An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

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Summary

Background The Bergamo province, which is extensively affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, is a natural observatory of virus manifestations in the general population. In the past month we recorded an outbreak of Kawasaki disease; we aimed to evaluate incidence and features of patients with Kawasaki-like disease diagnosed during the SARS-CoV-2 epidemic.

Methods All patients diagnosed with a Kawasaki-like disease at our centre in the past 5 years were divided according to symptomatic presentation before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic. Kawasaki-like presentations were managed as Kawasaki disease according to the American Heart Association indications. Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS) by the Paediatric Rheumatology International Trials Organisation criteria. Current or previous infection was sought by reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively.

Findings Group 1 comprised 19 patients (seven boys, 12 girls; aged 3·0 years [SD 2·5]) diagnosed between Jan 1, 2015, and Feb 17, 2020. Group 2 included ten patients (seven boys, three girls; aged 7·5 years [SD 7·5]) diagnosed between Feb 18 and April 20, 2020; eight of ten were positive for IgG or IgM, or both. The two groups differed in disease incidence (group 1 vs group 2, 0·3 vs ten per month), mean age (3·0 vs 7·5 years), cardiac involvement (two of 19 vs six of ten), KDSS (zero of 19 vs five of ten), MAS (zero of 19 vs five of ten), and need for adjunctive steroid treatment (three of 19 vs eight of ten; all p<0·01).

Interpretation In the past month we found a 30-fold increased incidence of Kawasaki-like disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. A similar outbreak of Kawasaki-like disease is expected in countries involved in the SARS-CoV-2 epidemic.

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Research in context

Evidence before this study
Kawasaki disease is an acute self-limiting vasculitis with specific predilection for the coronary arteries that affects previously healthy young infants and children. Despite half a century having passed since Kawasaki disease was first reported in Japan, the cause of this condition remains unknown. We did a PubMed database search to identify studies investigating the cause and pathogenesis of Kawasaki disease using the terms “Kawasaki disease”, “etiology”, “pathogenesis”, “intravenous immunoglobulin”, “corticosteroids”, “macrophage activation syndrome (MAS)”, and “KD shock syndrome”. All relevant articles were evaluated. The most accepted pathogenetic hypothesis supports an aberrant response of the immune system to one or more unidentified pathogens in genetically predisposed subjects. An infectious trigger, however, has not been identified.

Added value of this study
Shortly after the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to our region (Bergamo, Italy), we found a 30-fold increased incidence of Kawasaki disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. We therefore showed that SARS-CoV-2 might cause a severe form of Kawasaki-like disease.

Implications of all the available evidence
Outbreaks of Kawasaki-like disease might occur in countries affected by the SARS-CoV-2 pandemic, and might present outside the classic Kawasaki disease phenotype. This condition might be serious and requires prompt and more aggressive management. Future research on the cause of Kawasaki disease and similar syndromes should focus on immune responses to viral triggers.
troponin I, natural killer (NK) activity, and concentrations of interleukin 6 (IL-6). Electrocardiogram and echocardiogram were done in all children.

**Confirmation of SARS-CoV-2 infection**

Patients and caregivers had nasopharyngeal and oropharyngeal swab sampling, testing SARS-CoV-2 nucleic acid using reverse-transcriptase quantitative PCR assay; patients with a positive nasopharyngeal and oropharyngeal swab sampling test were considered confirmed cases of SARS-CoV-2 infection. The patients diagnosed more recently had a test for the qualitative detection of SARS-CoV-2 antibodies (IgM and IgG) through a lateral flow chromatographic immunoassay (NADAL COVID-19 IgG/IgM Test, Nal Von Minden, Moers, Germany). Positivity for IgM or IgG, or both, was considered consistent with an earlier infection with SARS-CoV-2.

