Evaluation of Endothelial Dysfunction in COVID-19 With Flow-Mediated Dilatation

Asli Kurtar Mansiroglu,[1] *Hande Seymen,*[1] *Isa Sincer,*[1] *Yilmaz Gunes*[1]
Abant Izzet Baysal University Hospital, Departamento de Cardiologia,[1] *Bolu – Turkey*

Abstract

Background: **Inflammation is known to play a crucial role in many diseases, including COVID-19.**

Objective: **Using flow-mediated dilatation (FMD), we aimed to assess the effects of inflammation on endothelial function in COVID-19 patients.**

Methods: **This study was conducted with a total of 161 subjects, of whom 80 were diagnosed with COVID-19 within the last six months (comprising 48 women and 32 men with a mean age of 32.10 ± 5.87 years) and 81 were healthy controls (comprising 45 women and 36 men with a mean age of 30.51 ± 7.33 years). We analyzed the findings of transthoracic echocardiography and FMD in all subjects. All results were considered statistically significant at the level of $p < 0.05$.**

Results: **The echocardiography and FMD of the COVID-19 group were performed 35 days (range: 25-178) after diagnosis. There was no statistically significant difference in echocardiographic parameters. Differently, FMD (%) was significantly higher in the control group (9.52 ± 5.98 vs. 12.01 ± 6.18, p=0.01). In multivariate analysis with the forward stepwise model, FMD was significantly different in the control group compared to the COVID-19 group (1.086 (1.026 - 1.149), p=0.04). A Spearman's correlation test indicated that FMD (r=0.27, p=0.006) had a weak positive correlation with the presence of COVID-19.**

Conclusion: **Our findings point to COVID-19-induced endothelial dysfunction, as assessed by FMD, in the early recovery phase.**

Keywords: **COVID-19/complications; Endothelial, Cells/infection; Endothelium Vascular/injuries; Diagnostic Imaging/methods; Echocardiography/methods; Ultrasonography/methods; Flow Dilatation; Myalgia; Olfaction Disorders; Taste Disorders.**

Introduction

A new type of coronavirus disease emerged in December 2019 and was named COVID-19 by the WHO. It primarily infects the respiratory tract and has spread rapidly around the world.[1]

As RNA viruses that can rapidly mutate and recombine, coronaviruses are known to primarily infect the respiratory tract or intestinal tract in humans and animals.[2] Coronaviruses enter the host cell by binding to the zinc peptidase angiotensin-converting enzyme 2, a surface molecule found in the endothelial cells of arteries and vessels, the respiratory tract epithelium, the arterial smooth muscle, the small intestinal epithelium, and immune cells.[3-5]

Endothelial activation and dysfunction develop as a result of endothelial cells being infected with COVID-19.[6] They lead to increased levels of pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-1, and interleukin-6), chemokines (monocyte chemoattractant protein-1), von Willebrand factor (vWF) antigen, vWF activity, anti-hemophilic factor (AHF), and acute-phase reactants (IL-6, C-reactive protein, and D-dimer).[6]

Although COVID-19 primarily affects the upper and lower respiratory tracts, the vascular endothelium is another known target. Endothelial dysfunction may be caused directly by the activity of the virus or by the resulting systemic inflammatory response. Flow-mediated dilatation (FMD), which is a non-invasive ultrasonographic method, has been widely used to evaluate endothelial dysfunction due to its simplicity and cost-efficiency.[7] Several studies have addressed the effect of FMD on various inflammatory diseases such as rheumatoid arthritis, peripheral vascular disease, coronary artery disease, diabetes mellitus, and hypertension. To date, as far as we know, there are only a few reports on FMD being used to evaluate COVID-19.[8,9]

In this study, we used FMD to investigate the potential abnormal effects of COVID-19 on the vascular function of patients recovered from a COVID-19 infection.

Mailing Address: Asli Kurtar Mansiroglu •
Abant Izzet Baysal University Hospital, Department of Cardiology –14280, Bolu, Turkey
E-mail: dr.asli.kurtar@gmail.com
Manuscript received June 28, 2021, revised manuscript Novermber 04, 2021, accepted December 08, 2021

DOI: https://doi.org/10.36660/abc.20210561

Methods

This single-centered study was carried out at Abant Izzet Baysal University Training and Research Hospital between October 2020 and February 2021. The study included 80 subjects diagnosed with COVID-19 within the last six months who did not require hospitalization and 81 healthy control subjects, with an age distribution of > 18 and < 45 years. All the COVID-19 patients were cured and free from symptoms at the time of study entry.

