



## Kawasaki Disease and COVID-19: Interrelation

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### ABSTRACT

**Background:** Kawasaki disease is a febrile disease with an unknown etiology, mostly affecting the children. It is a vasculitis with coronary artery dilations, rashes, swelling of hands, feet and lymph nodes and inflammation of lips, mouth and throat. It has possible association with SARS-COV-2 exposure. Their association increases the mortality by 15-30%.

The purpose of this article was to give a review of the literature on the association of Kawasaki disease with SARS-COV-2.

**Methods:** Review of articles including the case series, case reports, retrospective case control study, various clinical trials and RCTs available on PubMed, Google Scholar, Sci-hub and Medline database within the range of past 10 years has been performed for better analysis excluding the articles which were not including the specifications regarding association of Kawasaki disease with SARS-COV-2. Data on age at diagnosis, ethnicity, season, serological testing, RT-PCR reports, history and presentation of other diseases were taken from medical records.

**Results:** The mean number of consenting participants (n=109) were chosen for analysis. Therefore, it was concluded that the median of age of participants at diagnosis is 12 years. There is no prevalent association with asthma, diabetes and obesity but there were increased rates of dermatological conditions, oral mucosa manifestations, abdominal pain and heart diseases including myocarditis and vascular diseases including coronary artery disease, pericardial effusion and aneurysms. Majority of patients received anticoagulants, immunoglobulin, anti-inflammatory drugs and corticosteroids.

**Conclusion:** since the COVID-19 outbreak, the incidence of Kawasaki disease and MIS-C (multisystem inflammatory syndrome in children) is seen after 2-6 weeks of COVID-19 infection. With effective management plan and treatment, most of the patients recovered but complications developed. So, long term follow-ups are required.

**Keywords:** COVID-19, SARS-COV, Kawasaki disease, inflammatory syndrome, pediatrics, dermatological conditions, oral mucosal manifestations

### I. INTRODUCTION

Kawasaki disease 1<sup>st</sup> identified in 1960s by a Japanese pediatrician T. Kawasaki who described a group of children with similar symptoms: conjunctivitis, fever, enlarged lymph nodes of head and neck region <sup>(1)</sup>. It is an acute febrile systemic childhood vasculitis that affect medium and small sized blood vessels with coronary artery tropism <sup>(1, 2)</sup> patient typically present with fever, rash and swollen hands and feet <sup>(3, 4)</sup>. Recently, there has been growing concern over the potential association between Kawasaki disease and COVID-2019, the disease

caused by the novel coronavirus. This has raised significant alarm among healthcare professionals.

The symptoms of Kawasaki disease can be severe and potentially life-threatening, if left untreated it may cause heart complications and even death <sup>(4)</sup>.

The National Health Service issued a warning that a multisystem inflammatory syndrome which could be linked to COVID-2019 has led to a surge in the number of children requiring intensive care unit (ICU) admission <sup>(5)</sup>. Clusters of pediatric cases of severe systemic hyperinflammation and shock epidemiologically linked with COVID-19 were reported <sup>(6)</sup>. This has prompted researchers to investigate the possible connection between the two conditions and the mechanisms by which COVID-2019 may increase the risk of developing Kawasaki disease in children. As we delve into this topic, it is crucial to emphasize the importance of early detection <sup>(7)</sup> and treatment for Kawasaki disease. The diagnosis of KD is a clinical challenge, given its large variety of signs and symptoms since it may resemble other viral and bacterial infection <sup>(8)</sup>. Health officials have adjusted the clinical and epidemiological criteria used to identify cases as the MIS-C has evolved <sup>(9)</sup>.



In light of these developments, it is crucial for healthcare professionals to remain vigilant and it is critical to make the time distinction between classical Kawasaki disease and Kawasaki disease associated with COVID-2019<sup>(10)</sup>.

In this systematic review we will explore the current understanding of Kawasaki disease and its potential link to COVID-2019, as well as the implications for diagnosis, clinical manifestations and treatment. We have extracted the patient data and findings from literature review and meta-analysis.

### Abbreviations

CAD- Coronary artery disease ELN- Enlarged lymph nodes CRP- C-reactive proteins

BNP- Brain natriuretic peptide

NT-Pro BNP- N-terminal pro-hormone of brain natriuretic peptide

RT-PCR- reverse transcriptase polymerase chain reaction

IV-Ig- intravenous immunoglobulin

## II. RESULT

Around 184 potentially relevant studies met our initial criteria. Out of 184, 112 were removed as the studies were not about the topic, didn't report the desired outcome, papers which were duplicates or in other languages or about animal models and studies which were published before 2013. 72 articles with full text were reviewed (Search flow chart is presented in fig.1). Characteristics of the included articles are summarized in table 1.

Based on geographical region, 13 studies we included were from the USA, 8 studies were from UK, 8 from France, 5 from Europe, 8 from Italy, 4 from India, 4 from Brazil.

