Commentary

High dimensional cytokine panels reveal common SARS-CoV-2-related inflammation patterns across different latitudes

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COVID-19 can develop into a life-threatening hyperinflammatory disease in rare pediatric cases [1, 2]. Global efforts are ongoing to better understand protective immune responses against the SARS-CoV-2 virus and the immunopathological mechanisms underlying severe disease [3]. To our present knowledge, this hyperinflammatory syndrome shares clinical features with Kawasaki disease (KD) but usually affects children who are older than the typical patient with KD and who more often present with intestinal involvement and myocardial failure and shock [4, 5]. The pathogenesis of Multi Inflammatory Syndrome in Children (MIS-C) is still largely unknown, but an association with a previous history of SARS-CoV-2 (delay of 2–6 weeks from initial infection) suggest a role for adaptive immune responses and specific autoantibodies have been proposed [8]. However, little is known about the immunological mechanisms underlying COVID-19 severity. Imbalanced immune responses, partially caused by the impaired early type I interferon responses, seem to be the most likely determinant of the overall severity of acute COVID-19 [6].

The question of whether individuals in different parts of the world present a similar inflammatory signature upon SARS-CoV-2 infection, remains unknown. Subgroups of children affected by MIS-Care have been described [1, 2, 4, 5] and the optimal management of such cases is being worked out by collaborative networks of pediatricians in different high-income countries. Most MIS-C patients are treated with different strong immunomodulatory regimens such as high-dose of steroids, intravenous immunoglobulins and anti-cytokine therapies (i.e., Anakinra, Tocilizumab) in association with anti-coagulants to counter the microangiopathy and activation of both complement and endothelial factors (i.e., VEGF) were observed in MIS-C. Plasma cytokine levels also distinguished patients requiring pediatric intensive care admission from those without pediatric intensive care admission and a combination of cytokines enabled the clear separation of PIMS-TS patients from COVID-19 and controls [10]. These data are consistent and substantially in line with recent data published in EBioMedicine, and presents a multiplex immune assay analysis comparing the plasma biomarkers of groups of patients with different SARS-CoV-2-related pathological pictures: multisystem syndrome inflammatory, acute COVID-19 infection (COVID-19), SARS-CoV-2 seropositive, and control children admitted to a tertiary care children’s hospital in Chennai, India [10]. Extensive cytokine profiling was previously reported in other important recent publications (that evaluated immune responses in MIS-C compared with pre-pandemic Kawasaki disease and/or acute COVID-19 in European and USA cohorts through a systems biology approach [7–9]. In these studies utilizing principal component analysis (PCA) of circulating immune proteins, patients with MIS-C clustered separately from adults and children with acute COVID-19 or Kawasaki [8, 9]. Although there are now a number of published studies on cytokine profiles in patients with MIS-C, the study from Dr. Venkataraman [10] is the first reporting data from a low- or middle-income country. Comparison of plasma proteins measured between the groups of children with MIS-C, COVID-19 and controls showed marked elevation of a number of plasma cytokines in the MIS-C patients, but also identified elevation of a distinct pattern of proteins in the COVID19 patients as compared to controls. Significant differences in proinflammatory cytokines (IFNγ, IL2, TNF, IL1, IFNβ, IL6) as well as chemokines (i.e, CXCL-10) and endothelial factors (i.e, VEGF) were observed in MIS-C. Plasma cytokine levels also distinguished patients requiring pediatric intensive care admission from those without pediatric intensive care admission and a combination of cytokines enabled the clear separation of PIMS-TS patients from COVID-19 and controls [10]. These data are consistent and substantially in line with recent data published in other international study cohorts [7–9], suggesting the possibility to develop a common therapeutic strategy to target SARS-CoV2-related multisystem inflammatory syndrome in children across different latitudes. Since MIS-C was initially described as a complication of SARS-CoV-2 infection in children in early 2020, major efforts have been made in characterizing the clinical presentation and immune profile of this syndrome, studying both innate and adaptive immunity together...
with endothelial dysfunction and vascular inflammation as important contributors to pathophysiology [6-9]. These studies represent only an initial step in the search to understand MIS-C. To move forward in the field, future work will need to investigate larger numbers of treatment-naive MIS-C patients from different regions of the world, along with appropriate controls. In addition, studies have thus far focused on circulating immune perturbations; however, proteins released from tissue damage may also play a critical role in the pathogenesis of this disease. Finally, the genetic susceptibilities that predispose patients to MIS-C are unknown and currently under intensive investigation. The data generated by Dr. Venkataraman highlights the need for data sharing and cross-validation in all the countries affected to bring disease understanding to a new level. Harmonizing international collaborations representative of the different regions of the world, will help to accelerate the pace of advancement in MIS-C and make real change possible in the care and outcomes of this emerging condition.

Contributors
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Declaration of Competing Interest
The author reports no conflicts of interest.

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