



## Research article

# The landscape of hot topics and research frontiers in Kawasaki disease: Scientometric analysis

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## ABSTRACT

**Purpose:** Kawasaki disease(KD) is a vascular inflammatory disease that was first identified in 1967. Numerous studies have been conducted on KD and have yielded valuable recent insights. This current bibliometric analysis aimed to determine the intellectual landscape of research interest in KD.

**Methods:** Publications were collected from the Web of Science Core Collection. Bibliometric tools such as CiteSpace and VOSviewer were utilized to analyze the research focus, emerging trends, frontiers, and hot topics in this specific field.

**Results:** A total of 6122 articles on KD were retrieved. Pediatric Cardiology, Pediatrics International, and Pediatric Infections Disease Journal were the three most productive journals reporting KD development. The University of California San Diego was the most productive institution, with 230 publications. The USA was the most productive country, with 1661 articles in KD. SARS-CoV-2, diagnostic serum biomarkers, and risk factor prediction models for coronary arterial lesions and subtypes of KD are popular topics in KD research. Factors that induce smooth muscle cell transition to myofibroblastic cell, potentially halting the subacute/chronic vasculitis process and endothelial dysfunction in macrophage activation syndrome associated with KD were the frontiers in the study of KD.

**Conclusion:** KD has attracted widespread attention worldwide that has continued to increase since 1974. The most productive institution and country are the University of California San Diego and the USA, respectively. SARS-CoV-2, serum biomarkers, and prediction models are hot topics in this field.

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## 1. Introduction

Kawasaki disease (KD) is an acute systemic vasculitis. The Japanese pediatrician Tomisaku Kawasaki first reported KD in 1967. KD has been extensively reported globally in children of diverse racial and ethnic backgrounds [1,2]. The global incidence of KD is on the rise, with Japan exhibiting the highest reported incidence at 330.3 per 100,000 in 2015 [3–5]. KD also known as mucocutaneous lymph node syndrome, is predominantly characterized by high fever, mucocutaneous inflammation, and cervical lymphadenopathy. The cardiovascular system is the main structure affected, especially the coronary arteries [6,7]. The etiology and pathogenesis of KD remain largely elusive. Complex factors may be involved in the pathogenesis of KD, including genetic susceptibility, vaccine exposure, infectious agents, or other unknown stimulus triggers that activate the innate and adaptive immune system with overwhelming inflammation [3,8]. The diagnosis still relies on the initial clinical findings originally used to describe the disease over 50 years ago and the exclusion of other clinically similar conditions with known causes [9–11]. Timely initial treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary arterial aneurysms(CAAs) defined by absolute luminal dimensions to 4%. Untreated children in the acute phase of illness face a 20%–25% risk of developing CAA. Indeed, KD has replaced rheumatic fever as a leading cause of acquired cardiac disease in children in developed countries. Small and some medium-sized aneurysms may regress spontaneously, whereas large and giant aneurysms seldom regress [12,13]. According to the “JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in KD”, cardiovascular sequelae indicate endothelial dysfunction in coronary lesions, regardless of whether they regress. This dysfunction, combined with hemodynamic variations from persistent aneurysms, leads to thrombosis, calcification, coronary stenosis, and myocardial ischemia in early adulthood [11,14,15]. Furthermore, a minority of KD patients experience sudden death [16,17]. An in-depth pathology study of 41 KD patients, including 32 autopsies, 8 cardiac transplants, and an excised coronary aneurysm, revealed three linked pathological processes in KD vasculopathy [18]. The three linked processes include acute self-limited necrotizing arteritis(NA), subacute/chronic(SA/C) vasculitis, and luminal myofibroblastic proliferation(LMP). The NA process is characterized by neutrophilic infiltration in segments of the arterial wall. The SA/C process is associated with inflammatory cell infiltrates comprising lymphocytes, plasma cells, and eosinophils. LMP represents a unique process characterized by the proliferation of myofibroblasts derived from medial smooth muscle cells and the accumulation of their matrix products. Although initial research has suggested that inflammation originates in the luminal endothelium, ongoing studies have revealed that the adventitia is the primary site of acute vascular inflammation [17,18]. KD has attracted significant attention from researchers, leading to extensive studies investigating various aspects of this disease.

Bibliometric analysis is a popular and rigorous methodology for exploring and analyzing large amounts of scientific data for quantitative analyses [19]. Bibliometric analysis can help to revealing the evolutionary nuances of a specific field and elucidate emerging areas in a field, including with regard to individuals, institutions, countries and journals by creating infographics [20–22]. CiteSpace (Chaomei Cheng, version 5.8. R3) and VOSviewer (Leiden University’s Centre for Science and Technology Studies, version 1.6.17) have been widely applied to various subjects for bibliometric analysis, such as regenerative medicine, oncology, cardiovascular, neuroscience and stomatology [23–29]. CiteSpace software has evolved into a document visualization and analysis tool within the field of bibliometrics and data visualization. This program facilitates the visualization of basic knowledge and the identification of hotspots within a certain research field. It can also predict evolutionary trends and research frontiers. Another bibliometric software, VOSviewer, is utilized for constructing correlation networks and visualizing data. Notably, this software stands out for its graphics capabilities and its ability to process large-scale data.

