Early Short-Term Use of Different Doses of Corticosteroid in Hospitalized Pediatric Patients with Coronavirus Disease 2019 Pneumonia

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Abstract

Objective Encouraged by reports of favorable outcomes following the use of corticosteroids in patients with moderate-to-severe coronavirus 2019 (COVID-19) pneumonia, we aimed to present our experience with early short-term corticosteroid use at our center in pediatric patients with COVID-19 pneumonia.

Methods One hundred and twenty-nine pediatric patients were included in the study. Patients were divided into four groups according to the type and dose of corticosteroids given: Group 1 (those receiving dexamethasone 0.15 mg/kg/d); Group 2 (those receiving methylprednisolone 1 mg/kg/d); Group 3 (those receiving methylprednisolone 2 mg/kg/d); and Group 4 (those receiving pulse methylprednisolone 10–30 mg/kg/d).

Results Of 129 patients, 19 (14.7%) patients were assigned to Group 1, 30 (23.3%) patients to Group 2, 30 (23.3%) patients to Group 3, and 50 (38.8%) patients to Group 4. Thirty-two (24.8%) patients were followed in the pediatric intensive care unit (PICU), of whom 13 (10%) required mechanical ventilation, and 7 (%5.4) died. In Group 4, the hospitalization length was significantly longer than in other groups ($p < 0.001$, $p < 0.001$). No significant difference was found among the groups in terms of mortality ($p = 0.15$). The most common comorbidity was obesity (33%). A significant association was found between the presence of comorbidity and mortality ($p < 0.001$). All patients who died had an underlying disease. Cerebral palsy was the most common underlying disease among the patients who died. Worsening of lymphopenia was significant in patients with severe COVID-19 pneumonia at the time of transfer to the PICU ($p = 0.011$).

Conclusion Although children usually have a milder course of COVID-19 than adults, underlying diseases and obesity increase the severity of disease manifestations also in children. Further studies are needed to define the exact role of corticosteroids in COVID-19 patients.

Keywords
- Methylprednisolone
- dexamethasone
- COVID-19
- pneumonia
- lymphopenia
- pediatric

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How this Study Might Affect Research, Practice or Policy

Corticosteroids may be helpful in the treatment of moderate-to-severe coronavirus disease 2019 pneumonia in pediatric patients. Controlled clinical studies involving larger numbers of patients are needed to determine which of the corticosteroids is effective at which dose and its beneficial effect on mortality in pediatric patients.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a spectrum of respiratory disorders ranging from mild upper respiratory tract infection to fulminant pneumonia.[1]

Inpatient treatment of coronavirus disease 2019 (COVID-19) pneumonia involves primarily supportive care, oxygen therapy, and mechanical ventilation.[2,3] In the intensive care unit (ICU) setting, patient care involves noninvasive ventilation or high-flow nasal oxygen therapy.[4] Most guidelines recommend corticosteroids in moderate COVID-19 pneumonia only if there is rapid progression and to start supplemental oxygen if SpO2 is $<$94%. However, for severe disease in children, remdesivir, corticosteroid, and awake proning in older children, as well as high-flow nasal cannula (HFNC)/noninvasive ventilation (NIV)/invasive mechanical ventilation, inotropes and restrictive fluid therapy, have been advised. Dexamethasone (0.15 mg/kg/d, maximum 6 mg) and methylprednisolone (1–2 mg/kg/d) are the corticosteroids of choice. Similarly, in patients with multisystem inflammatory syndrome in children, apart from other supportive measures, intravenous immunoglobulin (IVIG) 2 g/kg over 24 to 48 hours should be added in case of life-threatening conditions, cardiac dysfunction, coronary involvement, or multiple organ dysfunction syndrome as recommended by the guidelines. If there is no improvement or worsening, then a repeat dose of IVIG or methylprednisolone at a dose of 10 to 30 mg/kg/d for 3 to 5 days is to be administered. Anakinra or infliximab can be tried in unresponsive cases to the treatment mentioned above.[5]

Some reports described the use of corticosteroids in children with critical illness, including patients with pneumonia.[6] In light of published reports of favorable results with the use of corticosteroids in patients with moderate-to-severe COVID-19 pneumonia, this study aimed to present our experience with early short-term use of corticosteroids in pediatric patients treated at our center and to evaluate how different doses of corticosteroids affect the laboratory and clinical parameters that are used for considering the transfer of the patient from hospital ward to pediatric intensive care unit (PICU).

