Observational Study

Medicine

OPEN

Lower brachial artery flow-mediated dilation is associated with a worse prognosis and more lung parenchymal involvement in Covid-19

Prospective observational study

Göksel Güz, MD[a], Serdar Demirgan, MD, PhD candidate[b,c,*].

Abstract

Severe acute respiratory syndrome coronavirus-2 is a highly infectious pathogenic coronavirus, which has appeared toward the end of 2019. The virus seen all over the world caused a pandemic of an acute respiratory disease named coronavirus disease 2019 (Covid-19). It has been shown that the virus that uses angiotensin-converting enzyme 2 receptors is causing endothelial dysfunction resulting in vascular inflammation and coagulopathy. It is possible to assess endothelial dysfunction by the flow-mediated dilatation (FMD) technique. Our study aimed to demonstrate the effect of endothelial dysfunction assessed using the FMD on prognosis and mortality in the patients hospitalized with the diagnosis of Covid-19.

In this prospective observational study, endothelial functions of 94 patients hospitalized due to the Covid-19 in the ward or intensive care unit (ICU) were evaluated by FMD. The relationship among endothelial dysfunction and prognosis of disease, biochemical parameters, lung involvement, and mortality was investigated.

We found that the FMD% values of the Covid-19 ICU patients compared to those followed up in the ward (2.66 ± 0.62 vs. 5.23 ± 1.46/$P < .001$) and those who died due to Covid-19 compared to those who were discharged alive (2.57 ± 0.22 vs. 4.66 ± 1.7/$P < .001$) were significantly lower. There were moderate negative correlation between FMD% and peak values of D-dimer ($r = –0.52$, $P < .001$), troponin ($r = –0.45$, $P < .001$), ferritin ($r = –0.47$, $P < .001$), lactate dehydrogenase ($r = –0.49$, $P < .001$), and white blood cells count ($r = –0.23$, $P = .024$). Lower FMD% was associated with higher lung parenchymal involvement ($P < .001$). The optimum cutoff point of FMD in predicting mortality was found to be 3.135% (sensitivity: 1, selectivity: 0.70).

According to our results, lower FMD% was associated with higher lung parenchyma involvement, ICU admission, and mortality rate in Covid-19 patients. The best cutoff point for predicting mortality of FMD was 3.135%. Nevertheless, largescale, multicenter studies are needed to evaluate lower FMD values as a risk factor for mortality in Covid-19.

Abbreviations: ACE2 = angiotensin-converting enzyme, Covid-19 = coronavirus disease 2019, CRP = C-reactive protein, CT = computed tomography, FMD = flow-mediated dilatation, ICU = intensive care unit, LDH = lactate dehydrogenase, RT-PCR = reverse transcription-polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, sVCAM-1 = soluble, vascular cell adhesion molecule 1, WBC = white blood cell, wVF = von Willebrand factor.

Keywords: Covid-19, endothelial dysfunction, flow-mediated dilatation, morbidity, mortality.

1. Introduction

Coronavirus disease 2019 (Covid-19), which is a major public health threat all over the world, is defined as a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] The disease has a wide clinical spectrum, ranging from asymptomatic to severe respiratory failure with a mortal course. Mortalities and morbidities are mostly due to respiratory failure. Atherothrombotic complications can be seen during the disease such as arrhythmias, myocardial infarction, renal failure, and cerebrovascular diseases. Endothelial dysfunction is held thought to be responsible for these atherothrombotic complications.[2] Angiotensin-converting enzyme 2 expressed in vascular endothelium and the respiratory epithelium is thought to be the primary mechanism of SARS-CoV-2 entry and infection. SARS-CoV-2 induces vascular injury after penetrating vascular endothelial cells. Vascular endothelial damage induced coagulation system activation and increased inflammatory response

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

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How to cite this article: Güz G, Demirgan S. Lower brachial artery flow-mediated dilation is associated with a worse prognosis and more lung parenchymal involvement in COVID-19: Prospective observational study. Medicine 2022;101:33(e30001).

