Heliyon 10 (2024) e23216

Contents lists available at ScienceDirect

Heliyon

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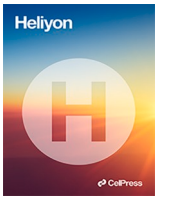

Research hotspots and emerging trends in the treatment of Sjogren's syndrome: A bibliometric analysis from 1900 to 2022

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ARTICLE INFO

Keywords:
Sjogren's syndrome
Sicca syndrome
Treatment
Therapy
Disease management
Bibliometric analysis

ABSTRACT

Objective: Sjogren's syndrome (SS) is an autoimmune disease that mainly affects the salivary and lacrimal glands and further leads to dry mouth and eyes. In recent years, knowledge about the treatment of SS is developing rapidly. This study aims to assess research progress on SS treatment using a bibliometric approach and to identify research hotspots and emerging trends in this area.
Methods: The publications related to the treatment of SS were retrieved from the Science Citation Index Expanded (SCI-E) database. The following search terms were used to extract document data: TS=(Sjogren* OR Sicca*) AND TS= (Treat* OR Therap* OR Disease Management). Articles and review articles published in English from 1900 to 2022 were selected. After the manual screening, the publication data were exported to a plain text file and applied for cooperative network analysis, keyword analysis, and reference co-citation analysis by using CiteSpace.
Results: A total of 2038 publications were included in the analysis from 571 journals by 9063 authors. The annual number of published studies and times cited showed an overall upward trend since 1992. There was a degree of national/regional collaboration in this area, but direct collaboration between institutions and authors was still lacking. The country with the highest number of publications was in the United States, followed by China and Japan. Five SS-related treatments as the research hotspots were summarized by analyzing keywords and references, including immunosuppressive and anti-inflammatory therapy, regenerative therapy, gene therapy, surgical treatment, and symptomatic treatment. Among them, B cells, T cells, mucosal-associated invariant T (MAIT) cells, mesenchymal stem cells (MSCs), rituximab, belimumab, cell-target therapy, and immunosuppressive and anti-inflammatory therapy were emerging trends in this field.
Conclusions: This study conducted a data-based and objective introduction to the treatment of SS from a fresh perspective. An analysis of the intellectual bases, research hotspots, and emerging trends in the field will contribute to future research and treatment decisions, which will ultimately benefit SS patients.

1. Introduction

Sjogren's syndrome (SS) is a systemic autoimmune disease characterized by ocular and oral dryness due to dysfunction of the

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https://doi.org/10.1016/j.heliyon.2023.e23216
Received 22 April 2023; Received in revised form 21 November 2023; Accepted 29 November 2023
Available online 12 December 2023

lacrimal and salivary glands [1]. In addition, fatigue, pain, and systemic complications are common in patients with SS [2]. SS can be divided into primary SS (pSS) which is not associated with other autoimmune diseases and secondary SS (sSS) coexisted with other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis [3]. A meta-analysis in 2015 indicated that the overall prevalence rate of pSS 60.82 (95 % CI 43.69 to 77.94) cases per 100 000 inhabitants [4].

Although great progress has been made in the pathophysiology of SS in recent decades, treatment decisions for SS remain challenging due to the lack of information on the efficacy and safety of different therapies [1,5]. EULAR recommendations on the treatment management of SS were published in 2019 to provide a basis for the homogeneous and consensual management of SS [5]. At present, a variety of therapeutic modalities have been applied or explored for the treatment of SS, such as topical oral and ocular therapies, oral muscarinic agonists, hydroxychloroquine, oral glucocorticoids, synthetic immunosuppressive agents, and biological therapies [5]. Although a large number of reviews and guidelines have summarized previous articles on SS treatment [6,7], the research hotspots and emerging trends in this field are still not reviewed objectively and systematically, which may limit the progress of scientific research and the designation of treatment guidelines in this field.

Bibliometrics was defined by Alan Pritchard in 1969 as the ability to effectively integrate retrospective information in a field of study, search for correlations between data and predict trends in future research [8,9]. Several bibliometric analyses of SS have been published in the past, but their studies have not focused on the treatment of SS [10–12]. CiteSpace is a web-based Java application for bibliometrics and visual analytics that is unique and influential in the field [13–15]. With some core concepts of CiteSpace (such as burst detection, betweenness, centrality, and heterogeneous networks), the Citespace can solve many practical problems: identifying the nature of research frontiers, tagging keywords, identifying emerging trends, turning points, key points and sudden changes in time [16,17]. This paper will summarize the intellectual bases, research hotspots, and emerging trends of SS through the CiteSpace to provide guidance and help for future research on the treatment of SS.

2. Materials and methods

2.1. Data acquisition and search strategy

Web of Science Core Collection (WOSCC) database (https://www-webofscience-com) is one of the most common academic database sources for bibliometric analysis [18]. In this study, Science Citation Index Expanded (SCI-E) database in the WOSCC was used for literature searching on December 21, 2022. The search query was set as follows: TS=(Sjogren* OR Sicca*) AND TS= (Treat* OR Therap* OR Disease Management). In this part, the Medical Subject Headings (MeSH) from PubMed, the wildcard character "*", and the field tag (TS) were applied to determine the search terms.

After searching, the retrieved publications were evaluated by two independent researchers (WP Song and XY Wang) according to inclusion and exclusion criteria. These two researchers were pre-trained and evaluated titles, abstracts, and keywords. In the event of disagreement between the assessments of two independent researchers, a third expert (H Wang) would make the final decision on whether to include the disputed records in subsequent analyses.

2.2. Inclusion and exclusion criteria

Publications that fully met the following conditions were included in the subsequent analysis, and the remaining articles were excluded:

(1) Articles and review articles related to the treatment of SS;

(2) Articles and review articles written in English;

[2] Articles and review articles published from 1900 to the present.

2.3. Data collection and statistical analysis

After literature searching and excluding, the detailed records were exported to a plain text file containing the author, title, source, abstract, keywords, addresses, cited references and use, and funding. The Analysis and Citation Report, the data analysis tool in WOS, was used for obtaining general information about the literature, including authors, affiliations, Countries/regions, publication years, and publication titles. Subsequent bibliometric and visualization analyses were performed with the CiteSpace software (Version 6.1 R6) based on the Java platform [19]. The dual-map overlay (Version 2.0) designed by Chen and Leydesdorff [20] in CiteSpace was applied for discipline and journal analysis. The cooperation network analysis was performed by using various node types (author,

Table 1
The configuration of CiteSpace.