The exclusion criteria were as follows: age > 45 years, any presence of coronary artery disease, left ventricle systolic dysfunction (EF < 50%), moderate to severe valvular disease, congenital heart disease, atrioventricular conduction abnormality, moderate to severe kidney or liver disease, thyroid disease, electrolytic imbalance, systemic inflammatory disease, or poor acoustic echocardiography window. The study protocol was approved by the Local Ethics Committee and a written informed consent form was signed by each subject before participation.

Based on the COVID-19 Diagnosis and Treatment Plan by the National Health Commission (7th edition), COVID-19 cases were classified into four clinical types: mild (characterized by mild clinical symptoms without pneumonia on radiological imaging), common (characterized by fever, involvement of the respiratory tract, and other symptoms with pneumonia on radiological imaging), severe (characterized by respiratory distress, respiratory rate of ≥ 30 times/min, oxygen saturation ≤ 93% at rest, PaO2/FiO2 ≤ 300 mmHg), and critical (characterized by respiratory failure requiring mechanical ventilation, shock, and failure of another organ requiring monitoring and treatment at an intensive care unit).[10]

Lung involvement was classified using the "total severity score" (TSS) based on an assessment of chest computed tomography (CT) imaging. For this purpose, the percentages of involvement calculated for each of the five lobes were converted into one of the following score categories: none (0%) (Score 0), minimal (1-25%) (Score 1), mild (26-50%) (Score 2), moderate (51-75%) (Score 3), and severe (76-100%) (Score 4). Finally, the sum of all the scores yielded a TSS value ranging from 0 to 20.[11]

Laboratory parameters were obtained from hospital medical records at COVID-19 infection diagnosis. Laboratory data from the control group were obtained at study entry.

Patients and control subjects were evaluated with echocardiography and brachial Doppler ultrasonography for FMD measurement at study entry.

Echocardiographic evaluation

We used a Vivid S6 4-Mhz transducer (GE Vingmed, N-3191 Horten-Norway) to perform the required echocardiographic procedures.

All echocardiographic images were obtained using continuous ECG monitoring by a single-blind cardiologist with the subjects in the left lateral position. We considered the mean of three consecutive cardiac cycles and measured left ventricular end-diastolic and end-systolic diameters, left ventricular posterior wall thickness, left ventricular septum thickness, and left atrium diameters. A biplane modfied simpson's method was applied for measuring left ventricular ejection fraction. We performed two-dimensional and pulsed Doppler measurements based on the American Society of Echocardiography criteria[12].

Ultrasonographic evaluation

The parameters were measured in a quiet, dark, and air-conditioned room (i.e. room temperature of 22 - 25°C) after a rest period of at least 15 minutes. In addition, subjects were asked to fast and to avoid exercising, smoking, and consuming alcohol or caffeine for at least 8 hours before FMD measurements. We used a 7.5 MHz linear array transducer (GE Healthcare, M4S-RS, Tokyo, Hino-Shi, Japan) to measure the brachial artery diameter at the antecubital fossa. The skin was marked with a pencil, and thus all measurements were performed on the same line. We started with the basal diameter and flow rate of the brachial artery and then increased the pressure up to 50 mmHg above systolic blood pressure, and waited for 5 minutes at this level, so the arm remained ischemic. Then cuff pressure was lowered, and the diameter and flow rate of the brachial artery were measured again at 1 minute after pressure decrease.

