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RESEARCH ARTICLE

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Evaluation of predictors of severe-moderate COVID-19 infections at children: A review of 292 children

Aybüke A. Kara[1] | Elif Böncüoğlu[1] | Elif Kıymet[1] | Kamile Ö. Arıkan[1] | Şahika Şahinkaya[1] | Mine Düzgöl[1] | Ela Cem[1] | Miray Çelebi[1] | Hasan Ağın[2] | Süleyman N. Bayram[1] | Behzat Özkan[3] | İlker Devrim[1]

[1]Department of Pediatric Infectious Diseases, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital, İzmir, Turkey

[2]Department of Pediatric intensive Care Ünit, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey

[3]Department of Pediatric Endocrinology, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey

Correspondence

Aybüke A. Kara, Department of Pediatric Infectious Diseases, University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Ismet Kaptan Mah. Sezer Doğan Sok. No.11 Konak, Izmir, Turkey.
Email: aybukeakaslan@hotmail.com

Abstract

Although the underlying disease is associated with a severe course in adults and laboratory abnormalities have been widely reported, there are not sufficient data on the clinical course of coronavirus disease 2019 (COVID-19) in children with pre-existing comorbid conditions and on laboratory findings. We aimed to describe the independent risk factors for estimating the severity of the COVID-19 in children. All children between 1 month and 18 years old who were hospitalized during the period of March 11–December 31, 2020, resulting from COVID-19 were included in the study. Patients were categorized into mild (group 1) and moderate + severe/critically (group 2) severity based on the criteria. Demographic characteristics, comorbidities, and laboratory variables between the two groups were compared. A total of 292 children confirmed to have COVID-19 infection were included in the study. The most common associated diseases were obesity (5.1%) and asthma bronchiale (4.1%). We observed that disease progressed more severely in patients with underlying diseases, especially obesity and asthma bronchiale (for patients with obesity odds ratio [OR] 9.1, 95% confidence interval [CI] 1.92–43.28, $p = 0.005$ and for patients with asthma bronchiale OR 4.1, 95% CI 1.04–16.80, $p = 0.044$). In group 2 patients, presence of lymphopenia and hypoalbuminemia, and also an elevation in serum levels of C-reactive protein, procalcitonin, and uric acid were detected and these results were statistically significant (p values; $p < 0.001$, $p = 0.046$, $p = 0.006$, $p = 0.045$, $p < 0.001$, respectively). The strongest predictor of moderate-severe COVID-19 infections in the children was uric acid, with an odds ratio of 1.6 (95% CI 1.14–2.13, $p = 0.005$) and lymphocytes with an odds ratio of 0.7 (95% CI 0.55–0.88, $p = 0.003$). Although children are less susceptible to COVID-19, the pre-existing comorbid condition can predispose to severe disease. In addition, lymphopenia and high uric acid are indicators that COVID-19 infection may progress more severely.

KEYWORDS

coronavirus, epidemiology, immune responses, lymphocyte, pandemics, virus classification

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease that was detected in December 2019 in Wuhan, China, and has become one of the worst infectious disease outbreaks of recent times, with over 96 million cases and 2 million deaths so far.[1] Clinical manifestations in children are not typical, and mainly milder.[2] The pediatric severe and life-threatening forms are rare excluding patients with multisystemic inflammatory syndrome associated in children (MIS-C)-associated with COVID-19.[3] Population data from China and Italy indicate that children are mildly affected in comparison with adults, representing approximately 5% of cases and less than 1% of admissions to hospital.[2,4] Moreover, the fatality rate of children with COVID-19 is extremely low (0%–0.69%)[5–7] compared with that of the adult population (8%–14.8%).[8] As the novel coronavirus continues to evolve, there are still many limitations to our knowledge of who exactly this virus would impact severely. In adults, comorbidities, including advanced age, diabetes mellitus, respiratory, or cardiovascular disease are associated with more severe disease and also a higher risk of mortality.[8,9] Currently, there are limited studies concerning the COVID-19 in children with comorbidity. Laboratory abnormalities in adults with mild and severe COVID-19 have been widely reported and appear to be somewhat consistent, but the majority of laboratory data on COVID-19 pediatric patients stems from case reports and case series. In this study, we aimed to describe the independent risk factors for estimating the severity of the COVID-19 in children.

