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Research article

Frontiers and hotspots evolution in cytokine storm: A bibliometric analysis from 2004 to 2022

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ABSTRACT

Background: As a fatal disease, cytokine storm has garnered research attention in recent years. Nonetheless, as the body of related studies expands, a thorough and impartial evaluation of the current status of research on cytokine storms remains absent. Consequently, this study aimed to thoroughly explore the research landscape and evolution of cytokine storm utilizing bibliometric and knowledge graph approaches.

Methods: Research articles and reviews centered on cytokine storms were retrieved from the Web of Science Core Collection database. For bibliometric analysis, tools such as Excel 365, CiteSpace, VOSviewer, and the Bibliometrix R package were utilized.

Results: This bibliometric analysis encompassed 6647 articles published between 2004 and 2022. The quantity of pertinent articles and citation frequency exhibited a yearly upward trend, with a sharp increase starting in 2020. Network analysis of collaborations reveals that the United States holds a dominant position in this area, boasting the largest publication count and leading institutions. Frontiers in Immunology ranks as the leading journal for the largest publication count in this area. Stephan A. Grupp, a prominent researcher in this area, has authored the largest publication count and has the second-highest citation frequency. Research trends and keyword evaluations show that the connection between cytokine storm and COVID-19, as well as cytokine storm treatment, are hot topics in research. Furthermore, research on cytokine storm and COVID-19 sits at the forefront in this area.

Conclusion: This study employed bibliometric analysis to create a visual representation of cytokine storm research, revealing current trends and burgeoning topics in this area for the first time. It will provide valuable insights, helping scholars pinpoint critical research areas and potential collaborators.

1. Introduction

Cytokines are polypeptides that function as intercellular mediators [1]. Cytokines perform critical functions in the immune system and engage in diverse physiological and pathological activities, such as tissue repair, blood coagulation, and inflammatory response, to maintain life [2–4]. However, when the body machine malfunctions and is in a state of disorder caused by infectious or non-infectious factors, it leads to the mass release of certain cytokines, thus damaging the body and tissues. This is also referred to as a cytokine storm

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[5]. A cytokine storm commonly occurs in several types of infections [6], and is primarily stimulated by an excessive pathogen burden, such as sepsis, and immune activation caused by long-term infection, such as hemophagocytic lymphoproliferative disease related to the Epstein-Barr virus (EBV) [7]. In addition, it can be caused by non-infectious factors, such as graft-versus-host reactions, autoimmune diseases like systemic lupus erythematosus, and cancer [8–10]. Recent research has established that a cytokine storm can be triggered by certain immunotherapies. Notably, this includes treatments such as chimeric antigen receptor T-cell immunotherapy (CAR-T) [11,12]. This response, often classified as cytokine release syndrome (CRS), involves the excessive activation of effector immune cells, leading to a substantial release of cytokines [7]. The potential mechanisms of the cytokine storm are complicated, including the dysregulated discharge of pro-inflammatory cytokines and disturbance of the negative feedback of high inflammation [13,14]. Cytokine storms induce excessive inflammatory and immune responses that can escalate into acute and critical diseases. These include acute conditions like disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). Ultimately, these reactions can progress to multiple organ failure syndrome (MODS), a critical and potentially fatal outcome [15–17]. Recent research indicates that cytokine storms are crucial in the progression of diseases like leptospirosis and Ebola virus disease [18, 19]. With the coronavirus disease 2019 (COVID-19) outbreak, the relationship between cytokine storms and COVID-19 has recently gained increasing attention [20–22].

Utilizing mathematical and statistical methods, bibliometric analysis performs qualitative and quantitative evaluations of scientific literature in a particular research area [23,24]. This approach can showcase the most recent advancements, pinpoint emerging topics, and forecast future directions in the research area, enabling researchers to identify and visualize the progression of research [25]. Bibliometric analyses have been applied in several research fields related to cytokine storms, including CAR-T cell therapy [26] and COVID-19 [27]. Despite the swift advancement of cytokine storm research over the last 20 years, the results require further expansion and confirmation. There are few studies that summarize the key information regarding cytokine storms, and bibliometric analysis remains limited in this area. Therefore, we employed VOSviewer and CiteSpace, two bibliometric tools, to perform a thorough bibliometric analysis of the publications. This was done to evaluate the general landscape of cytokine storm research, pinpointing trends and emerging topics from the past two decades, which enables researchers to achieve a more profound understanding of pertinent topics and acts as an essential asset for future collaborative studies.

2. Material and methods

2.1. Data source and retrieval method

This study employed a metrological analysis, leveraging data from the extensively used and comprehensive Web of Science Core Collection (WOSCC) database. Being a premier worldwide citation database, the WOSCC offers essential research articles, extensive analytical tools, and raw data for examination. The application of bibliometrics, supported by the WOSCC database, is progressively growing in different fields of study [28,29]. The Medical Subject Headings (MeSH) is extensively utilized in bibliometric studies due to its accuracy and the standardized categorization it provides for papers listed in the PubMed database [30]. In this study, we utilized the MeSH vocabulary to establish the search terms associated with cytokine storm, ensuring a more accurate and comprehensive retrieval of relevant literature. The search strategy employed was “TS = (“Cytokine Release Syndrome” OR “Cytokine Release Syndromes” OR “Cytokine Storm Syndrome” OR “Cytokine Storm” OR “Cytokine Storms”)”, covering the timeframe between January 1, 2004, and October 10, 2022, and restricted to "Article" and "Review" document types published in English. This approach identified 6647 articles. The search for relevant literature was finalized on October 10, 2022, to avoid data distortion from subsequent database updates.

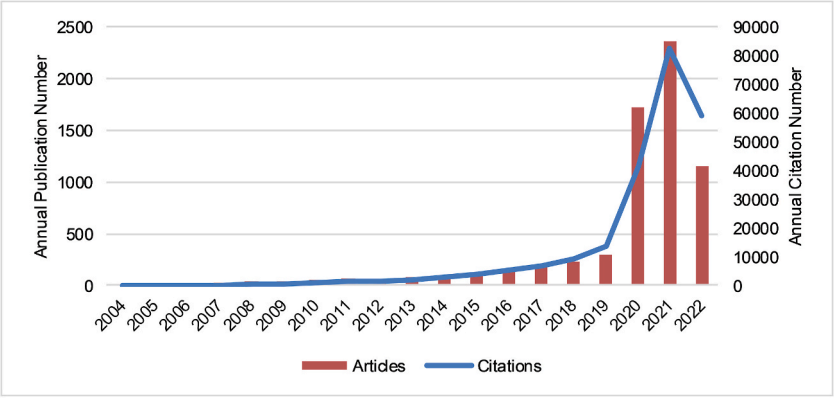
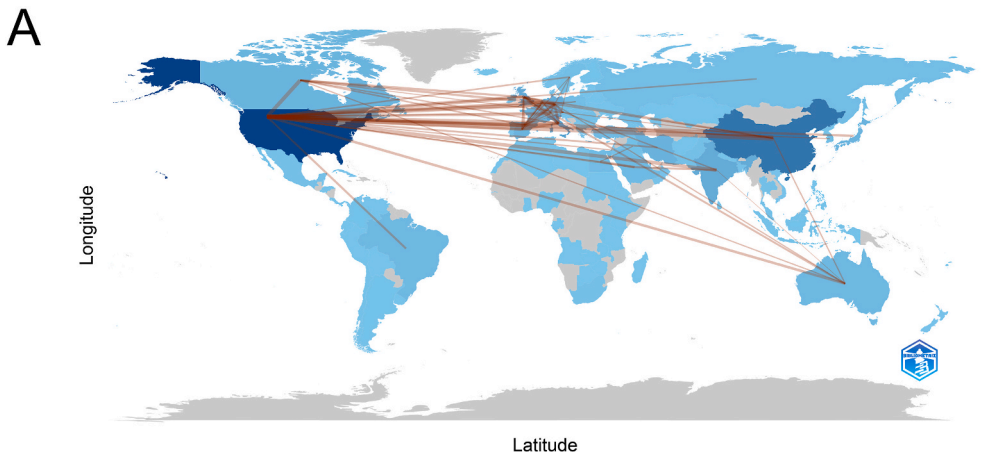
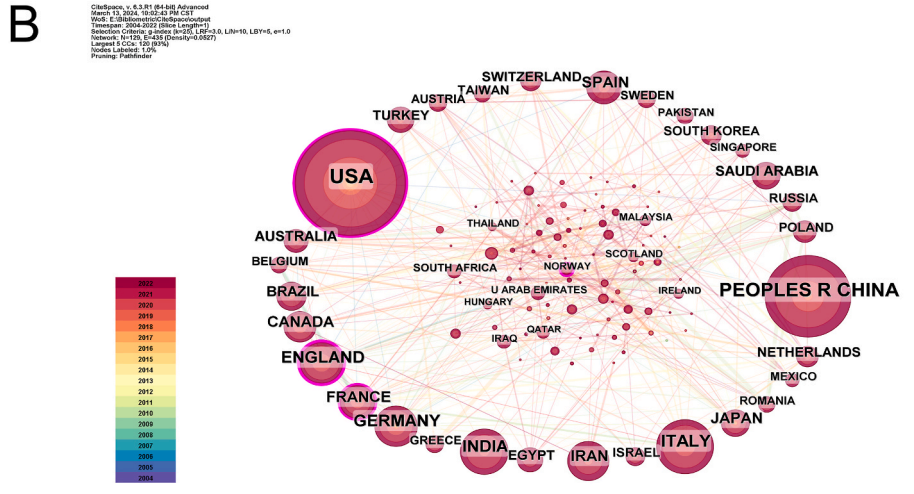


Fig. 1. Publication and citation trends related to cytokine storm research from 2004 to 2022. The data shows a general upward trend in the quantity of publications and their citation frequency, with a peak in 2021.