Navigating the research hotspots in KD research is challenging for researchers due to the rapidly expanding body of literature.

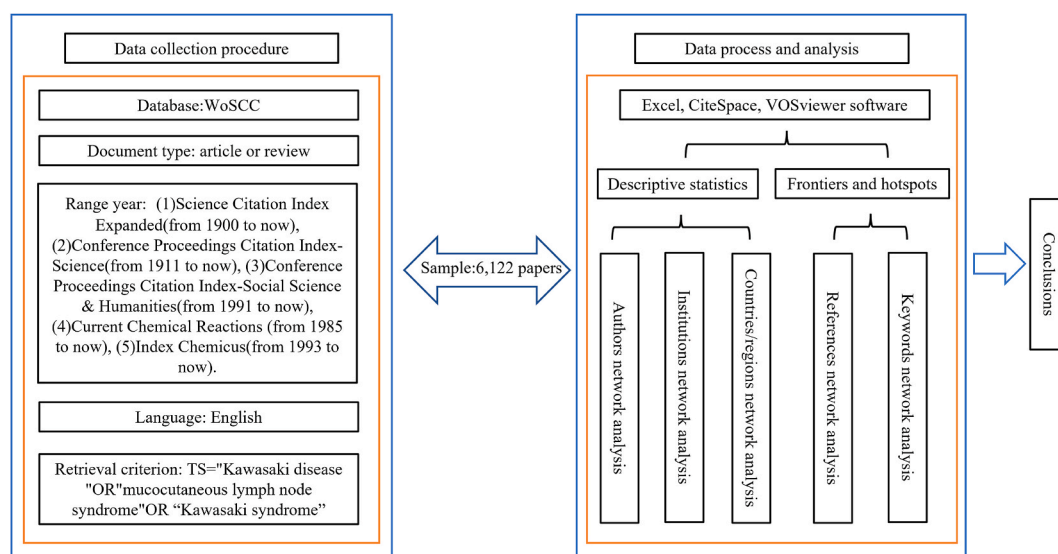


Fig. 1. Research steps included in this study. There were 6122 original research articles and review articles in the database.

However, identifying emerging literature can help mitigate confusion when new research challenges previous assumptions and expectations. Thus, staying abreast of the rapid body of literature is crucial. New discoveries arise from diverse areas and have the potential to fundamentally alter collective knowledge [30]. Chaomei Chen designed CiteSpace specifically to facilitate the detection of emerging trends and abrupt changes in the scientific literature. CiteSpace identifies emerging trends by computed indicators without any domain experts' intervention or prior working knowledge of KD. Our dataset was expanded through an index-based methodology, which is more robust than defining a rapidly growing field with a list of predefined keywords. This approach ensures the analysis's repeatability with new data and verifiability by different analyses.

## 2. Data and methods

### 2.1. Data collection and analysis

Literature about KD was retrieved from the Web of Science Core Collection database (WoSCC) [31]. WoSCC is one of the most comprehensive databases and offers enormous resources through an online access port, including many citation databases, but not all articles and journals are indexed [32].

The search query and the limitation strategy of the results are shown in Fig. 1. All studies were retrieved at May 25, 2023, to avoid bias caused by daily updates of the database. CiteSpace 6.2. R2, VOSviewer 1.6.18, Tableau 10.5, and Microsoft Excel 2021 were used to perform this bibliometric analysis and visualize references for KD research.

VOSviewer software is used to generate visual maps that construct a scientific knowledge network and display the structure and collaborations in the research field [33]. In our study, VOSviewer was employed to create density maps representing co-institutionalship, co-nationality, and keyword co-occurrence patterns. The visualization map generated by CiteSpace comprises nodes and lines, with nodes representing different entities, such as authors, countries/regions, institutions, references, and keywords. Larger nodes indicate a greater frequency of occurrence for the respective entity types. Microsoft Excel was used to create the table and determine the annual publication counts. Tableau was used to visualize the global distribution of publications.

### 2.2. Special terms

Note that centrality refers to the ability to serve as an intermediary throughout a relationship network [34]. In a network structure, nodes with centrality greater than 0.1 are important [35]. Keywords with high frequency and centrality are usually regarded as hot research topics in a given field. CiteSpace has the function of burst detection, indicating a sudden increase in terminology in the literature published in certain years. Such bursts are detected based on the literature and can be identified as the research frontier in certain fields [35,36]. The more influential the paper is, the higher the H-index is, regardless of where it is published. The H-index has been increasingly used in recent years to assess scholarly contributions and predict scientific achievements [37–39].