Materials and Methods

Between January 1 and September 30, 2021, 280 children ($\leq$19 years old) were hospitalized at the pediatric infectious diseases unit and PICU of Ankara City Hospital due to suspected COVID-19. Quantitative reverse transcription polymerase chain reaction test positivity for SARS-CoV-2 in a nasopharyngeal swab was used for the diagnosis. Among these patients, 129 were diagnosed with moderate-to-severe COVID-19 pneumonia and included in the study. Patients were risk stratified by severity of symptoms on presentation to the hospital as mild, moderate, or severe COVID-19. Patients without hypoxia or exertional dyspnea were considered to have mild COVID-19. Patients with pulmonary infiltrate on chest X-ray, respiratory distress who required oxygen support (oxygen saturation [SpO2] $\geq$90%, measured by fingertip pulse oximetry in room air) but not mechanical ventilation (noninvasive or invasive) were classified as having moderate COVID-19 pneumonia. Patients who required mechanical ventilation (noninvasive or invasive) with significant hypoxemia (SpO2 $\leq$90%) or who showed rapid clinical deterioration were classified as having severe COVID-19 pneumonia.[7]

Demographic and clinical data, comorbidities, and length of stay in the ward and PICU were recorded for all patients. Laboratory results (complete blood count, C-reactive protein [CRP], erythrocyte sedimentation rate, liver function tests (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase), interleukin-6 (IL-6), cardiac enzymes, and D-dimer results were retrieved from hospital records.

The severity of unilobar or multilobar pulmonary involvement was evaluated by chest X-ray and CT scan.

Underlying comorbidities were classified as follows.

- Obesity: Obesity was defined as having a body mass index (BMI) in the 85th percentile for age and gender, according to the World Health Organization's growth charts. BMI was calculated as kg/m^2. Anthropometric classification was performed as follows: (1) overweight: BMI of 25 to $<$30 kg/m^2; (2) grade 1, moderate obesity: BMI of 30 to $<$35 kg/m^2; (3) grade 2, severe obesity: BMI of 35 to $<$40 kg/m^2; and (4) grade 3, morbid obesity: BMI $\geq$ 40 kg/m^2.
- Congenital or acquired heart disease.
- Neurodevelopmental disorders.
- Chronic respiratory disease requiring respiratory support, such as asthma, reactive airway disease, or tracheostomy.
- Endocrine disorders, such as type 1 or type 2 diabetes mellitus and insulin resistance.
- Any syndrome (e.g., Down syndrome).
- Hematologic-oncologic malignancies.

Favipiravir was given to patients older than 12 years of age ($2 \times 1{,}600$ mg per oral loading dose, followed by 2×600 mg maintenance therapy orally for a total of 5 days) after obtaining consent from their parents. Additionally, the patients were given enoxaparin (100 U/kg/d subcutaneous, divided into two doses) as initial therapy unless contraindicated.

Pulse steroid therapy with methylprednisolone was administered at a dose of 10 to 30 mg/kg/d (maximum 1 g) for 3 to 5 days to patients with severe pneumonia and patients with moderate pneumonia who did not show any clinical improvement and/or whose respiratory symptoms worsened (defined

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as increased need for oxygen) within 24 hours. Then, these patients received maintenance treatment with methylprednisolone at a dose of 2 mg/kg/d (maximum 80 mg/d) for 10 days. Patients with moderate COVID-19 pneumonia were given corticosteroids for 5 to 10 days. Corticosteroid therapy included methylprednisolone at a dose of 1 to 2 mg/kg/d (maximum 80 mg/d) or dexamethasone at a dose of 0.15 mg/kg/d (maximum 6 mg/d).