FMD was calculated using the following equation:

FMD=100 x (maximum diameter at the 1st minute-baseline diameter)/baseline diameter.[13]

Statistical analysis

All statistical analyses were performed using SPSS 18.0 Statistical Package Software for Windows (SPSS Inc., Chicago, IL, USA). Normality data of the variables were evaluated with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were described using the mean and standard deviation; continuous variables without normal distribution were described using the median and interquartile range. The data are shown as numbers or percentages for qualitative variables. To analyze differences between independent groups, we used the Student's t-test (two-tailed) for normally distributed quantitative variables, the Mann-Whitney's U-test for variables without normal distribution, and the Chi-square test for qualitative variables. Spearman's correlation analyses were conducted to evaluate correlations between COVID-19 and lymphocyte level, neutrophil/lymphocyte ratio, glucose and creatinine levels, and FMD. For variables found to be significant in the univariate regression analysis, we employed multivariate logistic regression with the forward stepwise model to establish the independent prognostic factors of COVID-19. Spearman's correlation test was also performed between FMD and time elapsed from diagnosis. All results were considered statistically significant at the level of $p < 0.05$.

Results

Baseline clinical characteristics were similar between both groups. Among laboratory parameters, glucose,

creatinine, and neutrophil/lymphocyte ratio were significantly higher; lymphocyte counts were significantly lower in the COVID-19 group compared to the control group (Table 1).

Myalgia (65 %) and loss of smell and/or taste (61 %) were the most common symptoms in COVID-19 patients, whereas sweating was (8 %) the least common one (Table 2). None of the COVID-19 patients had a serious infection that required hospitalization. In our study, the patients belonged either to the mild type or the common type, according to the clinical classification, with TSS scores ranging from 0 to 5.

Echocardiography and FMD of the COVID-19 group were performed 35 days (25-178; IIQ: 38.5) after diagnosis. Echocardiographic measurements were similar between the two groups, whereas compared to the control group FMD (%), it was significantly lower in the COVID-19 patients (9.52 ± 5.98 vs. 12.01 ± 6.18, p=0.010) (Table 3). Spearman's correlation test showed that there was no statistically significant relation between FMD and the time elapsed after COVID-19 diagnosis (r=0.064; p=0.527).

Significantly different parameters in the univariate regression analysis (glucose, creatinine, lymphocyte, neutrophil/lymphocyte ratio, and FMD) were included in the multivariable regression analysis and only the FMD value was significantly different in the control group compared to the COVID-19 group (1.086 (1.026 – 1.149), p=0.04) (Table 4).

Spearman's correlation test showed that FMD (r=0.27, p=0.006) had a weak positive correlation with the presence of COVID-19.

Table 1 – Demographic and laboratory variables of the study population

Variables		COVID-19 (n= 80)	Control Group (n=81)	p
Demographics				
Age (years)		32.10±5.87	30.51±7.33	0.407
Male/Female (n(%))		32/48 (40/60%)	36/45 (44/56%)	0.313
SBP (mmHg) (IIQ)		105 (14)	110 (22)	0.307
DBP (mmHg) (IIQ)		70 (15)	70 (20)	0.343
Height (cm)		169.36±8.72	169.36±9.30	0.997
Weight (kg)		73.81±13.73	71.30±16.09	0.289
BMI (kg/m^2)		25.63±3.74	25.00±4.13	0.198
Hypertension n (%)	No	78 (97.5%)	79 (97.5%)	1.000
	Yes	2 (2.5%)	2 (2.5%)	
Diabetes mellitus n (%)	No	78 (97.5%)	81 (100.0%)	0.245
	Yes	2 (2.5%)	0 (0.0%)	
Hyperlipidemia n (%)	No	79 (98.8%)	80 (98.8%)	1.000
	Yes	1 (1.3%)	1 (1.2%)	
Family History of CAD n (%)	No	54 (67.5%)	59 (72.8%)	0.459
	Yes	26 (32.5%)	22 (27.2%)	
Smoking n (%)	No	61 (76.3%)	58 (48.7%)	0.502
	Yes	19 (23.8%)	23 (28.4%)	
Laboratory parameters				
Fasting Plasma Glucose (mg/dL) (IIQ)		93.50 (16.75)	91 (14)	0.038
Creatinine (mg/dL) (IIQ)		0.78 (0.19)	0.74 (0.11)	0.042
Hemoglobin (g/dL) (IIQ)		14.20 (2.05)	14.40 (1.95)	0.875
Hematocrit (%) (IIQ)		42.30 (5.51)	42.90 (5.40)	0.851
Platelet counts (K/uL) (IIQ)		250 (90.25)	263 (76.50)	0.659
Lymphocyte counts (K/uL) (IIQ)		1.83 (1.14)	2.24 (0.89)	0.017
Neutrophil counts (K/uL) (IIQ)		4.15 (2.12)	3.82 (1.73)	0.291
Neutrophil/ lymphocyte ratio (IIQ)		2.05 (1.63)	1.30 (1.06)	0.044

IIQ: Interquartile Range; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index.

