Gastrointestinal System Involvement in Pediatric Patients with Acute SARS-CoV-2 Infection

Akut SARS-CoV-2 Enfeksiyonu Olan Pediatrik Hastalarda Gastrointestinal Sistem Tutulumu

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ABSTRACT

Objective: The prevalence of gastrointestinal symptoms in coronavirus disease-2019 (COVID-19) has been reported widely. In this study, the prevalence of gastrointestinal system (GIS) involvement in pediatric COVID-19 and its effect on prognosis were investigated.

Methods: Children (aged 0-18 years) with acute COVID-19 were included in the study. The patients were grouped according to system involvement: isolated respiratory system (RS), isolated GIS, and combination of both (RS+GIS). These groups were compared in terms of demographic data, clinical characteristics, laboratory and imaging findings, and hospitalization.

Results: A total of 223 pediatric patients were included in the study. Of these patients, 19 were asymptomatic, 12 were diagnosed with a multisystem inflammatory syndrome in children, 21 had chronic disorders that may affect disease severity, and 27 had symptoms not related to RS or GIS. The remaining 144 patients were classified according to system involvement: 79 (35.4%), 14 (6.3%), and 51 (22.9%) had isolated RS, isolated GIS, and RS+GIS involvement, respectively. The GIS group was much younger than the RS group (median, 30 and 150 months, respectively, p=0.006). Three patients from the RS group were followed in the intensive care unit (ICU). Moreover, 17 (21.5%) and 4 (7.8%) patients from the RS group had severe-critical respiratory symptoms, in the RS+GIS group had severe-critical respiratory symptoms (p=0.039).

Conclusions: Our study showed that GIS involvement in children with COVID-19 is more prevalent than RS involvement in the younger age group. Respiratory symptom severity and ICU admission also decreased with accompanying GIS involvement. GIS involvement was still associated with a milder disease course after adjustment for age.

Keywords: Child, COVID-19, gastrointestinal system, SARS-CoV-2, disease severity

ÖZ

Amaç: Koronavirüs hastalığı-2019'da (COVİD-19) gastrointestinal semptomların prevalansı geniş bir değişkenlik içinde bildirilmiştir. Bu çalışmada, pediatrik COVİD-19'da gastrointestinal sistem (GİS) tutulumunun prevalansı ve hastalığın prognozuna etkisinin araştırılması amaçlanmıştır.

Yöntemler: Akut COVİD-19 olan 0-18 yaş arası çocuklar çalışmaya dahil edildi. Hastalar sistem tutulumlarına göre gruplandırıldı; izole solunum sistemi (SS), izole GİS ve her ikisinin kombinasyonu (SS+GİS). Bu gruplar demografik veriler, klinik özellikler, laboratuvar ve görüntüleme bulguları ve hastaneye yatış açısından karşılaştırıldı.

Bulgular: Toplam 223 çocuk hasta çalışmaya dahil edildi. On dokuzu asemptomatik, 12'si çocuklarda multisistem enflamatuvar sendrom tanısı aldı, 21'inde hastalık şiddetini etkileyebilecek kronik hastalıklar vardı ve 27'sinde SS veya GİS dışı semptomlar mevcuttu. Geriye kalan 144 hasta sistem tutulumuna göre sınıflandırıldı: 79'unda (%35,4) izole SS tutulumu, 14'ünde (%6,3) izole GİS tutulumu, 51'inde (%22,9) ise SS+GİS tutulumu birlikteydi. GİS grubunda olan hastaların SS grubundakilere göre daha genç olduğu görüldü (sırasıyla ortanca 30 ay ve 150 ay, p=0,006). Tamamı SS grubunda olan 3 hasta yoğun bakım ünitesinde takip edildi. SS grubundaki hastaların %21,5'inde ciddi kritik solunum semptomları varken SS+GİS grubunun %7,8'inde ciddi kritik solunum semptomları vardı (p=0,039).

Sonuçlar: COVİD-19 enfeksiyonu geçiren çocuklarda yaş azaldıkça GİS tutulumunun arttığı görüldü. GİS tutulumunun olması solunum semptomlarının şiddetini ve yoğun bakıma yatışını azalttığı tespit edildi. Yaştan bağımsız olarak da GİS tutulumunun daha hafif seyirli bir hastalık ile ilişkili olduğu görüldü.

