Cardiology in the Young

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Immune control in Kawasaki disease knowledge mapping: a bibliometric analysis

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Original Article

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Lu Zhang, Lifeng Shi and Ruijie Zhang have equal contribution.

Abstract

Background: Kawasaki disease is a systemic vascular disease with an unclear pathophysiology that primarily affects children under the age of five. Research on immune control in Kawasaki disease has been gaining attention. This study aims to apply a bibliometric analysis to examine the present and future directions of immune control in Kawasaki disease. *Methods:* By utilizing the themes "Kawasaki disease," "Kawasaki syndrome," and "immune control," the Web of Science Core Collection database was searched for publications on immune control in Kawasaki disease. This bibliometric analysis was carried out using VOSviewers, CiteSpace, and the R package "bibliometrix." *Results:* In total, 294 studies on immune control in Kawasaki disease were published in Web of Science Core Collection. The three most significant institutions were Chang Gung University, the University of California San Diego, and Kaohsiung Chang Gung Memorial Hospital. China, the United States, and Japan were the three most important countries. In this research field, Clinical and Experimental Immunology was the top-referred journal, while the New England Journal of Medicine was the most co-cited journal. The Web of Science Core Collection document by McCrindle BW et al. published in 2017 was the most cited reference. Additionally, the author keywords concentrated on "COVID-19," "SARS-CoV-2," and "multisystem inflammatory syndrome in children" in recent years. *Conclusion:* The research trends and advancements in immune control in Kawasaki disease are thoroughly summarised in this bibliometric analysis, which is the first to do so. The data indicate recent research frontiers and hot directions, making it easier for researchers to study the immune control of Kawasaki disease.

A Japanese paediatrician made the initial discovery of Kawasaki disease in 1967.[1] Kawasaki disease occurring in children below the age of 5 is mainly marked by systemic inflammation, and the incidence of Kawasaki disease varies by race and season.[2] Classic Kawasaki disease is characterised by a long-lasting fever that lasts for more than 5 days, diffuse inflammation of the mucous membranes (e.g. strawberry tongue, erythema and cracking of lips), bilateral nonsuppurative conjunctivitis, nonsuppurative cervical lymphadenopathy (≥1.5 cm in diameter), polymorphic rash, and vasculitic oedema of the extremities.[3–5] Approximately 20% of children who are not treated during the acute stage of the disease develop coronary artery aneurysms. Kawasaki disease has supplanted rheumatic fever as the main cause of heart illness in children in developed countries.[6]

Immune control refers to the interaction between immune molecules, immune cells, the immune system, and other systems of the body, constituting a regulatory network of mutual coordination and constraints, so that the immune response of the machine is at an appropriate level of intensity and quality, thus maintaining the stability of the internal environment of the body. The immune system consists of many immune cells and immune molecules, and their response to defence against foreign or non-self substances (antigen) is called the immune response, including innate and adaptive immune response.[7,8] Immune control avoids unnecessary or excessive responses that may impair physiological functions. According to several research, Kawasaki disease is brought on by a pathogen or unknown substance that triggers an abnormal immune response, leading to acute systemic immune injury of small and medium-sized vasculitis.[9,10] Both the innate and adaptive immune systems are activated in acute Kawasaki disease, according to the complicated picture of the immunological response that is developing. Superantigens (viral or bacterial) activate an immune response involving multiple T cells and B cells, triggering a cascade of cytokine amplification effects in the body, which ultimately leads to widespread vascular endothelial injury and dysfunction throughout the body. endothelial damage and dysfunction throughout the body.[11] The vascular lesion tissue of children with Kawasaki disease has a large number of infiltrating IgA-producing plasma cells, monocytes or macrophages, and CD8+ T cells.[12] Macrophage and antigen-specific T-lymphocyte activation and their interactions may be involved in this process, further

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illustrating the complexity of the immune reaction in the pathogenesis of Kawasaki disease.[13] Thus, the importance of immunoregulation in the pathogenesis of Kawasaki disease is indisputable, and the study of this link will help to elucidate the disease's pathophysiology.

Bibliometrics is a powerful tool for analysing the literature since it carefully examines the output and standing of publications on a particular study topic from both quantitative and qualitative perspectives.[14,15] By analysing the citation count, the author's worklist, publication mode, and national or thematic bibliography, it is possible to identify the leading direction of scholars, institutions, and the research field.[16,17] After analysis, we have access to comprehensive data on countries, organisations, journals, authors, references, keywords, etc. in the pertinent study field. VoSviewer, CiteSpace, and R package "bibliometrix" are popular bibliometric software for visualising literature analysis results and are frequently used in the medical fields of rheumatology, oncology, and thoracic surgery.[18–21] A study by Tan W et al. in 2022 summarised the research status of Kawasaki disease worldwide, but it omitted the specific research developments on immune control in Kawasaki disease.[22] Recently, many researchers have gradually increased the intensity of research on immune modulation, and the study of immune modulation in Kawasaki disease has also attracted attention. To address this critical knowledge gap, this study set out to perform a bibliometric analysis of publications on immune control in Kawasaki disease to pinpoint significant contributors to present research status and forecast research trends and future development opportunities in this subject.

Materials and methods

Data retrieval strategy

The connection between immune control and Kawasaki disease is the research object of this paper. The Web of Science Core Collection database (https://www.webofscience.com/wos/woscc/basic-search) is a vast and credible database that contains over 12,000 high-quality journals. We conducted a literature search through Web of Science Core Collection on August 15, 2023. The search formula is ([TS= (Kawasaki disease]) OR TS= (Kawasaki syndrome) AND TS= (immune control) and "articles" and "review" are selected as the document types (Fig. 1).

Data analysis

The 294 literatures were exported in plain text format. For the overall analysis, we utilised Microsoft Excel 2019, VOSviewer (version 1.6.19), the R package "bibliometrix" (version 4.3.1) (https://www.bibliometrix.org), and CiteSpace (version 6.2.R4).

Microsoft Excel 2019 was utilised to create data tables. The following analyses were mostly carried out by VOSviewer: analyses of countries, institutions, journals and co-cited journals, authors and co-cited authors, co-cited references, and analyses of keyword co-occurrence. Each node in the visualisation was created to represent a particular element, such as a journal, author, institution, country, or reference. The node colour and size, respectively, represent the category and quantity of these items, and the line thicknesses indicate how closely the pieces are related or co-cited.[23] The R package "bibliometrix" was implemented to analyse trends, thematic evolution, Single Country Publications scales, and Multi-country Publications scales, as well as to create a global distribution network of publications. The scientific impact of authors and journals was assessed using the h-index.[24] This is determined by analysing bibliometrics data through Bibliometrix Biblioshiny analysis.[22] Additionally, the Citation Bursts of references and dual-map overlay of journals were analysed using CiteSpace software.

Results

The trend of publication and citation

After conducting thorough research on the topic, we were able to retrieve a citation report from Web of Science Core Collection. The report indicated that there were 294 publications, with 7804 citing articles (without self-citations), 9850 times cited (without self-citations), as well as an h-index of 49. An overall upward trend in both the quantity of times cited and publications of immune control in Kawasaki disease research from 1991 to 2022 (Fig. 2). The quantity of publications is represented by a bar chart. Despite experiencing a few years of declining numbers, there is a clear trend of growth, highlighted by a sharp increase in numbers from 2018 to 2022. The times cited, represented by a line graph, show a continuous growth trend and a sharp increase from 2018 to 2022. It is worth noting that the greatest quantity of publications existed in 2022, but the citation frequency peaked in 2021. Because the most recent literature retrieved so far was published in June 2023, the quantity of times cited and publications for the second half of 2023 has not yet been reported, so the 2023 data reflect only the first half of the year.

Institutional and country/region analysis

The publications originated from a total of 616 institutions across 42 different countries/regions. As shown in Table 1, The United States leads all other countries/regions in terms of production with 77 publications altogether. China follows closely with 63 publications, followed by Japan with 46 and Taiwan with 28. Then, 42 countries and regions were sorted and displayed according to the number of publications equivalent to or above 1. There is a broad collaborative effort among numerous countries and regions (Fig. 3A). Examples include the tight ties between the United States, China, Taiwan, the Netherlands, Germany, Canada, and Italy; China also engages in active diplomatic relations with the Netherlands, Italy, and Australia. Collaboration among countries and regions in the immunomodulation of Kawasaki disease is also reflected in the geographic distribution map (Fig. 4A). According to Fig. 4B, China has the most Single Country Publications and Multi-country Publications numbers, followed by the United States. Intriguingly, Japan outperformed Germany in the Multi-country Publications and came in last in the Single Country Publications.