Table 2 – Symptoms experienced by the COVID-19 patients

Symptoms	Number	%
Myalgia	52/80	65
Loss of smell and/or taste	49/80	61
Weakness	33/80	41
Headache	32/80	40
Cough	28/80	35
Fever	25/80	31
Dyspnea	19/80	24
Sore throat	15/80	19
Nausea	15/80	19
Diarrhea	13/80	16
Sweating	7/80	8

Discussion

The purpose of this study was to assess the vascular repercussions of COVID-19 using impaired FMD as a surrogate marker of endothelial dysfunction. Our study demonstrated that the FMD value was lower in COVID-19 patients compared to the control group. These results point to vascular involvement by COVID-19, as assessed by FMD, even in mildly affected patients. Within the limits of our knowledge, this is the first study to show vascular endothelial dysfunction defined by impaired FMD among young patients recovering from a mild COVID-19 infection.

We found a significant reduction in FMD even in such mildly affected patients early after recovery. This raises the question of whether the disease may have long-term abnormal effects on vascular function. Similarly to our findings, Ergul et al.[8] included 63 COVID-19 patients two months after recovery and found COVID-19 infection and increased body mass index as independent predictors of endothelial dysfunction evaluated by FMD.[8]

Likewise, Riou et al.[9] found a significant decrease in FMD among 16 mild-to-moderate COVID-19 patients, whereas FMD tended to be lower among 9 severe-to-critical COVID-19 patients three months after disease onset.[9] Contrary to these reports, we studied mildly affected non-hospitalized COVID-19 patients 35 days (25-178) after disease onset.

Endothelial dysfunction, associated with oxidative stress, is known to be the earliest factor for many diseases.[14] Although inflammation is part of the body's normal repair response to healing and is essential in protecting our body from infections and dangerous environmental substances, it would be overly optimistic to say that it is completely beneficial. When it gets out of control, it can become detrimental and destructive to the body.[15] Likewise, it is known that systemically out-of-control inflammation is associated with adverse COVID-19 outcomes.[16]

In a study where FMD was used to predict future cardiovascular events in patients who had undergone coronary bypass surgery, the lowest event rate was determined in patients with normal FMD (>8%), while a moderate event rate and the highest event rate were

Table 3 – Echocardiographic measurements of the study population

Variables	COVID-19 (n= 80)	Control Group (n= 81)	p
Left atrium diameter (cm)	3.03±0.5	2.92±0.32	0.332
LVDD (cm)	4.48±0.45	4.45±0.42	0.281
LVSD (cm)	2.80±0.30	2.81±0.29	0.711
PW (cm)	0.96±0.14	0.96±0.13	0.550
IVS (cm)	0.92±0.16	0.90±0.14	0.742
EF (%)	67.27±5.02	65.90±4.64	0.151
Transmitral E wave (cm/s) (IIQ)	96.9 (23.3)	94.7 (22.5)	0.409
Transmitral A wave (cm/s) (IIQ)	68.0 (16.1)	69.0 (15.3)	0.533
Mitral DT (ms) (IIQ)	198 (45)	188 (57)	0.531
Lateral E' (cm/s) (IIQ)	12.2 (3)	12.5 (3.5)	0.414
Lateral A' (cm/s) (IIQ)	9.35 (2.5)	9.0 (3)	0.515
Lateral S' (cm/s) (IIQ)	9.5 (2)	10.0 (2.1)	0.066
TAPSE (cm) (IIQ)	2.19 (0.44)	2.16 (0.40)	0.537
sPAB (mmHg)	23.79±5.13	25.14±5.63	0.268
FMD (%)	9.52±5.98	12.01±6.18	0.010