## 3. Results and discussion

### 3.1. Analysis of research power

There were 6122 original research articles and review articles in the database.

#### 3.1.1. Journal statistics

Journals serve as chief conduits for science and technology. Leading journals, determined by the statistical analysis of relevant literature, expedite scholars' access to high-quality publications [40–42]. The top 10 journals with the most publications are shown in Table 1. Pediatric Cardiology (217 articles, H-index 31), Pediatrics International (186 articles, H-index 30), Pediatrics Infectious Disease Journal (178 articles, H-index 41), Journal of Pediatrics (175 articles, H-index 55), and Frontiers in Pediatrics (157 articles, H-index 18) were the most influential journals in terms of KD research. Pediatric Cardiology provided the largest number of studies;

**Table 1**  
Top 10 journals based on the number of articles about KD.

Rank	Journal	Number of articles	Average Citation Frequency per Paper	IF (2023)	JCR (2022)	H-index
1	Pediatric Cardiology	217	16.99	1.6	Q3	31
2	Pediatrics International	186	16.76	1.4	Q4	30
3	Pediatric Infectious Disease Journal	178	25.19	3.6	Q1	41
4	Journal of Pediatrics	175	36.93	5.1	Q1	55
5	Frontiers in Pediatrics	157	6	2.6	Q2	18
6	European Journal of Pediatrics	120	23.08	3.6	Q1	31
7	Cardiology in the Young	111	6.76	1	Q4	16
8	Pediatrics	101	69.91	8	Q1	51
9	Pediatrics Research	79	20.85	3.6	Q2	24
10	Clinical and Experimental Immunology	74	40.78	4.6	Q3	30

IF: Impact Factor; JCR: Journal Citation Reports Category Quartile.

Journal of Pediatrics and Pediatrics had the top two highest H-indexes. In addition, the cited journals were analyzed via CiteSpace, which revealed that Circulation (3723 total citations) was the most cited journal, followed by Pediatrics (3359 total citations) and the Journal of Pediatrics (3321 total citations). The Journals with centrality greater than 0.1 were Circulation (0.19), the Journal of Pediatrics (0.16) and The New England Journal of Medicine (0.15); these journals appear to publish crucial literature about the development of KD ([Supplementary material](#)).

### 3.1.2. Analysis of author distribution and collaboration

Researchers from all over the world have contributed to KD research. Authorship, as a strong bond, promotes academic collaboration and fostering research progress [43,44].

In total, 6122 authors were identified in this network. Authors with fifty or more papers in the KD field can be considered as productive authors. The top two authors were Burns J and Newburger J from the USA, with 212 and 121 articles, respectively. Of the top five citation papers published by Burns J and Newburger J, four were the same paper. These two individuals had close relationship in the study of KD. Newburger J had made enormous contributions to the treatment of KD with intravenous immunoglobulin (IVIG) administration. She reported that treatment with high-dose IVIG early during KD can reduce the occurrence of coronary artery lesions (CALs) [45]. Five years later, she further reported that a single large dose of IVIG is more effective than the normal regimen of four times infusions [46]. Kuo H and Huang Y from “Chinese Taiwan”, focused on genome-wide associated studies to determine gene susceptibility in KD and coronary artery aneurysm (CAA) formation. NAKAMURA Y participated in the 5th revision of diagnostic guidelines for KD, particularly in exploring the etiology of ITPKC functional polymorphisms associated with KD and providing epidemiology statistics on KD in Japan (Table 2).