**Treatment**

Risk of resistance to intravenous immunoglobulin treatment was ascertained according to the Kobayashi score. All patients were administered intravenous immunoglobulin at 2 g/kg. According to the RAISE study, based on risk stratification, patients were also treated with aspirin at 50–80 mg/kg per day (Kobayashi score <5) for 5 days or aspirin at 30 mg/kg per day plus methylprednisolone at 2 mg/kg per day for 5 days (Kobayashi score ≥5), followed by a tapering of methylprednisolone over 2 weeks. Aspirin was maintained until 48 h after defervescence, and then continued at an antiplatelet dose of 3–5 mg/kg per day for 8 weeks. The schedule for patients at risk of intravenous immunoglobulin resistance was adopted also in patients with KDSS or MAS. Response to treatment was defined as the normalisation of vital signs, CRP, and blood tests, and the resolution of symptoms and signs.

**Statistical analysis**

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). The study was approved by the Bergamo Ethics Committee (registration number 37/20, 25/03/2020).

**Role of the funding source**

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Between Feb 18 and April 20, 2020, ten patients (aged 7·5 years [SD 3·5]; seven boys, three girls), were diagnosed with Kawasaki disease (incidence ten per month), and comprised group 2. Admission to hospital occurred, on average, on day 6 of fever (range 4–8). Five (50%) patients presented with a classic form of the disease, and five (50%) presented with an incomplete form. Patients presenting with the classic form had non-exudative conjunctivitis, hand and feet anomalies (ie, erythema or firm induration, or both), and polymorphic rash. Four (80%) of five patients had associated changes of the lips or oral cavity, or both; patient 7 also had laterocervical lymphadenopathy (table 1).

In group 2, five (50%) of ten patients were diagnosed with incomplete Kawasaki disease, presenting with three or fewer clinical criteria associated with additional laboratory criteria (n=1) or an abnormal echocardiography (n=4). Two (20%) patients had bulbar non-exudative conjunctivitis; changes of the lips or oral cavity, or both; and polymorphic rash. One (10%) patient had only bulbar non-exudative conjunctivitis and polymorphic rash. In two (20%) patients, the echocardiography detected a left coronary aneurysm (>4 mm), reduced ejection fraction (48% and 40%), and mitral valve regurgitation; patient 1 also had pericardial effusion. Patient 2 met the diagnosis with four additional laboratory criteria (ie, hypoalbuminaemia, hypertransaminasemia, leucocytosis, and sterile pyuria).

Patients 4 and 5 diagnosed with incomplete Kawasaki disease, presented with non-exudative conjunctivitis associated with changes in the lips and oral cavity (patient 4), or polymorphic rash (patient 5). In these patients, echocardiography revealed left ventricular function depression, mitral valve regurgitation, and pericardial effusion; they also required inotropic support. Patient 4 had an underlying diagnosis of congenital adrenal hyperplasia.

Chest x-ray, done in all patients in group 2, was positive in five (50%) patients for minimal mono or bilateral infiltrates. Patients 1 and 10 had a chest CT and a confirmed bibasilar pulmonary thickening. Patients 2 and 7, who had meningeal signs, had an electroencephalogram that showed a slow wave pattern; patient 7 had a lumbar puncture revealing normal cerebrospinal fluid and the absence of SARS-CoV-2 in the cerebrospinal fluid.

Five (50%) of ten patients in group 2 met the criteria for KDSS because of hypotension and clinical signs of hypoperfusion. Two (20%) patients had diarrhoea and meningeal signs, four (40%) had only diarrhoea, and two (20%) had only meningeal signs (table 1). Mean ESR was 72 mm/h (SD 24), mean CRP 25 mg/dL (SD 15–3), and mean ferritin 1176 ng/mL (SD 1032). Full blood count showed a mean white cell count of 10·8×10⁹ per L (n=4). Two (20%) patients had bulbar non-exudative conjunctivitis and polymorphic rash. In two (20%) patients, the echocardiography detected a left coronary aneurysm (>4 mm), reduced ejection fraction (48% and 40%), and mitral valve regurgitation; patient 1 also had pericardial effusion. Patient 2 met the diagnosis with four additional laboratory criteria (ie, hypoalbuminaemia, hypertransaminasemia, leucocytosis, and sterile pyuria).

