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Creatine Kinase as a Predictor of Disease Severity in Children with COVID-19

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Abstract

Background: The majority of children with COVID-19 infection experience asymptomatic or mild disease, but some of them are at risk of developing severe illness. Determination of predictors of severe disease can help to prevent this form of disease in children. The aim of the current study was to determine the predictors of disease severity of COVID-19 infection based on laboratory markers and underlying conditions in children.

Methods: This cross-sectional study was conducted in Iran from May 2021 to March 2022. Thirty hundred and seventeen children under 18 years old with positive tests or pulmonary manifestations of COVID-19 referred to a teaching hospital in Tehran were included in the study. Demographic, laboratory, and clinical parameters of included children were measured. The participants were classified into three severity groups based on a severity-scoring protocol. Data was analyzed using SPSS software with chi-square, analysis of variance (ANOVA) tests, and linear generalized model. Statistical significance was considered at 0.05.

Results: Among 317 children, 186 patients (58.7%) were male. The mean age of the participants was 4.75 ± 4.47 years old. Examination of clinical factors showed cough (64%), Malaise (57.7%), and Tachypnea (35.3%) were the most frequent findings among the subjects. Employing the severity scoring protocol, most patients (69.1%) were classified into the mild group. There was a significant relationship between the severity of COVID-19 and the level of Hemoglobin, Aspartate Transaminase (AST), Alanine Transaminase (ALT), C-reactive protein (CRP), Lactate Dehydrogenase (LDH), Creatine Kinase (CK), D-dimer, Ferritin, and Fibrinogen (P<0.001). Creatine Kinase was found to be a predictor of COVID-19 severity in adjusted model. All underlying conditions, except asthma, were significantly associated with disease severity.

Conclusion: In our study, it was determined that CK could be considered a predictor of the severity of COVID-19 in children. These results suggest that integrating CK assessment into routine clinical protocols may aid healthcare providers in timely risk stratification and personalized patient care approaches.

Keywords: Covid-19, Pediatrics, Coronavirus, Biomarkers, Severity

Conflicts of Interest: *None declared*
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Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2, has had a major impact on global health, with millions of confirmed cases worldwide (1, 2). Although the pandemic has now come to an end, reviewing the clinical course and identifying predictors of severity in patients is crucial for future preparedness and management (3, 4).

During the pandemic, children were less affected than adults. However, it is clear that they were not immune to

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↑What is "already known" in this topic:
Identifying laboratory markers that predict the severity of the disease will help healthcare professionals prioritize high-risk patients, optimize resource allocation, and provide timely interventions to improve patient outcomes in future outbreaks. There are few comprehensive studies that specifically focus on children.

→What this article adds:
In our study, it was determined that CK could be considered as a predictor of the severity of COVID-19 in children. This suggests that integrating CK assessment into routine clinical protocols may aid healthcare providers in timely risk stratification and personalized patient care approaches.

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COVID-19 (5). The prevalence of this disease in children worldwide is 2.4%, but the incidence is higher in children with multisystem inflammatory disease, multiple organ failure, on chemotherapy, and at risk of shock (6). The severity of COVID-19 in children can range from mild illness or no symptoms to severe respiratory failure requiring intensive care (7). Children with this disease may present with a variety of symptoms. The most prominent ones are fever and gastrointestinal symptoms, such as abdominal pain, vomiting, and diarrhea, which occur in 70%–90% of them (5). Other symptoms include rash (50-60%), conjunctivitis (40-50%), peripheral edema (10-30%), and headache (30%) (8).

Laboratory markers play an important role in assessing disease severity and guiding clinical decision-making. The number of various blood cells, such as white blood cells, lymphocytes, neutrophils, platelets, and hemoglobin, can change, which can indicate the type and severity of the disease (9). Most patients had positive IgM and IgG antibody responses, indicating a postviral inflammatory response (10). In some studies, in children with COVID-19 and Multisystem Inflammatory Syndrome (MIS-C), a response with an increase in the level of cytokines, including interleukins 6, 10, 17 and tumor necrosis factor-alpha and Interferon-gamma, is determined (10, 11). Additionally, this inflammatory response was associated with the activation of neutrophils and macrophages, as well as endothelial dysfunction and microangiopathy (11). It has been proven in some studies that laboratory findings such as hyponatremia, hypoalbuminemia, high D-dimer, and inflammatory markers such as CRP (C-reactive protein), ESR (Erythrocyte Sedimentation Rate), and high ferritin were also associated with this disease (7, 8).