2 | METHODS

This analytical cross-sectional study was conducted in the University of Health Sciences Dr. Behçet Uz Children's Hospital in İzmir, Turkey, during the period of March 11–December 31, 2020. This current hospital is a 400-bed and tertiary care hospital with an annual approximately 600 000 outpatients and 24 000 hospitalizations.

All children between 1 month and 18 years old who were hospitalized only resulting from COViD-19 were included in the study. Newborns and cases whose data were not available were excluded from the study. Diagnosis of COVID-19 was documented by quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) positivity. The protocol of RT-PCR was consistent with the recommendation of the WHO.[10]

Demographic characteristics, pre-existing comorbidities, and laboratory parameters on admission were collected from the electronic database of the hospital. Of the comorbid diseases, obesity was defined as a body mass index (BMI) at or above the 95th percentile for children and teens of the same age and sex.[11]

The severity of COVID-19 was defined based on the clinical features, laboratory testing, and chest X-ray imaging, including asymptomatic infection, mild, moderate, severe, and critical cases.[12] Defining level of severity in COVID-19 is indicated in Table 1. According to this table, the severe and critically ill patient criteria were accepted as pediatric intensive care admission criteria. Patients were divided into two groups. Those with mild cases were determined as group 1, moderate and severe/critically cases as group 2, further demographic characteristics and laboratory variables between the two groups were compared and the effects of laboratory parameters on disease severity were investigated.

The laboratory variables included absolute lymphocyte count (ALC), thrombocyte count (PLT), C-reactive protein (CRP), procalcitonin, albumin level, uric acid level, D-dimer values, ferritin, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK), creatinine kinase-MB (CK-MB), and troponin.

2.1 | Statistical analysis

Categorical variables were analyzed using relative frequencies, numerical variables using median or mean (depending on whether they show normal distribution) values. Categorical variables were compared using Pearson χ^2 and Fisher's exact tests. Numerical variables were compared using the *t*-test or the nonparametric Mann–Whitney U test. Odds ratio (95% confidence interval [CI]) was calculated for risk factors for severity of the patients, and independent variables with $p < 0.05$ were included in the multivariate analysis. Adjusted

TABLE 1 Defining level of severity in COVID-19

Clinical category	Definition
Mild disease	Mild symptoms and normal or nonpneumonia findings on radiographic examination
Moderate disease	Respiratory symptoms and fever, with evidence of pneumonia on radiographic examination
Severe disease	Dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, PaO_2/FiO_2 ratio <300, and/or lung infiltrates >50% of the lung field within 24–48 h
Critically ill	Respiratory failure and mechanical ventilation required, septic shock, and/or multiple organ dysfunction/failure and requires ICU monitoring and treatment

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

TABLE 2 Underlying comorbid conditions of 292 children with COVID-19 infection

Comorbidities	Group 1	Group 2	Total, *N* (%)
Obesity	2	13	15 (5.1)
Asthma	3	9	12 (4.1)
Cardiac disease[a]	5	4	9 (3)
Neuro-developmental disease[b]	5	3	8 (2.7)
Congenital immunodeficiency and using of immunosuppressive drug[c]	3	4	7 (2.4)
Renal disease[d]	2	1	3 (1.02)
Hematologic disease[e]	2	0	2 (0.7)
Type 1 Diabetes mellitus	1	1	2 (0.7)
Metabolic disease[f]	1	1	2 (0.7)
Malignancy[g]	1	1	2 (0.7)
Hypertension	1	0	1 (0.35)
Celiac disease	1	0	1 (0.35)
Polycystic ovary syndrome	1	0	1 (0.35)
Skin[h]	0	1	1 (0.35)

[a]Dilated cardiomyopathy (2), atrial septal defect (ASD) (2), ventricular septal defect (VSD), mitral valve regurgitation, pulmonary stenosis, mitral valve prolapse, and asymmetric septal hypertrophy.

[b]Epilepsy (3), cerebral palsy (2), meningomyelocele, muscular dystrophy, and west syndrome.

[c]Severe combined immunodeficiency (SCID), hyperIgE syndrome, inflammatory bowel disease, familial mediterranean fever (FMF), juvenile idiopathic arthritis (JiA), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML) with bone marrow transplant.

[d]Bartter syndrome, henoch-schöenlein purpura, and vesicoureteral reflux.

[e]Thalassemia trait, chronic idiopathic thrombocytopenic purpura.

