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Gastrointestinal and Liver Manifestations in Children with COVID-19 and Their Relationship to Clinical Course

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What is already known on this topic?

- *Studies have shown that both adult and pediatric coronavirus disease 2019 (COVID-19) patients can present with gastrointestinal (GI) symptoms. In the literature, the relationship between GI symptoms and the severity of COVID-19 has been evaluated mostly in adult patients; data on children are limited.*

What this study adds on this topic?

- *The study results show that children with coronavirus disease 2019 (COVID-19) may present with only gastrointestinal (GI) symptoms. Most patients with liver involvement were under 5 years of age. Unlike adult cases, no relationship was detected between the severity of COVID-19 and GI symptoms or liver involvement.*

ABSTRACT

Objective: Coronavirus disease 2019 is a major health problem in all age groups. Although most clinical symptoms are respiratory, gastrointestinal symptoms are often reported. This is a major concern for children and has limited research coverage. In this study, we evaluated the frequencies of gastrointestinal symptoms and liver biochemical findings in children with coronavirus disease 2019 and their relationship with clinical course and length of hospital stay.

Materials and Methods: Demographic data, clinical, and laboratory findings of children with Coronavirus disease 2019 who were followed up by the Department of Pediatric Infectious Diseases between March 2020 and August 2020 were recorded. They were classified according to age groups as <5 years, 5-10 years, and >10 years. Laboratory findings were analyzed according to age groups. Demographic, clinical, and laboratory findings were compared in both situations, the presence of gastrointestinal symptoms and the presence of elevated liver enzymes. It was considered statistically significant if it was <.05.

Results: A total of 294 patients (median age 10 years [14 days to 18 years]) were enrolled in this study. Although fever is the most common symptom of coronavirus disease 2019, 15.6% of patients presented with acute gastroenteritis. Most patients with liver involvement (n = 130, 44.2%) were under 5 years of age (n = 74, 56.9%, $P < .001$). The patterns of abnormal liver test results were cholestatic (71.5%), hepatocellular (18.4%), and mixed (10%) types. Severe or massive elevation of aminotransferase or liver failure was not observed. No statistically significant difference was noted in outcomes, including length of stay, for patients with gastrointestinal symptoms ($P = .178$) or liver involvement ($P = .146$).

Conclusion: The presence of gastrointestinal symptoms or elevated liver enzymes does not affect the course of the disease in children with coronavirus disease 2019.

Keywords: Clinical outcome, children, coronavirus, COVID-19, gastrointestinal, liver, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is the global health threat of the century. Although COVID-19 affects all age groups, it often causes mild upper respiratory tract symptoms in children.[1] Severe acute respiratory syndrome coronavirus 2 requires the angiotensin-converting enzyme 2 (ACE-2) receptor to bind to the host cell. Immature immune systems and variations in the tissue expression of ACE-2 may lead to the development of different clinical signs in children.[2,3] The lung is the primary organ of involvement in SARS-CoV-2 infection, but extrapulmonary manifestations, such as gastrointestinal (GI) symptoms, have also been reported

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during the course of COVID-19. Notably, children have high rates of vomiting, abdominal pain, and diarrhea.[4] Intestinal tropism, direct cytopathic effects, and a cytokine storm response are considered to cause these symptoms.[2,5]

Coronavirus disease 2019 (COVID-19) also leads to varying degrees of liver injury, presenting with abnormal levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and slightly elevated bilirubin levels as well as elevated gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) levels.[6] Liver injuries, including hepatocellular, cholestatic, and mixed types, have also been reported.[7]

A mild rise in liver enzymes is commonly reported with COVID-19. Although high levels of transaminases are considered to be associated with the severity of the disease, the pathological mechanism of liver injury has not been clarified.[7] Immune-mediated mechanisms, endothelial cell infection and endotheliitis, vascular thrombosis, and direct cytopathic effects are considered possible causes in the pathogenesis of liver damage.[8,9] Because COVID-19 can decompensate underlying liver disease, patients with elevated transaminases should also be investigated for other liver diseases.[7,10] Rare manifestations of COVID-19 such as typical acute appendicitis, ileocolitis, and intussusception have also been reported as part of the clinical spectrum of SARS-CoV-2 disease in childhood.[11]

In this study, it was investigated whether the presence of GI symptoms and the presence of elevated liver enzymes in patients affected the clinical course and hospital stay of COVID-19.