Timely diagnosis of COVID-19 and its prognosis are of particular clinical importance, as delayed diagnosis can have irreversible consequences (12). Identifying laboratory markers that predict the severity of the disease will help healthcare professionals prioritize high-risk patients, optimize resource allocation, and provide timely interventions to improve patient outcomes in future outbreaks (13). Various studies have investigated associations between laboratory markers and disease outcomes in adult COVID-19 patients during the pandemic (14, 15). However, there are few comprehensive studies that specifically focus on children. Therefore, this paper aims to bridge this knowledge gap by providing an analysis of laboratory markers as predictors of severity in children with COVID-19. The three main objectives of the current study are investigating laboratory markers and their potential prognostic value for COVID-19 in children, determining the relationship between laboratory marker levels and disease severity, and finally, predicting the clinical course of disease in children suspected of having COVID-19 referred to an educational treatment center (Aliasghar Children's Hospital) in Tehran, Iran.

Methods

Study Design and setting

This cross-sectional study was conducted from May 2021 to March 2022 at Aliasghar Children's Hospital, Tehran, Iran.

Study population

All children between 1 month and 18 years old with positive COVID-19 or pulmonary manifestations of COVID-19 (based on PCR (Polymerase Chain Reaction) test, nasopharyngeal swabs, or lung CT (Computed Tomography) involvement according to the radiologist's report or positive serology which was defined as elevated IgM levels) referred to the hospital was included in the study. Children diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) syndrome were excluded from the study.

A convenient sampling method was employed. Sample size was calculated according to the rule of thumb, which is used in prediction models. Accordingly, 20-30 samples were considered for each variable of the model. Considering 10 variables for the final model, at least 200-300 cases were needed.

We evaluated the medical records of children with early symptoms of suspected COVID-19. Subsequently, 317 patients who met the inclusion criteria entered the study.

Data Collection

Child demographics included age, sex, weight, medical history, drug use, and laboratory parameters including White Blood Cell (WBC) count, hemoglobin, platelets (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), D-dimer, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), creatine kinase (CK), ferritin, troponin, fibrinogen, interlukin-6 (IL-6), procalcitonin, COVID-19 immunoglobulin M (IgM) serology, immunoglobulin G (IgG) were collected from the pediatric patient's medical record. In addition, clinical manifestations such as fever, fever duration, respiratory rate (RR), heart rate (PR), cough, weakness or lethargy, muscle pain, diarrhea, vomiting, loss of smell or taste, stomach upset, headache, dizziness, skin lesions, and unconsciousness, as well as need for respiratory support were recorded.

Using a scoring protocol designed by the Ministry of Health and Medical Education (MoHME) of Iran(16), the patients were classified into three severity groups. This scoring system employs host factors, clinical manifestations, co-morbidities, and laboratory parameters to determine a severity score for each patient. Accordingly, patients with scores of 4 or less were assigned to the "mild" group, while patients with scores from 5 to 7 and scores above seven were classified into "moderate" and "severe" groups, respectively. The parameters of the scoring system are presented in Table 1. Data was collected anonymously to maintain the confidentiality of study participants.

Data Analysis

Data were analyzed using SPSS version 22. Summary statistics such as frequency, mean, and standard deviation were used to describe the study population. According to the Central Limit Theorem, for sample sizes greater than 30, the distribution of sample means will tend to be normally distributed, regardless of the distribution of the population. Therefore, parametric statistical tests were em-

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Table 1. COVID-19 severity scoring protocol.