[f]Pheochromocytoma and Marfan syndrome.

[g]Neuroblastoma, new diagnosis chronic myeloid leukemia.

[h]Psoriasis.

odds rates for risk factors were determined by using these variables in a stepwise forward logistic regression model.

2.2 | Ethical consent

This study was approved by the Local Ethical Committee of Dr. Behcet Uz Children's Training and Research Hospital

3 | RESULTS

3.1 | Patients overview

As of December 31, 2020, a total of 730 children with RT-PCR positive for samples were detected in the study hospital, 348 of these patients were hospitalized and followed up, newborns and cases whose data were not available were excluded from the study, eventually, 292 patients concordance with the study design were included in this study. Of the patients, 152 (%52.1) were male and 140 (%47.9) were female. The median age of patients was 88 months (range: 1–215 months). Regarding the age distribution, 58 (19.9%) of the patients were under 1 year old, 61 (20.9%) were between 1 and 5 years old, 63 (21.5%) were between 5 and 12 years old, 110 (37.7%) were 13 years and older. The patients were classified into the severity of the disease as follows: 198 (67.8%) mild cases, 82 (28.1%), moderate cases, and 12 (4.1%) severe cases. The mean hospitalization duration was 5.1 ± 5.85 days (range: 1–56 days). Nine of 292 patients (3.0%) were admitted to the intensive care unit in the follow-up, four of them had invasive ventilation support. Of the patients, a 4.5-month-old patient died due to the underlying disease (dilated cardiomyopathy) 36th days following a recent COVID-19 infection

A pre-existing comorbid condition was present in 62 (21.2%) in the study group and five of the patients had more than one underlying disease. Among the patients, the most common associated disease was obesity (15 patients, 5.1%) and asthma bronchiale (12 patients, 4.1%) followed by congenital heart disease (9 patients, 3%), neuro-developmental disease (8 patients, 2.7%), and immunosuppressive status (7 patients, 2.4%). The associated comorbid diseases of the patients were reviewed in Table 1.

3.2 | Comparision of the mild and moderate-severe cases with COVID-19

We compared the patients with group 1 (mild) COVID-19 patients and group 2 (moderate-severe) COVID-19 patients.

3.3 | Demographic comparison

The rate of males was 65.8%. (100) and 34.2% (52) at group 1 and group 2. There was no significant difference regarding gender between the two groups ($p > 0.05$). The mean age of the patients in group 1 was 6.4 ± 5.7 years (range 1 months–17.9 years) and the mean age in group 2 was 11.5 ± 5.4 years (range 1 months–17.7 years), and significantly higher in group 2 ($p < 0.001$).

Underlying disease was present in 24 (38.7%) of the patients in group 1 and 38 (61.3%) of the patients in group 2, and significantly higher in group 2 ($p = 0.002$). The ratio of the asthma bronchiale patients was significantly higher in group 2 compared with group 1 (9 patients; 9.6% vs. 3 patients, 1.5% consecutively) ($p = 0.002$). The ratio of patients with obesity was 1.0% (two cases) in group 1 and 13.8% (13 cases) in group 2 and significantly higher in group 2 ($p < 0.001$). There was no statistical difference in terms of immunosuppression rates in these two groups ($p > 0.05$) (4.3% vs. 1.5%) (Table 2).

3.4 | Laboratory findings

The comparison of the laboratory variables between the two groups was summarized in Table 3. The mean absolute lymphocyte count was 3.05 ± 2.1 × 10^3/μl in group 1 and 2.07 ± 1.24 × 10^3/μl in group 2, significantly lower in group 2 ($p < 0.001$) (Table 3). The mean CRP and PCT values were 0.75 ± 1.8 mg/dl and 0.11 ± 0.61 ng/ml in group 1 and 2.1 ± 4.4 mg/dl and 3.9 ± 15.5 ng/ml in group 2. Both of the CRP and PCT values were significantly higher in group 2 compared with group 1 ($p = 0.0006$ and $p = 0.045$). The plasma albumin level was significantly lower in group 2 compared with group 1 ($p = 0.046$) (Table 3). The mean uric acid level was significantly higher in group 2 (4.2 ± 0.6 mg/dL) compared with group 1 (3.6 ± 1.2 mg/dl) ($p < 0.001$). There was no significant difference was present between these two groups regarding thrombocyte count, D-dimer values, ferritin, LDH, ALT, AST, CK, CK-MB, and troponin ($p > 0.05$) (Table 3).