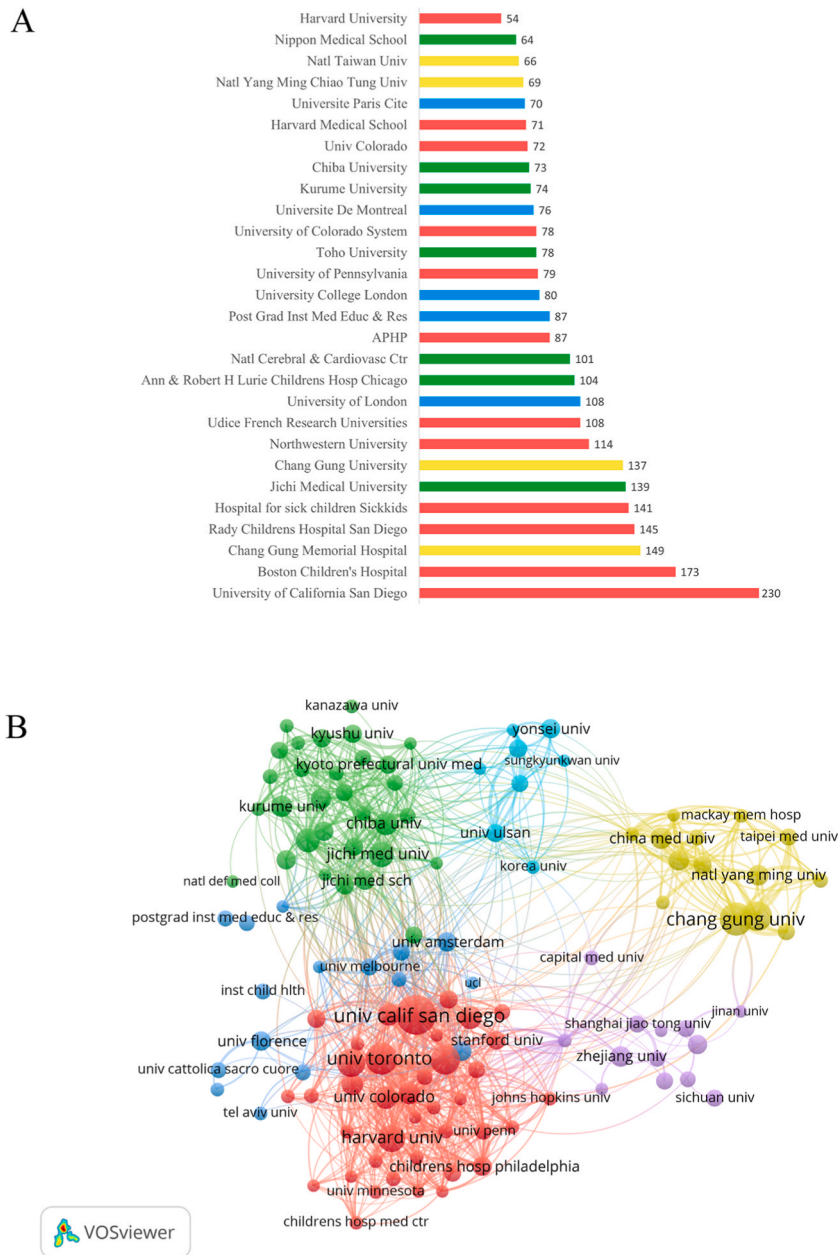
### 3.1.3. Analysis of institutional influence on publications on KD

An institution cooperation network map visualizes the distribution and collaboration among institutions [47,48]. The top 28 institutions are shown in Fig. 2A. The University of California San Diego was the most productive institution, with 230 articles, followed by Boston Children’s Hospital (173 articles) and Chang Gung Memorial Hospital (149 articles). Institutions with 20 or more publications were visualized: 121 institutions and 6 clusters with different colors are shown in Fig. 2B. The red cluster is the largest cluster, the University of California San Diego, Harvard University, and the University of Toronto group are in this cluster. Nearly half of the top 28 institutions belong to the red cluster (Fig. 2A), and most of the institutions in the red cluster are from the USA. This suggests that they built closer collaborative relationships within their cluster, focusing on similar research topics in KD. The USA emerged as the most influential country in KD research.

According to the high-citation articles from these productive institutions, the University of California San Diego reported that TNF- $\alpha$  and hnRNPL-related immunoregulatory lincRNA, this high-citation article report a long noncoding RNA that regulates TNF- $\alpha$  expression and play crucial roles in the innate immune response and inflammation in KD. In other paper, patients with KD shock syndrome exhibit more severe laboratory markers of inflammation, increased risks of coronary arterial lesions, greater cardiac structure or functional dysfunction and higher rates of resistance to immunoglobulin therapy [49,50]. These findings lay the groundwork for the clinical application of TNF- $\alpha$  monoclonal antibodies. A multicenter, randomized, double-blind, placebo-controlled trial did not find evidence indicating that the efficacy of pulsed corticosteroid therapy as a primary treatment can reduce the number of adverse events in KD patients [51]. Within the largest cluster (red cluster), high-citation articles from recent years, a study conducted at Boston Children’s Hospital examined the association between multisystem inflammatory syndrome (MIS) and coronavirus disease 2019(COVID-19) in children and adolescents. The results revealed that 40 % of these patients exhibited documented KD-like features [52]. Following the green cluster, institutions such as Jichi Medical University, Chiba University, Kurume University and Toho University, which are all located in Japan, this might have had the highest incidence rate of KD. Moreover, among the 28 institutions, 22

**Table 2**  
The most productive authors in the field of KD.

Rank	Author	Count	Proportion	Country/regions
1	BURNS J	212	1.79 %	USA
2	NEWBURGER J	121	1.02 %	USA
3	KUO H	120	1.01 %	Taiwan, China
4	NAKAMURA Y	111	0.93 %	Japan
5	SHULMAN S	101	0.85 %	USA
6	TREMOULET A	99	0.83 %	USA
7	HUANG Y	96	0.81 %	Taiwan, China
8	SINGH S	73	0.61 %	India
9	LEE J	68	0.57 %	Korea
10	WANG Y	66	0.56 %	China
11	YANAGAWA H	63	0.53 %	Japan
12	SHIMIZU C	63	0.53 %	USA
13	MCCRINDLE B	61	0.51 %	Canada
14	ROWLEY A	60	0.51 %	USA
15	ZHANG Y	52	0.44 %	China
16	YASHIRO M	51	0.43 %	USA
17	KATO H	50	0.42 %	Japan
18	KIM J	50	0.42 %	Korea



