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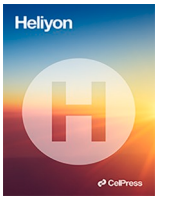

Research article

A bibliometric analysis of Kawasaki disease from 1974 to 2022

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ABSTRACT

Objective: To analyse the research history, development trends and current status of relevant literature in the field of Kawasaki disease, and to provide the basis for future directions in Kawasaki disease (KD) research.

Methods: Literature on Kawasaki disease published between January 1974 and December 2022 was searched for in the Web of Science database, and CiteSpace was used to perform visual analyses.

Results: The search yielded a total of 6950 articles. The number of publications related to Kawasaki disease showed an increasing trend. A collaborative network analysis revealed that the United States, Japan and mainland China were the most influential countries in this field. The University of California system contributed the most publications and the journal with the most publications was *Circulation*. JW Newburger was an authoritative author in this field. "Coronary artery lesion", "Intravenous immunoglobulin" (IVIG) and "Risk factor" were three prominent keywords. Keyword bursts changed from "TNF" and "IVIG", which focused on aetiology and treatment, to "Long term management", which emphasized the recovery period, and to "Kawasaki-like disease" and "Multisystem inflammatory syndrome" during the novel coronavirus pandemic. Trends of highly cited references indicated that landmark articles in different periods focused on Kawasaki disease guidelines, gene polymorphisms and multisystem inflammatory syndrome caused by the novel coronavirus.

Conclusion: The aetiology of Kawasaki disease remains unclear, but viral infection is likely to play an important role. The combination of evolving sequencing technologies, large-scale epidemiological investigations and prospective cohort studies is likely to be important in exploring Kawasaki disease and improving its prognosis in future.

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1. Introduction

Kawasaki disease is an acute, self-limiting vasculitis that mainly affects children under 5 years of age [1]. The medium-sized vessels are the most susceptible in this disease, especially the coronary arteries [2]. Without timely treatment, coronary artery injury may occur in 25% of children. Coronary artery injury and arterial stenosis can cause long-term complications, resulting in local thrombosis and leading to coronary heart disease or even death [3].

Kawasaki disease is an immune vasculitis. Since Furusho et al. [4] first began treating patients with Kawasaki disease with intravenous immunoglobulin (IVIG), which is commonly used in immune disorders, the incidence of coronary artery injury has decreased from 25% to 3%–5%, substantially improving the prognosis of patients with the disease. However, in subsequent treatment, 10%–20% of patients have IVIG resistance, and the incidence of coronary artery injury and coronary artery aneurysm in such children is significantly higher than that in IVIG-sensitive children. For IVIG-resistant patients, the early addition of immunosuppressants can reduce the incidence of coronary artery injury. Although progress continues to be made in the treatment of Kawasaki disease, scientists have not stopped exploring its aetiology. Recent evidence suggests that the novel coronavirus SARS-CoV-2 that emerged in 2020 has led to Kawasaki-like symptoms and multisystem inflammatory syndrome in children (MIS-C) in many infected children, highlighting a potential viral aetiology of Kawasaki disease [5]. MIS-C is a condition presenting with symptoms such as fever, inflammation and organ dysfunction, and it is thought to be related to COVID-19. MIS-C can lead to shock and multiple organ failure, requiring intensive care [6]. Recent studies have highlighted a significant correlation between Kawasaki disease and COVID-19, particularly in paediatric patients. It has been observed that children and adolescents with SARS-CoV-2 infection may develop MIS-C, which shares features with Kawasaki disease. This emerging link underscores the importance of Kawasaki disease research in the current global health landscape, especially considering the varied clinical presentations and the potential for long-term cardiovascular implications [6,7]. To promote the research of Kawasaki disease more effectively, we aimed to find a way to summarize development trends from previous research and identify important future research directions.

In bibliometric analysis, mathematical and statistical methods are used to analyse studies in specific research fields within a certain period of time and to evaluate both the quantity and quality of the literature [8]. This method allows for focus on the countries, institutions and authors associated with research in a specific field to evaluate the quantity of literature, and it can also be used to evaluate the quality of the literature through the number of citations. The research of keywords can provide readers with information on temporal trends and frontier research topics in a field [9].

Based on the characteristics of bibliometrics, we aimed to conduct a bibliometric analysis of the previously published literature on Kawasaki disease, to discover patterns, summarize the existing results and guide future research directions in Kawasaki disease.

2. Materials and methods

We conducted a literature search on the Web of Science (WOS) database. The keywords “Kawasaki disease” and “mucocutaneous lymph node syndrome” were selected for retrieval, with date of publication limited to January 1, 1973 to December 31, 2022. We excluded news reports, information, meeting abstracts and dissertations, obtaining a total of 6950 academic articles. These documents were exported in.txt format and then analysed.

CiteSpace, developed by Professor Chaomei Chen from the School of Computer and Information at Drexel University in the United States (US), is widely used for bibliometric analysis [10]. We used CiteSpace (version: 6.1.R6) for visual analysis, including country/region distribution analysis, author and region distribution analysis, keyword analysis and citation analysis. Using CiteSpace’s core features, we were able to identify key research frontiers and emerging trends. These features include burst detection, which identifies sudden increases in research activity; centrality, indicating the importance of a node in the network; and the analysis of heterogeneous networks, revealing complex relationships between different research elements [11]. Our methodology involved using CiteSpace’s

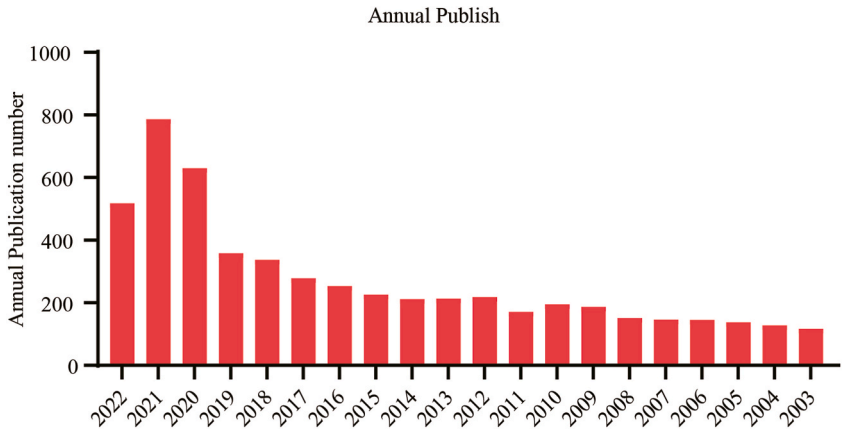


Fig. 1. Trend in the number of publications related to Kawasaki disease from 2003 to 2022.

advanced visualization capabilities to analyse literature comprehensively, thereby gaining insights into significant contributions and shifts in Kawasaki disease research over time.

3. Results

3.1. Annual publication trends

Fig. 1 and Table 1 illustrates the annual number of publications related to Kawasaki disease published in the past 20 years. In general, the number of publications has been increasing year by year. It decreased in 2011 and 2022, with 171 and 518 articles, respectively. The year with the highest number of publications was 2021, with a total of 787 articles.

