RESEARCH ARTICLE

Abdullah Solmaz[1]
Tugba Meliha Fatma Ercan[2]
Tugba Erat[3]
Filiz Solmaz[4]

[1]Department of Pediatrics, Faculty of Medicine, Harran University, Sanliurfa, Turkey
[2]Sanliurfa Provincial Health Directorate, Turkish Ministry of Health, Sanliurfa, Turkey
[3]Department of Pediatrics, Ankara City Hospital, Ankara, Turkey
[4]Department of Nursing, Faculty of Health Sciences, Harran University, Sanliurfa, Turkey

Corresponding Author:
Abdullah Solmaz
mail: dr.solmaz@hotmail.com

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konuralptipdergisi@gmail.com
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The Role of Some Parameters in Diagnosis in the Absence of PCR in the Children with COVID-19

ABSTRACT

Objective: Infectious diseases cause inflammation in the human body and produce numerical and functional changes in peripheral blood cells. Coronavirus disease-19 (COVID-19) is also an infectious disease diagnosed by the Polymerase Chain Reaction (PCR) test. However, PCR testing may not always be available. The aim of this study is to show the effect of numerical and functional changes in blood parameters on the diagnosis of COVID-19 in children.

Methods: In this retrospective study, 296 patients and 286 healthy children were included. Nasopharyngeal swabs were collected. The swabs were analyzed by Real-time PCR. Independent-t/Mann-Whitney-U tests were applied; Receiver Operating Characteristic (ROC) curves and logistic regression modelling were evaluated.

Results: Gender and age distributions of the groups were similar (p>0.05). There were significant differences between the two groups in terms of white blood cell (WBC) (p<0.001), neutrophil (p<0.001), thrombocyte (p<0.001), lymphocyte (p<0.001), mean platelet volume (MPV) (p=0.009), lactate dehydrogenase (LDH) (p=0.003), C-reactive protein (CRP) (p<0.001) and aspartate aminotransferase (AST) (p=0.002). It was found in ROC curve analyses, while LDH (p<0.001) and CRP (p<0.001) values were higher in patients, MPV (p=0.03), platelet (p=0.04), and neutrophil (p<0.001) values of them were lower. The best model in logistic regression was the model that included hemoglobin, neutrophil, lymphocyte, thrombocyte, LDH and CRP.

Conclusions: Rapid diagnosis of COVID-19 are crucial for public health. PCR, required for definitive diagnosis, may not always be achieved, so easier and cheaper methods are needed. This study supports the diagnosis of COVID-19 in the children in the absence of PCR.

Keywords: COVID-19, Children, Laboratory Parameters, Diagnosis.

COVID-19'lu Çocuklarda PCR Yokluğunda Tanıda Bazı Laboratuvar Parametrelerinin Rolü

ÖZET

Amaç: Enfeksiyon hastalıkları vücutta inflamasyon oluşturarak periferik kan hücrelerinde sayısal ve fonksiyonel değişikliklere neden olur. Coronavirüs hastalığı-19 (COVID-19), Polimeraz Zincir Reaksiyonu (PCR) testinin ile teşhis edilen bulaşıcı bir hastalıktır. Ancak PCR testi her zaman temin edilemeyebilir. Bu çalışmanın amacı, çocuklarda kan parametrelerindeki sayısal ve fonksiyonel değişikliklerin PCR olmadığı durumda COVID-19 hızlı teşhisine etkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 296 COVID-19 hasta ve 286 sağlıklı çocuk dahil edildi. Bilimsel araştırma için gereken izinler alındı. Değişkenlerin normal dağılımına uygunluğuna göre analizlerde bağımsız-t veya Mann-Whitney-U testleri uygulandı. Receiver Operating Characteristic (ROC) eğrileri ve lojistik regresyon modellemesi değerlendirildi.

Bulgular: Grupların cinsiyeti ve yaşı benzerdir (p>0.05). Beyaz küre (WBC) (p<0.001), nötrofil (p<0.001), trombosit (p<0.001), lenfosit (p<0.001), ortalama trombosit hacmi (MPV) (p=0.009), laktat dehidrojenaz (LDH) (p=0.003), C-reaktif protein (CRP) (p<0.001) ve aspartat aminotransferaz (AST) (p=0.002) açısından iki grup arasında istatistiksel olarak anlamlı farklılıklar bulunmaktadır. ROC eğrisine bakıldığında, hastalarda LDH (p<0.001) ve CRP (p<0.001) daha yüksekken MPV (p=0.03), trombosit (p=0.04) ve nötrofil (p<0.001) sonuçları daha düşüktür. Lojistik regresyonda en iyi model hemoglobin, nötrofil, lenfosit, trombosit, LDH ve CRP'yi içeren modeldi.