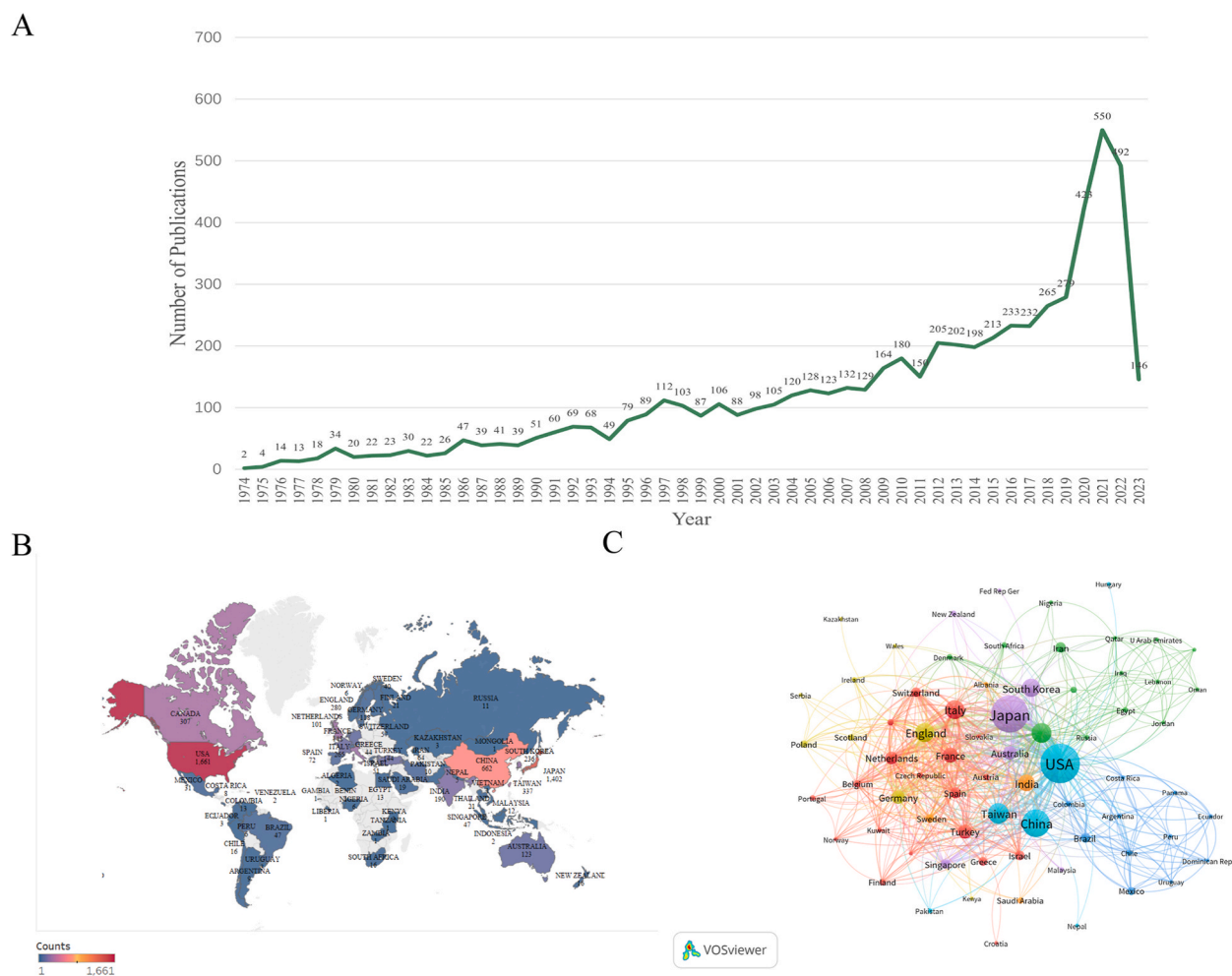
are universities, indicating that universities are the major research institution in this field.

3.1.4. Publications in international or regional distribution and collaboration

The number of published articles in the world reflects the status of the field [53]. As shown in Fig. 3A, the annual number of publications on KD has continued to increase since 1974. The number of publications has increased slowly, with no more than 100 studies published every year before 1996. The number of articles increased rapidly in 2012 and sharply after 2019. Moreover, there were 571 studies in 2021, suggesting that this field received considerable attention.

