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Evaluation of Inflammatory, Cardiac and Hematological Parameters in Hospitalized Children with COVID-19

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What is known on this subject?

The relationship between clinical symptoms such as inflammatory, haematological, cardiac and coagulation parameters, which are very common in adults, is still unclear in children with coronavirus disease-2019 (COVID-19).

What this study adds?

In our study, we aimed to improve the clinical approach while evaluating coagulopathy and myocarditis in children receiving treatment for COVID-19 pneumonia. In our study, it should be kept in mind that the incidence of pneumonia increased with age, and troponin values were high in the younger age group without pneumonia. Moreover, coagulation disorder is not a common finding in pediatric patients.

ABSTRACT

Objective: The relationship between clinical symptoms such as inflammatory and coagulation parameters, which are very common in adults, is still unclear in children with coronavirus disease-2019 (COVID-19). The aim of this study is to investigate the levels of inflammation and coagulation blood parameters and their correlation with pneumonia in COVID-19 pediatric patients.

Material and Methods: One hundred thirteen hospitalized COVID-19 pediatric patients were included in this study retrospectively. All patients' age, gender, number of hospitalization days, respiratory symptoms, laboratory parameters, thoracic computed tomography, polymerase chain reaction results were recorded. Patients were analyzed for pneumonia presence and absence.

Results: Gender distribution was 53% female, 47% male. Median age was 11.4 years. Hospitalization length was 4.5 days. Chest tomography was performed on 90 patients with respiratory complaints or symptoms, and COVID-19 pneumonia was detected in 62 patients (68.8%). There was a statistically significant difference in the length of hospitalization, age, white blood cell and troponin values between the patients with COVID-19 pneumonia and those without pneumonia ($p<0.001$, $p=0.008$, $p=0.048$, and $p=0.003$, respectively). When multivariate analysis was performed for these parameters, the probability of pneumonia was found to be 1.17 times higher for every additional year of age. Elevation of fibrinogen and D-dimer was not found to be statistically significant ($p=0.07$, $p=0.29$, respectively). There was no statistical difference between coagulation and inflammatory parameters in children with COVID-19 pneumonia. No cardiac complications or thrombosis were observed.

Conclusion: The finding that the risk of COVID-19 pneumonia increases with age draws more attention in terms of diagnosis and treatment. Coagulopathy was not detected in patients with COVID-19 pneumonia and no treatment is required. In addition, a detailed cardiac assessment is required in patients without COVID-19 pneumonia due to elevated troponin levels.

Keywords: Children, coagulation, COVID-19, D-dimer, pneumonia, troponin

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic was announced on 11 March 2020 in our country. In the literature, 1-5% of COVID-19 cases consist of pediatric patients (1,2). In the pediatric COVID-19 study conducted in China, 55% of cases were mild or asymptomatic, 40% were moderate, 5% were severe, and less than 1% were critically ill (3,4). Also, COVID-19 infection can cause significant cardiac and haematological alterationations in children (5,6,7).

The relationship between laboratory parameters, particularly pneumonia and myocarditis, in COVID-19 is important. White blood cell (WBC), C-reactive protein (CRP), D-dimer, fibrinogen, and troponin-I are the most commonly used laboratory markers. In adult COVID-19 patients, increases in lymphopenia, fibrinogen and D-dimer levels, and myocarditis frequency have been reported (8,9,10). The clinical importance of these parameters in pediatric patients is not clear.

In this study, our aim was to determine the changes in cardiac and haematological parameters of pediatric patients diagnosed with COVID-19 pneumonia and without pneumonia.