Received: 19 March 2022 / Received in final form: 30 May 2022 / Accepted: 23 June 2022

http://dx.doi.org/10.1097/MD.0000000000030001

lead to hypercoagulability. This is related to the atherothrombotic complications of Covid-19.[3,4]

The endothelium has a role in maintaining vascular homeostasis in the entire circulatory system. Norma-functioning vascular tonus is up to the balance of vasoconstrictor and vasodilator mediators that are released from the endothelium. The term endothelial dysfunction is mostly used to express the deterioration in endothelium-dependent vasodilation. In addition, the term endothelial dysfunction includes abnormalities in the relationships among leukocytes, platelets, regulatory substances, and endothelium, and conditions that lead to abnormal endothelial activation.[5] Endothelial dysfunction in Covid-19 can cause a pro-coagulatory state, which is a consequence of macro-and microvascular thrombotic events, and impair organ perfusions. Recently, pathology specimens from patients with severe Covid-19 have been shown to have viral inclusion structures in endothelial cells of the glomerular capillary rings and diffuse signs of endothelitis in the heart, lung, kidney, liver, and gastrointestinal tract.[6] As a result, the balance will shift in favor of vasoconstriction, inflammation, and thrombosis in a dysfunctional endothelium.[7] Endothelial function can be assessed by the flow-mediated dilatation (FMD) technique, which measures the dilation of brachial or coronary arteries in response to blood flow tension or external stimuli.[8,9]

In the current study, we aimed to investigate endothelial dysfunction evaluated by FMD in patients hospitalized in the ward or intensive care unit (ICU) due to Covid-19 and to investigate whether there is a relationship between FMD and prognosis of disease, biochemical parameters, lung involvement, and mortality.

2. Materials and Methods

A total of 107 patients with Covid-19 positivity detected by reverse transcription-polymerase chain reaction were recruited for this prospective observational study, and 94 patients were ultimately enrolled (Fig. 1). The inclusion criteria were as follows: age ≥18 years, a positive result on reverse transcription-polymerase chain reaction assay testing for SARS-CoV-2 on nasopharyngeal swab specimens at hospital admission, and informed written consent. Participants in a delirium state or with a recent history of endotracheal intubation were not included in the present study. Patients refusing to participate in the study, patients with a major cardiovascular disease, a solid tumor, renal failure patients on dialysis, active liver disease, and systolic blood pressure below 80 mm Hg were excluded from the study. Data were collected in the Medicana International Hospital between December 2020 and April 2021. Written informed consent was obtained from cooperative patients in ICU and ward, and was obtained from relatives of intubated and uncooperative patients. The study was approved by the ethics committee of Medicana International Hospital (021/03.11021).

2.1. Study protocol and procedures

Written informed consent was obtained from patients after being informed about FMD measurement. The FMD measurement was performed by placing a sphygmomanometer cuff on the 90° abducted right forearm of a supine positioned patient after resting for ≥10 minutes. The test was performed by an operator who was trained on FMD measurement and blinded to participants. Following the recommendations of the International Brachial Artery Reactivity Task Force, brachial artery diameter and blood flow velocity were monitored for 10 minutes with ultrasonography and a 10-MHz linear probe placed above the elbow bend. After 1 minute of baseline assessment, the cuff on the lower arm was inflated to 70 mm Hg above systolic blood pressure for 5 minutes. Brachial artery diameter and flow rate were monitored for 4 minutes after cuff deflating. By measuring