We have compiled a list of the top 10 institutions that are associated with immune control in Kawasaki disease (Table 1). Regarding the list of institutions, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University have 14 papers each, with the University of California San Diego following closely with 13 papers. Furthermore, Chongqing Medical University has 10 papers. We used VOSviewer to create a collaborative network based on the quantity and interactions of publications at each institution through filtering and visualising 49 institutions, where the number of publications has to be equal to or greater than 3 (Fig. 3B). Notably, every institution has a partnership or more with other institutions. For instance, there is a strong collaboration between Kaohsiung Chang Gung Memorial Hospital and

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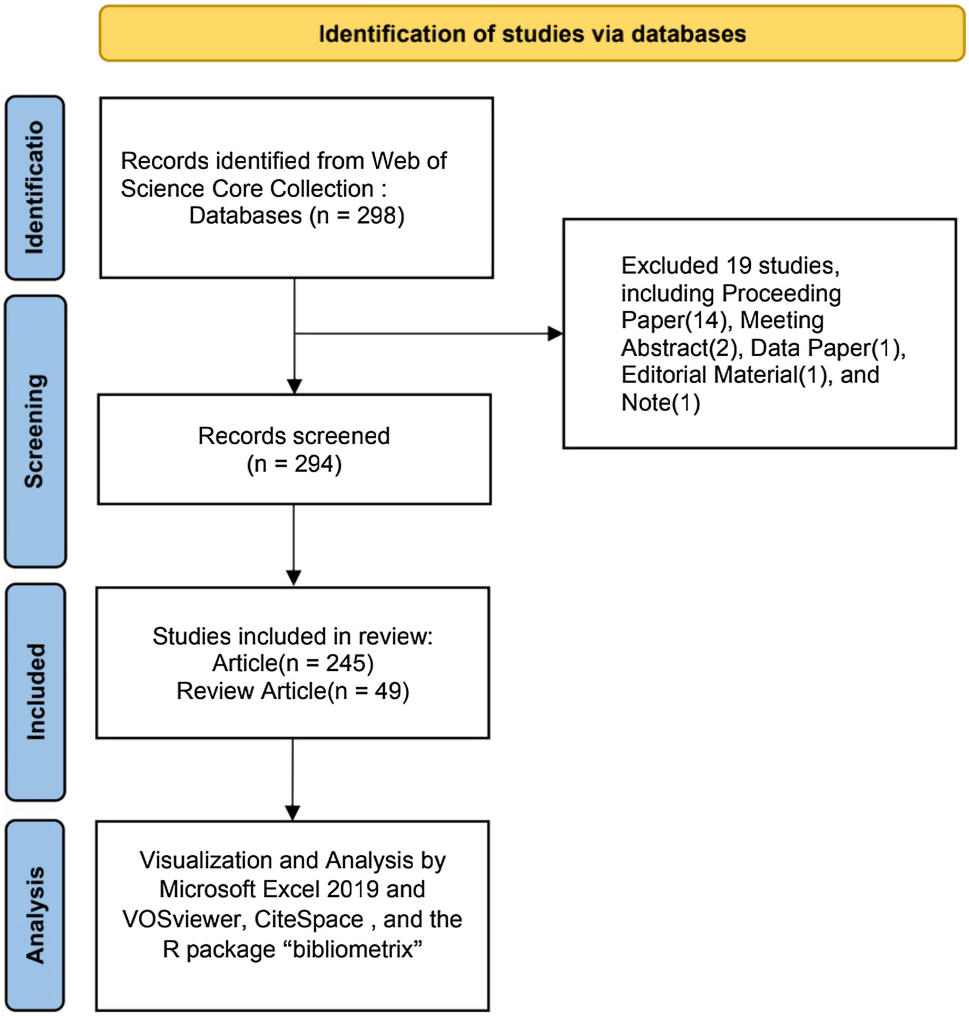


Figure 1. Flowchart for screening publications.

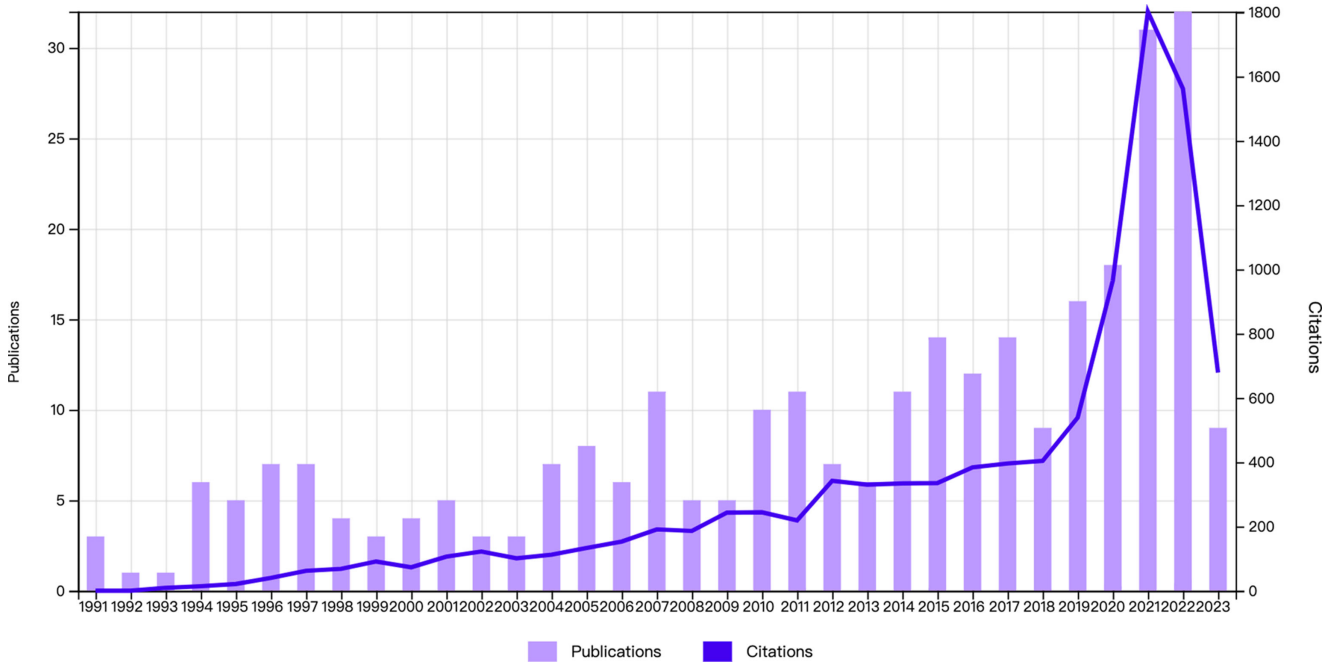


Figure 2. Times cited and publications over time of immune control in Kawasaki disease. The horizontal coordinate represents years, the right vertical coordinate shows the number of citations annually, and the left vertical coordinate shows the number of publications annually.

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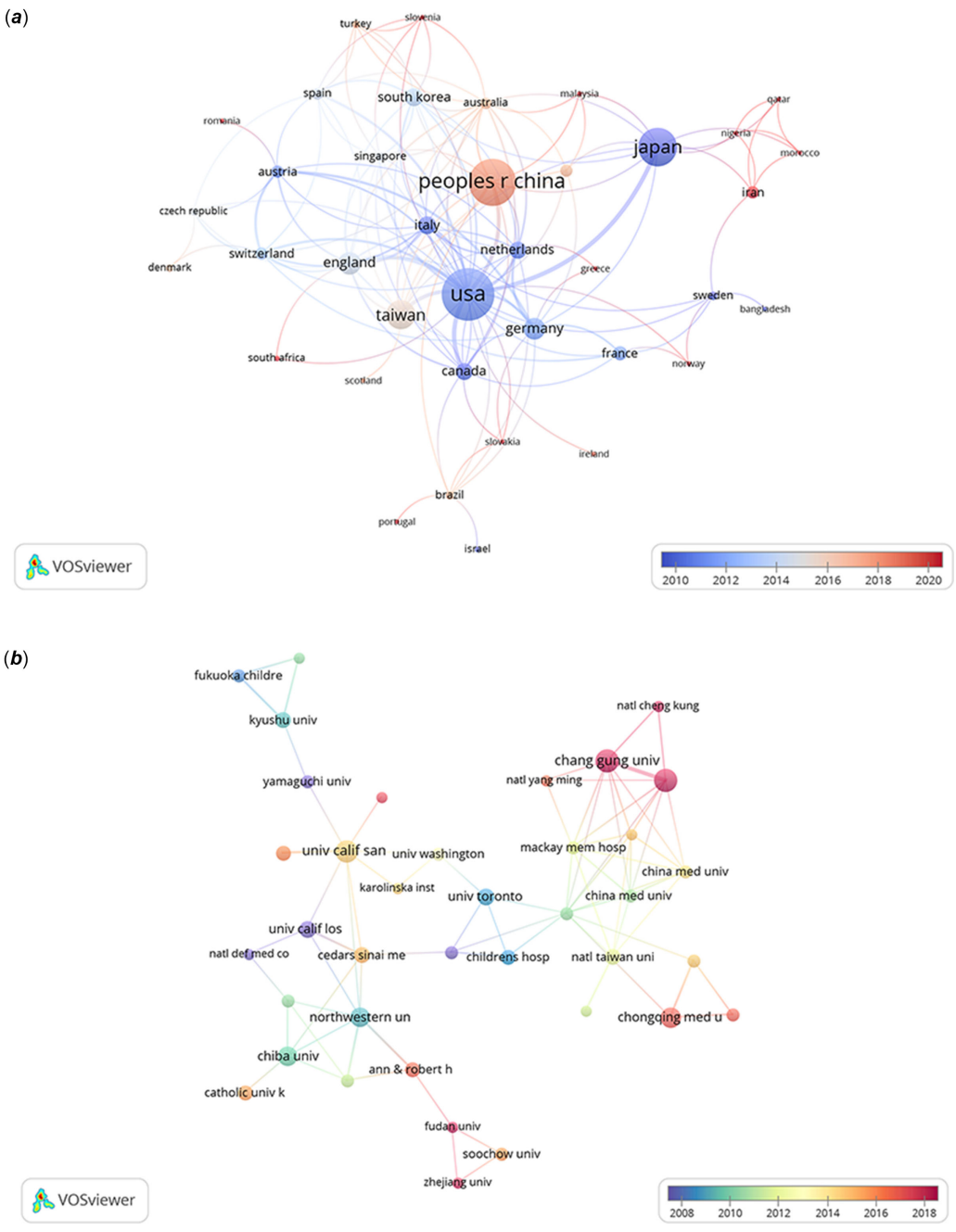


Figure 3. The visualisation of institutions and countries/regions engaged in immune control in Kawasaki disease (KD) research. (***a***) The network of countries/regions of immune control in KD by VOSviewer. (***b***) The network of institutions on immune control in KD by VOSviewer.

