Medical Science

25(118), December, 2021

Laboratory Markers in Egyptian Children with covid-19

Hanan Hanna[1]✉, **Hossam Hosny**[2]

To Cite:
Hanna H, Hosny H. Laboratory Markers in Egyptian Children with covid-19. Medical Science, 2021, 25(118), 3497-3504

Author Affiliation:
[1]Department of Basic Science, Faculty of Physical Therapy, Delta University for Science and Technology, Gamasa City, Egypt
[2]Consultant of Pediatric and New Born, Ministry of Health, Alexandria City, Egypt.

✉**Corresponding author**
Department of Basic Science, Faculty of Physical Therapy, Delta University for Science and Technology,
Gamasa City, Egypt
Email: hananagm@hotmail.com

Peer-Review History
Received: 16 November 2021
Reviewed & Revised: 19/November/2021 to 17/December/2021
Accepted: 19 December 2021
Published: December 2021

Peer-review Method
External peer-review was done through double-blind method.

ABSTRACT

Background: As Coronavirus disease 2019 (COVID-19) is a global pandemic infectious disease, medical staff all over the world are still struggling with the management of the disease. Biochemical and hematological changes can be considered as prognostic markers. *Methods:* A total of 65 Egyptian children positive covid-19 were enrolled, between 5-12 years. *Results:* White blood cell count was significantly low (mean= 4968±742.6, p≤0.001). Lymphocytopenia was significantly low (mean= 1529.9 ± 493.9, p≤0.001). N/L showed statistically significantly high (mean= 2.45± 0.72, p≤0.001), platelets showed statistically significantly low (mean= 196.7± 82.58, p≤0.001) both correlated to severity. Plat/Lymph showed a statistically significant difference between groups. CRP increased than normal (mean=12.14 ± 3.3, p≤0.001), and was negatively correlated with Lymphocyte %. D-dimer slightly increased than normal and showed statistical difference between groups. *Conclusion:* This study declares that pediatric COVID-19 showed various prognostics as CRP, thrombocytopenia, lymphopenia, neutrophil-to lymphocyte ratio, platelet-to lymphocyte ratio. As they are easily accessible, the majority of labs not expensive and showed a very good correlation with prognosis.

Keywords: Pediatric Covid positive; abnormal chemical test; hematological markers

1. INTRODUCTION

The COVID-19 pandemic is a global pandemic infectious disease causing mainly severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The Medical staff all over the world is still struggling with the manifestation, complication, and treatment, which become a real challenge. Initially, it starts as a mild respiratory illness, in some cases, interstitial pneumonia may progress into acute respiratory distress syndrome, even multiple organ failure (MOF) may occur in 10–15% of adults (World Health Organization (WHO), 2020). Likely, the progress of the disease in children is generally mild and has better progress compared to that in adults, which needs more explanation and more research. Although there were reporting few cases of severe or critical illness and even deaths have been documented in China and other countries (Ding et al., 2020). It is expected to continue to increase with the increase of

cases transmission and overall current disease prevalence (Henry et al., 2020). Most of the clinicians admitted that the recovery takes 7 to 14 days after the onset of the disease or even a few days. A single case was dead in China among 549 cases, in the age bracket of 10-19 years (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020), where 5.7%–20% of children were hospitalized in USA, while 0.58%–2.0% required pediatric intensive care admission (Centers for Disease Control and Prevention (CDC), 2020). The occurrence of severe disease and admission in ICU has been extremely rare among children (Ludvigsson, 2020).

COVID-19 initially has been divided into four types: mild, moderate, severe, and critical cases (National Health Commission of People's Republic of China, 2020). According to their manifestation and hospital admission days (mean duration of hospitalization 14 days). However, there was growing evidence that many pediatric patients with COVID-19 are asymptomatic or have very mild symptoms, having the ability to transmit the virus to others in the same way as symptomatic. Difficulties in screening for asymptomatic infections are a real challenge to protocols concerning controlling and prevention of this epidemic (Gao et al., 2021). The main mode of transmission of COVID-19 is through droplet and contact transmission and high-concentration aerosols. Transmission of droplets occurs when nearby people ingest or inhale infected droplets (Qiu et al., 2020). It has been proven that asymptomatic infections have the same infectivity as symptomatic infections (Chen et al., 2020). Uptill now Children and adolescents make up a small percent of COVID-19 cases.

