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Gastrointestinal and hepatic manifestations among hospitalized COVID-19 children

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Abstract

Background Gastrointestinal (GI) manifestations have been reported as the most extra-pulmonary manifestations of coronavirus disease 2019 (COVID-19). Recognizing the various manifestations, especially as presenting symptoms of COVID-19 is of great importance. We aimed to investigate the GI and hepatic manifestations of COVID – 19 in children, determining the factors associated with the disease severity and prognosis related to GI symptoms.

Methods In this retrospective study, children aged 1-month to 16-years who were admitted to Afzalipour Hospital in Kerman, Iran. for a period of one year (from October 2020 to October 2021) with the diagnosis of COVID-19 were included. The comparison of clinical symptoms and laboratory variables in the appendectomy and non-appendectomy groups were evaluated. Patients' information was extracted from the patient's medical record and analyzed in SPSS statistical. software.

Results A total of 163 patients (107 boy and 56 girls) with mean age of 4.35 ± 3.86 (range 0.08 to 16) years were included. The most frequent GI symptoms at the time of admission were watery diarrhea (46.6%), vomiting (45.4%), and abdominal pain (32.5%). There was no significant relationship between clinical symptoms and laboratory variables in the appendectomy and non-appendectomy groups, but the severity of COVID-19 was significantly associated with appendicitis ($P = 0.03$). There was no statistically significant relationship between liver enzyme levels and disease severity and pediatric intensive care unit admission.

Conclusions Although most COVID-19 patients present with GI manifestations, we could not determine the relationship between GI and hepatic manifestations and disease severity in this study.

Clinical trial number Not applicable.

Keywords COVID-19, Children, Gastrointestinal, Hepatic, Appendicitis

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Introduction

Coronaviruses are a large family of viruses that are known to be the main causes of respiratory infections in humans. Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) is a new type of this family that was introduced to the world in late 2019, and its related disease has been named as coronavirus disease-2 (COVID-19) [1]. The virus is highly contagious [2], spreading through the airways of affected patients during coughing, sneezing, talking and breathing, in the form of droplets or small aerosol particles [3]. The virus can also be excreted in the feces, which is a sign of direct GI involvement. So, the virus may be present in the stool while respiratory tests are negative [4]. However, SARS-CoV-2 affects various organs of the body such as the GI tract, nervous system, olfactory system, cardiovascular system, liver, kidneys, skin, and eyes [1]. GI manifestations have been reported as the most common extra-pulmonary manifestations of COVID-19 in children [5]. Some GI symptoms due to COVID-19 are common to those of other viral diseases. In some studies, the GI manifestations linked with severity [6]. GI symptoms may appear before respiratory symptoms, and even as the only presentation of disease [7].

Highlighting the types, frequencies and severity of GI manifestations may help in drawing the physicians' attention to make a correct and rapid diagnosis. In addition, the relationship between GI symptoms, laboratory parameters, and disease severity is not well understood in different communities. Finding these relationships may lead to better understanding of disease and its prognosis.

This study aimed to investigate the various GI and hepatic manifestations of COVID-19, as well as their relationship with the severity of the disease among hospitalized children.

Methods

This cross-sectional study was performed retrospectively on children aged 1-month to 16-years old who were admitted at Afzalipour Hospital, Kerman, southeastern Iran, with the diagnosis of COVID-19 (ICD10 Code: U.072 and U.071). Children with positive nasopharyngeal swab tests, using real-time reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 were considered as positive cases of COVID-19. Patients who were admitted to hospital from October 2020 to October 2021 were included in the study. Patients less than one month and old and more than 16 years old, patients with indeterminate diagnosis of COVID-19, and Patients with a history of underlying GI and hepatic diseases including chronic diarrhea, liver failure, hepatitis with other etiologies and inflammatory bowel disease (IBD) were excluded from the study. The comparison of clinical symptoms and laboratory variables in the appendectomy and non-appendectomy groups were evaluated.

