

Gastrointestinal Manifestation of COVID-19 in Pediatric Patients: A Literature Review

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Abstract

First reported in China on 31 December 2019, Coronavirus Disease 2019 (COVID-19) is primarily a respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that can manifest in other extrapulmonary organs such as the gastrointestinal tract. The GI symptoms that are commonly found in COVID-19 cases include diarrhea, nausea, vomiting, abdominal pain, and feeding difficulty. Of all ages, studies related to GI manifestation of COVID-19 in children is lacking compared to adults. The aim of this article is to review previous studies discussing the gastrointestinal manifestation of COVID-19 in pediatric patients by utilizing PubMed and Google Scholar as the primary database to find relevant and appropriate medical journals.

Keywords: COVID-19, SARS-CoV-2, pediatrics, gastrointestinal manifestation

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a highly infectious viral disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that primarily attacks the respiratory system. The World Health Organization (WHO) reported that this disease was discovered in Wuhan, China on 31 December 2019. In the following months, COVID-19 continue to spread around the world and was declared as a global pandemic by the WHO since March 2020 [1,2]. COVID-19 is known to affect all age groups from pediatric, adult, and geriatric. As of 19 December 2022, WHO has received reports of over 649 confirmed cases of COVID-19 worldwide, including more than 6,6 million deaths [3]. The number of cases of children under 18 years old infected with COVID-19 varies in different countries, where in the US, China, Italy, and Spain the percentage of pediatric COVID-19 cases comprise of 2%, 2.2%, 1.2%, and 0.8% respectively [4]. According to Ikatan Dokter Anak Indonesia (IDAI), 12.5% of COVID-19 cases in Indonesia were pediatric cases, with a case fatality rate of 3-5% [5].

The SARS-CoV-2 is mainly transmitted through respiratory droplets, aerosol particles, as well as fomite transmission from inanimate objects, with an incubation period of 2-14 days [6]. Unlike in adult patients, the clinical manifestation of COVID-19 in pediatric patients are generally mild or asymptomatic with several common symptoms such as fever, cough, shortness of breath, fatigue, and other flu-like symptoms [7]. Although it is most usually associated with respiratory illness, evidence shows that it can also have an impact on the gastrointestinal (GI) system, with a higher incidence found in pediatric age. In fact, GI manifestations are the most prevalent extrapulmonary manifestation of COVID-19 in pediatric patients, with a percentage of 32.5% compared to other extrapulmonary manifestations of COVID-19 [8]. The most common reported GI symptoms in pediatric patients with COVID-19 include nausea, vomiting, diarrhea, abdominal pain, and anorexia [9].

With the rapidly increasing number of published literatures regarding the clinical manifestations of COVID-19 in pediatric patients, differences in the GI manifestations among pediatric COVID-19 patients are found from various studies. The aim of this literature review is to summarize the current understanding of COVID-19 in pediatric patients

including the demographic characteristics, pathophysiology of the disease, risk factors, GI manifestations, as well as the diagnosis and treatment of the disease. 87

2. Overview of COVID-19 in Pediatric Patients

Coronaviruses (CoVs) are positive-stranded RNA viruses distinguished by their crown-like appearance under the electron microscope due to the presence of spike glycoproteins on the viral envelope. Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV) are the four genera of coronaviruses now recognized as belonging to the Orthocoronavirinae subfamily of the Coronaviridae family. The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which were previously linked to the SARS-CoV and MERS-CoV outbreaks, are subgenera of the new betaCoV known as SARS-CoV-2 [10]. Although recent findings by the WHO explaining the likely origins of SARS-CoV-2 were inconclusive, it is largely believed that this virus was generated from an animal, implying zoonotic transmission. Given the high degree of genomic similarities between the human SARS-CoV-2 genome and those of known animal coronaviruses, several genomic analyses showed that SARS-CoV-2 most likely developed from a strain found in bats [11].

2.1 Demographic Characteristics

Early in the pandemic, COVID-19 cases have been predominantly more common among adults over 15 years old while the confirmed cases of COVID-19 in children was fairly low. However, the number of confirmed COVID-19 cases among children has considerably grown overtime since they are not able to wear face masks or take other particular preventative and control measures [4]. In China, the predominant age group of pediatric patients with COVID-19 is 6 to 10 years with a median age of 7 years old [12]. According to a systemic review, the patients' mean ages ranged from 6.2 to 11 years, with a composite mean age of 7.9 years, across studies [13]. *Kementrian Kesehatan Republik Indonesia* (Kemenkes RI) reported that as of January 2021, the most prevalent age group of pediatric COVID-19 cases in Indonesia was 6 to 18 years, which was 8.9% of the total 11.6% of pediatric COVID-19 cases [14]. Another study also mentioned that the highest mortality among confirmed COVID-19 cases in pediatric age group in Indonesia was children aged 10 to 18 years (26%) [15]. These findings show that the predominant age group of pediatric patients infected with COVID-19 differ in several countries, which may be influenced by the research locations, total number of patients studied, and different waves throughout the COVID-19 pandemic.