Chang Gung University, and the collaboration between Kyushu University and Fukuoka Childrens Hospital is active.

Journal and co-cited journal analysis

Together, the research papers on immune control in Kawasaki disease were published in 2240 co-cited publications and 170 journals. The top 15 journals for immune control research in Kawasaki disease were then listed (Table 2). The majority of publications were published in Clinical and Experimental Immunology (n = 16), preceding Frontiers in Immunology (n = 13), European Journal of Pediatrics (n = 9), Plos One (n = 9), BMC Pediatrics (n = 6), and Frontiers in Pediatrics (n = 6), Pediatrics International (n = 6). Circulation (IF = 37.8) has the highest impact factor from the top 15 journals, subsequent to Frontiers in Immunology (IF = 7.3). After that, we filtered 22 journals based on the requirement that there be a minimum of three pertinent publications before mapping the journal visualisation (Fig. 5A). For instance, the journal Frontiers in Immunology has citation interactions among Clinical and Experimental Immunology, Frontiers in Pediatrics, Plos One, BMC Pediatrics, and other journals.

Six of the top 15 co-cited journals, listed in Table 2, were cited over 300 times, with The New England Journal of Medicine (co-citation = 489) as the most co-cited journal, thereafter Lancet (co-citation = 487), Journal of Pediatrics (co-citation = 379), Clinical and Experimental Immunology (co-citation = 368), Journal of Immunology (co-citation = 347), and Circulation (co-citation = 334). Additionally, Lancet has the highest impact factor (IF = 168.9) listed in Table 2, subsequent to The New England

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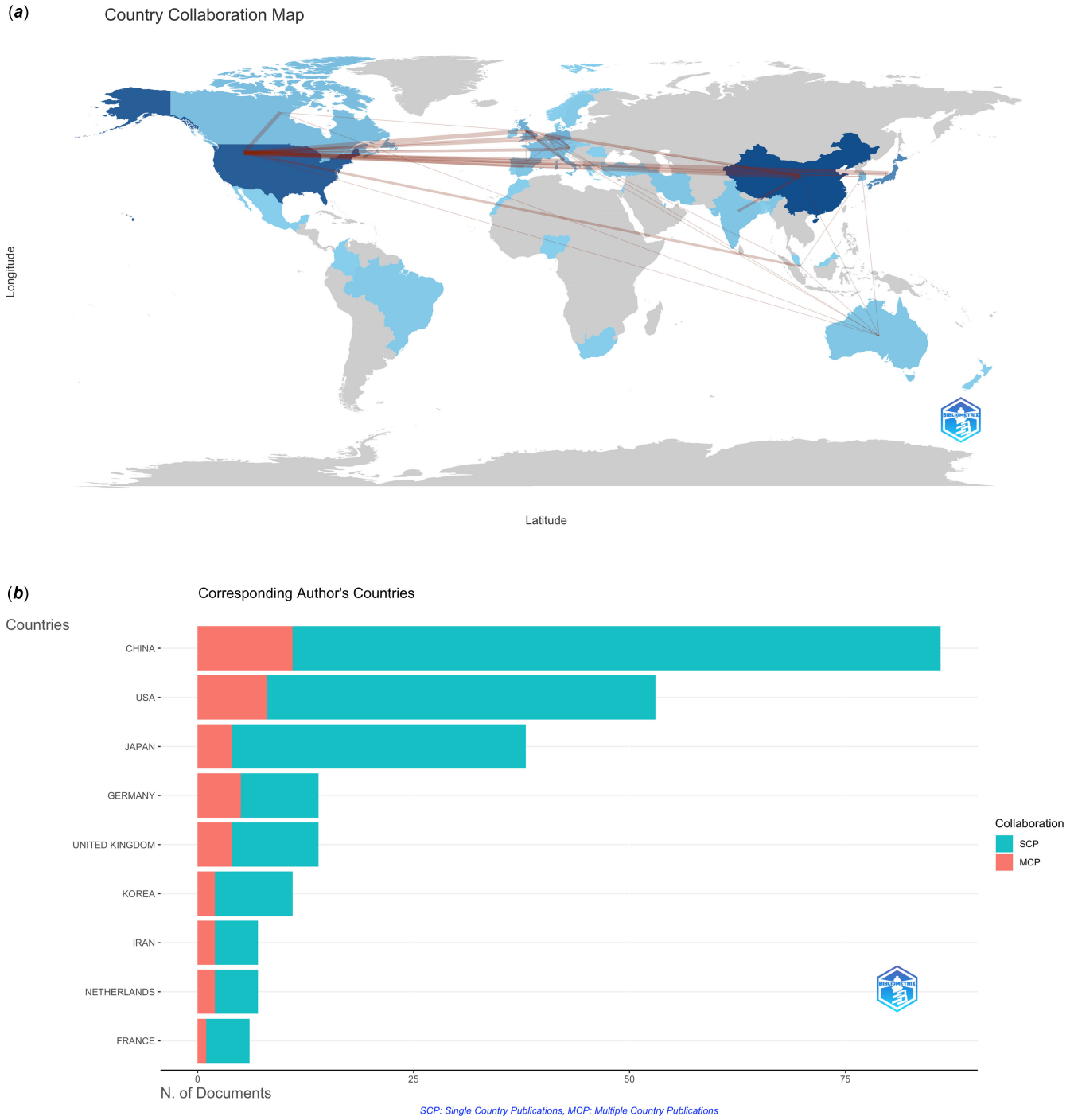


Figure 4. World research collaboration. (***a***) The geographical distribution and on the research of immune control in Kawasaki disease (KD). (***b***) Cooperative publishing on the research of immune control in KD. MCP, Multi-Country Publications; SCP, Single Country Publications.

Journal of Medicine (IF = 168.5), and Nature (IF = 64.8). According to Fig. 5B, Journals with no less than a co-citation of 100 were selected from the mapping of the co-citation network, which The New England Journal of Medicine has strong co-citation connections with Lancet, Clinical and Experimental Immunology, Journal of Clinical Investigation; Journal of Immunology has close cooperation with Circulation, etc.

A comprehensive way to display citation links between citing and cited journals is through the use of a dual-map overlay of journals. The clusters of citing and cited journals are separately on the left and right, and the primary citation path is represented by the orange and green paths (Fig. 6). From these paths, we observed that studies in Molecular/Biology/Immunology-journal are primarily cited by research in Tehnologije/Metalurgija/Midem-journal, and so on.

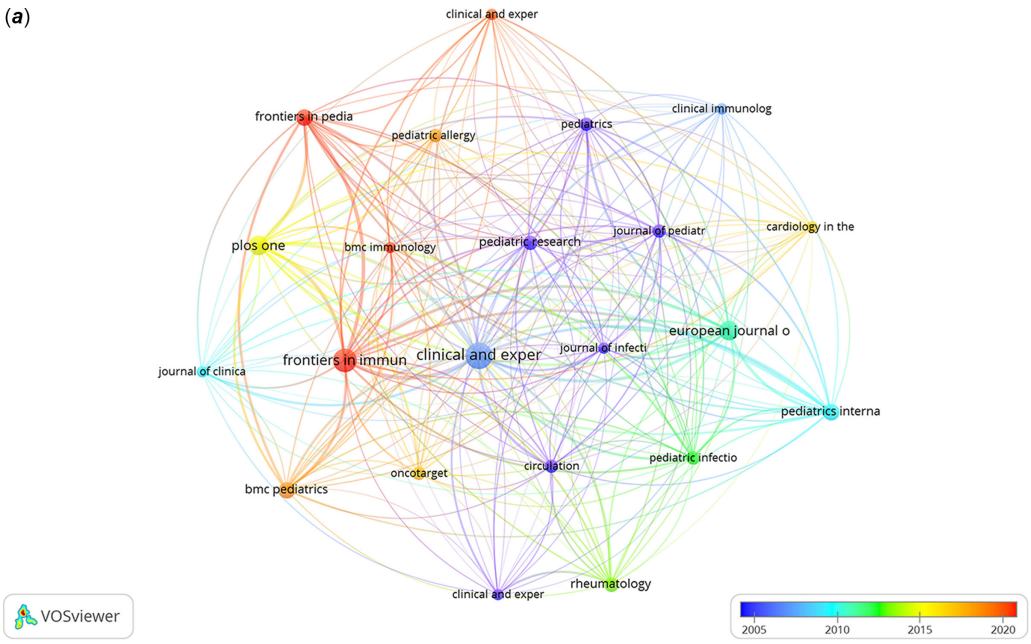
Author and co-cited author analysis

A bibliometric analysis conducted on immune control in Kawasaki disease enlisted a total of 1648 authors. Table 3 clearly shows that Kuo Ho-Chang is the leading author with 15 papers published.