Material and Methods

One hundred thirteen COVID-19 pediatric patients, aged 0-18 years, who were admitted to the pediatric pandemic service of the Health Sciences University between March 2020-March 2021 were analyzed retrospectively. The code U07.3, defined for COVID-19 according to the "International Classification of Diseases" coding system, was used to collect data. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Kütahya Health Sciences University Non-Interventional Clinical Research Ethics Committee (decision no: 2021/09-02, date: 26.05.2021). All patients' age, gender, length of hospitalization, laboratory parameters (WBC, neutrophil %, lymphocyte %, platelet, fibrinogen, D-dimer, CRP, troponin-I), thoracic computed tomography (CT), and polymerase chain reaction (PCR) were recorded. Thoracic CT was performed in patients with respiratory complaints or signs of pneumonia on physical examination or chest X-ray. Four patients who did not accept treatment were not included in the hospitalization portion of the study.

Before analysis, patients were divided into four subgroups. Groups 1 and 2 had pneumonia, while groups 3 and 4 had no pneumonia.

Group 1: Patients with both COVID-19 PCR positive with pneumonia [PCR (+), CT (+)],

Group 2: Patients with negative COVID-19 PCR test but was detected in CT with COVID-19 pneumonia [PCR (-), CT (+)],

Group 3: Patients with positive COVID-19 PCR test and without COVID-19 pneumonia [PCR (+), CT (-)],

Group 4: Patients with positive COVID-19 PCR test and no respiratory system complaints and findings [only PCR (+)]. CT was not performed in group 4 patients because of the absence of respiratory system complaints and findings.

Patients with clinically impaired general condition, persistent fever, abnormal blood parameters, respiratory distress, or COVID-19 pneumonia were hospitalized. Patients with respiratory failure or indication for intensive care unit hospitalization were excluded. COVID-19 pediatric patients were divided into two groups according to their clinical and radiological results: those with pneumonia and those without pneumonia. Patients with mild to moderate pneumonia were hospitalized and treated in accordance with the Turkish Ministry of Health Guidelines (11,12). Pediatric patients were classified as mild-moderate pneumonia in the guideline recommendation if they had a fever <38.5 °C, a respiratory rate <50 per minute, and mild respiratory distress the Turkish Ministry of Health's Pediatric Patient Treatment Protocol recommends 5 days of favipiravir treatment for COVID-19 pneumonia patients aged 15 years and older.

Statistical Analysis

Epidemiological, clinical, laboratory, and imaging characteristics of the patients were recorded with standard descriptive statistics. Statistical Package for the Social Sciences (version 25, SPSS Inc., Chicago, IL, USA) was used to analyze the data. The descriptive statistics of the numerical parametric variables were calculated as mean ± standard deviation, non-parametric variables as the median (25%-75% quartiles), and categorical variables as a percentage. We evaluated the normal distribution of the study parameters using the Shapiro-Wilk test. Subsequently, Student's t-test or Mann-Whitney U test was used to compare the groups. Laboratory parameters were compared between groups with and without respiratory system involvement by One-Way ANOVA or Kruskal-Wallis test. For the pairwise comparisons of the subgroups, a post-hoc test with Tukey honestly significant difference correction was used. P values based on two-sided tests were considered statistically significant at less than 0.05. Variables from the univariate logistic regression analysis with a statistical result of $p<0.250$ were included in the multivariate logistic regression analysis.

Results

In the epidemiological analysis of 113 COVID-19 pediatric patients, 60 (53%) were female and 53 (47%) were male. The median age was 11.4 (0.8-18) years and the hospital stay was 4.5 (1-19) days (Table 1).

When the laboratory values of all patients were evaluated, lymphopenia was found in 25% of patients, and fibrinogen, D-dimer, CRP, and troponin-I were higher than the normal reference range in 44%, 46%, 48%, and 13% of patients, respectively (Table 2). When the fibrinogen, D-dimer, and CRP values were evaluated in the subgroups, no statistically significant difference was found between the subgroups (Table 1).

As the subgroup laboratory values were evaluated, a statistically significant difference was found in age, WBC, and troponin-I values (p<0.001, p=0.006, and p=0.003 respectively) (Table 1). Additionally, we evaluated the comparison results in the subgroups; there was a statistically significant difference in WBC and troponin-I values between groups 1 and 4, with p=0.011 for WBC and p=0.008 for troponin-I, respectively (Table 1).