Patient information was entered into a data collection form designed by the researchers, which includes the following sections. The first part included demographic information including age, sex, weight, history of underlying disease, and history of contact with a patient with COVID-19. In the second part, the general symptoms of COVID-19 (fever, weakness and fatigue) and organ specific symptoms related to the GI tract such as watery diarrhea, dysentery, nausea, vomiting, abdominal pain, anorexia, constipation were included, and cases such as appendicitis, pancreatitis, elevated liver enzymes, hepatomegaly, cholecystitis, cholestasis, gallbladder hydrops, intussusception were recorded based on final diagnosis. Temperatures above 38.5 ° C (axillary) were considered as fever. Loose stools with a volume of more than 10 ml based on kg body weight per day for infants and more than 200 g per day in older children was considered as diarrhea. The increase of Alanine aminotransferase (Alt) and Aspartate aminotransferase (Ast) enzymes to more than 40 were considered as abnormal values in this study. Other liver tests were considered abnormal as following threshold: Gamma-glutamyl transpeptidase (GGT) > 85 U/L, and total bilirubin > 1.2 mg/dl [8–10]. The results of examinations and vital signs were assigned in the third part. The results of laboratory parameters, radiological findings, length of hospital stay, disease severity, disease outcome (discharge, death) were recorded in fourth and fifth parts, respectively.

According to the "National Guideline for Diagnosis and Treatment of COVID-19 in children and infants" [11], Patients were divided into 5 groups based on the severity of the disease.

Asymptomatic

They have no clinical signs in favor of COVID-19 but have a positive virological test.

Mild

They have clinical symptoms in favor of COVID-19 (fever, dry cough, fatigue, whooping cough, sore throat, headache, diarrhea, vomiting, lack of sense of smell or taste, but no respiratory distress) and abnormal imaging findings.

Moderate

These patients have clinical or imaging symptoms in favor of lower respiratory tract involvement but have an SPO2 > 94% in room air at sea level.

Severe

These patients need oxygen and have clinical signs in favor of lower respiratory tract infection, tachypnea,

respiratory involvement more than 50% on imaging and SPO2 < 94% in room air and Pao2 / Fio2 < 300 (partial pressure arterial oxygen to fraction of inspired oxygen ratio).

Critical

These patients enter the phase of respiratory failure, shock with or without dysfunction of several organs and cytokine storm and are admitted to the Intensive Care Unit (ICU). The condition of these patients is gradually deteriorating, and they need a ventilator.

All the information was completed by reviewing medical records of the patients.

Statistical analysis

The data were statistically analyzed after registration in the data collection form in SPSS statistical software. For statistical description of nominal and rank variables, frequency and ratio were used, and for quantitative variables, mean with standard deviation (SD) was used. For initial comparison of categorical variables between groups, Chi-squared test or Fisher's exact test was used. The independent t-test and Mann-Whitney test were used to compare quantitative variables in different groups of patients in the study (according to the normality of variables). To investigate the relationship between independent and dependent variables, logistic regression was used in two stages, first as a univariate to identify important variables (p-value > 0.2) and in the second stage as a multivariate model to determine the relationship between variables. Independent and independent measures are measured and reported. The effect of variables in logistic regression was reported as Odds ratio with 95% confidence interval and the significance of variables was determined using two-way Wald test and the maximum test error was considered 0.05.

Results

In this retrospective descriptive-analytical study, 163 patients including 56 girls (34.4%) and 107 boys (65.6%) were included. The mean age of children was 4.35 ± 3.86 (0.08-16) years. 31.28% of patients had a history of underlying disease. Congenital cardiovascular disease (10.64%), hematologic disease (6.38%), oncologic disease (6.38%), neurologic disease (23.4), renal disease (14.89%), were the most underlying diseases in patients.

The most frequent symptom was fever (89.6%), followed by anorexia in more than one half and cough in nearly one third of participants. Among GI symptoms (except for anorexia), diarrhea was the most common symptom (46.6%) and there was no case of olfactory and gustatory disorders in these patients. Frequency of other general symptoms and gastrointestinal symptoms are listed in Table 1.

21 cases (12.88%) had respiratory support, of which 10 were intubated. 36 patients (22.1%) were admitted to the Pediatric Intensive Care Unit (PICU) due to worsening of their respiratory symptoms as critical cases or Multisystem inflammatory syndrome of childhood (MISC). In terms of severity, 70 (43%) cases were moderate, 57 (35%) cases were severe, and 36 (22%) cases were critical. According to scientific criteria for the diagnosis of MIS-C, 62 patients (38%) were diagnosed with MIS-C and 12 patients (7.4%) were diagnosed as Kawasaki-like disease in the course of disease.