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Table 1. Top 10 countries/regions and institutions for immune control in Kawasaki disease research

Rank	Country/Region	Count	Institution	Count
1	USA	77	Chang Gung University (Taiwan)	14
2	China	63	Kaohsiung Chang Gung Memorial Hospital (Taiwan)	14
3	Japan	46	University of California San Diego (USA)	13
4	Taiwan	28	Chongqing Medical University (China)	10
5	England	19	Northwestern University (USA)	9
6	Germany	18	Chiba University (Japan)	9
7	Italy	13	University of Amsterdam (Netherlands)	8
8	South Korea	13	University of California Los Angeles (USA)	7
9	Canada	12	University of Toronto (Canada)	7
10	Netherlands	12	Cedars Sinai Medical Center (USA)	6



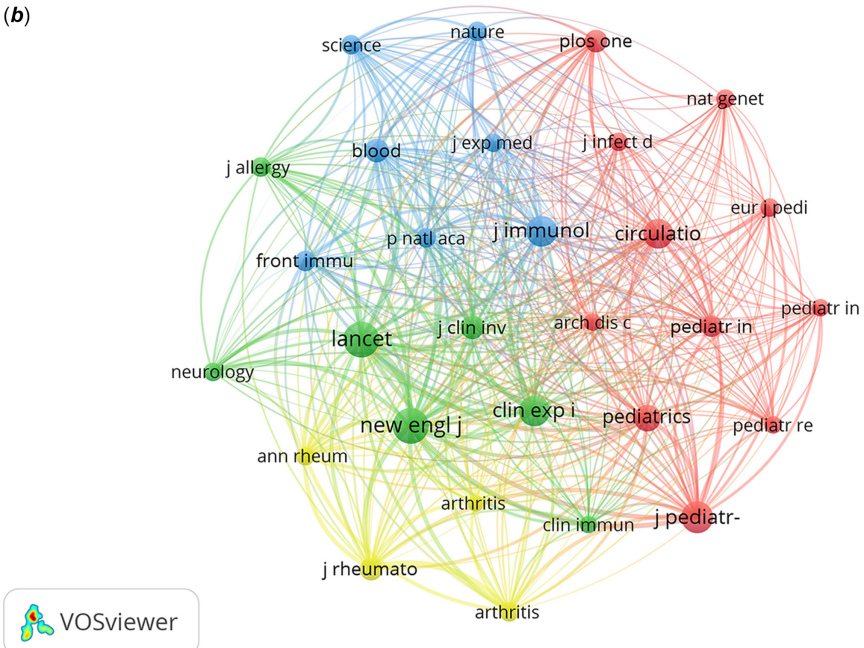


Figure 5. The visualisation of journals (***a***) and co-cited journals (***b***) engaged in immune control in Kawasaki disease research.

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Table 2. Top 15 journals and co-cited journals for immune control in Kawasaki disease research

Rank	Journal	Count	IF	Q	Co-cited journal	Count2	IF2	Q2
1	Clinical and Experimental Immunology	16	4.6	Q2	The New England Journal of Medicine	489	158.5	Q1
2	Frontiers in Immunology	13	7.3	Q1	Lancet	487	168.9	Q1
3	European Journal of Pediatrics	9	3.6	Q1	Journal of Pediatrics	379	5.1	Q1
4	Plos One	9	3.7	Q2	Clinical and Experimental Immunology	368	4.6	Q2
5	BMC Pediatrics	6	2.4	Q2	Journal of Immunology	347	4.4	Q2
6	Frontiers in Pediatrics	6	2.6	Q2	Circulation	334	37.8	Q1
7	Pediatrics International	6	1.4	Q4	Pediatrics	269	8	Q1
8	Pediatric Research	5	3.6	Q1	Journal of Clinical Investigation	213	15.9	Q1
9	Rheumatology	5	5.5	Q1	Blood	203	20.3	Q1
10	Circulation	4	37.8	Q1	Journal of Rheumatology	185	3.9	Q2
11	Journal of Pediatrics	4	5.1	Q1	Plos One	184	3.7	Q2
12	Oncotarget	4	5.168	Q2	Pediatric Infectious Disease Journal	166	3.6	Q3
13	Pediatric Allergy and Immunology	4	4.4	Q2	Frontiers In Immunology	157	7.3	Q1
14	Pediatric Infectious Disease Journal	4	3.3	Q3	Arthritis Rheum	145	8.955	Q1
15	Pediatrics	4	8	Q1	Nature	142	64.8	Q1

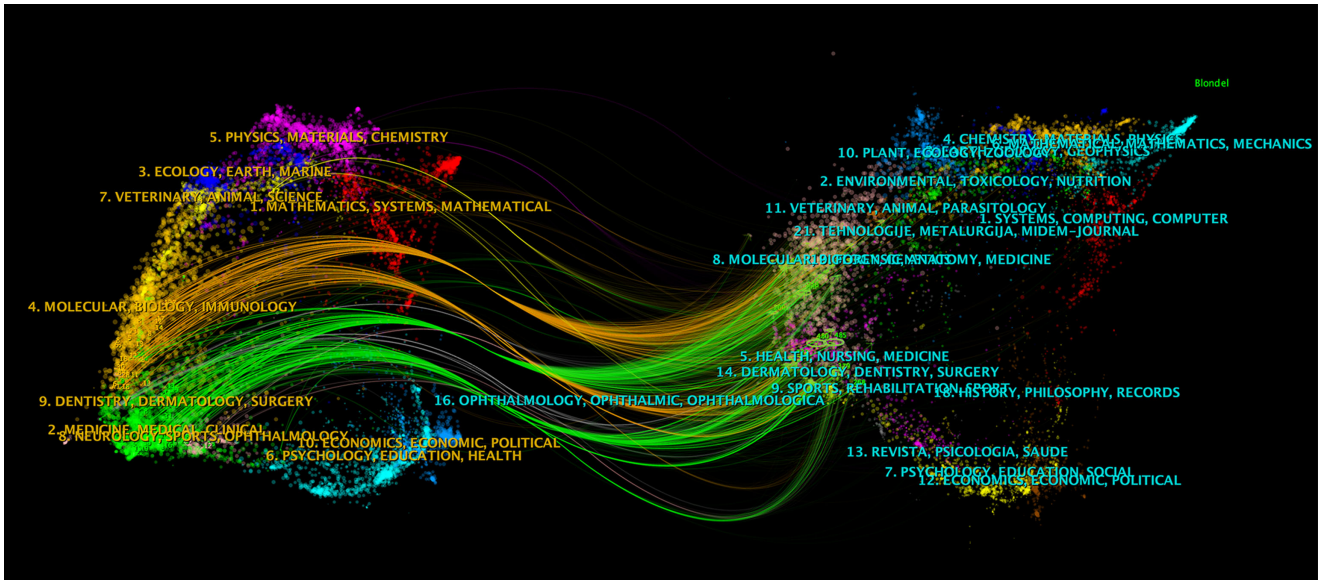


Figure 6. The dual-map overlay of journals on the research of immune control in Kawasaki disease.

Following closely is Huang Ying-Hsien with nine papers, while Burns Jane C and Yi Qijian have seven published papers each. Lee Kyung-Yil, Li Sung-Chou, and Tremoulet Adriana H have six papers each, and there are also a number of other authors who have published 5 papers. We have developed a cooperative network that involves authors who have a minimum of three papers published by VOSviewer (Fig. 7A). Nodes show how many papers each author has published, and the larger the node, the more papers published by the author. In addition, we noticed strong cooperation among several authors. For example, Kuo Ho-Chang has strong cooperation with Huang Ying-Hsien and Li Sung-Chou; Yu Hong-Ren has close cooperation with Yang Kuender D, etc.

In total, 37 of 8712 authors were cited over 20 times. As shown in Table 3, we observed that there are four authors whose names are Newburger JW, Rowley AH, Burns JC and Leung DYM were cited over 100 times. Newburger JW (n = 209) is the most co-cited author, subsequent to Rowley AH (n = 149), Burns JC (n = 129), and Leung DYM (n = 103). Next, we created a network graph of co-cited authors that were filtered to include only at least 20 co-citations (Fig. 7B). According to Fig. 7B, there are five authors—Newburger JW, Rowley AH, Burns JC, Onouchi Y, and Leung DYM—whose combined link strength is over 90.

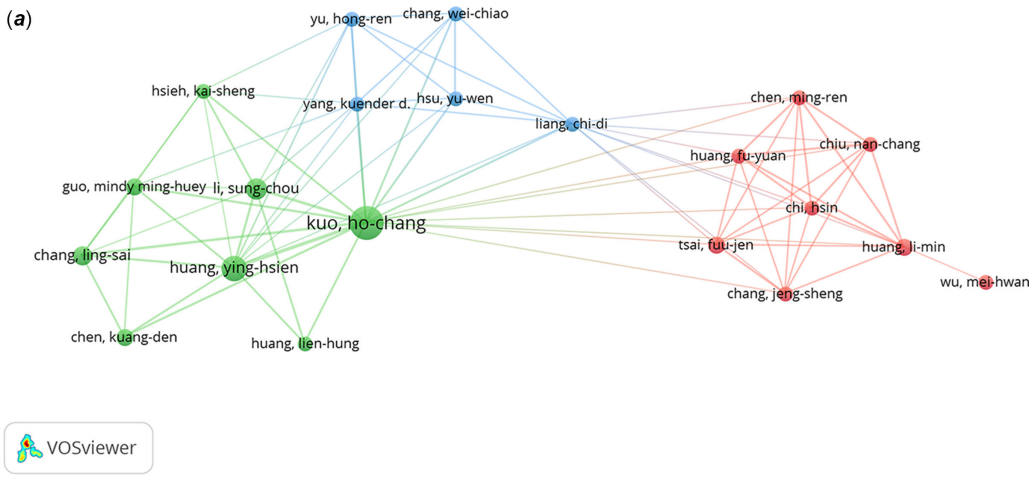
Reference analysis

Over the past few years, research on immune control in Kawasaki disease has generated 11,200 co-cited references. Figure 8A shows reference publication year spectroscopy, which describes the

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Table 3. Top 10 authors and co-cited authors for immune control in Kawasaki disease research