Anahtar kelimeler: Çocuk, COVİD-19, gastrointestinal sistem, SARS-CoV-2, hastalık şiddeti

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel strain of human coronavirus, emerged in December 2019 in Wuhan, China[1,2]. Named the coronavirus disease-2019 (COVID-19) by the World Health Organization, it was declared a pandemic in March 2020 after it infected more than 616 million people and led to the deaths of 6.5 million worldwide as of December 2021[3]. Although the clinical presentations of COVID-19 are predominantly respiratory, it also affects the gastrointestinal system (GIS).

The incidence of gastrointestinal symptoms has been reported in previous studies, ranging from 2% to 84% with a multisystem inflammatory syndrome in children (MIS-C) having the highest incidence[4,5]. Jin et al.[6] reported that gastrointestinal symptoms in adults were more frequent in severe than in mild COVID-19. Although COVID-19 has a lower mortality rate among children than adults, the effect of gastrointestinal symptoms on pediatric prognosis is unclear. In this study, we investigated the prevalence and characteristics of gastrointestinal symptoms in children with COVID-19 and the effect of GIS involvement on COVID-19 severity.

MATERIALS and METHODS

Study Population and Protocol

The study was conducted between March 2020 and February 2021 at a tertiary reference hospital. Children up to 18 years old and diagnosed with acute SARS-CoV-2 infection confirmed by a positive polymerase chain reaction (PCR) test were included in the study. The hospital records were retrospectively evaluated in terms of demographic data, symptoms, physical examination, laboratory and imaging findings at the time of COVID-19 diagnosis, hospitalization status, hospital stay, and mortality.

GIS involvement was defined as having nausea, vomiting, diarrhea, abdominal pain, or gastrointestinal bleeding, and respiratory system (RS) involvement was defined as having flu-like symptoms (nasal congestion, rhinorrhea, sore throat, etc.), cough, respiratory distress, or positive findings following a chest X-ray/computed tomography (CT). Patients with gastrointestinal symptoms related to other pathologies such as antibiotic use and other viral, bacterial, or parasitic infections were excluded.

MIS-C was diagnosed according to the case definition criteria of the Centers for Disease Control and Prevention[7].

Since it is a distinct entity related to SARS-CoV-2 infection, patients with MIS-C were further evaluated in terms of gastrointestinal symptoms.

After excluding asymptomatic cases, patients with MIS-C, and patients having other symptoms (fever, arthralgia, myalgia, loss of taste/smell, etc.; not accompanied by respiratory or gastrointestinal symptoms) and chronic disorders (hematological disorders, congenital heart disease, neurological disorders, severe asthma, rheumatological disorders, and type I diabetes mellitus), the remaining patients were divided into three groups: isolated RS involvement, isolated GIS involvement, and a combination of both (RS+GIS). These three groups were compared in terms of demographic data, clinical and laboratory findings, and COVID-19 severity.

Hospitalization status, hospital stay, and intensive care unit (ICU) admission were determined as the parameters to be used in assessing COVID-19 severity. While at the beginning of the pandemic, all patients who were positive in the PCR test had been hospitalized regardless of their symptoms because of the lack of knowledge about the prognosis of COVID-19 in children. Since hospitalization might not fully reflect disease severity, we also included RS severity criteria because it is the most responsible system for COVID-19 mortality and morbidity. Respiratory symptom severity was classified into four groups[8]:

1. Mild respiratory symptoms: Flu-like symptoms (nasal congestion, rhinorrhea, sore throat, etc.), chest X-ray and/or CT findings compatible with COVID-19 (consolidation, peripheral opacities, ground glass opacities, septal thickening, and pleural effusion) without a clinical sign of pneumonia.

2. Moderate respiratory symptoms: Clinical signs of pneumonia [cough/difficulty breathing + fast breathing (in breaths/min: <2 months, ≥60; 2-11 months, ≥0; 1-5 years, ≥40)] and no signs of severe pneumonia.

3. Severe respiratory symptoms: Clinical signs of pneumonia [cough or difficulty in breathing + fast breathing (in breaths/min): <2 months, ≥60; 2-11 months, ≥50; 1-5 years, ≥40] + at least one of the following: oxygen saturation <90% in room air or signs of severe respiratory distress (accessory muscle use, grunting, central cyanosis, or feeding difficulties).

4. Critical respiratory symptoms: Acute respiratory distress syndrome or need for invasive or non-invasive mechanical ventilation.