Sonuç: COVID-19'un PCR yokluğunda hızlı teşhisi halk sağlığı için çok önemlidir. Kesin tanı için gerekli olan Gerçek Zamanlı Polimeraz Zincir Reaksiyonu (RT-PCR) her zaman sağlanamayabilir, bu nedenle daha kolay ve daha ucuz yöntemlere ihtiyaç vardır. Sınırlı sayıda katılımcıya rağmen bu çalışma çocuklarda labaratuvar parametreleri ile Covid-19'da hızlı tanıyı desteklemektedir.

Anahtar Kelimeler: COVID-19, Çocuk, Laboratuvar Parametreleri, Tanı.

INTRODUCTION

Coronavirus disease-19 (COVID-19) has been recognized as a pandemic with the announcement of the World Health Organization (WHO) on March 12, 2020 (1). COVID-19 incidence in young children has increased over time due to not wearing a mask and not following social distance rules (2). Children with COVID-19 positive are thought to be carriers with mild symptoms or asymptomatic; they can play an important role in the spread of the disease (3,4). In the literature, it is emphasized even if most of the children with COVID-19 have mild symptoms or asymptomatic, in a part of them that have also a serious disease can cause morbidity or mortality (5).

In many diseases, peripheral blood cells undergo numerical and functional changes as response to inflammation in the body (6). It is still under investigation whether some parameters which can be easily obtained from peripheral blood counts, such as total white blood cell (WBC), neutrophil (polymorph nuclear leukocytes - PMNL), lymphocyte, platelet, mean platelet volume (MPV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and C-Reactive Protein (CRP), can quickly detect infectious or inflammatory diseases (7-9).

This study hypothesizes that it can be possible the diagnosis of COVID-19 disease with laboratory parameters in the absence of Polymerase Chain Reaction (PCR). Accordingly, this study aims to reveal effect of COVID-19 disease on the blood parameters, to evaluate the blood parameters of children and adolescents, to provide outcomes that can help diagnose quickly, when PCR test cannot be performed.

MATERIAL AND METHODS

Design of the Study: This study was planned as a retrospective descriptive study. All patients under the age of 18 (296 participants) who applied to the hospital in Şanlıurfa between September 1 and November 30, 2020 and were positive for the COVID-19 PCR test were included in the patient population group of the study. The control group consisted of 286 healthy children who applied to the general pediatric clinic for control evaluation between the same dates, without any diagnosis/signs of infection and negative COVID-19 PCR test. The participants in both groups were matched as much as possible in terms of age and gender; otherwords, the age and gender distribution of the participants in both groups was similar (Table 1).

Table 1. Patient and control groups' socio-demographic variables

Socio-demographic characteristics		**Patient**		**Control**		**P value**
		n	**%**	**n**	**%**	
Sex	Girl	141	47.6	137	47.9	0.95
	Boy	155	52.4	149	52.1	
	Total	**296**	**100.0**	**286**	**100.0**	
Age	0	26	8.8	20	7.0	0.82
	1	9	3.1	9	3.1	
	2	14	4.7	15	5.2	
	3	16	5.4	14	4.9	
	4	11	3.7	10	3.5	
	5	11	3.7	11	3.8	
	6	10	3.4	14	4.9	
	7	12	4.1	11	3.8	
	8	18	6.1	18	6.3	
	9	9	3.1	8	2.8	
	10	24	8.1	21	7.3	
	11	12	4.1	12	4.2	
	12	15	5.1	15	5.2	
	13	17	5.8	17	5.9	
	14	17	5.8	17	5.9	
	15	18	6.1	18	6.3	
	16	25	8.5	25	8.7	
	17	31	10.5	31	10.8	
	Total	**295**	**100.0**	**286**	**100.0**	

Sampling

Inclusion Criteria: The patients, who admitted to the hospital due to clinical symptoms similar to COVID-19, were younger than 18 years of age and had confirmed COVID-19 infection with RT-PCR, were included in the patient group.