Predictor	Predictive factor	Cut off	Score
Host factors	Age	<5	1
Clinical manifestations	Pulse Rate (Considering fever or dehydration)	Tachycardia according to age*	2
	Respiratory Rate	Tachypnea according to COVID 2 Algorithm in children**	2
	Temperature	> 38.5	1
		> 38.5 for > 5 days	2
Comorbidities	Obesity		2
	Hypertension	Uncontrolled	1
		Controlled	1
	Chronic lung disease	Chronic obstructive pulmonary disease	2
		Others (uncontrolled asthma, Pulmonary fibrosis)	1
	Immune deficiency	Bone marrow or solid organ transplant	2
		Other immunodeficiencies (HIV (CD4< 200 OR 15%), use of corticosteroids or other immunosuppressing agents)	1
	Cancer	Under chemotherapy	2
		In remission	1
	Hemoglobinopathy	Sickle cell disease	2
		Other hemoglobinopathies	1
	Chronic kidney disease		1
	Diabetes mellitus		1
	Cardiovascular disease		2
	Cerebrovascular disease		1
	Chronic liver disease		2
Lab tests	Lymphopenia	According to the COVID-19 algorithm in children*	2
	LDH	>500	2
	Or	245-500	1
	CRP	>70mg/L	2
		40-70mg/L	1

ployed in our study. The chi-square test was used to evaluate the relationship between categorical variables and COVID-19 severity. The exploration of the relationship between laboratory markers and COVID-19 severity was undertaken through the one-way ANOVA test. Following the identification of laboratory markers with significant associations with COVID-19 severity through the ANOVA test, further examination was carried out using a linear generalized model (ordinal regression) to find the predictors of COVID-19 severity. The significance level was considered less than 0.05.

Ethical approval

The Research Ethics Committee of the Iran University of Medical Sciences approved the study. (Code of Ethics: IR.IUMS.FMD.REC.1400.093)

Results

A total of 294 participants (92.7%) were Iranian, and the rest were Afghan. One hundred eighty-six patients (58.7%) were male, and the mean age of the participants was 4.75 ± 4.47 years (minimum age 1 month and maximum age 17 years). The mean length of hospital stays in the general ward and PICU were 5.68 ± 4.59 days and 3.00 ± 10.1 days, respectively. Nasopharyngeal samples were positive in 129 patients. In the chest CT of 187 patients (59%), there were manifestations of lung involvement. Employing the severity scoring protocol designed by the Ministry of Health and Medical Education of Iran, 219 (69.1%), 77 (24.4%), and 21(6.6%) patients were classified into mild, moderate, and severe groups, respectively.

The most common underlying conditions among the subjects included seizure (12.6%), cancer (9.1%), immunosuppressive medication within 6 weeks prior to the study (9.8%), and history of taking chemotherapy (8.5%). There was a significant relationship between all these underlying diseases and the severity of COVID-19, based on the results of the Chi-square test (P< 0.05) (Table 2). Other underlying conditions include diabetes, hypertension, asthma, sickle cell disease, cystic fibrosis, congenital immunodeficiency, congenital heart disease, cardiomyopathy, chronic liver disease, chronic lung disease, chronic kidney disease, HIV, chromosomal disease, myelopathies, history of dialysis were observed in 72 patients (22.7%). Of all the underlying conditions examined, there was no statistically significant association between asthma and the severity of COVID-19 (Not shown in the table).

Involvement of Chest CT was observed in 59% of patients. Using a Chi-square test, it was found that the relationship between chest CT involvement and COVID-19 severity was significant (P<0.001). However, a positive PCR test was not significantly associated with the severity of COVID-19 (Table 2).

In terms of clinical symptoms of the patients, cough (64%), Malaise (57.7%), and Tachypnea (35.3%) were the most common clinical findings. The mean of fever duration in the patients was 3.05 ±1.97 days. There was a significant relationship between the severity of COVID-19 and clinical parameters, including malaise (P:0.019), Tachypnea (P<0.001), Respiratory distress (P<0.001), Tachycardia

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Table 2. Demographic characteristics of hospitalized children with COVID-19 (n=317)

Variable	Total (n= 317)	Severity			
Number (percent)		Mild (n= 219)	Moderate (n=77)	Severe (n=21)	*P* value
Nationality (%)					
Iranian	294 (92.7%)	205 (93.6%)	69 (89.6%)	20 (95.2%)	0.458
Afghan	23 (7.3%)	14 (6.4%)	8 (10.4%)	1 (4.8%)	
Sex (%)					
Male	186 (58.7%)	127 (58%)	44 (57.1%)	15 (71.4%)	<0.001*
Female	131 (41.3%)	92 (42%)	33 (42.9%)	6 (28.6%)	
Underlying conditions (%)					
Seizure	40 (12.6%)	7 (3.2%)	22 (28.6%)	21 (52.4%)	<0.001*
Immunosuppressive drug user	31 (9.8%)	14 (6.4%)	15 (19.5%)	2 (9.5%)	0.004*
Cancer	29 (9.1%)	11 (5%)	16 (20.8%)	2 (9.5%)	<0.001*
History of Chemotherapy	27 (8.5%)	10 (4.6%)	16 (20.8%)	1 (4.8%)	<0.001*
Positive PCR test	129 (40.7%)	97 (44.3 %)	23 (29.9%)	9 (42.9%)	0.084
Chest CT involvement	187 (59%)	113 (51.6%)	57 (74%)	17 (81%)	<0.001*