**LVDD: left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; PW: posterior wall; IVS: interventricular septum; EF: Ejection fraction; IIQ: Interquartile Range; DT: deceleration time; E': peak early diastolic myocardial tissue velocity; A': peak late diastolic myocardial tissue velocity; S: mitral annular systolic myocardial velocity; FMD: Flow-mediated dilatation; TAPSE: tricuspid annular plane systolic excursion; sPAB: systolic pulmonary artery pressure.*

Table 4 – Independent predictors of COVID-19 by multivariate logistic regression analysis

	OR (95%CI)	p
Glucose	0.981 (0.957–1.005)	0.116
Lymphocyte	1.022 (0.646–1.616)	0.926
Neutrophil/lymphocyte ratio	0.895 (0.744–1.077)	0.240
Creatinine	0.093 (0.005–1.595)	0.101
FMD	1.086 (1.026–1.149)	0.004

*FMD: flow-mediated dilatation; CI: Confidence interval; OR: Odds ratio.

found in patients with an FMD value of 4 to 8% and <4%, respectively.[17] In another study, patients with an FMD less than 6.2% had significantly lower ankle/brachial index compared to those with an FMD greater than 6.2%.[18] In addition, Maruhashi et al.[19] showed that FMD had an inverse correlation with the Framingham Risk Score, commonly used as a risk calculator and an index of cumulative cardiovascular risk for assessing the probability of a heart attack or death from heart disease within 10 years.[19]

Independent predictive factors of mortality from COVID-19 include advanced age, comorbidities such as diabetes mellitus (DM), cardiovascular disease or cancer, and chronic obstructive pulmonary disease at presentation.[20] However, neither infants nor children showed a significant increase in both morbidity and mortality during the COVID-19 pandemic.[21]

With increased age and age-related diseases, the chronic inflammatory state becomes dominant, and the anti-inflammatory response of the immune system becomes erratic and unable to suppress the inflammatory episode in a timely and effective manner.[22] In our study, we aimed to exclude the effects of such advanced age-related inflammation by including subjects under the age of 45 years.

Although still within the normal range, the COVID-19 patients had significantly slightly higher levels of blood glucose and creatinine than those of the control group. During the acute phase of infection, blood glucose levels may rise abnormally in patients under COVID-19 stress, even if they are not diagnosed with diabetes mellitus. Renal function has been also reported to be abnormally affected. High levels of blood glucose in COVID-19 patients can predict worse outcomes regardless of a DM history.[23] Kidney disease is associated with increased mortality from COVID-19.[24] It was found that 14.4% of 701 hospitalized patients with COVID-19 had increased serum creatinine levels, 13.1% had a decreased glomerular filtration rate, and approximately 5% had acute kidney injury.[24] Histopathological findings revealed acute tubular injuries, different impairments of the glomeruli, tubular necrosis, and glomerulosclerosis.[25] Our finding of slightly increased blood glucose and creatinine levels may be an incidental finding but also may suggest subclinical kidney injury and/or ongoing stress.

Lymphopenia has been used in the diagnosis of COVID-19 and has been associated with a poor prognosis.[26] The severity of COVID-19 was also correlated with the neutrophil/lymphocyte ratio and the lymphocyte/CRP ratio.[27] Accordingly, compared to the control group, lymphocyte counts were decreased and NLR was increased in our mild COVID-19 study subjects.

Limitations

The main limitations of this study lie in the fact that it is single-centered and that it was conducted on a relatively small number of patients. The results are limited to an early point in time during the disease process and cannot be extrapolated to reflect long-term findings. Another limitation is that laboratory parameters were not measured simultaneously with FMD measurement. Due to the exclusion criteria and age limit, the study population was strictly selected, and therefore the results can not represent all COVID-19 patients.