Exclusion Criteria: The persons were excluded from the study if they had negative PCR test or had the Multisystem Inflammatory Syndrome in Childhood (MISC), chronic lung disease, diabetes mellitus, congenital heart disease, malignancy, immunodeficiency or recent traumatic history.

RT-PCR Test and Analyses: The nasopharyngeal swab samples were collected from the individuals with suspected COVID-19 infection. The samples were analyzed on the Real-time PCR device after nucleic acids were isolated, thus the samples which were positive for targeted DNA fragments were accepted as positive. Before of the treatments, the blood samples were taken from each participant. Complete blood counts were examined with an automatic blood counter (Abbott Celldyn-3500, IL, USA). Also, for some biochemical parameters, such as AST, ALT, LDH, and CRP, 2 cc venous blood samples were taken from each patient and the levels of the biochemical parameters were measured using a spectrophotometric chemical analyzer (Architect-C16000, Abbott Diagnostics, Abbott Park, IL, USA). There was not any sources of funding for analyzes in this research.

Ethics Declarations: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The scientific research permit from the Ministry of Health and the ethics committee approval from the Ethics Committee of Harran University were taken (Date: August 31, 2020, /No.: HRU/20.15.27).

Statistical Analysis: The data were analyzed using SPSS.v25. The normality of the variables was evaluated using Kruskal-Wallis and Shapiro-Wilk tests, histogram, scatter plot, and Skewness-Kurtosis values. In comparisons between the patient and control groups, the Independent t-test and the Mann-Whitney U test were used. Pearson and Fisher Chi-Square tests were used to compare the categorical data. ROC curve was used and the model was made with logistic regression modelling. P<0.05 was accepted significant.

RESULTS

There is no significant difference between control and patient groups in terms of gender and age (p>0.05) (Table 1). There is a significant difference between the patient and control groups for the WBC (p<0.001), neutrophil (p<0.001), platelet count (p<0.001), MPV (p=0.009), LDH (p=0.003), lymphocyte count (p<0.001), CRP (p<0.001), and AST (p=0.002) values (Table 2).

Table 2. Patient and control groups' some laboratory values

Variables*	Group	n	Mean†	SD†	SE†	T test† df†	T test† t†	p value
Hemoglobin	**Patient**	296	12.7341	1.36901	0.07957	579	0.898	0.369
	Control	285	12.5921	2.33505	0.13832	455.101	0.890	0.374
WBC*	**Patient**	296	6.4219	2.48329	0.14434	580	-5.746	**<0.001**
	Control	286	7.5905	2.42068	0.14314	579.954	-5.749	**<0.001**
PMNL*	**Patient**	296	2.7815	1.56230	0.09081	580	-6.361	**<0.001**
	Control	286	3.6084	1.57314	0.09302	579.010	-6.360	**<0.001**
Thrombocytes	**Patient**	296	277.1115	79.02935	4.59349	579	-5.230	**<0.001**
	Control	285	318.9344	111.55767	6.60811	510.108	-5.197	**<0.001**
MPV*	**Patient**	273	10.0886	1.00373	0.06075	549	2.636	**0.01**
	Control	278	9.7850	1.62248	0.09731	463.316	2.647	**0.01**
LDH*	**Patient**	212	276.6651	83.01034	5.70117	251	2.958	**0.003**
	Control	41	235.0488	79.44179	12.4067	58.185	3.048	**0.003**

Variables	Group	n	MR‡	SoR‡	U‡	Z‡	p value
Lymphocyte	**Patient**	295	261.30	77084.00	33424.000	-4.269	**<0.001**
	Control	285	320.72	91406.00			
CRP*	**Patient**	290	253.69	73569.00	15606.000	5.949	**<0.001**
	Control	162	177.83	28809.00			
AST*	**Patient**	293	238.53	69888.00	18598.000	3.153	**0.002**
	Control	155	197.99	30688.00			

* WBC: White Blood Cell; PMNL: Polymorphonuclear leukocytes; MPV: Mean Platelet Volume; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein; AST: Aspartate Aminotransferase; †SD: Std. deviation; SE: Std. error; df: Degree of freedom; t: Independent Sample T – Test
‡ MR: Mean rank; SoR: Sum of ranks; U:Mann Whitney U Test; Z:Z score

In ROC curve analysis, it is showed that LDH (p<0.001) and CRP (p<0.001) values are higher in the patient group while MPV (p=0.03), platelet (p=0.04), and neutrophil (p<0.001) are lower in the patient group. The values that have highest area under the curve are respectively CRP (0.741) and LDH (0.704) (Table 3). The ROC curves of the variables can be seen in Figure.