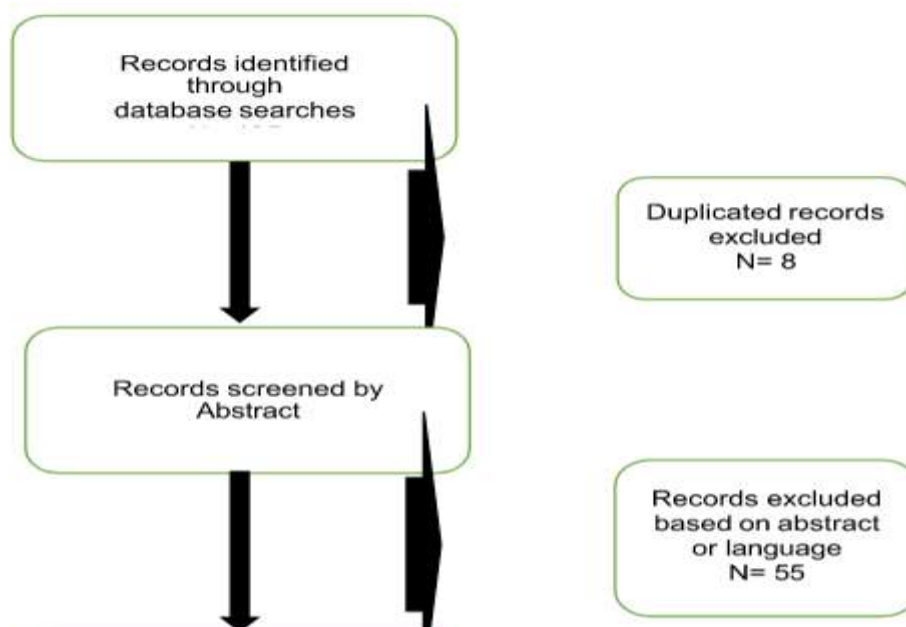
Apart from these, there were few studies from Spain, Iran, Romania, Pakistan, Turkey, Germany, South Africa, Sweden, Russia, Australia, China and New Zealand as well. In terms of study design, 21 were case reports, 28 case reviews and 18 case series. There were more than 1 outcome in most of the studies.

The mean number of consenting participants were 109. The median of age of participants at diagnosis was 12 years and the mean of age of participants at diagnosis was found to be 20.8 years.

Based on the pooled studies fever and dermatological manifestations were significantly associated with Kawasaki disease in association with Covid-19 in 25 papers. Respiratory symptoms, Gastrointestinal symptoms and Heart diseases also showed significant association with data in 51%, 82% and 43% studies respectively. Oral manifestations, conjunctivitis, neurological symptoms, maculopapular rash and peripheral edema were also associated with the data.

Apart from these, there were other symptoms like vomiting, hypotension, aneurysm, myocarditis, enlarged lymph nodes, pericardial effusion, coronary artery disease and joint pain were also seen in some studies.

Lab values including WBC count, erythrocytes sedimentation rate, ferritin levels, interleukins, D-dimers and C-reactive proteins were also taken into consideration



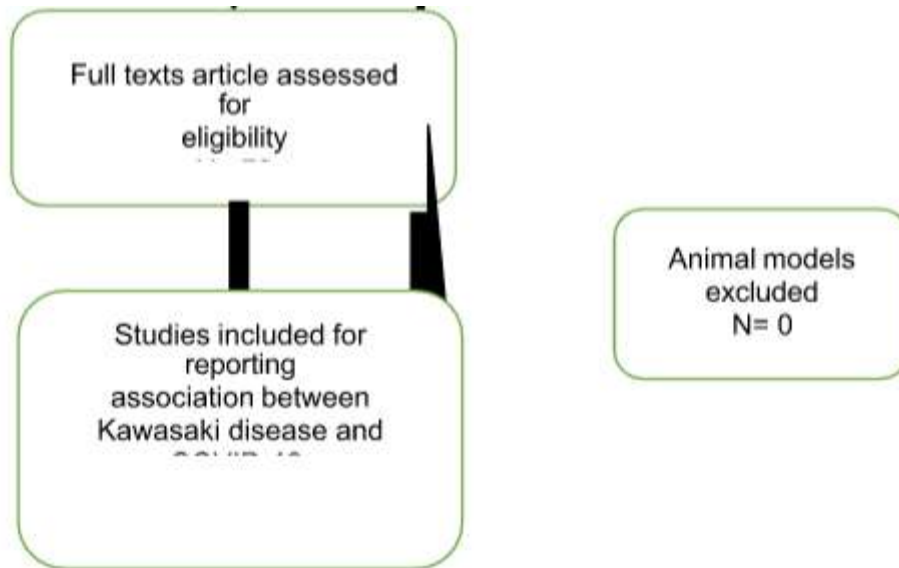


Fig 1. Search Flowchart

Full texts article assessed for Table 1. Characteristics of the included articles