To facilitate data analysis and comparisons, patients were divided into four groups according to the type and dose of corticosteroids given: Group 1 (those receiving dexamethasone 0.15 mg/kg/d); Group 2 (those receiving methylprednisolone 1 mg/kg/d); Group 3 (those receiving methylprednisolone 2 mg/kg/d); and Group 4 (those requiring pulse methylprednisolone 10–30 mg/kg/d).

Anakinra, tocilizumab, and convalescent plasma treatment were administered on a case-by-case basis to patients with severe COVID-19 who were followed in the PICU and showed significantly elevated levels of inflammatory markers (e.g., D-dimer and ferritin) and proinflammatory cytokines (e.g., IL-6).

Ethics approval for the study was obtained from the Institutional Review Board of Ankara City Hospital (No. E1-20-560), and informed consent was obtained for all study subjects.

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, United States). The one-sample Kolmogorov–Smirnov test was used to determine whether the data were distributed normally. Groups were compared using the one-way ANOVA or the Kruskal–Wallis H test as appropriate. As a result of these analyses, the groups showing a significant difference were compared pairwise using Duncan's multiple range test or Mann–Whitney U test. Bonferroni correction was applied for p-values < 0.0083 (i.e., 0.05/6 comparisons). The results were reported as mean $\pm$ standard deviation or median (min-max). Categorical variables were compared using Pearson's chi-squared test, Likelihood ratio, or Fisher's exact chi-square test, as appropriate. Spearman's rank correlation coefficient was used to examine the relationship between inflammatory markers, clinical parameters, and the dosage of corticosteroids. These results were expressed as counts and percentages. A p-value < 0.05 was considered statistically significant.

Results

Between January 1 and September 30, 2021, 129 pediatric patients diagnosed with moderate or severe COVID-19 pneumonia who met the inclusion criteria were included in the study. ►**Table 1** shows the laboratory abnormalities and clinical and demographic characteristics of patients with COVID-19 at the time of admission to the hospital. In our study, the male/female ratio was 74/55, and the median patient age was 15.2 years (1–222 months). Of 129 patients, 19 patients (14.7%) were assigned to Group 1; 30 patients (23.3%) to group 2; 30 patients (23.3%) to Group 3; and 50 patients (38.8%) to Group 4. The most common comorbidity was obesity ($n = 47$, 33%). Ninety-seven patients (75%) were treated in the ward, and 32 (24.8%) patients were followed in the PICU. Among PICU patients, 13 (10%) required mechanical ventilation, and 7 (5.4%) died due to acute respiratory distress syndrome (ARDS). Of the patients who died, 1 (14.2%) was in group 1, 1 (14.2%) was in group 3, and 5 (71.4%) patients were in group 4.

The clinical and demographic characteristics of patients treated with different types and doses of corticosteroids are shown in ►**Table 2**. When the first three groups (Groups 1, 2, and 3) were compared, no significant difference was found in the length of stay in the ward or PICU and mortality. The use of high-flow oxygen therapy and NIV was significantly more common in the pulse methylprednisolone group (Group 4) compared to the other groups ($p = 0.0001$ and $p = 0.003$, respectively). In Group 4, the length of hospital stay was significantly longer compared to the other groups ($p < 0.001$ and $p < 0.001$). No significant difference was found among all groups in mortality ($p = 0.15$) (►**Table 3**).

The comparison of laboratory parameters of PICU patients obtained on admission to the hospital and at the time of transfer to the PICU is shown in ►**Table 4**. Thirty-two (24.8%) of 129 patients were followed in the PICU. Seventeen (13.2%) patients were transferred to the PICU from the pediatric infectious diseases ward and fifteen (11.6%) from external centers. Seven (5.4%) patients died. Absolute lymphocyte counts were significantly reduced on admission to the PICU ($p = 0.011$). No significant difference was found in other parameters.