Study Design and Setting

This is a single-center, observational, retrospective case–control study conducted in the Pediatric COVID-19 Unit of the Faculty of Medicine at the University of Konya, Turkey, after receiving approval from the Selcuk University Faculty of Medicine Local Ethics Committee. Informed consent was obtained from the patient. Permission was also obtained from the Turkish Medicines and Medical Devices Institution, Republic of Turkey Ministry of Health (2020-08-29T21-00-02).

MATERIALS AND METHODS

Patients and Data

Using clinical data from March 22, 2020, to August 31, 2020, we retrospectively evaluated the data of 300 children who had been diagnosed with COVID-19 via real-time reverse transcription-polymerase chain reaction (RT-PCR) testing. Six patients with GI comorbidities (e.g., celiac disease, cystic fibrosis, inflammatory bowel disease, autoimmune hepatitis, Wilson's disease, and metabolic liver disease) were excluded from the study. Thirteen patients had comorbidities (e.g., asthma, autoimmune disease, malignancy, immunodeficiency, or Canavan diseases). The others were previously healthy according to their family history.

Coronavirus disease 2019 (COVID-19) was diagnosed based on clinical manifestations, a history of close contact, and SARS-CoV-2 real-time RT-PCR analysis of oropharyngeal or nasopharyngeal swab samples and positive findings of chest computed tomography (CT) according to COVID-19 guidance, as published by the Republic of Turkey Ministry of Health and the World Health Organization interim guidance. Only SARS-CoV-2 RT-PCR-positive cases were included in this study.

Children were divided into 2 subgroups according to the presence or absence of GI symptoms. They were then examined in 3 age groups (<5 years, 5-10 years, and >10 years). The following 5 clinical patient categories were applied according to symptoms and SARS CoV-2 RT-PCR positivity:

1. If the patient had SARS CoV-2 PCR positivity but no symptoms, it was considered an asymptomatic case.
2. If the patient had nasal stuffiness with discharge, sore throat, and cough, it was considered to be an upper respiratory tract infection (URTI).
3. If the patient had symptoms of cough, mucus, wheezing, and shortness of breath, but no pneumonia was found in the radiological examination, it was considered to be acute bronchitis.
4. If the patient had respiratory symptoms and radiological consolidation findings, it was considered to be pneumonia.
5. Acute gastroenteritis was applied if there was a rapid onset of diarrhea alongside other symptoms (e.g., nausea, vomiting, fever, and abdominal pain).

Laboratory parameters were evaluated at the patient's first admission to the hospital and prior to receiving medical treatment.

Serum AST, ALT, GGT, ALP, and bilirubin levels were evaluated according to normal reference ranges of the laboratory test kits recommended for our hospital. Serum liver tests were considered abnormal if levels were above the following thresholds: ALT > 35 U/L, AST > 35 U/L, GGT > 24 U/L, and total bilirubin (TBIL) >1.4 mg/dL. Serum ALP level was considered abnormal if it was >500 U/L in the 1-12 age group, >750 U/L in the 12-15 age group, or >150 U/L in those older than 15 years of age. Serum ALP and GGT values were evaluated for cholestatic liver injury if the ALP >1.5 × the upper limit of normal (ULN) and/or GGT >3 × ULN, according to the European Association for the Study of the Liver guidelines.[12]

Liver enzymes (e.g., AST and ALT), GGT, ALP, and TBIL were grouped by the upper limit of the normal range (<ULN) and abnormal range (>ULN). Aminotransferase elevations were defined as borderline (<2 × ULN), mild (2-5 × ULN), moderate AST/ALT 5–15 × ULN, severe AST/ALT >15 × ULN, and massive AST/ALT >10 000 IU/L. The R-factor value[13] was used to determine the likely type of liver injury (e.g., hepatocellular, cholestatic, or mixed) in patients with elevated aminotransferases and ALP or GGT. The R-factor value was calculated according to the formula, R = (ALT value/ALT ULN)/(ALP value/ALP ULN). In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, GGT level is used. If the R-factor values are >5, 2-5, or <2, they are defined as hepatocellular, mixed, or cholestatic, respectively.[14,15] Serum samples from children with high liver enzymes were screened for hepatitis A, B, and C. Laboratory data on admission were also evaluated, including complete blood count with differential routine biochemical tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, troponin, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and lactate dehydrogenase.

Children in all groups were evaluated in terms of demographics, admission symptoms, laboratory findings, and clinical outcomes.

