is a secondary analysis of the indexing of the literature, and this analytical technique may be inadequate for new publications that are poorly and inadequately indexed.Although our results show the most cited and important publications and keyword bursts over time, our study only summarises the most important and pervasive features of the development of the field and provides only a broad trajectory of the development of precision-targeted therapies for SLE.

6. Conclusion

In summary, the exploration of precision-targeted therapy for SLE is currently in a developmental phase, marked by a consistent annual growth in related research papers. Notably, the United States leads in both the quantity and quality of studies, exerting a significant guiding influence in this domain. Prior investigations have unveiled diverse therapeutic mechanisms and associated targets. Presently, the research emphasis is shifting towards validating phase III clinical trials of targeted drugs. The keywords “remission,” “validation,” and “PHASE-III” are poised to emerge as focal points in future research endeavors.

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Ethical approval

As this is a bibliometric study, it does not involve the collection of primary data from humans or animals. Instead, it is based on the analysis of existing literature and published data, which are publicly available and do not require ethical approval. This study follows standard practice in bibliometric analyses to ensure responsible use of data and respect for intellectual property rights. Therefore, we do not believe that ethical approval is required for this type of research.

Data availability statement

The data used in this study came from the Web of Science Core Collection database, which is an open access database from which anyone can access data. For access to the raw data used in the study, please contact the corresponding author.

CRediT authorship contribution statement

Zengze Yuan: Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **Weiqing Zhang:** Writing – original draft, Visualization, Software, Data curation. **Zhaokai Jin:** Visualization, Software, Data curation, Writing – original draft. **Yihan Wang:** Writing – review & editing, Visualization, Software, Conceptualization. **Zhiting Lin:** Writing – review & editing, Visualization, Software. **Zhimin Xie:** Writing – review & editing, Visualization, Software. **Xinchang Wang:** Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Xinchang Wang reports financial support was provided by The Second Affiliated Hospital of Zhejiang Chinese Medical University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that

could have appeared to influence the work reported in this paper.

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