The results of Spearman's rank correlation coefficients among inflammatory markers, clinical parameters, and the dosage of corticosteroids are shown in ►**Table 5**. Moving from Group1 to Group 4, length of stay in PICU, length of stay in the ward, and CRP positivity increased significantly ($p < 0.01$). No positive correlation was observed with IL-6.

All patients who died had an underlying disease, and a significant association was found between the presence of comorbidity and mortality ($p < 0.001$). The most common underlying disease among the deceased patients was cerebral palsy. Of the seven patients who died, four had cerebral palsy, one had Down's syndrome and obesity, one had Down's syndrome and congenital heart disease, and one had obesity and insulin resistance. There was no significant association between obesity grade and mortality ($p = 0.701$, ►**Table 6**).

Steroid-related side effects (hyperglycemia, bradycardia, and hypertension) did not occur in group 1 but were observed in five (16.7%) patients in group 2, one (3.3%) patient in group 3, and thirteen (26%) patients in group 4. None of the patients experienced thromboembolic events.

Discussion

The primary approach for the management of COVID-19 is to prevent disease-related complications. Among these complications, ARDS and cytokine release syndrome are characterized by increased tumor necrosis factor-α (TNF-α), interleukins (IL-1B, IL-2, IL-6, IL-8, IL-10), and interferon-γ (IFN-γ).[8] Death occurs as a result of an aberrant

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Table 1 Laboratory abnormalities and clinical and demographic characteristics of patients diagnosed with COVID-19 pneumonia at the time of admission

Age, months (median, min–max)	183 (1–222)
Male sex, *n* (%)	74 (57.4%)
Absolute lymphocyte count (10^3/μL), (median, min–max)	1,160 (240–9,330)
LDH (U/L), (median, min–max)	404 (155–1,688)
CRP (mg/dL), (median, min–max)	23 (2–196)
IL-6 (pg/mL), (median, min–max)	13.8 (0.6–1,792)
Procalcitonin (ng/mL), (median, min–max)	0.09 (0.01–641)
Ferritin (ng/mL), (median, min–max)	190 (17–3,372)
D-Dimer (mg/L), (median, min–max)	0.96 (0.19–35)
Treatment	
Favipiravir, *n* (%)	122 (94.6%)
Enoxaparin, *n* (%)	127 (98.4%)
Dexamethasone (0.15 mg/kg/d, max: 6 mg), *n* (%)	19 (14.7%)
Methylprednisolone (1 mg/kg/d), *n* (%)	30 (23.3%)
Methylprednisolone (2 mg/kg/d), *n* (%)	30 (23.3%)
Pulse methylprednisolone, *n* (%)	50 (38.8%)
Convalescent plasma, *n* (%)	9 (7%)
Intravenous immunoglobulin, *n* (%)	9 (7%)
Tocilizumab, *n* (%)	8 (6.2%)
Anakinra, *n* (%)	6 (4.7%)
Comorbidities ($n = 142$)	
Obesity	47 (33%)
Neurodevelopmental disorders (e.g., cerebral palsy)	17 (12%)
Insulin resistance, type 1 or type 2 diabetes mellitus	7 (4.9%)
Syndromic patients (e.g., Down's syndrome)	7 (4.9%)
Asthma or other chronic respiratory disease	4 (2.8%)
Congenital or acquired heart disease	2 (1.4%)
Hematologic-oncologic malignancies	1 (0.7%)
No comorbidities	57 (40%)
Body mass index	
Lean (malnourished)	5 (3.9%)
Normal	77 (59.7%)
Overweight	18 (14%)
Grade 1, moderate obesity	17 (13.2%)
Grade 2, severe obesity	6 (4.7%)
Grade 3, morbid obesity	6 (4.7%)
Need for supportive oxygen therapy	
Oxygen reservoir, *n* (%)	41 (31.7%)
High-flow oxygen, *n* (%)	51 (39.5%)
Noninvasive ventilation	24 (18.6%)
Mechanical ventilation, *n* (%)	13 (10%)
PICU admission, median length of stay, days (min–max)	7 (1–60)
Ward admission, median length of stay, days (min–max)	7 (1–30)