Rank	Author	Count	Co-cited authors	Count
1	Kuo Ho-Chang	15	Newburger JW	209
2	Huang Ying-Hsien	9	Rowley AH	149
3	Burns Jane C	7	Burns JC	129
4	Yi Qijian	7	Leung DYM	103
5	Lee Kyung-Yil	6	Onouchi Y	97
6	Li Sung-Chou	6	Kuo HC	93
7	Tremoulet Adriana H	6	Kawasaki T	91
8	Arditi Moshe	5	Dalakas MC	85
9	Chang Ling-Sai	5	Mccrindle BW	66
10	Liu Ruixi	5	Furukawa S	65



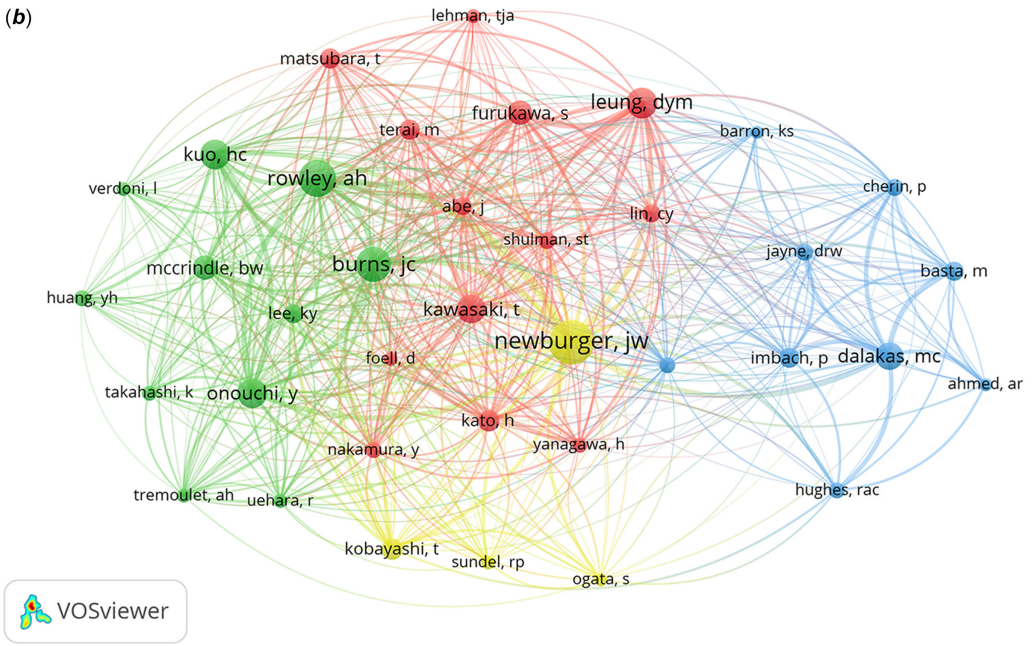


Figure 7. The visualisation of authors (***a***) and co-cited authors (***b***) engaged in immune control in Kawasaki disease research.

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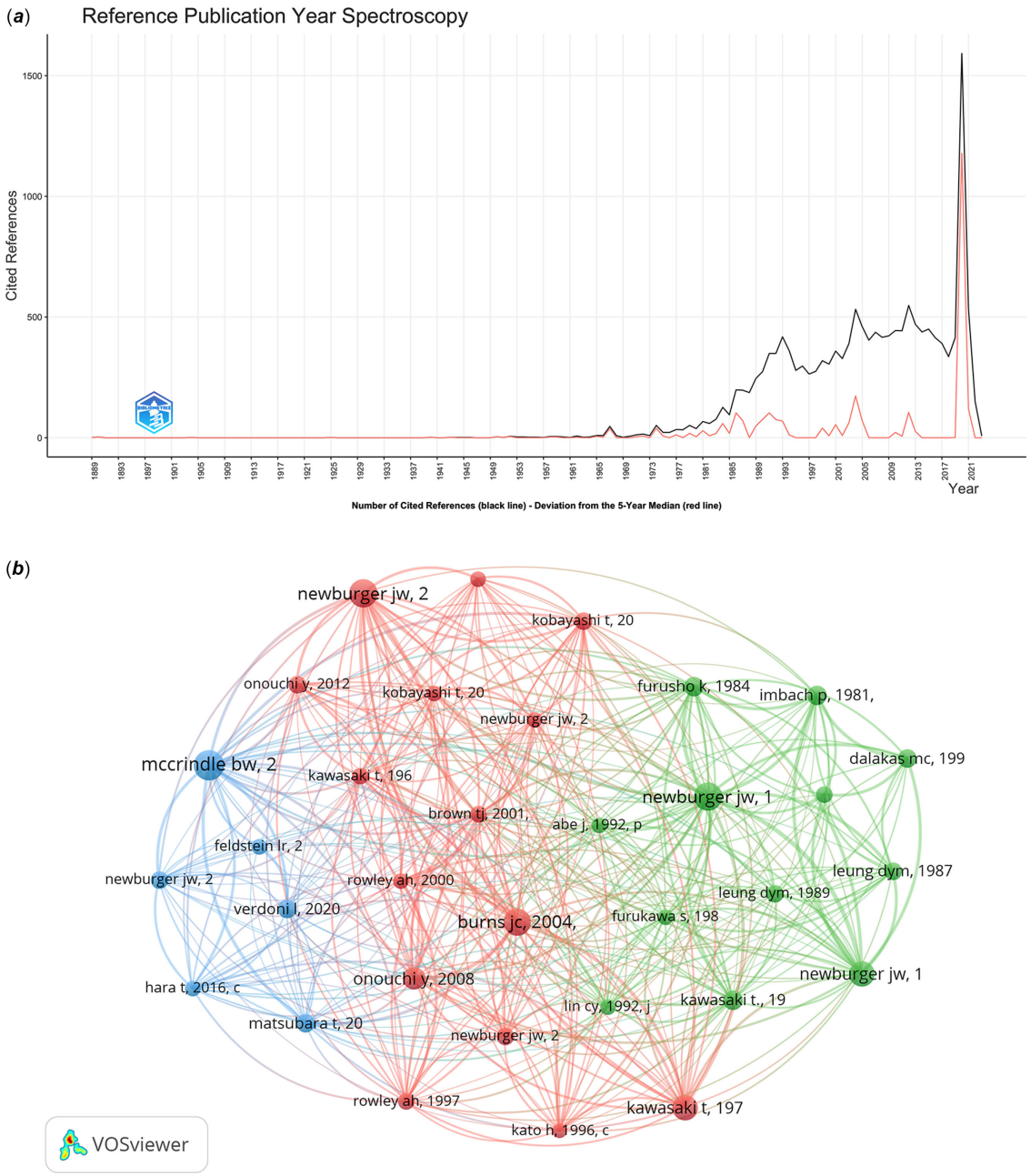


Figure 8. References analysis on the research of immune control in Kawasaki disease (KD). (***a***) Spectroscopy reference publication year. Red line, deviation from the 5-year median; Black line, number of cited references; (***b***) The visualisation of journals co-cited references on immune control in KD.

quantity and a deviation from the 5-year median of cited references. These two indicators both began to rise in 1973 and reached a high in 2020. The top 10 co-cited references were co-cited a minimum of 24 times including two references that were co-cited over 50 times (Table 4). To create the co-citation network (Fig 8B), we chose references with at least 15 co-citations. According to Fig. 8, "Burns JC, 2004, Lancet" shows close co-cited relationships with "Onouchi Y, 2008, Nat Genet" and "Kawasaki T, 1974, Pediatrics"; "McCrindle BW, 2017, Circulation" shows active co-cited relationships with "Newburger JW, 2004, Circulation," etc.

References with citation bursts are ones that have received several citations from scholars throughout time on a certain field. CiteSpace detected just four references with strong citation bursts in our research (Fig. 9). Figure 9 shows that each bar stands for a year; however, the red bar depicts a particularly high citation density. Citation bursts for references started to occur in 1993 and continued until 2023. These 16 references had endurance strengths ranging from 2 to 6 years, while their burst strengths generally varied from 3.66 to 14.84. Notably, McCrindle BW et al published the article "Diagnosis, Treatment, and Long-Term Management of KD," which has the strongest citation burst (strength = 14.84) in Circulation during 6 years (2018–2023). Subsequently, Verdoni L et al published the article "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study" in Lancet has the second-strongest citation bursts (strength = 7.74), which occurred from 2020 to 2023.

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Table 4. Top 10 co-cited references for immune control in Kawasaki disease research

Rank	Cited reference	Citations
1	McCrindle BW, 2017, Circulation, V135, Pe927	54
2	Newburger JW, 1991, New Engl J Med, V324, P1633	50
3	Newburger JW, 2004, Circulation, V110, P2747	48
4	Burns JC, 2004, Lancet, V364, P533	45
5	Kawasaki T, 1974, Pediatrics, V54, P271	40
6	Newburger JW, 1986, New Engl J Med, V315, P341	39
7	Onouchi Y, 2008, Nat Genet, V40, P35	33
8	Imbach P, 1981, Lancet, V1, P1228	25
9	Kawasaki T., 1967, Jpn J Allergy, V16, P178	25
10	Furusho K, 1984, Lancet, V2, P1055	24

Keyword analysis and topic trends

Research on immune control in Kawasaki disease has generated 703 author keywords and 961 keywords plus. We quickly identified research hotspots in this field through the co-occurrence analysis. The top 10 author keywords and keywords in studies on immunological control in Kawasaki disease are listed in Table 5. Among author keywords, Kawasaki disease featured more than 100 times, followed by intravenous immunoglobulin, COVID-19 and vasculitis which respectively showed up 28, 24 and 20 times. The top 10 keywords plus are different from author keywords. There were 10 keywords that appeared over 20 times. As shown in Table 5, expression, Kawasaki disease, gamma-globulin and immune globulin all showed up more than 30 times, followed by activation, association children, susceptibility, cells, and T cells all appeared more than 20 times.

