COVID-19-related multisystem inflammatory syndrome in children: *The plot thickens!*

Dear Editor,

We read with great interest, the article by Jain and colleagues, focusing on the '*must-knows*' of the COVID-19 infection in the pediatric age-group.[1] Although we appreciate the holistic nature of the discussion encompassing the intricacies of clinical presentation to the adoption of institutional standard operating protocols, the recent developments in the domain are worrisome, mandating elucidation.

In the later part of April 2020, a UK-based report of a cohort of eight children (in former good health) manifesting fever, cardiovascular shock and severe hyperinflammation, temporally linked to SARS-CoV-2 infection, bewildered the fraternity which was largely under the impression that the pediatrics were relatively spared by the viral enemy.[2] The Royal College of Paediatrics and Child Health (RCPCH) ascribed this condition to be a pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS), subsequently referred to as a multisystem inflammatory syndrome in children (MIS-C)

by the eminent Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), given a global rise in the number of cases.[3] The syndromic definition is centered around six key elements: pediatric age-group, fever-persistence, laboratory inflammatory-evidence, multisystem-involvement (at least two organs), serious illness necessitating hospitalization, and a temporal-association to COVID-19 infection/exposure.[3]

Pediatric anesthesiologists need to reflect upon certain important caveats (surfaced in a meta-analysis by Ahmed and colleagues[3]) pertaining to the recent clinical entity of MIS-C:

(i) Diagnostic-overlaps: Viral-inflammatory syndromes (MIS-C or PIMS-TS) can be potentially difficult to differentiate from other pediatric febrile illnesses like Kawasaki disease (KD) and toxic shock syndrome (TSS).[4] Nevertheless, Whittaker *et al*. recently outlined the important distinguishing features with major points such as the patients with PIMS-TS being older with higher total leukocyte counts, neutrophilia and elevated C-reactive protein in background of anemia and lymphocytopenia.[3]

(ii) Need for ICU admission: 470/662, as high as 71% of children included in the meta-analysis required an ICU admission with an associated 1.7% mortality rate (comparable to the mortality rate observed in adults aged 55-64 years with an underlying severe COVID infection). In all, 22.2% received invasive mechanical ventilation with an extracorporeal membrane oxygenation (ECMO) requirement in 4.4% of children.[3] Out of the 39 studies involved in the meta-analysis, the study by Feldstein *et al*. evaluated the largest patient cohort, revealing a 17% requirement of non-invasive ventilation.[5]

(iii) Association with hyperinflammatory shock: Consistent with the findings of Riphagen *et al*., hyperinflammatory shock demonstrated a strong association with MIS-C, supported by the need of vasopressor support and/or fluid resuscitation in 60.1%.[2,3]

(iv) Abnormal coagulation and cardiac biomarkers: Lower platelet levels and higher fibrinogen counts, D-dimer levels, cardiac troponins, B-natriuretic peptide (BNP) and alanine aminotransferase, constituted the noteworthy derangements.[5]

(v) Cardiovascular and other organ-complications: Cardiovascular involvement emerged as a remarkable feature with Feldstein *et al*. describing as high as 80% incidence.[5] The aforementioned meta-analysis also revealed echocardiographic abnormalities in 54% of children (most common being, ventricular dysfunction in 45.1%) with 8.1% of manifesting coronary artery aneurysms (a very peculiar KD-feature). Acute kidney injury resulted in 16.3% of the patients.[3] In addition, Feldstein *et al*. also highlighted thrombotic complications (deep venous thrombosis and pulmonary embolism) in 8 out of the186 patients included in their study.[5]

As we navigate through this epic pandemic, unprecedented challenges continue to transpire. In this context, MIS-C is a potentially dangerous clinical entity wherein an improved characterization of the epidemiology, clinical trajectory and treatment options (intravenous immunoglobulins, steroids, other immune-modulators, hemodynamic and ventilator support) backed by early recognition and multi-disciplinary management approach, can save the lives of these sick children, only to leave the physicians baffled for the time being to what the long-term sequel of such novel COVID-19-related clinical entities would be like.

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Conflicts of interest

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