Node type	Time slicing	Selection	Pruning
Authors Institution Country	1951–2022; Years per slice: 1	Top 100 %	No pruning
Keyword Reference	1992–2022; Years per slice: 1	g-index; k = 25	Pathfinder; Pruning the merged network

institution, and country). Keywords and cited references were applied for co-citation and burst analysis. The configuration of CiteSpace is shown in Table 1.

3. Results

3.1. General information

A total of 2038 of 7911 retrieved publications on the treatment of SS were screened and included for subsequent analysis, consisting of 1498 articles and 540 review articles (Fig. 1). The first literature among them was published in 1951 and reported a SS case treated with the adrenocorticotrophic hormone. From 1951 to 1991, the annual publication volume in this field did not exceed 10. The annual number of published studies and times cited showed an overall upward trend since 1992 and respectively peaked in 2020 (155 publications) and 2021 (7823 citations) (Fig. 2). The literature retrieval was performed on December 21, 2022, the number of publications and citations may not reflect the real situation in 2022.

3.2. Discipline and journal analyses

Publications on the treatment of SS were published in 571 journals. The top 3 journals with the greatest number of publications were *Annals of the rheumatic diseases* (58/2038, 2846 %), *Frontiers in immunology* (53/2038, 2.601 %), and *Clinical and experimental rheumatology* (49/2038, 2.404 %) **(Table 2)**. In terms of the Journal Citation Report (JCR), the top 10 journals were mostly classified into Q1/Q2 and classified as rheumatology. As for publisher location, all these 10 journals were in developed countries **(Table 2)**. Most of the journals (449/571, 78.634 %) published no more than 3 articles, among which 296 journals only had one publication record.

The dual-map overlay was used for discipline and journal analyses by applying the Blondel algorithm to assign journals to various

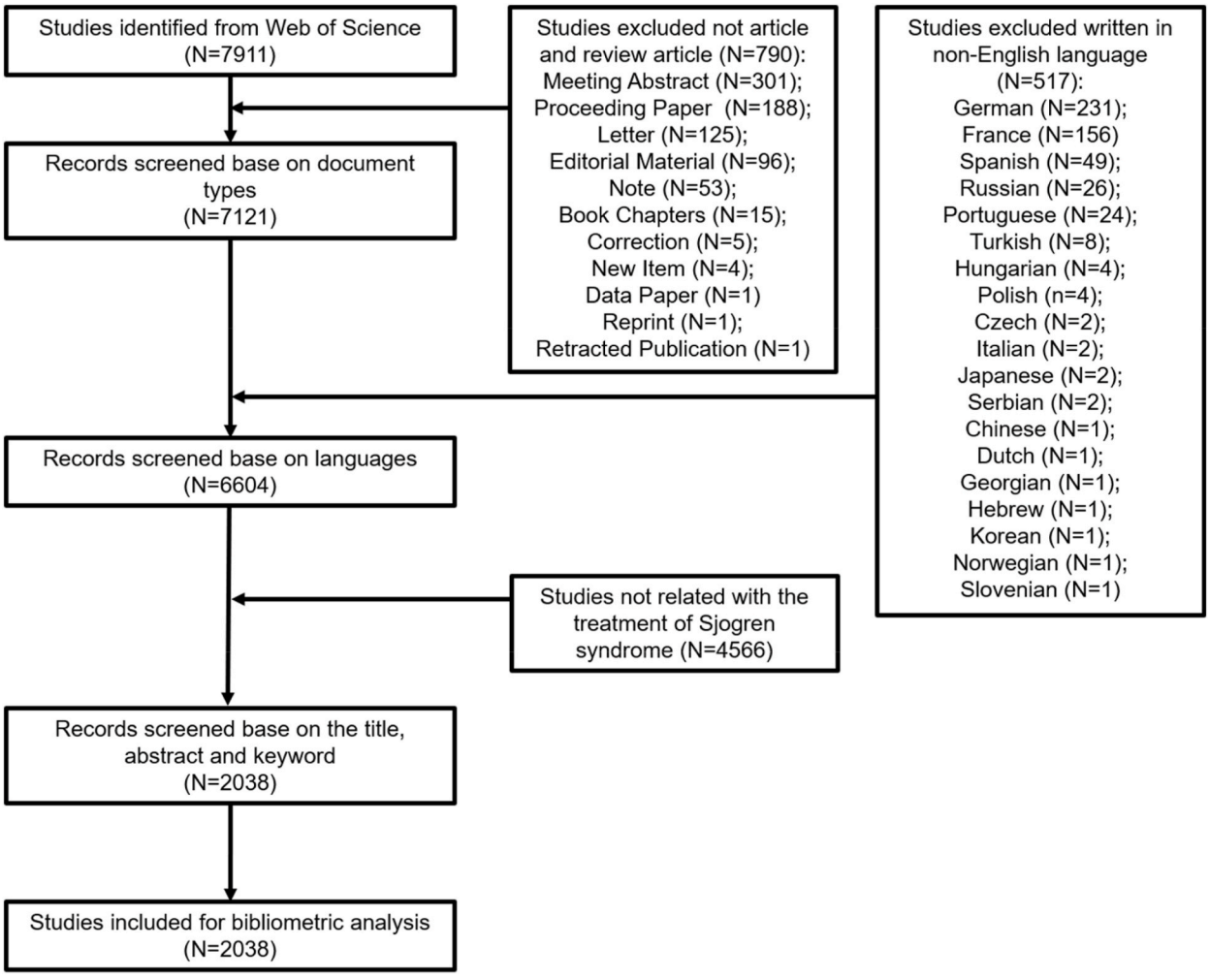

Fig. 1. Flowchart of the search strategy.

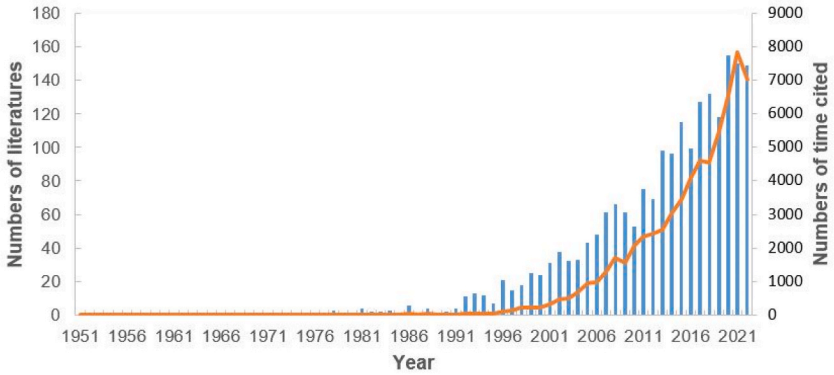

Fig. 2. The number of published studies and time cited over time. Numbers of literatures (blue), numbers of time cited (orange). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Top 10 journals with the largest number of published studies.