SN	Author	Year	Age at Diagnosis	Sex	Month/Season	Country
1	<u>Pragna Patel</u>	2021	21 years	Male: 154/219, Female: 65/219	NA	NA
2	Pedram Keshavarz	2021	9+-4.2 years	Male (61.6%) and female (37.5%) 1 unknown gender	NA	NA
3	Debjyoti Dhar	2021	8.9 ± 1.9	NA	NA	NA
4	Hsieh LE	2021	8.5 years	Male and female	May- November 2022	USA
5	<u>Seema Shah</u>	2021	11.096 years	Male (57%) female (43%)	NA	NA
	Claudio	2021		Male and		



6	Confroti	0	66 years	Female	NA	NA
7	<u>Kaiwei Liu</u>	2022	NA	NA	NA	US
8	<u>Sand Momtaz manah</u>	2020	NA	NA	NA	NA
9	K-H-LEE	2022	M(8-16 yrs) F(8-15 yrs)	M(n=24) F(n=21)	NA	NA
10	<u>Yuyi Tang</u>	2021	NA	NA	NA	US, EUROPE

11	Keren Paola Osorio-Mendea	2021	NA	NA	NA	NA
12	Ana Maria Jurca	2021	1 month - 17 years	n=26	December-April	Romania(Bucharest)
13	Naim Ouldali, MD	2020	1 month -15.5 years	230 [boys 134 (58%) girls 96(42%)	NA	NA
14	<u>V.O. Bitsadze</u>	2020	NA	NA	NA	Italy
15	<u>Anthony Zara</u>	2021	NA	n=375	NA	spain
16	Debjyoti Dhar	2021	8.9 ± 1.9 years.	ratio- 1.31 (n=833)	NA	NA
17	Francesca Sperotto	2020	21 years	NA	NA	UK, USA, India, Italy and France
18	Mohammad Javad Hosseini	2023	2 year	female	NA	Iran
	M.	202				



19	Verheyden	0	57 years	male	NA	NA
20	Yifan Que	2021	NA	NA	NA	NA
21	Tong Tong	2022	NA	NA	NA	France, Italy, sweden, Spain,UK,Russia,Pakistan
22	Eman A Toraih	2021	7.93-10 years	f(48.6%) m(51.4%)	NA	France,USA,UK,Italy
23	Kalai Wong	2022	M=24(6months-83yrs)	m=4 f=5	NA	NA
24	Parham Mardi	2021	6 months - 16.6 years	Total: 599; Males: 347(57.92%)	NA	USA , Europe, India, Brazil

25	Ummusen Kaya Akca	2020	2-10 years	1 male, 3 female	NA	Uk, Italy, USA, France
26	Monica O. Santos	2021	8.9 years (0.1 days- 20 years)	Male(10.27%)	NA	USA, UK, India, Turkey, France, Brazil, Germany, Spain, South Africa, Pakistan, Iran
27	Loubna Lamrani	2021	41.9± 31.3 months	58% male	NA	NA
28	Ji-Gan Wang	2021	<21yrs	Male:Female = 1.49:1	NA	Europe, USA
29	Raúl Bustos B	2021	<21 yrs	Male	NA	Europe, North America
30	Gianluigi Li Bassi	2021	62 year ( 52-71)	Male (510) and Female (235)	January - December	Africa, Asia, Australia and New Zealand, Europe, Latin America and the Caribbean, Northern America
						United States, China, France, Germany, the



31	Kamyar Nasiri	2023	0-18 years	Male and female	NA	UK, Romania, Saudi Arabia, Italy, Brazil and Iran
32	Li Jiang	2022	8.1 ± 2.37 years	Male and female	December 1, 2019, to July 31, 2021	NA
33	Silvia Ruvinsky	2022	6.6 years (6-7.4)	Male 60%, Female 40%	March 1, 2020 to June 30, 2021	Peru, Brazil, Argentina, Chile, Costa Rica, Colombia, Mexico, Venezuela, and other countries.
34	Mohamed Sabbour	2020	8.9 years	Males (n= 381) Female (n=292)	NA	USA, UK, France, Italy, India, Switzerland, Luxembourg, Israel, Turkey
35	Somayeh Jafrasteh	2023	8.8 years	15	NA	NA

36	Sunreet Randhawa	NA	7.9 years	3:2 (n=45)	NA	UK, France, USA, Italy, Switzerland
37	Ruwaa Samarrai	2021	NA	NA	NA	NA
38	Arianna Dondi	2022	14.7 years	M- 240 F- 240	NA	NA
39	Abel Emanuel Moca	2023	NA	NA	NA	NA

### III. METHODS

In this research paper the participants were informed about the procedures, potential benefits, risks by consent forms. These forms can also provide information regarding how participants could Access study results, counseling services and voluntary participation, researchers contact and information are included in Consent forms, along with Clear statement study's purpose. For conducting a comprehensive review on the topic, a systematic search was conducted on PubMed, and

Google Scholar databases. This search included various types of studies, such as case series, case reports, retrospective case control studies, clinical trials, and randomized controlled trials. The search spanned from 2013 to 2023 and focused on COVID-19 association with Kawasaki disease. Additionally, relevant systematic reviews and randomized control trials were examined for potential articles. Advanced search strategies were utilized in PubMed to gather all original studies that met the criteria. Different search terms were applied, including "COVID-19 disease association



with Kawasaki," "clinical findings of MIS-C in," "symptoms of COVID-19," and "treatment of COVID-19 in Kawasaki disease."