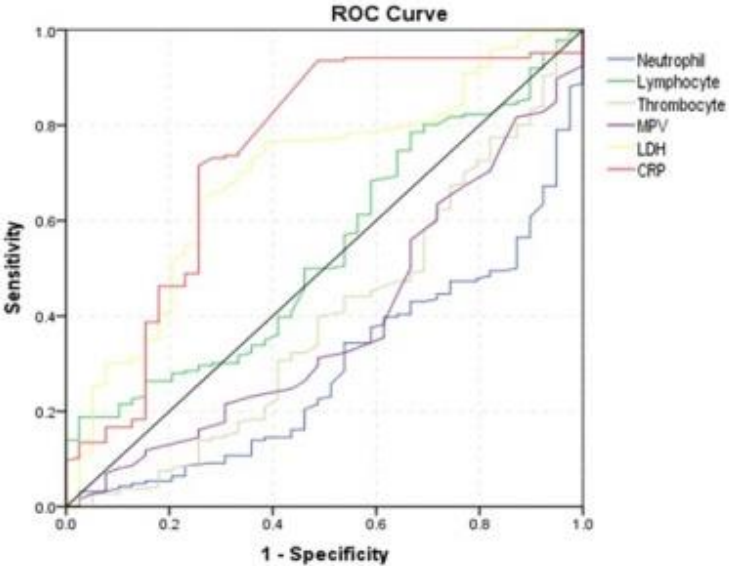

Figure 1. ROC curve for some laboratory parameters

Table 3. ROC curve of some laboratory values of patient and control groups

Variable	Diagnostic scan		ROC curve			p value
	Cut off	**Sensitivity**	**Specificity**	**Area**	**95% confidence interval**	
Neutrophil	**2.94**	0.39	0.39	0.291	0.208-0.374	**<0.001**
Lymphocyte	**2.17**	0.51	0.51	0.544	0.449-0.639	0.443
Thrombocyte	**285500**	0.44	0.46	0.393	0.291-0.496	**0.037**
MPV	**10.05**	0.37	0.39	0.390	0.293-0.487	**0.026**
LDH	**239.5**	0.69	0.69	0.704	0.614-0.793	**<0.001**
CRP	**0.74**	0.74	0.74	0.741	0.644-0.838	**<0.001**

First logistic regression models has be analyzed by including hemoglobin, PMNL, lymphocyte count, and platelet count. At second model, the MPV has be added to the model. In the third model, the regression analysis has included hemoglobin, PMNL, lymphocyte count, and platelet count, LDH and CRP. This last model is the most revealing of the models made (Table 4).

Table 4. Logistic regression models

Variables	B†	SE †	Wald	df†	p value	Exp(B)	95% CI† Lower	95% CI† Upper
Model 1								
Hemoglobin	0.035	0.046	0.565	1	0.45	0.966	0.882	1.058
Neutrophil	-0.307	0.062	24.811	1	**<0.001**	1.360	1.205	1.535
Lymphocyte	0.003	0.057	0.003	1	0.96	0.997	0.891	1.115
Thrombocyte	-0.004	0.001	11.759	1	**0.001**	1.004	1.002	1.006
Constant	1.627	0.695	5.475	1	0.02	0.197		
Model 2								
Hemoglobin	0.019	0.048	0.153	1	0.70	0.981	0.893	1.079
Neutrophil	-0.290	0.063	21.056	1	**<0.001**	1.337	1.181	1.514
Lymphocyte	0.005	0.059	0.006	1	0.94	0.995	0.886	1.118
Thrombocyte	-0.004	0.001	10.359	1	**0.001**	1.004	1.001	1.006
MPV	0.109	0.071	2.367	1	0.12	0.897	0.780	1.030
Constant	0.647	1.062	0.371	1	0.54	0.524		
Model 3								
Hemoglobin	0.141	0.124	1.292	1	0.26	0.869	0.681	1.107
Neutrophil	-0.351	0.123	8.106	1	**0.004**	1.420	1.115	1.807
Lymphocyte	0.429	0.207	4.295	1	**0.04**	0.651	0.434	0.977
Thrombocyte	-0.005	0.003	4.174	1	**0.04**	1.005	1.000	1.010
CRP	0.555	0.223	6.175	1	**0.01**	0.574	0.371	0.889
LDH	0.006	0.003	3.904	1	**0.048**	0.994	0.989	1.000
Constant	-0.675	1.938	0.122	1	0.72	1.965		