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Table 1 (*Continued*)

Patients followed at PICU, *n* (%)	32 (24.8%)
Patients followed at ward, *n* (%)	97 (75.2%)
Death, *n* (%)	7 (5.4%)

Table 2 Clinical and demographic characteristics of patients treated with different corticosteroid doses

Clinical and demographic characteristics	Group 1	Group 2	Group 3	*p*-Value[b]
	Dexamethasone *n* = 19	Methylprednisolone 1 mg/kg/d *n* = 30	Methylprednisolone 2 mg/kg/d *n* = 30	
Age, months[c]	174 (59–220)	172 (40–62)	143 (9–220)	0.077
High-flow oxygen, n (%)	4 (21.1%)	5 (16.7%)	4 (13.3%)	0.779
Non-invasive ventilation (NSIMV), n (%)	2 (10.5%)	1 (3.3%)	3 (10.0%)	0.496
Mechanical ventilation (MV), n (%)	1 (5.3%)	1 (3.3%)	2 (6.7%)	0.836
Comorbidities, *n* (%)[a]				
Obesity	6 (31.5%)	14 (46.6%)	7 (23.3%)	0.156
Neurodevelopmental disorders (e.g., cerebral palsy)	2 (10.5%)	1 (3.3%)	3 (10%)	0.496
Asthma or other chronic respiratory disease	1 (5%)	3 (10%)	0 (0%)	0.115
Insulin resistance, type 1 or type 2 diabetes mellitus	1 (5%)	3 (10%)	2 (6.6%)	0.807
Syndromic patients (e.g., Down's syndrome)	0 (0%)	1 (3.3%)	1 (3.3%)	0.572
Obesity				
Overweight	4 (21%)	5 (16.7%)	3 (10%)	0.546
Grade 1, moderate obesity	1 (5.3%)	8 (26.7%)	3 (10%)	0.075
Grade 2, severe obesity	0 (0%)	1 (3.3%)	1 (3.3%)	0.572
Grade 3, morbid obesity	1 (5.3%)	0 (0%)	0 (0%)	0.376
PICU admission, median length of stay, days (min–max)[c]	10 (7–13)	10.5 (2–19)	8 (4–36)	0.919
Ward admission, median length of stay, days (min–max)[c]	6 (3–11)	6 (2–12)	6 (4–13)	0.893
Death n (%)	1 (5.2%)	0 (0%)	1 (3.3%)	0.570

[a]Patients may have more than one comorbidity.
[b]Using Likelihood ratio test.
[c]Using Mann–Whitney test.

autoinflammatory response and severe systemic and tissue inflammation. Therefore, corticosteroids have been used to treat COVID-19 because of their potent anti-inflammatory effects.[9]

The results of the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial were announced via a press release on June 16, 2020 in the United Kingdom. In this large scale, open-label randomized study, 6,425 patients were enrolled, 2,104 patients were given dexamethasone (6 mg/d) treatment for up to 10 days, and 4,321 patients received usual care. Dexamethasone treatment was found to reduce mortality by one-third in patients who underwent mechanical ventilation. However, there was no benefit among those patients who did not receive respiratory support (rate ratio, 1.19 [%95 confidence interval [CI], 0.92–1.55]).[7] In a single center, observational study by Papamanoli et al, early administration (i.e., before mechanical ventilation) of methylprednisolone (median dose, 1.78 mg/kg/d) was associated with lower 28-day mortality or mechanical ventilation rates in patients with severe COVID-19 pneumonia. The authors reported that no effect was observed on mortality.[1] In the Brazilian open-label CoDEX (COVID-19–associated ARDS treated with DEXamethasone) study, the use of high-dose dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) therapy for moderate or severe ARDS caused by COVID-19 was associated with 6.6 ventilator-free days during the first 28 days versus 4 ventilator-free days in the standard care group (difference 2.6 days). However, there was no

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Table 3 Clinical course of patients treated with different corticosteroid doses