To select appropriate studies, inclusion and exclusion criteria were applied. This involved studies that review COVID-19 and its clinical findings, treatment and management, and also special inclusion of Kawasaki disease. These Studies don't involve animal models and also studies not published in English language were excluded.

We as reviewer extracted relevant data from the published articles on "COVID-19 association with Kawasaki disease". This included information such as author, publication year, country, study design, participant numbers, age at diagnosis, Sex, Month/Season and other comorbidities. The studies examined outcomes such as fever, shortness of breath, abdominal pain, diarrhea, vomiting, joint pain, aneurysm, myocarditis, CAD, heart diseases, Lymph node enlargement, Chest tightness, as Symptoms. Laboratory values, including blood test results, including lymphopenia, interleukin, ferritin, fibrinogen, C-reactive protein, BNP, D-dimer, Marker of Coagulation, spo<sub>2</sub>, N-pro BNP, Serological tests, RTPCR and pathological findings were also recorded. Reviewers also added the follow-up duration, discharge disposition and treatment provided to the participants. Mean values were preferred for lab results collection, and when mean values were unavailable, median values were calculated.

#### IV. DISCUSSION

The SARS-CoV-2 virus infection began in China in December 2019 and spread worldwide <sup>(5)</sup>. The symptoms of COVID-19 are more severe in adults than in children <sup>(11)</sup>. Because, in most cases, especially in children, COVID-19 is asymptomatic, they can transmit the virus to adults <sup>(12, 13)</sup>. Several studies have reported concurrent infections with Kawasaki and COVID-19 <sup>(6)</sup>.

As with the COVID-19 pandemic and its progress, the incidence of patients admitted with KD and other related diseases and symptoms such as KLD and MIS-C has increased, so that there have been several reports from different countries <sup>(3)</sup>. Moreover, up to now, there are large case series of KD related to COVID-19 in different countries, e.g., the United Kingdom (UK), Italy, the United States of America (USA), Turkey, and France <sup>(6)</sup>.

Kawasaki disease represents a pediatric vasculitis syndrome that affects multiple system <sup>(14)</sup>. The common presenting feature is mild flu in the majority of cases, followed by fever and GI

symptoms including abdominal pain and vomiting <sup>(5)</sup>. Atypical presentations at the forefront, like cutaneous lesions, erythematous maculopapular skin rashes, vesicular lesions related to COVID-19, vesicular rashes, neurological abnormalities, anosmia, venous thromboembolism, ocular involvement like conjunctivitis, oral mucosal changes (strawberry tongue, hyperemia of the lips and oropharynx, dry lips with crack), limb changes (redness, swelling or induration, non-pitting edema), and lymphadenopathy are frequent <sup>(15, 16, 5, 2)</sup>. Cardiac involvement (42%), being represented by: left ventricular dysfunction

(26%), coronary artery abnormalities (15%), atrioventricular valve regurgitation (30%), pericardial effusion, and one ECG anomaly

<sup>(12)</sup>. an anti-inflammatory drug containing 2 g/kg intravenous immunoglobulin IVIG and a high dose of acetylsalicylic acid was administered <sup>(6)</sup>.

Although more than 40 years of study have tried to explain it, the etiology of KD remains unidentified <sup>(7)</sup>. So far, researchers have been able to determine the immune response to a stimulus as a significant factor in the pathogenesis of the disease; however, researchers have not been able to identify the stimulus yet <sup>(17, 18)</sup>. One probable explanation is exposure to an infectious agent and subsequently triggering the immune system. This idea can explain the peak of KD cases in the winter <sup>(4)</sup>. With the incidence of the COVID-19 pandemic, the number of children who presented with KD symptoms increased dramatically <sup>(4)</sup>.

#### Demographics

**Time:** The occurrence of the disease can be seen to peak around the winters. The incidence is minimal around the time of spring. The frequency of occurrence of Kawasaki disease in the month from November to January is highest.

**Place:** Looking into the geographic extent of prevalence of the disease and its geographic variation, it is more common in the extra-tropical regions of the Northern hemisphere and few outbreaks have been observed in Japan without any clear cause.

**Age:** age group of 0-10 is the most susceptible to Kawasaki disease followed by the age group of 18-24 months being the highest.

**Ethnicity:** it is noted from the study, that children of any race can get the disease but the children of East Asia or afro-caribbean ancestry are more susceptible to the disease.

**Sex:** From the study, it has been noted that boys are slightly more likely to develop the



### Signs and Symptoms

After reviewing articles on Kawasaki disease and its association with COVID-19, it is apparent that the common clinical presentations found in the vast majority of patients typically involved fever, which is observed in approximately 64% of cases.

This persistent high fever lasting for at least five days is often accompanied by other distressing symptoms. Shortness of breath, medically known as dyspnea, is reported in about 25% of cases. This can be attributed to the inflammation of blood vessels supplying the lungs, leading to a condition called small vessel vasculitis.