As recorded by National statistics from countries in Asia, Europe, and North America showed that pediatric cases account only for 2.1–7.8% of confirmed COVID-19 cases (European Centre for Disease Prevention and Control (ECDC), 2021). A study from China reported that children younger than 10 years represent only 1% of COVID-19 cases, and the admitted children accounted for roughly 5% of total patients with COVID-19 (Kelvin and Halperin, 2020). It has been suggested that the lowered susceptibility in children is likely due to small number of angiotensin-converting enzyme 2 (ACE2) receptors in children, meaning that the virus has fewer receptors to bind to respiratory tract (Carsetti et al., 2020).

Children under the age of 20 have a level of susceptibility half that of adults, based on fitting a population-level model to data on clinically-reported cases (Davies et al., 2020). It is very important to recognize that children can carry the heaviest burden of viral respiratory diseases, but not necessarily affect them. Consequently, Covid-19 related infections vary widely in severity among children (Yılmaz et al., 2020).

2. METHODS

A total of 65 Egyptian children positive covid-19 were enrolled during July 2020 to December 2020; confirmed by clinical symptoms and PCR positive in a walk-in pediatric clinic, they were not admitted to the hospital. The age varies from 4 years to 12 years (mean 8.03 ± 2.18). This study was classified into two groups. Group I(Gp1), included 32 Mild symptoms covid-19 positive of comparable age, sex and socioeconomic status with the other group, group II(Gp II) included 34 positive moderate symptoms Covid -19 positive cases. Patients suffering from chronic diseases as inflammatory, endocrine, cardiovascular, hepatic, renal, or unusual dietary habits were excluded from the study.

Study design

All patients were subjected to the following: full history taking, full clinical examination, and investigations LDH, ALT, Iron IL 6, and Procalcotinin; using fully automated chemistry analyzer Cobas-C & Cobas. Biochemical and hematological tests have been done to correlate with diagnosis, prognosis and clinical symptoms associated of the disease.

The NLR is calculated as the absolute neutrophil count divided by the absolute lymphocyte count, while the PLR is calculated by platelet count divided by absolute lymphocyte count (Chan and Rout, 2020). PCR was done at Alexandria University Hospitals Clinical Pathology Lab. CRP was done using fully automated Nephelometric quantitative technique which is more specific than Latex, Ferritin was done using Immuilte 2000/Xpi. D-dimer was done using ELISA test. Complete blood cell count (hemoglobin) was analyzed using an automated blood cell counter (XE 2100). Chest radiograph (X-ray) and Computed Tomography (RCT) of the chest have been routinely used as imaging techniques in COVID-19 patients.

Sample number

Assuming that CI (confidence interval) = 95%, α error =5% ,cross-section study based on the previous situation in literature, was 8% among children (5-15yrs),so in Alexandria, the estimated sample size to achieve 95% confidence and avoid α error, was calculated (Calculator.net., 2021).

Symptoms

Children with CoV-19 positive are characterized by a broad spectrum of clinical manifestations that differ and can be categorized as follows:

Mild cases (group I) Mild clinical symptoms, such as fever, fatigue, cough, anorexia, malaise, muscle pain, sore throat, running nose, light headache. As far as no abnormal chest x-ray were found.

Moderate (group II): Clinical features (as before) in addition to lung affection evident by chest imaging showing mild pneumonia manifestation.

Close contact with a confirmed case in most cases, symptoms were mainly attributable to an upper respiratory tract infection or to mild pneumonia which was treated at home.