*Level of significance was considered as *P*<0.05 for the Chi-Square test.PCR: Polymerase Chain Reaction, CT: Computed Tomography

Table 3. Clinical symptoms and interventions in children with COVID-19 and the relationship with COVID-19 severity.

Variable	Total	Severity			
Number (percent)	(n=317)	Mild (n= 219)	Moderate (n=77)	Severe (n=21)	*P* value*
Symptoms (%)					
Cough	203 (64%)	131 (59.8%)	56 (72.7%)	16 (76.2%)	0.062
Malaise	183 (57.7%)	115 (52.5%)	53 (68.8%)	15 (71.4%)	0.019*
Tachypnea	112 (35.3%)	35 (16%)	58 (75.3%)	19 (90.5%)	<0.001*
Respiratory distress	108 (34.1%)	35 (16%)	54 (70.1%)	19 (90.5%)	<0.001*
Tachycardia	92 (29%)	24 (11%)	59 (64.9%)	18 (85.7%)	<0.001*
Diarrhea	71 (22.4%)	51 (23.3%)	14 (18.2%)	6 (28.6%)	0.510
Vomiting	70 (22.1%)	50 (22.8%)	16 (20.8%)	4 (19%)	0.878
Abdominal pain	54 (17%)	46 (21%)	6 (7.8%)	2 (9.5%)	0.019*
Myalgia	48 (15.1%)	34 (15.5%)	11 (14.3%)	3 (14.3%)	0.960
Nasal congestion	41 (12.9%)	32 (14.6%)	8 (10.4%)	1 (4.8%)	0.327
Intervention (%)					
Oxygen therapy	150 (47.3%)	68 (31.1%)	62 (80.5%)	20 (95.2%)	<0.001*
Intubation	33 (10.4%)	2 (0.9%)	20 (26%)	11 (52.4%)	<0.001*

*Level of significance was considered as p<0.05 for Chi Square test.

(*P*:0.001), as well as abdominal pain (*P*:0.019). However, the relationship between the severity of COVID-19 and other clinical symptoms was not statistically significant (Table 3).

Table 4 presents the laboratory data in patients, considering their severity categories. According to the results of the one-way ANOVA test, there was a significant relationship between the severity of COVID-19 and the level of Hemoglobin, AST, ALT, CRP, CK, LDH, D-dimer, Ferritin, and Fibrinogen (*P*: 0.02, 0.003, 0.002, 0.001, <0.001, <0.001, <0.001, <0.001¸0.01 respectively). However, the severity of COVID-19 was not significantly associated with other laboratory parameters (Table 4).

Table 5 presents the results of our generalized linear model (ordinal regression analysis) investigating the relationship between various laboratory markers and the severity of COVID-19. All laboratory markers with a significant relationship with COVID-19 severity (Table 4) were employed in this model, and the model aimed to identify significant predictors of COVID-19 severity. However, in our statistical analysis, we noted a collinearity between AST and ALT. In this case, including both AST and ALT could inflate the variance of the coefficient estimates, making it difficult to determine the individual effect of each variable on the outcome. Therefore, we chose to exclude ALT from our analysis to maintain the integrity of our statistical model.

Additionally, C-reactive protein (CRP) and lactate dehydrogenase (LDH) were also excluded from the analysis. Both CRP and LDH are integral components of our severity scoring system, which categorizes patients based on various clinical and laboratory parameters. Since these markers are already utilized as predictors within the severity score, including them as separate predictors in our statistical models would create redundancy. Thus, we opted to focus on other independent variables that did not overlap with the severity scoring criteria.