In this period a variety of GI conditions were experienced in the context of COVID-19. However, 20 patients (12.2%) presented with acute abdominal pain including appendicitis in 14 cases, Intussusception in two cases, Henoch shöenlien purpura (HSP) in two cases, pancreatitis and gall bladder hydrops each in one patient. In addition, two cases developed to Inflammatory Bowel Disease (IBD) and three revealed evidence of new-onset food sensitivity to gluten in the course of disease. The

Table 1 Frequency of general and GI signs & symptoms in hospitalized children with COVID-19

General Signs & symptoms	Frequency	Frequency percentage	Gastrointestinal Signs &symptoms	Frequency	Frequency percentage
Fever	146	89.6	Watery Diarrhea	76	46.6
Anorexia	87	53.4	Vomiting	70	45.4
Weakness	47	28.8	Abdominal pain	53	32.5
Cough	46	28.2	Constipation	7	4.3
Rash	30	18.4	Bloody diarrhea	4	2.5
Headache	19	11.7	Odynophagia	2	1.2
Conjunctivitis	14	8.6			
Respiratory Distress	13	8			
Myalgia	9	5.5			
Sore throat	8	4.9			
Redness around the eyes	8	4.9			
Olfactory & Gustatory Dysfunction	0	0			

cases with IBD were a seven-year-old boy with early presentation of knee arthritis following COVID-19 and a 10-year-old girl that both developed to IBD during few weeks later.

Ultrasound findings

In 77 (47.2%) patients, abdominal ultrasound was performed in the course of disease, while 42 (54.5%) were normal. Other results were free fluid in abdominal cavity (19 cases), lymphadenopathy (14 cases), appendicitis (14 cases), intussusception (two cases), and gallbladder hydrops (one case). In one case, an increase in the thickness of the entire colon wall (ascending, transverse, descending), and in another one, there was an increase in the thickness of the terminal ileum and colon wall from the cecum to the splenic flexion were found compatible with the diagnosis of HSP.

Findings of patients with appendicitis

Fourteen patients were diagnosed as appendicitis and underwent appendectomy. The mean age of these patients was 8.02 ± 3.37 years. Seven cases (63.6%) were girl and two patients (18.2%) had previous underlying disease. In one patient, the appendix perforation resulted to the peritonitis, and in another one complicated as phelegmon. A seven-year-old patient underwent laparoscopic appendectomy due to hemodynamic instability after reductions of intussusception for three times. Five out of these cases (35%) were admitted to PICU due to deterioration of general condition and the severity of the disease was assessed as critical. There were no cases of severe heart failure or cardiac involvement in these patients. All patients were discharged from the hospital in good general condition.

Comparison of studied variables according to appendectomy status

In the first step, the frequency of the studied variables in the two groups of people with and without appendectomy were examined, the results are as follows: The mean age of children with appendicitis was 6.99 ± 3.49 years (range 0.8 to 13.67) and in the group of people without appendicitis was 4.1 ± 3.8 years (range 0. 8 to 15); There was a significant difference between the two means ($P = 0.006$). Table 2 contains a description of the other variables studied in these two groups. In the second step, univariate logistic regression method was used to investigate the independent effect of each of the variables on appendectomy.

The multivariate logistic regression method was used to determine simultaneous effect of variables (that P Value is less than is 0.2 in the univariate model) on appendectomy.

The results of both models are described in Table 3. According to the results in Table 3, disease severity has a significant relationship with the diagnosis of appendicitis in these patients ($P = 0.03$).

Comparison of the studied variables according to the status of liver enzymes

In this study, 40.2% and 31.5% of cases had increased aminotransferases of AST and ALT values above 40, respectively. The maximum values of AST and ALT were 320 U/L and 450 U/L, respectively. However, none of the patients did not experience liver failure.

According to the results shown in Table 4, there is no statistically significant relationship between the level of liver enzymes and the severity of the disease, diagnosis, and hospitalization in ICU among affected children.