The sex distribution of pediatric patients with COVID-19 varies in different countries, hence the correlation between sex distribution and prevalence of COVID-19 can yet to be determined. Based on a comprehensive systematic review, the number of male pediatric patients of COVID-19 are greater than the female, which comprises of 56% of the total patients [16]. Similar result was found in China where the prevalence of male pediatric patients is higher than female pediatric patients with COVID-19. Studies in Indonesia, however, found several different findings where some hospital had more female patients than the male, while others had more male patients than the female [17,18]. Nevertheless, the percentage difference between the number of male and female patients in several studies is not substantial. Different research locations as well as the total number of patients in each study may affect these results.

2.2 Pathophysiology and Risk Factors

Coronaviruses are positive-sense, single-stranded RNA viruses that are enveloped and around 30 kb in size. These viruses affect a wide spectrum of host species, which may be broadly categorized into the genera alpha, beta, delta, and gamma based on their genomic structures. The beta coronavirus family includes the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV [10]. Five stages generate the virus's life cycle with the host: attachment, penetration, biosynthesis, maturation, and release. SARS-CoV-2 enter the host cells using its viral spike glycoproteins by endocytosis or membrane fusion after binding to host receptors (penetration) called as Angiotensin-Converting Enzyme 2 (ACE-2) receptor. Once the viral contents are released into the host cells, viral RNA reaches the nucleus for replication. Viral proteins are produced using viral mRNA (biosynthesis). Then, after maturation, additional virus particles are produced and discharged [19].

In the human body, the alveolar epithelial cells in the lungs have the highest expression of ACE2 receptors. The involvement of the ACE-2 receptor in the lung parenchyma is believed to be significant for both the severity of the illness and subsequent transmission. Numerous extrapulmonary tissues, such as the GI tract, heart, liver, and kidney, also express ACE-2 receptors. The luminal surface of differentiated epithelial cells in the small intestine has been reported to have high quantities of ACE-2 receptors, but levels in the crypt cells and colon are lower. In the digestive tract, ACE-2 is known to have a number of roles, including the absorption of amino acids and the preservation of gut homeostasis [9]. Based on a study, SARS-CoV-2 RNA was discovered in biopsies taken from the rectum, duodenum, oesophagus, and stomach of patients confirmed with COVID-19. Due to the GI tract's involvement during COVID-19, malabsorption, an imbalance in intestinal secretions, and stimulation of the enteric nervous system may occur. This may be caused by direct viral damage and/or an inflammatory immunological response [20]. In addition, it is noted in several studies that pediatric patients with COVID-19 tend to have a milder clinical course than adult patients. This finding may be influenced by the smaller number of ACE-2 receptors present in children compared to adults [17].

Children are far less likely than adults to have comorbidities including diabetes, hypertension, and cardiovascular disease. The primary risk factors for COVID-19 infection in the pediatric population have been identified as close contact with a family member who are also infected with COVID-19 and a history of travel to or living in an endemic region. A variety of comorbidities and underlying illnesses, including hydronephrosis, leukemia, and intussusception, were present in the few pediatric patients who required ICU hospitalization and those who died [21]. Several studies in Indonesia also mentioned the presence of various underlying medical conditions in pediatric patients with COVID-19 such as malnutrition and malignancy, which may affect their clinical course and severity of illness [5,15,22].

2.3 Gastrointestinal Manifestation

Significant differences in the frequency of GI manifestations in adult COVID-19 patients have been found by several study groups. Research from Europe and the United States revealed a prevalence of 55% and 35-61%, respectively, whereas studies from China and Hong Kong found a range of 8.7 to 26% of COVID-19 patients having GI symptoms [9]. In pediatric population, the GI manifestations of COVID-19 also have a various range of prevalence, with the most common reported GI symptoms being nausea, vomiting, diarrhea, abdominal pain, and anorexia or feeding difficulties.