Gastrointestinal symptoms are also commonly seen in Kawasaki disease. Abdominal pain affecting 38%, diarrhea affecting around 38% of patients, and vomiting, reported in 25% of cases, can cause significant discomfort and lead to dehydration. These symptoms are thought to arise due to the involvement of blood vessels supplying the gastrointestinal tract. Another cardiovascular manifestation of Kawasaki disease is hypotension, affecting approximately 25% of patients. Moreover, aneurysms, which are abnormal bulges in the blood vessels, occur in about 28% of cases. These aneurysms can lead to serious complications if left untreated.

Joint pain, or arthritis, is seen in around 15% of Kawasaki disease cases. This can cause significant discomfort, limiting the child's mobility and daily activities. Along with joint pain, peripheral effusion, or swelling in the hands and feet, is observed in few patients. These symptoms are likely caused by the immune system's response to the inflammation. disease than the girls. Out of the 39 papers 56.4% are males, 48.7% are females and 38.46% are not mentioned.

Furthermore, Kawasaki disease can also affect the heart, leading to potentially severe complications. Myocarditis, inflammation of the heart muscle, occurs in approximately 30% of cases. Heart disease, including coronary artery disease, is reported in 43% and 23% of patients, respectively. These cardiac manifestations highlight the importance of early detection and treatment to prevent long-term complications.

Enlarged lymph nodes, or lymphadenopathy, are also common in Kawasaki disease, affecting around 33.3% of patients. The lymph nodes, part of the immune system, become swollen due to the body's inflammatory response. While lymphadenopathy can occur in various conditions, its presence in conjunction with other symptoms can aid in the diagnosis of Kawasaki disease.

It is essential to note that the percentages provided above are not fixed values but rather represent the frequency with which these signs and symptoms have been observed in previous studies. Each case of Kawasaki disease can present differently, and the severity of symptoms may vary. Prompt recognition and medical intervention are crucial for successful management of this condition.

In conclusion, Kawasaki disease is a complex condition that affects multiple systems within the body. The signs and symptoms mentioned above, along with the collected data, serve as valuable references for healthcare professionals in diagnosing and treating this challenging disease. Further research is needed to unravel the mysteries surrounding Kawasaki disease and develop more effective strategies for its prevention and management.

Table 2. Common signs and symptoms

SNo	Author	Fever	abdomial pain	diarrhea	heart diseases	enlarged lymph nodes
1	<u>Pragna Patel</u>	197/205 (96%)	95/199 (48%)	102/197 (52%)	present	29/187 (16%)
2	Pedram Keshavarz	46/133 (34.5%)	present	NA	present	NA
3	Debjyoti Dhar	NA	NA	present	NA	NA
4	Hsieh LE	present	NA	NA	NA	NA
5	<u>Seema Shah</u>	present	NA	present	NA	present





6	Claudio Confroti	present	NA	NA	NA	NA
7	<u>Kaiwei Liu</u>	present	NA	NA	present	29/187(16%)
8	<u>Sand Momtaz manah</u>	NA	NA	NA	NA	NA
9	K-H-LEE	100%	30/31(97%)	14/21(67%)	Present	5/30(17%)
10	<u>Yuyi Tang</u>	100%	84%	84%	NA	10-60%
11	Keren Paola Osorio- Mendea	NA	NA	NA	NA	NA
12	Ana Maria Jurca	present (88%)	NA	NA	present in 11pts(42%) [left ventricular dysfunction(26%) , atrioventricular valve regurgitation(30%%)	NA
13	Naim Ouldali, MD	NA	NA	NA	NA	NA
14	<u>V.O. Bitsadze</u>	NA	NA	NA	NA	present
15	<u>Anthony Zara</u>	NA	NA	NA	present	NA
16	Debjoyti Dhar	NA	NA	NA	present	NA

17	Francesca Sperotto	present	present	present	present	NA
18	Mohamma d Javad Hosseini	Present	NA	NA	NA	NA
19	M. Verheyden	present (upto 38.7°C)	present	NA	NA	NA
20	<u>Yifan Que</u>	high	NA	NA	NA	NA
21	<u>Tong Tong</u>	NA	NA	NA	NA	NA
22	<u>Eman A Toraih</u>	present (82.4%)	present (79.4%)	present (79.4%)	NA	acute nonpurulent cervical lymphadenopathy(28.5%)
23	<u>Kalai Wong</u>	NA	present	NA	NA	present