Statistical analysis of the data

IBM SPSS version 20.0 was used in analysis data using (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov was used to verify the normality of distribution of variables; Comparisons between groups for categorical variables were assessed using the Chi-square test (Fisher). Student t-test was used to compare two groups for normally distributed quantitative variables Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. The significance of the results was judged at the 5% level.

3. RESULTS

Sixty-six patients were included in our study (table 1, aging ranging from five to twelve years, they were divided into 2 groups according to their symptoms. All of them were treated at home. Thirty-five patients (53%) were male, and Thirty-one (47%) were female, had no previous disease. Covid-19 infection was confirmed with Viral RNA was detected by PCR. As for ALT, CRP, ESR, HBG, WBC, lymphocyte, and platelet counts; results showed a significantly statistically positive higher difference between Groups ($p \leq 0.001$).

As for IL6, Procalcitonin, Ferritin, Iron, Neutrophils did not show any significant difference. D dimer was normal in mild cases and slightly elevated in moderate cases. As for Routine laboratory blood tests alterations are infrequent and less specific in the diagnosis of CoviD-19, as shown in several published studies.

Table 1 Comparison between mild and moderate according to different parameters

	Total (n = 66)	Mild (n = 34)	Moderate (n = 32)	p
Sex				
Male	35 (53%)	15 (44.1%)	20 (62.5%)	0.135
Female	31 (47%)	19 (55.9%)	12 (37.5%)	
Age (years)				
Mean ± SD.	8.03 ± 2.18	7.91 ± 2.33	8.16 ± 2.05	0.653
Weight (kg)				
Mean ± SD.	22.92 ± 5.70	23.15 ± 5.97	22.69 ± 5.47	0.746
LDH (U/l)				
<140	11 (16.7%)	9 (26.5%)	2 (6.3%)	0.028*
140 – 280	55 (83.3%)	25 (73.5%)	30 (93.8%)	
Mean ± SD.	171.17 ± 25.82	164.53 ± 26.39	178.22 ± 23.59	0.030*
ALT (U/L)				
<34M OR <22F	34 (51.5%)	34 (100%)	0 (0%)	<0.001*
>34M OR >22F	32 (48.5%)	0 (0%)	32 (100%)	
Mean ± SD.	28.52 ± 11.17	19.06 ± 4.42	38.56 ± 6.21	<0.001*
CRP (mg/l)				
<3	0 (0%)	0 (0%)	0 (0%)	–
>3	66 (100%)	34 (100%)	32 (100%)	
Mean ± SD.	12.14 ± 3.3	9.53 ± 1.81	14.91 ± 1.99	<0.001*
IL6 (pg/ml)				

<5	66 (100%)	34 (100%)	32 (100%)	–
>5	0 (0%)	0 (0%)	0 (0%)	
Mean ± SD.	2.82 ± 0.66	2.69 ± 0.58	2.96 ± 0.71	0.098
Procalcitoninpct-Q	0 (0%)	0 (0%)	0 (0%)	–
D-Dimer (ng/ml)				
<250	31 (47%)	31 (91.2%)	0 (0%)	<0.001*
>250	35 (53%)	3 (8.8%)	32 (100%)	
Mean ± SD.	266.53 ± 92.68	185.15 ± 34.94	353 ± 41.59	<0.001*
ESR				
<22M OR <29F	6 (9.1%)	6 (17.6%)	0 (0%)	FEp=
>22M OR >29F	60 (90.9%)	28 (82.4%)	32 (100%)	0.025*
Mean ± SD.	52.58 ± 21.50	35.03 ± 12.74	71.22 ± 10	<0.001*