Table 2 Comparison of studied variables between appendectomy and non-appendectomy groups in hospitalized children with COVID-19

Variables				Appendicitis				*p*-value
		Total		Yes		No		
		Frequency	Percent	Frequency (14)	Percent (8.6)	Frequency (149)	Percent (91.4)	
Sex	Male	107	65.6	7	50	100	67.1	0.242
	Female	56	34.4	7	50	49	32.9	
Underlying Disease	Yes	52	39.1	2	14.3	50	33.6	0.229
	No	111	68.1	12	85.7	99	66.4	
Fever	Yes	146	89.6	13	92.9	133	89.3	1.000
	No	17	10.4	1	7.1	16	10.7	
Abdominal Pain	Yes	53	32.5	13	92.9	40	26.8	0.000
	No	110	67.5	1	7.1	109	73.2	
Vomiting	Yes	74	95.4	11	78.6	63	42.3	0.011
	No	89	54.6	3	21.4	86	57.7	
Disease severity	moderate	70	42.9	1	7.1	69		0.004
	Sever	52	31.9	9	64.3	4	28.9	
	Critical	41	25.2	4	28.6	37	24.8	

Table 3 Evaluation of the factors affecting the incidence of appendicitis in hospitalized children with COVID-19

Variables		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*. V	OR (95% CI)	*P*. V
Age		1.19 (1.04,1.35)	0.011	1 (0.98,1.02)	o.75
WBC		0.99 (0.96,1.03)	0.87	-	-
Age	Male	*	0.21	*	0.56
	Female	2.04 (0.67,6.14)		1.84 (0.49,6.88)	
Underlying Disease	No	*	0.15	*	0.05
	Yes	0.33 (0.07,1.5)		0.17 (0.03,1)	
Fever	No	*	0.68	*	-
	Yes	1.56 (019,12.76)		-	
Disease severity	Moderate	*		*	
	Severe	14.4 (1.76,118)	0.013	11.1 (1.14,107)	0.03
	Critical	7.54 (0.8,69)	0.077	7.17 (0.61,83.6)	0.11

Statistical comparison of patients with and without GI symptoms

121 cases (74.24%) of patients had GI symptoms and 42 cases (25.76%) had no GI symptoms. Results of comparison of descriptive variables between patients with and without GI symptoms are shown in Table 5. According to the results, the average values of alkaline phosphatase (Alp), Phosphorus (P), Direct Bilirubin (Bill-D), Creatinine (Cr) were significantly different between patients with and without GI symptoms.

Inflammatory bowel disease (IBD) and Covid-19

A 7-year-old boy with a history of left knee arthritis was admitted due to diarrhea, abdominal pain, and limping. The PCR test of the synovial fluid was positive for COVID-19. According to the patient's history and persistent diarrhea, a colonoscopy was performed for the patient. The diagnosis was Crohn's Disease.

Discussion

In this study, 163 patients aged one-month to 16-years old with COVID-19 who admitted at Afzalipour hospital during one-year period were retrospectively evaluated for GI symptoms, laboratory results, and outcome. In the present study, watery diarrhea followed by vomiting were the most common GI symptoms. The results are similar to some studies conducted in Iran and other parts of the

Table 4 Comparison of studied variables in hospitalized children with COVID-19, in terms of increased liver enzymes

Variables	Category	AST			ALT		*p*-value
		Less than 40	More than 40	*p*-value	Less than 40	More than 40	
Total		**64(59.8)**	**43(40.2)**		**74(68.5)**	**34(31.5)**	
Severity	Moderate	18(28.1)	18(41.9)	0.352	26(35.1)	10(29.4)	0.682
	Severe	24(37.5)	13(30.2)		24(32.4)	14(41.2)	
	Critical	22(34.4)	12(27.9)		24(32.4)	10(29.4)	
Diagnosis	MISC	35(54.7)	16(37.2)	0.052	37(50)	14(41.2)	0.719
	Kawasaki-like disease	4(6.3)	3(7)		4(5.4)	3(8.8)	
	Appendicitis	4(6.3)	0(0)		3(4.1)	2(5.9)	
	COVID-19	21(32.8)	24(55.8)		30(40.5)	15(44.1)	
ICU Hospitalization	Yes	17(26.6)	12(27.9)	1.000	18(24.3)	11(32.4)	0.484
	No	47(73.4)	31(72.1)		56(75.7)	23(67.6)	