3.5 | Logistic regression analysis of factors affecting the severity of the COVID-19 infections

In this part, the logistic regression was performed in two different models. One model included the variables including age, obesity, and asthma bronchiale (possible predisposing factors) and the second model included the laboratory tests including lymphocyte count, CRP, PCT, albumin, and uric acid.

The first model of binary logistic regression was calculated to predict moderate-severe COVID-19 disease based on age, presence of obesity, and presence of asthma bronchiale. The full model containing all predictors was statistically significant, ($\chi^2 = F$ (3, 292) = 62.3, $p < 0.001$) indicating that the model was able to distinguish between the moderate-severe COVID-19 cases and mild COVID-19 cases. As shown in Table 4, three of the independent variables made a unique statistically significant contribution to the model (presence of obesity, presence of asthma, and older age). The strongest predictor of moderate-severe COVID-19 infections in the children was obesity, recording an odds ratio of 9.1 followed by the presence of asthma bronchiale with an odds ratio of 4 1. This indicated that the children with obesity were 9.1 times and children with asthma bronchiale were 4.1 times more likely to have moderate-severe COVID-19 infection than mild COVID-19 infections. The odds ratio of 1.011 for age, indicating that for every additional month of age were 1.011 times likely to have moderate-severe COVID-19 infections.

The second model of binary logistic regression was calculated to predict moderate-severe COVID-19 disease based on lymphocyte count, CRP, PCT, albumin, and uric acid. The full model containing all predictors was statistically significant, ($\chi^2 = F$ (6, 292) = 62.4, $p < 0.001$) indicating that the model was able to distinguish between the moderate-severe COVID-19 cases and mild COVID-19 cases. As shown in Table 5, two of the independent variables made a unique statistically significant contribution to the model (lymphocyte and uric acid value). The strongest predictor of moderate-severe COVID-19 infections in the children was uric acid, with an odds ratio of 1.6, and lymphocyte with an odds ratio of 0.7. The odds ratio of 1.6 for uric acid, indicating that for every additional increase of uric acid by 1 mg/dL, were 1.6 times likely to have moderate-severe COVID-19 infections. The odds ratio of 0.70 for lymphocyte count less than 1, indicating that for every additional lymphocyte increase were 0.70 times less likely to have severe-moderate COVID-19 infections controlling for other factors in the model (Table 6).

4 | DISCUSSION

Large clinical studies evaluating the severity of the disease COVID-19 with comorbidity in children are not available yet. In this cross-sectional study, we evaluated the effect of COVID-19 on pediatric patients with comorbidities. Among the 292 patients hospitalized, 21.2% had a pre-existing comorbid condition. Obesity (5.1%) and asthma bronchiale (4.1%) were the most common underlying diseases. Considering the severity of the disease according to the laboratory parameters at the hospital admission, lymphopenia, and uric acid elevation has may serve as an early warning indicator for moderate and severe diseases

Obesity and asthma bronchiale are important risk factors for severity and mortality in adult patients.[13,14] The risk factors that link obesity to COVID-19 demonstrated for adults are also present among children: chronic subclinical inflammation, impaired immune response, and underlying cardiorespiratory diseases.[15] Studies in animal models show that rats fed a high-fat diet have increased expression of angiotensin-converting enzyme 2 (ACE-2) in the lungs, which may support the assumption of the greater severity of the disease among obese individuals.[16] In a study of 48 children admitted

TABLE 3 Comparing the severity of the disease in patients with and without comorbidity

	Group 1 (*N*:198)	Group 2 (*N*:94)	*p* value
Comorbid condition present	24 (38.7%)	38 (61.3%)	**0.000**
Obesity condition present	2 (1%)	13 (13.8%)	**0.000**
Asthma condition present	3 (1.5%)	9 (9.6%)	**0.002**
Congenital immunodeficiency and using of immunosuppressive drug	3 (1.5%)	4 (4.3%)	>0.05

Note: Group 1: Mild cases; Group 2: Moderate + severe cases.