A systematic review that analyzed numerous studies from several different countries discovered 9.5% of pediatric patients with COVID-19 were presented GI symptoms [16]. Higher prevalence was found in a study by Puoti et al. [9], which reported that the total prevalence of GI symptoms in pediatric COVID-19 cases is up to 84.1%, where diarrhea is the most prevalent symptom (up to 56.8%), followed by vomiting (up to 50%), nausea (up to 34.3%), abdominal pain (up to 27.3%), and feeding difficulties (up to 23%). In Indonesia, a few studies discovered that the prevalence of GI manifestations of COVID-19 in pediatric patients range from 9 to 31% [17,22]. Consistent with other studies, the most common GI symptoms in pediatric COVID-19 in Indonesia includes diarrhea, nausea or vomiting, abdominal pain, and anorexia or loss of appetite. Hepatic injury is also found in some cases.

The correlation between GI manifestation and the illness severity of COVID-19 remains inconclusive. In up to 10% of children, GI manifestations may be the only sign of COVID-19, be the first symptoms of COVID-19 to present, start before respiratory symptoms, or occur later in the course of the disease [9]. Age and ACE-2 expression in the small intestine are positively correlated, with ACE-2 mRNA expression rising with older age. Children may thus have lower levels of ACE-2 receptor expression than adult patients, making them more susceptible to ACE-2-downregulation and increased vulnerability to GI manifestation such as diarrhea. For this reason, several authors hypothesize that, despite the equal variety of prevalence of GI symptoms in children and adults, children's GI symptoms are often linked to SARS-CoV-2 infection as a primary reaction due to the modest expression of ACE2 and hence reflect milder symptoms [23].

There is detectable viral RNA in the patients' feces in approximately 50% of cases with COVID-19. Live virus has been discovered in the feces of COVID-19 patients using electron microscopy [24]. In China, a study using epidemiologic and environmental data suggested that fecal aerosols produced during flushing may have been the cause of a cluster of cases, raising the potential of SARS-CoV-2 fecal-aerosol transmission [25]. Although the prospect of

fecal-oral transmission has been raised by the discovery of active viral RNA in the linings of the GI tract and in feces, this method of transmission has not been proven. 89

2.5 Diagnosis and Treatment

At least two of the clinical symptoms of COVID-19 (fever, respiratory symptoms, gastrointestinal symptoms, or exhaustion), as well as supporting laboratory findings such low to normal leukocytes, elevated CRP, and abnormalities on a chest X-ray or CT, are utilized to make a clinical diagnosis. As a standard procedure, RT PCR testing is done to diagnose COVID-19. Understanding the COVID-19 history of the adults around the patient is also important to note when diagnosing a pediatric COVID-19 case. According to the Handbook released by IDAI in December 2020, cases involving children and neonates are classified as suspected cases, probable cases, confirmed cases, and close contacts according to the COVID-19 [14].

The clinical condition and severity of the illness determine how pediatric COVID-19 patients are treated. Children who are suspected of having COVID-19 must be isolated in a separate room or self-isolated at home. While severe cases are managed in the PICU, confirmed cases can be treated in the standard inpatient room among other confirmed patients. The requirement for mechanical breathing, shock needing vasopressor medications, changes in mental state, multiorgan dysfunction, and the presence of intubation indication are reasons for pediatric COVID-19 patients to be hospitalized in the PICU [14]. The pharmacologic medications necessary for treating COVID-19 in pediatric patients are mostly symptomatic medications such as antipyretics and analgesics, as well as other drugs to treat the respiratory, GI, or other symptoms present in the patient. Vitamin, minerals, and other supplements are also recommended to be given as a supportive addition to improve the patient's condition.

3. Conclusion

COVID-19 is a viral infectious disease caused by SARS-CoV-2 that affects not only the respiratory system, but also other extrapulmonary organs such as the GI tract. High distribution of ACE-2 receptors in the epithelial cells lining the GI tract play a significant role in the pathogenesis of GI manifestation of COVID-19 in pediatric patients. The predominant GI manifestation in pediatric COVID-19 cases include nausea, vomiting, diarrhea, abdominal pain, and anorexia, with varying prevalence in different studies. In contrast to adult population, the ACE-2 receptors expression in children's GI tract is lower in quantity, which may explain the milder clinical course of COVID-19 in pediatric cases despite the equal variety of prevalence of GI symptoms between children and adult.