Treatment Approach

All patients were isolated and given bed rest, and they were monitored for heart rate, blood pressure, and oxygen saturation. They also received supportive care. Hypoxemia and electrolyte imbalances were treated with supplemental oxygen and fluid replacement therapy according to their clinical conditions.

Although there is no accepted specific antiviral treatment regimen, 7 patients with pneumonia were treated with favipiravir. The decision to start favipiravir therapy was based on the clinical symptoms of the patients and the clinical experience of the medical team. The specific treatment protocol was defined as favipiravir (1.600 mg orally twice a day on day 1, then 600 mg orally twice a day for a total of 5 days) according to patient symptoms, hypoxemia, chest CT findings, and acute phase reactants (e.g., albumin, procalcitonin, C-reactive protein, fibrinogen, and ferritin). Antibiotics were used as needed, and the decision was based on the discretion of the patients' healthcare providers.

Statistical Analysis

All statistical analyses were performed using *R* v.3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https ://www.r-project.org). To assess the normality of the data, the Shapiro–Wilk normality test and Q–Q plots were used. Levene's test was also used to check the homogeneity of the variances. Numerical variables were presented as mean ± standard deviation or median (interquartile range: 25th-75th percentile) as appropriate. Additionally, categorical variables were described as number (n) and percentage (%). Fisher–Freeman–Halton, Pearson chi-squared, Kruskal–Wallis, and Welch's *F* tests were run to determine whether there was a statistically significant difference or association between age groups according to the clinical characteristics and laboratory findings of the patients. Moreover, Yates's continuity correction chi-squared, Mann–Whitney, and Welch/independent sample *t*-tests were conducted to examine whether there was a statistically significant difference or association between patients with and without GI symptoms with demographic characteristics and laboratory examinations. Multiple comparisons of numerical variables found to be significant as a result of Kruskal–Wallis and Welch's *F* tests were performed with Bonferroni-adjusted Dunn and Games–Howell tests, respectively. Pairwise comparisons of categorical variables found to be significant as a result of Fisher–Freeman–Halton or Pearson chi-squared tests were conducted alongside a 2-proportion Z-test. A 2-tailed *P*-value less than .05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of Children with COVID-19

A total of 294 patients (146 male, 148 female, median age 10 years [14 days to 18 years]) were enrolled in this study. Of these, 186 patients (63.2%) represented family cluster cases. Two neonates were born to mothers with COVID-19, and PCR tests were positive on days 3 and 7 after birth.

The clinical characteristics of patients according to age groups are given in Table 1. The most common symptoms were fever (71.1%), cough (39.5%), and diarrhea (15.6%). However, fever and vomiting were more common in children <5 years old; cough was more common in children older than 10 years (P = .001, P = 0.004, and P = .005, for fever, vomiting, and coughing, respectively). Although asymptomatic cases (11.7% vs. 4.1%) were more common in children under 5 years of age, pneumonia (4.8% vs. 0%) was common in children >10 years. The proportions of URTI, acute bronchitis, and pneumonia were 70.4%, 3.4%, and 2.7%, respectively. Two neonates and 7 obese adolescents with asthma presented with acute bronchitis. Two of 8 patients presenting with moderate pneumonia had immunosuppression, and the rest were obese adolescents with asthma. Bacterial coinfection (e.g., bacteremia or urinary tract) was detected in previously healthy patients (n = 6) under 5 years old. Three children in the 5-10-year group presented with acute appendicitis symptoms and reactive mesenteric lymph nodes.

Table 1. Clinical Characteristics of the Patients According to the Age Groups

	Age Groups			
Characteristics	**<5 Years (n = 94, 31.9%)**	**5-10 Years (n = 53, 18%)**	**>10 Years (n = 147, 50%)**	***P***
Diagnose				.040[1]
Asymptomatic (n = 23, 7.8%)	11 (11.7)[a]	6 (11.3)	6 (4.1)[b]	
URTI (n = 207, 70.4%)	61 (64.9)	38 (71.7)	108 (73.5)	
Acute bronchitis (n = 10, 3.4%)	3 (3.2)	0 (0)	7 (4.8)	
Acute pneumonia (n = 8, 2.7%)	0 (0)[a]	1 (1.9)	7 (4.8)[b]	
Acute gastroenteritis (n = 46, 15.6%)	19 (20.2)	8 (15.1)	19 (12.9)	
Symptoms at admission				
Fever (n = 209, 71.1%)	79 (84)[a]	40 (75.5)	90 (61.2)[b]	.001[2]
Cough (n = 116, 39.5%)	25 (26.6)[a]	21 (39.6)	70 (47.6)[b]	.005[2]
Diarrhea (n = 49, 16.7%)	20 (21.3)	9 (17)	20 (13.6)	.296[2]
Abdominal pain (n = 16, 5.4%)	4 (4.3)	6 (11.3)	6 (4.1)	.114[2]
Vomiting (n = 10, 3.4%)	7 (7.4)[a]	1 (1.9)	2 (1.4)[b]	.040[1]