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Table 1: Clinical and laboratory features of ten patients with Kawasaki-like disease who presented over 1 month during SARS-CoV-2 epidemic (group 2)

| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Date of onset | March 17, 2020 | March 27, 2020 | March 28, 2020 | April 3, 2020 | April 3, 2020 | April 4, 2020 | April 4, 2020 | April 6, 2020 | April 10, 2020 | April 11, 2020 | April 14, 2020 |
| Age, years | 8·2 | 7·0 | 2·9 | 7·7 | 7·5 | 16·0 | 5·0 | 9·2 | 5·5 | 5·5 |
| Sex | Male | Male | Female | Female | Male | Male | Male | Male | Male | Male |
| Type of Kawasaki disease | Incomplete | Incomplete | Incomplete | Incomplete | Classic | Classic | Classic | Incomplete | Classic | Classic |
| Other symptom | Diarrhoea, meningeal signs | Diarrhoea, meningeal signs | Diarrhoea | Diarrhoea | Diarrhoea | Meningeal signs | Diarrhoea | Meningeal signs | Diarrhoea, drowsiness |
| ESR, mm/h | ... | 60 | 39 | 108 | 97 | ... | 51 | 84 | 81 | 54 |
| Lymphocytes, ×10⁹ per L | 803 | 1060 | 970 | 930 | 450 | 790 | 1870 | 860 | 420 | 460 |
| Blood culture | Sterile | Sterile | Sterile | Sterile | Sterile | Sterile | Sterile | Sterile | Sterile |
| Chest x-ray | Pneumonia | Pneumonia | Pneumonia | Normal | Normal | Normal | Pneumonia | Normal | Pneumonia |
| Echocardiography | Abnormal | Normal | Normal | Abnormal | Abnormal | Abnormal | Normal | Abnormal | Abnormal |
| Aneurism >4 mm | No | No | No | No | No | No | No | No | No |
| Ejection fraction | >55% | >55% | >55% | >55% | >55% | >55% | >55% | >55% | >55% |
| Mitral valve regurgitation | Yes | No | Yes | Yes | No | Yes | No | Yes | Yes |
| Pericardial effusion | Yes | No | No | No | No | No | No | No | No |
| Kobayashi ≥5 | Yes | No | No | No | No | No | Yes | Yes | Yes |
| <12 months | No | No | No | No | No | No | No | No | No |
| Kawasaki disease signs at day 4 | No | No | No | No | No | No | No | No | No |
| CRP >10 mg/dL | Yes (9) | Yes (31) | Yes (15) | Yes (48) | Yes (52) | No (7) | Yes (24) | Yes (24) | Yes (12) |
| Neutrophils >80% | Yes (80) | Yes (89) | Yes (77) | Yes (90) | Yes (90) | No (79) | Yes (83) | Yes (83) | Yes (83) |
| Platelets ≥100 ×10⁹ | Yes (119) | Yes (121) | Yes (66) | Yes (142) | Yes (113) | Yes (121) | Yes (138) | Yes (192) | Yes (142) |
| Sodium ≤133 mEq/L | Yes (131) | Yes (130) | Yes (132) | Yes (128) | Yes (129) | No (133) | No (115) | Yes (133) | Yes (122) |
| ALT >100 U/L | No (32) | No (79) | No (46) | No (82) | No (78) | Yes (733) | No (41) | No (63) | No (20) |
| MAS* | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Ferritin >684 ng/mL | Yes (1183) | Yes (893) | Yes (1972) | Yes (3213) | Yes (2027) | No (199) | No (449) | No (307) | No (341) |
| Platelets ≤10 ×10⁹ | Yes (119) | Yes (121) | Yes (66) | Yes (142) | Yes (113) | Yes (121) | Yes (138) | Yes (192) | Yes (151) |
| AST >48 IU/L | No (30) | Yes (120) | Yes (63) | Yes (174) | Yes (89) | Yes (237) | Yes (50) | Yes (51) | Yes (30) |
| Triglycerides ≥156 mg/dL | Yes (434) | Yes (367) | Yes (263) | Yes (198) | Yes (161) | Yes (200) | Yes (171) | No (29) | Yes (23) |
| Fibrinogen ≤360 mg/dL | Yes (465) | No (599) | No (506) | No (924) | No (759) | Yes (313) | No (637) | No (759) | No (489) |
| KDSS* | No | No | No | No | No | No | No | No | No |
| Hypotension | No | No | No | No | No | No | No | No | No |
| SBP ≤20% basal | No | No | No | No | No | No | No | No | No |
| Peripheral hypoperfusion | No | No | No | No | No | No | No | No | No |
| CPK, nv | 16 | 84 | 76 | 247 | 89 | 119 | 79 | 40 | 59 |
| Troponin I, nv | 111 | 188 | ... | 200 | 3557 | 4906 | 12 | 36 | <3 |
| proBNP, nv ≥1 ng/mL | 1870 | 952 | 1519 | 2072 | 1656 | 108 | 247 | 2957 | 129 |
| Nasal swab for respiratory pathogens | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
| Nasal swab for SARS-CoV-2 | Negative | Positive | Positive | Positive | Positive | Positive | Negative | Positive | Positive |
| Serology for SARS-CoV-2 (IgG, IgM) | Negative, negative | Positive, positive | Positive, positive | Positive, positive | Positive, positive | Positive, negative | Positive, negative | Positive, positive | Positive, negative |
| Serology (days from onset) | 30 | 18 | 16 | 11 | 10 | 10 | 8 | 7 | 4 |