The number of publications and the distribution of nations or regions can help in understanding the geographical position of a nation or region and the cooperative relationships between nations in terms of KD research [54,55]. The distribution of publications





**Fig. 3. Visualization map of publications involving KD.** A: The annual number of publications on KD research from January 1974 to September 2020. B: Word map of the country/region distribution map based on frequency. C: Collaboration network of main countries/regions.

indicated that the number of KD studies was extremely uneven in different countries and regions. The majority of countries and regions exhibited low numbers of publications. Fig. 3B shows that the USA (1,661), Japan (1,402) and the Chinese mainland (662) ranked as the top 3 countries in terms of the number of research publications. This suggests that these countries have invested significant resources in KD study, resulting in substantial rewards. In Fig. 3C, blue and purple are the two largest clusters. The USA, Chinese mainland, and Chinese Taiwan region exhibited strong cooperation with each other, while Japan showed closer collaboration with South Korea and Australia.

### 3.2. Emerging trends and hot topics

With the theory of scientific change, research frontiers may signal the emergence of a new scientific paradigm. Consequently, many scientists have committed themselves to exploring these frontiers, recognizing their significant potential for advancement [56]. Xue Zhang et al. proposed that emerging research has the potential to develop into research frontiers, and specific conditions may elevate certain frontiers to become highly sought-after research topics [57]. In this study, we employed keyword co-occurrence and reference co-citation maps to illustrate the emerging research trends, explore the research frontiers, and identify hot topics in KD.

#### 3.2.1. Analysis of keywords in the Co-citation network

The literature keywords serve as the core and main contents. Keywords with high frequency helped us to uncover popular research in the KD field [58–60]. As illustrated in Fig. 4, keywords occurred more than 20 times, and 325 keywords were present in the landscape. We excluded the keywords Kawasaki disease and children because we used “Kawasaki disease” as the retrieval term in this study. Finally, the top 5 high-frequency keywords were, diagnostic criteria (712 times), intravenous immunoglobulin therapy (687 times), risk factors (497 times), aneurysm (380 times), and management (377 times). These high-frequency keywords suggest that the



### Top 72 Keywords with the Strongest Citation Bursts

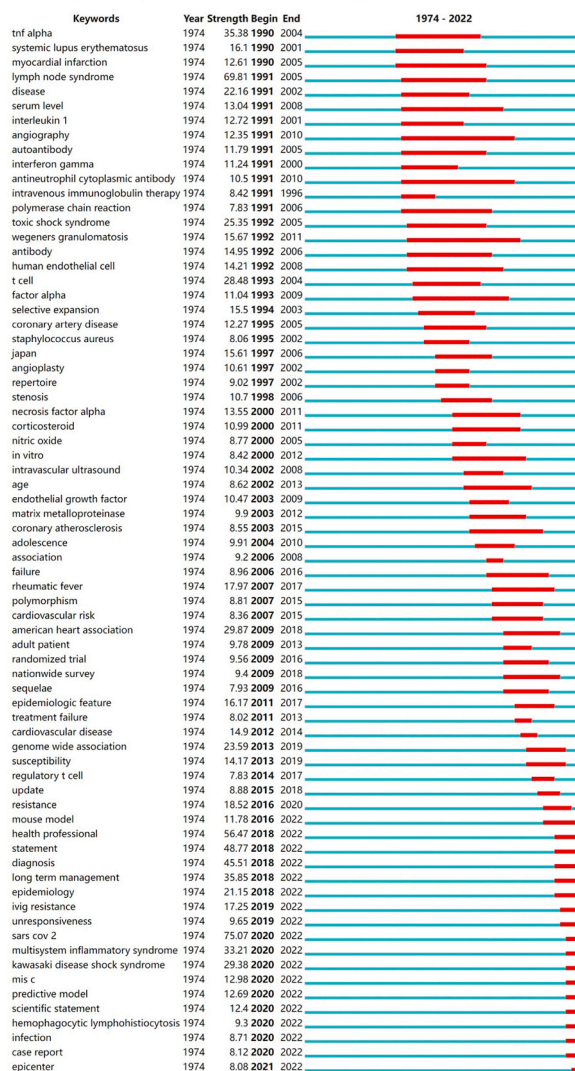


Fig. 5. Top 72 strongest citation bursts of keywords.

factors that induce smooth muscle cell transition to myofibroblastic, which potentially halts the SA/C vasculitis process, remain unknown.