It is demonstrated that among the laboratory markers investigated, only CK exhibited a statistically significant relationship with COVID-19 severity (*P*=0.035). For each unit increase in CK, there was a 1.3% increase in the odds of moving to a higher COVID-19 severity category. The remaining markers, including AST, D-dimer, Ferritin, Fibrinogen, and Hemoglobin, did not demonstrate statistically significant associations with COVID-19 severity (Table 5).

The Receiver Operating Characteristic (ROC) curve was developed to evaluate the model's ability to distinguish between moderate or severe cases and mild cases. Among the variables assessed, the one with the highest Area Under the

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Table 4. Laboratory findings in children with COVID-19 and the relationship with COVID-19 severity

Variable	Total	Severity			
Mean (SD)	(n=317)	Mild (n= 219)	Moderate (n=77)	Severe (n=21)	*P* value*
WBC (µ/l)	8.3 (5.4)	8.4 (5.1)	7.6 (5.1)	9.3 (8.5)	0.382
Lymph (%)	32.5 (21.5)	34.2 (21.3)	28.3 (20.5)	30.1 (25.7)	0.104
PMN (%)	56.3 (23.8)	56.9 (22.4)	55.6 (26.4)	52.9 (28.4)	0.738
Hb (mg/dl)	11.1 (1.99)	11.2 (1.7)	10.8 (2.2)	10.1 (2.7)	0.022*
PLT (mm^3/µl)	253.0 (137.7)	259.9 (131.8)	232.2 (147.7)	257.9 (158.7)	0.311
AST (IU/L)	66.7 (149.4)	47.7 (36.8)	107.3 (280.8)	115.3 (159.7)	0.002*
ALT (IU/L)	49.8 (155.3)	30.6 (33.4)	83.5 (249.5)	126.2 (343.4)	0.003*
ALP (IU/L)	544.8 (482.8)	540.5 (473.6)	562.4 (549.3)	524.8 (299.8)	0.926
ESR (mm/hr)	23.6 (23.7)	22.2 (21.6)	25.1 (27.8)	32.9 (27.5)	0.120
CRP (mg/dl)	42.1 (35.0)	38.1 (34.3)	47.2 (35.1)	65.0 (32.4)	0.001*
CK (U/L)	148.3 (183.1)	130.8 (119.0)	157.8 (223.7)	295.6 (399.6)	<0.001*
LDH (U/L)	626.9 (303.4)	586.0 (226.7)	700.4 (409.9)	797.2 (446.5)	<0.001*
CK-MB (IU/L)	28.0 (17.8)	28.5 (18.4)	24.8 (14.8)	34.8 (20.3)	0.060
D-dimer (ng/ml)	484.8 (544.1)	429.8 (508.5)	525.9 (483.4)	907.0 (862.8)	<0.001*
Ferritin	238.5 (199.1)	219.3 (195.5)	255.3 (167.4)	400.5 (268.8)	<0.001*
Troponin	0.08 (0.13)	0.07 (0.09)	0.09 (0.21)	0.10 (0.09)	0.384
Fibrinogen	75.9 (178.3)	56.3 (141.0)	114.7 (249.8)	138.6 (185.7)	0.018*
IL-6	2.1 (10.7)	2.0 (12.0)	1.7 (6.9)	4.3 (6.8)	0.597
Procalcitonin	0.04 (0.3)	0.02 (0.2)	0.06 (0.3)	0.15 (0.5)	0.139

*The level of significance was considered as p<0.05 for the ANOVA test.
WBC: White Blood Cell; PMN: Polymorphonuclear neutrophil; Hb: Hemoglobin; PLT: Platelet; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; CK: Creatine kinase; LDH: Lactate Dehydrogenase, CK-MB: Creatine Phospho-kinase-MB; IL-6: Interleukin-6.

Table 5. Ordinal Regression Analysis of Laboratory Markers as Predictors of COVID-19 Severity in Children

Variable	Exp (B)	Confidence Interval 95%		*P*-value
		Lower	upper	
AST	1.000	0.998	1.001	0.699
CK	1.003	1.000	1.005	0.035*
D dimer	1.000	0.999	1.001	0.845
Ferritin	1.001	0.999	1.004	0.278
Fibrinogen	0.999	0.095	1.003	0.736
Hemoglobin	0.639	0.389	1.050	0.077

*Level of significance was considered as *P*<0.05 for ordinal regression analysis.