ESR=erythrocyte sedimentation rate. CRP=C-reactive protein. MAS=Macrophage Activation Syndrome. ALT=alanine aminotransferase. AST=aspartate aminotransferase. KDSS=Kawasaki disease shock syndrome. SBP=systolic blood pressure. CPK=creatine phosphokinase. BNP=B-type natriuretic peptide. nv=normal values. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. IVIG=intravenous immunoglobulin. mPDN=methylprednisolone. *Test done shortly after high-dose IVIG.
Hypertriglyceridaemia was shown in seven (87%) of eight tested patients in group 2 (239 mg/dL [SD 108]); fibrinogen was high in nine (90%) of ten patients (621 mg/dL [182]), as was D-dimer in eight (80%) of ten patients (3798 ng/mL [SD 1318]). Laboratory criteria predicted intravenous immunoglobulin-resistance in seven (70%) of ten patients. MAS was diagnosed in five (50%) of ten patients. Troponin I was elevated in five (55%) of nine tested patients (1004 ng/L [SD 1862]), creatine phosphokinase in one (10%) of ten patients (85 IU/L [64]), and proBNP in all ten patients (1255 ng/L [929]; tables 1, 2).

For four (40%) of ten patients in group 2, IL-6 was increased (177·1 pg/mL [SD 137·4], normal values (nv) <3·4). NK count was measured in four (40%) patients, and was reduced in all (62 [SD 35]; nv 200–600×10⁹ per L). Blood culture was sterile in all patients.

Nasopharyngeal and oropharyngeal swab sampling for SARS-CoV-2, available from Feb 24, 2020, was positive in two (20%) of ten patients in group 2 (table 1). All patients were tested at least twice. Serology for SARS-CoV-2 antibodies, available from April 13, 2020, was investigated in all patients in group 2; eight (80%) of ten patients were IgG positive, and three (31%) were also IgM positive. Patient 6, who had a negative serology, was tested shortly after discharge, treatment with aspirin at an antiplatelet dose is ongoing, and a follow-up echocardiogram is scheduled at 8 weeks.

From Jan 1, 2015, to the start of the epidemic on Feb 24, 2020, 31 health-care personnel from the Paediatric Department, Hospital Papa Giovanni XXIII (Bergamo, Italy) had serology testing. Nine (29%) of 31 were IgG positive, and three (10%) were also IgM positive, corresponding to the expected rate of exposure (85 1U/L [64]), and proBNP in all ten patients (1255 ng/L [929]; tables 1, 2).

