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The Relationship between Liver Enzyme Levels and Severity of Lung Involvement in Children with COVID-19 Infection

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Abstract

Background: COVID-19 can affect multiple organs, including the lungs and liver. Elevated liver enzymes are often observed in these patients, and a chest CT scan is typically used to assess the extent of lung involvement.
The aim of this study was to determine the frequency of liver enzyme elevation in children infected with COVID-19 and evaluate the type and severity of lung involvement based on chest CT scan findings. Additionally, the study aimed to identify any relationship between hepatic enzyme abnormalities and the severity of lung involvement based on imaging findings.

Methods: A cross-sectional study was conducted on all patients under 18 years of age who were admitted to Hazrat Ali Asghar Children's Hospital from March 2020 to September 2022 with a confirmed COVID-19 infection by PCR test. Normal laboratory values for aspartate transaminase (AST) and alanine transaminase (ALT) were 8-33 U/L and 10-40 U/L, respectively. Mild, moderate, and severe increases in ALT were defined as 40-200 U/L, 200-800 U/L, and more than 800 U/L respectively. Similarly, mild, moderate, and severe increases in AST were defined as 33-165 U/L, 165-660 U/L, and more than 660 U/L, respectively. Continuous data between two groups were compared using an independent t-test, while comparisons across multiple groups were analyzed via one-way ANOVA. Associations between categorical variables were assessed using the Chi-square or Fisher's exact test.

Results: The present study included 320 patients, with 186 (58.12%) male and 134 (41.88%) female cases. No cases of clinical hepatitis were observed during the study. In terms of ALT values, 264 (82.5%) patients had normal levels, while 56 (17.5%) had subclinical hepatitis. Specifically, 51 (16%)cases were classified as mild, 4 (1.2%) as moderate, and 1 (0.3%) as severe in terms of increased ALT levels. It is important to note that all patients showed improvement in AST and ALT levels during the course of treatment. A chest CT scan was performed in 192 cases, accounting for 60% of the total. Out of these, 110 patients (57.3%) had a normal CT scan, while 49 (25.5 %), 23 (12%), and 10 (5.2%) cases showed mild, moderate, and severe pulmonary involvement, respectively. Additionally, 4 (2%) cases had pleural effusion. Regarding the type of involvement, 27 (14%), 37 (19.3%), and 18 (9.4%) cases presented with typical, indeterminate, and atypical findings on the chest CT scan. No significant relationship was found between liver enzyme abnormalities and the severity of lung involvement based on imaging findings.

Conclusion: Liver enzyme values do not appear to predict the severity of lung involvement in pediatric COVID-19 patients.

Keywords: Covid-19, Liver enzyme, Lung, Pediatrics

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Introduction

The coronavirus 2 (SARS-CoV2) was first identified as the cause of the COVID-19 disease in late December 2019 in China (1). Shortly after, the World Health Organization declared it a pandemic in March 2020 (2). By April 2024, the virus had infected millions of people and caused the deaths of over 7 million individuals worldwide (3). Studies

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↑What is "already known" in this topic:
COVID-19 can affect multiple organs, including the lungs and liver. Lung involvement and respiratory symptoms are major concerns for patients with COVID-19, with chest CT scans often used to evaluate the extent of lung involvement. Elevated liver enzymes are commonly observed in these patients.

→What this article adds:
This study evaluated the relationship between liver function test levels and the degree of lung involvement indicated by imaging results. The findings suggest that the levels of liver enzymes are not able to predict the severity of lung involvement in pediatric patients with COVID-19.

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on COVID-19 patients have shown symptoms related to the digestive system, such as diarrhea, nausea, and vomiting (4). The most frequently reported gastrointestinal symptom of COVID-19 is diarrhea (5). However, a review study found that anorexia was the most common gastrointestinal symptom in adults, while diarrhea was the most common in both children and adults. Moreover, vomiting was more prevalent in children compared to adults. Abdominal pain and gastrointestinal bleeding were reported more frequently in patients with critical conditions due to long-term hypoxemia. Cell necrosis caused by tissue hypoxia damages the mucosal cells of the gastrointestinal tract, resulting in ulceration and bleeding (4).

The liver may also be affected by this disease as increased liver enzymes are commonly observed in these patients (6).

Lung involvement and respiratory symptoms are major concerns in patients with COVID-19, with chest CT scans often used to evaluate the extent of lung involvement. Several studies have investigated the radiological findings of COVID-19 patients, revealing changes visible in the CT scan in 69 to 89% of cases. Among these findings, Ground Glass Opacification(GGO) is the most common, as reported in various studies. While the RT-PCR test is a diagnostic tool for this disease, a CT scan can be useful for both diagnosis and determining the appropriate treatment for patients (7).