SD: Standard deviation t: Student t-test

χ^2: Chi square test FE: Fisher Exact

p: p value for comparing between the mild and moderate

*: Statistically significant at $p \leq 0.05$

Data presented in the table 2 showed; the white blood cell count was reduced than normal and was significantly different between groups (mean= 4968±742.6, p≤0.001). Lymphocytopenia; cell reduced than normal and was significantly different between groups (mean=1529.9 ± 493.9, p≤0.001). N/L (figure 1) showed a statistically significant difference between groups table 3 (mean= 2.45± 0.72, p≤0.001) showing higher level in group two. Also, platelets showed significant differences between groups (mean= 196.7± 82.58, p≤0.001) which was decreased more in group two. Plat/Lymph (figure 2) showed statistically significant difference between groups (mean=110.5 ± 36.22, p≤0.001) showing high ratio in group two. CRP increased than normal and was significantly statically different between groups (mean=12.14 ± 3.3, p≤0.001), and was negatively correlated with Lymphocyte % (table 3). D-dimer slightly increased than normal and was significantly statically different between groups (mean= 266.53 ± 92.68, p≤0.001), and was negatively correlated with Lymphocyte % (table 3).

Table 2 Comparison between mild and moderate according to different parameters

	Total (n = 66)	Mild (n = 34)	Moderate (n = 32)	p
Ferritin				
Mean ± SD.	204.6 ± 102.83	183 ± 94.85	227.5 ± 107.4	0.075
Iron (µg/ml)				
0.33 – 1.93	66 (100%)	34 (100%)	32 (100%)	–
>1.93	0 (0%)	0 (0%)	0 (0%)	
Mean ± SD.	1.08 ± 0.25	1.05 ± 0.23	1.12 ± 0.27	0.313
HBG (g/dl)				
<11.5	27 (40.9%)	3 (8.8%)	24 (75%)	<0.001*
11.5 – 13.5	39 (59.1%)	31(91.2%)	8 (25%)	
Mean ± SD.	11.73 ± 0.92	12.39 ± 0.73	11.04 ± 0.48	<0.001*
WBC				
Mean ± SD.	4968.4 ± 742.6	5273.2 ± 651.2	4644.5 ± 703.3	<0.001*
Neutrophilis %				
Mean ± SD.	3438.5 ± 486.17	3359.4 ± 383.18	3522.5 ± 570.21	0.181
Platelets				
Mean ± SD.	196.7 ± 82.58	272.5 ± 34.61	116.3 ± 7.21	<0.001*
Lymphocyte				
Mean ± SD.	1529.9 ± 493.9	1913.9 ± 382.9	1122 ± 148.1	<0.001*
Lymphocyte %				
Mean ± SD.	30.38 ± 6.67	36.09 ± 4.08	24.31 ± 1.33	<0.001*
N/L				

Mean ± SD.	2.45 ± 0.72	1.8 ± 0.3	3.13 ± 0.24	<0.001*
Plat/lymp				
Mean ± SD.	110.5 ± 36.22	132.9 ± 30.32	86.59 ± 25.1	<0.001*

SD: Standard deviation t: Student t-test U: Mann Whitney test

χ^2: Chi square test

p: p value for comparing between mild and moderate

*: Statistically significant at p ≤ 0.05

Table 3 Correlation between Lymphocyte % with CRP and D Dimer

	Lymphocyte %					
	Total (n = 66)		Mild (n = 34)		Moderate (n = 32)	
	r	p	r	p	r	p
CRP (mg/l)	-0.721	<0.001*	0.047	0.793	0.024	0.898
D-Dimer (ng/ml)	-0.827	<0.001*	-0.175	0.323	0.110	0.548