* MPV: Mean Platelet Volume; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein
†B: beta; SE: Std. Error; df: Degree of freedom; Cl: Confidence interval

DISCUSSION

COVID-19 disease progresses with mild symptoms or asymptomatic in children (3, 4). Due to the high risk of transmission of the virus, it is important to diagnose the disease early and rapidly. Some blood parameters, which are fast and cheaply obtainable, could be useful in the diagnosis of COVID-19. In this study, the role of widely accessible, fast and cheap blood parameters, such as WBC, PMNL, platelet and lymphocyte counts, MPV, ALT, AST, CRP and LDH, have be evaluated in the absence of PCR in the diagnosis of COVID-19 patients.

The literature show that COVID-19 patients have different laboratory results (10-16). Shen et al. (10) have found that their leukocyte count was normal or low while their lymphocyte count was low. Chen et al. (11) also have found that lymphocyte count was significantly low in the patients with COVID-19; moreover, they found that the WBC, PMNL and platelet count were low, but it was not statistically significant. Liu et al. (12) have showed a significant decrease in lymphocyte count in adult patients with Covid-19; it is inversely proportional to the viral load in the respiratory tract and the severity of the disease. In our study, while it is not detected a significant difference in hemoglobin value between patient and control groups, WBC, neutrophil, thrombocyte, lymphocyte values are in patients less than controls. These findings suggest that although COVID-19 infection is a viral infection, it can cause different outcomes in blood parameters compared to many infections.

A similar situation exists for biochemical parameters, also. In our study, it is seen MPV, LDH, CRP, and AST values are in patients higher than the control group, significant. However, Xia et al. (13) have reported ALT value increased in 25% of the patients and CRP value increased in 45% of the cases. Zhang et al. (14) have determined while the CRP value of 59% of the cases and LDH of 82% of the cases had an increase, there is no significant difference in ALT. Cai et al. (15) have stated CRP of 30% of the cases, ALT of 10% of them, AST of 20% of them, LDH value of 30% of them are increasing. Wang et al. (16) have determined while CRP increased in 9.7% of the cases, it decreased by 3.2% of them. They have reported ALT increased in 22% of the patients and AST increased in 22% of the cases. So, it should be kept in mind that different results may be seen in different patient groups before making a quick and erroneous decision while evaluating the disease.

In this study, While ROC Curve analysis of lymphocyte count did not give significant results, the area under the curve of the MPV was below 0.40, and it was found that CRP (0.74) and LDH (0.70) have highest area under the curve (Table 3; Figure). While Gumus et al. (17) stated that there was a difference in the MPV and lymphocyte count values between the patient and control groups, Seyit et al. (18) showed that the sensitivity of LDH and CRP was 60% and 66%, respectively, and similar to the results of our study, they found that there was no difference between the patient and control groups in the MPV. Due to the different results in the literature, regression modeling was performed to include more than one parameter in this study (Table 4). The model to which LDH and CRP parameters were added was found to be more explanatory compared to the model with basic CBC parameters. In the literature, it is underlined, LDH levels in COVID-19 patients are seen high and these results are associated severe disease, infection-related lung damage, and hospitalization as it plays a role in the energy mechanism in all cells is an important enzyme (19-21). Especially, owing to tissue damage in lung diseases, such as pulmonary fibrosis, LDH levels increase, and these results are accepted that support to viral infection (21). In a study, in which mortality modelling of COVID-19 infection is made, increase of LDH level is evaluated that associates with COVID-19 mortality (22). So, serum LDH may be a biomarker to detect patients have high risk.

Some results are also reported for CRP; it is emphasized that high CRP level may be important in grading the severity of the disease (18). Particularly, in the literature, it is mentioned CRP correlates lung damage and pneumonia in the early stage of the disease (23) and it is higher with mild versus severe disease (24). While a meta-analysis's results, it is seen that levels of white blood cell count elevated in this patients, another meta-analysis's results showed that while lymphocytes were decreased, inflammation markers were increased in COVID-19 infection (23, 24). On account of, in light of all these data, it is considered that in the absence of PCR, the evaluation of some laboratory parameters, such as neutrophil, lymphocyte and thrombocyte, primarily CRP and LDH, may be quite useful in the diagnosis of COVID-19 and early isolation, and early initiation of treatment.

