Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. May 2020.(1)

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BACKGROUND – THE STUDY QUESTION?	
Background	• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that is highly contagious, spreads rapidly. In adults, the illness is characterized by severe interstitial pneumonia while in children the respiratory involvement causes a more benign illness with rare mortality and causes mild to severe respiratory illness (COVID-19), including pneumonia and acute respiratory distress syndrome (2). • At least 10% of the Italian population had been exposed to the SARS-CoV-2 virus with the city of Bergamo having the highest rate of infections and deaths in the country, hindering this city a natural epidemiological setting. Traditionally, common human coronaviruses had been isolated in up to 6% and 8% of children in a hospital and ambulatory setting, respectively (2). • Kawasaki disease is an acute, vasculitis with specific predilection for the coronary arteries that affects previously healthy young infants and children. To this date, the cause of this disease remains unknown but evidence suggest that an infectious trigger is likely to be a contributing case(3) • Notably, the incidence of the disease varies according the geographical location. Northeastern Asian countries have a 10-30 times higher incidence of KD than in North America and Europe. For instance it is 308 cases per 100,000 children in Japan compared to 14.7 cases per 100,000 children in Italy(4). • In fact, past studies has suggested that coronavirus family might represent one of the triggers of Kawasaki disease with SARS-CoV-2 being a particularly virulent strain able to elicit some powerful immune response in the host.
Previous trials	• The association between two other coronaviruses (HCoV-NL63 and HCoV-229E) and Kawasaki disease had been investigated by serological tests and found that HCoV-229E antibody positivity was higher in patients with Kawasaki disease. Nevertheless, the immunofluorescence assay detected no difference in HCoV-NL63 antibody positivity between patients with the disease and controls.(3) Another coronavirus (HCoV-New Haven (NH) from the same species as HCoV-NL63) was associated with Kawasaki disease in 73% of patients (i.e., 8 of 11 patients were PCR positive for HCoV-NH) compared to less than 5% of control patients (5). However, in a subsequent study from Taiwan all 53 pediatric patients with Kawasaki disease had negative PCR results for both HCoV-NL63 and HCoV-NH (6). • Human bocavirus and enterovirus have significant correlations with monthly patterns of KD occurrence (p=0.032 and p=0.007, respectively) and influenza virus correlated with KD occurrence with borderline significance (p=0.063). Interestingly, coronaviruses was not well correlated with KD occurrence; r2=0.115 (p=0.505)(7).

	• While there is no evidence to suggest that HCoV infection can cause heart injury, myocardial injury caused by coronavirus infection is one of the main factors contributing to poor prognosis(3,7).	
Why this study?	• To describe the incidence and features of Kawasaki-like disease presenting in the COVID-19 era. Therefore, epidemiological areas with COVID-19 should be be diligent about diagnosis and management of this disease if a correlation was in fact, proven.	
Null Hypothesis	• There is no difference in incidence or features of Kawasaki-like disease after COVID-19 pandemic compared to before	
GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	There was no funding source for this study	•
Trial design	• Retrospective, cohort, single center study	• As this is not a multi-center study and does not extend to a larger epidemiological area, several cofounders can be contributing to the assumed correlation
Objectives	• To determine if the incidence and features of Kawasaki disease had been impacted by the COVID-19 pandemic	
Enrollment	• Patients diagnosed with Kawasaki disease per the 2017 American Heart Association Guideline including both classic and incomplete types or Kawasaki disease shock syndrome (KDSS) or macrophage activation syndrome (MAS) per stated criteria from a single tertiary academic medical center in Italy • Patients were enrolled for the study between January 1, 2015 to April 20, 2020	• Clinical criteria based on the most current American Heart Association Guidelines were used to constitute epidemiological case definition of Kawasaki disease. Principal clinical features as well as additional laboratory and echocardiographic findings supported the diagnosis of Kawasaki disease (i.e., incomplete Kawasaki disease). While there is no diagnostic test available, criteria for diagnosis is standardized and credible. ,. Several pediatric illnesses can manifest with Kawasaki-like symptoms such as like toxic shock syndrome, streptococcal scarlet fever, Stevens-Johnson syndrome, systemic-onset juvenile idiopathic arthritis to name a few. It is not possible to definitely exclude a relationship between the corona viruses and these disorders.

