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COMMENT

Multisystemic Inflammatory Syndrome in Children: a step towards a better understanding of this entity

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As pediatricians, we all have to deal with new childhood inflammatory disorder due to COVID 19: the Multisystem Inflammatory Syndrome in Children (MIS-C). The recent article by Savorgnan et al. on the physiologic profiles associated with MIS-C proposed a classification through the "MIS-C severity score" (MSS). The authors also identified a combination of seven variables collected during the first 3 h of admission in the PICU that contributes to stratify MIS-C severity with an area under the receiver operating characteristic curve (AUC) >0.90. This work represents an important first step in the development of a MIS-C severity score and is a call for collaborative groups to validate the prediction model through multicenter studies and thereby refine the management of MIS-C.

IMPACT:

- The recent article by Savorgnan et al. on physiologic profile associated with MIS-C represents an important first step in the development of an MIS-C severity score and is a call for collaborative groups to validate the prediction model through multicenter studies and thereby refine the management of MIS-C.
- Our manuscript helps in the methodology interpretation of the manuscript by Savorgnan et al.
- And our manuscript promotes collaborative work on MIS-C.

A new childhood inflammatory disorder characterized by an unusual febrile illness, significant elevation of inflammatory markers, and multisystem involvement emerged during the coronavirus disease 2019 (COVID-19) pandemic with the distinction of developing within 4 weeks of the onset of COVID-19 symptoms.[1] The first case definition of this condition, named Multisystem Inflammatory Syndrome in Children (MIS-C), was described in late April 2020.[2] Subsequently the U.S. Center for Disease Control and Prevention[3] and the World Health Organization[4] published their own definitions. From that day to the end of September 2022, PubMed has recorded around 2000 indexed published articles, mainly describing the epidemiology of MIS-C, clinical presentations, and its management.

The clinical symptoms of MIS-C have often been compared to those of Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS)[1,5] given some similarities of their profiles. Further studies reported that MIS-C, unlike KD and TSS, usually occurs between 6 and 12 years, predominantly in non-Hispanic black children, and is most often associated with significantly elevated inflammatory markers, thrombocytopenia, lymphopenia, left ventricular dysfunction, shock, gastrointestinal, and neurological symptoms.[1,5] Once it was demonstrated that MIS-C pathophysiology and epidemiology was different from that of acute COVID-19 infection, KD, and TSS, a therapeutic approach tailored to this clinical entity and severity of illness is necessary to avoid exposing the child to inadequate/excessive therapies and unnecessary burdening of resources.

The recent article by Savorgnan et al.[6] on the physiologic profiles associated with MIS-C proposed a classification through the "MIS-C severity score" (MSS). From a 1-year retrospective single-center study including 152 children with MIS-C, the score was based on hospital or Pediatric Intensive Care Unit (PICU) admission and the need for vasoactive drugs with/without mechanical ventilation. Moreover, they identified a combination of seven variables, which are routinely collected in patients with MIS-C suspicion and include respiratory rate, creatinine blood level, international normalized ratio, brain natriuretic peptide, white blood cells, ferritin, and albumin. They were collected during the first 3 h of admission in the PICU that help to stratify MIS-C severity with an area under the receiver operating characteristic curve (AUC) >0.90. A significant association of "severe MIS-C" was found with older patients (more than 12 years old), lower initial left ventricular function, prolonged hospital stay, tachycardia, tachypnea, and hypotension. As described in the literature,[7] it was also reported that brain natriuretic peptide, troponin, procalcitonin, creatinine, and ferritin were at least twofold higher in children with severe MIS-C. Finally, they were also able to describe the course of MIS-C: MSS worsened on days two and three, and improved on days four and five, under treatment usually combining steroids and immunomodulators (intravenous immune globulin or Anakinra).

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Early estimation of disease severity scores converts a data set into objective values and is routinely used in medicine. Once validated, these scores are used to improve quality of care, compare treatment effectiveness, optimize patient outcomes, and risk stratify in observational research and benchmarking. An additional step is the development of a probability model that provides the likelihood of an event occurring based on the score. The probability model refines the ability of the score in comparing different groups of patients. However, its accuracy depends on certain characteristics: (1) being based on routinely recorded variables, (2) having a high level of discrimination, (3) being well calibrated, and (4) being widely applicable.[8]

The MSS score uses routinely recorded variables and has a high level of discrimination, i.e., it accurately differentiates between patients with mild or severe MIS-C with an AUC >0.90. The challenge is the calibration of the model, which consists of its ability to correctly estimate the absolute risk. In the Savorgnan et al.[6] study, 70% of the children received immunomodulators, including Anakinra, and steroids within the first 48 h, which is not necessarily the standard practice seen in all MIS-C cohorts given the diversity of diagnostic and therapeutic options available. In the context of calibration assessment, it is important to understand the risk of the overall population by including data from a wide variety of patients (by age, diagnostic criteria, comorbidities, and management) and multiple PICUs (from different hospitals and countries), which will help distinguish risk across groups and various combinations of predictors.[9] In addition, changes in disease prevalence and improvements in diagnosis and treatment may lead to "calibration deterioration" of the model, making periodic review and updating of established scoring systems important.

Severity scores are usually developed for diseases with short-term life-threatening or long-term functional sequelae in order to intervene early and avoid unfavorable outcomes. This does not seem to be the scenario for MIS-C, as it presented with low mortality, short length of stay, and infrequent cardiovascular sequelae as demonstrated for Savorgnan et al.[6] Meanwhile, in the context of the COVID-19 pandemic that required quick and precise decisions for an uncertain disease, it seemed reasonable to rely on a less conservative therapy targeting some "similar" pathological entities. However, 2 years after the onset of the disease with the emergence of more robust knowledge on the topic, the need to refine therapy seems quite plausible to us, and at this point the severity scores seem valuable once they may allow a more accurate classification of patients.

Discrimination based on disease severity, combined with quantification of risk for a given outcome, can motivate discussions about health care as well as optimization of resource allocation. As a growing area of interest, considerable attention has been given to potential sources of error and strategies to improve the accuracy of outcome predictions. As medical data become increasingly digitized and thus easily analyzable, the interest and potential for using these data to develop useful clinical decision support systems are growing.[10] The work of Savorgnan et al.[6] represents an important first step in the development of a MIS-C severity score and is a call for collaborative groups to validate the prediction model through multicenter studies and thereby refine the management of MIS-C.

DATA AVAILABILITY

No data are used for this manuscript.

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COMPETING INTERESTS

ADDITIONAL INFORMATION

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