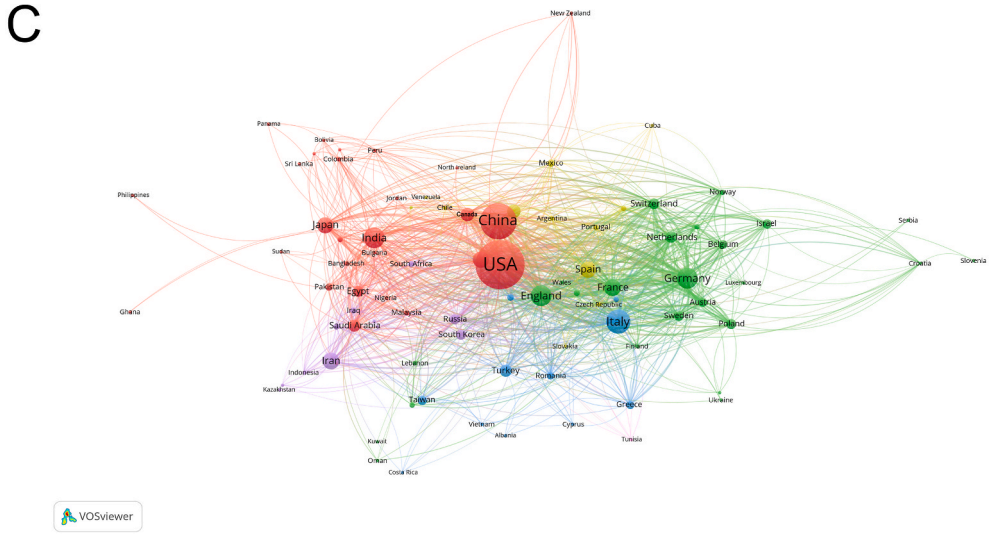


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Fig. 2. Analysis of countries/regions engaged in cytokine storm-associated research. (A) Identification of countries/regions engaged in cytokine storm-associated research, with connections representing collaborations and links between them. (B) CiteSpace analysis of the collaboration network of countries and regions, where node size signifies co-occurrence frequency, and links denote the co-occurrence relationship. (C) VOSviewer visualization of the collaborative network of countries and regions. Countries and regions with more than one publication are displayed, with nodes symbolizing the countries and regions in various clusters, and node size indicating their occurrence frequency.

2.2. Bibliometric analysis

This study employed two bibliometric and visualization analysis tools, namely CiteSpace and VOSviewer, to investigate publication patterns in our field of interest. CiteSpace, a leading software frequently used for bibliometric studies, was developed by Chaomei Chen [31]. On the other hand, VOSviewer, developed by Nees Jan van Eck et al., was primarily utilized for analyzing bibliometric network graphs [32]. These software programs were utilized for collaborative analysis and visualization of countries/regions, institutions, authors, and journals. Specifically, CiteSpace 6.3.R1 (64-bit) Advanced was used to conduct journal citation analysis, generate keyword timeline diagram, perform reference analysis, and carry out high-burst citation analysis. Meanwhile, VOSviewer 1.6.18 was utilized for analyzing author cooperation and keyword co-occurrence relationships. Moreover, we employed Bibliometrix (a tool for R-Studio) to evaluate worldwide spread of pertinent studies and the development of keywords, while using Microsoft Excel 365 to depict the trends in articles and citations across the years. Data originally used in this study, sourced from publicly accessible databases, required no ethical approval.

3. Results

3.1. Annual publication volume and cited trends

Between 2004 and 2022, Fig. 1 illustrates the annual publication count and citation frequency for relevant publications. The quantity of annual publications associated with cytokine storm is growing, with 2021 having the highest publication count at 2352. In general, the annual citation frequency for cytokine storm-associated publications exhibited a growing trend, with a gradual rise prior to 2019 and a sharp increase following 2020. In 2021, the literature showed the highest annual frequency of citations at 82476 (Fig. 1). Notably, because of the search time, we were unable to obtain all publications and citations in 2022. However, as of the study's date, the annual count of publications and citations stood at 1148 and 58881, respectively, reflecting the rapid growth of annual publications and citations in 2022.

3.2. Country/region distribution

This research encompassed 84 countries/regions, mainly focused in the Northern Hemisphere. Fig. 2A shows the national cooperation network among countries/regions. Significantly, the primary focus of inter-regional links was between North America and Europe, followed by North America and East Asia. Additionally, robust connections were clearly present between Oceania and the regions of North America, Europe, and East Asia (Fig. 2A). The leading ten countries/regions, ranked by publications and citations frequency, are listed in Tables 1 and 2. The United States led in terms of publication count (2317), trailed by China (1283) and Italy (594). The United States also exhibited the greatest citation frequency (124209), followed by China (45188). Fig. 2B and C illustrate the global collaboration among countries with a substantial publication count. In the collaborative network analysis performed using CiteSpace, a node's radius grew proportionally to its contribution, depicted by the quantity of publications in the cytokine storm research area. The width of the nodes' inner circles, distinguished by colors, represents the article count for each corresponding year. The links between nodes signify the collaborative associations among countries and regions, with the link thickness positively related to the co-occurrence frequency. A node's betweenness centrality, which quantifies its occurrence frequency on the shortest paths among other nodes, is directly represented by the size of its encircling purple circles. Nodes displaying a betweenness centrality greater than 0.1 are connected to over 10 % of other nodes. These nodes exert substantial influence through the significant resources they control within their networks [33]. The United States, China, and Englandwere the primary research centers for cytokine storms, and

Table 1
Top 10 countries/regions ranked by publication count.

Rank	Countries/regions	Publications	Centrality
1	USA	2317	0.17
2	China	1283	0.02
3	Italy	594	0.01
4	England	441	0.26
5	Germany	429	0.10
6	India	425	0.03
7	Iran	289	0.03
8	France	282	0.14
9	Spain	265	0.03
10	Japan	262	0.09

Table 2
Top 10 countries/regions ranked by citation frequency.

Rank	Countries/Regions	Citations	Centrality
1	USA	124209	0.17
2	China	45188	0.02
3	Germany	25921	0.10
4	Italy	24125	0.01
5	England	22204	0.26
6	France	19405	0.14
7	Canada	15010	0.09
8	Spain	10368	0.03
9	Australia	9512	0.06
10	Japan	8425	0.09

had close cooperation with Italy, Canada, and Germany. Notably, England (0.26), the United States (0.17), and France (0.14) showed high betweenness centrality, suggesting that these countries significantly influenced cytokine storm research (Fig. 2B). VOSviewer's worldwide cooperative network revealed that countries and regions can be grouped into five clusters based on their collaboration level, represented by different colors (Fig. 2C). Within these blocks, nodes with shared attributes, such as co-authorship, were grouped together into clusters, visually indicated by the same color. The five blocks of countries/regions are as follows: the United States, China, Canada, Japan, India, etc. (red); England, Germany, Switzerland, France, the Netherlands, etc.(green); Italy, Greece, Turkey, etc. (blue); Spain, Mexico, etc. (yellow); and Iran, Russia, South Korea, etc. (purple).

3.3. Institutional analysis

Tables 3 and 4 present the leading ten institutions based on publication volume and citation frequency. The University of Pennsylvania had the highest article count (174), trailed by the Huazhong University of Science and Technology (127). Of the foremost ten institutions with the highest number of publications, six are located in the United States, making it the most represented country. Institutions in China account for three of these, coming next in the list. The University of North Carolina was the most active entity (23730), trailed by the University of Texas MD Anderson Cancer Center (12083) and the National Cancer Institute (10443). The United States was abode to all of the leading ten institutions based on citation frequency. Notably, for the University of California System and Universite Paris Cite, the betweenness centrality are 0.10 and 0.09 respectively, significantly higher than those of other institutions, which do not exceed 0.08. This indicates that these two institutions exerted significant influence on the field of cytokine storm research.

Fig. 3A depicts the proportion of publications published by institutions in relation to the total publication count from 2004 to 2022. Research institutions were analyzed to map the global spread of cytokine-storm-associated publications and to explore potential collaborative opportunities. In CiteSpace, the University of California System was highly productive and held the greatest centrality. In addition, institutions such as Universite Paris Cite and University of Wurzburg also had high centrality, indicating extensive cooperation with academic institutions worldwide (Fig. 3A). In VOSviewer, institutions were classified into five closely related blocks based on the level of collaboration (Fig. 3B): Huazhong University of Science, Zhejiang University, etc. (red); University of Pennsylvania, Emory University, etc. (blue); Memorial Sloan Kettering Cancer Center, The University of Maryland, etc. (yellow); University of Milan, University of Toronto, etc. (green); Harvard Medical School, Tehran University of Medical Sciences, etc. (purple).

The temporal distribution of the publications from each institution is illustrated in Supplementary Fig. 1. Nodes with a color tendency towards yellow suggest a more recent overall publication date, while nodes with a color inclination towards purple imply an earlier overall publication date. The results showed that Shahid Beheshti University of Medical Sciences and Tehran University of Medical Sciences are emerging forces in cytokine storm research. Over the past few years, the research output of the University of Pennsylvania and University of Cambridge in the field of cytokine storms has been relatively small. Notably, the temporal distribution of publications in Supplementary Fig. 1 shows a concentration between 2019 and 2021, which can be linked to the sharp increase in scholarly output observed after 2019.

Table 3
Top 10 institutions ranked by publication count.

Rank	Institution	Publication	Centrality
1	Univ Penn	174	0.03
2	Huazhong Univ Sci & Technol	127	0.01
3	Harvard Med Sch	117	0.03
4	Univ Texas Md Anderson Canc Ctr	102	0.02
5	Mem Sloan Kettering Canc Ctr	90	0.03
6	Univ Washington	81	0.02
7	Mayo Clin	79	0.02
8	Zhejiang Univ	77	0.01
9	Univ Tehran Med Sci	76	0.04
10	Chinese Acad Sci	69	0.01

Table 4
Top 10 institutions ranked by citation frequency.

Rank	Institution	Citations	Centrality
1	Univ Penn	23730	0.03
2	Univ Texas Md Anderson Canc Ctr	12083	0.02
3	Nci	10443	0.02
4	Mayo Clin	9349	0.02
5	Univ Washington	9020	0.02
6	H Lee Moffitt Canc Ctr & Res Inst	8921	0.01
7	Fred Hutchinson Canc Res Ctr	8355	0.03
8	Mem Sloan Kettering Canc Ctr	8256	0.03
9	Dana Farber Canc Inst	7307	0.04
10	Harvard Med Sch	7094	0.03

3.4. Journal analysis

Frontiers in Immunology had the highest publication count (317) in cytokine storm-associated research, trailed by International Journal of Molecular Sciences (117), Frontiers in Pharmacology (97), and Blood (65) (Supplementary Tables 1 and 2). In the Journal Citation Reports (JCR), among the top ten journals ranked by publication count, four are categorized under Q1, and six have an impact factor (IF) above 5. The New England Journal of Medicine and Blood were the most frequently cited journals, with 18481 and 9785 articles, respectively. All journals among the leading ten based on citation frequency were listed in the Q1 JCR and had an IF exceeding 8. Notably, two of the leading ten journals based on publication count were also among the top ten journals by citation frequency, suggesting their substantial impact in this field.

