

**EDITORIAL**

# Gastrointestinal Manifestations of COVID-19: Are They Associated with Severe Disease in Children

Syed Shafi Ahmed Muaz

COVID-19 is a highly contagious disease that was first reported in Wuhan, Hubei Province, China in December 2019.<sup>1</sup> Ever since the COVID-19 pandemic has hit the world the landscape of its clinical manifestations has been changing and its gastrointestinal (GI) features are now being recognised more frequently.<sup>2,3</sup>

Similar to the respiratory tract, SARS-CoV-2 binds to GI tract cells via the ACE-2 and TMPRSS2 cell receptors in the intestine causing release of cytokines. Fecal shedding of the virus has been demonstrated, which may continue even after nasopharyngeal swabs become negative. Recently, GI symptoms have come to the fore with the recognition of multisystem inflammatory syndrome (MIS-C), a manifestation of COVID-19 with systemic hyperinflammation and multi-organ failure. In the largest series of MIS-C, 84.1% had GI symptoms [abdominal pain (75%), vomiting (56%), diarrhea (40%)].<sup>4</sup>

The exact mechanism of GI involvement in COVID-19 is unknown. The probable mechanism may be due to the interaction between ACE2 and the COVID-19 virus, as these receptors are abundantly present in small and large intestines.<sup>5</sup> Other possible mechanisms include inflammatory responses such as cytokine storms, drug side effects and finally, the dysregulation of intestinal flora through immune mechanisms.<sup>6</sup> COVID-19 leads to various degrees of liver injury, presenting with abnormal levels of alanine aminotransferase (ALT), aspartate amino-transferase (AST) and albumin accompanied by slightly elevated bilirubin levels as well as elevated gamma-glutamyltransferase and alkaline phosphatase levels (ALP). Liver injury may

be due to the cytopathic effects of the virus. Virus binding to ACE2 receptors in hepatocytes especially, cholangiocytes, and there occurs an immune-mediated inflammation. Another possible factor may be the high positive end-expiratory pressure level that can cause hepatic congestion by increasing right atrial pressure. Indeed, drug-induced liver injury caused by COVID-19 treatment should be carefully considered.<sup>7</sup>

Among the COVID-19 patients, a wide range of GI symptoms have been reported. A recent research work in China confirmed that more than 80% of the patients experienced digestive symptoms to some extent, including diarrhea, diminished appetite, nausea, vomiting, abdominal pain and gastrointestinal bleeding during their hospitalization.<sup>8,9</sup> Lu et al<sup>10</sup> reported that diarrhea and vomiting were observed in 8.8% and 6.4% in a cohort study of children with COVID-19 infection.

A systemic review and meta-analysis showed that gastrointestinal symptoms are common in children with COVID-19 with nearly a quarter of patients exhibiting at least one gastrointestinal symptom. The most common gastrointestinal symptom was diarrhoea, followed by vomiting and then abdominal pain.<sup>11</sup>

Another intriguing GI manifestation is a “surgical” abdomen clinically mimicking appendicitis. Imaging showed features of terminal ileitis, ileo-colitis and/or mesenteric lymphadenitis, all patients improving with conservative management.<sup>12</sup> In a cohort study in Hong Kong, 15 COVID-19 patients out of 59 presented gastrointestinal (GI) symptoms. The presence of the RNA molecules of the virus in the patient’s stool was tested, and 48% had positive results. In some patients, the stool result remained positive even after the

respiratory samples became negative. This study recommended that health care workers should take extra precautions during sampling from GI secretion and conducting endoscopic procedures in COVID-19 patients.<sup>13</sup>

A systematic review showed that the gastrointestinal tract was the system more frequently associated to the multisystem inflammatory syndrome in children (MIS-C), a severe spectrum of disease in children.<sup>14</sup> Laboratory-confirmed COVID-19 pediatric patients with gastrointestinal manifestations, particularly vomiting, had a severe systemic involvement and high mortality rate. Moreover, cardiac abnormalities were a relevant finding in this setting. Pediatric COVID-19 patients, mainly in those with underlying conditions and gastrointestinal manifestations, may have a severe and systemic involvement, with high mortality rate.

Gastrointestinal involvement had high levels of serum biomarkers, indicating acute inflammation, predominantly with increase of fibrinogen and D-dimer parameters. The elevated levels of these parameters have been also correlated with cytokine storm, multi-organ dysfunction and unfavorable outcome in severe patients with COVID-19.<sup>15</sup> de Paula et al<sup>16</sup> evaluated 83 patients with laboratory-confirmed COVID-19, both by real-time RT-PCR exam and serological test and aimed to compare demographic and anthropometric data, underlying conditions, clinical characteristics, exams, treatments, and outcomes in laboratory-confirmed pediatric COVID-19 patients with and without gastrointestinal signs and symptoms. Therefore, they suggested that laboratory-confirmed COVID-19 pediatric patients with digestive signs/symptoms require attention for hyperinflammation condition and cardiac abnormalities. Multicenter study conducted in 15 hospitals including 101 COVID-19 pediatric inpatients showed that GI symptoms were present in 57% and were the first manifestation in 14%. Adjusted by confounding factors, those with GI symptoms had higher risk of pediatric intensive care unit admission. GI symptoms are predictive of severity in COVID-19 children admitted to hospitals.<sup>17</sup>

So gastrointestinal symptoms are frequent in COVID-19 pediatric patients admitted to hospital. The

spectrum of GI manifestations of pediatric COVID-19 may range from mild non-specific symptoms to severe symptoms mimicking a “surgical” abdomen, which may occur even in the absence of respiratory symptoms. These symptoms are also predictive of severity, regardless to other confounding factors and associated with severe systemic involvement and high mortality rate. GI symptoms had higher risk of pediatric intensive care unit admission. It is important for pediatricians to be aware of these clinical presentations and maintain a high index of suspicion for COVID-19, especially in those who have been exposed to a COVID-19 patient.

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