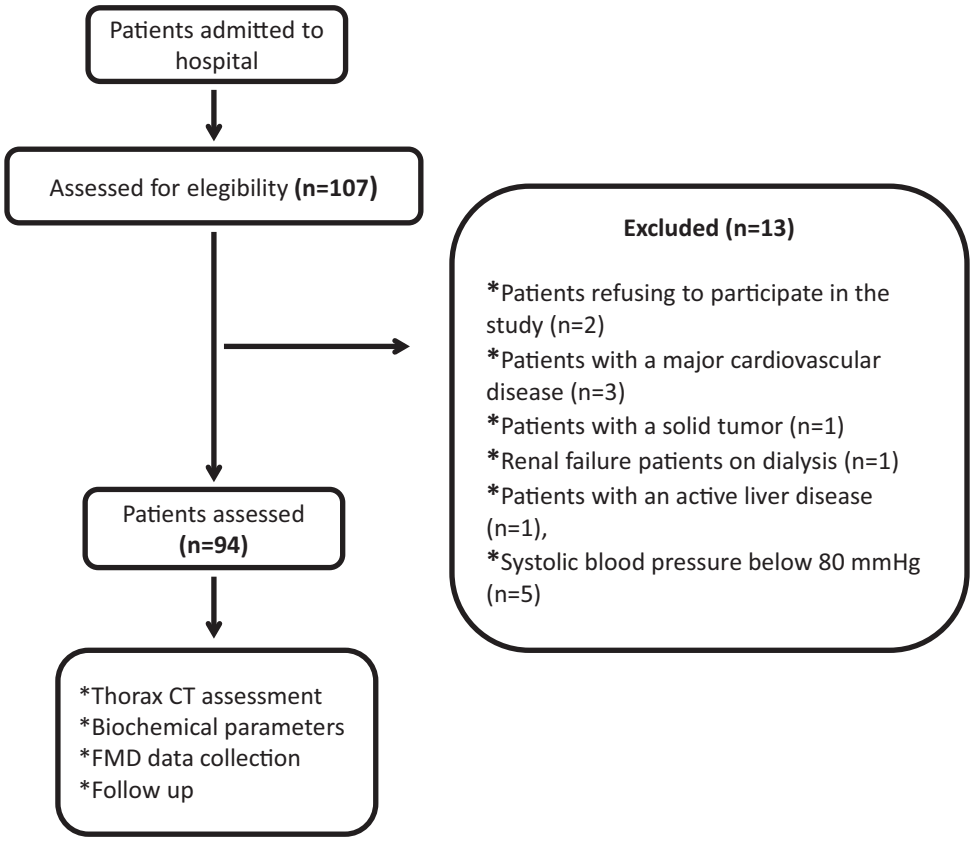

Figure 1. Study flow diagram. CT = computed tomography, FMD = flow-mediated dilatation.

the maximal diameter of the brachial artery recorded during reactive hyperemia induced by arm ischemia the FMD is calculated as a percentage.[10] All FMD measurements were performed within the first 24 hours of hospitalization. The average of 3 measurements of the basal and post-hyperemic diameters of the brachial artery was used for statistical analysis; FMD% was calculated as 100 × ([post-hyperemia diameter – basal diameter]/basal diameter).

Thorax computed tomography (CT) of the patients taken during hospitalization was evaluated by the same radiologist. Thorax CT with the highest lung parenchyma involvement was evaluated for all patients. Patients with >50% lung parenchyma involvement in thorax CT were considered as Thorax CT 3, while patients with less than 25% lung parenchyma were considered as Thorax CT 1. A total of 25% to 50% lung parenchyma involvement was accepted as Thorax CT 2.[11] The patients were grouped according to their gender, where the patients followed up (ward/ICU), the prognosis of the disease (discharged alive/non-survivors), involvement of the lung parenchyma (Thorax CT 1/Thorax CT 2/Thorax CT 3), and groups were compared in terms of FMD%. Peak values detected during hospitalization of the patients of ferritin, C-reactive protein (CRP), D-dimer, troponin, lactate dehydrogenase (LDH), and white blood cell count (WBC) were recorded. The effect of these values on mortality was evaluated. At the same time, the correlation of these biochemical parameters with FMD% was examined. The correlation between FMD% and mortality was also evaluated.

2.2. Primary and secondary outcomes

The primary outcome was to evaluate the relationship between FMD% and prognosis of the disease, involvement of the lung parenchyma, and mortality. In addition, the optimum cutoff point of FMD% for predicting mortality was calculated. The secondary outcome was a correlation between biochemical parameters and FMD%. The changes in FMD% according to gender and age were also evaluated.

