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Gastrointestinal Symptoms and Liver Dysfunction in Children with Covid 19 Infection

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Abstract:

Background: *Although, the primary organ of involvement are lungs in Coronavirus disease 2019 (COVID-19), however liver, and gastrointestinal (GI) involvement is being increasingly reported in the emerging data from various centers across the world.*

Objective: *To observe the gastrointestinal symptoms and liver dysfunctions in children with Covid 19 infection.*

Methods: *This retrospective observational study was conducted in children with Covid 19 RT PCR positive, aged between 0 and 15 years admitted from March 2020 to March 2022. Data of 103 consecutive children were collected retrospectively. We analyzed the clinical and laboratory data of 101 children after exclusion 2 children as associated acute HAV infection and liver cirrhosis using Statistical Package for Social Science (SPSS) for Windows version 29.*

Results: *A total of 101 children with Covid 19 were analyzed in this study. Of these 101 children, 61 were male. The mean age was 5.4 years (SD 4.9). 44 children had gastrointestinal presentation in the form of vomiting, diarrhea, abdominal pain. Most common gastrointestinal presentation were nausea and vomiting (34.7%), then diarrhea (21.8%), abdominal pain (15.8%), hepatosplenomegaly (3%), ascites and jaundice 1% in each respectively. Total 17(16.8%) patients presented with gastrointestinal manifestations without any respiratory symptoms or any other coinfections including 10 acute gastroenteritis, 4 acute gastritis, 2 dysenteries (bloody stool) with stool culture negative and 1 intussusception. Liver dysfunctions were found in 16(15.8%) patients in the form of raised ALT (16) or AST (4) or low albumin (10). All 10 children with low albumin had MIS-C. None of them developed liver failure. There was statistically no significant difference between covid 19 children with GI symptoms and without GI symptoms clinically and biochemically except longer hospital stays more frequent in GI symptoms group (p=0.03).*

Conclusion: *Gastrointestinal symptoms may be a presenting clinical feature even without any respiratory symptoms in Covid 19 children. Liver dysfunction is uncommon in children with mild Covid 19 infections. If liver dysfunction is found, we think that it may progress to more severe infection like MIS-C or associated with co infection.*

Keywords: *Children, Covid19, Gastrointestinal symptoms, Liver dysfunctions.*

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Introduction:

The novel coronavirus (SARS-CoV-2) outbreak started in China in December 2019. The rapid transmission of the infection and its virulence forced the World Health Organization to declare the associated disease (COVID-19) an international public health emergency. Previously the typical clinical picture of children with COVID-19 is a mild or even asymptomatic disease, with practically no associated mortality. The most common symptoms are fever, dry cough, and dyspnea. However, as knowledge of COVID-19 has progressed, symptoms affecting any other organ or system have been described.[1]

There are so many adult studies where they showed GI symptoms not so frequent in covid 19 patients.[2-4] However, there are paucity of studies specific in children with Covid 19 which showed covid 19 associated GI manifestations. In our country, no such studies have been done. Therefore, this retrospective study has undertaken to see the incidence of GI manifestations and liver dysfunction in hospital admitted Covid 19 Bangladeshi children.

Materials and Methods:

This is a retrospective observational study. We conducted the study in children with Covid 19 RT PCR positive children between 0 and 15 years of age admitted to the Department of Pediatrics at Evercare hospital, Dhaka a tertiary care hospital of Bangladesh from March 2020 to March 2022. A total of 103 children with Covid 19 were admitted in pediatric ward, cabin or PICU in this period. Two were excluded as they have other liver diseases, 1 acute viral hepatitis and another 1 was a case of chronic liver disease. Data were collected retrospectively from the medical record department of hospital software after approval from institutional ethical committee.

At the end of study the data were analyzed using Statistical Package for Social Science (SPSS) for Windows version 29 (IBM, Chicago, USA).Descriptive statistics were used for demographic and baseline data and were presented as mean ± standard deviation (SD), number or percentage. The Chi-square test was used for categorical variable. P values <0.05 was considered as significant.

Results:

A total of 101 children after 2 exclusions with Covid 19 were included in this study. All patients were confirmed Covid 19 RT PCR. Of these 101 children, 61 were male and 40 were female. The study included 53(52.5%) children under 5 years, 29(28.7%) children between 5 to 10 years and more than 10 years 19(18.8%) children. The mean age was 5.4 years (SD 4.9). Most patients are under 5 years old.

40 children had simple covid 19 infection and 61 had covid 19 with serious illness in the form of severe involvement or associated with coinfection. 17 children had MIS-C, 10 patients had pneumonia, associated with dengue fever, febrile seizure and seizure disorder were found in 5 patients in each respectively. Typhoid fever and UTI were also associated in 2 patients in each respectively.