No.	Journals	Counts	% of 580	Country	Categories	2021 IF	JCR-c
1	*Annals of the Rheumatic Diseases*	58	2.846	England	Rheumatology	28.003	Q1
2	*Frontiers in Immunology*	53	2.601	Switzerland	Immunology	8.787	Q1
3	*Clinical and Experimental Rheumatology*	49	2.404	Italy	Rheumatology	4.862	Q2
4	*Rheumatology*	42	2.061	England	Rheumatology	7.046	Q1
5	*Arthritis Research & Therapy*	40	1.963	England	Rheumatology	5.606	Q1
6	*Journal of Autoimmunity*	40	1.963	England	Immunology	14.511	Q1
7	*Arthritis and Rheumatology*	37	1.816	USA	Rheumatology	15.483	Q1
8	*Clinical Rheumatology*	34	1.668	England	Rheumatology	3.650	Q3
9	*International Journal of Molecular Sciences*	32	1.570	Switzerland	Biochemistry & Molecular Biology Chemistry, Multidisciplinary	6.208	Q1
10	*Cornea*	30	1.472	USA	Ophthalmology	3.152	Q2

Abbreviations: IF, impact factor**; JCR-c,** Journal Citation Reports category.

clusters [21,22]. As shown in Fig. 3, the clusters on the left side and right side respectively displayed citing journals and cited journals, and the colored curves represented the pathway from citing map to cited map [23]. The beginning and ending positions of curves showed how the literature in the field built on past works [24]. Publications on this field primarily appeared from two regions of the citing map: Molecular/Biology/Immunology in orange and Medicine/Medical/Clinical in green. The orange-colored curve indicated that the publications belonging to Molecular/Biology/Immunology journals primarily cited those in Molecular/Biology/Genetics

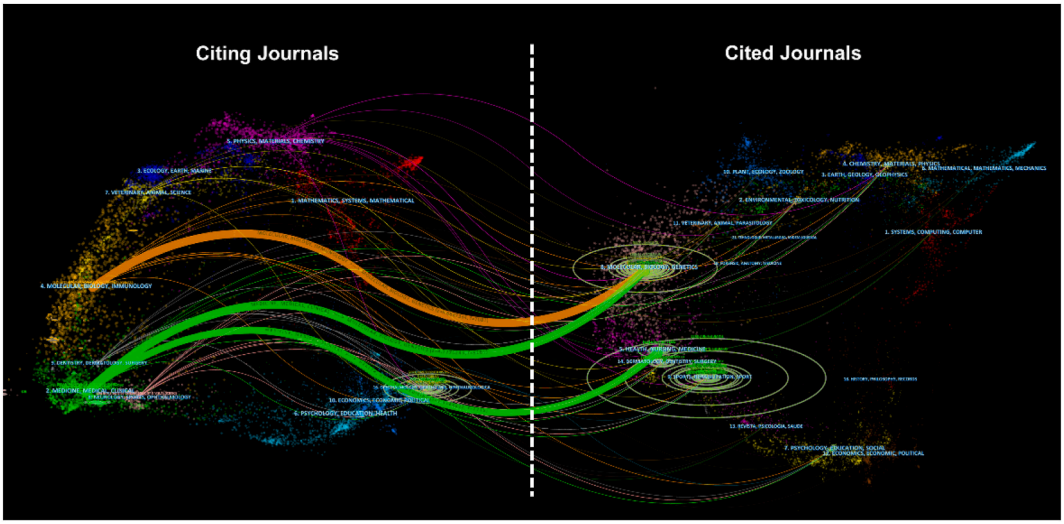

Fig. 3. The dual-map overlay of journals on the treatment of Sjogren's syndrome generated by CiteSpace. The clusters on the left side and right side respectively displayed citing journals and cited journals. The colored curves represented the pathway from citing map to cited map.

journals. The green-colored curve showed that the publications from Health/Nursing/Medicine journals mainly cited the publications from the journals labeled Molecular/Biology/Genetics and Health/Nursing/Medicine (Fig. 3).

3.3. Cooperation network analysis

The cooperative visualization maps were regenerated by CiteSpace software. The nodes in the cooperative visualization maps represented the authors, institutions, and countries/regions in this field. The size of the nodes indicated the number of publications and the connections between them showed cooperation. The greater size of the nodes and the thicker links of the connections represented the larger amount of published literature and cooperation.

3.3.1. Distribution of countries/regions

A total of 66 countries and regions contributed to the publications on the treatment of SS. As shown in Fig. 4 A, there is a degree of direct cooperation between countries/regions. The United States contributed the greatest counts of cooperation (567/2038, 27.822 %), followed by China, Japan, and Italy (Fig. 4 B). Besides, the United States also peaked at between centrality (BC) of cooperation (0.36), indicating that inter-country cooperation of the United States in this field is at a relatively high level (Fig. 4 C). France, England, Mexico, and Italy were also with a BC of cooperation greater than 0.1 (Fig. 4 C). Among the top 10 countries in terms of the number of cooperation and BC, developed countries play a dominant role.

3.3.2. Distribution of institutions

The authors from 2293 institutions published studies in this field. The University of Groningen contributed to the most publication (64/2038, 3.140 %), followed by the National Institute of Dental and Craniofacial Research (NIDCR) and Harvard University (Fig. 5A. B). The Charite and Johns Hopkins University ranked first in BC with 0.08. and none of the institutions was with a BC higher than 0.1 (Fig. 5C). The institution cooperation visualization map was relatively sparse showing the shortage of direct inter-institution cooperation, even among the institutions with high-publication institutions (Fig. 5A). For example, there was only a small amount of direct collaboration on the treatment of SS between the top 5 institutions with the highest publications.

3.3.3. Distribution of authors

A total of 9063 authors participated in the publications on the treatment of SS. Mariette X (41/2038, 2.012 %), Bootsma H, Pers J, Vissink, A, and Saraux A are the five authors who have published the most papers in this field (Fig. 6 A.B). A total of 55 authors have published more than 10 pieces of literature in this field. As shown in Fig. 6C, direct collaborations were relatively scattered among authors, which was consistent with the low BC of all authors (less than 0.05).