Conclusion

This study showed a decrease in FMD in young patients who were mildly affected by COVID-19 in the early recovery phase. Therefore, this parameter may be used as a marker for COVID-19-induced endothelial dysfunction. Undoubtedly, routine cardiovascular monitoring in patients with a history of COVID-19 may identify patients at risk of future cardiovascular events. To better understand the possible cardiovascular effects in these patients, larger-scale studies including long-term follow-up should be considered.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Mansiroglu AK, Seymen H, Sincer I, Gunes Y; Statistical analysis: Sincer I.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the bant Izzet Baysal University Hospital under the protocol number 2021/89. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-6. doi: 10.1007/s12098-020-03263-6
2. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660-94. doi: 10.1128/CMR.00023-07.
3. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016;3(1):237-61. doi: 10.1128/CMR.00023-07.
4. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112-6. doi: 10.1038/nature03712
5. Hamming I, Timens W, Bulthuis M, Lely A, Navis Gv, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7. doi: 10.1002/path.1570
6. Zhang J, Tecson KM, McCullough PA. Endothelial dysfunction contributes to COVID-19-associated vascular inflammation and coagulopathy. Rev Cardiovasc Med. 2020;21(3):315-9. doi: 10.31083/j.rcm.2020.03.126.
7. Agewall S. Is impaired flow-mediated dilatation of the brachial artery a cardiovascular risk factor? Curr Vasc Pharmacol. 2003;1:107-9. doi: 10.2174/1570161033476745.
8. Ergül E, Yılmaz AS, Öğütveren MM, Emlek N, Kostakoğlu U, Çetin M. COVID 19 disease independently predicted endothelial dysfunction measured by flow-mediated dilatation. Int J Cardiovasc Imaging. 2022;38(1):25-32. doi: 10.1007/s10554-021-02356-3.
9. Riou M, Oulehri W, Momas C, Rouyer O, Lebourg F, Meyer A, et al. Reduced Flow-Mediated Dilatation Is Not Related to COVID-19 Severity Three Months after Hospitalization for SARS-CoV-2 Infection. J Clin Med. 2021;10(6):1318. doi: 10.3390/jcm10061318
10. Pei-Fang Wei, editors. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl). 2020, 5;133(9):1087-95. doi: 10.1097/CM9.0000000000000819
11. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol. 2020;30(8):4407-16. doi: 10.1007/s00330-020-06817-6.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1007/s00330-020-06817-6.
13. Korkmaz H, Onalan O. Evaluation of endothelial dysfunction: flow-mediated dilation. Endothelium. 2008;15(4):157-63. doi: 10.1080/10623320802228872
14. Daiber A, Steven S, Weber A, Shuvaev VV, Muzykantov VR, Laher I, et al. Targeting vascular (endothelial) dysfunction. Br J Pharmacol. 2017;174(12)1591-619. doi: 10.1111/bph.13517.
15. Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci. 2017;11:316. doi: 10.3389/fnhum.2017.00316
16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. doi: 10.1016/S0140-6736(20)30628-0.
17. Gokce N, Keaney Jr JF, Hunter LM, Watkins MT, Menzoian JO, Vita JA. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. Circulation. 2002;105(13):1567-72. doi: 10.1161/01.cir.0000012543.55874.47.
18. Brevetti G, Silvestro A, Di Giacomo S, Bucur R, Di Donato A, Schiano V, et al. Endothelial dysfunction in peripheral arterial disease is related to increase in plasma markers of inflammation and severity of peripheral circulatory impairment but not to classic risk factors and atherosclerotic burden. J Vasc Surg. 2003;38(2):374-9. doi: 10.1016/s0741-5214(03)00124-1
19. Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, et al. Relationship between flow-mediated vasodilation and cardiovascular risk factors in a large community-based study. Heart.2013;99(24):1837-42. doi: 10.1136/heartjnl-2013-304739.
20. Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: A comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. PLoS One. 2020;15(12):e0243191. doi: 10.1371/journal.pone.0243191
21. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr. 2020;179(7):1029-46. doi: 10.1007/s00431-020-03684-7.
22. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. Front Immunol. 2018;9:586. doi: 10.3389/fimmu.2018.00586
23. Cai Y, Shi S, Yang F, Yi B, Chen X, Li J, et al. Fasting blood glucose level is a predictor of mortality in patients with COVID-19 independent of diabetes history. Diabetes Res Clin Pract. 2020;169:108437. doi: 10.1016/j.diabres.2020.108437
24. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829-38. doi: 10.1016/j.kint.2020.03.005.
25. Kissling S, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, et al. Collapsing glomerulopathy in a COVID-19 patient. Kidney Int. 2020;98(1):228-31. doi: 10.1016/j.kint.2020.04.006
26. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care. 2020;8:36. doi: 10.1186/s40560-020-00453-4.
27. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020;92(10):1733-4. doi: 10.1002/jmv.25819