Statistical Analysis

The IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY, USA) was used for all the statistical analyses. The Kolmogorov-Smirnov test and histograms were used to test the normality of data distribution. Continuous variables were expressed as medians [interquartile range (IQR) 25th-75th percentiles], and categorical variables were expressed as numbers (percentages). Categorical variables were compared using a chi-square test, and numerical variables were compared using the Mann-Whitney U test.

The Kruskal-Wallis test was conducted to compare COVID-19 involvement groups (isolated RS, isolated GIS and RS+GIS involvement groups). Subsequently, the Mann-Whitney U test was performed to test the significance of pairwise differences. A p-value of <0.05 was considered statistically significant. The possible factors identified by univariate analysis were further entered into the logistic regression model to determine the predictors of COVID-19 severity.

The study was approved by the University of Health Sciences Turkey, Istanbul Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (decision no: 80, date: 24.03.2021).

RESULTS

Patient Characteristics

During the study period, a total of 719 children suspected of SARS-CoV-2 infection were admitted to our clinic. Of these, 322 patients had SARS-CoV-2 PCR positivity, from which a further 99 patients who lacked complete data were excluded (Figure 1).

The study population included 223 patients. The median age of the patients was 10 (IQR, 2.6-1.4) years, and 126 (56.5%) were male. A total of 57 (25.5%) patients with chronic conditions, which comprised allergic diseases (asthma, allergic rhinitis, or atopic dermatitis) in 27 (12.1%) patients, hematological disorders (leukemia, thalassemia, and immune thrombocytopenic purpura) in 9 (4%), congenital heart disease in 7 (3.1%), neurological disorders in 7 (3.1%), endocrine disorders (congenital
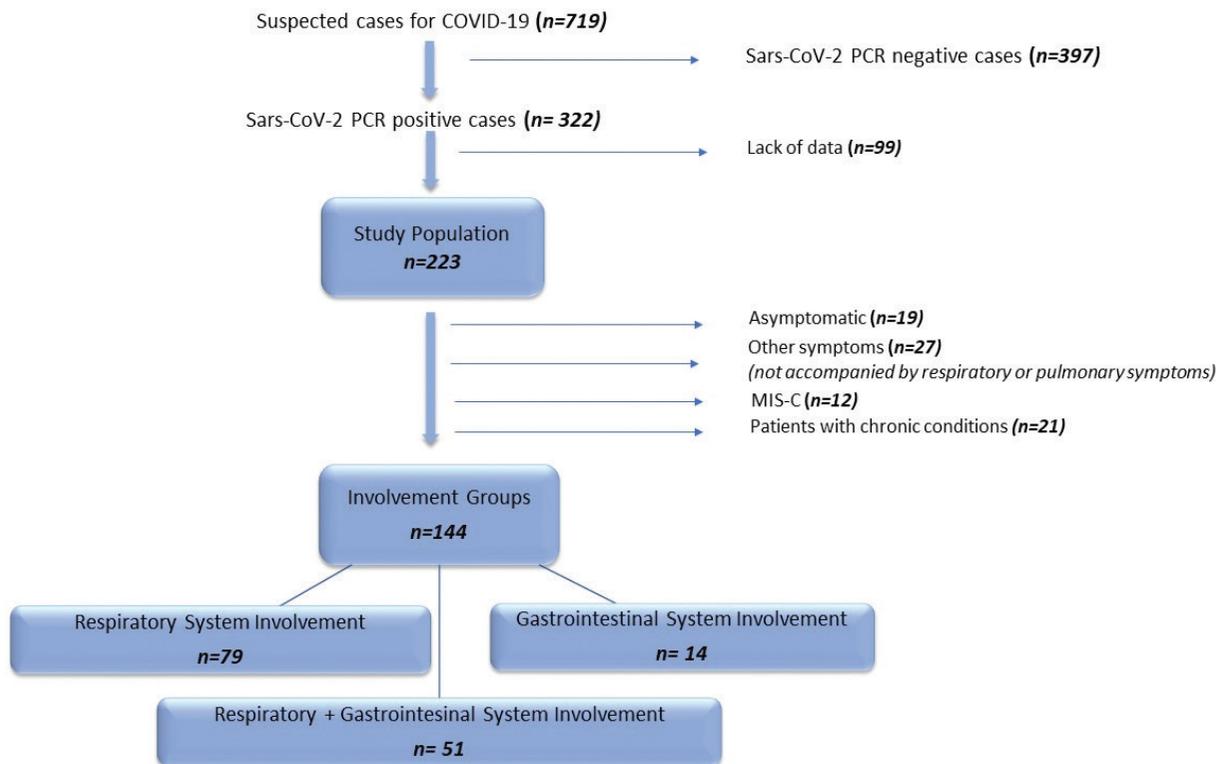
Figure 1. Flowchart of the study population. Other symptoms included fever, arthralgia, myalgia, flu-like symptoms, loss of smell/taste, etc., which were not accompanied by pulmonary or gastrointestinal symptoms.