24	<u>Parham Mardi</u>	Present	NA	NA	Present	NA
25	<u>Ummusen Kaya Akca</u>	Present	NA	NA	NA	NA
26	<u>Monica O. Santos</u>	Present	present	present	present	NA
27	<u>Loubna Lamrani</u>	NA	Present	Present	NA	NA
28	<u>Ji-Gan Wang</u>	Present (99.91%)	NA	NA	Present	NA
29	<u>Raúl Bustos B</u>	present	NA	NA	NA	NA
30	<u>Gianluigi Li Bassi</u>	NA	NA	NA	Present (chronic cardiac disease)	NA
31	<u>Kamyar Nasiri</u>	Present	Present	Present	Present	Present
32	<u>Li Jiang</u>	Present	Present	Present	Present (mitral regurgitation)	Present (cervical lymphadenopathy)
33	<u>Silvia Ruvinsky</u>	Present	Present (47%)	Present (60%)	Present	Present (6%)
34	<u>Mohamed Sabbour</u>	Present (98%)	Present (N=557, 83)	Present (N=557, 83%)	Present	Present (mesenteric or mediastinal lymphadenopathy)
35	<u>Somayeh Jafrasteh</u>	present	present	present	NA	NA
36a	<u>Sunreet Randhaw</u>	NA	NA	present	present	present
37	<u>Ruwaa Samarrai</u>	NA	NA	NA	NA	NA
38	<u>Arianna Dondi</u>	NA	NA	NA	NA	NA

Abel						
39 Emanuel Moca	present	NA	NA	NA	NA	NA

Diagnosis

Regarding the correlation between COVID- 19 and Kawasaki illness, a clinical diagnosis can be made based on certain criteria.

Gathering case history involves asking about the main grievances, their characteristics, and how long they have persisted. Frequent patient presentations include fever (64%), rash, conjunctivitis, tachycardia, hypertension (25%) or shock, dyspnea (25%), diarrhea (41%), vomiting (25%).

Oropharyngeal hyperemia and lip or tongue symptoms are frequently seen. There may also be neurological symptoms, such as weariness, headaches, and changes in mental state.

Testing abnormalities include anemia, leukocytosis, neutrophilia, ferritin and fibrinogen elevated, lymphopenia elevated (60-85%), interleukin elevated, high levels of several enzymes and markers of inflammation and cytokine activation, as well as markers indicating



coagulopathy or disseminated intravascular coagulation.

These findings are used to make a laboratory diagnosis. Furthermore, a sizable portion of cases show positive findings from serological testing for COVID-19 and confirmatory testing using RT-PCR. Reports on blood tests for patients indicate raised D-

dimer levels, hematological abnormalities such as neutrophilia and lymphopenia, and increased inflammatory markers (C reactive protein). It is also discovered that there are aberrant levels of biomarkers for cardiac dysfunction, such as pro-brain natriuretic peptide and troponin. Numerous studies' results indicate that elevated levels of specific biomarkers, such as troponin, B-type natriuretic peptide, and C-reactive protein, are frequently observed in COVID- 19 patients. Most

individuals had lymphopenia, or a reduction in specific types of white blood cells. D-dimer and ferritin levels were also frequently reported to be elevated.

Abnormalities on their chest imaging, such as opacities or infiltrates. In certain cases, echocardiography showed a lower left ventricular ejection fraction, which suggests heart failure. Inflammation of the heart muscle, known as myocarditis, was found in several of the patients. A large proportion of patients had myocarditis, or inflammation of the heart muscle. Furthermore, some of the patients developed coronary artery dilatation or aneurysm. RT-PCR testing and serology were used to confirm COVID-19 infection; a significant proportion of individuals tested positive for the virus or had antibodies against it.

Table 3a. Lab Values

SNo	Author	lymphopenia	interleukin	ferritin	fibrinogen	C-reactive protein
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1	<u>Pragna Patel</u>	94/109 (86%)	61/62 (98%)	150/165 (91%)	93/102 (91%)	176/195 (90%)
2	Pedram Keshavarz	NA	present 412.2+-82.5	present 1036.6+-108.3	NA	present 226.5+-12.4
3	Debjyoti Dhar	NA	NA	NA	NA	NA
4	Hsieh LE	NA	NA	82-1441	NA	0.8-31.3
5	<u>Seema Shah</u>	NA	NA	not reported or normal	NA	normal
6	Claudio Confroti	NA	NA	NA	elevated	elevated
7	<u>Kaiwei Liu</u>	NA	NA	NA	NA	75.40%
8	<u>Sand Momtaz manah</u>	NA	NA	70.30%	NA	146-253 mg/L(Increased)
9	K-H-LEE	NA	NA	elevated	6.67±1.70(33)	NA
10	<u>Yuyi Tang</u>	Elevated	NA	abnormal 86%	NA	NA
11	Keren Paola Osorio- Mendea	NA	NA	NA	NA	NA
12	Ana Maria Jurca	NA	NA	NA	NA	NA



13	Naim Ouldali, MD	NA	NA	NA	NA	NA
14	V.O. Bitsadze	NA	NA	NA	NA	NA
15	Anthony Zara	NA	NA	NA	NA	NA
16	Debjyoti Dhar	NA	NA	NA	NA	NA
17	Francesca Sperotto	present	elevated (IL- 6)	elevated	elevated	elevated
18	Mohammad Javad Hosseini	NA	NA	NA	NA	elevated
19	M. Verheyden	elevated	NA	elevated	NA	elevated
20	Yifan Que	NA	NA	elevated	NA	NA
21	Tong Tong	NA	NA	NA	NA	NA
22	Eman A Toraih	mean=0.93×10 <sup>9</sup> /L	elevated-mean=189.67	elevated mean =763.24 ng/mL	elevated- mean =763.24 ng/mL	elevated-mean = 215.58 mg/L