3.2. Distribution and citation bursts of countries/regions

We analysed the 10 countries/regions with the highest number of published articles on Kawasaki disease (Table 2). The United States (US) led Kawasaki disease research with the highest number of published articles (1702) and the highest centrality score (0.35), followed by Japan (1419 articles) and mainland China (719 articles). These results are consistent with previous studies that revealed the US to be a global scientific powerhouse, whereas Japan and China are located in East Asia and have a high incidence of Kawasaki disease (Fig. 2a) [1]. We further studied the citation patterns of articles published in each country. Articles quoted earlier were mainly from the US, then articles published in Japan were widely cited. The citation frequency of relevant articles from mainland China and Taiwan has increased significantly in the past 20 years (Fig. 2b). The research conducted in various countries and regions aimed to provide insights into the worldwide distribution of collaborative studies and foster possibilities for further collaboration. We observed that the cooperation between countries/regions could be categorized into three major clusters. Firstly, there was significant collaboration between the US and East Asian countries (such as China, Japan and South Korea), with a substantial number of publications. Secondly, there was notable cooperation among European nations (such as France and Italy). Lastly, there was cooperation involving the United Kingdom and certain Commonwealth countries, such as India and Canada (Fig. 2c and Table 3).

3.3. Analysis of institutions

The institution with the highest number of publications was the University of California system (306), followed by Harvard University (238), which is consistent with the finding that the US published the most articles. No research institutions in mainland China were listed (Fig. 3a and Table 4). The findings of the CiteSpace analysis of the collaboration networks revealed that the top 10 institutions with the highest number of publications were grouped into several clusters based on the degree of collaboration. The clusters are distinguished by different colours in the relevant figures (Fig. 3b and Table 5). The cooperation between institutions could be divided into five groups: (1) Harvard University and Boston Children's Hospital, in the US; (2) the University of Toronto and Hospital for Sick Children, in Canada; (3) the University of California system in the US and the UDICE research universities in France; (4) Jichi Medical University in Japan; and (5) Chang Gung Memorial Hospital in Taiwan. Several other institutions demonstrated high centrality, such as the University of Toronto (0.05), implying that these institutions network significantly in Kawasaki disease research.

Table 1
Annual publication number for the last 20 years on Kawasaki disease.

Year	Publication number
2022	518
2021	787
2020	630
2019	359
2018	338
2017	279
2016	254
2015	226
2014	212
2013	214
2012	219
2011	171
2010	195
2009	187
2008	151
2007	146
2006	145
2005	138
2004	128
2003	117

Table 2
Top 10 publish country of frequency and the corresponding centrality.

Frequency	Centrality	Country
1702	0.35	USA
1419	0.1	JAPAN
719	0.01	PEOPLES R CHINA
348	0.24	CANADA
338	0.01	TAIWAN
327	0.1	ITALY
316	0.2	ENGLAND
265	0.03	SOUTH KOREA
255	0.02	INDIA
252	0.08	FRANCE

3.4. Analysis of journals

We examined the Kawasaki-disease-related citation status of journals to assess which journals held significant influence in Kawasaki disease research. The top five most cited journals were *Circulation* (4081 citations), *Pediatrics* (3643), *Journal of Pediatrics* (J PEDIATR-US) (3562), *Lancet* (3231) and The *New England Journal of Medicine* (NEW ENGL J MED) (2972) (Fig. 4a and Table 6). The CiteSpace visualization depicts the journals in which literature related to collaboration was published, along with the connections between them (Fig. 4b and Table 7). Articles published in the same cluster of journals tended to have similar research directions in Kawasaki disease. The clustering was determined by the similarity of the journals and is divided into three categories. The dark blue cluster includes *Circulation*, *Pediatrics* and *Lancet*, which focused on risk factors for Kawasaki disease. The green cluster includes *PLOS ONE*, *Journal of Immunology* (J IMMUNOL), *Clinical and Experimental Immunology* (CLIN EXP IMMUNOL) and *Journal of Clinical Investigation* (J CLIN INVEST). The light blue cluster includes *Pediatric Cardiology* (PEDIATR CARDIOL), *American Journal of Cardiology* (AM J CARDIOL) and *Journal of the American College of Cardiology* (J AM COLL CARDIOL), and the focus of this cluster is on coronary artery aneurysm in Kawasaki disease.

3.5. Analysis of keyword frequency

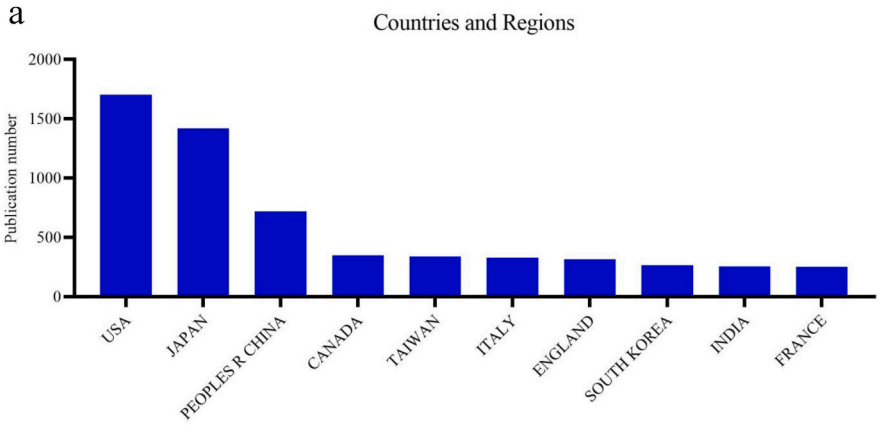
As keywords are core to article content, we studied the frequency of keywords in the literature related to Kawasaki disease. Table 8 shows that the top 10 keywords ranked by frequency were “Kawasaki disease” (3745), “Children” (1165), “Diagnosis” (780), “Intravenous immunoglobulin” (448), “Management” (432), “Coronary artery aneurysm” (423), “Therapy” (354), “Long term management” (336), “Coronary artery lesion” (313) and “Risk factor” (310). In addition, we analysed the betweenness centrality of the keywords, which is a CiteSpace algorithm that reflects the importance of keywords. The results revealed “Coronary artery lesion”, “Intravenous immunoglobulin” and “Risk factor” as three important keywords. This suggests that in the development of relevant studies, scholars are most concerned about coronary artery injury, gammaglobulin and risk factors for poor prognosis.

3.6. Analysis of keyword clusters

We used the keyword clustering network in CiteSpace to divide keywords into nine clusters. We found that the keywords “Coronary artery aneurysm”, “T cell” and “Refractory Kawasaki disease” had highest frequency (Fig. 5a). CiteSpace software forms clusters based on shared or similar keywords across articles. Larger clusters encompass more related articles, indicating a greater importance of those keywords. Notably, coronary artery aneurysm is one of the most serious complications of Kawasaki disease, and refractory Kawasaki disease is prone to coronary artery aneurysm formation, with T cell levels closely related to Kawasaki disease prognosis [12]. The results indicated that the main problem faced currently in Kawasaki disease treatment is how to reduce refractory Kawasaki disease incidence, to thereby reduce the formation of coronary artery aneurysm.