2.3. Statistical analysis

Quantitative data were summarized as mean ± standard deviation and median (minimum-maximum), and categorical data were summarized as frequency and percentage, n (%). The conformity of the quantitative data to the normal distribution was examined using the Shapiro-Wilk test. The relation between FMD% values and quantitative data was examined with the Spearman correlation coefficient. Mann–Whitney *U* test or Kruskal-Wallis test was used for comparisons between groups in terms of quantitative data. After the Kruskal-Wallis test, Dunn post hoc test was used for pairwise comparison of the groups. The chi-square test or Fisher exact test was used for comparisons between groups in terms of categorical data. The performance of FMD% values in predicting exitus was examined with the receiver operating curve (ROC). The best cutoff point was determined as the value corresponding to the maximum Youden index (J = Sensitivity + Selectivity – 1). $P < .05$ value was accepted as statistically significant. R statistical programming language version 3.6.1, R Core Team (R Foundation for Statistical Computing, Austria) is used for analysis. The pROC library was used in the R program for ROC analysis.

3. Results

A total of 107 patients diagnosed with Covid-19 were recruited for this study, and 94 patients were ultimately enrolled (Fig. 1). Only 1 patient recruited for the study had a known previous chronic obstructive pulmonary disease before being diagnosed with Covid-19. The patient was not excluded from the study because there was no appearance compatible with Covid-19 in the previous thorax CT of this patient. Other patients had no history of lung disease. Of the patients included in the study, 4 had diabetes mellitus type 2, 36 had hypertension, 1 had coronary artery disease, 2 had chronic heart failure, and 2 had chronic kidney disease. Patients refusing to participate in the study (n = 2) and patients with a major cardiovascular disease (n = 3), a solid tumor (n = 1), renal failure patients on dialysis (n = 1), active liver disease (n = 1), and systolic blood pressure below 80 mm Hg (n = 5) at the time of measurement were excluded from the study. Of the 94 patients included in the study, 55 (58.5%) were male, and 39 (41.5%) were female. The mean age was 56.8 ± 13.9 (median: 56.5, min:22, max:92). Among patients hospitalized with Covid-19, ICU patients tended to be older than patients in the ward.[12,13] In addition, length of stay was lower in the patients followed up in the ICU (Table 1).

There was no statistically significant difference between genders in terms of mortality (8 [14.5%] vs 6 [15.4%]; $P = .910$). While all of the 62 patients hospitalized in the ward were discharged alive, 18 (56.3%) of the 32 patients hospitalized in the ICU were discharged alive ($P < .001$). In addition, none of the patients in the Thorax CT 1 group, 1 (3%) patient in the Thorax CT 2 group and 13 (40.6%) patients in the Thorax CT 3 group died ($P < .001$). The distribution of comorbidities by discharged alive and non-survivors was presented in Table 1, Supplemental Digital Content, http://links.lww.com/MD/H14.

In males, FMD% was lower than in females ($P = .023$). The FMD% of the patients in ICU was significantly lower than the patients in the ward (2.66 ± 0.62 vs 5.23 ± 1.46, respectively; $P < .001$). In addition, FMD% was significantly higher in patients discharged alive compared to patients who died (4.66 ± 1.7 vs. 2.57 ± 0.22, respectively; $P < .001$). The comparison of the groups in terms of FMD% was given in Table 2.

When lung involvement parenchyma groups were compared in terms of FMD%, it was observed that all 3 groups were statistically different from each other ($P < .001$). According to Dunn post hoc analysis, patients in the Thorax CT1 group have higher FMD% than patients in Thorax CT2 and Thorax CT3 groups ($P = .019$, $P < .001$, respectively). Moreover, patients in the Thorax CT2 group have higher FMD% than the patients in the Thorax CT3 group ($P = .001$) (Table 3).

Moderate negative correlations were found between FMD% and age ($r = –0.32$, $P = .002$), d-dimer ($r = –0.52$, $P < .001$), troponin ($r = –0.45$, $P < .001$), ferritin ($r = –0.47$, $P < .001$), LDH ($r = –0.49$, $P < .001$), and WBC ($r = –0.23$, $P = .024$). There was no statistically significant correlation between FMD% and CRP values ($r = –0.15$, $P = .138$).