23	Kalai Wong	NA	NA	NA	NA	NA
24	Parham Mardi	present	NA	Elevated	NA	Elevated
25	Ummusen Kaya Akca	present	NA	Elevated	NA	Elevated
26	Monica O. Santos	NA	NA	NA	NA	NA
27	Loubna Lamrani	NA	Elevated	NA	NA	20.8 ± 14.8
28	Ji-Gan Wang	elevated(61.5 1%)	elevated(89. 3%)	elevated( 90%)	elevated (87.01%)	elevated (98.5%)
29	Raúl Bustos B	Present	NA	elevated	NA	elevated
30	Gianluigi Li Bassi	NA	NA	NA	NA	0:7-1.4 mg/dl
31	Kamyar Nasiri	NA	NA	NA	NA	NA
32	Li Jiang	NA	NA	Elevated	Elevated	Elevated
33	Silvia Ruvinsky	Lower	Elevated	Elevated	NA	Elevated



34	Mohamed Sabbour	Elevated	Elevated	Elevated	NA	Elevated (78%)
35	Somayeh Jafrasteh	NA	NA	NA	NA	NA
36	Sunreet Randhawa	Present	NA	elevated	NA	NA
37	Ruwaa Samarrai	NA	NA	NA	NA	NA
38	Arianna Dondi	NA	NA	NA	NA	NA
39	Abel Emanuel Moca	NA	NA	NA	NA	NA

Table 3b. Lab Values

SNo	Author	BNP	D-dimer	markers of coagulopathy	N-pro BNP
1	<u>Pragna Patel</u>	56/76 (74%)	138/151 (91%)	176/195 (90%)	53/59 (90%)
2	Pedram Keshavarz	NA	NA	NA	NA
3	Debjyoti Dhar	NA	NA	NA	NA
4	Hsieh LE	10-2590	1.31-12.77	NA	NA
5	<u>Seema Shah</u>	NA	elevated or not reported	normal pr not reported	NA
6	Claudio Confroti	NA	elevated	elevated	NA
7	<u>Kaiwei Liu</u>	NA	NA	NA	NA
8	<u>Sand Momtaz manah</u>	3.354-5.743 pg/ml (Elevated)	2.060-5.208 (increased)	NA	46.50%
9	K-H-LEE	NA	NA	NA	NA
10	<u>Yuyi Tang</u>	NA	NA	NA	elevated
11	Keren Paola Osorio-Mendea	NA	NA	NA	NA
12	Ana Maria Jurca	NA	NA	NA	NA
13	Naim Ouldali, MD	NA	NA	NA	NA
14	<u>V.O. Bitsadze</u>	NA	NA	NA	NA



15	<u>Anthony Zara</u>	NA	NA	NA	NA
16	<u>Debjyoti Dhar</u>	NA	NA	NA	NA
17	<u>Francesca Sperotto</u>	NA	elevated	NA	NA
18	<u>Mohammad Javad Hosseini</u>	NA	NA	NA	NA
19	<u>M. Verheyden</u>	NA	elevated	NA	NA
20	<u>Yifan Que</u>	NA	NA	NA	NA
21	<u>Tong Tong</u>	NA	NA	NA	NA
22	<u>Eman A Toraih</u>	elevated	elevated-mean=3.79 µg/mL	elevated	elevated mean = 5648.78 pg/mL
23	<u>Kalai Wong</u>	NA	NA	NA	NA
24	<u>Parham Mardi</u>	Elevated	NA	NA	NA
25	<u>Ummusen Kaya Akca</u>	Elevated	Elevated	NA	NA
26	<u>Monica O. Santos</u>	NA	NA	NA	NA
27	<u>Loubna Lamrani</u>	Elevated	Elevated	NA	Elevated
28	<u>Ji-Gan Wang</u>	NA	NA	NA	Elevated (89.7%)

29	<u>Raúl Bustos B</u>	NA	elevated	NA	NA
30	<u>Gianluigi Li Bassi</u>	NA	0.8-4.7 mg/l	NA	NA
31	<u>Kamyar Nasiri</u>	NA	NA	NA	NA
32	<u>Li Jiang</u>	NA	Elevated	NA	Elevated
33	<u>Silvia Ruvinsky</u>	Elevated	Elevated	NA	NA
34	<u>Mohamed Sabbour</u>	Elevated	Elevated	NA	NA
35	<u>Somayeh Jafrasteh</u>	NA	NA	NA	NA
36	<u>Sunreet Randhawa</u>	NA	elevated	NA	NA
37	<u>Ruwaa Samarrai</u>	NA	NA	NA	NA



38	Arianna Dondi	NA	NA	NA	NA
39	Abel Emanuel Moca	NA	NA	NA	NA

### Management and Treatment

The management and treatment of Kawasaki disease (KD) associated with COVID-19, or Multisystem Inflammatory Syndrome in Children (MIS-C), follows the general principles of treating KD along with COVID-19 where combinations of medication and therapies are done.