Data were described as number (n) and percentage (%).
Different small superscript in each row denotes that statistically significant difference between age groups.
[1]Fisher–Freeman–Halton test
[2]Pearson chi-square test
URTI, upper respiratory tract infection.

Laboratory Characteristics and Liver Function Tests of Children with COVID-19

Demographic characteristics and laboratory examination data of the patients with GI manifestations are given in Table 2. The age and gender distributions of patients with and without GI symptoms were similar (P = .089 and P = .366, respectively).

Although the white blood cells (WBCs; 7400 [IQR, 5.450-9.750] vs. 5900 [IQR, 4.800-8.000], P =.003), platelet count (294.57 ± 77.05 vs. 255.27 ± 60.30, P = .002), and lactate dehydrogenase (LDH; 285 [IQR, 227-337] vs. 253 [IQR, 209-305], P = .029) were significantly higher in patients with GI symptoms, the hemoglobin (13.37 ± 1.50 vs. 12.78 ± 1.56, P = .015) and troponin (2 [IQR, 2-2.3] vs. 2 [IQR 2-4.25], P = .018) values were lower than patients without GI symptoms. However, the differences in absolute neutrophil, lymphocyte, eosinophil counts, ESR, CRP, procalcitonin, AST, ALT, GGT, ALP, TBIL, indirect bilirubin, albumin, INR, aPTT, and D-dimer values were not statistically significant between GI-symptom groups (all P-values > .05).

The laboratory results of patients with COVID-19 per age group are given in Table 3. Although the WBC, lymphocyte, and ESR values were significantly higher in children under 5 years of age than those aged 5-10 years and older than 10 years, there was no significant difference between children aged 5-10 years and older than 10. Children under 5 years had lower hemoglobin levels than children aged 5-10 years and children older than 10, whereas children aged 5-10 years had lower hemoglobin levels than children older than 10 years. The platelet levels were significantly higher in children under 5 years and 5-10 years than in children older than 10 (Table 3).

In our study, about 44.2% (n = 130) of the children had abnormal liver test results. The patients frequently presented with abnormal AST (n = 98, 33.3%), GGT (n = 26, 8.9%), ALP (n = 19, 6.6%), ALT (n = 15, 5.1%), direct bilirubin (n = 11, 3.8%), TBIL (n = 11, 3.8%), and indirect bilirubin (n = 10, 3.4%) test results. Abnormal AST levels were significantly higher in children under 5 years of age (76.6%) compared with children aged 5-10 years (28.3%) and older than 10 years (7.5%). It was also higher in children aged 5-10 years compared with children older than 10 years. Abnormal ALT levels were significantly higher in children under 5 years of age (9.6%) compared to children aged 5-10 years (0%).

Abnormal ALP levels were significantly higher in children older than 10 years of age (12.2%) compared with children aged 5-10 years (1.9%) and under 5 years (0%). However, there was no significant difference between the abnormal ALP levels of children aged 5-10 years and children under 5. Bilirubin values (e.g., total, direct, and indirect) lower or higher than normal limits were not found to be significantly different between age groups (P = .920, P = .105, and P = .929, respectively).

The percentage of borderline, mild, and moderate elevations of AST was 29.5% (n = 87), 2.7% (n = 8), and 1% (n = 3), respectively. The percentage of borderline, mild, and moderate elevations of ALT was 2% (n = 6), 2% (n = 6), and 1% (n = 3), respectively. Severe or massive elevations of aminotransferase were not observed.