While the minimum cluster size was set as 3, the author keywords from Web of Science Core Collection literature were categorised into 9 classes with red and green clusters having the highest number of keywords (Fig. 10A). The red clusters of author keywords include "Multisystem Inflammatory Syndrome in Children (MIS-C)", "SARS-CoV-2", "children", "COVID-19", "cytokines", "immunopathology", "autoantibodies", and so on. And the green clusters of author keywords include "intravenous immunoglobulin", "vasculitis", "immunomodulation", "myositis", "dermatomyositis", etc. The Network visualisation of author keywords shows that Kawasaki disease has close relationships with vasculitis intravenous immunoglobulin and COVID-19. According to the Density visualisation of author keywords (Fig. 10C), the link between nodes is stronger when they are close to one another and darker in colour when there are more occurrences of the keyword. As shown in Figure 10C, we found the strongest correlation between Kawasaki disease and vasculitis. While the minimum cluster size was 10, the Web of Science Core Collection literature's keywords plus were divided into 3 groups (Fig. 10B). Words like "expression," "association," "children," "diagnosis," "susceptibility," "coronary artery lesions," and others are included in the red clusters of keywords plus. The green keywords plus clusters include "KD," "gamma-globulin," "therapy," "idiopathic thrombocytopenic," "systemic lupus-erythematosus," and so on. Words like "activation," "T cells," "lymph-node syndrome," "tumor-necrosis-factor," "receptor," and others are included in the blue clusters of keywords plus. In addition, Kawasaki syndrome has a close relationship with idiopathic thrombocytopenic purpura, gamma-globulin, and immune globulin through combination with the network visualisation (Fig. 10B) and density visualisation (Fig. 10D) of keywords plus. It was found that gamma-globulin and immune globulin have a strong correlation and more occurrence times.

According to Figure 11A, an author keywords trend topic, from 1995 to 2022, immunological study predominated, with the leading keywords being immunomodulation, intravenous immunoglobulin, and vasculitis. Additionally, these three terms—MIS-C, COVID-19, and SARS-CoV-2—appeared frequently during the course of the last 3 years (2019–2021), making them very likely to be representative of the areas of immune regulation in Kawasaki disease that are currently the focus of research. According to Figure 11B, the keywords plus trend topic, from 1995 to 2015, studies mostly concentrated on T cells and immune globulin, and the leading keywords were T cells, gamma-globulin, intravenous gamma-globulin, immune globulin, and guillain-barre syndrome. Since 2014, researchers have begun to actively explore the genome-wide association of immune control in Kawasaki disease, and the main keywords were activation, association, infection, protein, and pathogenesis.

Sankey diagrams: Three-field plots for the study of immune control in Kawasaki disease

The communication interactions between different elements are visualised using the three-field plot, which combines rectangles to represent the elements and connects them with lines. With the help of this tool, it is possible to visualise the relationships among the literature sources, author keywords, cited sources, main authors, nations/regions, and affiliations. Additionally, the communication between multiple components increases as the size of the rectangle increases. Figure 12 displays the cited references on the left, the authors in the centre, and the author keywords on the right. These three elements are interrelated, and comprehending their connection is crucial to fully exploiting a research paper's potential. According to the analysis, the authors who frequently studied immune control in Kawasaki disease were identified through the use of cited references and author keywords. Utilising scrutiny of the most frequently cited references, authors, and author keywords, it can be found that five authors Kuo HC, Burns JC, Shulman ST, Shimizu C, and Huang YH, five author keywords, namely "Kawasaki disease," "intravenous immunoglobulin," "coronary artery lesions," "vasculitis," and "intravenous immunoglobulin," which originated from five cited reference, "Newburger JW 2004 Circulation," "Burns JC 2004 Lancet," "McCrindle BW 2017 Circulation," "Onouchi Y 2008 Nat Genet," and "Newburger JW 1991 New Engl J Med."

Discussion

The current research analysed study tendencies and focused on the area of immune control in Kawasaki disease using bibliometric analytic techniques and visualisation tools as technical support. There exists an increased overall tendency both in the quantity of publications and times cited, which have two periods, from 1991 to 2022. First, both of them rose gradually between 1991 and 2017. Then, they erupted starting in 2018, but mainly between 2020 and 2021 (during the COVID-19 outbreak). Briefly, Since the last several years, there has been a large increase in publications and citations, which suggests that more researchers are becoming interested in related research and that the study of immune control

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Table 5. Top 10 keywords for research immune control in Kawasaki disease

Rank	Author keyword	Frequece	Keyword plus	Frequece
1	Kawasaki disease	129	Expression	39
2	Intravenous immunoglobulin	28	Kawasaki-disease	38
3	COVID-19	24	Gamma-globulin	36
4	Vasculitis	20	Immune globulin	32
5	Coronary artery lesions	14	Activation	32
6	Intravenous immunoglobulin	13	Association	28
7	Inflammation	12	Children	26
8	Children	11	Susceptibility	24
9	Immune system	6	Cells	23
10	Coronary aneurysm	6	T cells	21

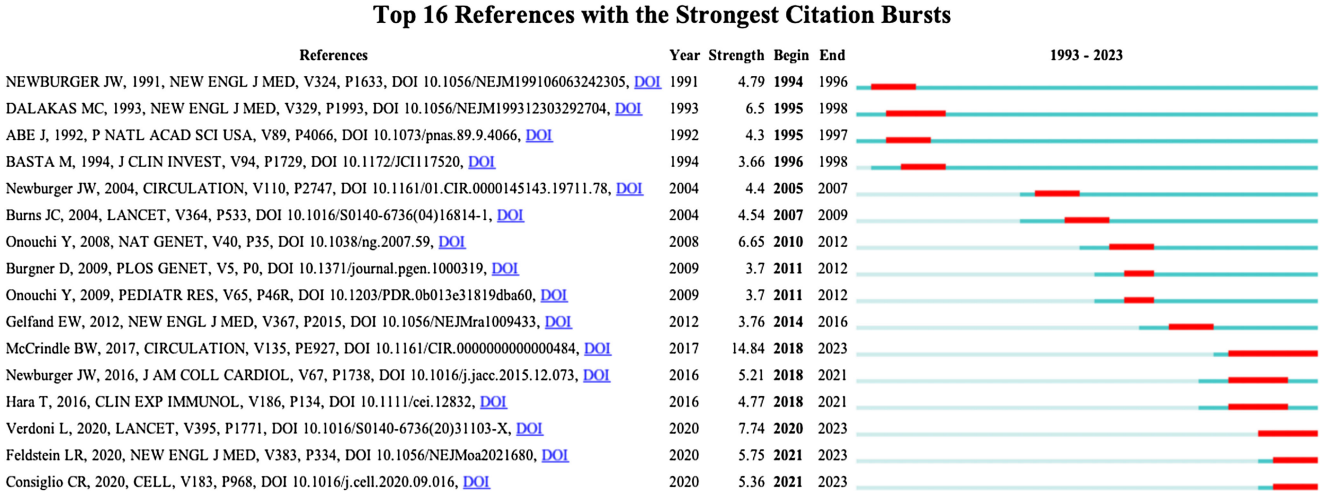


Figure 9. Top 16 references with the strongest citation bursts. A red bar indicates high citations in that year.

in Kawasaki disease is currently in an explosive phase. In addition, the results of a different Google tendency research on Kawasaki disease and COVID-19 are consistent with the apparent rise in citation volume. This may be connected to the ongoing identification of Kawasaki disease symptoms in the wake of the COVID-19 outbreak.[25,26]

In total, 42 different countries/regions represented by a total of 616 institutions were represented in the publications. The highest level of collaboration (n = 14) was demonstrated by Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, who also developed collaborative networks with one another. Although the scope and depth of collaboration between institutions fails to be optimal, it has cooperative links between some countries/regions. Kawasaki disease research is more cooperative in the aforementioned three countries when looking at word cooperation networks and the chart. In terms of Single Country Publications and Multi-country Publications numbers, China was at the forefront, and subsequence to the United States and Japan. A good deal of the top 10 highest-productivity nations remained developed nations as is probably related to their access to more adequate research funding, while several were developing countries. Additionally, the study discovered that the Web of Science database publications on immune control in Kawasaki disease research were primarily from China, the United States, and Japan. Northeast Asia has a high frequency of Kawasaki disease.[27] Data from questionnaire inquiries conducted in 2017 indicate that the overall incidence of Kawasaki disease in China is increasing, with an incidence of 46.3–55.1 per 100,000 children below the age of 5 in China, though 28.58–60.08 per 100,000 children under the age of 5 in Taiwan.[28,29] This has gradually raised the awareness of Kawasaki disease in this populous country. The Shaanxi Provincial Diagnosis and Treatment Center of Kawasaki disease drafted the first expert consensus in China in 2021 to control the administration of intravenous immunoglobulin for Kawasaki disease.[30] Since Japan was the primary nation to discover and thoroughly research Kawasaki disease, there was obviously an abundance of interest in the research. Because of an absence of data, the African continent was displayed as grey on a visualisation illustrating the frequency of Kawasaki disease worldwide. According to research from Egypt, an African nation, potentially undiagnosed or untreated Kawasaki disease may be widespread there.