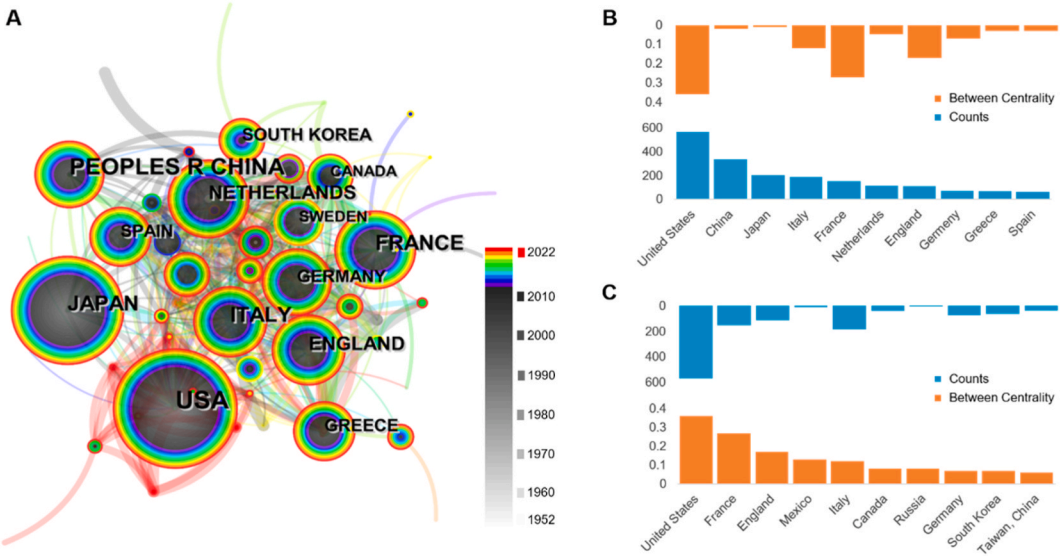

Fig. 4. Cooperation network analysis of countries/regions. A. Cooperation network map of countries/regions. The size of the nodes indicated the number of publications and the connections between them showed cooperation. Various colors represent the year of cooperation; B. Top 10 countries/regions with the largest numbers of publications. Counts (blue), between centrality (orange); C. Top 10 countries/regions with the highest between centrality of cooperation. Counts (blue), between centrality (orange). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

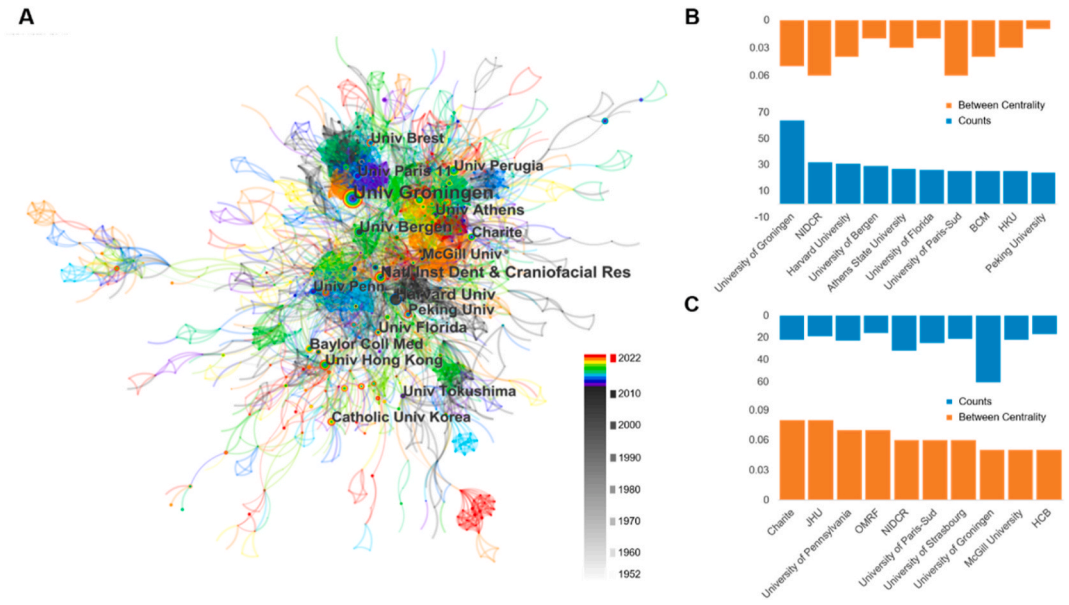

Fig. 5. Cooperation network analysis of institutions. A. Cooperation network map of institutions. The size of the nodes indicated the number of publications and the connections between them showed cooperation. Various colors represent the year of cooperation; B. Top 10 institutions with the largest numbers of publications. Counts (blue), between centrality (orange); C. Top 10 institutions with the highest between centrality of cooperation. Counts (blue), between centrality (orange). **Abbreviations: BCM**, Baylor College of Medicine; **HCB**, Hospital Clinic of Barcelona; **HUK**, The University of Hong Kong; **JHU**, Johns Hopkins University; **NIDCR**, National Institute of Dental and Craniofacial Research; **OMRF**, Oklahoma Medical Research Foundation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

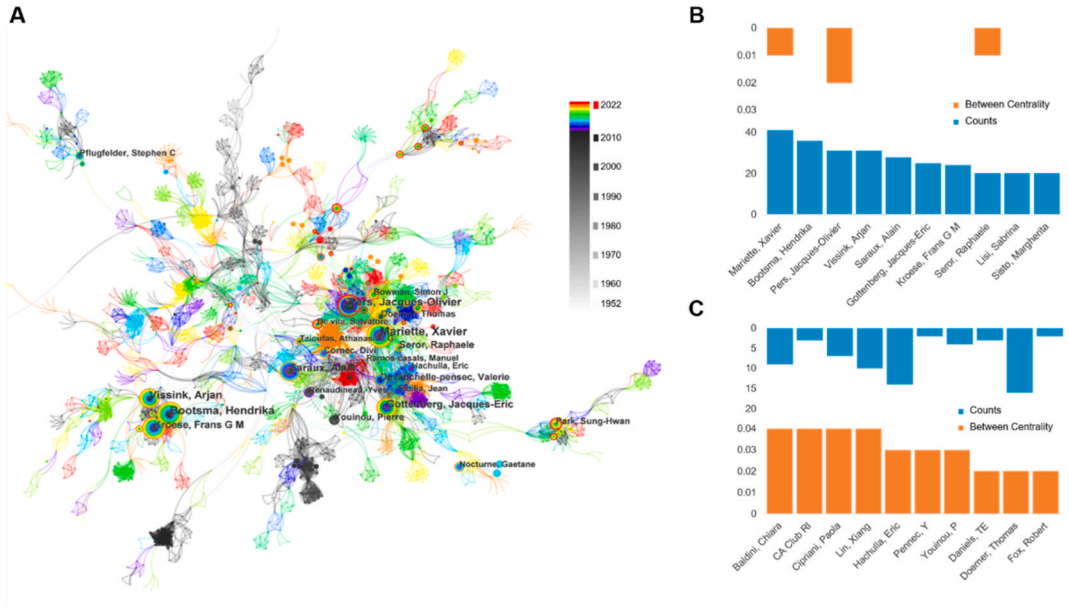

Fig. 6. Cooperation network analysis of authors. A. Cooperation network map of authors. The size of the nodes indicated the number of publications and the connections between them showed cooperation. Various colors represent the year of cooperation; B. Top 10 authors with the largest numbers of publications. Counts (blue), between centrality (orange); C. Top 10 authors with the highest between centrality of cooperation. Counts (blue), between centrality (orange). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.4. Keyword analysis