The CiteSpace analysis revealed that the periodic network consisted of a relatively large number of journals with extensive connections among them. Nature and Journal of Clinical Investigation were highly productive institutions with high betweenness centrality values. Nature Medicine, Nature Immunology, and Journal of Clinical Oncology also exhibited high centrality values, indicating their extensive cooperation with other journals (Fig. 4A). The visualization generated by VOSviewer depicted the journals that published literature on cytokine storms, as well as their associations and connections with each other. These journals, organized by their co-citation frequency, were divided into four distinct groups, each sharing similar research themes (Fig. 4B). The green block had studies focused on clinical research and experiments (New England Journal of Medicine and Nature Medicine, etc.), tumor-related fields (Lancet Oncology, Journal of Clinical Oncology, and Journal of Hematology & Oncology, etc.), and blood-related fields (Blood and Blood Advances, etc.); the red block concentrated on clinical studies and interventions, including (Lancet, Clinical Infectious Diseases, and the Journal of the American Medical Association, etc.); the yellow block emphasized autoimmunity (Annals of Rheumatic Diseases, and Arthritis Research and Therapy, etc.); and the blue cluster's studies mainly focused on biochemistry and molecular biology (Frontiers in Immunology, Journal of Immunology, and Cell Research, etc.).

To investigate how knowledge evolves, we conducted an examination of knowledge trajectory focusing on the interactions of citations and co-citations. This analysis was specifically applied to explore relationships between journals that cite others and those that are cited [34]. By utilizing a dual-map overlay of journals, we illustrated the subject coverage, citation trajectory modifications, and movements in academic hubs across scholarly journals [34,35] (Fig. 4C). The cited journals mainly belonged to the disciplines of molecular biology, biology, immunology, medicine, medicinal biology, which represent research frontiers with the latest advancements and cutting-edge research. The cited journals were largely from the areas of molecular biology, biology, genetics, health, nursing, and medicine, forming a knowledge base that provided foundational understanding and support for this research.

3.5. Author analysis

The 6647 publications included in this study were published by 21866 authors. Supplementary Tables 3 and 4 list the ten authors who lead in both publication count and frequency of citations. Authors with several publications were Stephan A. Grupp (33), He Huang (29), Carl H. June (28), and Yongxian Hu (23). Carl H. June had the highest citation count (12185), trailed by Stephan A. Grupp (11962) and David L. Porter (10135). Notably, Stephan A. Grupp and Carl H. June led in both publication count and citation frequency, establishing themselves as influential authorities in this area. Moreover, among the leading ten authors based on publication count or citation frequency, Jianfeng Zhou (138) and Stephan A. Grupp (120) exhibited the greatest total link strength (TLS). TLS represents the total number of co-occurrences between one author and other authors. This highlights the importance of and substantial contributions to the field.

Collaborative authorship serves as a formal means of knowledge sharing among scholars, whereas co-authorship analysis enables the examination of interactions among researchers within a specific research domain. The collaboration network among authors of cytokine storm-related publications was visualized using VOSviewer (Fig. 5). This network assists in identifying potential research collaborators and industry experts. Based on the connectivity of the authors, they were generally divided into 11 blocks: the authors in the red blocks were Xin Li and Qi Deng, etc.; the authors in the orange blocks were Jianfeng Zhou and Liting Chen, etc.; the authors in the light green blocks were Lei Yu and Depei Wu, etc.; the authors in the purple block were Yang Liu, Jing Li, and Yao Wang, etc.; the authors in the pink block were Ming Shi and Ying Wang, etc.; the authors in the yellow block were Edward M. Behrens and Gerhard Zugmaier, etc.; the authors in the blue block were Stephan A. Grupp and Carl H. June, etc.; the authors in the brown block were

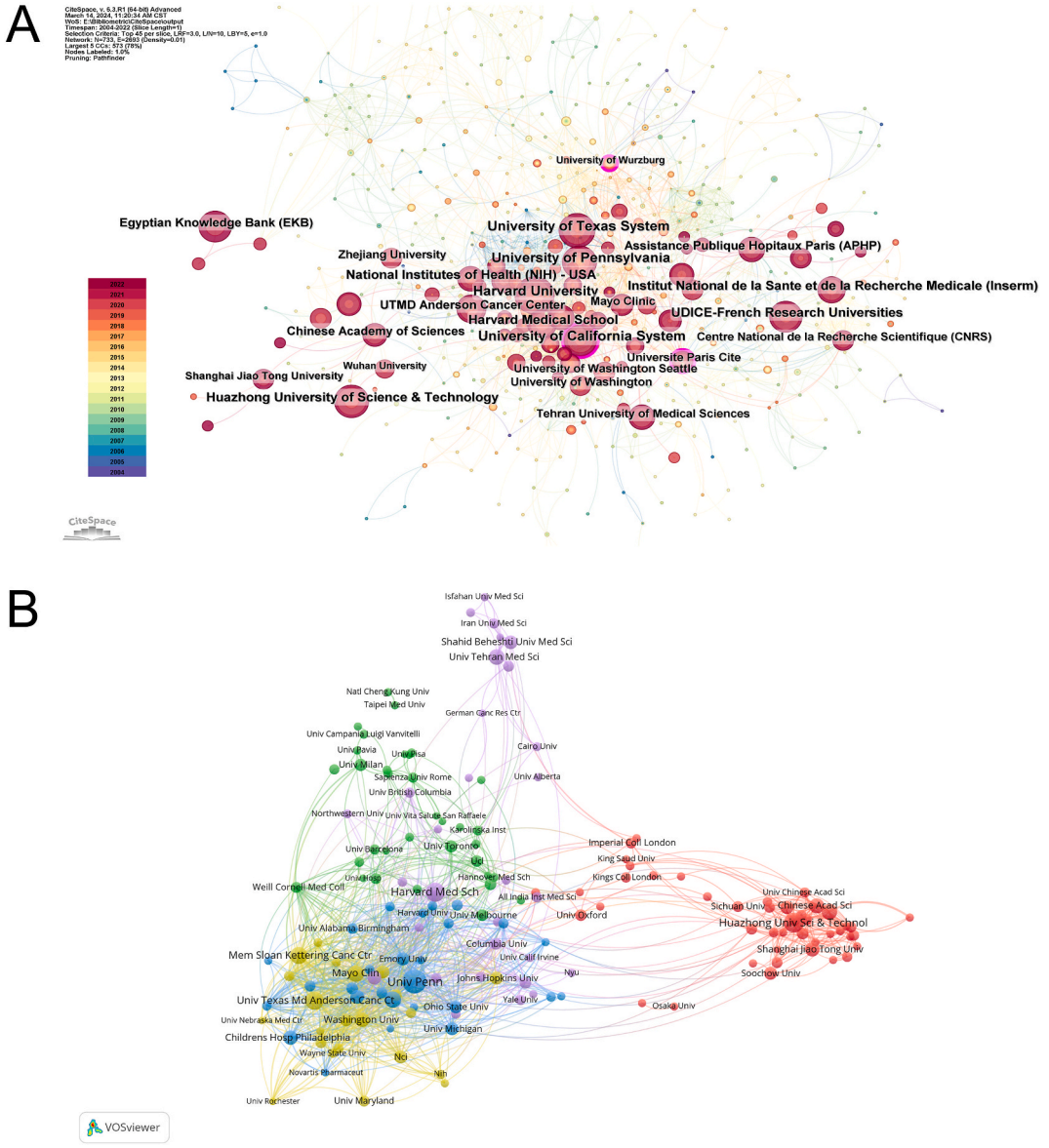

Fig. 3. Analysis of cytokine storm-related institutions. (A) CiteSpace depiction of the cooperative network among institutions. Node size signifies co-occurrence frequencies, links denote co-occurrence relationships, and nodes with purple outer circles indicate high centrality. (B) VOSviewer visualization of the collaborative network of institutions. Institutions with more than 5 publications are displayed. Nodes with various colors symbolize institutions in different clusters, and node size represents their occurrence frequency. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Cameron J. Turtle and Stanley R. Riddell, etc.; the authors in the green block were Frederick L. Locke and Sattva S. Neelapu, etc.; and the authors in the cyan blocks were Jae H. Park and Michel Sadelain et al. These blocks constituted two major clusters. The first cluster primarily included red, orange, purple, and pink blocks, whereas the second cluster mainly included blue, brown, cyan, green, and yellow blocks. Notably, these two clusters are connected by pink and red blocks, indicating that the authors of these blocks play a bridging role.