Fig. 5 illustrates the TNF- $\alpha$  burst from 1990 to 2004. However, in recent years, the focus of TNF- $\alpha$  studies has shifted toward the monoclonal antibody inhibitor infliximab. Infliximab has been used to treat patients with uncontrolled inflammation in KD. Researchers have also explored other biomarkers, such as the angiotensin converting enzyme-2 (ACE2) receptor, and investigated the ACE2 and STING pathways as potential contributors to endothelial dysfunction in coronary arterial lesions in KD patients [65–67]. In addition to risk factor model, researchers have developed risk prediction models for CALs and prediction models for the diagnosis of KD subtypes. Earlier identification these KD subtypes of KD, such as MIS, KD shock syndrome, or IVIG resistance, will enable prompt treatment to reduce cardiovascular sequela.

“Mouse models” another citation burst term, is shown in Fig. 5. Three factors, namely, low availability of human tissues in KD or KD-CAA, unknown etiological agents, and incomplete understanding of the mechanisms involved in CAA sequelae, limit our understanding of the pathophysiology of KD. Therefore, it is critical to utilize experimental animal models mimicking the features of KD. Researchers utilized animal models (LCWE or CAWS models) to investigate the mechanisms involved in cardiovascular disease and inflammation via potential new biomarkers, endothelial dysfunction, and smooth muscle cell transformation. The accepted mouse models may not be a hot topic or frontiers in KD research.

#### 3.2.2. Network of references in Co-citation mapping

Scientific philosophers propose that the advancement of science unfolds through a sequence of scientific revolutions, including



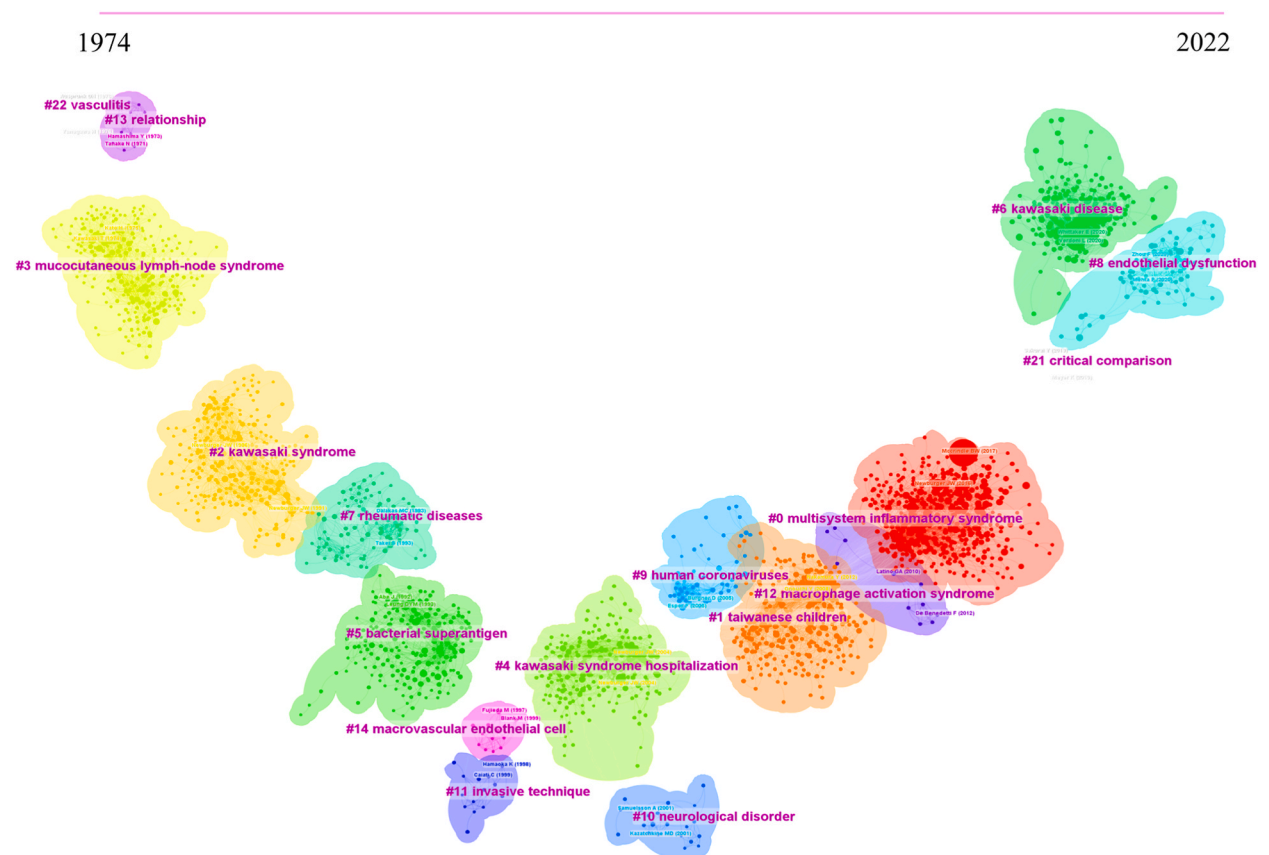
phases of normal science, crises, and breakthrough revolutions. As science evolves, a new paradigm has emerged to replace the existing paradigm [56]. The co-citation network reveals the basic literature, and the essential knowledge base measures the strength of two articles that have been cited in the same article [68–70]. In this study, only references cited more than 50 times are displayed in the co-citation map. Finally, a total of 17 co-citation clusters were identified, with a modularity of 0.7972, which suggested the high quality of the cluster divisions (Fig. 6). The labels in the clusters were automatically generated from titles based on label-adding technology within CiteSpace clustering [71].

