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Letter to the editor

Kawasaki or Kawasaki-like disease? A debate on COVID-19 infection in children

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ABSTRACT

Kawasaki disease (KD) is an inflammatory syndrome which is generally observed among children. Considering the significant number of COVID-19-positive children presenting with the manifestations of typical/atypical KD, it has been mentioned as a possible complication of COVID-19 infection among the children. However, many of the reported cases do not completely fill the clinical diagnostic criteria, which has made some researchers use the term "Kawasaki-like disease" instead of KD for this state. The current manuscript aims to review the key studies in the field, address the ongoing conflict, and indicate the objective requirements of the further studies.

Dear Editor,

Kawasaki disease (KD) is a form of vasculitis, usually observed among children less than five years old, which affects the middle-sized arteries. Since the delay in diagnosis of KD leads to life-threatening complications, such as coronary artery abnormalities, valvular heart diseases, Kawasaki disease shock syndrome (KDSS), and macrophage activation syndrome (MAS), an early and accurate diagnosis of KD is vital. For this purpose, diagnostic criteria have been introduced to clinically define KD, including the presence of fever for five days or more, along with at least four of the following five features [1]:

1. Conjunctivitis: Bilateral, dry, and painless
2. Cervical lymphadenopathy: Unilateral, tender, and over 1.5 cm
3. Polymorphous exanthema: Rash through trunk and extremities
4. Mucosal changes: Including strawberry tongue, hyperemia of lips, or erythema of oropharynx
5. Changes in extremities: From erythema and painful edema to desquamation

A fever of fewer than five days, accompanied by two or three of the mentioned criteria is considered as incomplete (atypical) KD [1]. Also, the diagnosis could be confirmed with less than four features, if coronary artery aneurysm is present.

Since the declaration of COVID-19 pandemic, there have been numerous reports of COVID-19-positive children, presenting with typical/atypical KD manifestation. Since the KD is unknown in etiology, SARS-CoV-2 has been considered to be a cause for KD among children [2]. In general, even the number of patients presenting with clinical manifestations of KD are dramatically increased; for example, a rise of 497% in KD patients was observed in a hospital in France during the previous months [3]. However, many of the reported cases do not completely fill the clinical diagnostic criteria. Therefore, some researchers have suggested the term "Kawasaki-like disease" instead of KD. Similarly, there have been novel explanations too. Diorio et al. assessed the data of twenty-four patients with positive SARS-CoV-2 RT-PCR or serum immunoglobulin G, and observed that the children infected with SARS-CoV-2 might not show the signs and symptoms of COVID-19, but develop the clinical features of so-called, Multisystem Inflammatory Syndrome in Children (MIS-C); suggesting that MIS-C and COVID-19 are different and separate presentations of infection with SARS-CoV-2 [4]. Although the reports of patients with both MIS-C and COVID-19 manifestations make this hypothesis less likely, the essence of the fact that SARS-CoV-2 could result in such complications cannot be ignored [5]. Table 1 presents some of the main studies reporting COVID-19-positive children with clinical features in favor of KD.

As seen, there is excessive conflict regarding this issue. Although substantial evidence suggests that the present condition may be different from other pediatric inflammatory disorders, we still cannot draw a precise line between them and separate similar disorders assuredly [6]. Since the diagnosis of KD is exclusively based on clinical judgement, large-scale studies are best tools to define the current inflammatory disorder or even improve the previous definition of KD, as they benefit from a greater population, along with an integrated and equivalent clinical evaluation of patients.

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Declaration of Competing Interest

The author declares no competing interests.

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Appendix A

Table 1
Main studies reporting COVID-19-positive patients with clinical features in favor of KD.