Table 2. Demographical Characteristics and Laboratory Examination of the Patients According to Gastrointestinal Manifestations

	Patients		
Variables	**Without GI Symptoms (n = 247)**	**With GI Symptoms (n = 47)**	***P***
Demographical characteristics			
Age (months)	125 (45.5-184.5)	84 (16.5-177)	.089[3]
Gender (Female/Male)	121 (57.4) / 126 (51)	27 (57.4) / 20 (42.6)	.366[2]
Laboratory examination			
WBCs (K/μL)	5900 (4800-8000)	7400 (5450-9750)	.003[3]
Absolute neutrophil count (K/μL)	2900 (1940-4400)	3500 (2550-5500)	.101[3]
Absolute lymphocyte count (K/μL)	1900 (1200-2800)	2400 (1450-3850)	.018[3]
Absolute eosinophil count (K/μL)	55 (0-100)	0 (0-179)	.851[3]
Hemoglobin (g/dL)	13.37 ± 1.50	12.78 ± 1.56	.015[1]
Platelet count (K/μL)	255.27 ± 60.30	294.57 ± 77.05	.002[4]
ESR (mm/hr)	5 (2-14)	6 (2-18)	.390[3]
C-reactive protein (mg/L)	2.70 (1.50-5.53)	3.10 (1.84-12.40)	.119[3]
Procalcitonin (ng/L)	0.50 (0.50-0.50)	0.50 (0.41-0.50)	.168[3]
AST (U/L)	28 (23-38.5)	32 (25-40.5)	.160[3]
ALT (U/L)	15 (12-20)	16 (12-20.5)	.560[3]
GGT (U/L)	12 (10-16)	12 (10-19)	.639[3]
ALP (U/L)	191 (92-245.5)	163 (79-232.5)	.363[3]
Total bilirubin (mg/dL)	0.39 (0.28-0.58)	0.39 (0.29-0.56)	.885[3]
Indirect bilirubin (mg/dL)	0.28 (0.20-0.42)	0.30 (0.22-0.44)	.308[3]
Albumin (mg/dL)	4.44 ± 0.31	4.43 ± 0.38	.897[1]
INR	1.05 ± 0.11	1.01 ± 0.12	.353[1]
aPTT	29.36 ± 3.85	30.40 ± 4.49	.531[1]
D-dimer (ng/mL)	300 (228-442)	290 (212-534)	.840[3]
LDH (U/L)	253 (209-305)	285 (227-337)	.029[3]
Troponin (ng/L)	2 (2-2.3)	2 (2-4.25)	.018[3]

Data were presented as mean ± standard deviation or median (interquartile range: 25th percentiles-75th percentiles), and were described as number (n) and percentage (%), as appropriate.
[1]Independent samples t-test.
[2]Yates continuity correction chi-square test.
[3]Mann–Whitney U-test.
[4]Welch's t-test.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; GGT, Gamma-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; aPTT, activated partial thromboplastin time; WBCs, white blood cells.

High levels of ALT were reported in patients with 46.6% (n = 7) with 1-2 × ULN, 13.3% (n = 2) with 2-3 × ULN, and 40%

Table 3. Laboratory Results of the Patients with COVID-19 According to the Age Groups