Table 2: Comparison between patients with Kawasaki-like disease presenting before and after the SARS-CoV-2 epidemic

| Parameter                      | Group 1 | Group 2 | p value |
|--------------------------------|---------|---------|---------|
| Time of presentation          | Until February, 2020 | March–April, 2020 | NA |
| Number of patients            | 19      | 10      | NA      |
| Age at onset, years           | 3.0 (2.5) | 7.5 (3.5) | 0.00035 |
| Incidence                     | 0.3 per month | 10 per month | <0.00001|
| Sex                           | NA      | NA      | 0.43    |
| Female                        | 12      | 3       | NA      |
| Male                          | 7       | 7       | NA      |
| Incomplete Kawasaki disease   | 0/19 (31%) | 5/20 (50%) | 0.43    |
| CRP, mg/dL                    | 16 (3) (8.0) | 25 (15.3) | 0.05    |
| ESR, mm/h                     | 82 (29) | 72 (24) | 0.38    |
| White cell count, ×10⁹ per L  | 19.4 (6.4) | 10.8 (6.1) | 0.0017 |
| Neutrophils                   | 71.9% (12.2) | 84.5% (5.7) | 0.034   |
| Lymphocytes, ×10⁹ per L       | 3.0 (1.8) | 0.86 (0.4) | 0.0012  |
| Haemoglobin, g/dL             | 10.8 (2.0) | 11 (1.2) | 0.79    |
| Platelets, ×10⁹ per L         | 457 (96) | 130 (32) | <0.0001 |
| Albumin, g/dL                 | 3.3 (0.5) | 3.2 (0.3) | 0.55    |
| Sodium, mmol/L                | 134.7 (1.6) | 130.8 (3.9) | 0.0011  |
| AST, IU/L                     | 120 (218) | 87 (70) | 0.64    |
| ALT, IU/L                     | 92 (122) | 119 (217) | 0.67    |
| Ferritin, ng/mL               | 187 (83) | 1176 (1032) | 0.011   |
| Triglycerides, mg/dL          | 230 (108) | 230 (108) | 0.87    |
| Fibrinogen, mg/dL             | 543 (300) | 621 (182) | 0.51    |
| D-dimer, ng/mL                | 3244 (943) | 3798 (3118) | 0.52    |
| CPK, IU/L                     | 61 (28) | 85 (64) | 0.19    |
| Troponin I, ng/L              | 1004 (1862) | 1004 (1862) | 0.87    |
| proBNP, ng/mL                 | 1255 (929) | 1255 (929) | 0.87    |
| Kobayashi score ≥5            | 2/19 (10%) | 7/10 (70%) | 0.0021  |
| MAS                            | 0/10 (0%) | 5/10 (50%) | 0.021   |
| KDSS                          | 0/10 (0%) | 5/10 (50%) | 0.021   |
| Abnormal echocardiography     | 2/19 (10%) | 6/10 (60%) | 0.0089  |
| Adjunctive steroid treatment  | 4/19 (16%) | 8/10 (80%) | 0.0045  |
| Inotropes treatment           | 0/19 (0%) | 2/10 (20%) | 0.11    |
| Response to treatment         | 19/19 (100%) | 10/10 (100%) | 1       |

Data are mean (SD) or n/N (%), unless otherwise stated. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; NA=not applicable; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; AST=aspartate aminotransferase; ALT=alanine aminotransferase; CPK=creatine phosphokinase; BNP=B-type natriuretic peptide; MAS=Macrophage Activation Syndrome; KDSS=Kawasaki disease shock syndrome.
To rule out the possible effect of number of referrals to the emergency department in different periods, we calculated incidence corrected for number of patients seen at the emergency department. We found that in the past 5 years, from January, 2015, to December, 2019, 98 572 patients had been evaluated, with a mean of 1642 (SD 280) per month, compared with 283 patients per month during the study period—approximately six-fold lower. With these figures, the incidence of Kawasaki disease in group 1 was 0·019% (95% CI –0·002 to 0·0019), compared with 3·5% (3·5 to 3·6) in group 2 (odds ratio 184; p<0·0001; figure). To rule out the possible effect of a change in the geographical catchment area in the prepandemic (group 1) versus the pandemic (group 2) period, we reviewed the place of residence of all our patients with Kawasaki disease and drew a referral map, showing that all but one came from the Bergamo province (appendix p 1).