In the patients died, age ($P = .014$), d-dimer ($P < .001$), troponin ($P < .001$), ferritin ($P = .002$), WBC ($P = .001$), and LDH ($P < .001$) were higher than patients discharged alive (Table 4). However, FMD% ($P < .001$) was lower in the patients who died due to the Covid-19. In terms of

Table 1

Demographics of patients followed up in the ward and ICU.

Patient's characteristics	Ward (n = 62)	ICU (n = 32)	*P*
Age	54.35 ± 14.07 54(22–82)	61.63 ± 12.55 60 (39–92)	**.016**
Male/female	34 (54.8)/28 (45.2)	21 (65.6)/11 (34.4)	*.315*
Length of stay (d)	7.7 ± 4 7(3–26)	4.86 ± 2.28 5 (2–9)	**.005**

The mean ± standard deviation along with median (minimum-maximum) for age and length of stay, n (%) for gender were given. *P* values were obtained by Student *t* test and chi-square test. $P < .05$ was accepted as statistically significant.

Patients who followed up in the ICU tended to be older than patients who followed up in the ward. In addition, the length of stay was lower in the patients followed up in the ICU.

ICU = intensive care unit.

Table 2

Comparison of the flow-mediated dilatation % values according to gender, where the patients followed up, and prognosis of disease.

Male (n = 55)	Female (n = 39)	*P*
4.08 ± 1.7 4.34 (2.17–8.1)	4.74 ± 1.75 5.12 (2.17–9.09)	**.023**
Ward (n = 62)	**ICU (n = 32)**	
5.23 ± 1.46 5.26 (2.17–9.09)	2.66 ± 0.62 2.5 (2.17–4.87)	**<.001**
Discharged alive (n = 80)	**Nonsurvivors (n = 14)**	
4.66 ± 1.7 5 (2.17–9.09)	2.57 ± 0.22 2.56 (2.22–2.94)	**<.001**

The mean ± standard deviation and median (minimum-maximum) values were given. P values were obtained by Mann-Whitney *U* test. $P < .05$ was accepted as statistically significant.
In males, FMD% was lower than in females. The FMD% of the patients in ICU was significantly lower than the patients in the ward. In addition, FMD% was higher in patients discharged alive compared to patients who died.
ICU = intensive care unit.

Table 3

Comparison of flow-mediated dilatation% values between lung parenchyma involvement groups.

Thorax CT 1	Thorax CT 2	Thorax CT 3	*P*
5.85 ± 1.54 5.4 (2.5–9.09)	4.33 ± 1.35 4.87 (2.22–6.06)	3.02 ± 1.05 2.56 (2.17–5.71)	**<.001**

The mean ± standard deviation and median (minimum–maximum) values were given. *P* values were obtained by Kruskal-Wallis test. According to Dunn post hoc test, $P = .019$ for comparison of Thorax CT 1 group with Thorax CT 2 group, $P < .001$ for comparison of Thorax CT 1 group with Thorax CT 3 group, and $P = .001$ for comparison of Thorax CT 2 group with Thorax CT 3 group. $P < .05$ was accepted as statistically significant.
Patients with >50% lung parenchyma involvement in thorax CT were considered as thorax CT 3, whereas patients with less than 25% lung parenchyma involvement were considered as thorax CT 1. 25–50% lung parenchyma involvement was accepted as thorax CT 3.
Patients in the thorax CT1 group have higher FMD% than patients in thorax CT2 and thorax CT3 groups. Moreover, patients in the Thorax CT2 group have higher FMD% than the patients in the Thorax CT3 group.
FMD = flow-mediated dilatation, Thorax CT = thorax computed tomography.

CRP values, there was no statistically significant difference between the 2 groups ($P = .675$) (Table 4).