	Age Groups			
Laboratory Results	**<5 Years (n = 94, 31.9%)**	**5-10 Years (n = 53, 18%)**	**>10 Years (n = 147, 50%)**	***P***
WBCs (K/μL)	7500 (5400-10000)[a]	5800 (4800-7700)[b]	5700 (4700-7100)[b]	<.001[1]
Neutrophil (K/μL)	2600 (1600-4700)	3100 (2300-5300)	3000 (2300-4350)	.055[1]
Lymphocyte (K/μL)	3200 (2200-5000)[a]	1600 (1000-2400)[b]	1800 (1200-2275)[b]	<.001[1]
Eosinophil (K/μL)	55 (0-100)	0 (0-100)	0 (0-100)	.611[1]
Hemoglobin (g/dL)	12.33 ± 1.14[a]	12.97 ± 1.00[b]	13.99 ± 1.54[c]	<.001[2]
Platelet (× 10^3/L)	285.24 ± 74.05[a]	269.74 ± 53.08[a]	243.58 ± 56.77[b]	<.001[2]
ESR (mm/h)	3 (2-7.75)[a]	7 (4-14)[b]	7 (2-16.5)[b]	.010[1]
C-reactive protein (mg/L)	2.55 (1.40-6.65)	3.40 (2-5.30)	2.85 (1.60-6.03)	.822[1]
Procalcitonin (ng/L)	0.50 (0.24-0.70)	0.50 (0.50-0.60)	0.50 (0.50-0.50)	.180[1]
AST (U/L)	42 (36-48.75)[a]	31 (27-37)[b]	23 (19-28)[c]	<.001[1]
Abnormal AST levels (n = 98, 33.3%)	72 (76.6)[a]	15 (28.3)[b]	11 (7.5)[c]	<.001[3]
ALT (U/L)	17.5 (14-23.75)[a]	15 (12-17)[b]	14 (11-19)[b]	<.001[1]
Abnormal ALT levels (n = 15, 5.1%)	9 (9.6)[a]	0 (0)[b]	6 (4.1)	.028[4]
GGT (U/L)	11 (9-15.25)[a]	12 (11-13)[a]	13 (11-17)[b]	.006[1]
Abnormal GGT levels (n = 26, 8.9%)	14 (15.2)[a]	2 (3.8)[b]	10 (6.8)[b]	.030[3]
ALP (U/L)	209 (140.5-247.5)[a]	233 (212-257)[b]	121 (73-211)[c]	<.001[1]
Abnormal ALP levels (n = 19, 6.6%)	0 (0)[a]	1 (1.9)[a]	18 (12.2)[b]	<.001[3]
Total bilirubin (mg/dL)	0.35 (0.25-0.46)[a]	0.34 (0.27-0.48)[a]	0.45 (0.32-0.63)[b]	<.001[1]
Abnormal total bilirubin levels (n = 11, 3.8%)	4 (4.3)	2 (3.8)	5 (3.4)	.920[4]
Indirect bilirubin (mg/dL)	0.26 (0.18-0.35)[a]	0.24 (0.19-0.30)[a]	0.33 (0.23-0.47)[b]	<.001[1]
Abnormal indirect bilirubin levels (n = 10, 3.4%)	6 (6.5)	0 (0)	4 (2.7)	.105[4]
Direct bilirubin (mg/dL)	0.08 (0.06-0.11)[a]	0.08 (0.06-0.13)[a]	0.11 (0.08-0.15)[b]	<.001[1]
Abnormal direct bilirubin levels (n = 11, 3.8%)	4 (4.2)	2 (3.8)	5 (3.4)	.929[4]

Data were presented as mean ± standard deviation or median (interquartile range: 25th percentiles-75th percentiles), and were described as number (n) and percentage (%), as appropriate.
[1]Kruskal–Wallis test.
[2]Welch's *F* test.
[3]Pearson chi-square test.
[4]Fisher–Freeman–Halton test.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; ULN, upper limit of normal; WBCs, white blood cells.

(n = 6) with more than 3 × ULN. High levels of AST were reported in patients with 88.7% (n = 87) with 1-2 × ULN, 5.1% (n = 5) with 2-3 × ULN, and 6.1% (n = 6) with more than 3 × ULN.

There is no consensus on the COVID-19 liver injury classifications. In an adult study, liver abnormalities were classified as hepatocellular (high AST/ALT activities), cholestatic (high ALP/GGT activities), and mixed types.[16] In our study, based on the patterns of abnormal liver test results (n = 130, 44.2%), 71.5% (n = 93) were cholestatic, 18.4% (n = 24) were hepatocyte, and 10% (n = 13) were mixed. All abnormal liver result types were statistically significantly more frequent under 5 years of age ($P < .001$). No patient had liver failure at their follow-up evaluations as liver enzymes recovered within 5-60 days. All patient coagulation measures and kidney function results were normal. There were no differences in liver function tests (e.g., serum albumin level or INR) or clinical outcomes in groups with and without GI symptoms ($P > .05$). Only one adolescent with Canavan disease died due to acute respiratory distress syndrome. However, liver function tests were normal at admission, and AST and ALT levels increased following intensive care. The other patients were discharged from the hospital without complications.

DISCUSSION

In the early course of the COVID-19 pandemic, respiratory symptoms were the most frequently reported complaint in patients with SARS-CoV-2. Over time, patients were found to present with different clinical symptoms.

In our study, as with others, there was no gender or age dominance in COVID-19 patients.

Guo et al[17] found that the male-to-female gender ratio was 1.2 : 1, and a median age of 7years was found in children with COVID-19. The study by Cura et al[18] in Turkey reported that 48.2% of 220 infected children were boys with a median age of 10 years.

Like our findings, the study by Turan et al[19] reported that 131 (66.2%) children had a history of family contact. Moreover, children with COVID-19 were infected by close family clustering or a history thereof.