The average age at onset was 3·0 years (SD 2·5) in group 1 versus 7·5 years (3·5) in group 2 (p=0·0003). In group 1, 14 of 19 patients were white, versus eight of ten patients in group 2. The mean body-mass index of patients in group 1 was 15·93 kg/m² (SD 1·72) versus 19·11 kg/m² (SD 3·21) in group 2 (p=0·0016). Two patients tested in group 1 had a negative serology for SARS-CoV-2 versus eight of ten positive patients in group 2 (one of the two negative patients was tested after high-dose intravenous immunoglobulin); five (50%) of ten patients had been in contact with confirmed COVID-19 cases. Group 2 had a significantly lower white cell count, lymphocyte count, and platelet count when compared with group 1 (table 2). Group 2 also differed significantly from group 1 for increased rate of markers of severity. An abnormal echocardiogram was recorded in six (60%) of ten patients of group 2 versus two (10%) of 19 patients in group 1 (p=0·0089); fulfilment of criteria for KDSS and MAS was found in five (50%) of ten patients in group 2, and in none of the patients in group 1 (p=0·021). Seven (70%) patients in group 2 met the criteria for a Kobayashi score of 5 or more, compared with two (10%) of 19 patients in group 1 (p=0·0021). Adjunctive steroid treatment was required in four (16%) of 19 patients in group 1 versus eight (80%) of ten patients in group 2 (p=0·0045; table 2).

**Discussion**

Despite half a century having passed since Tomisaku Kawasaki first reported his 50 cases in Japan, the cause of Kawasaki disease remains unknown. The most accepted hypothesis supports an aberrant response of the immune system to one or more unidentified pathogens; however, the search for the infectious triggers has been disappointing. In Japan, during three epidemics recorded in 1979, 1982, and 1986, the highest Kawasaki disease incidence was seen in January, potentially suggesting that factors during winter months may trigger Kawasaki disease.25,26 In 2010, the incidence of Kawasaki disease in Japan was 239·6 per 100 000 children younger than 5 years, compared with 20·8 per 100 000 in the USA.27 A 2-year retrospective survey done in northeastern Italy calculated an incidence of 14·7 cases per 100 000 children younger than 5 years.28 We report a high number of Kawasaki-like disease cases in the Bergamo province following the SARS-CoV-2 epidemic, with a monthly incidence that is at least 30 times greater than the monthly incidence of the previous 5 years, and has a clear starting point after the first case of COVID-19 was diagnosed in our area. Group 2, diagnosed after SARS-CoV-2 appeared, showed evidence of seroconversion to the virus in the majority of patients.
In the past 20 years, viruses of the coronavirus family have been proposed as possibly implicated in the pathogenesis of Kawasaki disease. In 2005, a group from New Haven (CT, USA) identified a novel human coronavirus, designated New Haven coronavirus (HCoV-NH), in the respiratory secretions of eight of 11 children with Kawasaki disease versus one of 22 controls tested by RT-PCR. A serological test was not done. This report was followed by commentaries expressing a mixed sense of interest and scepticism. The arguments against this association were expressed by a group from Japan, who did a retrospective study on nasopharyngeal swab samples from 19 children with Kawasaki disease and 208 controls with respiratory tract infections, and found RNA sequences of HCoV-NH in five (2%) of 208 controls versus zero of 19 children with Kawasaki disease.