PI: Pulmonary involvement, COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, PCR: Polymerase chain reaction, MIS-C: Multisystem inflammatory syndrome in children

hypothyroidism or type 1 diabetes) in 5 (2.2%), and rheumatological disorders in 2 (0.9%). None of the patients had a known chronic GIS disorder. Moreover, 91 (40.8%) patients were hospitalized for a median of 7.5 (IQR, 5-10) days, and 14 (6.5%) of them were treated in the ICU. All patients were discharged with no complications. Detailed clinical characteristics of the patients are provided in Table 1.

Comparison of Patients According to RS and GIS Involvement

In this study, 19 children were asymptomatic, 27 had symptoms not accompanied by RS or GIS involvement, and 12 were diagnosed with MIS-C. In addition, 27 (12.1%) patients had chronic conditions that may contribute to the severity of SARS-CoV-2 infection: hematological disorders (leukemia, thalassemia, and immune thrombocytopenic purpura) in 9 (4%) patients, congenital heart disease in 7 (3.1%), neurological disorders in 5 (2.2%), severe asthma in 2 (0.9%), rheumatological disorders in 2 (0.9%), and type I diabetes in 2 (0.9%). Six of these 27 patients with chronic disorders did not have any symptoms during the COVID-19 course. Thus, the remaining 144 patients were classified based on respiratory and gastrointestinal symptoms. A total of 79 (35.4%) patients had isolated RS involvement, 14 (6.3%) had isolated GIS involvement, and 51 (22.9%) patients had both RS+GIS. The median ages were 150 (IQR, 55-184) months for the RS group, 98 (IQR, 27-192) months for the RS+GIS group, and 30 (IQR, 18-138) months for the GIS group. Pairwise comparisons revealed a significant difference in age between the GIS group and both the RS group and RS+GIS groups (p=0.006 and p=0.046, respectively).

Comparison of the three groups did not reveal any differences in terms of laboratory findings, such as leukocyte, lymphocyte, and platelet numbers and levels of hemoglobin, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, procalcitonin, albumin, fibrinogen, and d-dimer. The ferritin level was significantly higher in the RS group (median, 64 ng/mL IQR, 37-138 ng/mL) than both the RS+GIS (median, 41 ng/mL; IQR, 17-86 ng/mL) and the GIS (median, 40 ng/mL; IQR, 20-52 ng/mL) groups (p=0.012 and p=0.051, respectively) (Table 2).

Although not statistically significant, the hospitalization rates also varied, i.e., 48% for the RS group, 39% for the RS+GIS group, and 21% for the GIS group (p=0.151), respectively, and their median durations were 7.5 (IQR, 5.2-9) days, 7.5 (IQR, 6-9.7) days, and 5 (IQR, 4-6) days (p=0.097), respectively. A total of 14 patients were admitted to the ICU, of which 11 were diagnosed with MIS-C. Three (5.4%) patients in the RS group and none in both the GIS+RS group and GIS group were followed up in the ICU (p=0.169) (Table 2).

A total of 130 patients having respiratory symptoms were classified according to disease severity: 68 (52%) had mild respiratory symptoms, 41 (32%) had moderate symptoms, 16 (12%) had severe symptoms, and 5 (4%) had a critical illness. Severe-critical RS involvement was observed in 17 (21.5%) patients in the RS group and 4 (7.8%) in the RS+GIS group (p=0.039) (Table 2). As GIS involvement was present in the younger age group and COVID-19 was associated with a severe course in older patients, logistic regression analysis was performed including age and GIS involvement. Accompanying GIS involvement was associated with a milder disease course after adjustment for age. Isolated RS involvement was associated with a 3.1-fold increased risk for COVID-19 severity (Table 3).