Clinical course	Group 1 dexamethasone $n=19$	Group 2 Methyl prednisolone 1 mg/kg/d $n=30$	Group 3 Methyl prednisolone 2 mg/kg/d $n=30$	Group 4 Pulse methyl prednisolone $n=50$	*p*-Value
Age, months[c]	174.1[a] ± 37.7	172.3[a] ± 40.5	143.87[b] ± 60.1	173.62[a] ± 49.1	**0.042**
High-flow oxygen, n (%).%[e]	4 (21.1%)	5 (16.7%)	4 (13.3%)	38 (76%)	**0.0001**
Noninvasive ventilation (NSIMV), n (%)%[e]	2 (10.5%)	1 (3.3%)	3 (10.0%)	18 (36%)	**0.003**
Mechanical ventilation (MV), n (%)%[e]	1 (5.3%)	1 (3.3%)	2 (6.7%)	9 (18%)	0.11
Anakinra, n (%) %e	2 (10.5%)	0 (0%)	0 (0%)	4 (8%)	**0.049**
Tocilizumab, n (%)%[e]	0 (0%)	0 (0%)	0 (0%)	8(16%)	**0.001**
Comorbidities n%[e]					
Obesity[e]	6 (31.5%)	14 (46.6%)	7 (23.3%)	20 (40%)	0.244
Neurodevelopmental disorders (e.g., cerebral palsy)[e]	2 (10.5%)	1 (3.3%)	3 (10%)	11 (22%)	0.078
Asthma or other chronic respiratory diseasee	1 (5%)	3 (10%)	0 (0%)	0 (0%)	**0.04**
Insulin resistance, type 1 or type 2 diabetes mellitus[e]	1 (5%)	3 (10%)	2 (6.6%)	1 (2%)	0.463
Syndromic patients (e.g., Down's syndrome)e	0 (0%)	1 (3.3%)	1 (3.3%)	5 (10%)	0.225
Obesity					
Overweighte	4 (21%)	5 (16.7%)	3 (10%)	6 (12%)	0.778
Grade 1, moderate obesity [e]	1 (5.3%)	8 (26.7%)	3 (10%)	5 (10%)	0.116
Grade 2, severe obesitye	0 (0%)	1 (3.3%)	1 (3.3%)	4 (8%)	0.374
Grade 3, morbid obesity[e]	1 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0.275
Side effects [e]					
None	17 (89.5%)	25 (83.3%)	26 (86.7%)	32 (64%)	
Steroid-related side effects (including hypertension, hyperglycemia, and bradycardia)	0 (0%)	5 (16.7%)	1 (3.3%)	13 (26%)	**0.002**
Other (including abnormal liver function tests, hemorrhage, and rash)	2 (10.5%)	0 (0%)	3 (10%)	5 (10%)	
Length of stay in PICU[d]	1.05[b] / 0 (0-13)	0.70[b] 0 (0–19)	1.87[b] / 0 (0–36)	4.68[a] /0 (0–60)	<**0.001**
Length of stay in ward[d]	6 [b] (3–11)	6 [b] (2–12)	5.50 [b] (0–13)	10 [a] (0–30)	<**0.001**
Death n%[e]	1 (5.2%)	0 (0%)	1 (3.3%)	5 (10%)	0.15

PICU: Pediatric intensive care unit.
[a,b]Different superscript letters within a column indicate significant differences; same superscript letters indicate similarity.
[c]Using one-way ANOVA and Duncan's multiple range test.
[d]Using Kruskal–Wallis H test.· Mann-Whitney U test was used for pairwise comparisons (Bonferroni correction was applied for which *p*-values <0.0083 (i.e., 0.05/6 comparisons).
[e]Using likelihood ratio test. Note. Statistically significant values are written in bold.

difference in mortality at 28 days.[10] In the Metcovid study, no effect on mortality was reported with the administration of 0.5 mg/kg methylprednisolone twice daily for 5 days in COVID-19 patients who required oxygen support or mechanical ventilation.[11]

Similarly, in our study, there was no significant difference between dexamethasone (0.15 mg/kg/d for 10 days) and methylprednisolone (1 mg/d and 2 mg/kg/d for 10 days) treatments in terms of length of stay in the ward and PICU, and mortality. The length of stay in the ward and PICU was longer, and the use of high-flow oxygen, noninvasive mechanical ventilation, and treatment with anakinra and tocilizumab were significantly more common in the group given pulse steroid therapy with methylprednisolone.