According to ROC Curve analysis in predicting mortality of FMD, the best cutoff point of FMD value was 3.135% (Fig. 2). Sensitivity and selectivity values corresponding to ROC curve cutoff points were presented in Table 2, Supplemental Digital Content, http://links.lww.com/MD/H16. While the FMD of all patients (14/14) who died was below 3.135%, only 24 of the 80 discharged patients had an FMD value below 3.135% (Table 5).

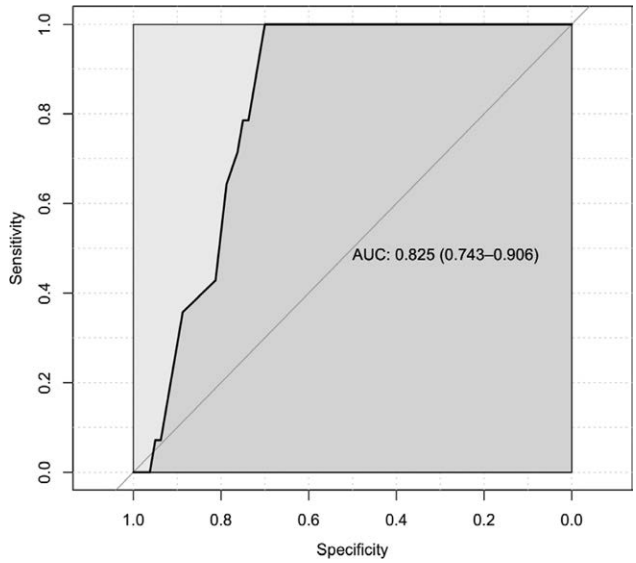

Figure 2. ROC curve in predicting mortality of FMD%. According to Youden index (Youden J = Sensitivity + Selectivity – 1). The best cutoff point of FMD value is 3.135% (Sensitivity = 1, Selectivity = 0.70). AUC = area under the curve, FMD = flow-mediated dilatation, ROC = receiver operating curve.

4. Discussion

To our knowledge, this is the first study demonstrating the best cutoff point of FMD% in predicting mortality in patients diagnosed with Covid-19. It is also the first study in which patients were objectively grouped according to lung parenchyma involvement and compared in terms of FMD%. Indeed, in some recent studies in which FMD was evaluated in patients with recent or ongoing Covid-19,[14,15] however, the correlation between FMD% and biochemical parameters of the patients such as d-dimer, troponin, ferritin, LDH, and WBC has not been directly evaluated.

Five main results of the current study deserve discussion: in the patients who died FMD% was lower than patients discharged alive, the FMD% of the patients in ICU was lower than

Table 4

Comparison of the age and peak values of the biochemical parameters between discharged alive and nonsurvivors.

Biochemical parameters and age of the patients	Discharged alive (n = 80)	Nonsurvivors (n = 14)	*P*
Age	55.19 ± 13.32 55.5 (22–82)	66.21 ± 14.18 65.5 (44–92)	**.014**
D-dimer (ng/mL)	594.34 ± 444.09 461 (112–3130)	2212.14 ± 1699.43 1320 (790–6890)	**<.001**
Troponin (ng/mL)	18.41 ± 20.8 12 (0–121)	194.79 ± 283.25 85.5 (13–1078)	**<.001**
Ferritin (ng/mL)	1323.6 ± 584.58 1309.5 (334–2000)	1838.93 ± 279.03 2000 (1228–2000)	**.002**
CRP (mg/dL)	9.13 ± 6.36 8 (0.1–31.01)	10.07 ± 6.88 8.2 (0.1–23)	0.675
WBC (/μL)	11954 ± 4533.58 12300 (1920–23900)	15735.71 ± 6009.05 14500 (2900–25500)	**.007**
LDH (UI/L)	664.39 ± 317.82 640.5 (145–1902)	1321.07 ± 612.16 1150 (573–2862)	**<.001**

The mean ± standard deviation and median (minimum-maximum) values were given. *P* values were obtained by Mann-Whitney *U* test. $P < .05$ was accepted as statistically significant.
In the patients died, age, d-dimer, troponin, ferritin, WBC, and LDH were higher than patients discharged alive.
CRP = C-reactive protein, LDH = lactate dehydrogenase, WBC = white blood cell count, UI = International Unit.