3.7. Keywords with citation bursts

By analysing keyword trends over time, we could further understand the progress of Kawasaki disease research. The 10 keywords with the strongest citation bursts are shown in Fig. 5b. Around 1990 the most important keywords were “Tumour necrosis factor” and “Intravenous gamma globulin”, indicating that research in this period was mainly focused on the release of inflammatory factors such as TNFα and intravenous gamma globulin, which was an important treatment for Kawasaki disease. Later, long-term management related to disease prognosis received great attention with the publication of the two significant Kawasaki disease guidelines by the American Heart Association (AHA) in 2004 and 2017 [12, 13]. With the subsequent COVID-19 pandemic in 2020, significant numbers of infected children developed MIS-C and Kawasaki disease-like symptoms, which seemed to confirm that viral infection may be one of the causes of Kawasaki disease.



b

Top 5 Countries with the Strongest Citation Bursts

Countries	Year	Strength	Begin	End	1974-2022
USA	1976	43.2	**1976**	1996	
JAPAN	1974	70.12	**1993**	2005	
FRANCE	1980	9.46	**1997**	2008	
TAIWAN	1987	15.6	**2010**	2015	
PEOPLES R CHINA	1999	40.07	**2019**	2022	

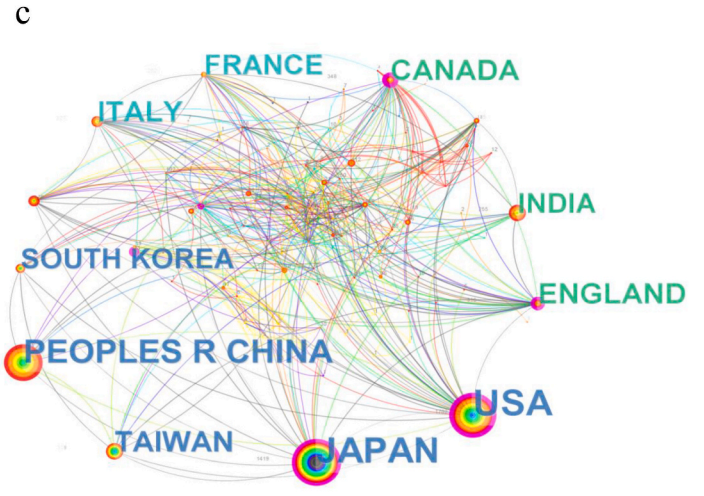


Fig. 2. Distribution of publications related to Kawasaki disease by country. (a) Trend in the number of publications related to Kawasaki disease by different countries. (b) Strength of citation bursts of publications related to Kawasaki disease. (c) Analysis of collaborative network visualization of countries/regions in Cite Space. The top 10 countries/regions are indicated. The different colour nodes represent the countries/regions in different clusters, and the size of the nodes indicates the significance of each node within its respective cluster. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Clustering of countries.

Cluster	Country	Size	Label of cluster
1	USA et al.	26	Kawasaki disease
2	CANADA et al.	23	pediatric inflammatory multisystem syndrome
3	ITALY et al.	21	skin manifestation

3.8. Analysis of highly cited references

Number of citations is one of the most important indicators for evaluating the value of literature. In our study, the 10 references with the highest number of citations in the last 20 years were identified using CiteSpace. Table 9 shows that the most cited reference was titled "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals", which was published by the AHA in 2017 and had a total of 1221 citations [12]. The least cited reference was titled "Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort", with a total of 166 citations [13]. As shown in Table 9, all 10 articles were published in the last 6 years. It is worth noting that eight highly cited references showed an explosive trend in citations in 2020 [5,13–19]. In 2020, as SARS-CoV-2 spread across the world, many infected children had Kawasaki disease-like syndromes, especially MIS-C. These articles tended to be widely cited because most of them were reports of multicentre prospective cohort studies, suggesting that the publishing of high-quality, highly cited clinical research articles reflects the research hotspots and the use of persuasive, well-designed studies.

3.9. Distribution of authors and references by citation bursts

Co-cited authorship analysis reveals where the works of two authors are cited by a third author concurrently in the literature. The examination of authors with the most co-citation frequencies in collaborative research offers a visual representation of the research prowess of these authors and the hotspots in collaborative studies. Authors with over 500 published co-citations were categorized into five clusters (Fig. 6a and Table 10). Detailed citation information is shown in Fig. 6b and Table 11. The five clusters include the authors L Verdoni L (orange); BW Mccrindle, H Kato H and ASuzuki (purple); T Kobayashi, Y Nakamura and R Uehara (green); H Yanagawa and T Kawasaki (grey); and DYM Leung, AH Rowley, JW Newburger and JC Burns (black). To discover the research hotspots and development trends of Kawasaki disease over the last 20 years, we studied the references with citation bursts (Fig. 6c). Based on the findings, we divided the citation trends of the references into five phases. In the first stage (2005–2009), the landmark articles were the Kawasaki disease guidelines [20] published by the AHA in 2004 and a review by Burns et al. [21] published in *Lancet*, which marked the formation of a clear guideline for the diagnosis, treatment and management of Kawasaki disease. Another article that was not highly cited but of great significance in the development of Kawasaki disease treatment was that of Kobayashi et al. [22], who in 2006 constructed a prediction model of IVIG unresponsiveness in patients with Kawasaki disease, which played a key role in the subsequent treatment of Kawasaki disease patients with gammaglobulin non-response. In the second stage (2008–2013), the landmark article was written by Onouchi et al. [23], and demonstrated that ITPKC functional polymorphism had an important relationship with Kawasaki disease susceptibility and formation of coronary artery aneurysm. In the third stage (2013–2018), Kobayashi et al. [24] published an article on treatment with immunoglobulin plus prednisone for the prevention of coronary artery abnormalities in Kawasaki disease, and Nakamura et al. [25], Uehara et al. [26] and Makino et al. [27] published articles on multicentre large-scale epidemiological investigations of Kawasaki disease. These articles were important for updating previous conclusions that hormone therapy is not recommended for Kawasaki disease. However, the aetiology of the disease was still unclear, despite several large-scale epidemiological investigations. In the fourth stage (2018–2019), the AHA Kawasaki disease guideline, reinforced in 2017, became the landmark article of this phase [12]. In the fifth stage (2020–2022), with the outbreak of COVID-19 Verdono et al. reported that many children had Kawasaki disease-like symptoms [5], which has greatly influenced research on the aetiology of Kawasaki disease.