44 children had gastrointestinal presentation in the form of vomiting, diarrhea, abdominal pain. Most common gastrointestinal presentation were nausea and vomiting(33.7%), then diarrhea (21.8%), abdominal pain (15.8%), hepatosplenomegaly (3%), ascites and jaundice 1% in each respectively (Table I). A total of 17(16.8%) patients presented with gastrointestinal manifestations without any respiratory symptoms or any other coinfections including 10 acute gastroenteritis, 4 acute gastritis, 2 dysentery and 1 intussusception.

Table I

Gastrointestinal presentation of Covid 19 children (N=101)

Parameters	Number	%
Overall gastrointestinal findings	44	43.6
Nausea and vomiting	35	34.7
Diarrhea	22	21.8
Abdominal pain	16	15.8
Jaundice	1	1
Hepatosplenomegaly	3	3
Ascites	1	1

Liver dysfunctions were found in 16(15.8%) patients in the form of raised ALT (16) or AST (4) or low albumin (10). Among the raised ALT 10 were MIS-C, 2 associated with typhoid co-infection, 2 Dengue hemorrhagic fever and 2 remdesivir induced. Children with low albumin who hadMIS-C (Table II).

Table II

Liver dysfunction in Covid 19 disease

Liver function test	Number	%
Raised ALT	16/59	27.1
Raised AST	4/16	28.6
Raised bilirubin	1/11	9
Low albumin	10/20	50

Data are presented as n (%), ALT, alanine amino-transferase, AST, aspartate aminotransferase.

There was no statistically significant difference between covid 19 children with GI symptoms and without symptoms regarding age, gender, clinical,

biochemical profiles except longer hospital stay where p value significant (0.03) (Table III).

Table III

Demographic, clinical, laboratory features and outcome of covid 19 children

Parameters	All patients n (101)	With GI symptoms n (44)	Without symptoms n (57)	p value
Age years (Mean ±SD)	5.4(4.9)	4.43(4.01)	6.1(4.8)	0.05
Age groups				
<5 years	53(52.5)	27(61.4)	26 (45.6)	
5-10 years	29(28.7)	12(27.3)	17 (27.9)	0.171
>10 years	19(18.8)	5(1.4)	14 (24.6)	
Sex	101	44	57	
Female	40(39.6)	16	24	0.56
Male	61(60.4)	28	33	
Fever				
Yes	87(86.1)	41(40.6)	46(80.7)	0.08
No	14(13.9)	3(6.8)	11(19.3)	
CRP (N)	98(97)	44(100)	54(94.7)	
Normal<0.33	40(40.8)	16(36.4)	24(44.4)	
Mildly raised <3	38(38.8)	19(43.2)	19(35.2)	0.67
Very high >3	20(20.4)	9(20.5)	11(20.4)	
Ferritin(N)	50(49.5)	24(54.5)	26(45.6)	
Normal	32(64)	14(58.3)	18(69.2)	0.42
raised	18(36)	10(41.7)	8(30.8)	
D-dimer(N)	63(62.3)	31(70.4)	32(56.1)	
Normal<500	20(31.7)	5(16.1)	15(46.9)	
Raised<1000	12(19)	6(19.4)	6(18.8)	0.17
Highly raised>1000	31(49.2)	20(64.5)	11(34.4)	
Hospital stays.	101	44	57	
<8 days	85(84.2)	33(75)	52(91.2)	0.03
>8 days	16(15.8)	11(25)	5(8.8)	

Data are presented as n (%), n/N (%) and N is the total number of patients with available data. P value refers to the comparison between patients with GI symptoms and those without GI symptoms

Discussions:

Covid 19 infection is less severe in children, presented as an asymptomatic or mild disease course to rarely, life-threatening conditions.[5,6]

According to an adult study, GI symptoms are not frequent, nausea/vomiting is seen in around 5% patients and diarrhea in 3.8%.[2] However, in the study by Fang et al, up to 79% of patients had GI involvement with predominant symptoms being anorexia, diarrhea, nausea/vomiting, abdominal pain, and GI bleed.[3] Approximately 10% of patients with the GI symptoms can also precede fever and dyspnea by 1-2 days.[4] There is a recent meta-analysis of 57 studies[7]that has reported the prevalence of diarrhea in 7.7%, nausea/vomiting in 7.8%, and abdominal pain in 3.6% of patients. These studies are not specific to children.However, a systemic review in a pediatric cohort with Covid 19 showed that the commonest GI symptoms were diarrhea—19.08% [95% confidence interval (CI) 10.6–28.2], nausea/vomiting 19.7% (95% CI 7.8– 33.2) and abdominal pain 20.3% (95% CI 3.7–40.4). The presence of diarrhea was significantly associated with a severe clinical course with a pooled OR of 3.97 (95% CI 1.80–8.73; $p < 0.01$).[8]

In the presented study we found that 43.7% of patients have gastrointestinal manifestations. Among them the most common was nausea and vomiting 34.7%, diarrhea 21.8%, abdominal pain 15.8%, jaundice 1%, hepatosplenomegaly 3% and ascites 1 %. Findings are almost similar with previous studies.The presented study also found that 17 patients presented with gastrointestinal manifestations without any respiratory symptoms or any other coinfections including 10 acute gastroenteritis, 4 acute gastritis, 2 dysentery and 1 intussusception.