Chest tomography was performed in 90 patients with respiratory complaints or symptoms, and COVID-19 pneumonia was detected in 66.6% of patients who required tomography.

In the analysis of 113 COVID-19 pediatric patients according to the presence of pneumonia, there was a statistically significant difference between the length of hospital stay and age (p<0.001, p=0.008, respectively). Mean age was 13.9 years, length of hospitalization was 5.2 days in the pneumonia groups (Table 3). Mean age and length of hospitalization were higher in the pneumonia groups. When fibrinogen, D-dimer, and CRP were evaluated according to pneumonia, there was a statistically significant difference in WBC and troponin-I levels (p=0.048 and p=0.003, respectively) (Table 3). When multivariate analysis was performed for these parameters, the probability of pneumonia was found to be 1.17 times higher with increasing age (Table 4).

Table 1. Epidemiological and laboratory parameters of COVID-19 pediatric patients

	Group 1 (n=40)	Group 2 (n=20)	Group 3 (n=28)	Group 4 (n=25)	p value
Age (years)	15.4 [2.0; 18.0]	15.2 [1.7; 17.9]	14.4 [3.1; 18]	2.7 [0.1; 17.1]	<0.001
Hospitalization day	5.1 [1; 19]	4.6 [1; 18]	3.1 [1; 16]	3.1 [1; 8]	0.071
WBC (x10^3)	6.0 [4.7; 8.2]	7.4 [5.2; 13.3]	6.3 [4.9; 10.6]	9.8 [7.0; 12.5]	**0.006**[b]
Neutrophil (%)	57.8±16.3	61.0±22.3	60.8±15.4	50.2±23.6	0.187[a]
Lenfocyte (%)	31.9±12.7	30.3±21.6	29.0±14.7	39.6±23.0	0.168[a]
Thrombocyte (x10^3)	233.2±60.6	366.0±270.3	256.7±67.2	268.3±71.3	0.160[a]
CRP (mg/L)	4 [1.2; 15.9]	10.2 [2.8; 87.8]	4.7 [2.0; 13.9]	7.1 [1.4; 19.6]	0.463[b]
Fibrinogen (mg/dL)	358 [272; 418]	383.5 [342.5; 567]	338.2 [302.2; 360]	318 [291.4; 353.7]	0.07[b]
D-dimer (ng/mL)	420 [262; 798]	850 [345.5;1829]	367 [317; 757]	679.5 [380; 1098]	0.289[b]
Troponin-I (ng/L)	1.4 [0.5; 2.8]	3.2 [1.8; 13.8]	2.6 [1.7; 6.2]	5.5 [2.1; 11.7]	**0.003**[b]

Values are presented as median [minimum; maximum], p values were calculated with Kruskal-Wallis test. The significant results were represented as bold; values are presented as mean ± SD, median [25-75% quartiles], p values were calculated with [a]: One-Way ANOVA or [b]: Kruskal-Wallis test. The significant results represented as bold and pairwise group comparison results were as represented below; for WBC: 1 vs. 4: p=0.011 (post-hoc test: Tukey HSD), for troponin: 1 vs. 4: p=0.008 (post-hoc test: Tukey HSD), COVID-19: Coronavirus disease-2019, n: Number, WBC: White blood cell, CRP: C-reactive protein, SD: Standard deviation

Table 2. Evaluation of laboratory parameters of all patients

Laboratory parameters	Mean + SD (reference range)	Laboratory parameters	Median [IQR] (reference range)
Thrombocyte (10^3/uL)	254.1±77.6 (130-400)	**CRP (mg/L)**	6.8 [32.6] (<5)
Neutrophil %	57.7±19.2 (41-73)	**Fibrinogen (mg/dL)**	352 [105.1] (180-350)
Lymphocyte %	32.4±17.7 (19-44)	**D-dimer (ng/mL)**	568.5 [588.5] (170-550)
		Troponin-I (ng/L)	2.1 [3.8] (0-19.8)
		WBC (10^3/uL)	6.2 [5.4] (5.2-12.4)