Although clinical findings in children tend to be mild, they may present with different systemic involvements. Guo's study indicated incidence rates of fever (77.9%), cough (32.4%), and diarrhea (4.4%).[17] Incidence rates of fever (40.5%), cough (5.9%), diarrhea (7.7%), and vomiting (4.1%) were reported by Cura et al.[18] In our study, the most asymptomatic cases included children under 5 years of age, and cough was more common among those >10 years ($P < .001$). The high rate of acute gastroenteritis in our study may be related to the frequency of COVID-19 testing in children who present with diarrhea.

Although children are less susceptible to COVID-19 than adults, underlying medical problems (e.g., genetic, neurological, or metabolic conditions; congenital heart disease; asthma; malignancies; obesity; and immunosuppression) and very young age are considered risk factors for severe cases. The most common comorbidities in our patients were asthma (n = 6), obesity (n = 7), autoimmune disease (n = 2: autoimmune hemolytic anemia and familial Mediterranean fever), malignancy (n = 2: hepatoblastoma and lymphoma), immunodeficiency (n = 2: nuclear factor-kappa B essential modulator deficiency and antibody deficiency), and Canavan disease (n = 1). These patients presented with acute bronchitis or pneumonia. All adolescents presenting with lower respiratory tract infections were obese and had asthma. A meta-analysis showed that the severity of COVID-19 was higher in children with asthma.[5,20] Öner et al[21] demonstrated that pediatric hematology–oncology patients have relatively favorable outcomes with COVID-19 because they are already under close monitoring. We observed that apart from asthma and obesity, immunosuppressive conditions and autoimmunities were risk factors. In such cases, patients should be closely monitored as clinical deterioration may occur. However, there were no statistically significant elevations of liver enzymes in COVID-19 children with underlying diseases compared with previously healthy children ($P > .05$). Unlike adult patients, liver enzymes may not predict COVID-19 severity.

In our study, patients with bacterial coinfections (2%) were younger than 5 years of age and were previously healthy. All patients had high WBCs, CRP, and procalcitonin values and were discharged without complications. Although specific rates of pediatric patients have not yet been reported, bacterial infections were found to be more common in critically ill adult COVID-19 patients (6.9%).[22] There were no statistically significant differences in liver enzyme elevation and GI manifestations in the patient ($P > .05$). Procalcitonin was found to be high in 80% of Chinese pediatric patients, and 40% of these patients had coinfections.[23] High leukocyte, CRP, procalcitonin, and LDH levels were detected in 8 severe pediatric cases in China, and half of these had abnormal liver function test results.[24] In our study, WBC, CRP, and procalcitonin levels were high in immunosuppressed patients with pneumonia and those with bacterial coinfections. In others, there were no statistically significant differences between lymphopenia, liver enzyme elevation, or hospitalization rates ($P > .05$). Bacterial coinfections should be considered with COVID-19 patients who are immunosuppressive or with high acute phase reactants.

The notion that GI symptoms are prognostic indicators is controversial. In adults, GI symptoms and liver injuries have been associated with severe COVID-19.[25] However, another study found no differences in clinical outcomes in adults with or without GI symptoms.[2] In a meta-analysis, the prevalence of GI manifestations of COVID-19 in children was 32.5%. The most common symptoms are diarrhea, vomiting, and abdominal pain.[3] In our study, diarrhea was a symptom in all age groups, and it lasted for an average of 5 days. White blood cells, platelet count, and LDH levels were significantly higher in patients with GI symptoms. The results suggest that this may have been due to dehydration.

Although our patients with GI symptoms had good prognosis, we should be careful about symptoms that may progress in severity. Tullie et al[26] reported on 8 children with COVID-19 presenting with symptoms of atypical appendicitis. Terminal ileitis and mesenteric adenitis were later confirmed via radiological imaging, and no surgical intervention was required. However, the children's clinical status progressed to multisystemic inflammatory syndrome. In our study, 3 patients had mesenteric reactive lymphadenopathy via abdominal ultrasonography. Clinical signs of multisystem inflammatory syndrome in children or acute COVID-19 infection can mimic an acute surgical-like abdomen.