Early recognition and diagnosis of KD associated with COVID-19 is needed for timely management which includes attention for symptoms of KD such as prolonged fever, conjunctivitis, rash, and mucous membrane changes<sup>(19)</sup>.

Multidisciplinary care involving pediatric rheumatologist, infectious disease specialists, cardiologist and critical care teams should be provided for comprehensive evaluation and management of KD associated with COVID-19<sup>(19, 20)</sup>.

Immunomodulatory therapy such as Intravenous immunoglobulin (IVIGs)<sup>(19, 20, 21, 22, 23)</sup> corticosteroids<sup>(19, 20, 24)</sup> and biological agents have been employed in the management and treatment. IVIGs and corticosteroids is the primary treatment for KD and is also utilized for MIS-C based on severity of case. Most of the patients were treated with IVIG and if inflammatory markers persisted, steroids were added<sup>(24)</sup>. IVIG administration requires slower infusion to reduce the risk of fluid overload<sup>(21)</sup>. It has been demonstrated to decrease the risk of coronary artery abnormalities and improve patient outcomes, whereas, if inflammatory markers persist after IVIG treatment then additional corticosteroids are considered which further suppresses the inflammatory response.

Biological agents such as anakinra (anti-IL-1) or tocilizumab (anti-IL-6)<sup>(24)</sup> can be given for the patient with persistent fever and elevated inflammatory markers to mitigate the inflammatory process<sup>(24)</sup>.

Children presenting with hemodynamic instability may require acute resuscitation and pediatric resuscitation guidelines as a Cardiac support. Those with ventricular dysfunction and cardiogenic shock may require smaller fluid boluses and evaluation of signs of fluid overload before each administration<sup>(21)</sup>.

Medication like combination of antibiotics (ampicillin-sulbactam and azithromycin), antiviral medication (oseltamivir) and hydroxychloroquine, lopinavir/ ritonavir, aspirin or clexane, and acetylsalicylic acid therapy before discharge is provided<sup>(23)</sup>.

Other supportive care encompasses various measures such as fluid management therapy, oxygen therapy, respiratory support<sup>(24)</sup> and plasmapheresis<sup>(20)</sup>.

Careful exclusion of other etiologies including cutaneous manifestations, with other conditions, is important for accurate diagnosis and appropriate management. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) has been proposed as a biomarker for the diagnosis of Kawasaki disease and may be useful in identifying incomplete Kawasaki disease in children<sup>(22)</sup>. Close monitoring for cardiac complications, including coronary artery aneurysms, is essential and long term follow-up is often recommended to assess the resolution of vasculitis and to monitor for potential late sequelae<sup>(20)</sup>.

Overall, it is important to note the management and treatment of KD associated with COVID-19 requires medicine strategies, therapies, long-term follow-up and management should be individualized based on the patient's clinical presentation severity of illness.

### Prognosis

Kawasaki disease is a condition which has definite management and treatment plans, making it a disease with excellent prognosis but in the absence of coronary artery disease. Patients with underlying heart disease seem to be a vulnerable population at high risk if they contract COVID-19.

The prognosis of Kawasaki disease depends on the early diagnosis and treatment plan.

Younger patients have longer prodromal periods and better outcomes than the older age group. Prognosis is associated with initial RT-PCR and serological testing for COVID-19 and CSF culture for Kawasaki disease and severity of fever and rashes.

According to the CDC, if a patient does not develop a coronary artery aneurysm, they will recover fully. The mortality from Kawasaki disease



is less than 0.5% with the highest risk in the first year after disease onset.

## V. CONCLUSION

Our case review systematically summarized and evaluated the clinical signs and symptoms, treatment and prognosis of the patients with Kawasaki disease and its potential link to COVID-2019. Based on the currently limited data, we concluded that the incidence of children presenting with a severe inflammatory syndrome like Kawasaki disease, with fever and gastrointestinal symptoms as the primary symptoms and multisystem involvement, particularly cardiovascular systems are increased during the COVID-19 pandemic. To differentiate COVID-19 symptoms and KD symptoms, recent guidelines recommend additional testing such as PCR testing of SARS-COV-2, serological test and inflammatory markers. It is important to note the management and treatment of KD associated with COVID-19 requires medicine strategies, therapies, long-term follow-up and management should be individualized based on the patient's clinical presentation severity of illness. Multidisciplinary care should be provided for comprehensive evaluation and management of KD associated with COVID-19 and further research to explore the possible causal correlation between Kawasaki disease and COVID-19 are urgently needed.

## Limitations

Several limitations needed to be noted in this meta-analysis. To begin with, the results were possibly impacted by potential

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- [4]. confounding factors. We extracted median from included studies when they were available and calculated mean when only raw data was accessible. Our meta-analysis was limited to publications written in English and there is the possibility of unidentified articles in other databases.
- [5]. Also, we did not include unpublished literature. Large heterogeneity was found in this meta-analysis, which may derive from characteristics of population, study design, measurement of age at diagnosis, seasons and country.
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The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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#### **Author's Contribution**

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.