SD: Standard deviation, CRP: C-reactive protein, WBC: White blood cell, IQR: Interquartile range

Table 3. Evaluation of epidemiological and laboratory parameters of patients with and without COVID-19 pneumonia

	COVID-19 pneumonia (n=60)	COVID-19 without pneumonia (n=53)	p value
Age (year)	15.2 [13.1; 16.8]	8.6 [3; 14.8]	**<0.001[b]**
Hospitalization (day)	5.2 [3; 6]	3.1 [1; 5]	**0.008[b]**
WBC (10^3/uL)	6.2 [4.4; 8.9]	7.7 [5.2; 12.2]	**0.048[b]**
Neutrophil (%)	58.9±18.3	56.3±20.3	0.474[a]
Lenfocyte (%)	31.3±15.8	33.6±19.8	0.489[a]
Thrombocyte (10^3/uL)	245.3±84	264.3±69.1	0.195[a]
CRP (mg/L)	4.6 [1.5; 19.8]	6.2 [1.9; 18.9]	0.795[b]
Fibrinogen (mg/dL)	375.2 [291; 448]	330 [302; 363]	0.108[b]
D-dimer (ng/mL)	476 [262; 889]	526 [331; 894.5]	0.671[b]
Troponin-I (ng/L)	2 [0.8; 4.5]	3.1 [2; 9.2]	**0.024[b]**

Values are presented as mean ± SD, median [25-75% quartiles], p values were calculated with [a]Student's t-test or [b]Mann-Whitney U test. The significant results represented as bold. COVID-19: Coronavirus disease-2019, n: number, WBC: White blood cell, CRP: C-reactive protein

Table 4. Multivariate logistic regression analysis of epidemiological parameters of patients with and without COVID-19 pneumonia

	Xep (β)	95% CI		p value	Wald statistic
		Lower	Upper		
Age	1.138	0.981	1.321	0.089	2.894
Hospitalization day	1.177	1.086	1.275	**<0.001**	15.955

Variables from the univariate logistic regression analysis with a statistical result of p<0.250 were included in the multivariate logistic regression analysis. Age groups, sex, hospitalization day, lymphocyte count, neutrophil count, platelet count, D-dimer, fibrinogen, C-reactive protein, and troponin levels were evaluated in the analysis. COVID-19: Coronavirus disease-2019, CI: Confidence interval

Discussion

Leukopenia, lymphocytopenia, high CRP level, high D-dimer, and fibrinogen levels were detected in most of the studies conducted on COVID-19 infection (13,14,15). Especially in pediatric patients, more detailed clinical studies are required to determine the relationship between these parameters and age, pneumonia, myocarditis, and coagulopathy.

In some review studies, it was reported that: 56% of the patients were male; mean age was 8.9±0.5 years; 86.5% were PCR positive; and the length of hospital stay was 11.6±0.3 days (16). In our study, it was observed that the gender distribution was similar, the average age was higher, and the length of hospitalization was shorter than reported in the literature. The difference in the length of stay was thought to be because the ministry's guideline recommended the treatment period as 5 days (11,12).

When we evaluate the laboratory parameters, it has been reported that leukocyte and fibrinogen levels were found to be normal, while lymphocyte, D-dimer, and CRP values were found elevated in children with COVID-19 (16). It was reported that D-dimer elevation was not found to be statistically significant in 10 studies included in the analysis (17). Our study results were similar to those reported in the literature. In addition, although the CRP, fibrinogen, and D-dimer levels were above the normal reference range in our study, the difference was not statistically significant. None of these patients had clinical signs of a coagulopathy.

