



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

patients still in the hospital (94 [37%]) at the end of follow-up. The multivariable Cox model analysis showed that history of chronic pulmonary disease had the highest adjusted hazard ratio (aHR) for mortality (aHR 2.94 [95% CI 1.48–5.84]). Other independent predictors of death were history of chronic cardiovascular disease (aHR 1.76 [95% CI 1.08–2.86]), older age (aHR 1.31 [95% CI 1.09–1.57]), higher concentrations of IL-6 (aHR 1.11 [95% CI 1.02–1.20] per decile increase), and higher concentrations of D-dimer (aHR 1.10 [95% CI 1.01–1.19] per decile increase) on admission. There appear to be no differences by sex. The association of mortality with higher concentrations of IL-6 and D-dimer is particularly relevant for two reasons. First, it confirms the key pathogenic role played by the activation of systemic inflammation and endothelial-vascular damage in the development of organ dysfunction. Second, it provides the rationale for the design of clinical trials for measuring the efficacy of treatment with immunomodulating and anticoagulant drugs.

The study by Cummings and colleagues¹⁰ shows that clinicians can produce high-quality research even when facing an overwhelming clinical workload. However, despite providing important insights, this work leaves us with some unanswered questions. While waiting for the availability of a COVID-19 vaccine, further studies are required to improve and personalise patient treatment, with particular attention to the role of initial non-invasive respiratory support strategies, timing of intubation, optimal setting of mechanical ventilation, and efficacy and safety of immunomodulating agents and anticoagulation strategies.

GG reports personal fees from Biotest, Draeger, Fisher & Paykel, Maquet, Merck Sharp & Dohme, and Pfizer, all outside the area of work commented on here. AZ declares no competing interests.

**Giacomo Grasselli, Alberto Zanella*
giacomo.grasselli@unimi.it

Dipartimento di Anestesia, Rianimazione ed Emergenza-Urgenza, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy (GC, AZ) and Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy (GC, AZ)

- 1 WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. March 11, 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020> (accessed May 5, 2020).
- 2 Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA* 2020; **323**: 1545.
- 3 Azoulay E, Pochard F, Chevret S, et al. Compliance with triage to intensive care recommendations. *Crit Care Med* 2001; **29**: 2132–36.
- 4 Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region — case series. *N Engl J Med* 2020; published online March 30. DOI:10.1056/NEJMoa2004500.
- 5 Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; published online April 6. DOI:10.1001/jama.2020.5394.
- 6 Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. *JAMA* 2020; published online April 24. DOI:10.1001/jama.2020.7202.
- 7 Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA* 2020; published online April 22. DOI:10.1001/jama.2020.6775.
- 8 Wang Y, Lu X, Chen H, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am J Respir Crit Care Med* 2020; published online April 8. DOI:10.1164/rccm.202003-0736LE.
- 9 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.
- 10 Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020; published online May 19. [https://doi.org/10.1016/S0140-6736\(20\)31189-2](https://doi.org/10.1016/S0140-6736(20)31189-2).
- 11 Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol* 2020; **7**: e362–63.

Kawasaki-like disease: emerging complication during the COVID-19 pandemic



Children have to date borne a minimal medical burden in the global COVID-19 pandemic. Epidemiological data from many countries show that children are a small minority of those who test positive. Children younger than 18 years have made up only 1.7% of national cases in the USA,¹ 1% of cases in the Netherlands,² and 2.0% of a large observational cohort in the UK.³ Whether these proportions reflect lower susceptibility among children versus adults,⁴ or similar infection rates, but

much higher proportions with asymptomatic disease, is unclear.⁵ Studies from several countries have confirmed that severe illness and death due to COVID-19 among children are rare,^{1,6} with accurate estimates unavailable because of an absence of true population denominators. Attention has now shifted to the vulnerability of children for two reasons. First, the degree to which children transmit COVID-19 is key to how countries reopen communities after lockdown. Second, new

Published Online
May 13, 2020
[https://doi.org/10.1016/S0140-6736\(20\)31129-6](https://doi.org/10.1016/S0140-6736(20)31129-6)
See [Articles](#) page 1771



Jill Lehmann Photography/Getty Images

concerns about a novel severe Kawasaki-like disease in children related to COVID-19, including Lucio Verdoni and colleagues⁷ description of an outbreak in Italy in *The Lancet*, change our understanding of this disease in children.