GIS involvement was found in 8 (67%) of children diagnosed with MIS-C, with symptoms of diarrhea, vomiting, nausea, abdominal pain, and loss of appetite appearing in 5 (42%), 5 (42%), 3 (25%), 2 (17%), and 2 (17%) patients, respectively.

Table 1. Clinical characteristics related to coronavirus disease-2019.	
Clinical characteristics	**n (%)**
Asymptomatic	19 (8.5)
Fever	137 (61.4)
Respiratory symptoms	148 (66.4)
Cough	100 (44.8)
Flu-like symptoms (nasal congestion, rhinorrhea, sore throat, etc.)	39 (17.5)
Respiratory distress	24 (10.8)
Gastrointestinal symptoms	73 (32.7)
Diarrhea	44 (19.7)
Nausea	37 (16.6)
Vomiting	31 (13.9)
Abdominal pain	22 (9.9)
Loss of appetite	22 (9.9)
Gastrointestinal bleeding	1 (0.4)
Other	
Malaise	24 (10.8)
Headache	16 (7.2)
Loss of smell/taste	11 (4.9)
Arthralgia	7 (3.1)
Rash	6 (2.7)
Myalgia	3 (1.3)

Table 2. Comparison of patients according to the respiratory system and the gastrointestinal system involvement.

		Isolated RS involvement (n=79)		RS+GIS involvement (n=51)	Isolated GIS involvement (n=14)	p
Age [months (median) (IQR)]		150 (55-184)		98 (27-192)	30 (18-138)	0.033
Sex	Female	34 (43%)		24 (47%)	6 (43%)	0.896
	Male	45 (57%)		27 (53%)	8 (57%)	
Fever		42 (53%)		35 (68%)	9 (64%)	0.200
Hospitalization		38 (48%)		20 (39%)	3 (21%)	0.151
Hospital stay (days)		7.5 (5.2-9)		7.5 (6-9.7)	5 (4-6)	0.097
ICU admission		3 (3.8%)		0	0	0.169
Respiratory symptom severity	Mild-moderate	62 (78.5%)		47 (92.2%)		0.039*
	Severe-critical		17 (21.5%)	4 (7.8%)		
Laboratory findings [(median) (IQR)]						
Hemoglobin (g/dL)		12.6 (11.4-14.3)		12.8 (11.7-14.3)	11.6 (11-12.3)	0.052
Leukocyte (/mm³)		6605 (5010-9175)		7665 (5575-9665)	6865 (5662-9187)	0.420
Neutrophil (/mm³)		2905 (1875-3995)		3900 (2000-5775)	2560 (1687-3987)	0.208
Lymphocyte (/mm³)		2100 (1600-4100)		2600 (1625-4025)	3000 (1900-5375)	0.557
Eosinophil (/mm³)		80 (37.5-173)		45 (10-162)	120 (52-467)	0.063
Thrombocyte (/mm³)		277,000 (214,250-312,750)		260,500 (221,000-327,000)	251,000 (178,000-372,000)	0.840
AST (IU/L)		23.5 (18.2-36.7)		29 (20-40)	35 (19-47)	0.197
ALT (IU/L)		13 (11-23)		14 (10-20)	17.5 (10-24)	0.829
Albumin (g/dL)		4.6 (4.3-4.8)		4.4 (4.3-4.7)	4.4 (4.4-4.6)	0.789
CK (IU/L)		94 (69-135)		121 (26-144)	81 (64-238)	0.230
LDH (IU/L)		258 (203-343)		283 (215-374)	297 (241-355)	0.440
CRP (mg/dL)		2.6 (0.57-10.5)		0.95 (0.4-7.2)	1.5 (0.6-8.7)	0.442
Procalcitonin (ug/L)		0.06 (0.04-0.09)		0.06 (0.04-0.13)	0.09 (0.05-0.15)	0.294
Ferritin (ng/mL)		64 (37-138)		41 (17-86)	40 (20-52)	0.019
Fibrinogen (mg/dL)		273 (224-339)		279 (220-312)	275 (198-313)	0.786
INR		1.05 (1.00-1.12)		1.04 (1.00-1.10)	1.00 (1.00-1.15)	0.923
D-dimer (mg/L)		0.43 (0.25-0.78)		0.45 (0.26-0.96)	0.5 (0.27-1.24)	0.868

The Kruskal-Wallis test was conducted to investigate differences between the three groups. *The chi-square test was performed between the RS and GIS+RS groups. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CK: Creatine kinase, ICU: Intensive care unit, CRP: C-reactive protein, RS: Respiratory system, GIS: Gastrointestinal system, INR: International normalized ratio, LDH: Lactate dehydrogenase, IQR: Interquartile range

Table 3. Logistic regression model for age and involvement groups affecting COVID-19 severity.