Table 6. Diagnostic Accuracy of the Laboratory Variables for moderate or severe cases

Variable	Area Under Curve	Standard Error	Confidence Interval 95%		*P*-value
			Lower	Upper	
AST	66.8	0.085	0.503	0.834	0.048
CK	59.1	0.086	0.422	0.759	0.286
D dimer	66.3	0.083	0.500	0.825	0.825
Ferritin	64.1	0.077	0.489	0.792	0.098
Fibrinogen	52.0	0.086	0.352	0.689	0.810
Hemoglobin	34.9	0.087	0.177	0.520	0.520

Curve (AUC) was AST, achieving an AUC of 66.8% significanltly. Other variables' AUC values are detailed in Figure 1 and Table 6.

Discussion

Despite the formal declaration of the end of the COVID-19 epidemic, ongoing cases continue to manifest, signifying a persistent impact. Learning from this pandemic is essential to prepare for future outbreaks, especially for vulnerable pediatric populations with weaker immune systems (17).

The definition of COVID-19 disease severity varies across studies. In a study by Zachariah et al. (18), disease severity was measured using hemodynamic markers and the need for mechanical ventilation. Dong et al. selected respiratory symptoms, including dyspnea or hypoxemia, as the parameters for determining disease severity (19). However, in the present study, as well as in a study by Armin et al (20), disease severity was determined based on the scoring protocol of the Ministry of Health and Medical Education of Iran (16). Employing this severity scoring protocol, the majority of patients (69.1%) were classified into the mild group, reflecting a pattern observed in children with generally milder disease manifestations. Aligned with previous research, a 2020 systematic review supported milder disease severity and more favorable prognostic outcomes among children affected by COVID-19 (6).

Several studies highlight the significance of clinical factors like cough in assessing COVID-19 severity in children (21, 22). Our study mirrors established clinical symptoms of pediatric COVID-19, notably highlighting the prominence of cough, malaise, and tachypnea, aligning with prior research.

An association between the severity of COVID-19 and

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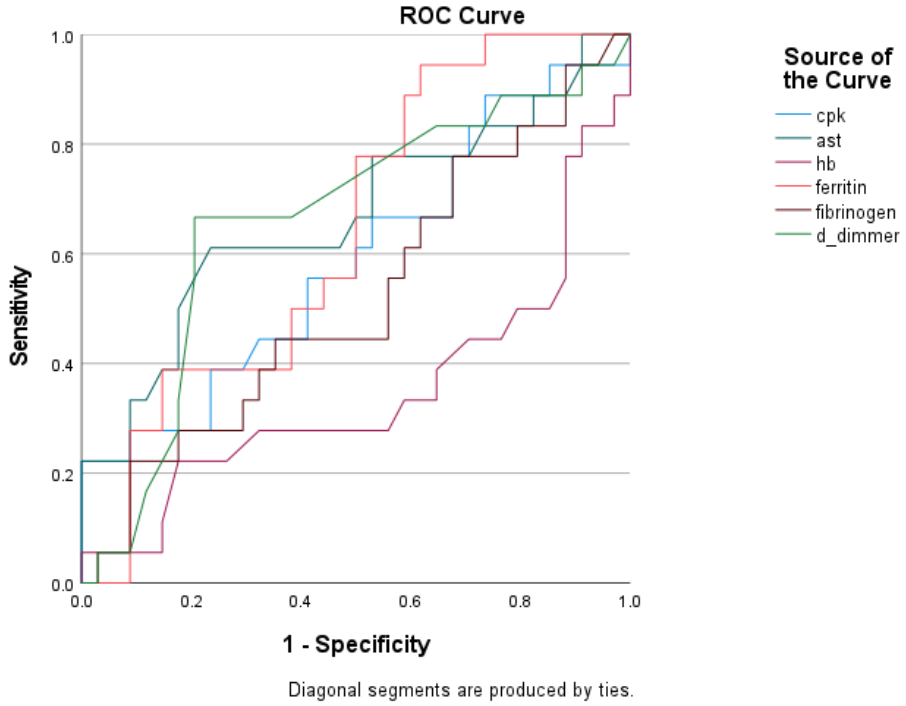

Figure 1. Receiver Operating Characteristic (ROC) curve of the Laboratory Variables for moderate or severe cases

all the underlying medical conditions we investigated was observed in our study, except for asthma. In the study of Graff et al., the presence of an underlying disease, particularly obesity, diabetes, immunodeficiency, and sleep apnea, was found to be a significant predictor of a more severe form of COVID-19. However, in their study, unlike our study, it was found that there is a relationship between asthma and disease severity. This can be because the average age of the patients in their study was higher, and the prevalence of asthma was higher in these age groups (23).