TABLE 4 Comparing the laboratory parameters in patients with mild versus moderate + severe

	N	Group 1 (*N*:198)	*N*	Group 2 (*N*:94)	*p* value
ALC, 10^3/μl	198	3.05 ± 2.1 (0.35–11.31)	93	2.07 ± 1.24 (0.24–6.33)	**<0.001**
PLT, 10^3/μl	198	275.95 ± 943.59 (32.80–634.0)	94	260.60 ± 1138.29 (14.0–678.0)	>0.05
CRP, mg/dl	198	2.1 ± 4.4 (0–16)	94	0.75 ± 1.8 (0.02–25)	**0.006**
Procalcitonin, ng/ml	142	0.11 ± 0.61 (0.01–7.21)	69	3.9 ± 15.5 (0.01–75)	**0.045**
D-Dimer, ng/ml	179	304.26 ± 405.75 (70–3512)	88	482.34 ± 939.23 (41–6960)	>0.05
Ferritin, μg/L	130	113.65 ± 326.70 (1–2660)	69	164.58 ± 358.20 (6.4–2119)	>0.05
LDH, IU/L	137	275.69 ± 222.63 (117–2630)	74	290.70 ± 291.16 (118–1788)	>0.05
Uric acid, mg/dL	141	3.6 ± 1.2 (0.5–8.1)	76	4.2 ± 0.6 (1.6–12.4)	**<0.001**
AST, IU/L	197	36.50 ± 43.17 (9–562)	94	43.00 ± 132.61 (9–1279)	>0.05
ALT, IU/L	198	23.82 ± 41.23 (6–543)	94	31.57 ± 80.34 (6–743)	>0.05
Albumin, g/dL	187	4.32 ± 0.37 (2.7–4.9)	90	4.17 ± 0.60 (2.2–5.4)	**0.046**
CK, IU/L	166	137.97 ± 171.05 (26–1418)	81	181.46 ± 573.72 (26–4850)	>0.05
CK-MB, ng/ml	180	2.10 ± 2.15 (0–16.1)	88	1.92 ± 5.03 (0–39.7)	>0.05

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatinine kinase; CK-MB, creatinine kinase-MB; CRP, C-reactive protein; LDH, lactate dehydrogenase; PLT, thrombocyte count.

Note: Group-1: Mild cases. Group-2: Moderate + severe cases.

TABLE 5 Logistic regression analysis of invariable factors affecting the severity of the COVID-19 infections

	B	Odds ratio	% 95 CI	*p* value
Presence of obesity	2.212	9.132	1.927–43.281	0.005
Presence of asthma	1.431	4.183	1.041–16.808	0.044
Age (months)	0.011	1.011	1.007–1.016	0.00

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

to the intensive care unit, 7 (15%) were obese, and obesity was found to be remarkable comorbidity, especially in older children.[17] From the perspective of asthma bronchiole, it is unclear whether it affects COVID-19 sensitivity or severity in children. In a systematic review of whether asthma bronchiale is associated with higher COVID- 19 risk or severity in children, only two reports described asthma bronchiale or recurrent wheeze as a COVID-19 risk factor.[18] Paradoxically, asthma bronchiale may also be protective as the ACE2 receptor, required for coronavirus infection, maybe underexpressed in the lungs of atopic children.[19] A retrospective review of COVID-19 cases in children with asthma bronchiale in Spain noted no demographic differences between asthmatic children with probable COVID-19 and those without infection, including lung function, need for oral steroids, other measures of asthma bronchiale control, or comorbidities.[20] In this study, it was seen that both asthma and obesity were riskier in terms of moderate and severe disease development. Moreover, the children with obesity were 9.1 times and children with asthma bronchiale were 4.1 times more likely to have moderate-

TABLE 6 Logistic regression analysis of laboratory tests affecting the severity of the COVID-19 infections

	B	Odds ratio	% 95 CI	*p* value
ALC, 10^3/µl	−0.357	0.700	0.551–0.889	0.003
CRP, mg/dl	0.227	1.255	0.981–1.606	0.071
Procalcitonin, ng/ml	0.360	1.433	0.257–7.982	0.682
Uric acid, mg/dL	0.446	1.562	1.142–2.137	0.005
Albumin, g/dL	−0.975	0.377	0.129–1.100	0.074

Abbreviations: ALC, absolute lymphocyte count; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

severe COVID-19 infection. But the effects of pediatric obesity and asthma on COVID-19 are not yet adequately studied and some data are inferences due to the lack of a considerable number of studies published on this subject in this age group. İn this regard, further larger-scale data are required in pediatric populations.