Another group from Japan explored the association between two different coronaviruses (HCoV-NL63 and HCoV-229E) and Kawasaki disease by serological tests. The immunofluorescence assay detected no difference between two different coronaviruses (HCoV-NL63 and HCoV-229E) antibody positivity between patients and controls, whereas HCoV-229E antibody positivity was higher in patients with Kawasaki disease. Given the pathogenesis of the disease, serology testing seems a more reliable tool than RT-PCR in detecting the cause of infection. This suggests that the coronavirus family might represent one of the triggers of Kawasaki disease, SARS-CoV-2 being a particularly virulent strain able to elicit a powerful immune response in the host.

In this study, the clinical and biochemical features of patients with Kawasaki disease diagnosed during the COVID-19 pandemic appeared to differ from our historical cohort of patients; therefore, we have classified these patients as Kawasaki-like disease. From a clinical perspective, they were older, had respiratory and gastrointestinal involvement, meningeal signs, and signs of cardiovascular involvement. From a biochemical perspective, they had leucopenia with marked lymphopenia, thrombocytopenia, and increased ferritin, as well as markers of myocarditis. Similar clinical features are shared by patients with COVID-19. Additionally, these patients had a more severe disease course, with resistance to intravenous immunoglobulin and need of adjunctive steroids, biochemical evidence of MAS, and clinical signs in keeping with KDSS.

The proinflammatory effect of SARS-CoV-2 has been reported in adults with the most severe respiratory complications of COVID-19. Many of these patients have a constellation of features classified under the term cytokine storm, such as fever, lymphopenia, elevated transaminases, lactate dehydrogenase, D-dimer, and ferritin, in keeping with MAS. Likewise, MAS is a form of cytokine storm, and might affect patients with Kawasaki disease. All these elements supported the need to start adjunctive steroids. In our experience, this treatment is effective and safe, and should be considered by physicians treating patients with Kawasaki-like presentations in the context of the COVID-19 pandemic.

Evidence of contact with the virus was confirmed by the presence of antibodies against SARS-CoV-2 in eight of ten patients in group 2. It is possible that in the remaining two patients, who both had a negative serology, confounding factors played a role. One patient was tested just after an infusion of high-dose immunoglobulins. Additionally, qualitative antibody testing is reported to have a sensitivity of 95% and a specificity of 85–90% when compared with PCR test by nasal swab. It is also possible that this patient represents an unusual presentation of Kawasaki disease outside of SARS-CoV-2 epidemic, as seen in previous years. Only two patients in group 2 presented a positive nasopharyngeal and oropharyngeal swab sampling for SARS-CoV-2. This finding and the positivity of IgG antibodies suggest a late onset of the disease compared with the primary infection, due to the host immune response. This might be the reason why, in the past, no active viral infection could be shown in this disease. All these results and considerations support the hypothesis that the immune response to SARS-CoV-2 is responsible for a Kawasaki-like disease in susceptible patients.

We believe these findings have important implications for public health. The association between SARS-CoV-2 and Kawasaki-like disease should be taken into account when it comes to considering social reintegration policies for the paediatric population. However, the Kawasaki-like disease described here remains a rare condition, probably affecting no more than one in 1000 children exposed to SARS-CoV-2. This estimate is based on the limited data from the case series in this region.

This study has the limitations of a relatively small case series, requiring confirmation in larger groups. Genetic studies investigating the susceptibility of patients developing this disease to the triggering effect of SARS-CoV-2 should be done. Nonetheless, we reported a strong association between an outbreak of Kawasaki-like disease and the SARS-CoV-2 epidemic in the Bergamo province of Italy. Patients diagnosed with Kawasaki-like disease after the viral spreading revealed a severe course, including KDSS and MAS, and required adjunctive steroid treatment. A similar outbreak of Kawasaki-like disease is expected in countries affected by the SARS-CoV-2 pandemic.