Keywords represent the focus of an article or authors and can reflect hotspots and emerging trends in a research field [25]. After preliminary extraction and manual sorting, a total of 1146 keywords were filtered out. The keywords with a frequency higher than 40 or a BC greater than 0.05 were listed in Supplemental Tables S1 and S2. The keyword with the highest frequency and BC was SS which was the same as the research topic in this study. Studies in this field mainly focus on treating dry mouth (xerostomia), dry eye, and keratoconjunctivitis sicca caused by SS, as well as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis associated with SS. Several cell types such as B cells, T cells, regulatory T cells (Treg), and dendritic cells (DCs) were targeted spots for treating SS. Additionally, other keywords related to the treatment of SS including rituximab and cytokine were also adopted by numerous studies. By investigating the time distribution of keywords, burst keyword analysis screens out keywords with high-frequency change, to analyze the research frontiers and development trends in this field. As shown in Fig. 7A, research on therapies in this field shifted from early rituximab treatment and artificial tears to mesenchymal stem cells (MSCs), abatacept treatment, and therapies targeting T cells, B cells, and cytokine.

In order to better reflect the research hotspots and emerging trends in this field, high-frequency keywords (the top 15 levels of the most cited or occurring keywords from each slice) were used to generate keyword co-occurrence networks and clustering network maps. The clustering effect is significant and reasonable ($S = 0.8515$, $Q = 0.5752$). Immunosuppressive therapy (#4) and surgical treatment (#8) were the clusters related to the treatment of SS produced by high-frequency keywords (Fig. 7 B.C).

3.5. Reference co-citation analysis

Articles cited by later studies at the same time are defined as reference co-citations which can reflect the relationship and structure between references and reveal research interest and emerging trends in an academic field [26]. The top 10 ranked cited references by citation counts and BC were listed in Supplemental Tables S3 and S4. Two consensuses on the classification criteria for SS [27,28] and multiple clinical trials using rituximab and belimumab received more co-citation counts [29–33]. The in vitro study by Ittah et al. [34] about the up-regulated effect of IFN-α stimulation on the expression of B cell-activating factor of the tumor necrosis factor family (BAFF) in salivary gland epithelial cells obtained the highest BC (Supplemental Table S4). The studies by Groom et al. [35] and Devauchelle-Pensec et al. [36] were ranked second and third in BC.

As shown in Fig. 8 A, the consensus on rheumatism classification for primary SS developed by the American College of Rheumatology/European League in 2016 had the strongest burst strength of reference co-citations [28]. The reference co-citation burst of this reference and the other 5 references continued until 2022 (Fig. 8 A). The 5 references included two reviews related to SS [37,38], one recommendation for the management of SS with topical and systemic therapies [5], one that summarized the role of B cells in the pathogenesis of primary SS [39], and one randomized controlled study of rituximab therapy for treating SS [33]. The timeline cluster map of co-citations is shown in Fig. 8 B. The clusters related to the treatment of SS with log-likelihood ratio (LLR) labels were as followed: mucosal-associated invariant T (MAIT) cells (#1), transitional B cell (#2), cell-target therapy (#3), gene therapeutics (#5),

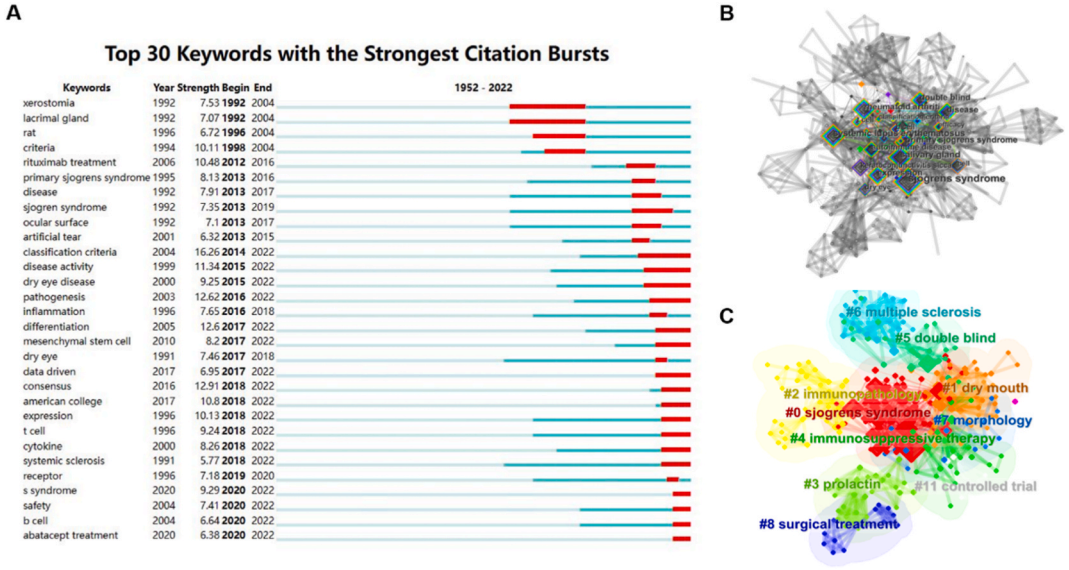

Fig. 7. Visualization map of keyword analysis. A. Top 30 keywords with the strongest citation bursts. The red line in this part indicates years when keywords burst and the green line represents the time range when keywords were used less frequently; B. Co-occurrence network map of high-frequency keywords; C. Cluster network map of high-frequency keywords. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