		• The period of time to differentiate between group 1 and 2 was appropriate and suitable for the peak of the pandemic in the targeted geographical location
METHODS		
Inclusion criteria	• Pediatric population • Diagnosed with Kawasaki disease, Kawasaki disease shock syndrome (KDSS) or macrophage activation syndrome (MAS)	• Although its general common knowledge that pediatric population are all patients who are less than 18 years of age, a direct age cut off was not stated in the paper.
Exclusion criteria	• None stated	• Would have been helpful to exclude patients who have been diagnosed in the past with some illness that mimic Kawasaki disease such as toxic shock syndrome, streptococcal scarlet fever, Stevens-Johnson syndrome, systemic-onset juvenile idiopathic arthritis
Interventions	• No intervention was used in this study: non applicable	• This is acceptable as this study was done to determine a correlation between an exposure and outcome rather than an experimental intervention
Monitoring	• No intervention was used in this study: therefore no monitoring parameters: non applicable	• This is acceptable as this study was done to determine a correlation between an exposure and outcome rather than an experimental intervention

Primary Endpoints	• The incidence of Kawasaki disease measured as number of cases per month	• Incidence is a suitable epidemiological measure as it correlated the number of cases within a specific time period which is appropriate for a pandemic peak. A figure provided by authors have also demonstrated the incidence per trimester. • Would have been helpful to elaborate more in the method section on “incidence corrected for number of patients seen in the emergency department” as well as methods to “rule out the possible effect of change in the geographical catchment area in the prepandemic”
Secondary Endpoints	• Features of Kawasaki disease	• The authors included defined quantitative criteria for features of the disease such as fever, mucositis, rash, extremity changes, lymphadenopathy, cardiovascular findings, arthritis, CRP, ESR, WBC, ferritin, lymphocytes as well as treatment that may impact outcomes such as IVIG and steroids

Statistical analyses	• The Student's *t* test, the χ2 method, and Fisher's exact test were done when appropriate for statistical analysis to compare continuous and categorical variables. • A p value of <0·05 was chosen as cutoff for significance. Data were analysed with SPSS (version 20.0) and GraphPad Prism (version 5.00 for Mac).	• For such a small size, reporting medians rather than means and using Mann-Whitney test rather than student T test is mandated for better reporting of data variables particularly as it is not expected to be parametric within a pandemic • All statistical analyses were performed using an outdated version of SPSS
RESULTS		
Enrollment	• 29 total patients enrolled: 19 group 1 and 10 group 2	• Small sample size but impressive for such a rare disease. In addition, enrollment size is acceptable for the incidence documented in Italy (i.e. 15 cases per 100,000)

Baseline characteristics	• Group 1: from January 1, 2015 to February 17, 2020, 19 children (incidence 0・3 per month; seven boys, 12 girls, mean age 3 years [SD 2・5]) • Group 2: from February 18, 2020 to April 20, 2020, 10 children (incidence 10 per month; seven boys, three girls, mean age 7.5 years [SD 3・5]) • Statistical significance in the age of onset of Kawasaki-like illness 3.0 vs 7.5 years (p = 0.00035)	• The authors included defined quantitative criteria for features of the disease such as fever, conjunctivitis, etc as stated in the AHA guideline.
Primary Outcome	• The incidence of Kawasaki disease was higher in group 2 compared to group 1; 10 per month vs. 0.3 months (P< 0.00001)	• Although group 2 included 2 patients that have been included within the specified time restriction and period, they had tested negative for COVID-19 per all diagnostic criteria. Nevertheless, this was not an exclusion criteria for group 2.