Author (Country)	Study population	Patients presented with KD/ KLD/MIS-C, with laboratory-confirmed COVID-19 diagnosis (PCR, IgG)	Mean age (Range)	Sex (Female: Male)	Confirmed infected patients with complete classic criteria of KD*	Notes		
						Clinical presentations of classic KD in patients	Other significant clinical presentations	Laboratory features
Chiotos et al. (USA) [7]	6	6	8.5 (5y-14y)	5:1	0	None of the patients presented with the classic KD. All patients presented with prolonged fever. Also, fissured lips/strawberry tongue was observed in half of the patients. Fever was present mostly for 5–6 days. Initial echocardiography showed low ventricular function in 4 patients, which were all normal in the final echocardiography. One patient was reported with coronary artery dilation.	Abdominal pain (5/6), diarrhea (4/6), and neurological symptoms, including headache, altered mental status, irritability (4/6) were the most common. Acute kidney injury (serum creatinine $\geq$ x1.5 upper limit of normal) was reported in 4 patients. One patient had cerebral edema on head CT. Five out of 6 patients were in need of mechanical ventilation.	All patients had elevated levels of CRP and procalcitonin. Elevated levels of ferritin (5/6), BNP (5/6), D-dimer (5/6), leukocyte count (4/6), lactate dehydrogenase (3/6), troponin (2/6) were observed among the patients. All patients had hyponatremia, and lymphocytopenia and thrombocytopenia were present in four and two patients, respectively.
de Farias et al. (Brazil) [8]	23	11	6.03 (7 m-11y)	2:9	4	Duration of fever was variable from 4 to 23 days. Abnormal echocardiography (mild and medium aneurysms) was reported in 7 patients.	Multi-organ dysfunction (2 or more organs) was reported in all patients. Two deaths were reported, which were related to neurologic and respiratory comorbidities, being underweight, and toxic shock syndrome. Seven out of 11 patients were in need of mechanical ventilation	Hypofibrinogenemia, hypoalbuminemia, hyperlactatemia, elevated CRP, and elevated D-dimer levels were observed in all patients (11/11). Ferritin and troponin levels were elevated in 7 of 11 patients. Lymphocytopenia was observed in 7 patient and lymphocytosis in one patient.
Heidemann et al. (USA) [9]	3	3	6 (5y-7y)	1:2	1	Prolonged fever was observed in 2 of 3 patients. Echocardiography showed decreased left ventricular function in all patients. Dilation was reported in one patient in the left coronary artery and the proximal left anterior descending coronary artery.	Abdominal pain and hypotension were reported in all patients. Tachycardia was reported in 2 patients. One patient had an experience of 1-min syncope, and one other had lethargy at the time of admission. Diarrhea, vomit, chest pain, and difficulty in breath were present in one of the patients. Two of the 3 patients were in need of mechanical ventilation.	Hyponatremia and lymphocytopenia were reported in all patients, along with elevated levels of CRP, ferritin, and troponin. Elevated levels of fibrinogen, D-dimer, and leukocyte count were reported in two patients. Hypochloremia was reported in one patient.
Ouldali et al. (France) [3]	10	8	10.2 (1.5y-15.8y)	6:4	6	Abnormal echocardiography was reported in 6 patients; Myocarditis was present in 5 patients, pericarditis in one patient, and coronary dilation in one patient.	Four patients developed KDSS. Six patients were admitted to PICU. Length of hospital stay varied from 4 days to 27 days (mean: 13.1). No data is available on	Elevated levels of CRP and low sodium concentration were observed among the patients. Aspartate aminotransferase and alanine aminotransferase concentrations were normal. Thrombocytosis

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Table 1 (*continued*)