SARS-CoV-2 binds to the ACE-2 receptor and enters endothelial cells, some cholangiocytes, and centrilobular hepatocytes via the ACE-2 protein.[27] Abnormalities in liver tests have been reported in 14-53% of hospitalized patients. A meta-analysis has shown that liver injury may be associated with a severe form of COVID-19 in adults.[28] However, data on abnormal liver enzymes in children with COVID-19 are rare. Slight increases in ALT or AST have been reported in 15.6-29% of children. The underlying mechanisms of abnormal liver enzymes in pediatric patients are not as clear as in adults. The effects of ACE-2 receptors, antiviral drugs, and cytokine levels remain controversial in children.[29] In a meta-analysis of 551 laboratory-confirmed pediatric COVID-19 patients, 9% presented with increased ALT, and 18% exhibited high levels of AST.[3] Another meta-analysis suggested that the liver involvement prevalence was 1.9% among children.[30]

In our study, the rates of AST, GGT, ALP, ALT, direct bilirubin, TBIL, and indirect bilirubin elevation were 33.3%, 8.9%, 6.6%, 5.1%, 3.8%, 3.8%, and 3.4%, respectively. The percentages of abnormal AST, ALT, and GGT were common in patients under 5 years of age. Like our findings, Zhou et al[29] suggested that COVID-19-related liver involvement is more prevalent among children aged 0-3 years than in other age groups as liver immaturity predisposes patients to a higher risk of abnormal

liver enzymes. Most had abnormal aminotransferase within the borderline (<2 × ULN) and only a few had abnormal liver test results higher than 2 × ULN. However, the elevation in aminotransferase >3 × ULN was 2%, and massive or severe aminotransferase elevations did not develop.

Data on liver function tests in children with COVID-19 have thus far been limited to AST and ALT. In an adult study that included 417 COVID-19 cases, 90% showed mild abnormal liver enzymes, and patients with elevated ALT, AST, GGT, and TBIL levels >3 × ULN during hospitalization accounted for 10.4%, 5.7%, 11.6%, and 2.8%, respectively.[16] Adult studies have reported that patients with severe COVID-19 have significant elevations of GGT, direct bilirubin, and TBIL, with moderate elevations of ALP. Alterations in liver function tests could possibly be caused by the dysfunction of cholangiocytes, which can become infected by SARS-CoV-2.[27] Regarding patterns of abnormal liver tests, in our study, mainly cholestatic (n = 93, 71.5%) liver injury was detected. However, the percentages of hepatocellular and mixed types of liver injuries were 18.4% (n = 24) and 10% (n = 13), respectively. Cholestatic liver injury was more common in children under 5 years of age, which may be related to differences in the distribution of ACE-2 in the liver and biliary tract. In the study of Cai et al.[16] patients (n = 417, including children) who were classified with hepatocellular and cholestatic liver injury were at 3-fold greater risk of developing severe COVID-19.[16] In our study, patients with cholestatic liver injuries required more hospitalization than those with hepatocellular types (P =.05).

The 14-day-old neonate presenting with low-grade fever was diagnosed via RT-PCR. His mother had no symptoms, and the test was negative. In routine examinations, elevations of AST (414 U/L), ALT (431 U/L), and GGT (580 U/L) were found. Otherwise, liver function tests (e.g., serum albumin level and INR) were normal. Serum AST, ALT, and GGT levels improved over 2 months. Therefore, SARS-CoV-2 should be considered in differential diagnoses as a viral agent causing hepatitis.

Viral hepatitis markers (e.g., anti-HAV IgM, HBsAg, total anti-HBc, and anti-HCV serological) were negative in children with elevated liver enzymes, and they recovered spontaneously without specific treatment within 5-60 days. No liver side effects were observed in those using favipiravir therapy (n = 7). Additionally, there was no significant relationship between abnormal liver enzymes and acute phase reactants or in the clinical course of patients (P > .05).

This study has some limitations. First, it is a retrospective, single-centered study. Because the number of moderate and critical cases was small, we could not compare disease severity with abnormal liver function. Additionally, the increase in AST levels may be due to COVID-19 or other factors, such as myositis or hepatotoxic drugs (i.e., paracetamol), which patients may have used before being admitted. Additional studies are needed to confirm the effects of GI and liver involvement in children with COVID-19.

CONCLUSION

In our study, GI and liver manifestations occurred at considerable rates in patients with COVID-19; however, less was seen in the respiratory system. We suggest that COVID-19 should be kept in mind in differential diagnoses of gastroenteritis and liver enzyme abnormalities. Unlike adult studies, there was no relationship between COVID-19 severity and GI symptoms or liver involvement.

Ethics Committee Approval: This study was approved by Ethics committee of Selçuk University, (Approval No: 70632468-050.01.04-57148).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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