The majority of papers were published in Clinical and Experimental Immunology (n = 16), subsequence to Frontiers in Immunology (n = 13). Clinical and Experimental Immunology,

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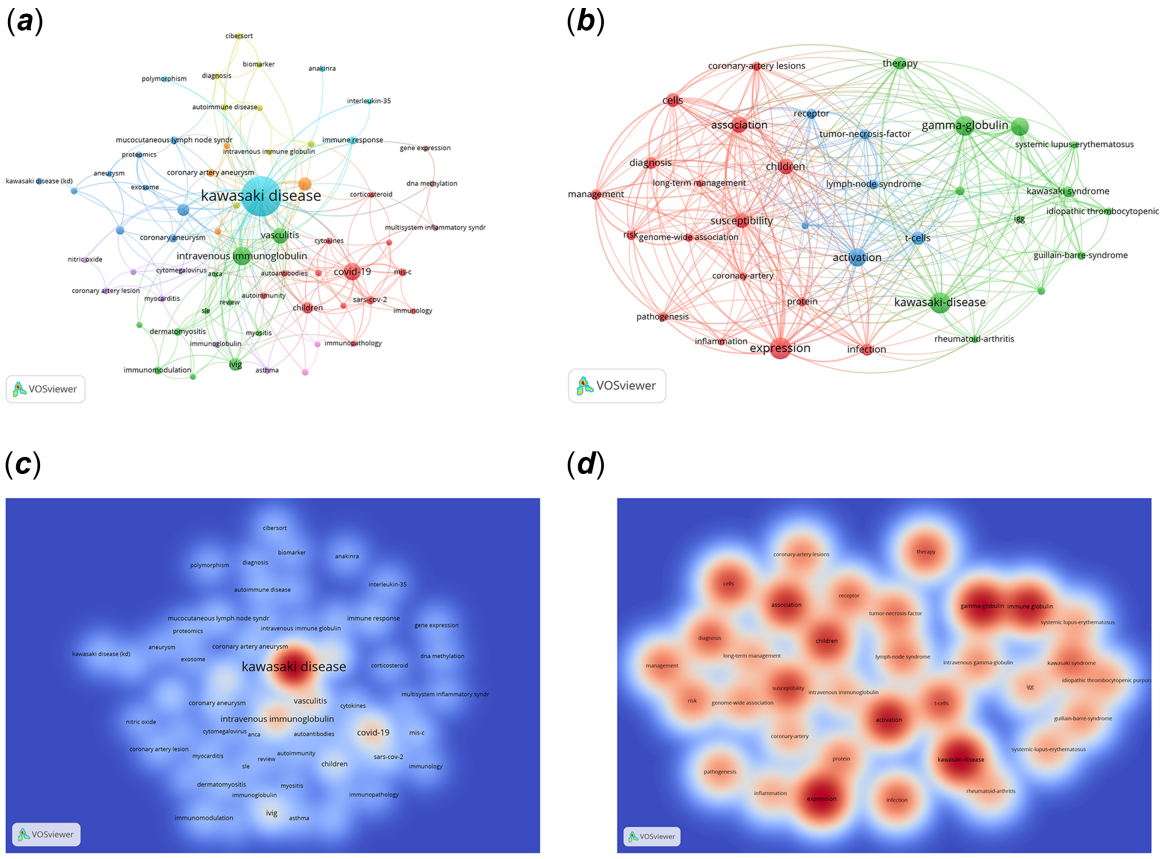


Figure 10. The visualisation of author keywords and keywords plus publishing research involved in researching immune control in Kawasaki disease. (***a***) Network visualisation of author keywords. (***b***) Network visualisation of keyword plus. (***c***) Density visualisation of author keywords. (***d***) Density visualisation of keywords plus.

Frontiers in Pediatrics, Plos One, BMC Pediatrics, and other publications all have active citation connections with Frontiers in Immunology. The three journals having the largest number of co-citations were The New England Journal of Medicine (Co-citation = 489), Lancet (Co-citation = 487), and Journal of Pediatrics (Co-citation = 379). What's more, Lancet and The New England Journal of Medicine Lancet frequently co-cite one another. However, compared to other publications, the majority of the cited articles on the Kawasaki disease study originate from co-cited journals, like Nature, Lancet, and The New England Journal of Medicine, with higher impact factors. While it may be more challenging to publish immune control in Kawasaki disease study articles in high-impact factor journals, doing so may result in greater attention and citations.[31] Additionally, the majority of the recent studies on immunological control in Kawasaki disease have been published in publications devoted to pediatrics and immunology.

The most prolific author is Kuo Ho-Chang, who has 15 papers published. Huang Ying-Hsien comes in second with nine papers, followed by Burns Jane C and Yi Qijian, who each have seven papers published. With Huang Ying-Hsien and Li Sung-Chou, Kuo Ho-Chang works closely; Yu Hong-Ren works closely with Yang Kuender D. Thirty-seven authors were referred to more than 20 times out of the total 8712 authors who had been cited. Over 100 times were cited for Newburger JW, Rowley AH, Burns JC, and Leung DYM. Newburger JW (n = 209) has earned the most co-citations, subsequence to Rowley AH (n = 149), Burns JC (n = 129), and Leung DYM (n = 103), indicating that their study findings are widely followed and acknowledged. Five authors had connection strengths over 90, including Newburger JW, Rowley AH, Burns JC, Onouchi Y, and Leung DYM. The information presented above will make it easier for future researchers studying immunological control in Kawasaki disease to pinpoint key research groups with more accuracy and speed and to consult pertinent parties in a focused manner.

It is possible to think of co-cited references as the foundation for study in a field because they are citations being cited in tandem through numerous other publications. 11,200 co-cited references were produced by the study's findings on immune control in Kawasaki disease. The deviation from the 5-year median and the quantity of cited references both grew starting in 1973 and peaked in 2020. The top 10 co-cited citations included two with over 50 citations each. "Burns JC, 2004, Lancet" displays close co-cited links with "Onouchi Y, 2008, Nat Genet" and "Kawasaki T, 1974, Pediatrics"; "McCrindle BW, 2017, Circulation" displays active co-cited relationships with "Newburger JW, 2004, Circulation." Due to their high frequency of citation in recent years, citation bursts for references are indicative of developing fields of study.[32] We performed a citation burst analysis on less than 300 citations from 1993 to 2023, 16 references saw substantial spikes in citations. The article "Diagnosis, Treatment, and Long-Term Management of KD" by McCrindle BW et al. had citation bursts during the last 6 years (2018–2023), and it had the strongest citation burst (strength = 14.84). "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study" is the reference that has the second-strongest citation bursts (strength = 7.74), which occurred from 2020 to 2023. Generally, all of these citations have endurance ranging

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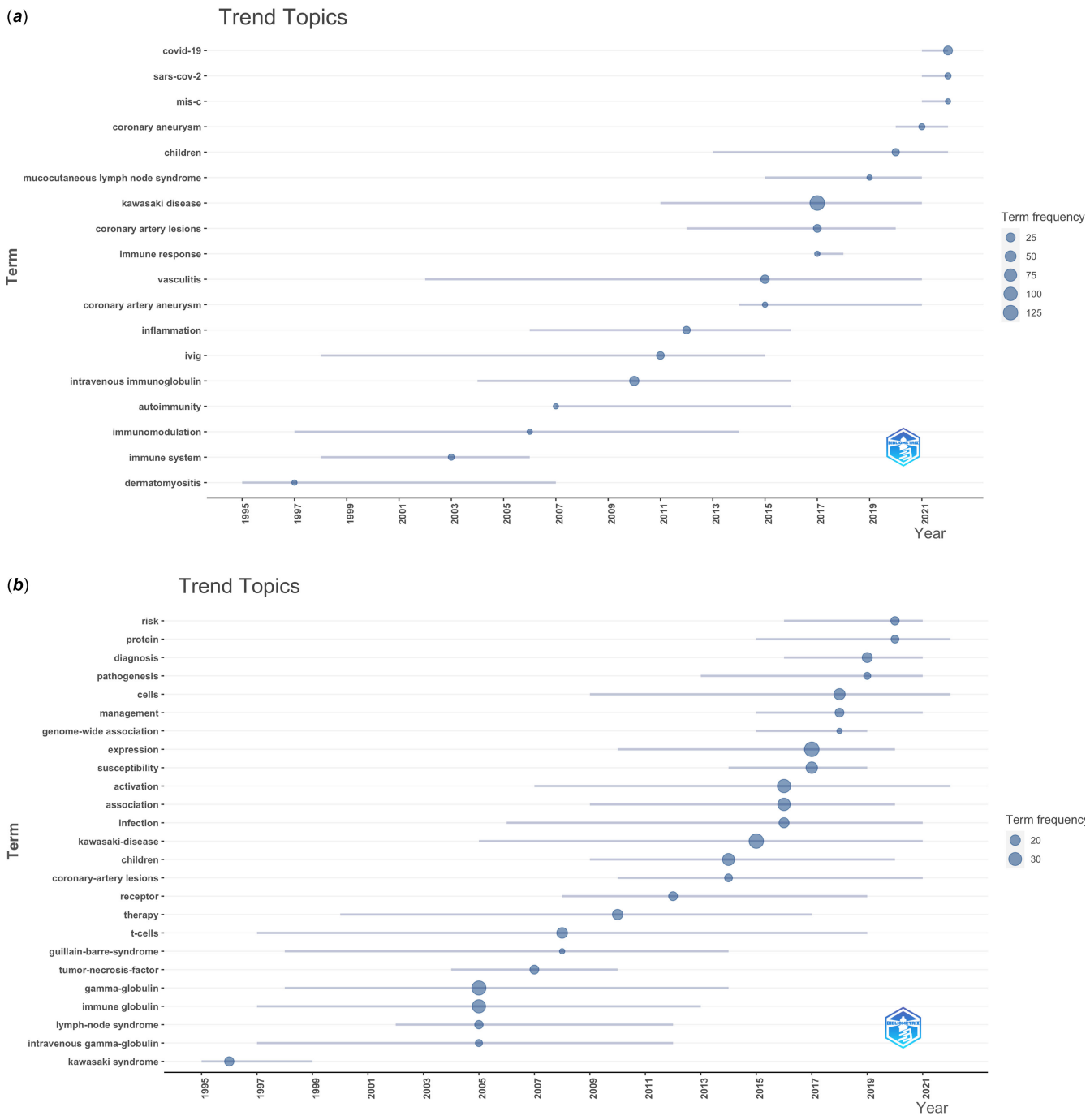


Figure 11. Trend topic analysis of keywords (***a***) and keywords plus (***b***) on immune control in Kawasaki disease research. IVIG, intravenous immunoglobulin.

from 2 to 6 years, while their burst strengths vary from 3.66 to 14.84.