r: Pearson coefficient

*: Statistically significant at p ≤ 0.05

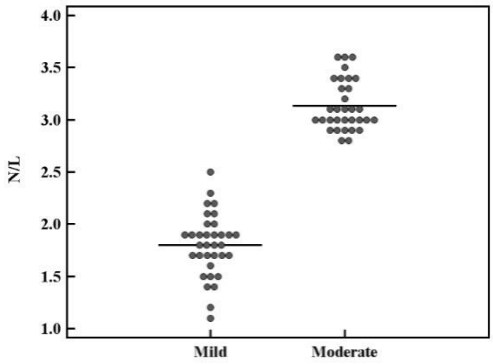

Figure 1 Comparison between mild and moderate groups according to N/L

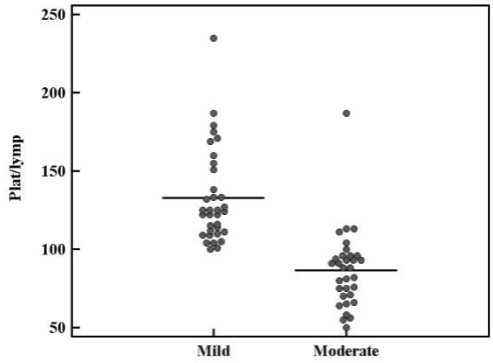

Figure 2 Comparison between mild and moderate groups according to Plat/Lymp

4. DISCUSSION

In terms of laboratory abnormalities, Covid -19 showed a variety of abnormal chemical, and hematological values which was unique than other viruses; lymphopenia, thrombocytopenia and elevated CRP were present in the majority of patients included in

our study, making a possible correlation with diseases severity and level of abnormal labs findings. 1070 specimens were collected from 205 patients from China, most of the bronchoalveolar samples showed positive result, followed by sputum specimen, nasal swabs, pharyngeal swabs, feces, blood, where blood was the least one to show positive results. However, none of the urine samples tested was positive (Wang et al., 2020). This indicates different samples which can be used; in our study pharyngeal swab was used, as it was more accessible in a pediatric walk-in clinic.

According to Wei et al., (2020) higher circulating levels of LDH, D-dimer, C-reactive protein, and IL-6 are also correlated with severe, disease emphasizing that the rapid decline in T lymphocytes and significant increases in the levels of inflammatory factors can be clinical warnings of severe infection. Which relate with our results in terms of CRP, D- Dimer shows a significant difference between groups. However, LDH and IL-6 did not show increased level properly because our patients were not sever cases or hospitalized cases. Similar results were found with other researchers in the pediatric patient.

Tang et al., (2020) reported that a positive Correlations of abnormal coagulation factors and fatal prognosis. As significant high levels of D-dimers, fibrin degradation products, prothrombin, and partial thromboplastin times compared to the survivor one. However, Bhattacharjee and Banerjee (2020) concluded in a systemic review done on 45 cases that thrombocytopenia is associated with moderate to severe Covid-19, however, bleeding symptoms are not associated with most of the cases. According to Henry (2020) lymphopenia is clearly associated with disease severity; especially non–survivor patients have had significantly lymphopenia than survivors stating that following lymphocytes may be an important factor for recovery, which completely agrees with our results.

Neutrophil/lymph ratio (NLR) could be a valuable biomarker to recognize severe COVID-19 patients; this was clear in our study as there was a difference between groups; however, it remains unclear to what extent the significance of NLR would predict the occurrence of severing progress. Similarly in a systemic review done by Yasuhara et al., (2020) studying different laboratory abnormality in children thrombocytopenia, lymphopenia and leucopenia was observed. Zhang et al., (2020a) Stated lymphopenia was seen in 75.4% of patients. They also found a positive correlation between eosinophil and lymphocyte numbers on the first day after hospital admission. Cai et al., (2021) emphasized the decreased lymphocyte, thrombocyte, and eosinophils in a cohort study done on 12,862 COVID-19 cases from 21 hospitals. They emphasize the validation of a clinical indicator from a relatively simple blood test, namely neutrophil-to-lymphocyte ratio (NLR)>6.11 which are effective to assess treatment, however, if NLR ≤6.11 was not associated with reduced mortality rate. This gives the NLR a value in predicting all-cause mortality. Also, this was evident in our study showing the positive correlation between NRL and the severity of cases and indirectly reflecting a patient's inflammatory state.