The aim of this study was to determine the frequency of gastrointestinal symptoms and abnormal liver function tests in children with COVID-19 infection. Additionally, the study aimed to investigate the type and severity of lung involvement in chest CT scans to establish any potential relationship between GI manifestations, abnormal liver function tests, and the severity of lung involvement as indicated by imaging results.

Methods

Population

In this current cross-sectional study, all patients under the age of 18 who tested positive for COVID-19 based on PCR results and were hospitalized at Hazrat-e Ali Asghar Children's Hospital in Tehran, Iran, were included. These cases were part of a descriptive cross-sectional study approved by the ethics committee of Iran University of Medical Sciences and conducted from March 2020 to the end of September 2022. Patients diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) were excluded.

The normal laboratory values for AST and ALT were 8-33 U/L and 10-40 U/L respectively. Mild increases (less than 5 times the normal limit) in AST ranged from 33-165 U/L, while moderate increases (5-20 times the normal limit) and severe increases (more than 20 times the normal limit) ranged from 165-660 U/L and more than 660 U/L respectively. Mild, moderate, and severe increases in ALT were 40-200 U/L, 200-800 U/L, and more than 800 U/L respectively. Subclinical hepatitis was defined as an increased ALT without clinical symptoms.

The severity and type of pulmonary involvement were assessed and recorded by a single radiologist based on the chest CT scan findings of the patients. To determine the severity of involvement, each lobe of the lung was assigned a score from one to five based on the percentage of involvement. A score of 1 indicated involvement of less than 5% of the lobe, while a score of 2 indicated involvement of 5-25% of the lobe. Scores 3 and 4 indicated an involvement of 26-49% and 50-75% of the lobe, respectively. A score of 5 indicated involvement of more than 75% of the lobe. The numerical scores ranged from 0 to 25, with scores of 1-5 considered mild, 6-14 considered moderate, and 15-25 considered severe. To classify the type of lung involvement, it was categorized into four types (8,9): typical (bilateral distribution, peripheral and/or subpleural GGOs and/or consolidation), indeterminate (unilateral peripheral or peripheral and central GGOs and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, multifocal or diffuse GGOs and/or consolidation without specific distribution), atypical (unilateral segmental or lobar consolidation, central unilateral or bilateral GGOs and/or consolidation, single round consolidation, pleural effusion, lymphadenopathy), and negative (no chest radiographic findings suggestive of pneumonia).

Statistical methods

The data were presented as mean (SD) and frequency (percentages). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. To compare binomial continuous data, an independent t-test was used. Comparison between multiple groups was conducted using a one-way ANOVA test. The Chi-square or Fisher exact test was used to assess the association between categorical variables. The data were analyzed using SPSS version 22 statistical software. A *p*-value of less than 0.05 was considered statistically significant.

Results

The present study included 320 patients under the age of 18 with COVID-19 infection. The mean age of the participants was 5.55 ± 4.78 years, ranging from 2 days to 17 years. Among the 320 patients, 186 (58.12%) cases were male, and 134 (41.88%) cases were female.

A total of 241 cases (75.3%)showed elevated liver function tests. Specifically, increased AST and ALT levels were observed in 186 (58.1%) and 56(17.5%) patients, respectively. Additionally, 48(15%) cases had elevated levels of both ALT and AST.

There was no significant relationship between sex and abnormal LFTs (*P*=0.618), including abnormal AST (*P*=0.767) and abnormal ALT (*P*=0.836).

While there was no significant relationship between age and abnormal ALT (*P*=0.342), there was a significant relationship between age and abnormal AST (*P*=0.001).

Out of 56 cases with abnormal ALT, 34(60.7%) were male and 22(39.3%) were female. The mean values for AST and ALT were 60.11 ± 150.21 (6-2200) and 37.44 ±84.76 (5-1400) U/L respectively.

There was no significant relationship between the severity of pulmonary involvement based on imaging and abnormal LFTs (*P*=0.227) [including ALT (*P*=0.08) and AST

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Table 1. Characteristics of the cases