4. Discussion

4.1. Overview of progress in Kawasaki disease research

A total of 6950 articles on Kawasaki disease from 1973 to 2022 were included in the bibliometric analysis. Fig. 7 presents a summarized history of the development of publications related to Kawasaki disease, including milestone publications. The first literature in English on Kawasaki disease was published in 1974, introducing research in the field [28]. Then, in 1986, Newburger et al. [29] used aspirin plus gammaglobulin to treat patients with Kawasaki disease. Standardized treatment guidelines were developed in 2004 and reinforced in 2017 [12,20], with which diagnosis of incomplete Kawasaki disease, initial treatment of high-risk children who do not respond to gammaglobulin, and long-term management protocols were advanced. These significant improvements in treatment were associated with a predictive model of gammaglobulin unresponsiveness in patients with Kawasaki disease constructed by Professor Kobayashi in 2006 for the Japanese population [22]. To improve the prognosis of IVIG-resistant patients, the use of safer and more aggressive treatment has been repeatedly studied. For example, in 1984 Furusho and colleagues added corticosteroid to the initial treatment, and this was found to neither increase the side effects of the drug nor improve prognosis [4]. Despite this, opinion on the addition of corticosteroid in Kawasaki disease treatment has long been divided [30,31]. In the large-scale prospective cohort study

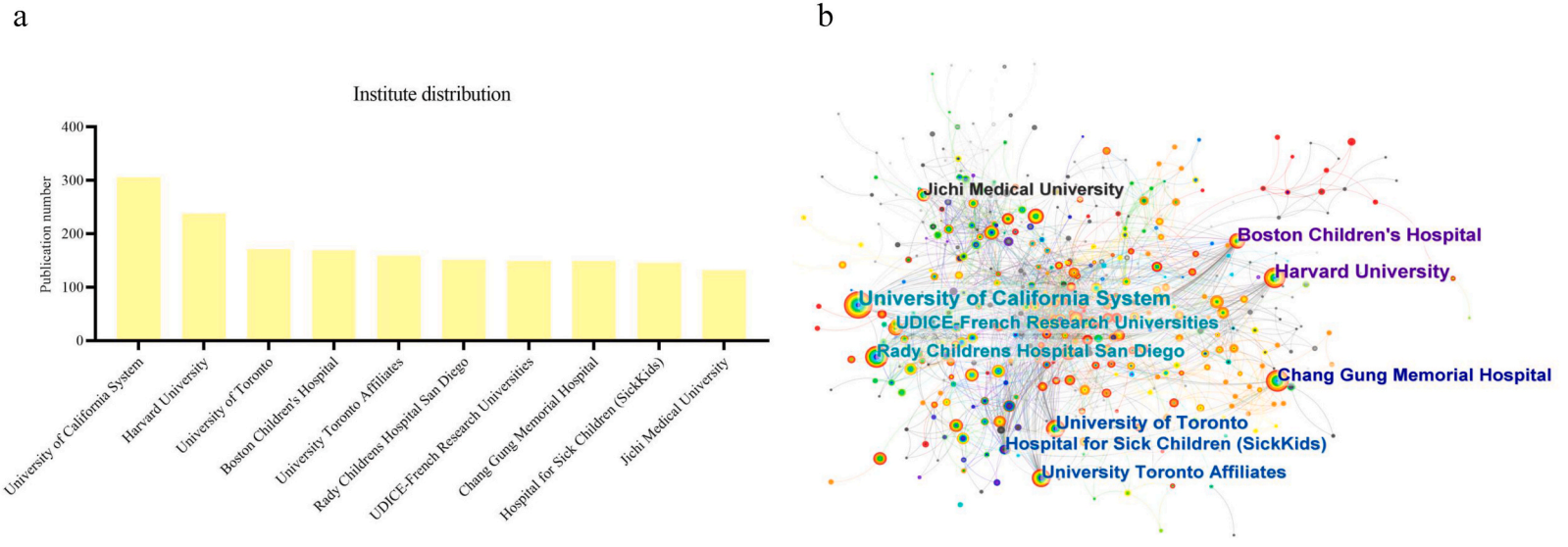


Fig. 3. Analysis of collaborative studies. (a) Distribution of publications related to Kawasaki disease by institution type. (b) Analysis of collaborative network visualization of institutions in CiteSpace. The top 10 institutions are indicated. The different colour nodes represent the different country/regional clusters, and the size of the nodes indicates the significance of each node within its respective cluster. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Top 10 Institute of frequency and the corresponding centrality.

Frequency	Centrality	Institution
306	0.02	University of California System
238	0.04	Harvard University
171	0.05	University of Toronto
169	0.02	Boston Children's Hospital
159	0.1	University Toronto Affiliates
151	0.04	Rady Childrens Hospital San Diego
149	0.03	UDICE-French Research Universities
149	0.02	Chang Gung Memorial Hospital
146	0.02	Hospital for Sick Children (SickKids)
132	0.01	Jichi Medical University

Table 5
Clustering of institution.

Cluster	Country	Size	Label of cluster
1	University Toronto Affiliate et al.	75	common treatment
2	Jichi Medical University et al.	70	giant coronary aneurysm
3	University of California system et al.	66	mouse model
4	Boston Children's hospital et al.	66	Kawasaki syndrome
5	Chang Gung Memorial Hospital et al.	47	population-based study

by Kobayashi et al. in 2012, based on Kawasaki disease being an immune vasculitis, predictive models were used to select high-risk children, and the early addition of the immunosuppressant prednisolone to high-risk children further reduced incidence of non-response to gammaglobulin and coronary artery injury [24]. At this time, the aetiology and pathogenesis of Kawasaki disease attracted more attention in research and publication. Onouchi et al. published a landmark article on gene polymorphism research in which they described isolating the ITPKC gene from 1222 SNPs in 94 patients with Kawasaki disease and 564 healthy controls. The ITPKC gene may influence Kawasaki disease susceptibility and the formation of coronary artery aneurysms by negatively regulating the Ca^{2+}/NFAT signalling pathway in T cells [23]. Since Onouchi's article, many similar articles on gene polymorphisms have been published, and, to date, a total of 62 SNPs suspected of affecting susceptibility to Kawasaki disease have been found in 12 related studies.

4.2. IVIG resistance models, global epidemiological insights and trends in Kawasaki disease literature

Nakamura et al. [25], Uehara et al. [26] and Makino et al. [27] conducted large-scale multicentre epidemiological surveys on Kawasaki disease in Japan, the US, Europe and other Asian countries and regions. The seasonal peaks of Kawasaki disease incidence in Japan, Korea and Taiwan are in December and January (winter) and June and July (summer). However, in mainland China, the peak incidence of Kawasaki disease varies greatly because of its vast size. Most regions experience cases in spring and summer; for example, seasonal patterns in Beijing are similar to Japan and Korea. The highest incidence of Kawasaki disease in Shanghai is from May to August, while in Sichuan it is from March to May. However, in the US and European countries peak incidence occurs in the winter. An exact pathogen closely associated with Kawasaki disease infection has still not been identified, and a focus on viral infections such as influenza virus is needed. Early in the COVID-19 pandemic, researchers such as Verdono et al. [5] identified an increase in MIS-C and Kawasaki-like symptoms among children, which reinforced the idea that viral infection might be an important cause of Kawasaki disease.