References

1. Lee IC, Huo TI, Huang YH. Gastrointestinal and liver manifestations in patients with COVID-19. *Journal of the Chinese Medical Association*. 2020 Jun;83(6):521–3.
2. Puoti MG, Rybak A, Kiparissi F, Gaynor E, Borrelli O. SARS-CoV-2 and the Gastrointestinal Tract in Children. *Front Pediatr*. 2021 Feb 22;9:617980.
3. WHO Coronavirus (COVID-19) Dashboard [Internet]. World Health Organization. World Health Organization; [cited 2022Dec20]. Available from: <https://covid19.who.int/>
4. Baghizadeh Fini M, Seraj B, Ghadimi S. COVID-19 in Pediatric Patients: A Literature Review. *IJSRDMS*. 2020 Oct; 2(4): 126-130.
5. Hartoyo E, Ariyani R, Fitri L, Nurfahmayati T, Qotrunnada SA, Rahmiati R. Studi Deskriptif dan Analitik COVID-19 pada Anak di Rumah Sakit Umum Daerah Ulin Banjarmasin. *SP*. 2022 Feb 26;23(5):290.
6. Silangen KT, Waleleng BJ, Wantania FEN. Gejala Gastrointestinal pada Pasien COVID-19. *e-CliniC*. 2021 Mar 14;9(2):279–86.
7. Patel NA. Pediatric COVID-19: Systematic review of the literature. *American Journal of Otolaryngology*. 2020 Sep;41(5):102573.
8. Pousa PA, Mendonça TSC, Oliveira EA, Simões-e-Silva AC. Extrapulmonary manifestations of COVID-19 in children: a comprehensive review and pathophysiological considerations. *Jornal de Pediatria*. 2021 Mar;97(2):116–39.
9. Puoti MG, Rybak A, Kiparissi F, Gaynor E, Borrelli O. SARS-CoV-2 and the Gastrointestinal Tract in Children. *Front Pediatr*. 2021 Feb 22;9:617980.
10. Chan JFW, Kok KH, Zhu Z, Chu H, To KKW, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020 Jan 28;9(1):221–36.
11. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med*. 2020 Mar 17;1–3.
12. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. 2020 Jun 1;145(6).
13. Patel KP, Patel PA, Vunnam RR, Hewlett AT, Jain R, Jing R, et al. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. *Journal of Clinical Virology*. 2020 Jul;128:104386.
14. Hadiyanto ML. Gambaran hingga tatalaksana COVID-19 pada anak. *Intisari Sains Medis*. 2021 Apr 30;12(1):250–255.
15. Pudjiadi AH, Putri ND, Sjakti HA, Yanuarso PB, Gunardi H, Roeslani RD, et al. Pediatric covid-19: Report from Indonesian Pediatric Society Data Registry. *Frontiers in Pediatrics*. 2021 Sep 23;9.
16. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine*. 2020 Jul;24:100433.
17. Lambe GM, Mu'ti A, Buchori M. KARAKTERISTIK PASIEN COVID-19 PADA ANAK DI RSUD AJI MUHAMMAD PARIKESIT TENGGARONG TAHUN 2020. *Verdure: Health Science Journal*. 2022 Mar 31;4(1):27–33.
18. Angelina, Novriandina S, Dewi AC. Profil Klinis dan Luaran Pasien Anak dengan Covid-19 yang Dirawat di Ruang Isolasi Rumah Sakit Umum Daerah Balaraja Selama Gelombang Ketiga. *Sari Pediatri*. 2022 Oct;24(3):141–50.
19. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clinical Immunology*. 2020 Jun;215:108427.
20. Kariyawasam JC, Jayarajah U, Riza R, Abeysuriya V, Seneviratne SL. Gastrointestinal manifestations in COVID-19. *Transactions of The Royal Society of Tropical Medicine and Hygiene*. 2021 Mar 16;trab042.
21. Alsohime F, Tamsah MH, Al-Nemri AM, Somily AM, Al-Subaie S. COVID-19 infection prevalence in pediatric population: Etiology, clinical presentation, and outcome. *Journal of Infection and Public Health*. 2020 Dec;13(12):1791–6.
22. Anam MS, Wistiani W, Sahyuni R, Hapsari MMDEAH. Profil Klinis, Laboratorium, Radiologis dan Luaran Pasien COVID-19 Pada Anak di RSUP Dr. Kariadi Semarang. *Medica Hospitalia : Journal of Clinical Medicine*. 2020 Aug 28;7(1A):130–6.

23. Vuille-dit-Bille R, Liechty K, Verrey F, Guglielmetti L. SARS-CoV2 receptor ACE2 gene expression in small intestine correlates with age. *Amino Acids*. 2020;52:1063–5. 91
24. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020 Mar 17;323(11):1061–9.
25. Kang M, Wei J, Yuan J, et al. Probable Evidence of Fecal Aerosol Transmission of SARS-CoV-2 in a High-Rise Building. *Ann Intern Med*. 2020;173(12):974–980.