Contributors
IV and LD’A made substantial contributions to the conception or design of the work. LV and AM drafted the work. IV, AM, AG, LM, MR, MC, EB, and LD’A gave final approval for the Article to be published. IV, AM, AG, LM, MR, MC, EB, and LD’A agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AM, AG, LM, MR, MC, and EB acquired, analysed, or interpreted data for the Article. AG, LM, MR, MC, and EB revised the Article critically for important intellectual content. LD’A prepared the final draft and critically revised the Article for important intellectual content.

Declaration of interests
We declare no competing interests and no financial support for this study.
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References
1. Ministero della Salute. Nuovo coronavirus: cosa c’è da sapere. http://www.salute.gov.it/por/nuovocoronavirus/ (accessed April 15, 2020).
2. Flaxman S, Mishra S, Gandy A, et al. Estimating the number of infections and the impact of nonpharmaceutical interventions on COVID-19 in 11 European countries. https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-11-europe-npi-impact/ (accessed March 30, 2020).
3. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. 2019. N Engl J Med 2020; 382: 727–33.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
5. Yonker LM, Shen K, Kinane TB. Lessons unfolding from pediatric cases of COVID-19 disease caused by SARS-CoV-2 infection. Pediatr Pulmonol 2020; 55: 1085–86.
6. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020; published online March 16. DOI:10.1542/peds.2020-0702.
7. Nicastro E, Mazza A, Gervasoni A, Di Giorgio A, D’Antiga L. A pediatric emergency department protocol to avoid intra-hospital dispersal of SARS-CoV-2 during the outbreak in Bergamo, Italy. J Pediatr 2020; published online April 21. DOI:10.1016/j.jpeds.2020.04.026.
8. Xiao F, Tang M, Zhong X, Liu Y, Li X, Shang H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020; 158: 1831–13.
9. Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol 2020; published online April 15. DOI:10.1002/art.41285.
10. D’Antiga L. Coronavirus and immunosuppressed patients. The facts during the third epidemic. Liver Transplant 2020; published online March 20. DOI:10.1002/lt.25756.
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033–34.
12. Kawasaki T, Kosaki F, Okawa S, Shigenobu I, Yamagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974; 54: 271–76.
13. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1996; 94: 1379–85.
14. Kanegaye JT, Wilder MS, Molkara D, et al. The genetics of Kawasaki disease. Pediatr Res 2009; 123: e781–89.
15. Wang W, Gong F, Zhu W, Fu S, Zhang Q. Macrophage activation syndrome in Kawasaki disease: more common than we thought? J Infect Dis 2005; 191: 351–52.
16. Kawasaki T, Kosaki F, Okawa S, Shigenobu I, Yamagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974; 54: 271–76.
17. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1996; 94: 1379–85.
18. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009; 123: e781–89.
19. Wang W, Gong F, Zhu W, Fu S, Zhang Q. Macrophage activation syndrome in Kawasaki disease: more common than we thought? J Infect Dis 2005; 191: 351–52.
20. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005; 191: 499–502.
21. McIntosh K. Coronavirus in the limelight. J Infect Dis 2005; 191: 489–91.
22. Elhbarza T, Endo R, Ma X, Ishiguro N, Kikuta H. Lack of association between New Haven coronavirus and Kawasaki disease. J Infect Dis 2005; 192: 351–52.
23. Esper F, Shapiro ED, Landry ML, Kahn JS. Reply to van der Hoek and Berkhourt. Elhbarza T, et al. J Infect Dis 2005; 192: 353.
24. Turnier JL, Anderson MS, Heier HR, Jone PN, Glode MP, Dominguez SR. Concurrent respiratory viruses and Kawasaki disease. Pediatrics 2015; 136: e609–14.
25. Shirato K, Imada Y, Kawai M, Nakagaki K, Matsuura Y, Taguchi F. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. J Med Virol 2014; 86: 2146–53.
26. McGregor D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autimmune Rev 2020; published online April 3. DOI:10.1016/j.autrev.2020.102357.
27. Mollot EJ, Bearer CF. COVID-19 in children and altered inflammatory responses. Pediatr Res 2020; published online April 3. DOI:10.1038/s41590-020-0883-y.
28. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.