The number of publications related to Kawasaki disease has generally shown an increasing trend year by year, proportional to the increasing incidence of Kawasaki disease [12]. The increase in Kawasaki-disease-related publications goes beyond mere numbers; it reflects a growing global awareness and research interest. This surge, particularly since the COVID-19 pandemic, reflects a significant rise in Kawasaki disease cases, heightening attention to this condition. Improvements in diagnostic techniques and greater awareness have led to many febrile illnesses previously attributed to other causes now being recognized as Kawasaki disease. This trend not only underscores the evolving complexities in clinical presentations and management strategies but also highlights the dynamic nature of research in this field, emphasizing the need for continued research and innovation to address these emerging challenges. The US has produced the most publications on Kawasaki disease, with the three institutions with the most publications being the University of California, Harvard University and the Boston Children's Hospital, all of which are located in the US. Kawasaki disease guidelines published by the AHA in 2004 and reinforced in 2017 [12,20] suggest that the US still has significant advantages in the Kawasaki disease research field. Japan, where the diagnosis of Kawasaki disease was first clarified, has the second highest number of publications in the field and has the largest number of patients with Kawasaki disease in the world. However, only one of the top 10 research institutions in terms of publication numbers was in Japan, Jichi medical university, suggesting that despite the high Kawasaki disease incidence in the country, research institutions are scattered. However, many landmark articles in the field have been published from Japan. In 1974, Kawasaki's team published the article "A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS)

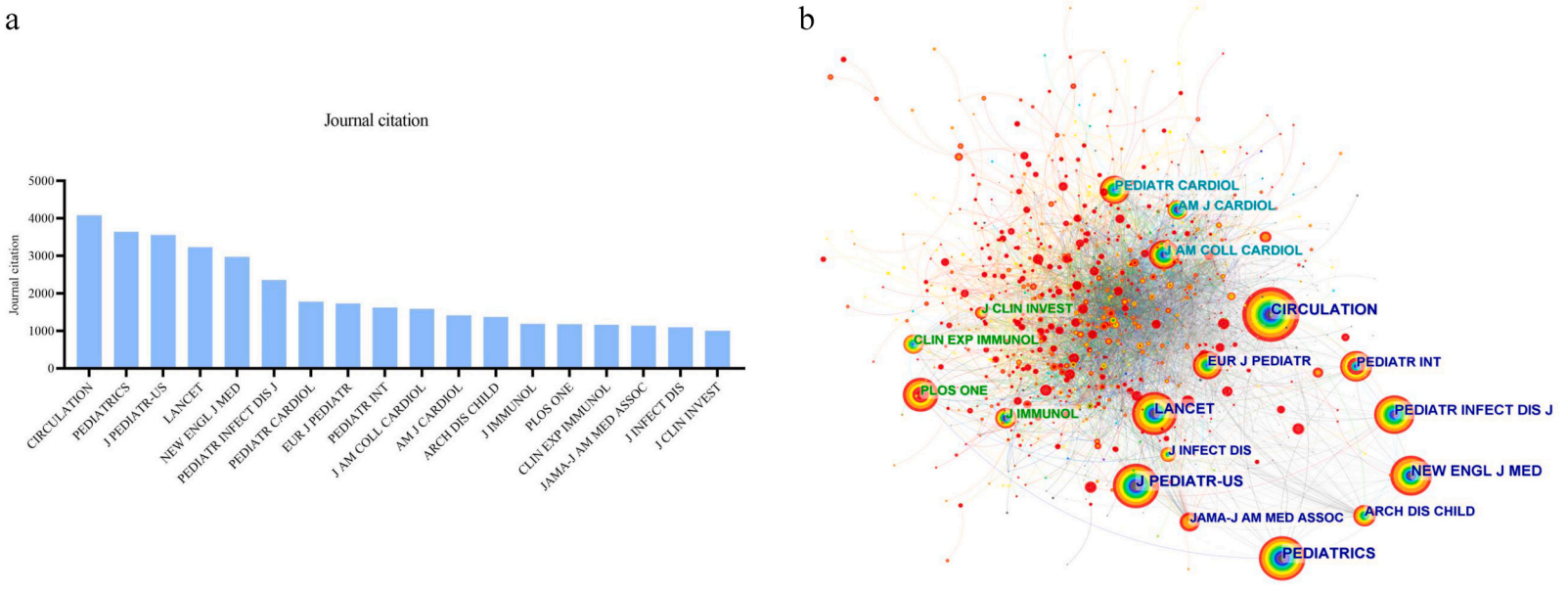


Fig. 4. Journal analysis. (a) Distribution of citations related to Kawasaki disease by journal. (b) Analysis of collaborative network visualization of journal citations in CiteSpace. More than 1000 citations are indicated. The different colour nodes represent the journals in different clusters, and the size of the nodes indicates the significance of each node within its respective cluster. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 6
More than 1000 citations journal of frequency and the corresponding centrality.

Frequency	Centrality	Journal
4081	0.01	CIRCULATION
3643	0	PEDIATRICS
3562	0	J PEDIATR-US
3231	0.01	LANCET
2972	0	NEW ENGL J MED
2361	0.01	PEDIATR INFECT DIS J
1780	0.01	PEDIATR CARDIOL
1734	0.02	EUR J PEDIATR
1627	0	PEDIATR INT
1595	0	J AM COLL CARDIOL
1414	0	AM J CARDIOL
1379	0.03	ARCH DIS CHILD
1190	0.02	J IMMUNOL
1186	0	PLOS ONE
1163	0.01	CLIN EXP IMMUNOL
1138	0.06	JAMA-J AM MED ASSOC
1100	0.02	J INFECT DIS
1006	0.02	J CLIN INVEST

Table 7
Clustering of cited journal.

Cluster	Journal	Size	Label of Cluster
1	PLOS ONE et al.	288	Kawasaki disease
2	Pediatric Cardiology et al.	246	coronary artery aneurysm
3	Circulation et al.	222	risk factor

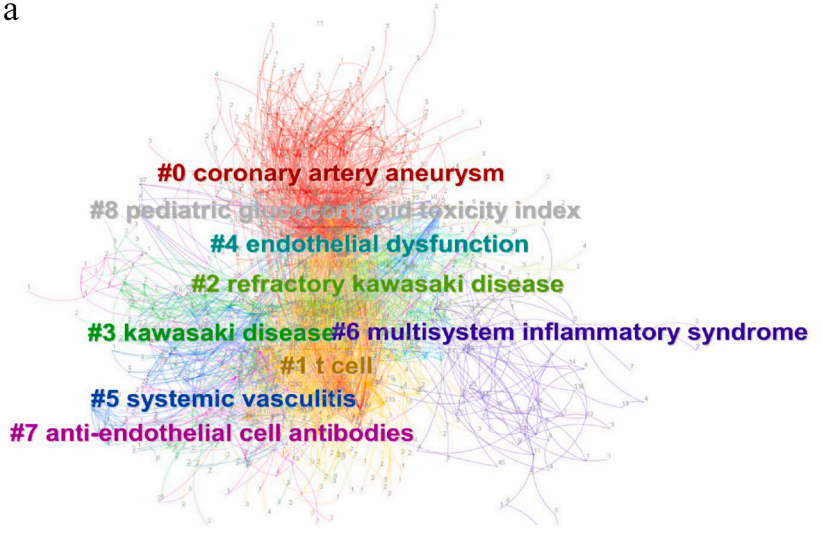
Table 8
Top 10 keywords in terms of frequency and the corresponding centrality.