Variable	Subgroups	Live (N:311)	Death (N:9)	Total (N=320)	*P* value
AST	Normal	131 (42.1%)	3(33.3%)	134 (41.9%)	0.312
	Mild	171(55%)	5(55.6%)	176(55%)	
	Moderate	6(1.9%)	1(11.1%)	7(2.2%)	
	Severe	3(1%)	0(0%)	3(0.9%)	
ALT	Normal	258(83%)	6(66.7%)	264(82.5%)	0.106
	Mild	49(15.8%)	2(22.2%)	51(16%)	
	Moderate	3(0.9%)	1(11.1%)	4(1.2%)	
	Severe	1(0.3%)	0(0%)	1(0.3%)	
GI manifestations	Abdominal pain (age≥2 years)	9(2.9%)	0(0%)	9(2.8%)	0.771
	Vomiting	56(18%)	1(11.1%)	57(17.8%)	0.708
	diarrhea	54(17.4%)	3(33.3%)	57(17.8%)	0.372
Variable	Subgroups	Live(N=187)	Death(N=5)	Total(N=192)	
Severity of involvement in CT	Normal	108(57.75%)	2(40.0%)	110(57.3%)	0.061
	Mild	48(25.7%)	1(20%)	49(25.5%)	
	Moderate	23(12.3%)	0(0%)	23 (12%)	
	Severe	8 (4.25%)	2 (40%)	10(5.2%)	
Type of involvement in CT	Normal	108(57.75%)	2(40.0%)	110(57.3%)	0.293
	Typical	27(14.4%)	0(0%)	27 (14 %),	
	Indeterminate	34(18.25%)	3(60%)	37(19.3%)	
	Atypical	18(9.6%)	0(0%)	18(9.4%)	
Variable	Subgroups	Live (N:311)	Death (N:9)	Total (N=320)	P value
AST	Normal	131 (42.1%)	3(33.3%)	134 (41.9%)	0.311
	Mild	171(55%)	5(55.6%)	176(55%)	
	Moderate	6(1.9%)	1(11.1%)	7(2.2%)	
	Severe	3(1%)	0(0%)	3(0.9%)	
ALT	Normal	258(83%)	6(66.7%)	264(82.5%)	0.107
	Mild	49(15.8%)	2(22.2%)	51(16%)	
	Moderate	3(1%)	1(11%)	4(1.2%)	
	Severe	1(0.3%)	0(0%)	1(0.3%)	
GI manifestations	Abdominal pain (age≥2 years)	9(2.9%)	0(0%)	9(2.8%)	0.772
	Vomiting	56(18%)	1(11.1%)	57(17.8%)	0.706
	diarrhea	54(17.4%)	3(33.3%)	57(17.8%)	0.371
Variable	Subgroups	Live(N=187)	Death(N=5)	Total(N=192)	
Severity of involvement in CT	Normal	108(57.75%)	2(40.0%)	110(57.3%)	0.062
	Mild	48(25.7%)	1(20%)	49(25.5%)	
	Moderate	23(12.3%)	0(0%)	23 (12%)	
	Severe	8 (4.25%)	2 (40%)	10(5.2%)	
Type of involvement in CT	Normal	108(57.75%)	2(40.0%)	110(57.3%)	0.293
	Typical	27(14.4%)	0(0%)	27 (14 %),	
	Indeterminate	34(18.25%)	3(100%)	37(19.3%)	
	Atypical	18(9.6%)	0(0%)	18(9.4%)	

(*P*=0.34)], gastrointestinal symptoms (*P*=0.28), but death (*P*=0.05).

The mean AST/ALT ratio was 1.79± 1.24. There was no significant relationship between the AST/ALT ratio and gastrointestinal symptoms (*P*=0.199) or the severity of lung involvement (*P*=0.939).

No clinical hepatitis cases were observed during the study. However, based on ALT levels, 17.5% of cases had subclinical hepatitis (16 % mild, 1.2% moderate. and 0.3% severe) (Table 1). All patients showed improvement in AST and ALT levels during treatment.

Out of 320 cases, 51 cases (16%) had an underlying disease, with hematologic malignancy being the most common. In total, 5 cases with underlying disease (4 cases with hematologic malignancy and one case with cyanotic heart disease) and 4 cases without known underlying disease died.

A chest CT scan was performed in 192 (60%) cases. The characteristics of pulmonary CT scans based on severity and type of involvement are shown in Table 1. In total, 4 (2%) cases had pleural effusion.

The most common gastrointestinal symptoms were vomiting (18%) and diarrhea (17.4%) (Table 1). There was no significant difference between gender and the severity or type of lung involvement in the CT scan (*P*=0.262).

Discussion

Although the respiratory system is the primary site of infection, COVID-19 can also impact many other organs. It appears that hepatic involvement and GI manifestations are more common than initially reported (10).

It is important to note that this study only focused on hepatic involvement and gastrointestinal symptoms without considering respiratory symptoms. The higher frequency of certain gastrointestinal symptoms in our study compared to previous studies might be attributed to changes in the virus's behavior over time (11). The most common gastrointestinal symptoms observed in our study were vomiting and diarrhea, which align with several other studies. However, some studies have identified abdominal pain as the most common gastrointestinal symptom (11). According to a

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systematic review, the prevalence of gastrointestinal symptoms ranged from 0% to 88% (12). Pooled analyses revealed that gastrointestinal symptoms were common in pediatric COVID-19 cases, with nearly a quarter of patients experiencing at least one gastrointestinal symptom (12). The most common gastrointestinal symptoms were diarrhea, followed by vomiting and abdominal pain (12).