Kawasaki disease is a rare acute paediatric vasculitis, with coronary artery aneurysms as its main complication. The diagnosis is based on the presence of persistent fever, exanthema, lymphadenopathy, conjunctival injection, and changes to the mucosae and extremities.^{8,9} Verdoni and colleagues describe ten cases (seven boys, three girls; aged 7.5 years [SD 3.5]) of a Kawasaki-like disease occurring in Bergamo, Italy, at the peak of the pandemic in the country (Feb 18 to April 20, 2020), a monthly incidence some 30-fold higher than observed for Kawasaki disease across the previous 5 years. Bergamo was the city with the highest rate of infections and deaths in Italy at that time. Within the cluster were five children who had features similar to Kawasaki disease (ie, non-purulent conjunctivitis, polymorphic rash, mucosal changes, and swollen extremities); however, another five children presented with fewer than three of the diagnostic clinical signs and were older than patients with classic Kawasaki disease. There was also a high proportion of shock, with five of ten children presenting with hypotension requiring fluid resuscitation, and two of ten children needing inotropic support. Two of ten children had a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR swab and eight of ten had a SARS-CoV-2-positive serology test; however, these tests were not done contemporaneously with the

episode, so the clinical relevance is unclear. The majority of patients with Kawasaki disease respond well to intravenous immunoglobulin; however, 10–20% require additional anti-inflammatory treatment.⁹ In this cohort, eight of ten children received high-dose corticosteroids in addition to intravenous immunoglobulin. These differences raise the question as to whether this cluster is Kawasaki disease with SARS-CoV-2 as the triggering agent, or represents an emerging Kawasaki-like disease characterised by multisystem inflammation. The diagnosis of Kawasaki disease is based on clinical and laboratory criteria and is hindered by the lack of a diagnostic test. Understanding the pathophysiology of this emerging phenomenon might provide welcome insights into our understanding of Kawasaki disease.

Anecdotally, clinicians across Europe have identified clusters of similar cases. In the UK, paediatricians have identified a small group of children presenting with shock and a multisystem inflammation to critical care units, some of whom have coronary artery aneurysms, and a further group of less severely ill children with a Kawasaki-like disease, who respond to a variety of immunomodulatory treatments, including intravenous immunoglobulin, corticosteroids, and biologics such as infliximab and anakinra (Whittaker E, unpublished). Long-term echocardiogram data on coronary artery aneurysms are pending. In response to this cluster in London, UK, we notified the National Health Service of the emergence of an unusual disorder, and an alert was issued on April 25. On the basis of the review of clinical and laboratory features, a case definition of the syndrome we have provisionally called paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was formulated by experts in the UK and published by the Royal College of Paediatrics and Child Health.¹⁰ Correspondence¹¹ in *The Lancet* on May 7, 2020, describing nine children with PIMS-TS requiring critical care in south London highlights the severe end of the spectrum of this disease.

The recognition of this disease late in the first pandemic wave might relate to its rarity and the difficulty of recognising uncommon syndromes in fragmented health-care systems rapidly reorganising to deal with a pandemic. Alternatively, it might reflect a mechanism for PIMS-TS. Alternatively, it suggests that the mechanism for the Kawasaki-like disease described

here and PIMS-TS might represent post-infectious inflammatory syndrome, which might be antibody or immune-complex mediated, particularly because in this Italian cohort there was little evidence of viral replication. For prospective studies, measuring antibody at the time of presentation, as well as consenting patients for appropriate research samples, will be essential to elucidate the mechanism of this syndrome.