Frequency	Centrality	Keyword
3745	0	Kawasaki disease
1165	0.03	Children
780	0.01	Diagnosis
448	0.03	Intravenous immunoglobulin
432	0.01	Management
423	0.02	Coronary artery aneurysm
354	0.02	Therapy
336	0	Long term management
313	0.04	Coronary artery lesion
310	0.03	Risk factor

prevailing in Japan" in *Pediatrics*, which was the first English-language publication on Kawasaki disease [28]. In addition, in 2006, Kobayashi et al. constructed a prediction model for patients with Kawasaki disease who did not respond to initial treatment with gammaglobulin. Kobayashi's team also conducted the first large-scale prospective cohort study of prednisolone plus gammaglobulin in high-risk children unresponsive to gammaglobulin [24]. Mainland China had the third highest number of publications, but no institutions there were among the top 10 research institutions in terms of number of publications. It is worth noting the lack of highly cited literature on Kawasaki disease from mainland China and the absence of landmark publications on Kawasaki disease diagnostics and treatment. In a word, Kawasaki disease research and high-quality literature in the field is lacking in China, although citation bursts from references suggest that attention to Kawasaki disease in the literature in China has increased significantly in recent years, and we hope that China will make further breakthroughs in Kawasaki disease in future.

In the keyword analysis, we filtered the top 10 keywords in terms of frequency and selected the three most important keywords "Coronary artery lesion", "Intravenous immunoglobulin" and "Risk factor", based on their betweenness centrality. Of these keywords, coronary artery lesion has always attracted much attention. In the history of Kawasaki disease research, major advances in treatment have been made to reduce the occurrence of coronary artery lesion. For example, intravenous gammaglobulin has been the initial treatment for Kawasaki disease since it was proposed in 1986. After discussion of the optimal gammaglobulin dose [32,33], 2 g/kg as a single dose was eventually recommend by the AHA [12], as higher plasma concentrations of gammaglobulin were associated with a lower incidence of coronary artery lesion [34]. In 2006 "Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease" by Kobayashi et al. proposed the keyword "risk factor", and subsequently a large number of articles related to prediction models were published [22]. However, owing to the risk of bias of the model and genetic background differences, the

a



b

Top 10 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End
Tumor necrosis factor	1990	38.82	**1990**	2004
Lymph node syndrome	1991	78.96	**1991**	2006
Intravenous gamma globulin	1991	49.47	**1991**	2007
American heart association	2003	34.92	**2008**	2018
Health professional	2006	55.65	**2018**	2022
Statement	2009	49.47	**2018**	2022
Long term management	2006	36.68	**2018**	2020
Covid 19	2020	55.19	**2020**	2022
Multisystem inflammatory syndrome	2020	47.94	**2020**	2022
Kawasaki like disease	2020	38.71	**2020**	2022

Fig. 5. Keyword analysis. (a) Keyword analysis of Kawasaki disease-related references and clustering of references based on similarity between references. (b) The top 10 references with the strongest citation bursts related to keywords of Kawasaki disease.

Table 9
Top 10 most cited references.

Citations	Centrality	Author, fear	Article title	Magazine (impact factor)
1221	0.66	McCrindle BW, 2017	Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association	CIRCULATION (39.918)
524	0.66	Verdoni L, 2020	An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study	Lancet (202.731)
372	0.15	Whittaker E, 2020	Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2	JAMA (157.335)
357	0.01	Riphagen S, 2020	Hyperinflammatory shock in children during COVID-19 pandemic	Lancet (202.731)
340	0.14	Feldstein LR, 2020	Multisystem Inflammatory Syndrome in U.S. Children and Adolescents	N Engl J Med (176.079)
266	0.09	Belhadjer Z, 2020	Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic	CIRCULATION (39.918)
260	0.01	Toubiana J, 2020	Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study	BMJ (93.333)
245	0.01	Dufort EM, 2020	Multisystem Inflammatory Syndrome in Children in New York State	N Engl J Med (176.079)
192	0	Newburger JW, 2016	Kawasaki Disease	J Am Coll Cardiol (27.203)
166	0	Pouletty M, 2020	Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort	Ann Rheum Dis (27.973)

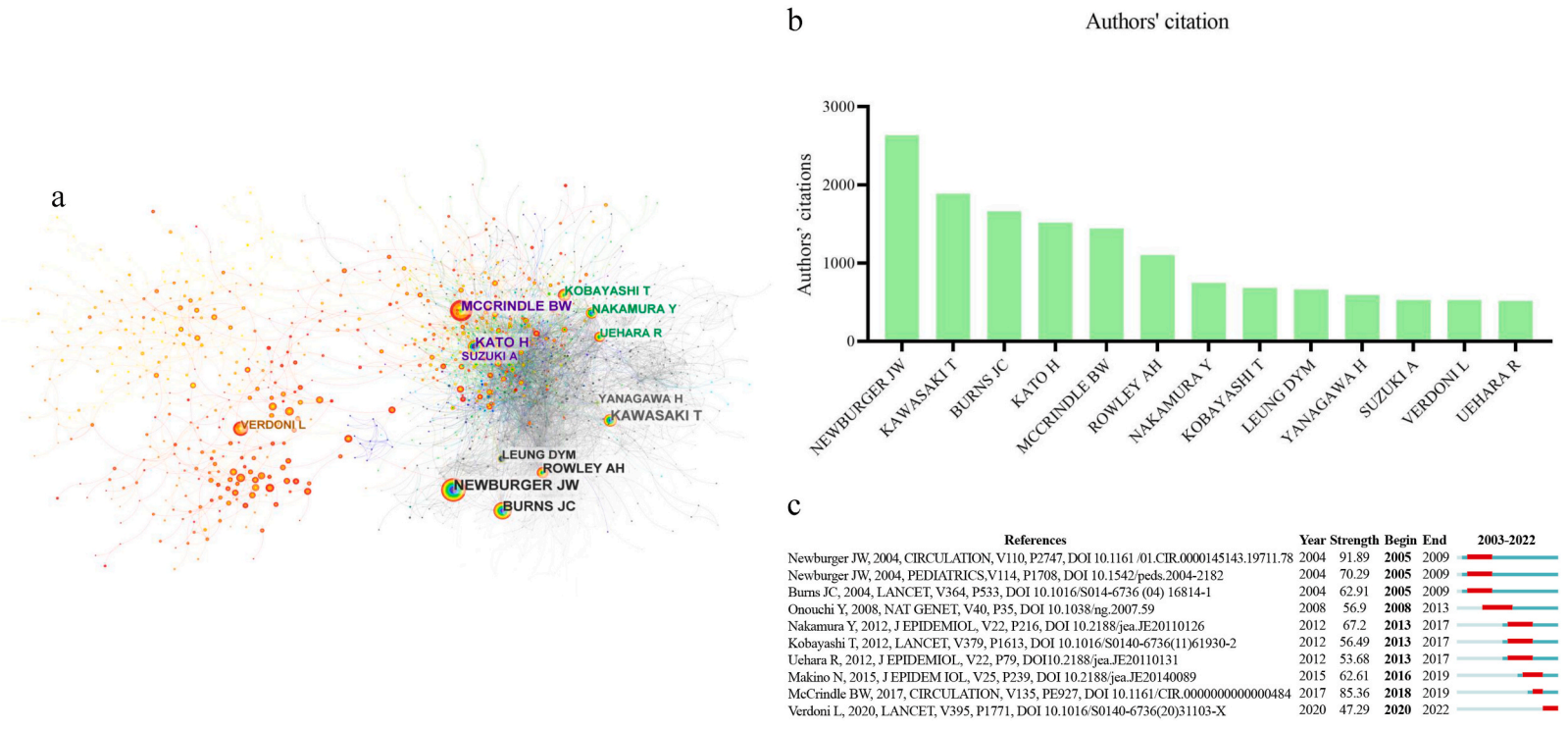
Japanese predictive model is inefficient when applied to the North American population [35]. Therefore, there is currently no predictive model composed of identified risk factors that can be used universally across populations. This limitation is attributed to several factors: (1) models in which many predictive factors are derived from continuous variables converted to binary ones, such as serum sodium levels, and models built on varied genetic backgrounds can introduce bias [2]; (2) diverse genetic backgrounds across populations and differences in IVIG production techniques by different countries and companies affects IVIG efficacy, potentially leading to varied outcomes in predictive modelling and treatment efficacy [36]; and (3) there is a current lack of robust biological markers in predictive model construction. Addressing these issues requires more research, particularly involving high-throughput sequencing, single-cell RNA sequencing and animal model research [37]. Integrating more biological markers and genetic backgrounds into the optimization of prediction models is essential to reduce selection bias and develop more universal and effective predictive models for Kawasaki disease.