Huang et al., (2021) Summarized that the incidence of leukocytosis, lymphopenia, and elevated CRP, PCT, AST, and LDH levels, was increased among patients with severe COVID-19 when compared with patients with moderately severe disease, which is very important in monitoring the patients. Sproston and Ashworth (2018) Reported that evidence suggests that CRP is not only an inflammatory marker of inflammation or infection, but it also induce IL-6 and TNF-α, as there are correlated together especially in moderate and sever cases of infection. That is why CRP should be considered as potential marker for monitoring of cases. Hematological changes are a common finding among patients with Covid-19, remarkably comprising thrombocytopenia and lymphopenia (Liu et al., 2020). The exact mechanism of hematopoiesis induced by this coronavirus is not yet well understood, but scientific evidence proved by several systemic reviews the trueness of this association (Mehrpouri, 2021). As for platelet, it decreases gradually mostly due to platelets expressing ACE2 and TMPRSS2 which Covid-19 could directly activate platelets via the interaction of Spike protein and platelet, causing lowering level (Zhang et al., 2020b).

5. CONCLUSION

This study declares that most children with COVID-19 had a good prognosis, especially mild cases to moderate. Up till now the role of children in the transmission of infection is less prominent than that of adults although they can transmit without being symptomatic. Various prognostic marker has been used in this pandemic; using CRP, thrombocytopenia, lymphopenia, neutrophil-to- lymphocyte ratio, platelet-to lymphocyte ratio. As NLR was the most promising predictive factor for critical illness incidence of COVID-19 pneumonia, which is not highlighted in the routine test; it is time to emphasize the use of this simple mathematic ratio as well as using plat/Lymph ratio as both can be associated to assess prognosis.

Acknowledgments

We thank all patients who participated and contributed samples to the study

Authors' contributions

All the authors contributed evenly with regards to data collecting, analysis and drafting.

Informed consent

All patients signed an informed consent form.

Ethics Committee

The study protocol was approved by the Ethics Committee of the Medical Research Institute, Alexandria University. (Approval number: 0105231).

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there are no conflicts of interest.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Bhattacharjee S, Banerjee M. Immune Thrombocytopenia Secondary to COVID-19: a Systematic Review. SN Compr Clin Med 2020:1-11.
2. Cai J, Li H, Zhang C, Chen Z, Liu H, Lei F, Qin JJ, Liu YM, Zhou F, Song X, Zhou J, Zhao YC, Wu B, He M, Yang H, Zhu L, Zhang P, Ji YX, Zhao GN, Lu Z, Liu L, Mao W, Liao X, Lu H, Wang D, Xia X, Huang X, Wei X, Xia J, Zhang BH, Yuan Y, She ZG, Xu Q, Ma X, Wang Y, Yang J, Zhang X, Zhang XJ, Li H. The Neutrophil-to-Lymphocyte Ratio Determines Clinical Efficacy of Corticosteroid Therapy in Patients with COVID-19. Cell Metab 2021; 33(2):258-69.
3. Calculator.net. Sample Size Calculator. 2021. Available from: https://www.calculator.net/sample-size-calculator.html. [Accessed in: Oct, 2021].
4. Carsetti R, Quintarelli C, Quinti I, Piano Mortari E, Zumla A, Ippolito G, Locatelli F. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? Lancet Child Adolesc Health 2020; 4(6):414-6.
5. Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(14):422-6.
6. Chan AS, Rout A. Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19. J Clin Med Res 2020; 12(7):448-53.
7. Chen Y, Wang AH, Yi B, Ding KQ, Wang HB, Wang JM, Shi HB, Wang SJ, Xu GZ. Epidemiological characteristics of infection in COVID-19 close contacts in Ningbo city. Zhonghua Liu Xing Bing Xue Za Zhi 2020; 41(5):667-71.
8. Davies NG, Klepac P, Liu Y, Prem K, Jit M. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020; 26(8):1205-11.
9. Ding Y, Yan H, Guo W. Clinical Characteristics of Children with COVID-19: A Meta-Analysis. Front Pediatr 2020; 8:431.
10. European Centre for Disease Prevention and Control (ECDC). COVID-19 situation dasshoard. 2021. Available from: https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html#global-overview-tab. [Accessed in: Oct, 2021].
11. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, Singh AR, Li S, Tarquinio KM, Jaggi P, Oster ME, Zackai SP, Gillen J, Ratner AJ, Walsh RF, Fitzgerald JC. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020; 383(4):334-46.
12. Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, Ma K. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect 2021; 54(1):12-6.
13. Henry BM, Benoit SW, de Oliveira MHS, Hsieh WC, Benoit J, Ballout RA, Plebani M, Lippi G. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. Clin Biochem 2020; 81:1-8.
14. Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. Lancet Respir Med 2020; 8(4):e24.
15. Huang Y, Zhang Y, Ma L. Meta-analysis of laboratory results in patients with severe coronavirus disease 2019. Exp Ther Med 2021; 21(5):449.