*Data were shown frequency (percent)

Table 5 Comparison of descriptive variables in hospitalized children with COVID-19, according to the presence or absence of GI symptoms

Variables				GI Manifestations				*p*-value
		Total		Yes		No		
		No.	Percent	No. (121)	Percent (74.2)	No. (42)	Percent (25.8)	
Sex	Male	107	65.6	80	66.1	27	64.3	0.852
	Female	56	34.4	41	33.9	15	35.7	
Underlying Disease	Yes	52	39.1	37	30.6	15	35.7	0.568
	No	111	68.1	84	69.4	27	64.3	
Fever	Yes	146	89.6	110	90.9	36	85.7	0.382
	No	17	10.4	11	9.1	6	14.3	
Disease Severity	Mild	70	42.9	51	42.1	19	45.2	0.285
	Moderate	52	31.9	36	29.8	16	38.1	
	Critical	41	25.2	34	28.1	7	16.7	

world [4, 12–14]. A meta-analysis of 78,798 patients also found that diarrhea was the most common GI symptom [13]. In a meta-analysis of 59 patients with COVID-19 in Hong Kong, 17.6% had GI complaints, while viral shedding was found in stools of 48.1% of participants [15]. One study found that the presence of GI symptoms, especially diarrhea, was directly related to an increase in positive RNA virus or SARS-CoV-2 loading, which was seen in about half of patients. It is reported that stool PCR test for COVID may be positive for 33 to 47 days (another study averaged 11 days) [16] after the initial illness and even after the throat test was negative [17].

Enterocytes in the small intestine and colon include the highest concentration of Angiotensin Converting Enzyme (ACE2) receptor, through which the virus enters the cell. However, it is not clear whether inflammatory disease in these areas is due to direct virus damage to the cell or due to the systemic effect of the disease [17]. It seems that diarrhea caused by SARS-Cov-2 does not appear to cause damage to colon epithelial cells; however, inflammatory infiltration of lymphocytes has been found in the esophagus, stomach, colon, and liver of adults affected with SARS-CoV-2 infection. These findings suggest that GI symptoms reflect the body's immune response to the virus rather than direct virus damage. Pediatricians and gastroenterologists should be sensitive to other conditions that cause diarrhea (such as enteroviruses), viral hepatitis, and diarrhea caused by immunosuppressive therapy [18]. An article written by Karimi et al. Provides advice on diarrhea caused by COVID-19. It is recommended that physicians should be aware that the absence of respiratory symptoms in children with diarrhea does not rule out COVID-19. It should be noted that the vomiting and feces of patients should be considered infected and the necessary hygiene and precautions should be taken when performing procedures such as endoscopy and colonoscopy. In patients who present with diarrhea, nausea, vomiting, and abdominal pain, five-days after the onset of lower respiratory symptoms, COVID-19 should be considered as the main differential diagnosis [19].

Appendicitis in patients with Covid-19 disease

In this study, 14 patients were admitted with a diagnosis of appendicitis. According to the literature, COVID-19 and MIS-C, both can present with abdominal pain in 30% of cases and mimic appendicitis, which can sometimes lead to misdiagnosis [20]. In a study from Latin American, four patients with MIS-C and acute abdominal pain were treated non-surgically and had no specific complication at all, so appendicitis is probably not the cause of abdominal pain in this study. Given that no specific finding of appendicitis was found in the four patients who underwent appendectomy, the inflammatory response, rather than appendicitis, is probably the cause of abdominal pain [20].

In the present study, a 9-year-old boy presented with severe abdominal pain and high-grade fever. The possibility of appendicitis was raised on ultrasound, but due to the clinical condition and history of contact with a person with COVID-19, with the diagnosis of MIS-C, he underwent appropriate non-surgical treatment and after a few days, both the fever and abdominal pain were resolved.