Identifying keywords with citation bursts can help us capture research hotspots for Kawasaki disease at different stages. Early studies in Kawasaki disease focused on factors such as “tumour necrosis factor” and “intravenous gamma globulin”. A key finding in 1990 linked high TNFα levels to coronary artery issues, but traditional treatments often did not yield good outcomes [38]. The 2017 AHA guidelines therefore recommended treatment with infliximab for resistant cases. The evolution in treatment keywords reflects a shift from early control of inflammatory factors such as TNFα using IVIG to a more precise medical approach and long-term management in treating Kawasaki disease, emphasizing the benefits of precision medicine for individual patients.

4.3. Influence of COVID-19 on Kawasaki disease research and incidence

Since the COVID-19 outbreak in 2020, many COVID-19-infected children have developed symptoms of MIS-C and Kawasaki-like disease. The incidence of Kawasaki disease in Italy increased significantly post-COVID-19 [39], while in Japan, a decrease in incidence was observed, possibly due to mask wearing and different genetic responses to viruses [7,40]. These contrasting trends highlight the need for further research into the immunological responses in different ethnic groups. MIS-C and Kawasaki disease both involve multiple organs but differ in the age groups they affect and their treatments. Kawasaki disease primarily affects children under 5 years, whereas MIS-C has a broader age range, including adolescents and adults [19]. Both can lead to coronary artery injury, with MIS-C affecting 10%–20% of patients [41,42]. In terms of treatment, MIS-C also differs from Kawasaki disease. In addition to antiplatelet agents, gammaglobulin and the TNFα receptor antagonist infliximab, anticoagulant agents (heparin, warfarin, argatroban, etc.) and IL-1 receptor antagonists (anakinra) and IL-6 receptor antagonists (tocilizumab) have been used in the treatment of MIS-C [13,18,19]. In addition, long-term management depends on the level of cardiac involvement, but this requires further supportive prognostic data [42].

In Kawasaki disease research, keywords such as “T cells” and endothelial cell-related terms such as “Endothelial dysfunction” and “Anti-endothelial cell antibodies” are important. Unlike previous treatments, anti-endothelial antibody therapies are closely linked to the mechanisms of coronary artery damage in Kawasaki disease. T cells, particularly certain cytotoxic T cell subgroups, are significant in the Ca+/NFAT signalling pathway and are elevated during the disease’s acute phases [43]. Studies have shown that cyclosporine, a drug used in the treatment of refractory Kawasaki disease, is closely associated with inhibition of the Ca+/NFAT signalling pathway in T cells. High-throughput sequencing shows elevated cytotoxic T-lymphocyte markers in Kawasaki disease [44]. Endothelial dysfunction has always been an important complication of Kawasaki disease because it can cause local platelet aggregation and even thrombosis [12]. Recent studies have found that endothelial dysfunction is associated with the novel coronavirus infection [45] and



References	Year	Strength	Begin	End	2003-2022
Newburger JW, 2004, CIRCULATION, V110, P2747, DOI 10.1161 /01.CIR.0000145143.19711.78	2004	91.89	**2005**	2009	
Newburger JW, 2004, PEDIATRICS,V114, P1708, DOI 10.1542/peds.2004-2182	2004	70.29	**2005**	2009	
Burns JC, 2004, LANCET, V364, P533, DOI 10.1016/S014-6736 (04) 16814-1	2004	62.91	**2005**	2009	
Onouchi Y, 2008, NAT GENET, V40, P35, DOI 10.1038/ng.2007.59	2008	56.9	**2008**	2013	
Nakamura Y, 2012, J EPIDEMIOL, V22, P216, DOI 10.2188/jea.JE20110126	2012	67.2	**2013**	2017	
Kobayashi T, 2012, LANCET, V379, P1613, DOI 10.1016/S0140-6736(11)61930-2	2012	56.49	**2013**	2017	
Uehara R, 2012, J EPIDEMIOL, V22, P79, DOI10.2188/jea.JE20110131	2012	53.68	**2013**	2017	
Makino N, 2015, J EPIDEM IOL, V25, P239, DOI 10.2188/jea.JE20140089	2015	62.61	**2016**	2019	
McCrindle BW, 2017, CIRCULATION, V135, PE927, DOI 10.1161/CIR.0000000000000484	2017	85.36	**2018**	2019	
Verdoni L, 2020, LANCET, V395, P1771, DOI 10.1016/S0140-6736(20)31103-X	2020	47.29	**2020**	2022	

Fig. 6. Analysis of author networks. (a) Collaborative network visualization of authors in CiteSpace. The figure shows the authors with more than 500 citations. The different colour nodes represent the authors in different clusters, and the size of the nodes indicates the frequency of their occurrence. (b) Distribution of citations related to Kawasaki disease by authors. (c) The top 10 references with the strongest citation bursts. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 10
Clustering of references based on similarity between references.