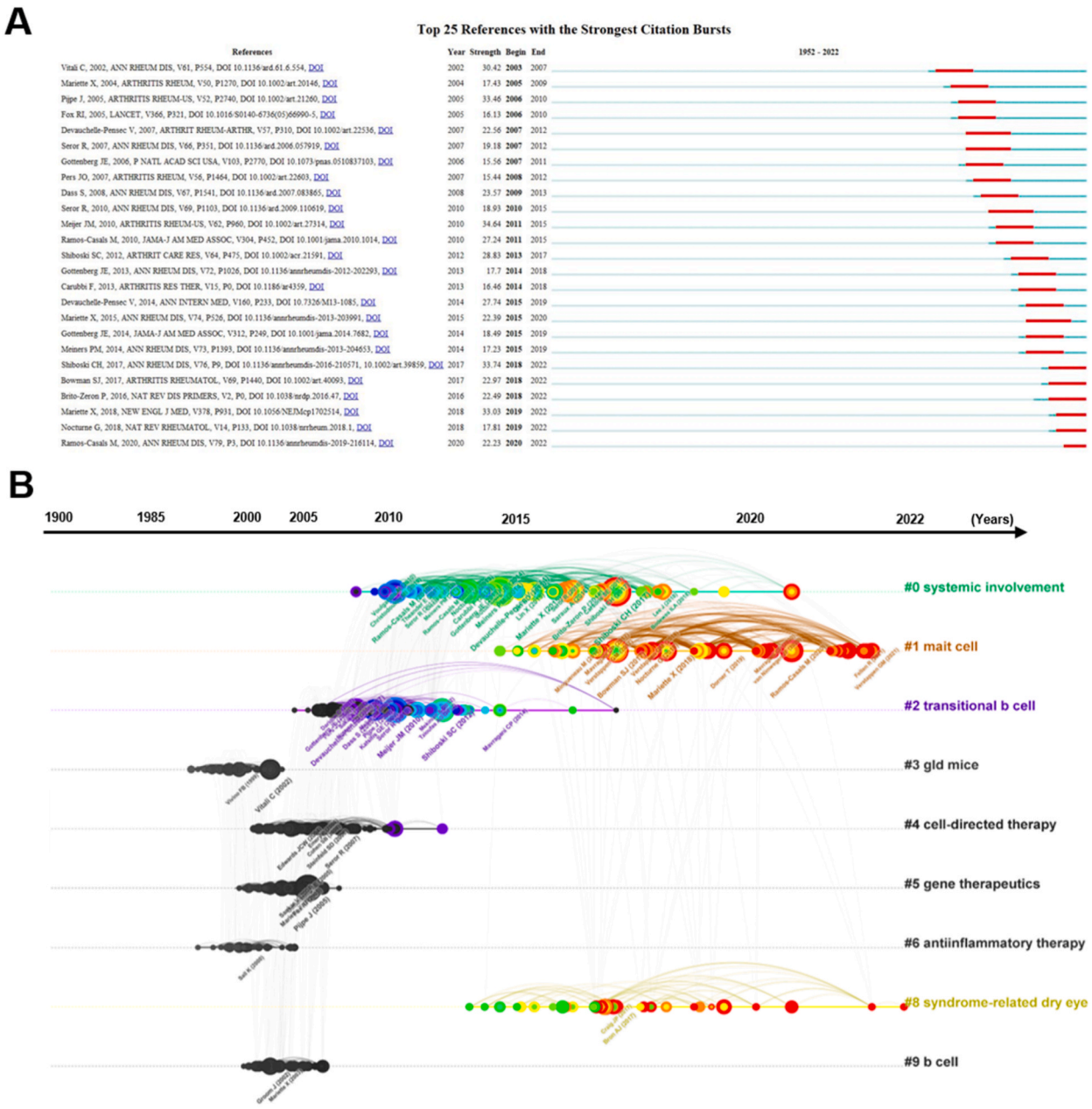

Fig. 8. Visualization map of reference co-citation analysis. A. Top 25 references with the strongest citation bursts. The red line represents years when keywords burst, and the green line indicates years when keywords were used less frequently. B. Timeline cluster map of co-citations. The timeline is shown near the top of the figure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

anti-inflammatory therapy (#6), and B cell (#9). The most representative keywords under different labels of each cluster are shown in Supplemental Table S5. MAIT cells (#1) was the cluster with the most recent nodes, which might be associated with B cells and rituximab identified in reference burst analysis together as the emerging trend in this field.

4. Discussion

4.1. Intellectual bases of the studies on the treatment of SS

Based on the principles of bibliometrics and CiteSpace software, the publications in the field of SS treatment were analyzed and visualized through the publication and citation situation, discipline and journal, cooperation network, keywords, and references. The

annual publications and citations in this field gradually increased since the first publication in 1951 and peaked in 2021. This indicated that the treatment of SS was valuable for research and had received persistent and increasing attention from academics and researchers.

Disciplinary and journal analysis of publications in a field can help to learn the disciplinary distribution, track research progression, and contribute to future article submissions in this field. The top 8 journals with the largest number of publications were in the categories of rheumatology and immunology, suggesting the attention of these kinds of journals to the treatment of SS. In addition, the journals with the labels molecular/biology/immunology, and medicine/medical/clinical were the main areas on the left side of the dual-map overlay, indicating that journals with the same labels were highly interested in publishing articles in this field.

Scientific cooperation was defined as researchers collaborating to generate new scientific knowledge [40] and was divided into 3 levels, including the cooperation between authors, institutions, and countries/regions. In bibliometric analysis, sociality and academic output are equally important for evaluating the importance of nodes in collaborative networks. The important evaluation index of sociality is BC. When BC is greater than 0.1, the node is considered to be the central node, which can have a great impact on research in this field. Only a small number of direct collaborations were found among authors and institutions, which might be due to the ability of authors and institutions to conduct independent research activities in this field. The cooperations between countries/regions were denser, especially among developed countries. For example, the United States is the node with the highest number of publications counts and BC, and the countries with which it works most closely are Canada and Japan. In addition, the most of top ten countries/regions in terms of publication counts and BC were developed countries/regions except China, Mexico, and Russia. This is partly related to the fact that researchers in developed countries had easier access to research funding support and commanded better basic research facilities [41]. On the other hand, developed countries tend to face more severe aging problems than developing countries [42]. The higher prevalence of SS in the elderly population provides a stronger impetus for research in this area in developed countries [43]. Increased cooperation between countries can accelerate the development of the discipline and produce more high-quality publications. To advance the treatment of SS, enhanced cooperation between countries, especially between developed and developing countries, remains an urgent need.

4.2. Research hotspots and emerging trends on the treatment of SS

Based on the analysis of keywords and co-cited references, several research hotspots related to SS treatment were summarized including immunosuppressive and anti-inflammatory therapy (cell target therapy, B cells, T cells, Treg, MAIT cells, DCs, MSCs, rituximab, belimumab, abatacept, IFN-α, BAFF), regenerative therapy (MSCs), gene therapy, surgical treatment, and symptomatic treatment (artificial tears). Among them, B cells, T cells, MAIT cells, MSCs, rituximab, belimumab, cell-target therapy, and immunosuppressive and anti-inflammatory therapy were emerging trends in this field.