Author (Country)	Study population	Patients presented with KD/KLD/MIS-C, with laboratory-confirmed COVID-19 diagnosis (PCR, IgG)	Mean age (Range)	Sex (Female: Male)	Confirmed infected patients with complete classic criteria of KD*	Notes		
						Clinical presentations of classic KD in patients	Other significant clinical presentations	Laboratory features
						No other data is presented on KD-related clinical symptoms	the clinical symptoms at the time of admission. None of the patients was in need of mechanical ventilation.	was observed among the patients (no further information reported).
Shahbaznejad et al. (Iran) [10]	10	6	5.37 (13 m-12y)	4:6	1	Mean of fever presence was 9.4 days (ranging from 6 to 12 days) among all patients. Skin rash was the most common KD-related clinical symptom (8/10). Echocardiography was performed for all patients, and abnormal coronary artery (3/10) and low cardiac ejection fraction (3/10) were recorded.	Gastrointestinal symptoms (vomit, abdominal pain, diarrhea) were present in 9 of 10 patients. Pleural effusion and intra-abdominal fluid were present in four and five patients, respectively. Two patients developed acute kidney injury. Mean of total hospital stay was 11 days (ranging from 3 to 24 days).	CRP > 10 mg/L was reported in all patients. Lymphocyte count <1000/μL was reported in 8 of 10 patients, hemoglobin <10 g/dL was reported in 8 of 10 patients, platelet count <100,000/μL was reported in 3 of 10 patients, ESR > 30 mm/h was reported in 9 of 10 patients, and albumin <3 g/dL was reported in 8 patients.
Toubiana et al. (France) [11]	21	19	NA (Median: 7.9)	12:9	11	Median of fever among the 21 patients was five days. Conjunctival injection, rash, and oral cavity/lip changes were the most common among the patients with complete KD. Dilation of coronary arteries was observed in 5 out of 21 patients. No aneurysm was reported.	Gastrointestinal symptoms were present in all patients. Neurological manifestations were observed in 18 of 21 patients. Myocarditis and serous effusion were present in 16 and 12 of 21 patients, respectively. Eight patients of 21 had abnormalities in chest radiography/CT, including ground-glass opacity, local patchy shadowing, and interstitial abnormalities. Eleven of 21 patients were in need of mechanical ventilation.	An increase in levels of the following laboratory findings was reported among the study population: White blood cell count, neutrophil count, platelet count, procalcitonin, interleukin-6, and alanine aminotransferase. Meanwhile, levels of albumin, sodium concentration, lymphocyte count and hemoglobin were decreased.
Verdoni et al. (Italy) [12]	10	8	7.45 (2.9y-16y)	3:7	5	Abnormal echocardiography was reported in 6 patients. Two patients were reported with aneurysm, and pericardial effusion was reported in four patients.	KDSS was observed in five patients, all with hypotension and mostly (4/5) with peripheral hypoperfusion.	Compared with normal values, the following variables were increased: Ferritin (9/10, considering the 140 ng/mL as upper normal limit), ESR (8/10), and troponin (5/10). Meanwhile, hyponatremia and thrombocytopenia were observed in 8 patients. A mean lymphocyte count of 0.86×10^9/L, mean AST level of 87 IU/L, mean fibrinogen level of 621 mg/dL, and mean ProBNP level of 1255 ng/L were reported. Also, blood culture was obtained, which was sterile in all patients.

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Table 1 (*continued*)

Author (Country)	Study population	Patients presented with KD/ KLD/MIS-C, with laboratory-confirmed COVID-19 diagnosis (PCR, IgG)	Mean age (Range)	Sex (Female: Male)	Confirmed infected patients with complete classic criteria of KD*	Notes		
						Clinical presentations of classic KD in patients	Other significant clinical presentations	Laboratory features
Whittaker et al. (UK) [13]	58	45	NA (Median: 8)	3:10	8 (13)**	Other than fever, the most common symptoms of classic KD among the patients were conjunctival injection (11/13), and rash (10/ 13). Coronary artery aneurysm was observed in 3 of 13 patients.	Shock (25/45, defined as needing inotrope support or fluid resuscitation over 20 mL/kg), diarrhea (25/ 45), and abdominal pain (24/45), were the most common. Vomit was another common gastrointestinal manifestation (20/ 45). Neurological complications of headache (13/45) and confusion (5/45) were also significant. Acute kidney injury was reported in 13 patients. One death was reported among the patients. Twenty of the 45 patients were in need of mechanical ventilation.	The following values were increased: Leukocyte count, Neutrophile count, CRP, Ferritin, Lactate dehydrogenase, troponin, NT-ProBNP, and the coagulation markers of fibrinogen and D-dimer. Lymphocyte count, platelet count, hemoglobin, and albumin were decreased among the patients.

AST = aspartate transaminase. BNP = brain natriuretic peptide. COVID-19 = coronavirus disease-2019. CRP = c-reactive protein. CT = computed tomography. ESR = erythrocyte sedimentation rate. IgG = immunoglobulin G. KD = Kawasaki disease. KDSS = Kawasaki disease shock syndrome. KLD = Kawasaki-like disease. MIS-C = multisystem inflammatory syndrome in children. NA = not available. NT-proBNP = N-terminal pro-brain natriuretic peptide. PCR = polymerase chain reaction. PICU = pediatric intensive care unit. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Classic criteria of KD are presented in the main text.

** Thirteen patients had the classic definition of KD, 8 of which were laboratory-confirmed infected. The data were reported among the 13 patients.

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Mohammad-Salar Hosseini[a,b,*]

[a] *Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*

[b] *Student Research Committee, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*

[*] Corresponding author at: Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Golgasht Street, 5166/ 15731 Tabriz, EA, Iran.

E-mail address: hosseini.msalar@gmail.com.