Intriguingly, there are few reports of severe disease in immunocompromised patients with COVID-19 despite receipt of immunosuppressive agents and chemotherapies. In a review of how SARS-CoV-2 affects immunocompromised adults and children, cancer was most frequently linked with a more severe clinical course, but overall patients prescribed immunosuppression appeared to have a favorable outcome, as compared with a general population and a better outcome compared with those with other comorbidities.[21,22] Similarly, in the results of this study, no significant difference was evaluated in immunosuppressive patients in terms of moderate-severe disease development. Despite these results, we still think that clinicians should be more alert and closely monitor in terms of deterioration in immunosuppressive patients until publications with larger series come out.

Based on currently available data, it is not possible to document a pattern of laboratory values in pediatric COVID-19 according to the severity of the disease. In both SARS and the Middle East respiratory syndrome (MERS), lymphopenia was a predominant feature, due to a combination of viral particle-induced cytoplasmic damage and apoptosis.[23,24] Henry et al.[25] reviewed 2020 case reports and case series providing laboratory data on pediatric cases of COVID-19. In that review, 69.6% of the children had a normal leukocyte count and the researchers commented that the absence of lymphopenia in children could be partially explained by milder disease. In the study from China, moderate cases (19 patients) compared with mild cases (17 patients) were associated with, a decrease in lymphocyte counts, higher levels of procalcitonin, and increased D-dimer levels.[26] Laboratory data from eight severe pediatric cases showed normal or increased leukocyte count, and high levels of CRP, procalcitonin, and lactate dehydrogenase.[27] In a study of 67 children, admission to an ICU was associated with higher levels of CRP, procalcitonin, and an increased platelet count.[28] As a result, although a distinct pattern of laboratory findings has not emerged as being associated with severity of the disease in pediatric cases of COVID-19, similar to other studies, also in this study indicated that lymphopenia, high CRP, and high procalcitonin levels can be a guide in determining the severity of the disease. In fact, lymphopenia was found as a stronger predictor of moderate to severe COVID-19 infections in children with an odds ratio of 0.7. In addition, in this study hypoalbuminemia and high uric acid levels were found to be associated with moderate-severe disease differently from similar studies. Moreover, for uric acid the odds ratio was 1.6, which means for every additional increase of uric acid by 1 mg/dL, were 1.6 times likely to have moderate-severe COVID-19 infections.

Although all age groups were infected with SARS-CoV-2, the youngest (<1 year) and oldest children/young adults (15–25 years of age) were more likely to be hospitalized.[29] İn this study, we found an association between increased age and worse outcomes. In a recently published multicenter study from Turkey, similar to this study, the moderate disease was observed with a higher rate in patients over the age of 15 ($p < 0.01$) [30] Another study of 177 children from the Children's National Hospital in Washington, DC reported that the adolescents and young adults were more commonly to have critical illness than the younger children, supporting our study.[29]

This study has several limitations. First its retrospective design therefore all laboratory parameters of interest were not available in the patients included in the study. Secondly, comorbid condition groups did not contain enough patients therefore cannot be extolled as representing all children with comorbidities. İn the future, prospective studies with larger series in children with comorbidities will better demonstrate the effect of COVID-19 in children with comorbidity.

5 | CONCLUSION

COVID-19 infection was seen to have a more severe course in children with underlying diseases especially obesity and asthma bronchiale. Additively, observed that lymphopenia and uric acid are indicators that COVID-19 infection may progress more severely. We recommend clinicians must be more aware of deterioration in the children with comorbidities and monitor lymphocyte count, and uric acid levels as predictors for severe infection.

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CONFLICT OF INTERESTS

All the authors declared that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Aybüke A. Kara, Elif Kıymet, Elif Böncüoğlu, Şahika Şahinkaya, Ela Cem, Kamile Ö. Arıkan, and İlker Devrim performed the research. Aybüke A. Kara, Süleyman N. Bayram, and İlker Devrim designed the research study. Mine Düzgöl, Miray Çelebi, Behzat Özkan, and Hasan Ağın contributed essential reagents or tools. Aybüke A. Kara,

Süleyman N. Bayram, and İlker Devrim analyzed the data. Aybüke A. Kara, Süleyman N. Bayram, and İlker Devrim wrote the paper. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

ORCID

Aybüke A. Kara https://orcid.org/0000-0002-9212-5155

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