Risk factor	Regression coefficient	Standard error	Wald x^2 value	p-value	OR	95% CI for OR Lower	95% CI for OR Upper
Age	0.005	0.003	2.237	0.135	1.00	0.998	1.012
Involvement group*	1.132	0.593	3.651	0.056	3.10	0.971	9.916

*Involvement group includes isolated RS involvement and RS+GIS involvement. Age and involvement group were included in logistic regression analysis. Isolated RS involvement was associated with a 3.1-fold increased risk for COVID-19 severity. COVID-19: Coronavirus disease-2019, CI: Confidence interval, OR: Odds ratio, RS: Respiratory system, GIS: Gastrointestinal system

DISCUSSION

Various symptoms have been documented in COVID-19 among both adults and children. The RS appears to be the main target for SARS-CoV-2; however, gastrointestinal symptoms have increasingly been reported, especially in pediatric patients[4,9]. Available data for gastrointestinal symptoms in children are sparse; furthermore, there is a wide variance in the prevalence of specific gastrointestinal symptoms. Badal et al.[10] reported 6% incidence of gastrointestinal symptoms in their study of 1810 children, whereas Giacomet et al.[11] 24.3% in children with severe COVID-19. In our study, GIS was the most frequently involved extrapulmonary system, with a prevalence of 32.7%.

In our study population, isolated GIS involvement was reported in 6.2% of children, with diarrhea as the most common (19.7%) gastrointestinal symptom, similar to the literature. Giacomet et al.[11] reported isolated gastrointestinal symptoms in 12% of patients with mild and moderate COVID-19 and 25% of patients with severe or critical COVID-19. The low percentage of isolated GIS manifestation can be explained by our hospital being a tertiary referral hospital for children and patients having milder symptoms visiting primary care physicians.

A limitation of this study concerns its retrospective nature. Patients who were not hospitalized (those who were asymptomatic or just had mild symptoms, such as fever, malaise, and flu-like symptoms) might later have developed respiratory or gastrointestinal symptoms; therefore, some cases with RS or GIS involvement might have been missed.

When comparing the groups, those in the GIS group were much younger than those in the RS group. Similar to our findings, Xiong et al.[12] analyzed 244 children and showed a younger age in patients with GIS symptoms than in those with non-GIS symptoms.

Moreover, 21% of the patients followed in the ICU were in the RS group and the remaining 79% had MIS-C. In addition, the percentage of severe-critical respiratory symptoms was higher in the RS group than in the RS+GIS group. In the study by Xiong et al.[12], a comparison of patients with gastrointestinal and non-gastrointestinal symptoms did not reveal any difference in terms of disease severity. On the contrary, Han et al.[13] described a subgroup of patients with mild COVID-19 having gastrointestinal symptoms. They reported a higher positivity rate in stool RNA for COVID-19 in patients with digestive symptoms than in those respiratory symptoms, together with a longer delay before viral clearance and delayed diagnosis. However, in a study involving 204 adult patients, digestive symptoms became more pronounced as disease severity increased[14,15]. Additionally, in a meta-analysis of 15,305 patients, abdominal pain was reported more frequently in severe COVID-19 patients than in non-severe patients.

CONCLUSION

This study highlights the presence and features of gastrointestinal symptoms in children with COVID-19. Thus, GIS involvement is more prominent in younger patients and GIS involvement is associated with milder pediatric COVID-19.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Istanbul Kanuni Sultan Suleyman Training and Research Hospital Ethics Committee (decision no: 80, date: 24.03.2021).

Informed Consent: Retrospective study.

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Author Contributions

Surgical and Medical Practices: O.K.S., B.B., Z.O., S.O., G.O., G.G., Concept: O.K.S., B.B., Design: O.K.S., B.B., Data Collection and/or Processing: O.K.S., B.B., Z.O., S.O., G.O., G.G., Analysis and/or Interpretation: O.K.S., B.B., Literature Search: O.K.S., B.B., Z.O., S.O., G.O., G.G., Writing: O.K.S., B.B.

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