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Table 4 Comparison of laboratory parameters on hospital admission and PICU admission for patients followed at PICU

Laboratory parameters (Median. min–max)	On hospital admission	On PICU admission	*p*-Value[a]
CBC (10^3/μL)	6,535 (4,290–34,470)	8,845 (2,850–17,760)	0.836
Absolute neutrophil count (10^3/μL)	4,295 (2,620–29,680)	6,250 (1,940–16,220)	0.717
Absolute lymphocyte count (10^3/μL)	1,495 (840–3,800)	780 (280–2,700)	**0.011**
Platelets (10^3/μL)	175.000	211.500	0.196
	(30.000–312.000)	(61.000–351.000)	
AST (U/L)	60.5 (16–2,477)	52.5 (13–1,476)	0.163
ALT (U/L)	49.5 (16–1,399)	55.5 (14–893)	0.196
LDH (U/L)	428 (286–993)	491 (332–1,222)	0.438
CRP (mg/dL)	37 (4–196)	73 (7–212)	0.393
IL-6 (pg/mL)	36.8 (19.7–303)	24.4 (2.7–130)	1.000
Procalcitonin (ng/mL),	0.1 (0.1–641)	0.34 (0.03–12)	1
Ferritin (ng/mL)	550 (49–3,372)	440 (211–2,000)	0.273
D-Dimer (mg/L)	1 (0.2–7)	1.43 (0.3–15)	0.678
Pro-BNP (ng/L)	79 (35–7,318)	697 (12–3,863)	0.700

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CBC, complete blood count; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; PICU, pediatric intensive care unit.
[a]Using Mann–Whitney U test. Note. Statistically significant values are written in bold.

This difference may be related to the use of more intensive treatments for patients with severe COVID-19 pneumonia who were expected to be transferred to the PICU. There was no difference in mortality among the groups. Due to the lack of a control group in our study, we could not provide data on the optimal steroid dose that reduces overall mortality and the need for ventilation. This is one of the limitations of our study. In our clinical practice, we observed that glucocorticoids could be beneficial in treating patients with moderate-to-severe COVID-19 pneumonia. Clinical studies with a larger sample size are warranted to determine which corticosteroid dose is effective for pediatric patients and the frequency of adverse events.

High visceral adiposity in obese individuals is known to induce higher levels of local and systemic inflammatory cytokines such as IL-6 and CRP.[12] Elevation of these cytokines is mediated by increased production of proinflammatory macrophage populations, which are observed in obese individuals.[13] These cytokines have been positively correlated with COVID-19 severity.[14] Elevated cytokine levels in obese individuals may contribute to increased susceptibility to severe infection. However, childhood obesity is likely to contribute to severe COVID-19 disease through additional mechanisms. Several studies in adults reported that COVID-19 patients with a BMI of $\geq$35 kg/m^2 require invasive mechanical ventilation more frequently than patients with mild COVID-19.[15] The presence of comorbidities is a risk factor for developing severe COVID-19 in pediatric patients. In our study, the most common comorbidity was obesity, and two (6%) obese patients died. A large meta-analysis confirmed that childhood obesity was associated with a worse prognosis of COVID-19 infection.[16] We also think childhood obesity is probably associated with a worse prognosis of COVID-19. Cerebral palsy was diagnosed in four of our patients who eventually died. Respiratory dysfunction is the leading cause of morbidity and mortality in patients with chronic neurological disorders. Since these patients experience deterioration of respiratory function, such as decreased pulmonary capacity and persistent cough, this seems likely to be related to COVID-19 mortality.