The frequency of COVID-19 infection showed a male predominance in our study. According to available studies, males may be more susceptible to COVID-19 infection. Based on recent epidemiological studies, the higher incidence of COVID-19 infection in males and individuals of Asian descent may be attributed to a higher expression level of ACE-2 receptors (13,14).

Our study revealed that chest CT scans were performed on 60% of patients infected with COVID-19, with 57.75% of the scans showing normal results. During the early stages of the COVID-19 pandemic, CT scans were performed more frequently, especially when guidelines for diagnosing and managing COVID-19 infection in pediatrics were unclear or lacking.

Although the increased AST to ALT levels in our study were not statistically significant, this may be attributed to the COVID-19 infection itself or accompanying myositis (15).

According to a study by Di Giorgio et al., the most common presentation of liver involvement in COVID-19 infection was an increase in liver transaminases (16). Therefore, SARS-CoV-2 is considered a possible cause of acute non-icteric hepatitis, even in children with mild respiratory symptoms (17).

In our study, we found that sex did not have any relationship with increased LFTs. This result is not consistent with the findings of Feng et al.'s study, where they hypothesized that infected men are more likely to develop COVID-19-associated liver dysfunction than infected women. The differences in sex-related findings between these studies may be attributed to the age of the cases studied (18). Additionally, older age was associated with a higher likelihood of liver damage/dysfunction in their study. We also observed a relationship between age and abnormal AST values (P=0.001) in our study.

The concentration of ACE2 receptors on bile duct epithelial cells may be 20 times higher than in hepatocytes. Therefore, it can be concluded that during SARS-CoV-2 infection, bile duct epithelial cells might be more involved and damaged than hepatocytes. However, significant increases in circulating levels of serum alkaline phosphatase, bilirubin, or gamma-glutamyl transferase (which may reflect bile duct injury) have been rarely reported in COVID-19 patients (19). Since our study focused on pediatric cases and serum alkaline phosphatase levels can also originate from the bones, we were unable to evaluate this aspect. Additionally, none of the cases showed clinical signs of jaundice.

In Armin et al.'s study, abnormal AST and ALT tests were reported in 62% and 58% of the patients, respectively (1). In Kiani et al.'s study, an increase in ALT and AST levels was observed in 32% and 35% of the cases, respectively. Consistent with our study, the increase in AST levels was higher than ALT values. However, this increase was not significant in our study.

Lavoza et al. reported that liver damage in uncomplicated cases of COVID-19 is mostly temporary and usually resolves without treatment (20). Our study confirmed their findings.

Our study found no relationship between LFT levels and the severity of lung involvement based on imaging. Esmaili et al.'s study also demonstrated that children with elevated liver enzymes did not exhibit more respiratory involvement than those without elevated liver enzymes. Additionally, there was no significant relationship between pulmonary involvement and abnormal increase in AST and ALT levels (21). Our results are also consistent with the study by Gulsum Alkan et al., which showed that the presence of GI symptoms or an increase in liver enzymes had no effect on the course of the disease in children infected with the COVID-19 virus (15). The study also found that there was no significant difference in the increase of liver enzymes between children with underlying diseases and healthy children infected with COVID-19. It was observed that, unlike adult patients, liver enzymes could not predict the severity of COVID-19 infection (15).

However, some studies have yielded conflicting results. In the study by Armin et al., a significant relationship was found between elevated liver enzymes and the severity of the disease. They concluded that liver enzymes could predict the severity of COVID-19 (14). Similarly, the study by Boregowda et al. also indicated that abnormalities in liver enzymes could suggest a severe COVID-19 infection and predict mortality (22). Further research is needed to clarify this issue.

It is important to acknowledge that this study had some limitations. The cases included were limited to confirmed COVID-19 cases that were tested for LFTs. Impacting the sample size. Additionally, some characteristics of study participants, such as social characteristics and exposure information, were not available.

Conclusion

Based on the results of our study, it appears that the severity of lung involvement in pediatric COVID-19 patients may not be predicted by liver enzyme levels.

Authors' Contributions

SS and KA wrote the first draft. YA performed the statistical analysis. ZE reported the radiological results. SS, YA, KA, ZE, and MA all contributed

to conceptualization and critical revision for accuracy. YA is the guarantor of this study.

Ethical Considerations

This study was approved by the ethics review committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1400.056).

Acknowledgment

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Conflict of Interests

The authors declare that they have no competing interests.

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