3.6. Keyword analysis

Being a summary of the article's central themes, keywords can be employed to examine the leading edges of cytokine storm research. Supplementary Table 5 presents the leading 20 keywords based on their occurrence frequency. "COVID-19" (2532) was the most frequently appearing keyword, trailed by "severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]" (1458). Furthermore, "cytokine storm" (1165) and "inflammation" (516) were frequently appearing keywords, suggesting that these areas were hotspots in

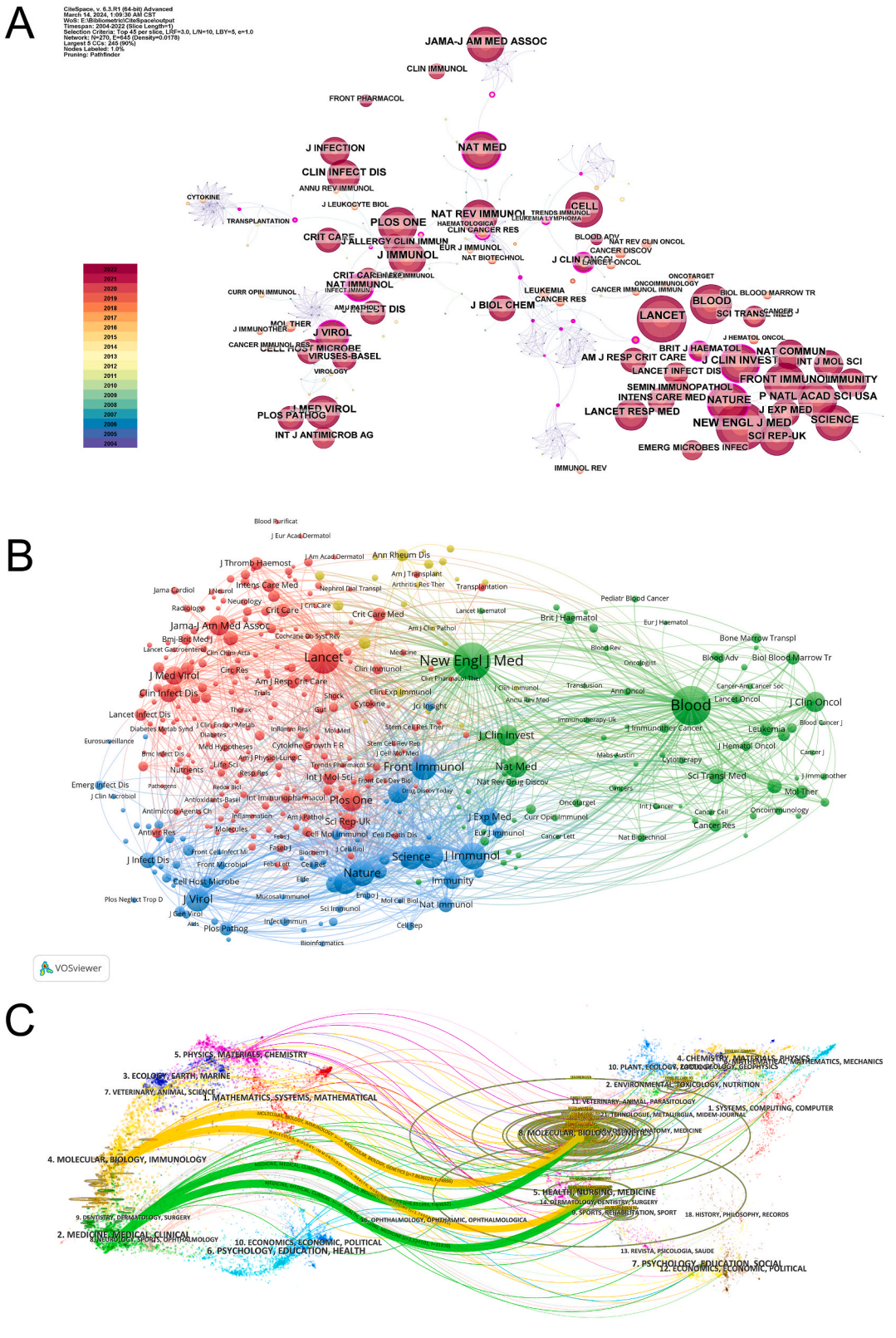

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Fig. 4. Analysis of cytokine storm-related journals. (A) CiteSpace depiction of the cooperative network among institutions. The size of the nodes represents the frequency of co-occurrences, while the links illustrate the relationships between these co-occurrences. (B) VOSviewer visualization of the collaborative network of journal citations. Nodes with various colors symbolize countries/regions in different clusters, and node size signifies occurrence frequency. (C) Dual-map overlay of journals. Journals that cite others are located on the left, those that are cited are on the right, and the relationships between them are depicted through colored paths. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

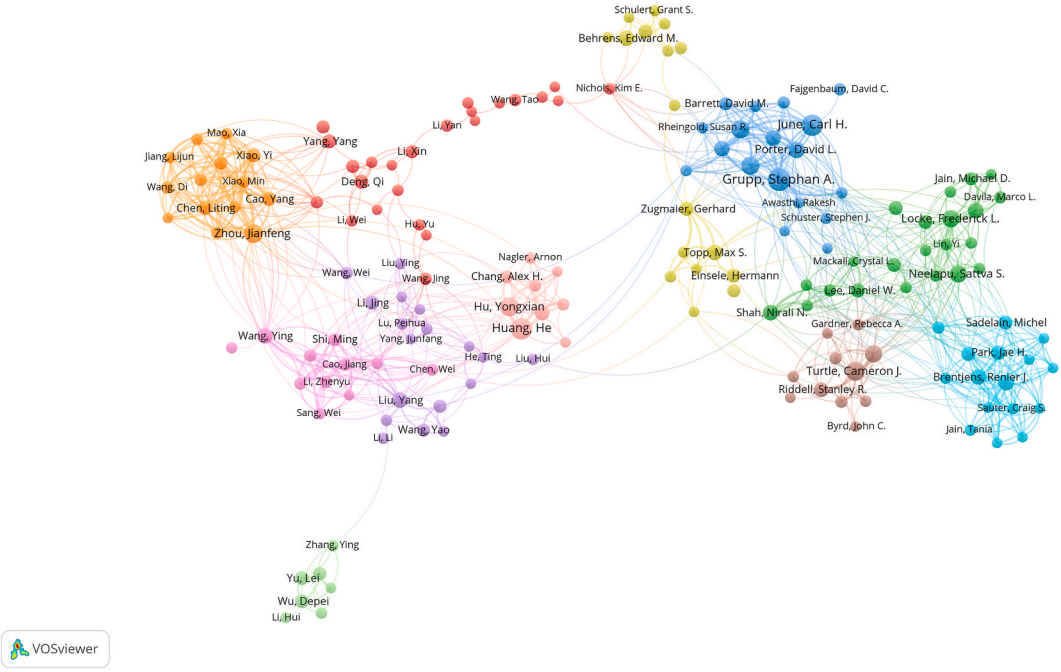

Fig. 5. VOSviewer visualization of the collaborative network of authors. Authors who have produced over 8 publications are shown, with nodes in diverse colors symbolizing authors in distinct clusters, and the size of nodes indicating their appearance frequency. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cytokine storm-associated research. It is noteworthy that among the leading 20 keywords based on occurrence frequency, the top three keywords' TLS rankings corresponded with their frequency rankings. Specifically, COVID-19 (4887), SARS-CoV-2 (3239), and Cytokine Storm (2383) exhibited high TLS values, reflecting their significant presence and importance in the analyzed literature.

VOSviewer was employed to illustrate the keywords' co-occurrence network graph (Fig. 6A). The connections among various keywords signify a co-occurrence relationship. According to the research focus, the keywords were grouped and primarily categorized into three clusters: the red cluster's keywords were associated with coronavirus (COVID-19 and SARS-CoV-2, etc.); the green clusters' keywords were associated with immunotherapy (cell therapy, t-cell therapy, and chimeric antigen receptor, etc.); and the blue clusters' keywords were associated with inflammation (hyperinflammation, interleukin-6 [IL-6], and sepsis, etc.). It is worth noting that the red cluster's keywords were strongly connected to the other clusters, indicating that there was a cross-field among the research directions. The time distribution of each keyword is illustrated in Supplementary Fig. 2, which displays the average appearance time of each keyword in different colors. Specifically, a color nearer to yellow implies a later appearance, whereas a color nearer to purple implies an earlier appearance. These findings suggest that research on SARS-CoV-2, COVID-19 are prominent topics in the field of cytokine storm research. However, in recent years, keywords such as apoptosis, sepsis, chimeric antigen receptor, and toxicity have received less focus. Notably, the average occurrence of these keywords was also concentrated between 2019 and 2021, which may be associated with the significant increase in publications observed after 2019.

CiteSpace's timeline graph illustrates the keywords that are most frequently used in each cluster over various periods (Fig. 6B). The cluster's size is inversely related to the number succeeding the "#". #0 (dendritic cell) was the largest. In this area, cytokine release syndrome was among the earliest-emerging keywords, while biomarkers were among the most recent research targets. #2 (expression) was another large cluster that appeared at an early stage. In this field, the research frontier is the keyword inhibition, protein, and mechanisms. Notably, six of the eight clusters are ongoing, including #0 (dendritic cells), #1 (cytokine release syndrome), #3 (COVID-19), #4 (molecular docking), #6 (hemophagocytic lymphohistiocytosis) and #7 (acute lymphoblastic leukemia), suggesting that studies in these fields are continuing. Furthermore, #3 (COVID-19) and #7 (acute lymphoblastic leukemia) appeared the latest, and the main keywords were pneumonia, inflammatory cytokines, and signaling pathways, which are the frontier hotspots of cytokine storm-related research.

Fig. 7A shows the frequencies of the top ten keywords over time. From 2004 to 2019, the frequency of each keyword increased gradually. However, from 2019 to 2022, the frequency of keywords increases rapidly. Notably, the keyword cytokine storm showed the fastest growth rate. Moreover, the frequency of COVID-19 and coronavirus rapidly increased since 2019, highlighting that they are major research hotspots in the field of cytokine storms. Fig. 7B illustrates the annual heat values of keywords from 2004 to 2022, calculated as the frequency of occurrence in a given year divided by the total occurrences for that year. Keywords such as monoclonal antibody and necrosis factor-alpha have shown relatively lower annual heat values in recent years. In contrast, terms like infection, activation, coronavirus, and COVID-19 have exhibited higher annual heat values, suggesting that these keywords symbolize nascent cutting-edge fields.

3.7. Analysis of highly cited literature

The ten most highly cited articles and the ten articles with the greatest annual average citations are showcased in Supplementary Tables 6 and 7, respectively. The most frequently cited article was "Chimeric antigen receptor T cells for sustained remissions in leukemia" (Shannon L. Maude et al., 2014) (3127). This study highlights the efficacy of T cell therapy, modified by a chimeric antigen receptor that targets CD19, in treating patients with relapsed and refractory acute lymphoblastic leukemia (ALL) [36]. "Axicabtagene ciloleucel CAR T-Cell therapy in refractory large B-Cell lymphoma" (Sattva S Neelapu et al., 2017) (2406) was also a high cited article. This multicenter study found that individuals with refractory large B-cell lymphomawho underwent axi-cell CAR-T cell therapy exhibited elevated rates of long-lasting responses. The safety profile of this intervention encompassed myelosuppression, CRS, and neurological adverse events [37]. The article that accrued the highest annual average number of citations was "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status" (Yan-Rong Guo et al., 2020) (693.67). This review offers a summary of the latest progress in studies on the epidemiological aspects, disease mechanisms, and clinical symptoms of COVID-19. It also explores the current therapeutic options and scientific developments aimed at countering the new coronavirus pandemic [38].