The epidemiological and laboratory values of the patients were evaluated within COVID-19 pneumonia groups. There was a statistically significant difference in age, WBC, and troponin-I values. Mean age was highest in patients with pneumonia. WBC and troponin-I values were higher in patients who had only fever and not pneumonia. Myocardial injury, also defined by increased troponin levels in patients with COVID-19, is thought to occur due to non-ischemic myocardial processes, particularly hypoxia, sepsis, systemic inflammation, and severe respiratory tract infection (8). In our study; cardiological examinations and echocardiographic findings of the patients with elevated troponin were found to be normal and no treatment was required.

In a study conducted in Turkey, it was found that 182 (42.5%) patients underwent thoracic CT imaging, and COVID-19 was confirmed in 38 (32.7%) (18). In our study, 54.8% of the hospitalized patients were found to have COVID-19 pneumonia

on CT. In both studies, the incidence of pneumonia is high because because pneumonia is one of the major criteria for hospitalization. Considering the patients with pneumonia, there was a statistically significant difference found between age, hospitalization day, WBC, and troponin-I levels. In the detection of WBC elevation and troponin elevation in younger children, it is important to consider that they tend to have many viral infections. It is possible that repeated viral exposure may boost the immune system when it responds to severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2) (1,19,20). Also, the distribution and affinity of the angiotensin-converting enzyme receptor and SARS-CoV-2 are different according to age (21,22,23). When multivariate analysis was performed for these parameters, the probability of pneumonia was found to increase by a factor of 1.17 with increasing age (Table 4). In older children with pneumonia, hospitalization time was also longer. The recommendation of a 5-day favipiravir treatment for patients aged 15 years and older in the Turkish Ministry of Health pediatric patient treatment protocol was thought to be the reason for this (11,12).

It is known that D-dimer is significantly elevated in patients with severe and fatal COVID-19 (24). Although adults have high D-dimer and pulmonary embolism risk, the correlation of these factors with the severity of the disease in patients with COVID-19 pneumonia remains under investigation (13,14). However, the utility of D-dimer and its clinical effect in pediatric patients are not known. In a pediatric study from Turkey, it was reported that the mean D-dimer value was higher than the references (25). In our study, the elevation of fibrinogen and D-dimer was not found to be statistically significant. Anticoagulant therapy was not administered in these patients. No thrombotic complications were observed in this study. However, there was no correlation between coagulopathy and the severity of the disease in patients with COVID-19 pneumonia.

Study Limitations

This study at the beginning of the pandemic-which was a major health problem at the time- comprehensively examined the issue. During the pandemic period, different treatment methods were recommended and applied by countries and clinics. We think that this study will contribute to the literature because it is a single-center study. in addition, in pediatric patients with COVID-19, there are few studies that have been evaluated in detail in terms of coagulopathy and blood parameters, especially in patients with pneumonia. Due to the limited number of patients and the different diagnostic and treatment protocols in different countries, we think that the different results that emerged include diverse experiences and are remarkable.

Conclusion

The finding that the risk of COVID-19 pneumonia increases with age draws more attention in terms of diagnosis and treatment. Since there was no significant difference in the COVID-19 pneumonia patients among the parameters showing a tendency to thrombosis, further investigation is warranted to understand the underlying mechanisms. It was thought that the presence of pneumonia did not increase the risk of coagulopathy. Therefore, we believe that there is no need for more aggressive anticoagulant therapy in the presence of diffuse pneumonia. Troponin-I levels may be higher in young children without COVID-19 pneumonia; therefore, it was thought that close follow-up was required for myocarditis. Also, more detailed epidemiological data are needed regarding pediatric patients related to COVID-19.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and the Kütahya Health Sciences University Non-Interventional Clinical Research Ethics Committee (decision no: 2021/09-02, date: 26.05.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.G., R.Ö., Z.Y., O.S., C.H.Ç., Y.Y., Concept: D.G., Design: D.G., R.Ö., Data Collection or Processing: D.G., R.Ö., Z.Y., O.S., C.H.Ç., Y.Y., Analysis or Interpretation: D.G., R.Ö., Literature Search: D.G., Writing: D.G., R.Ö.

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