16. Kelvin AA, Halperin S. COVID-19 in children: the link in the transmission chain. Lancet Infect Dis 2020; 20(6):633-4.
17. Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. Ann Hematol 2020; 99(7):1421-8.
18. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020; 109(6):1088-95.
19. Ma A, Cheng J, Yang J, Dong M, Liao X, Kang Y. Neutrophil-to-lymphocyte ratio as a predictive biomarker for moderate-severe ARDS in severe COVID-19 patients. Crit Care 2020; 24(1):288.
20. Manti S, Licari A, Montagna L, Votto M, Leonardi S, Brambilla I, Castagnoli R, Foiadelli T, Marseglia GL, Cardinale F, Caffarelli C, Tosca MA, Cravidi C, Duse M, Chiappini E. SARS-CoV-2 infection in pediatric population. Acta Biomed 2020; 91(11-s):e2020003.
21. Mehrpouri M. Hematological Abnormalities in Patients With COVID-19: An Emerging Approach to Differentiate Between Severe COVID-19; Compared With Non-Severe Forms of the Disease. Acta Med Iran 2021; 59(3):126-32.
22. Naja M, Wedderburn L, Ciurtin C. COVID-19 infection in children and adolescents. Br J Hosp Med (Lond) 2020; 81(8):1-10.
23. National Health Commission of People's Republic of China. Diagnosis and treatment plan of Corona Virus Disease 2019 (tentative sixth edition). Glob Health J 2020; 4(1):1-5.
24. 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(6):689-96.
25. Sproston NR, Ashworth JJ. Role of C - reactive protein at Sites of Inflammation and Infection. Front Immunol 2018; 9:754.
26. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18(4):844-7.
27. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. Turk J Med Sci 2020; 50(Si-1):592-603.
28. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) - China, 2020. China CDC Wkly 2020; 2(8):113-22.
29. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. Jama 2020; 323(18):1843-4.
30. Wei YY, Wang RR, Zhang DW, Tu YH, Chen CS, Ji S, Li CX, Li XY, Zhou MX, Cao WS, Han MF, Fei GH. Risk factors for severe COVID-19: Evidence from 167 hospitalized patients in Anhui, China. J Infect 2020; 81(1):e89-e92.
31. World Health Organization (WHO). WHO-China Joint Mission, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Geneva: WHO; 2020.
32. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. Pediatr Pulmonol 2020; 55(10):2565-75.a
33. Yılmaz K, Gozupirinççioğlu A, Aktar F, Akın A, Karabel M, Yolbas I, Uzel VH, Şen V. Evaluation of the novel coronavirus disease in Turkish children: Preliminary outcomes. Pediatr Pulmonol 2020; 55(12):3587-94.
34. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020a; 75(7):1730-41.
35. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, Liu M, Zhao X, Xie Y, Yang Y, Zhang S, Fan Z, Dong J, Yuan Z, Ding Z, Zhang Y, Hu L. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol 2020b; 13(1):120.