Co-citation analysis investigates the associations among scholarly works by assessing the frequency of their co-occurrence in reference lists. CiteSpace's timeline graph displays the most prevalent references for each cluster across time (Fig. 8). The initial cluster, #4 (TGN1412), appeared before 2005 and persisted until 2015. Clusters #1 (acute lymphoblastic leukemia) and #5 (macrophage activation syndrome) also emerged early but were no longer active. In 2019, several new clusters emerged, including the #0 (COVID-19), #3 (thrombosis), #6 (tocilizumab), and #7 (ACE2) clusters. Clusters #0, #2, and #6 are currently active, indicating ongoing research on these topics. Notably, among all the clusters, the relatively recent #0 (COVID-19) exhibited the largest magnitude, signifying its immense popularity and potential.

Fig. 9 unveils the 25 most influential references that have experienced the most powerful and explosive citation bursts. The burst of highly cited literature refers to the extraction of cited literature with a high-frequency change rate at a certain time from numerous subject-cited studies by examining the frequency of the cited literature [39]. The initial pair of citation bursts appeared in 2007, entitled "Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412" and "Fatal outcome of human influenza A (H5N1) was associated with high viral load and hypercytokinemia." Notably, "Chimeric antigen receptor T cells for sustained remissions in leukemia" were the papers with the strongest outbreak (strength = 161.26), and its outbreak lasted until 2019. The article by Daniel W. Lee et al., titled "Current concepts in the diagnosis and management of cytokine release syndrome" (strength = 146.62) and the article by Marco L. Davila, titled "Efficacy and toxicity management of 19-28z CAR T Cell therapy in B cell acute lymphoblastic leukemia" (strength = 142.47), also had high explosive power. The results showed that the largest number of new citation bursts occurred in 2014, 2016, and 2018 (five). These results indicate that highly impactful articles during these years contributed to a surge in related research in the field.

4. Discussion

4.1. General information

This research examined 6647 publications related to cytokine storm sourced from 1586 journals and involving 21866 authors within the WoSCC database, spanning the period from January 1, 2004 to October 10, 2022. In 1993, James L. Ferrara et al. firstly used the term "cytokine storm" to characterize the acute graft-versus-host disease (GvHD) of engraftment syndrome that occurs after allogeneic stem cell transplantation [8]. Over the past three decades, the field has witnessed a continuous increase in related publications, particularly since the COVID-19 outbreak, which has resulted in an exponential surge in cytokine storm research. Notably, the count of publications published in 2021 is approximately 32 times greater than that published in 2011. Following the emergence of COVID-19 in 2019, publications and citations in this area have steadily increased. Our analysis revealed that post-2019, there has been an increased frequency in the occurrence of keywords such as "ACE2," "oxidative stress," and "vitamin D," in addition to the potential influence of COVID-19. This trend suggests that these factors may also have contributed to the surge in research activity within this domain during this period. As of October 10, 2022, the count of searchable documents reached 1148 and the quantity of citations reached 58881 (71 % of 2021), suggesting that research hotspots related to this field may be rising. Overall, this growth not only reflects the importance of cytokine storms in clinical and basic research but also highlights their urgency in global health crises, particularly throughout the COVID-19 outbreak.

The country analysis indicated that the publication volume and betweenness centrality were the two most important indicators. A central value greater than or equal to 0.10 indicated that these nations served as connectors in the worldwide collaboration network.

As demonstrated in Tables 1 and 2, and Fig. 2B, England and the United States have emerged as pivotal nations in this research field. Notably, the United States has achieved the highest number of publications and citations, marking it as a leader in academic output. Meanwhile, China has also demonstrated significant scholarly activity, ranking second in both publications and citations. Of the leading ten institutions based on publication count, six were situated in the United States, while three originated from China. Moreover, all of the leading ten institutions with respect to volume of citation were found in the United States, with the University of Pennsylvania significantly outperforming other organizations. Having a centrality score of 0.26, England demonstrated the greatest centrality among all nations, with the United States following closely at a centrality of 0.17, indicating its leading role in worldwide cytokine storm research cooperation. Countries, including Canada, France, and the United States, have been actively engaged in extensive cytokine storm research and cooperation. The distribution of research forces revealed by bibliometric analysis facilitates collaborative research between different countries and institutions, jointly promoting the development of this field.

Supplementary Tables 3, 4, 6, and 7 show the high-impact authors and documents. Shannon L. Maude, affiliated with the Children's Hospital of Philadelphia, published an article titled "Chimeric antigen receptor T cells for sustained remissions in leukemia" in New

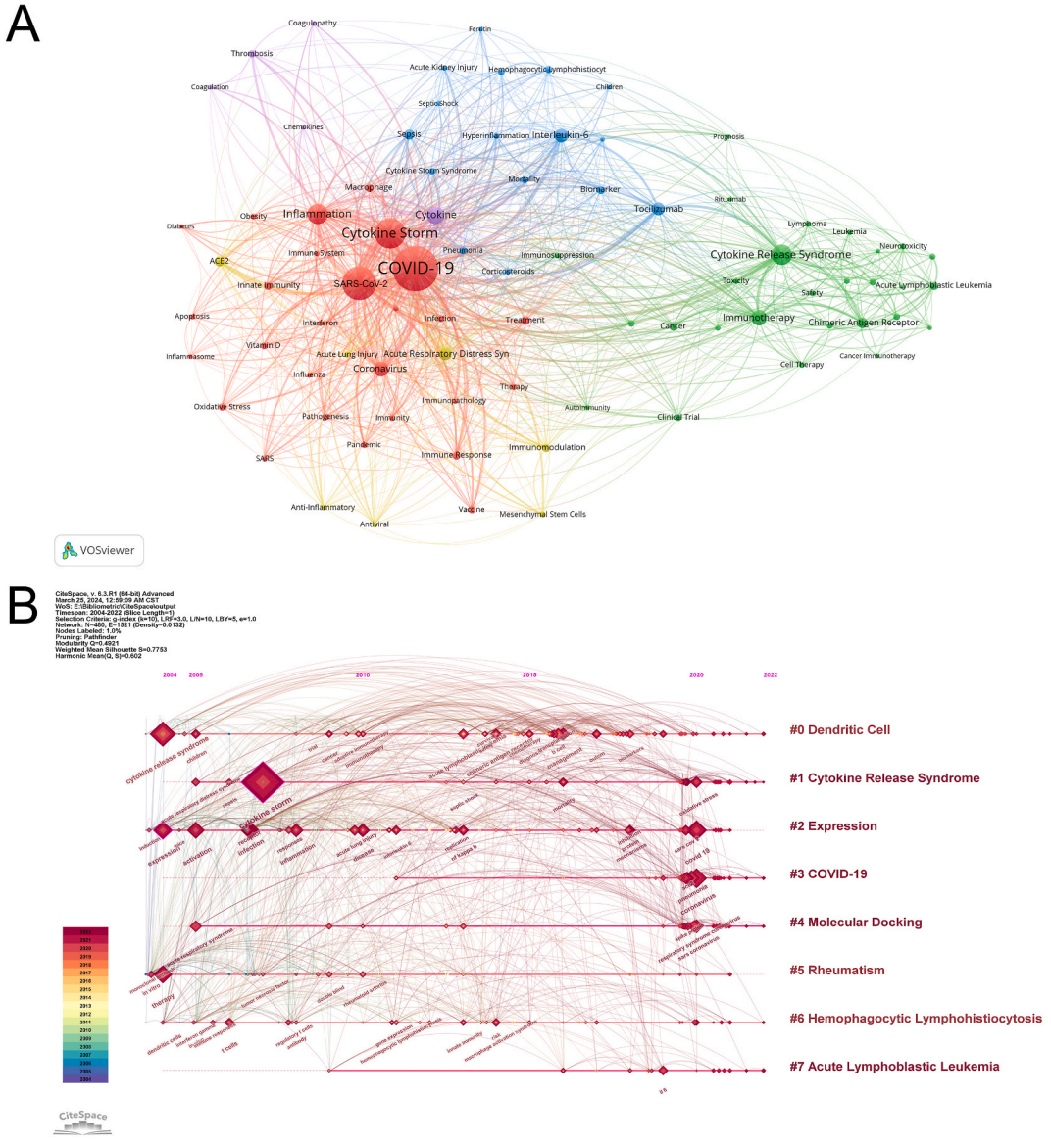

Fig. 6. Analysis of cytokine storm-related keywords. VOSviewer visualization of the collaborative network of keywords. Keywords appearing over 15 times are shown, with nodes colored differently to represent various keyword groups, and the size of each node reflecting how frequently each keyword occurs. (B) Timeline display of keyword trends. Horizontal lines represent different clusters, with cluster #0 as the most significant. The size of each node represents the frequency of co-citations, while the links between nodes depict the co-citation connections. The year a node first appears marks the beginning of its co-citation.

England Journal of Medicine in 2014". This groundbreaking article, which explored CRS, reported unprecedented success in patients receiving chimeric antigen receptor-modified T cells targeting CD19. Remarkably, this article was cited more often than any other in this area of research. Stephan A. Grupp was ranked as the most prolific author, with a substantial publication count and the second-highest citation frequency. Notably, "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status" by Yan-Rong Guo et al. ranked fifth in citation volume and demonstrated the greatest average annual citation volume. Similarly, "The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19" authored by Qing Ye et al. ranked tenth in citation frequency and secured the second position regarding average annual citation frequency, signifying its recent and noteworthy impact within the field.

Turning attention to journals, Frontiers in Immunology stood not only among the most prolific journals but also ranked third in citation frequency. Blood secured the fourth rank by publication volume and second position regarding citation volume. These journals have been crucial in spreading cytokine storm-associated research. Notably, among the ten most frequently cited journals, The New England Journal of Medicine and Nature Medicine signified publications in the medical field. Journal of Clinical Oncology and Lancet fall under the clinical domain. Frontiers in Immunology and Journal of Medical Virology are aligned within the field of immunology, thereby supporting the findings of the dual-map analysis presented in Fig. 4C.