While some studies assert the role of markers like CRP and lymphopenia in predicting severity, others argue that markers such as ferritin, LDH, CRP, procalcitonin, and D-dimer are essential in indicating severe COVID-19 cases (24, 25). In the study by Shahbaznejad et al., lymphopenia and neutrophilia were common in their subjects (26). In the study by Dufort et al., in 95 children with COVID-19 and fever, increases in CRP, D dimer (91%), and troponin (71%) were observed (8). Furthermore, in another study conducted in China of 1099 patients, 83.2% had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia. CRP, ALT, AST, and d-dimer were increased in most of the patients in their study (27). In the study by Armin et al., it was found that there is a significant relationship between ferritin, LDH, and liver enzyme changes, as well as increased CRP with disease severity (28). Similar findings regarding the relationship between disease severity and elevated CRP and liver enzymes have also been observed in studies in adults. In the study by Graff et al., it was established that elevated CRP is a predictor of increased disease severity in children (23). In the present study, elevated levels of AST, ALT, CRP, LDH, CK, D-dimer, ferritin, and fibrinogen are consistently associated with disease severity, reinforcing existing knowledge. Particularly, CK emerges as a robust predictor, complementing recent findings on its prognostic value (29).

Our study establishes a significant association between Creatine Kinase (CK) levels and the severity of COVID-19 in children. The observed correlation suggests CK's potential as a predictor for the severity of illness in pediatric patients affected by COVID-19. Elevated CK levels could serve as an early warning sign. However, evaluating CK in conjunction with other potential biomarkers might fortify its predictive value and improve risk assessment models for pediatric COVID-19 cases.

While we utilized a severity protocol to gauge COVID-19 severity in pediatrics, our method lacked a specific tool for children. This underscores the necessity for a tailored scoring system designed explicitly for assessing COVID-19 severity in children, considering their distinct circumstances. While some tools exist in other countries, it's imperative to develop a scoring system customized to the situation of Iranian children affected by COVID-19. This tailored tool could better address the unique aspects of the disease in this specific population.

The comprehensive analysis of our study underscores the intricate relationship between clinical symptoms, laboratory markers, and disease severity in pediatric COVID-19. This holistic understanding provides crucial insights for clinicians, urging a nuanced approach to managing pediatric cases. These findings hold promising implications for guiding clinicians in risk stratification, treatment planning, and monitoring disease progression in pediatric COVID-19 cases. Further research validating and refining the role of CK and other identified markers in larger cohorts could contribute significantly to enhancing predictive models and

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optimizing patient care strategies. Another recommendation is to compare the patients' laboratory findings with their pre-COVID tests.

Conclusion

In our study, it was determined that CK could be considered as a predictor of the severity of COVID-19 in children. These results suggest that integrating CK assessment into routine clinical protocols may aid healthcare providers in timely risk stratification and personalized patient care approaches. Furthermore, the levels of Hemoglobin, AST, ALT, CRP, LDH, D-dimer, Ferritin, and Fibrinogen are significantly associated with COVID-19 severity.

Authors' Contributions

AN conceived the manuscript topic. MN developed the study design and the data analysis. TH conducted the data collection and interpretation of results and drafted the manuscript. MRB was a major contributor to writing the manuscript and data collection. AN and MN reviewed and commented on the manuscript draft. All authors read and approved the final manuscript.

Ethical Considerations

This study was approved by the Research Ethics Committee of the Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.FMD.REC.1400.093); all the procedures of the study were approved, including verbal informed consent. All participants were informed regarding the aim and objectives of the study, and verbal informed consent was obtained from all of the participants prior to participation. All methods were carried out in accordance with relevant guidelines and regulations.

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Conflict of Interests

The authors declare that they have no competing interests.

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