Many studies have shown that lymphopenia is a distinctive finding in patients infected with SARS-CoV-2, even in the early stages of the disease.[17,18] Decreased peripheral blood lymphocyte count is an early indicator of severe or critical COVID-19. Multiple studies show lymphopenia in a substantial portion of COVID-19 patients.[19,20] Lymphopenia may be caused by viral attachment or immune injury from inflammatory mediators. Also, the exudation of circulating lymphocytes into inflammatory lung tissues may cause lymphopenia.[21] Lymphopenia has been associated with disease severity; thus, lymphocyte count can be used as a predictor of increased risk of in-hospital mortality and ICU admission. Consistently, in our study, we found a significant decrease in lymphocyte counts when we compared laboratory parameters on admission to the hospital and at the time of transfer to the PICU. These data corroborate our findings.

Steroid-related side effects were more common among patients given pulse steroid therapy, but it should be noted that since our study was retrospective, it may not fully reflect the actual frequency.

In conclusion, in addition to immunomodulatory therapies, there is a need for a specific antiviral therapy that can suppress viral replication and can be administered orally as prophylaxis before hospitalization or after exposure. Until

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Table 5 The results of Spearman's rank correlation coefficients among inflammatory markers, clinical parameters, and the dosage of corticosteroids

Variables	Length of stay in PICU	Length of stay in ward	Comorbidities	CBC	CRP	IL-6	Procalcitonin	Ferritin	Sedimentation	D-dimer
Different doses of corticosteroid	**0.363**[b]	**0.330**[b]	−0.050	0.128	**0.305**[b]	0.100	0.002	0.219	0.050	0.151
Length of stay in PICU	1.000	0.030	−0.141	**0.193**[a]	**0.291**[b]	**0.391**[b]	**0.451**[b]	**0.287**[a]	−0.237	**0.321**[b]
Length of stay in ward		1.000	−0.090	−0.080	0.134	−0.075	**−0.278**[a]	0.092	−0.162	**−0.217**[a]
Comorbidities			1.000	−0.058	0.022	0.168	0.110	−0.123	0.170	0.131
Complete blood count				1.000	0.164	**0.319**[b]	−0.003	0.141	0.101	0.064
C-reactive protein					1.000	**0.521**[b]	**0.380**[b]	**0.409**[b]	**0.414**[b]	0.116
Interleukin-6 (IL-6)						1.000	**0.372**[b]	0.206	0.190	**0.275**[a]
Procalcitonin							1.000	0.164	−0.017	0.168
Ferritin								1.000	0.062	0.145
ESR									1.000	−0.104
D-dimer										1.000

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate, IL-6, interleukin-6; PICU: pediatric intensive care unit.
Note: Spearman's Rank Correlation coefficient was used.
Note: Values in bold letters show significant correlations.
[a]$p < 0.05$.
[b]$p < 0.01$.

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Table 6 Association of comorbidity and obesity with survival status

	Survival status		*p*-Value
	Dead ($n = 7$)	Alive ($n = 122$)	
Comorbidity present	7 (100%)	63 (51.64%)	**<0.001**
Obesity present	2 (28.57%)	50 (40.98%)	0.701

Note: Using Fisher's exact test. Note. Statistically significant values are written in bold.

effective drugs are discovered, corticosteroids may be helpful in the treatment of moderate-to-severe COVID-19 pneumonia in pediatric patients. Moreover, the absence of severe steroid-related side effects makes steroid therapy a convenient treatment option for both patients and clinicians. Controlled clinical studies with a larger sample size are needed to demonstrate the true effect of corticosteroids on mortality and to determine which corticosteroid is effective at which dose in the treatment of pediatric patients.

Conflict of Interest
None declared.

Author Contributions
S.Ö. and B.G. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

S.Y., A.G., T.E., A.Y., Ö.G., L.G., Ö.M., P.B., S.E., G.B., and A.Ö.P. designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

F.U. performed statistical analyses.

All authors read and approved the final version of the manuscript.

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