Previous studies also reported that pediatric covid 19 may also present with GI manifestations without any respiratory symptoms.[9-11] Early reports in children suggested that some patients presented with watery diarrhoea as the first symptom although diarrhea usually begins 1-8 days after the disease onset.[9] A study in a Spanish cohort has been confirmed, where 25 out of 101 patients presented GI symptoms in absence of respiratory symptoms, and GI symptoms were the first disease manifestation.[10] This findingis slightly higher than our findings. Other study reported, diarrhea and abdominal pain were the presenting symptoms in 37% and 25% of patients, respectively.[12]

Diarrhoea, nausea, vomiting, and abdominal pain are the gastrointestinal symptoms in children with Covid 19 and GI involvement seems extremely relevant in the novel multisystem inflammatory syndrome in children (MIS-C) that follows SARS-CoV-2 infection.[13-15] In the presented study there were 15 children with MIS-C who all have GI manifestations. This finding is like other studies.

Angiotensin-converting enzyme 2 (ACE2), which is present on host cells in gastrointestinal tract. Spike protein of SARS-CoV-2 contains two subunits, S1 and

S2[16] Virus is attached to the cell membrane by S1 subunit, and S2 subunit is involved in the fusion of cell membranes by using ACE2.[17] For priming this process, serine proteases, mainly Transmembrane protease serine 2 (TMPRSS2) is required.[18] Binding of SARS-CoV-2 with ACE2 may alter gut microbiota, interfere with innate immunity, and inhibit dietary tryptophan absorption, leading to diarrhea.[19] High-ACE2 receptor staining in the cytoplasm of gastric, duodenal, and rectal epithelial cells of COVID-19 infected patients have been demonstrated,[20] supporting viral entry and GI symptoms of diarrhea, abdominal pain, and nausea/ vomiting.Most common liver injury in Covid 19 is raised liver transaminases around 14-53% cases. [1,4,21-22] Most of the cases are mild and transient elevated amino transaminase. However, raised liver enzymes are rarely associated with increased mortality.[22] The mechanism is unclear, and various factors like pre-existing chronic liver disease, drug toxicity, ischemic hepatitis secondary to hypotension and, rarely, direct injury by SARS-CoV-2 is implicated. ACE2 receptors and TMPRSS2 are expressed in cholangiocytes and hepatocytes, and viral binding to these receptors may result in entry of SARS-CoV-2 in liver cells.[23,24] However, only a small percentage of hepatocytes express ACE2 receptors (~2.6%).[25] In our study, we also found gastrointestinal manifestations though common however liver dysfunction found only small percentages of children which support the above evidence. We found liver dysfunctions were found in 16(15.8%) patients in the form of raised ALT (16) along with elevated AST (4) and low albumin (10). Among the raised ALT 10 were Covid 19 associated MIS-C, 2 associated with typhoid co-infection, 2 Dengue hemorrhagic fever and 2 remdesivir induced. Children with low albumin were all who developed MIS-C. Gastrointestinal symptoms are increasingly recognized to be associated with the presentation of MIS-C. In 2 reported series of 35 and 44 pediatric patients with MIS-C, more than 80% showed some type of digestive involvement.[26,27] Giacomet V et al also found in their study, gastrointestinal symptoms were more frequently associated with severe and critical phenotype.[28] Covid 19 associated acute live failure is rare. Weber et al.[27] reported an older patient with covid 19 developed liver failure. None of the Covid 19 children in the presented studydeveloped liver failure.

In the presenting study, there was no statistically significant difference between covid 19 children with GI symptoms and without symptoms regarding age, gender, clinical, biochemical profiles. However, who have GI symptoms need prolonged hospital stays where p value significant (0.03).

As a limitation of the study, it is single center study, the data were retrospectively retrieved.

In conclusion, gastrointestinal symptoms are frequent in COVID-19 pediatric patients admitted to hospital. Eventually, Covid 19 children may presented with isolated GI manifestations. These symptoms are also predictive of severity, may need prolonged hospital stay regardless to other confounding factors. Liver dysfunction is uncommon in mild covid 19 infections in children. If liver dysfunction is found, we can think it may progress to more severe infection like MIS-C or associated with coinfection.

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