Secondary Outcomes	Features of the disease: • The average age at onset was 3·0 years in group 1 versus 7·5 years in group 2 (p=0・0003). • The mean body-mass index of patients in group 1 was 15・93 kg/m2 versus 19・11 kg/m2 in group 2 (p=0・0016). • In group 1, 14 of 19 patients were white, versus eight of ten patients in group 2 (P=xx). • In group 1, WBC were higher than group 2; 19.4 versus 10.8 (P=0.0017) • In group 1, lymphocyte count was higher than group 2; 3 versus 0.86 (P=0.0012) • In group 1, platelets were higher than group 2; 96 versus 32 (P=0.0001) • In group 1, Kobayashi score equal to or higher 5 were lower than group 2; 70% versus 10% (P=0.0021) • In group 1, incidence of MAS was lower than in group 2; 0% versus 50% (P=0.021) • In group 1, incidence of KDSS was lower than in group 2; 0% versus 50% (P=0.021) • In group 1, abnormal echocardiography was lower than in group 2; 10% versus 60% (P=0.0089) • In group 1, adjunctive steroid treatment was lower than in group 2; 16% versus 80% (P=0.0045)	• Several features that are indicative of Kawasaki disease (ferritin, WBC, ESR, chestxray) are also well correlated with COVID-19 prognosis, therefore establishing a direct definitive relationship between the severity of illness of Kawasaki disease as opposed to COVID-19 is not possible. • Findings of more frequent KDSS, MAS, Kobayashi score as well as abnormal ECG in group 2 corresponds with observed finding of higher adjunctive steroid treatment use per AHA guidance of increased IVIG resistance risk. Adjunctive steroid use in group 1 corresponds to established rate (i.e., 10-20%) of IVIG resistance in patients with Kawasaki disease.
Adverse Effects	• Non applicable as this is not an intervention study	• This is acceptable as this study was done to determine a correlation between an exposure and outcome rather than an experimental intervention with possible adverse events

AUTHORS' CONCLUSIONS

- There was a 30-fold increase in the incidence of Kawasaki-like disease in children after COVID-19 (February, 2020) compared to children before the pandemic.
- Children diagnosed with Kawasaki-like disease after COVID-19 (February, 2020) showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, features of MAS, and had a higher incidence of a severe form of Kawasaki disease.

GENERALIZABILITY/CRITIQUE/DISCUSSION

- Even though some statistical significance was observed between the 2 groups, the small sample size is too small to draw conclusions and these criteria might demolish when extrapolated to a larger population with different geographical locations

- The incidence prior to the pandemic varies significantly among geographical locations, which suggests a complex collection of triggers and confounders to the disease itself that may be independent of COVID-19. In fact, it is possible that COVID-19 is a confounder between another biological trigger (exposure) and the ultimate outcome (Kawasaki disease). The results would be more credible had the authors included other geographical distinct areas, nevertheless; the authors have adjusted for that in the results in appendix 1.

- The features of Kawasaki disease can overlap with features of COVID-19 particularly for most diagnostic/lab variables. However, leukopenia, lymphocytopenia and thrombocytopenia were notably decreased among patients presenting during the local SARS-CoV-2 epidemic and are not classic laboratory findings for Kawasaki disease though have been observed in common human coronavirus infections (2).

- Given the above critique, particularly the small sample size and the single geographical location the ability to make meaningful conclusions concerning the incidence in the treatment of COVID-19 is severely limited. Emergence of similar patterns from the United Kingdom, United States, France, and Switzerland do provide further association between COVID-19 and Kawasaki-like illness, thus large-scale observational studies will be needed to address causal relationship of the diseases based on clinical, laboratory, and cardiovascular findings, as well as serologic testing (8-12).

References:

1. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet.

2. Zimmerman P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J 2020; 39:355-368.

3. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyama S, Taguchi F. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. Journal of medical virology. 2014;86(12):2146-53.. .

4. Kim GB. Reality of Kawsaki disease epidemiology. Korean J Pediatr 2019;62:292-296.

5. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. 2005a. AT Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 191:499–502

6. Chang LY, Chiang BL, Kao CL, Wu MH, Chen PJ, Berkhout B, Yang HC, Huang LM. 2006. Lack of association between infection with a novel human coronavirus (HCoV), HCoV-NH, and Kawasaki disease in Taiwan. J Infect Dis 193:283–286.

7 Zhao M, Wang M, Zhang J, Ye J, Xu Y, Wang Z, et al. Advances in the relationship between coronavirus infection and cardiovascular diseases. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2020;127:110230.

8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet 2020.

9. NYC Health. Pediatric multi-system inflammatory syndrome potentially associated with COVID-19. https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf. Accessed May 26, 2020.

10. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal B, et al. Hosp Pediatr 2020; doi: 10.1542/hpeds.2020-0123.

11. Deza Leon MP, Redzepi A, McGrath E, Abdel-Haq N, Shawaqfeh A, Sethuraman U, et al. J Pediatric Infect Dis Soc 2020; doi: 10.1093/jpids/piaa061.

12. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Circulation 2020; doi: 10.1161/CIRCULATIONAHA.120.048360.