Cluster	Author	Size	Lable of cluster
1	Newburger JW et al.	239	coronary angiography; following Kawasaki disease; endothelial dysfunction; coronary artery bypass; acute myocardial infarction
2	Kobayashi T et al.	233	to-lymphocyte ratio; resistant Kawasaki disease; post raise; risk score; predicting coronary artery aneurysm
3	Kawayashi T et al.	230	mucocutaneous lymph-node syndrome; acute febrile mucocutaneous lymph-node syndrome; new disease; coronary-artery involvement; infantile polyarteritis nodosa
4	Mccrindle BW et al.	198	t cell; peripheral blood mononuclear cel; streptococcal superantigen; iia trial; skin diseases
5	Verdoni L et al.	190	multisystem inflammatory syndrome; inflammatory syndrome; Kawasaki disease; cov-2 infection; systematic review

Table 11
Top 10 cited author of frequency and the corresponding centrality.

Frequency	Centrality	Author
2635	0.01	NEWBURGER JW
1889	0.01	KAWASAKI T
1667	0.02	BURNS JC
1520	0.01	KATO H
1444	0.06	MCCRINDLE BW
1100	0.04	ROWLEY AH
748	0.02	NAKAMURA Y
680	0.01	KOBAYASHI T
661	0.04	LEUNG DYM
593	0.05	YANAGAWA H

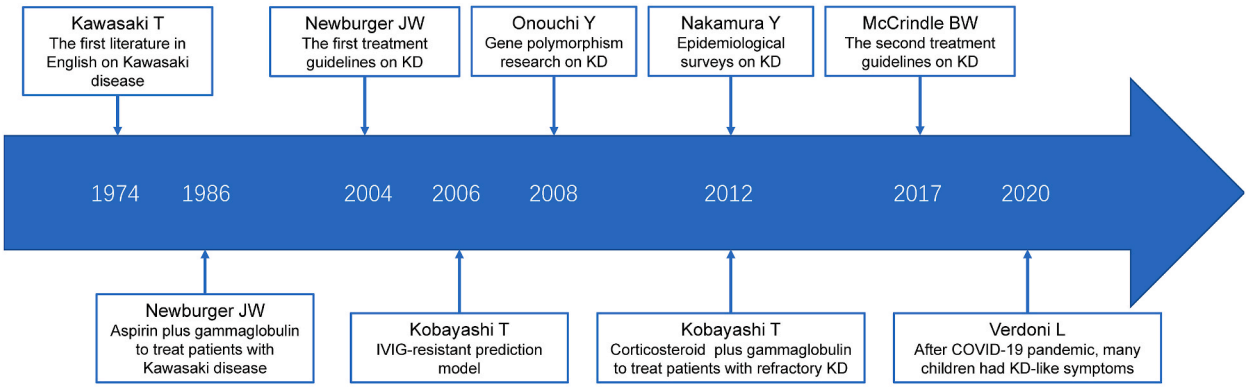


Fig. 7. The history of the development of publications related to Kawasaki disease, including milestone publications.

the formation of coronary aneurysms [46]. Further research is needed to understand the way in which these T-cell subgroups interact with endothelial cells, causing endothelial dysfunction.

5. Current challenges and prospects in Kawasaki disease research

The future application of high-throughput sequencing, including single-cell RNA sequencing, will likely enhance our understanding of the mechanism and aetiology of Kawasaki disease. These advanced technologies will aid in identifying more meaningful biological markers for diagnosis and treatment, and in exploring how immune cells interact with endothelial and smooth muscle cells to cause coronary aneurysm formation [37]. Furthermore, experimental animal models are providing valuable insights into coronary artery lesions in Kawasaki disease [47], revealing potential new targets for future therapeutic interventions.

Advantages and limitations

To our knowledge, this study is the first to use bibliometric analysis to analyse the diagnosis, treatment and research developments of Kawasaki disease in the past 50 years. The scientific algorithms of CiteSpace provided us with hotspots and frontiers in the field, and our data analysis process was objective. However, this research had some limitations. Firstly, owing to limitations in CiteSpace identification, data could only be obtained from the WOS database, which may have led to important literature in other databases

Key point summary

1. Corticosteroid use: Despite past controversies, following Kobayashi's 2012 study [24], corticosteroids are increasingly recognized for early use in high-risk IVIG-resistant Kawasaki disease patients.
2. IVIG resistance predictive models: The current overreliance on IVIG resistance predictive models developed in Japan may not be universally applicable.
3. Biological markers: Current Kawasaki disease (KD) diagnosis primarily relies on clinical symptoms. There is a pressing need for more research on specific biological markers, to improve diagnostic accuracy.
4. Long-term and cardiac management in Kawasaki disease: Long-term management strategies in Kawasaki disease care, particularly those based on cardiac involvement, are a critical focus. The 2017 AHA guidelines highlight the need for long-term management, yet there is a gap in specific guidance tailored to the level of cardiac involvement in Kawasaki disease patients [12].
5. The relationships between COVID-19, MIS-C and Kawasaki disease: Observations indicate a potential link between COVID-19 and Kawasaki disease. A major gap exists in pathogenic evidence or laboratory markers for MIS-C, which presents with Kawasaki-like symptoms in the context of COVID-19. Understanding why different genetic backgrounds lead to significant variations in Kawasaki disease incidence triggered by COVID-19 is crucial. The complex relationships between these conditions necessitates further focused research to elucidate their mutual impact and underlying mechanisms.
6. Role of T cells and endothelial cells: Limited research has been conducted on the interaction between T cells and endothelial cells and its influence on endothelial cell phenotype transformation in Kawasaki disease.
7. High-throughput and single-cell RNA sequencing: Deep single-cell studies could uncover more biomarkers and assist in mechanistic research.
8. Animal model research: More studies are needed on coronary artery lesions and biological markers in Kawasaki disease using animal models.

being overlooked. Secondly, articles published very recently, especially in 2022, may have lacked sufficient citation frequency because of the short time for which they had been available, and this may have affected the evaluation of their citation weight. Finally, only English-language literature was included in this study, thus we may have ignored some important non-English literature.

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.

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CRediT authorship contribution statement

Lei Xu: Writing – original draft, Conceptualization. **Jiaying Zhang:** Writing – original draft, Conceptualization. **Jinfeng Dong:** Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Qiaobin Chen:** Supervision, Methodology, Data curation. **Shurong Ma:** Supervision, Methodology, Data curation. **Jiangqi Jiang:** Validation, Methodology, Data curation. **Yiming Zheng:** Supervision, Methodology, Data curation. **Wenyu Zhuo:** Supervision, Methodology, Data curation. **Xuan Tang:** Supervision, Methodology, Data curation. **Yang Gao:** Supervision, Methodology, Data curation. **Xuan Li:** Methodology, Data curation. **Fang Yang:** Methodology, Data curation. **Guoping You:** Methodology, Data curation. **Haitao Lv:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Hongbiao Huang:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation, 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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