4.2.1. Immunosuppressive and anti-inflammatory therapy

SS is a systemic autoimmune disease with inflammation, characterized by lymphocytic infiltration and sicca symptoms of secretory glands [3,44]. The pathophysiology of SS had made tremendous progress in the last few decades, and innate immunity, especially the interferon signaling pathway, plays an important role in the early stage of the disease [45]. On the other hand, the adaptive immune system plays a central role in the development of SS, such as the sustained activation of B cells and the immunomodulatory activity of T cells (e.g., Th1, Th17, Treg) [2]. Salivary gland epithelial cells play a dual role in the pathogenesis of SS, as they are both targets of autoimmune processes and triggers of immune activation. These cells can produce a variety of cytokines (e.g., IL-21 and BAFF) [34] and promote B-cell activation along with other factors (e.g., crosstalk between T cells and B cells) [1]. Different therapeutic targets can be applied to SS patients for the inflammatory and immune processes involved in the knowledge of the pathophysiology of SS.

Over the past decade, B-cell targeted therapies have been the most promising investigational agents in SS(39). Achieving B-cell depletion and inhibiting cytokines critical to B-cell development or activation are the primary modalities of B-cell targeted therapies. The first anti-CD20 monoclonal antibody that has been tested in SS is rituximab [46]. While several open-label studies and randomized controlled trials (RCTs) supported the improvement effects of rituximab on fatigue, dryness, pain, and salivary gland echostructure in patients with SS [29,32,36,47–49], satisfactory efficacy targeted to SS were not observed in two larger multicenter RCTs [30,33]. In the study from France enrolling 120 patients with pSS from 14 hospitals, the primary endpoint by using rituximab (improvement of at least 30 mm in 2 of 4 visual analogue scales (VASs) by week 24, including global disease, pain, fatigue, and dryness) was not met [30]. Another study from the United Kingdom included 133 pSS patients from 25 rheumatology clinics, in which rituximab did not improve any other outcome measures (including fatigue, dry mouth, tear flow rate, and quality of life) except for unstimulated saliva flow [33].

Belimumab, a monoclonal antibody targeting BAFF, was evaluated in an open-label trial with belimumab in patients with pSS (BELISS). In the BELISS trial, targeting BAFF with belimumab successfully normalized B cell frequency, phenotype, and functions in patients with pSS [50]. After 24 weeks (per 4 weeks) of belimumab treatment, 18 out of 30 patients with pSS in the subject met the primary endpoint of the improvement in two of five items by week 28: dryness, fatigue, pain, systemic disease activity, and/or B cell activation biomarker [31]. A new strategy for the treatment of pSS in combination with rituximab and belimumab is currently being investigated. It was found that near-complete depletion of $CD20^+$ B cells in small salivary glands and a greater and more persistent depletion of peripheral $CD19^+$ B cells were observed with belimumab + rituximab compared with rituximab or belimumab monotherapy [51].

The activation and migratory state of T cells are the likely key step in the pathogenesis of SS, and T cells have been logical and key targets for the treatment of SS [52–54]. Abatacept is a selective costimulatory modulator that blocks the interaction between CD80/CD86 on antigen-presenting cells and CD28 on T cells, further limiting the activation of T cells and T cell-dependent B cell

hyperactivity [53,55]. Several open-label and prospective observational studies have reported beneficial effects of abatacept on SS disease activity [56–59], but the results of two phase III RCTs with a larger scale did not show any significant clinical efficacy of abatacept compared with placebo in patients with early and moderate-to-severe pSS [55,60]. The role of Treg cells in the pathogenesis of SS remains controversial and is manifested as an increase, decrease, or no change in amounts [54]. Several studies have presented the driving role of Th17/Treg imbalanced in SS progression [61–64]. Although no change in SS activity was observed, short-term treatment with low-dose IL-2 restored the Th17/Treg ratio in SS patients [65]. MAIT cells are the kind of innate-like T cells abundant in human, which can mount immune response with/without antigens stimulation [66,67]. It was reported that the altered function of MAIT cells in the salivary gland of SS patients may lead to local immune response disorders, triggering autoimmune damage to glandular tissue and the development of dry symptoms [68,69]. The emerging roles of MAIT cells in the pathogenesis of SS may be the target and approaches of clinical intervention in the future.

In general, circulating DCs are divided into two main categories: myeloid DCs (mDC), which play an antigen-presenting role, and plasmacytoid DCs (pDC), which are the main producers of type I IFN (e.g., IFN-α and IFN-β) [70,71]. Infiltrating pDCs and activated type I IFN signaling pathways can be found in the salivary glands of SS patients [72]. IFN signaling may affect multiple aspects of SS pathophysiology, including lymphocyte infiltration into exocrine glands, autoantibody production, and glandular cell apoptosis [73]. In addition, pDCs can secrete a variety of other inflammatory cytokines, such as TNFα and IL-6 [74,75]. A variety of therapies targeting IFN pathways and DCs are currently being explored for the treatment of SS, such as hydroxychloroquine, RSLV-132, BX795, ILT7, and tofacitinib [76–78].

MSCs are capable of producing potent immunomodulatory effects on both adaptive and innate immune responses through intercellular contacts and the release of soluble factors [79]. Recently, salivary gland-derived MSCs (SGMSCs) have been characterized and shown to have the ability to immunomodulatory [63,80]. Some evidence suggested that the immunomodulatory capacity of SGMSCs and bone marrow MSCs (BMSCs) from SS patients was defective [80,81]. Reports showed improved salivary secretion and reduced lymphocyte infiltration in the salivary glands of patients and mice with SS after intravenous or infra-peritoneal injection of MSCs [82]. Supplementing exogenous MSCs or extracellular vesicles derived from MSCs can be a potential novel treatment strategy for SS [63,79,80,83].

4.2.2. Regenerative therapy

In addition to immunomodulatory capabilities, MSCs have tissue repair, homing capacity toward injured tissue, and multidirectional differentiation capabilities, including osteogenic, adipogenic, and salivary gland-like cells [80,84,85]. SGMSCs from SS patients have a defect in salivary gland-like cell differentiation compared to normal individuals [80]. The transfer of MSCs and their derived cells may be a promising method to restore hypo-salivary function by reconstructing damaged salivary glands. Currently, a variety of MSCs including SGMSCs, BMSCs, adipose-derived stem cells (ADSCs), and dental pulp stem cells (DPSCs) have been reported to have salivary gland regenerative potential [85–87]. However, it remains controversial whether these MSCs differentiate directly into salivary gland epithelial cells or whether their soluble factors induce residual cell regeneration [85]. Besides, it has been found that the proliferation and differentiation of salivary gland progenitor cells (SGPCs) in SS patients are significantly decreased, and the application of SGPCs to rescue damaged salivary glands may be a choice for SS treatment [88,89].