This study has some limitations, also. Although it is tried to match the patient and control groups as much as possible, as in all case-control studies, it has not be possible to match them completely. On the other hand, it is seen that the evaluation of the laboratory findings, as well as the clinical picture, increases the chance of diagnosis.

CONCLUSION

Consequently, the diagnosis of the disease in the absence of PCR, and treatment and isolation of COVID-19 patients are very important for the protection of both the individual and the public health. This study and other similar studies can provide valuable information that can contribute to diagnosis and intervention in some countries, which cannot perform the PCR or pediatric patients before receiving RT-PCR test results of patients with suspected COVID-19.

REFERENCES

1. Jiatong S, Wenjun L. Epidemiological characteristics and prevention and control measures of Corona Virus Disease 2019 in children. J Trop Med. 2020;20(2):153-6.
2. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. Jama. 2020;323(13):1313-4.
3. Kemelbekov K, Ospanova E, Baimakhanova B, Zharylkap Z, Klara Z, Zhuldyz Y, et al. Epidemiological characteristics of new coronavirus diseases: Features of risk factors and clinical features of the child population. Electron J Gen Med. 2020;17:252.
4. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: An observational cohort study. Lancet Infect Dis. 2020;20:689-96.
5. Gumus H, Ozcan Y, Kazanasmaz H, Demir A, Guzelcicek A. Clinical Characteristics of COVID-19 Infection in the Pediatric Age Group. Electron J Gen Med. 24;18(5):308.
6. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2011;140(6):883–99.
7. An I, Ucmak D. Evaluation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, mean platelet volume, and C-reactive protein in patients with psoriasis vulgaris. Dicle Med J. 2018;3:327–34.
8. An I, Ucmak D, Ozturk M. Evaluation of neutrophil-to-lymphocyte ratio, platelet to lymphocyte ratio and mean platelet volume in patients with lichen planus. Ann Med Res. 2019;26:161–4.
9. An I, Ucmak D, Ozturk M, Aksoy M, Yildiz I, Ucan E. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume and C-reactive protein values in psoriatic arthritis patients. Ann Med Res. 2019;26:894–8.
10. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel Coronavirus infection in children: Experts' consensus statement. World J Pediatr. 2020;16:223-31.
11. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel Coronavirus. World J Pediatr. 2020;16:240-6.
12. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364-74.
13. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 20202;55(5):1169-74.
14. Zhang C, Gu J, Chen Q, Deng N, Li J, Huang L, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. PLOS Med. 2020;17(6):e1003130.
15. Cai J, Xu J, Lin D, Xu L, Qu Z, Zhang Y, et al. A case series of children with 2019 novel coronavirus infection: Clinical and epidemiological features. Clin Infect Dis. 2020;71(6):1547-51.
16. Wang D, Ju XL, Xie F, Lu Y, Li FY, Huang HH, et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. Chinese J Pediatr. 2020;58(4):269-74.
17. Gumus H, Demir A, Yukkaldiran A. Is mean platelet volume a predictive marker for the diagnosis of COVID-19 in children?. Int J Clin Pract. 2020;00:e13892.
18. Seyit M, Avci E, Nar R, Senol H, Yilmaz A, Ozen M, et al. Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID-19. Am J Emerg Med. 2021;40:110-4.
19. Kurt Yüksel M, editor. COVID-19 sürecinde biyobelirteç olarak laktat dehidrogenaz: COVID19 Sürecinde Biyobelirteçlerin Klinik Pratikte Kullanımı. Ankara: Türkiye Klinikleri; 2021.
20. Memikoglu O, Genc V, editors. COVID-19: Tanı ve İzlemde Laboratuvar Testleri. Ankara: Ankara Üniversitesi Basımevi; 2020.
21. Kishaba T, Tamaki H, Shimaoka Y, Fukuyama H, Yamashiro S. Staging of acute exacerbation in patients with idiopathic pulmonary fibrosis. Lung. 2014;192:141-9.
22. Yan L, Zhang H, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell. 2020;2:283-8.
23. Ghayda RA, Lee J, Lee JY, Kim DK, Lee KH, Hong SH, et al. Correlations of Clinical and Laboratory Characteristics of COVID-19: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2020;17(14):5026.
24. Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, et al. Association of elevated inflammatory markers and severe COVID-19: A meta-analysis. Medicine. 2020;99(47):e23315.