The label represents the gist in the whole cluster. Fig. 6 clearly shows the pattern changes in the study of KD over time. Cluster #0 was the largest cluster and was labeled “multisystem inflammatory syndrome (MIS)”. The core members in cluster #0 represent major landmarks related to the MIS. Notably, after excluding highly cited reviews, we found that the two highly cited articles in this cluster were related phase 3 clinical trials. Tremoulet, A.H et al.’s article entitled “Infliximab for intensification of primary therapy for Kawasaki disease” [72], and Hamada, H et al.’s article entitled “Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin” [73].

We specifically focused on the most recent clusters because they reveal the emerging trends in the study of KD. The most recently formed clusters are cluster #6 and cluster #8.

In cluster #6, all of the 5 most highly cited articles were related to KD and SARS-CoV-2. The most cited article is an observational cohort study on the association between SARS-CoV-2 and a severe Kawasaki-like disease outbreak in Italy. This study revealed a high incidence of a severe form of KD during the SARS-CoV-2 epidemic [63]. In contrast, the second cited article suggested that pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 differs from KD or KD shock syndrome [74]. The emergence of SARS-CoV-2 in 2019 prompted extensive research to investigate whether it acts as an etiological factor in KD.

Researches in cluster #8 focused on investigating endothelial dysfunction in macrophage activation syndrome (MAS) associated with KD. In the acute phase of KD, patients who present with presenting with fever accompanied by splenomegaly, hyperferritinemia, thrombocytopenia, and elevated aspartate aminotransferase levels should be considered to have MAS complicating KD. In recurrent KD, if similar clinical features recur within 1 month, MAS-complicating KD should be considered. Treatment in these patients should involve multiple combinations of anti-inflammatory agents. Coronary abnormalities and fatal cardiovascular events were notably prevalent. Research has suggested that the inflammation and coagulation are likely responsible for ongoing endothelial dysfunction



**Fig. 6.** Co-citation network cluster visualization in KD references. Cluster #0 was the biggest cluster and the #6, and #8 were the newest clusters in the field of KD.

and lead to poor outcomes in patients with cardiovascular complications [75,76].

#### 4. Conclusions and prospects

This scientometric analysis of the KD literature spanned from 1974 to 2023 (until May 25th). In total, 6122 original studies and review articles were included in this study. Researchers have increasingly directed their attention toward KD. The number of publications increased slowly, and no more than 100 studies were published before 1996. A rapid increase occurred in 2012, and a sharp increase occurred after 2019. There were 571 studies in 2021. The USA held the utmost influence, while Japan and China emerged as the primary driving forces in the realm of KD studies. Journals such as the *Journal of Pediatrics*, *Pediatrics*, *Pediatric Cardiology*, and *Circulation* have exerted significant influence and made substantial contributions to the advancement and process of KD research. Burns J, Newburger J, Kuo H, Nakamura Y, and Huang Y were the principal authors who played a pivotal role in advancing the development of KD as a prominent research field. The University of California San Diego, Boston Children's Hospital, and the Chang Gung Memorial Hospital were all significant institutions.

In addition to examining the current state of KD research, this study explored future directions by investigating emerging trends and identifying key areas for further investigation. SARS-CoV-2, diagnostic serum biomarkers, and risk factor prediction models for CALs and subtypes of KD, such as MIS, KD shock syndrome, or IVIG resistance, are popular topics in KD research. Factors that induce smooth muscle cell transition to myofibroblastic cells, potentially halting the SA/C vasculitis process and endothelial dysfunction in MAS associated with KD, were the frontiers in the study of KD.

As research progresses and new frontiers emerge, some of these frontiers have become hot topics with advancements. However, over time, the latter tend to fall behind the former. Furthermore, novel approaches other than a single biomarker may be required for laboratory standard testing for KD diagnosis in the future due to the potential complexity of its pathogenesis. Additionally, the research fervor surrounding "SARS-CoV-2" may gradually dissipate as the pathogenic intensity decreases due to virus mutations.

#### Ethics declaration

Not applicable. This study used existing data from published studies and did not involve any direct experimentation or studies on living beings.

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#### Data availability statement

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

#### CRediT authorship contribution statement

**Mengling Li:** Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zaiyong Zheng:** Writing – review & editing, Visualization, Validation, Software, Resources, Methodology, Conceptualization. **Qijian Yi:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, 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.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e29680>.

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