4.2. Hotspots and frontiers

Analyzing keywords aided in comprehending the cutting-edge and popular subjects in cytokine storm research. As depicted in Supplementary Table 5, the prevailing high-frequency keywords like COVID-19, cytokine storm, SARS-CoV-2, and inflammation, predominantly revolved around the subject of novel coronavirus pneumonia, indicating its current status as a research hotspot. This observation is further confirmed by the findings shown in Fig. 6B. Notably, the keyword cluster "#3COVID-19" emerged as a prominent and more recent cluster, underscoring the contemporary significance of COVID-19 as a focal point of investigation (Fig. 6B). Both "COVID-19" and "coronavirus" first appeared in 2020 and subsequently exhibited a rapid escalation in frequency. This trend is closely aligned with the growth trajectory observed in the volume of publications and citation of cytokine storm-related literature, indicating that the exponential surge in COVID-19 research may serve as a catalyst for the expansion of the cytokine storm field (Fig. 7A). Supplementary Table 6 shows that among the ten highly cited articles, eight were directly linked to CAR T-cell therapy, highlighting the ongoing significance of CRS induced by CAR T-cell therapy as a research focus. This perspective was further supported

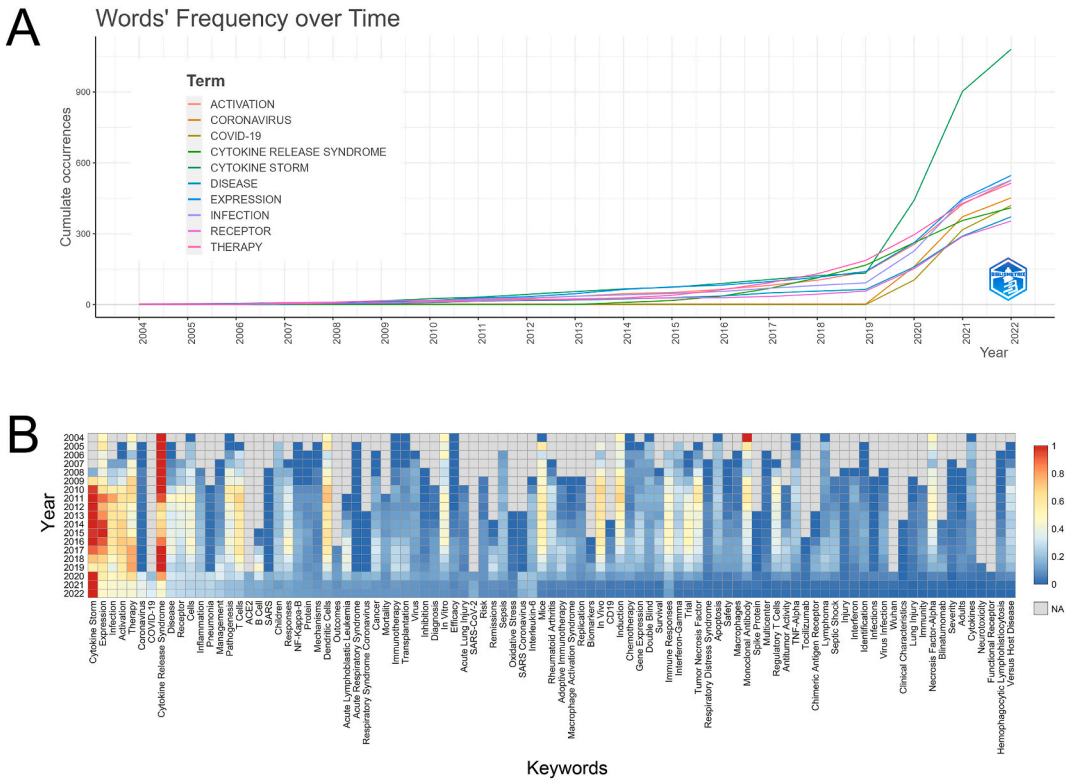

Fig. 7. Analysis of research field trends based on cytokine storm-associated keywords. (A) The temporal distribution of keyword frequencies spanning the years 2004–2022. (B) A heatmap examination, conducted annually, of keywords associated with cytokine storm from 2004 to 2022. To calculate the annual heat value for each keyword, the yearly occurrence count is divided by the total occurrence count within that year. Subsequently, the values are transformed using min-max normalization.

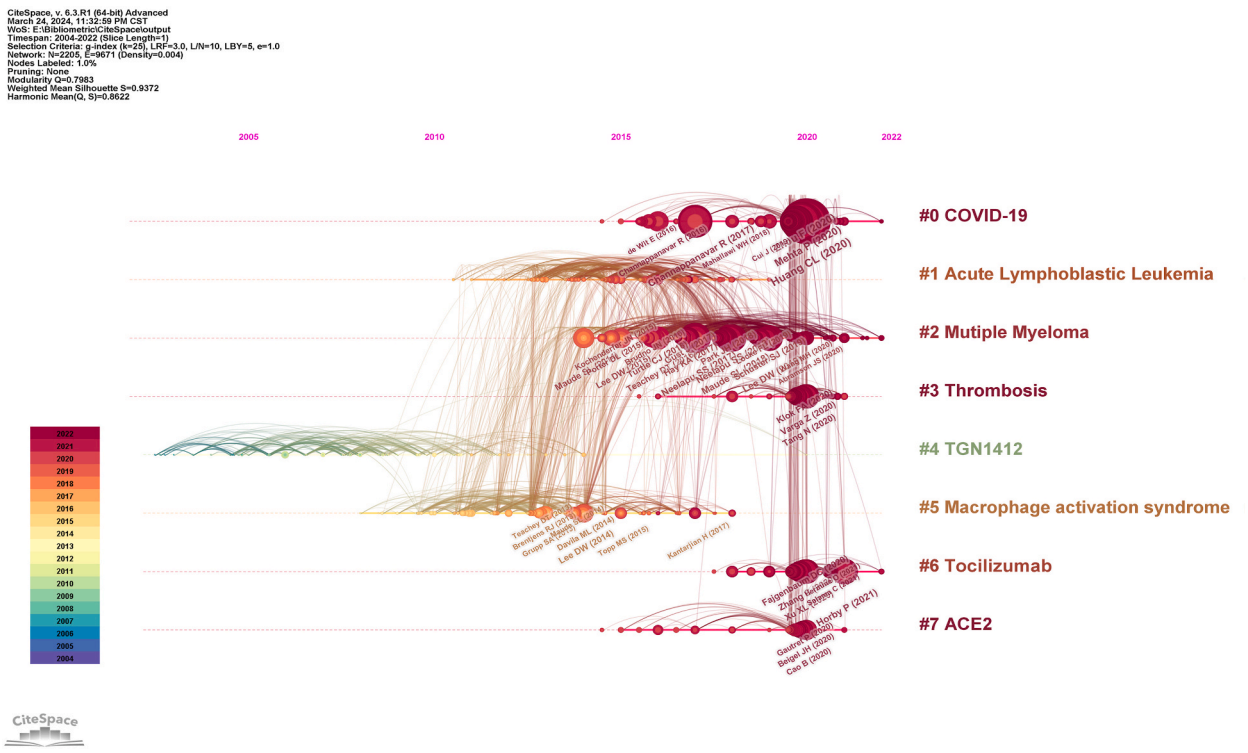

Fig. 8. Timeline view of author's co-citation of cytokine storm-related references. Publications that share a significant number of references are more likely to exhibit homogeneity and form clusters. Horizontal lines represent different clusters, with cluster #0 as the most significant. The size of each node represents the frequency of co-citations, while the links between nodes depict the co-citation connections. The year a node first appears marks the beginning of its co-citation.

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2004 - 2022
Suntharalingam G, 2006, NEW ENGL J MED, V355, P1018, DOI 10.1056/NEJMoa063842, DOI	2006	37.1	**2007**	2011	
Grupp SA, 2013, NEW ENGL J MED, V368, P1509, DOI 10.1056/NEJMoa1215134, DOI	2013	92.29	**2013**	2018	
Brentjens RJ, 2013, SCI TRANSL MED, V5, P0, DOI 10.1126/scitranslmed.3005930, DOI	2013	66.49	**2013**	2018	
Porter DL, 2011, NEW ENGL J MED, V365, P725, DOI 10.1056/NEJMoa1103849, DOI	2011	36.87	**2013**	2016	
Lee DW, 2014, BLOOD, V124, P188, DOI 10.1182/blood-2014-05-552729, DOI	2014	146.62	**2014**	2019	
Davila ML, 2014, SCI TRANSL MED, V6, P0, DOI 10.1126/scitranslmed.3008226, DOI	2014	142.47	**2014**	2019	
Maude SL, 2014, CANCER J, V20, P119, DOI 10.1097/PPO.0000000000000035, DOI	2014	76.94	**2014**	2019	
Teachey DT, 2013, BLOOD, V121, P5154, DOI 10.1182/blood-2013-02-485623, DOI	2013	57.2	**2014**	2018	
Kochenderfer JN, 2012, BLOOD, V119, P2709, DOI 10.1182/blood-2011-10-384388, DOI	2012	39.33	**2014**	2017	
Maude SL, 2014, NEW ENGL J MED, V371, P1507, DOI 10.1056/NEJMoa1407222, DOI	2014	161.26	**2015**	2019	
Lee DW, 2015, LANCET, V385, P517, DOI 10.1016/S0140-6736(14)61403-3, DOI	2015	119.84	**2015**	2019	
Kochenderfer JN, 2015, J CLIN ONCOL, V33, P540, DOI 10.1200/JCO.2014.56.2025, DOI	2015	75.6	**2015**	2019	
Porter DL, 2015, SCI TRANSL MED, V7, P0, DOI 10.1126/scitranslmed.aac5415, DOI	2015	78.06	**2016**	2019	
Turtle CJ, 2016, J CLIN INVEST, V126, P2123, DOI 10.1172/JCI85309, DOI	2016	70.87	**2016**	2019	
Topp MS, 2015, LANCET ONCOL, V16, P57, DOI 10.1016/S1470-2045(14)71170-2, DOI	2015	43.72	**2016**	2019	
Brudno JN, 2016, J CLIN ONCOL, V34, P1112, DOI 10.1200/JCO.2015.64.5929, DOI	2016	38.11	**2016**	2019	
Sotillo E, 2015, CANCER DISCOV, V5, P1282, DOI 10.1158/2159-8290.CD-15-1020, DOI	2015	33.78	**2016**	2019	
Teachey DT, 2016, CANCER DISCOV, V6, P664, DOI 10.1158/2159-8290.CD-16-0040, DOI	2016	64.76	**2017**	2019	
Brudno JN, 2016, BLOOD, V127, P3321, DOI 10.1182/blood-2016-04-703751, DOI	2016	47.26	**2017**	2019	
Turtle CJ, 2016, SCI TRANSL MED, V8, P0, DOI 10.1126/scitranslmed.aaf8621, DOI	2016	41.39	**2017**	2019	
Maude SL, 2018, NEW ENGL J MED, V378, P439, DOI 10.1056/NEJMoa1709866, DOI	2018	48.13	**2018**	2019	
Neelapu SS, 2017, NEW ENGL J MED, V377, P2531, DOI 10.1056/NEJMoa1707447, DOI	2017	43.97	**2018**	2019	
Neelapu SS, 2018, NAT REV CLIN ONCOL, V15, P47, DOI 10.1038/nrclinonc.2017.148, DOI	2018	43.36	**2018**	2019	
Hay KA, 2017, BLOOD, V130, P2295, DOI 10.1182/blood-2017-06-793141, DOI	2017	37.24	**2018**	2019	
Schuster SJ, 2017, NEW ENGL J MED, V377, P2545, DOI 10.1056/NEJMoa1708566, DOI	2017	33.94	**2018**	2019	