Keyword analysis on immune control in Kawasaki disease has generated 703 author keywords and 961 keywords plus. Among author keywords, Kawasaki disease, intravenous immunoglobulin, COVID-19, and vasculitis were the most common keywords. we found the strongest correlation between Kawasaki disease and vasculitis. Among keywords plus, expression, Kawasaki disease, gamma-globulin, and immune globulin, which were the most common keywords, all showed up more than 30 times. It was found that gamma-globulin and immune globulin have a strong correlation and more occurrence times. According to a trend topic analysis of keywords, the research mostly concentrated on T cells. During the course of the last three years (2019–2021), SARS-CoV-2, COVID-19, and MIS-C appeared frequently. In short, COVID-19, globulin, and vascular disease are all closely associated to with Kawasaki disease. Kawasaki disease mostly affects newborns and young children and results in systemic vascular inflammation. The Centers for Disease Control in the US suggested MIS-C, a new illness linked to COVID-19, in May 2020.[33] Clinical symptoms, such as modest pulmonary indications but substantial and severe systemic inflammation, are present in certain SARS-CoV-2-infected infants who have been given the diagnosis of MIS-C.[34,35] Kawasaki disease may be brought on by SARS-CoV-2.[36]

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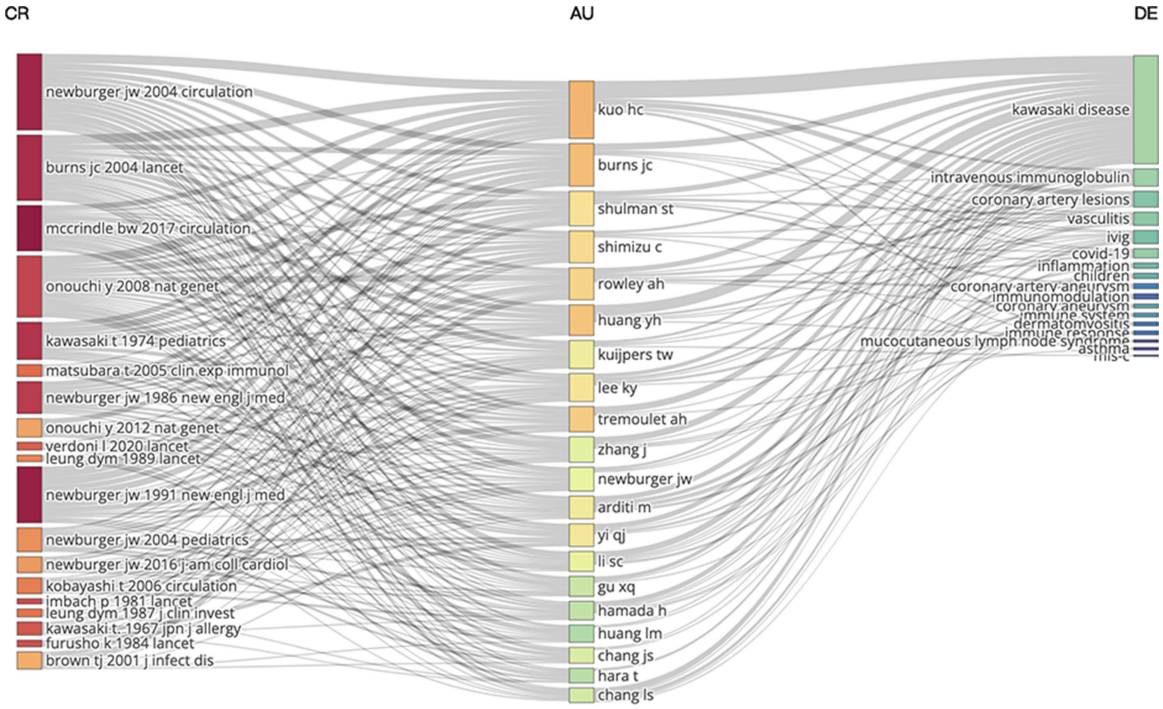


Figure 12. Three-field plots on immune control in Kawasaki disease research. CR, cited references; AU, authors; DE, author keywords.

These Kawasaki disease cases in children caused by SARS-CoV-2 typically present at a later age and are clinically distinguished by myocarditis development. Italian COVID-19 patients are at a greater risk of suffering more severe Kawasaki-like symptoms, and they frequently need adjuvant glucocorticoid medication.

The primary contributing causes to the acute phase of Kawasaki disease include immunological problems, aberrant T and B cell activation, and the creation of several inflammatory agents, including anti-endothelial cell autoantibodies, which result in vascular inflammatory injury. Here are some of the mechanisms associated with immune control in Kawasaki disease. T helper Cell 1 and T helper Cell 2 play important roles in cellular and humoral immunity, respectively, and both are integral to the acute stage of Kawasaki disease. After intravenous immunoglobulin treatment, TNF-α levels were significantly lower in patients without coronary artery lesions or intravenous immunoglobulin responders, but increased in patients with coronary artery lesions or intravenous immunoglobulin non-responders; IFN-γ level was elevated in patients suffering coronary artery lesion compared with patients without coronary artery lesion both before and after intravenous immunoglobulin therapy.[37–39] T helper Cell 17 exerts a pro-inflammatory effect through the production of Interleukin-17, which acts on a variety of cells, inducing the expression of cytokines like granulocyte/macrophage colony-stimulating factor, TNF-α, Interleukin-6, and Interleukin-8, along with chemokines and metalloproteinases, which in turn prolongs inflammation, thus playing a key role in autoimmune and allergic responses.[40,41] T helper Cell 17/Treg imbalance was found to be present in patients with Kawasaki disease. Many cells, such as smooth muscle cells, epithelial cells, endothelial cells, fibroblasts, adipocytes, B cells, and monocytes, all express Cluster Of Differentiation 40 (CD40), and Cluster Of Differentiation 40 Ligand (CD40L), which is up-regulated upon CD40 activation and binds to CD40 to transmit signals pertaining to cell activation or development, has been found expressed on the surface of platelets and Cluster of differentiation 4+ T cells.[42] CD40L expression has been reported to be elevated in the acute phase of Kawasaki disease and is significantly elevated in Kawasaki disease patients with coronary artery lesions.[43] In individuals having acute Kawasaki disease, neutrophils are prone to establish a neutrophil extracellular trap, and the expression of vascular endothelial growth factor A and hypoxia-inducible factor 1 is increased by neutrophil extracellular trap, causing continuous endothelial injury, which in turn leads to endothelial proliferation.[44] In addition, the interaction between neutrophil extracellular trap and peripheral blood mononuclear cells leads to vascular injury in Kawasaki disease patients.[45] The dysregulation of the immune system may be a factor in the low level of natural killer group 2 member D observed during the acute stage of Kawasaki disease.[46] Allograft inflammatory factor 1 may have a variety of functions in Kawasaki disease patients, including activation of antigen-specific T lymphocytes, macrophage activation, and type I interferon response. In a mouse model of Kawasaki disease caused by vasculitis generated by *Lactobacillus casei* cell wall extract, it was demonstrated that activation of cysteoaspartase-1, Interleukin-1β, and Interleukin-1 α can promote Kawasaki disease vasculitis.[47,48] The importance of the abnormal immune response in the pathophysiology of Kawasaki disease is beyond dispute, and research into this connection will assist not only in understanding the pathogenesis of Kawasaki disease but also in creating novel therapeutic medications that will increase the effectiveness of current Kawasaki disease treatments.

This study has a number of distinctive benefits. First, we used bibliometrics to conduct a thorough analysis of research on immunological control in Kawasaki disease for the first time, which involved performing a macro-level analysis of variables such as institution, country, journal, author, and keywords. Second, our analysis approach is extremely likely to prove impartial because we utilised three bibliometric tools simultaneously for the study,

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including CiteSpace and VOSviewer both have been extensively employed in the bibliometrics community. To further ensure that articles written in languages other than English are not left out, our data are multilingual. Finally, bibliometric analysis, as opposed to traditional reviews, offers a more thorough understanding of the hotspots and frontiers.

Of course, there are some limitations. First, additional databases are not taken into consideration when analysing the data for this study; as a result, some pertinent studies may be missed. Second, we only counted articles and reviews as studies, which might have underrepresented other types of papers.

Conclusions

In conclusion, the amount of pertinent research published each year reflects the growing interest in immune control and Kawasaki disease. This bibliometric analysis describes the research development on the investigation of immunological control in Kawasaki disease for the first time and offers a qualitative and quantitative evaluation of essential bibliometric data. The largest contributions to this field have come from China, the United States, and Japan, whose cooperation is more frequent and publications are greatly focused. Study on immune control in Kawasaki disease has recently concentrated on SARS-CoV-2, COVID-19, and MIS-C. The findings of bibliometric analysis offer researchers a more straightforward and efficient way to get the most recent data on immune control in Kawasaki disease research.

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Ethics approval. The data are all from the public database Web of Science, which does not involve ethical issues.

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