Although there have been cases of pseudo-appendicitis, several other articles have suggested that appendicitis may present as a complication after COVID-19 infection [21]. The underlying cause of appendicitis is still unknown. Inflammation due to the immune system response to mesenteric lymphadenopathy probably causes obstruction of the appendix duct and the continuation of appendicitis. However, acute abdominal pain can be one of the confusing symptoms of COVID-19, which can be led to unnecessary surgical interventions. On the other hand, delay in the diagnosis of appendicitis can lead to perforation or complication of the appendix [20].

One study showed that the number of cases of appendicitis complication increased during the coronavirus pandemic, but the duration of surgery and length of hospital stay did not differ from that of the pre-corona pandemic period [22]. Therefore, in cases of acute abdominal pain in a patient suspected to COVID-19, it is important to perform the sufficient and adequate investigations for early diagnosis of appendicitis. A study by Yuk et al. On more than thousand patients with appendicitis showed that children with appendicitis had a higher mean age than patients without appendicitis. Although laboratory factors such as C-reactive protein (CRP) and leukocyte count were higher in appendicitis patients, they did not differ, significantly. In multivariate analysis, age over 5-years was associated with a higher risk of appendicitis and respiratory distress syndrome has been associated with decreased risk of appendicitis [20]. In our study mean age of patients with appendicitis was higher than other patients. The factors affecting the incidence of appendicitis were investigated using multivariate analysis. According to the results, only the severity of COVID-19 had a significant relationship with the diagnosis of appendicitis in patients, which means the higher possibility of appendicitis occurrence in severe cases of COVID-19. However, due to the small number of cases of appendicitis in this study, by increasing the number of samples, more accurate results can be obtained and perhaps a significant relationship can be found between appendicitis and other possibilities.

Comparison of studied variables according to the status of liver enzymes

In this study, 40.2% of participants had AST values above 40 and 31.5% had ALT values above 40. In the study of Bolia et al. liver damage is mentioned as another extrapulmonary manifestation of COVID-19, which occurs more in severe cases of the disease [23]. A new study found that nearly half of the 99 COVID-19 patients had 19 liver problems that were associated with elevated transaminases [24]. A meta-analysis of 551 cases with COVID-19 elevated liver function tests reported in a number of patients [25]. In a study by Syed et al. a case of liver failure was reported in an 11-year-old boy following SARS-CoV-2 infection [26]. Some articles have reported the incidence of liver damage from the age of 55-days to 65-years, and the rate of liver damage in various studies has varied from 4.8 to 78% [27]. In a study conducted at Mazandaran University, Iran; changes in liver enzymes in patients with COVID-19 and their relationship with disease prognosis were investigated [28]. A study in Shanghai found that up to 37.2% of patients had abnormal liver tests at the time of admission. Elevated liver enzymes have been reported to be a common phenomenon in patients with COVID-19, which is associated with increased hospitalization duration and disease severity [29]. There appear to be differences between children and adults with SARS-CoV-2 infection in terms of elevated liver enzymes. Increased liver enzymes are more common in adults. In some studies, increase in liver enzymes has not been a common phenomenon in children, which may partly be due to the protective mechanisms of immune system during childhood resulted to less severe courses [30, 31]. However, various mechanisms have been proposed for hepatic impairment in patients with COVID-19, but its exact pathophysiology is not clear.

The most important possible mechanisms include: 1) Inflammatory response in the Covid-19 (especially IL-6, IL-10, IL-2R, TNF-alfa, 2) Hypoxia and ischemia due to weakening of the circulatory system, formation of microthrombi, 3) Direct virus attack on cholangiocytes, 4) drug-induced liver damage [29].

One study reported an increase in liver enzymes in the second week of hospitalization in adults, but in children there was usually an increase in enzymes at the time of admission, indicating that drug-induced liver enzymes were less likely to occur [30]. In the study that conducted by Doki et al. A slight increase in liver enzymes was reported and it was shown that there was no difference between patients with increased liver enzymes and bilirubin compared to patients with no increase in these cases [32]. However, in our study, there is no statistically significant relationship between the level of liver enzymes and the severity of the disease, diagnosis, and hospitalization in the ICU.

Comparison of groups with and without Gastrointestinal symptoms

In the present study, 121 cases (74.24%) of patients had GI symptoms and 42 cases (25.76%) had no GI symptoms. Clinical symptoms and contextual variables in the two groups of people with and without GI symptoms were not significantly different.