Fig. 9. References ranked in the top 25 for citation outbreaks.

by the keyword analysis presented in Fig. 6B, where keywords such as "#6 hemophagocytic lymphohistiocytosis," "#1 cytokine release syndrome," and "#7 acute lymphoblastic leukemia" support the aforementioned viewpoint. Fig. 6A showed that previous studies have focused on several prominent topics, including the novel coronavirus (COVID-19 and SARS-CoV-2, etc.), clinical treatment (immunotherapy, monoclonal antibody, cell therapy, and prognosis, etc.), and biomarkers (IL-6, IFNs, and ACE2, and ferritin, etc.). Notably, tocilizumab, classified as a monoclonal antibody, has emerged as a significant and relatively recent cluster, underscoring the current interest in targeted therapies for cytokine storms (Fig. 6A and Supplementary Fig. 2). Notably, the timeline diagram analysis revealed that larger clusters such as "#0 dendritic cell" and "#2 expression" pertained to the mechanisms of cytokine storm, indicating that research in this domain was still in progress and has significant potential for further exploration. In summary, these findings reveal the pivotal importance of both COVID-19 and CAR-T therapy in the study of cytokine storms and emphasize the significance of research hotspots such as related biomarkers and clinical treatments for understanding and managing complex immune responses. This not only identifies current research priorities but also sets the direction for future therapeutic strategies and medical advancements.

4.2.1. Cytokine storm and COVID-19

Disrupted adaptive immune reactions and uncontrolled innate inflammatory responses triggered by SARS-CoV-2 have been implicated as the underlying causes of cytokine storms in patients with COVID-19 [40]. Upon invasion by respiratory epithelial cells, SARS-CoV-2 swiftly triggers pathogenic T helper 1 (TH1) cells, prompting them to release inflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 [41]. Notably, GM-CSF induces the stimulation of $CD14^{+}CD16^{+}$ monocytes and downstream signaling pathways, leading to substantial production of cytokines [42]. Furthermore, during the initial phases of SARS-CoV-2 infection, the production of IFNs is suppressed, which hamper the antiviral response and potentially facilitates the excessive release of inflammatory cytokines [43]. The onset of a cytokine storm in COVID-19 patients is often indicative of disease exacerbation [44]. Huang et al. demonstrated that patients with severe COVID-19 display elevated levels of serum inflammatory cytokines, including granulocyte colony-stimulating factor (G-CSF) and TNF-α, compared to non-severe patients [45]. In addition, critically ill COVID-19 patients consistently exhibit significantly elevated levels of ILs, TNF-α, IFN-γ, and other inflammatory cytokines [46,47]. IL-6 has emerged as a predictive indicator for the progression of COVID-19 [48]. Additionally, increased expression levels of serum chemokines, including CXCL2 and CXCL10, have been discerned to exhibit a robust association with severe manifestations of COVID-19 [49–51].

The pronounced elevation of cytokine levels can result in severe metabolic disturbances and tissue damage within the body, resulting in an unfavorable prognosis for individuals afflicted with COVID-19 [52–54]. Extensive research has shed light on the mechanisms by which cytokine storms induce bodily harm in COVID-19 patients. Compelling evidence suggests that cytokine storms can precipitate severe lung injury characterized by lung endothelial cell apoptosis, disruption of the epithelial cell barrier, and pulmonary edema, ultimately culminating in ARDS [43,55]. ARDS, which is triggered by a cytokine storm, can precipitate fatality in patients with severe COVID-19 [43]. Moreover, cytokine storms have been linked to multi-organ damage and subsequent organ failure in patients with COVID-19 [56]. Ahmadian et al. showed that the extensive release of cytokines and chemokines induced by SARS-CoV-2 infection indirectly leads to acute kidney injury (AKI) by disrupting renal tubular and endothelial function, in addition to causing lung injury [57]. Evidence suggests that cardiac injury in patients with COVID-19 may be linked to a cytokine storm, resulting from an unbalanced response between TH1 cells and T helper 2 (TH2) cells following SARS-CoV-2 infection [58,59]. Similarly, research supports the association between cytokine storm induced by COVID-19 and related injuries in distant organs such as the liver, brain, and intestines [60–62]. Moreover, cytokine storm-related coagulation abnormalities are closely linked to the deterioration of patients with COVID-19 [15,63,64]. The elevated expression of serum inflammatory cytokines, including IL-6 and TNF-α, induces pulmonary endothelial cells, macrophages, and neutrophils to express tissue factor, leading to widespread pulmonary coagulation and microvascular thrombus formation [65]. Notably, IL-6 has been shown to induces tissue factor expression, enhances fibrinogen and platelet production, and serves as a crucial activator in the development of coagulopathy in patients with severe COVID-19 [63]. Extensive pulmonary coagulation can lead to diffuse pulmonary intravascular coagulopathy (PIC), which ultimately triggers ARDS onset [63]. Furthermore, COVID-19-induced thrombotic microangiopathy is closely associated with fatal extrapulmonary conditions, including atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria, acute coronary syndrome (ACS), and myocardial injury [66,67]. Pneumonia-associated coagulation may also heighten the likelihood of DIC as COVID-19 worsens [68].

4.2.2. Emerging cytokine storm-related biomarkers

In the realm of clinical practice, pinpointing robust and reliable biomarkers for cytokine storms is paramount for evaluating patients' disease risk and prognostic outcomes. Such identification facilitates the swift selection of suitable therapeutic strategies by clinicians. Recently, there has been a concentrated focus on biomarkers related to cytokine storms, namely inflammatory cytokines, Angiotensin-converting enzyme-2 (ACE2), and ferritin, as depicted in Supplementary Fig. 2 and Supplementary Table 5. Characterized by abnormally high levels of inflammatory cytokines, a cytokine storm occurs [69]. Various studies have underscored the significance of inflammatory cytokines, including interleukins, interferons, TNF-α, and chemokines, as diagnostic markers for assessing cytokine storm severity [48,50,70]. Notably, IL-6 emerges as a focal point of research within the cytokine storm spectrum. IL-6's value extends beyond the scope of COVID-19, enriching the evaluation of cytokine release syndrome linked to CAR-T cell therapy and other diseases [71]. Specifically, in COVID-19, IL-6 is considered the most accurate marker for tracking disease progression and predicting mortality among cytokines associated with cytokine storms [72]. IL-6 often demonstrates enhanced predictive power for disease progression over non-cytokine inflammatory markers like C-reactive protein, highlighting its critical role in cytokine storm evaluation [73]. ACE2 is crucial for viral infection, serving as the primary receptor for SARS-CoV-2 to enter cells [74]. The viral entry into lung epithelial cells

via ACE2-mediated endocytosis leads to the detachment of membrane-bound ACE2. This detachment may interfere with inflammatory regulation, potentially initiating a cytokine storm [75]. The rise in circulating ACE2 levels post-detachment has propelled research into soluble ACE2 (sACE2) as a cytokine storm monitoring biomarker [74]. Studies have shown sACE2's utility in tracking cytokine storms, particularly in severe COVID-19 instances. For example, Chamorro et al. demonstrated sACE2 levels in COVID-19 patients as an early severe infection biomarker [76]. In addition, sACE2 levels might predict prognosis in severe COVID-19-related cytokine storms. Mortaz et al. observed that recovery in severe COVID-19 cases was marked by increased sACE2 levels, with circulating cytokines unaffected [77]. Additionally, Patel et al. noted a correlation between plasma ACE2 activity in COVID-19 survivors and disease severity, with higher activity in severe cases, suggesting a strong link between plasma ACE2 activity and the progression and severity of the disease [78]. Ferritin serves as a vital mediator in immune dysregulation, with hyperferritinemia occurring in severe instances, such as severe COVID-19 onset. Elevated ferritin levels can directly induce inflammation and are a significant cytokine storm development risk factor [79–81]. Evidence supports ferritin's potential in predicting cytokine storms and disease progression. A retrospective analysis in Wuhan, China, revealed that individuals who did not survive COVID-19 exhibited significantly higher concentrations of ferritin and IL-6 than those who recovered, with these levels rising as the disease worsened [82]. Additionally, studies from Italy and other regions have linked high ferritin levels with adverse results in severe COVID-19 cases [83–85]. The study by Melo et al. also indicates that elevated ferritin levels could act as an indicator of systemic inflammation and negative outcomes in COVID-19 cases [86]. Moreover, biomarkers like leukocytes, neutrophils, lymphocytes, procalcitonin, D-dimer, and lactate dehydrogenase are promising for assessing cytokine storm-related diseases' risk and prognosis [81,86,87]. These biomarkers could provide more comprehensive insights for clinical decision-making, although additional studies and validation are required to precisely establish their applications.