In addition, MSCs and other types of stem cells combined with organoid technology hold the promise of replacing whole organs for tissue regeneration [90,91]. In 2018, Tanaka et al. [92] applied embryonic stem cells successfully generated orthotopically functional salivary in mice with the characteristics of mature salivary glands. Another of their studies used human iPSCs to successfully regenerate salivary gland-like organs in vitro and to form mature salivary glands penetrated by host vessels and nerves after transplantation in parotid gland-defective severe combined immunodeficient mice [93].

4.2.3. Gene therapy

Gene therapy is the treatment through transferring genetic material into the cells of patients, which had been explored for the treatment of salivary gland diseases since the early 20th century [94]. The therapeutic agent can be administered for gene transfer by retrograde infusion through the main excretory ducts of the glands or by intravenous injection [95,96]. There is no clear and coherent understanding of the pathogenesis of SS, and current attempts at gene therapy related to SS are based on animal models [95]. Therapies based on different vectors (e.g., adeno-associated virus and adenovirus) and targeting different transfer genes (e.g., IL-10, IL-27, and aquaporin 5) have shown alleviating effects on SS [96–99]. Notably, the immune response and toxicity induced by different vectors may pose an ongoing challenge for gene therapy of SS [100,101].

4.2.4. Surgical treatment

Although parotid and minor salivary gland surgery are often performed clinically in patients with suspected SS for diagnostic purposes, surgical treatments such as superficial or parotidectomy are uncommon in non-malignant diseases [102]. Obstructive salivary gland diseases associated with SS could be treated with interventional salivary gland endoscopy and could be combined with endoscopy-assisted surgical interventions, irrigation of the duct system, and mechanical dilation [103–105]. superficial or total parotidectomy should be considered when chronic salivary adenitis associated with SS causes severe pain, excessively frequent episodes, or a poor response to nonsurgical treatment [106,107]. The risk of non-Hodgkin's lymphoma due to SS is another clinical manifestation that may lead to surgical intervention [102]. Temporary or permanent facial nerve damage, postoperative pain, and persistent inflammation of residual parotid tissue that may result from surgical treatment should be taken into account [102,108].

4.2.5. Symptomatic treatment

Except for the early stages of the disease, dysfunction will remain stable over a long period of time with a chronic course, and no studies have shown that available therapies can completely reverse glandular dysfunction and thus cure sicca symptoms [109]. Based on this, the primary treatment for SS should be topical therapies to relieve the patient's symptoms, such as tear and saliva substitutes, analgesics, and saliva stimulants [1,5].

Artificial tears and eye gels/ointments are the first-line therapy for ocular dryness and can reduce friction between the eyelids and eyeballs by lubricating and adding the volume to the tear volume lake [5,110]. In 2016, A Cochrane review on the application of artificial tears for dry eye syndrome indicated their safe and effective means [111].

4.3. The guiding value for further clinical practice

Notably, all of the emerging trends in the field of treatment of SS are related to immunosuppressive and anti-inflammatory therapy. Unlike other common treatments available for symptomatic relief (e.g., oral pilocarpine and cevimeline), immunosuppressive and anti-inflammatory therapy is expected to directly target the pathogenic pathways and prevent further progression of SS [1]. Although some immunosuppressive and anti-inflammatory therapies have not achieved the desired clinical outcomes [55,60], more appropriate clinical trial paradigms should be applied to evaluate the results of these treatment options, such as better definition of subgroups of patients to be recruited, more strictly use of the new ACR/EULAR criteria, clearer definitions of disease activity, and more appropriate endpoints for success [112,113]. In summary, based on the results of this study, immunosuppression and anti-inflammatory therapy remain the focus of clinical practice and scientific research for SS therapy in the future, and more rigorously designed and suitable trials are needed to enrich knowledge in this field.

4.4. Limitations

Consistent with other bibliometric analyses, there are some limitations in this study: (I) Only English publications in the WOSCC database were analyzed in this study, which may have resulted in some key articles not being included. (II) Although different selection criteria and pruning were used in the various parts, the visualization results of the bibliometric analysis were still determined by the size of the threshold. This study did not compare the results of visual analysis under different thresholds. (III) In this study, although the researchers manually merged synonyms or similar words in authors and keywords, they could not guarantee that they had eliminated the bias associated with synonyms and similar words. (IV) Only two types of publications were included in this study: articles and review articles. Therefore, the results of this study cannot be applied to publications other than these two types of publications. (V) The literature search for this study was conducted on December 21, 2022, which may have resulted in inaccurate results for the analysis of 2022. (VI) Some recently published high-quality articles may have low citation counts due to insufficient time since publication, which may affect the results of the analysis. Nevertheless, we believe that this study reflects the hot spots and emerging trends in the treatment of SS, and through this study, future researchers will be able to more quickly understand the current state of research in this field and choose their research directions more effectively.

5. Conclusions

In conclusion, a variety of therapies, including immunotherapy and anti-inflammatory therapy, have been applied or explored for the treatment of SS with increasing attention and funding. This bibliometric study provides a new perspective on the treatment of SS and summarizes research hotspots and emerging trends in this field. Immunosuppressive and anti-inflammatory therapy is expected to continue to be a focus of future clinical practice and scientific research. This will not only help future researchers to acquire a knowledge base in the field, but also provide direction and ideas for their research, and ultimately contribute to the advancement of research on SS treatment.

Data availability statement

Data associated with this study has not been deposited into a publicly available repository. Data included in article/supplemental materials/referenced in the article.

Funding

This research was supported by the National Natural Science Foundation of China (82201084), the China Postdoctoral Science Foundation (2022M722232), Beijing Postdoctoral Research Foundation (2023-ZZ-020) and the Miaopu Project of Beijing Tiantan Hospital, Capital Medical University (2023 MP10).

CRediT authorship contribution statement

Wenpeng Song: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis. **Hao Wang:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Xiaoyan Wang:** Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This research was supported by the National Natural Science Foundation of China (82201084), the China Postdoctoral Science Foundation (2022M722232), and the Miaopu Project of Beijing Tiantan Hospital, Capital Medical University (2023 MP10). We thank Professor Chen for the excellent tool "CiteSpace" for bibliometric analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23216.

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