In the study of Montazeri et al. that was conducted on 611 patients with COVID-19, there was no significant difference in the incidence or severity of respiratory distress between patients with or without GI symptoms [33]. However, in another study conducted in China, patients with GI symptoms became more severely ill, developed more respiratory distress, and were more likely to be hospitalized or admitted to the ICU [34]. Intestinal involvement of COVID-19 has been reported in 25–50% of studies. The length of hospital stays, the duration of high liver enzymes-coagulopathy, and high inflammatory markers in patients with diarrhea were longer than patients without diarrhea, with worse prognosis [19].

In a case-control study, patients with GI symptoms/elevated liver enzymes were less likely to die or be admitted to the ICU than those without GI symptoms or hepatic enzymes impairments [13]. In another study conducted by Ramachandar et al. no significant relationship was found between laboratory values in the two groups with and without GI symptoms. Patients with GI symptoms had a higher mortality rate, but the relationship was not significant [12]. In this study, none of the underlying factors and symptoms of the disease were significantly different between the groups with and without GI symptoms. Only the mean values of Alp, Bill-D, and Cr in the two groups were significantly different. Of course, the number of cases reported with Bill-D was small, and it is best to repeat the results with a larger sample size. The difference between the results of this study and other studies can be due to the difference between patients in terms of mean age, underlying disease, and evaluation time. Studies have shown that after the onset of clinical and laboratory symptoms of COVID-19, the GI tract can act as a central nucleus for the re-immune activity of SARS-CoV-2 infection [15, 35]. However, despite several other studies we did not found a comprehensive list of risk factors for ICU admission in this study. Patients with critical courses including five patients with appendicitis and 31 patients with MISC were enrolled to the ICU. There was no relationship between transaminase elevation and ICU admission. However, disease severity has a significant relationship with the diagnosis of appendicitis in our study ($P = 0.03$). In a German nationwide inpatient study of 3360 hospitalized pediatric patients with COVID-19, obesity, diabetes mellitus, pneumonia, acute respiratory distress syndrome, MISC, heart failure, myocarditis, kidney failure, and liver disease were associated

with an ICU admission [36]. Risk factors for ICU admission in a France study were also MISC, respiratory forms, underlying conditions, and being younger than seven years [37].

Conclusions

Based on this and previous studies, the COVID-19 can present with a variety of GI symptoms. Some manifestations, such as mild diarrhea and vomiting can be treated with supportive care, but some other manifestations, such as abdominal pain can be misleading and, if not given enough attention can lead to poor diagnosis and untimely treatment. Complications such as liver damage should also be managed and treated in a timely manner. More serious GI diseases such as pancreatitis should also be considered by physicians.

In this study, there was no difference between the group with and without GI symptoms in terms of disease severity, laboratory values and outcome. However, since GI symptoms are not specific and can be seen in other patients such as IBD, other intestinal infectious diseases, antibiotics consumers, etc., physicians should note that they suspect COVID-19 even in patients who have previously had GI symptoms. Nevertheless, disease severity has a significant relationship with the diagnosis of appendicitis in our patients, partly due to inflammatory mechanisms separated it from non-affected patients.

Limitations and suggestions

1. The present study was retrospective and based on the information in the medical records. Therefore, the lack of information in the patients' hospital records has led to the loss of important information about the symptoms and course of the disease. Given that there is a possibility of a new wave of COVID-19 disease, it is suggested to prepare a standard data collection form for systematic collection of information about patients. It may be completed at the time of hospitalization.
2. Due to the fact that the present study was conducted in one center, there was not enough sample size for special cases such as appendicitis or pancreatitis, so to increase the internal validity and generalizability of the study results, it is better to do a multi-center study at the level or province.

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Author contributions
"All authors involved in searching process and data collection, designed the body of article, and wrote the results and conclusions."

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
All patients' information was recorded anonymously and the information was provided to the research group confidentially. This research has been approved by the ethics committee of Kerman University of Medical Sciences (Code: IR.KMU.AH.REC.1400.207). Written informed consent was obtained from the parents of patients.

Consent for publication
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Competing interests
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