4.2.3. Treatment of cytokine storm

As mentioned previously, cytokine storm treatment methods have become popular in recent years. Anti-inflammatory drugs are important treatment modalities for cytokine storms [88]. Corticosteroids, including glucocorticoids and dexamethasone, exert an anti-inflammatory effect by modulating the transcription of genes that suppress inflammation and reducing the production of inflammatory cytokines [89]. In several clinical trials of CAR-T cell therapy, corticosteroids have often been used to treat CRS in patients [90–92]. Corticosteroids are also potential therapeutics for the COVID-19-associated cytokine storm [93]. Ye et al. proposed that the timely administration of glucocorticoids to suppress excessive inflammation during the early stages of an inflammatory cytokine storm can effectively prevent the onset of ARDS and safeguard organ function in patients [43]. Because of the impact of glucocorticoid administration timing and dosage on the prognosis of critically ill patients, several studies have advocated cautious consideration of their clinical application [43]. Accumulating evidence in recent years validate the effectiveness of anti-cytokine treatment as a superior approach for managing cytokine storms. This therapeutic approach involves the inhibition of cytokine production and neutralization of released cytokines [13]. Studies on anti-IL-1β monoclonal antibodies, including anakinra, for treating COVID-19, demonstrate their clinical advantages in cytokine storm management [94–96]. Additionally, the interleukin-6 receptor (IL-6R) inhibitor tocilizumab has demonstrated positive effects in addressing cytokine storms accompanied by CAR-T cell therapy [97]. Considering the critical role of IL-6 in the development of cytokine storms triggered by SARS-CoV-2, tocilizumab has potential to treat COVID-19-associated cytokine storms [98–100]. Furthermore, anti-cytokine therapies targeting TNF, IFN-γ, and IL-18 are also considered promising in managing cytokine storm [13,101]. Because of the involvement of various signaling pathways in cytokine storm development, the selective inhibition of relevant pathways represents another therapeutic avenue [102]. Janus kinases (JAKs) mediate several cytokine-related pathways, including the IFNs, IL-6, IL-12, and GM-CSF pathways, rendering JAK inhibitors promising strategies for addressing cytokine storms [103,104]. Evidence suggests that JAK inhibitors mitigate inflammatory cytokine production, reduce lung cell susceptibility to viral infections, and treat cytokine storm in COVID-19 patients [40]. Cao et al. successfully employed the JAK inhibitor ruxolitinib in treating patients with COVID-19, leading to a notable decrease in seven cytokine levels and enhanced clinical outcomes [105]. Notably, caspase inhibitors exhibit anti-inflammatory and organ-protective effects in ischemia/reperfusion and sepsis models [106]. Current evidence supports the notion that inhibiting caspases can effectively alleviate the severity of cytokine storms in patients with COVID-19, suggesting their promise as treatment options [107]. Additionally, antioxidants, stem cell therapy, intravenous immunoglobulin (IVIG), and chloroquine has demonstrated potential in managing COVID-19-associated cytokine storms [13, 108–110].

Due to the complexities of clinical practice, evaluating the pros and cons of cytokine storm treatments is essential. Although corticosteroids have shown efficacy in treating severe cases of cytokine storms, they also pose certain risks [111]. Studies have indicated a significant increase in mortality when corticosteroids are used for severe SARS-CoV-2 infections, possibly due to prolonged viral clearance and bacterial infections associated with immunosuppression [112]. To mitigate these risks, clinicians require precise timing and treatment dosing. For instance, the timely administration of glucocorticoids to suppress excessive inflammation during early onset cytokine storms in COVID-19 patients can effectively prevent the onset of ARDS. Additionally, short-term high-dose glucocorticoid therapy should be considered in patients showing progressive worsening of oxygenation indices, quick radiographic advancement, and heightened inflammatory responses [43]. Notably, evidence suggests that for COVID-19 patients not requiring ventilator support, anti-cytokine therapy tends to provide greater benefits than corticosteroids [113,114]. Moreover, unlike corticosteroids, anti-cytokine therapies demonstrate greater safety in several instances. Research indicates that, in specific clinical scenarios, the therapeutic effects of tocilizumab are relatively rapid and do not affect virus-specific antibody responses, even in cases of high viral load, suggesting its relative safety in treating cytokine storms in patients with COVID-19 [69,115]. Furthermore, the short half-life of anakinra enhances its safety and suitability for the therapy of patients experiencing severe and acute cytokine storms [21, 116]. In addition, the outstanding efficacy and safety of pathway inhibitors have been reported in numerous studies. Pathway

inhibitors, which inhibit the production of multiple cytokines, may possess broader anti-inflammatory activity than cytokine inhibitors targeting single cytokines [117]. Notably, the safety of cytokine pathway inhibitors such ruxolitinib has been validated by numerous preclinical models and clinical data [118–120]. However, it should not be overlooked that in certain circumstances, anti-cytokine therapies and cytokine pathway inhibitors may lead to adverse outcomes. For instance, tocilizumab may exacerbate the neurotoxicity associated with CRS [69,121]. Moreover, owing to their involvement in various physiological mechanisms beyond immune responses, inhibiting pathways such as JAK/STAT may lead to unforeseen side effects [116]. Thus, considering the safety limitations of anti-cytokines and pathway inhibitors in specific situations, clinicians should closely monitor the safety of drugs and adjust their treatment plans accordingly. For example, when the short-term efficacy of drugs such as tocilizumab is unclear, or when there is a risk of exacerbating underlying conditions such as neurological diseases, Lee et al. suggest that supplementation or switching to corticosteroid therapy may be preferable [69]. Notably, the simultaneous use of multiple therapies showed significant interactions and may represent another valuable treatment strategy. For instance, a meta-analysis suggested that compared to standard treatment, concurrent use of corticosteroids and tocilizumab can further reduce the short-term mortality rate of COVID-19 hospitalized patients [122]. In conclusion, although cytokine therapy remains a focal point in current discussions, further research is needed to overcome the shortcomings of existing therapies and develop safer and more effective treatments. Additionally, considering the advantages and disadvantages of various cytokine storm therapies, researchers should explore the optimal therapies, timing, and dosages based on differing circumstances to guide clinical treatments.

4.3. Future perspectives

The trend analysis of keywords in our study reveals emerging topics and current popular research directions in the field of cytokine storms, which aids in forecasting future research trends. Our annual heatmap analysis of keywords demonstrates that terms such as "COVID-19," "expression," "activation," "therapy," and "infection" have appeared more frequently in recent years. Correspondingly, results from timeline analysis of keyword occurrences indicate that research in areas related to COVID-19, expression, molecular docking, and dendritic cells continues to be active. This indicates that, under current trends, these keywords are expected to remain central to research interests in the coming years. Upcoming studies ought to concentrate on understanding the mechanisms of cytokine storms in severe COVID-19 instances and refining therapeutic strategies to enhance treatment efficacy and boost survival rates in patients. Additionally, given the current research trends, exploring the role of cytokine storms in global health crises, especially within the framework of COVID-19, is poised to become a principal focus in upcoming advancements.

Nevertheless, it is crucial to recognize that despite the significant potential of many research directions, there is still a shortfall in related studies. For instance, ACE2, as a crucial target in COVID-19 and a biomarker for related cytokine storms, has emerged as a topic of interest in recent years. Yet, research in this area remains comparatively sparse. Subsequent research ought to delve deeper into the function of ACE2 within cytokine storms linked to COVID-19, as well as its utility in diagnosing and treating the disease. Additionally, emerging keywords related to cytokine storm mechanisms, such as "oxidative stress," also lack sufficient research. Given the critical role of oxidative stress in various diseases and its yet-to-be-fully-elucidated relationship with cytokine storms, future research should delve deeper into the molecular regulatory networks between these two, potentially revealing new therapeutic targets.

4.4. Limitations

This research pioneered the application of bibliometric visualization to examine cytokine storm-associated studies over the last two decades. Nevertheless, it is crucial to acknowledge that this study still has several limitations. Firstly, data analysis was solely conducted using CiteSpace and VOSviewer. Different bibliometric analysis tools may yield varying results, and future studies could employ other software for cross-validation. Secondly, the WOSCC database was the sole source of all the bibliographic data for this research. While the WOSCC database carries authority and comprehensiveness, it might unavoidably result in the omission of relevant articles on cytokine storm from alternative databases like PubMed, Cochrane Library, and Google Scholar. Thirdly, there is an inherent time lag in article publication, and the latest developments in the field may not be fully captured. Continuous tracking of the latest research trends is necessary for a more up-to-date understanding of the field. Lastly, the time frame of this study was limited to October 10, 2022, and only English-language articles and reviews were included, which could introduce potential biases into the results. Future research could expand the analysis to include more in-depth examinations of key literature, authors, and institutions in the field of cytokine storms.

Despite these limitations, this original bibliometric study offers valuable insights into cytokine storms, identifying strengths, weaknesses, leading entities, historical trends, and future directions. It also provides essential data on current trends, guiding research efforts, and facilitates a deeper understanding through sub-topic clustering. On one hand, this study clarifies the forefront of biomarkers and treatments related to cytokine storms, offering valuable insight for clinical practitioners. On the other hand, future researchers can use our findings to quickly grasp the field's current status and choose their research directions based on these identified hotspots and trends.

5. Conclusions

Using bibliometric analysis, this study provides a summary of current trends, prevalent subjects, and cutting-edge areas in cytokine storm-associated studies during the previous 20 years. The quantity of research and its citation frequency associated with cytokine storms have consistently increased over the years, with a notable surge from 2020 onwards. The United States stands as a central

country in cytokine storm research, exerting significant influence in the field and engaging in extensive collaboration with other countries/regions. Prominent journals in this area include the New England Journal of Medicine, Frontiers in Immunology, and Blood, with Stephan A. Grupp emerges as a leading author in the field. COVID-19, cytokine storm mechanisms, cytokine storm-related biomarkers, and their treatments are popular subjects in this area, with the connection between cytokine storms and COVID-19 likely to be a primary focus for future research. These findings provide a comprehensive view of the broader research landscape, allowing clinical practitioners and new researchers to gain valuable insights.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this article does not contain any studies with human participants or animals. Informed consent was not required for this study because this article does not contain any studies with human participants.

Consent to publish

Not applicable.

Data availability statement

The original contributions presented in this study are included in the article and its supplementary materials. No data were deposited in any publicly available repositories. Further inquiries can be directed to the corresponding authors.

CRediT authorship contribution statement

Junyi Shen: Writing – original draft, Visualization, Software, Formal analysis. **Jiaming Li:** Writing – original draft, Software, Formal analysis. **Yuqi Lei:** Writing – original draft. **Zhengrui Chen:** Writing – original draft. **Lingling Wu:** Writing – review & editing. **Chunyan Lin:** Writing – review & editing, Supervision, Resources, 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30955.

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