Although the Article suggests a possible emerging inflammatory syndrome associated with COVID-19, it is crucial to reiterate—for parents and health-care workers alike—that children remain minimally affected by SARS-CoV-2 infection overall. Understanding this inflammatory phenomenon in children might provide vital information about immune responses to SARS-CoV-2 and possible correlates of immune protection that might have relevance both for adults and children. In particular, if this is an antibody-mediated phenomenon, there might be implications for vaccine studies, and this might also explain why some children become very ill with COVID-19, while the majority are unaffected or asymptomatic.

In the UK, a British Paediatric Surveillance Unit study has been rapidly opened to explore the extent of PIMS-TS nationally. Two COVID-19 priority studies in the UK (DIAMONDS [Central Portfolio Management System 45537] and ISARIC [UK Clinical Research Network 14152]) are collaborating to ensure that every child with this emerging syndrome has the opportunity to consent to take part in a study exploring mechanisms. International discussions are underway to facilitate standardised approaches to the investigation and management of these children, including treatment strategies to prevent long-term adverse outcomes such as coronary artery aneurysms.

RMV is President of the Royal College of Paediatrics and Child Health. EW is Secretary of the British Paediatric Allergy Immunity and Infection Group. She is a member of the PIMS-TS Study Group.

*Russell M Viner, Elizabeth Whittaker
r.viner@ucl.ac.uk

Population, Policy & Practice Research Department, UCL Great Ormond Street Institute of Child Health, London WC1N 1EH, UK (RMV); and Paediatric Infectious Diseases, Imperial College Healthcare NHS Trust and Section of Paediatric Infectious Diseases, Department of Medicine, Imperial College London, London, UK (EW)

- 1 Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 422–26.
- 2 Children and COVID-19. Amsterdam: National Institute for Public Health and the Environment (RIVM), 2020. <https://www.rivm.nl/en/novel-coronavirus-covid-19/children-and-covid-19> (May 5, 2020).
- 3 Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. *medRxiv* 2020; published online April 28. DOI:10.1101/2020.04.23.20076042 (preprint).
- 4 Zhang J, Litvinova M, Liang Y, et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. *Science* 2020; published online April 29. DOI:10.1126/science.abb8001.
- 5 Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis* 2020; published online April 27. [https://doi.org/10.1016/S1473-3099\(20\)30287-5](https://doi.org/10.1016/S1473-3099(20)30287-5).
- 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 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. *Lancet* 2020; published online May 13. [https://doi.org/10.1016/S0140-6736\(20\)31103-X](https://doi.org/10.1016/S0140-6736(20)31103-X).
- 8 Dietz SM, van Stijn D, Burgner D, et al. Dissecting Kawasaki disease: a state-of-the-art review. *Eur J Pediatr* 2017; **176**: 995–1009.
- 9 McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017; **135**: e927–99.
- 10 Royal College of Paediatrics and Child Health. Guidance—Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, 2020. <https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19> (May 5, 2020).
- 11 Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; published online May 7. [https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1).

For the DIAMONDS study see <https://diamond-project.eu/consortium/>

For the ISARIC study see <https://isaric.tghn.org/clinical-characterisation-protocol-ccp/>

Attacks against health-care personnel must stop, especially as the world fights COVID-19



Physicians, nurses, and other front-line health-care workers have been celebrated in many countries as heroes for their work during the COVID-19 pandemic. Yet not everyone appreciates their efforts and contributions. Since the beginning of this pandemic, headlines have also captured stories of health-care personnel facing

attacks as they travel to and from health-care facilities. Nurses and doctors have been pelted with eggs and physically assaulted in Mexico.¹ In the Philippines, a nurse was reportedly attacked by men who poured bleach on his face, damaging his vision.² Across India, reports describe health-care workers being beaten, stoned, spat

Published Online
May 20, 2020
[https://doi.org/10.1016/S0140-6736\(20\)31191-0](https://doi.org/10.1016/S0140-6736(20)31191-0)