Table 5

Comparison of the number of discharged alive and nonsurvivors according to the flow-mediated dilatation% value grouped by cutoff point.

Cutoff point of FMD%	Discharged alive (n = 80)	Nonsurvivors (n = 14)	*P*	Relative risk (95% CI)
FMD%*				
>3.135	56 (70)	0 (0)	**<.001**	1.58 (1.24–2.02)
≤3.135	24 (30)	14 (100)		

*Grouped by cutoff point found using Youden index. Sensitivity 100% and selectivity 70%.

While the FMD of all patients (14/14) who died was below 3.135%, only 24 of the 80 discharged patients had an FMD value below 3.135%.

CI = confidence interval, FMD = flow-mediated dilatation.

the patients in the ward, the risk of the composite endpoint of death was significantly higher in patients with FMD <3.135% compared with those with FMD ≥3.135%, as the amount of lung parenchyma involvement increased (according to thorax CT classification), the FMD% decreased, and there was a negative correlation between FMD% and d-dimer, troponin, ferritin, LDH, and WBC values in the patients hospitalized with the diagnosis of Covid-19.

The vascular endothelium is a delicate single-cell layer that covers all blood vessels and plays an important structural and functional role in the development of cardiovascular and cerebrovascular diseases. A properly functioning endothelium is essential for healthy vascular function, while endothelial dysfunction is associated with various diseases.[16] Additionally, endothelial dysfunction has a great role in the development of thrombotic complications. A systematic review and meta-analysis of FMD evaluating endothelial functions both found that brachial FMD has significant predictive value for future cardiovascular events after adjusting for other risk factors.[13] It is known that endothelial functions are impaired in patients with Covid-19 and that impaired endothelial functions are responsible for increased thrombotic complications. It has been suggested that multiple parameters may have the potential prognostic capacity to differentiate adverse outcomes in general populations of hospitalized Covid-19 patients.[17,18] High troponin, d-dimer, and ferritin levels are the most significant laboratory parameters for poor prognosis.[19,20] Similarly, we found that higher troponin, d-dimer, ferritin, WBC, and LDH peak levels were associated with poor prognosis of hospitalized Covid-19 patients. As in our study, Lombardi et al[21] reported that the elevated troponin levels were a predictor of hospital mortality in a multicenter study including patients diagnosed with Covid-19. In addition, the current study demonstrated that there was a negative correlation between FMD% and d-dimer, troponin, ferritin, LDH, and WBC. This is consistent with the association between low FMD% and poor prognosis detected in the present study.

Our study reached some important similar results, with minor contrasts, with the study of Bianconi et al.[14] In these 2 studies, lower FMD values were associated with higher ICU admission and death. The finding of reduced FMD values in patients with more severe Covid-19 manifestations is consistent with the results of previous studies, which have demonstrated a significant and direct association between Covid-19 severity and different direct/indirect measures of endothelial function other than FMD.[22–26] All these findings may indicate that endothelial dysfunction can be both a cause and a consequence of severe Covid-19. In this line of evidence, noninvasive measurements of endothelial function may be an important tool to detect systemic endothelial dysfunction in the early stages of Covid-19.[15] The most important difference between our study from Bianconi et al[14] is that we detected a lower FMD cutoff value (3.135% vs 4.4%). Our FMD cutoff value was also lower than the study of Oliveira MR et al (3.135% vs 3.43%).[15] This is because we calculated the FMD% cutoff to estimate mortality, while others calculated the FMD cutoff value without distinguishing between severe disease and mortality. We think that the present study has important results because it gives the FMD% cutoff value that can be used to predict mortality in the patients diagnosed with Covid-19.

In the current study, patients were grouped according to Covid-19-related lung parenchyma involvement[11] and compared in terms of FMD%. We found that as the severity of lung parenchyma involvement increased in the patients, the FMD% decreased. While the mean FMD value was 3.02% in patients with lung parenchyma involvement over 50 percent, it was about 5.85% in the patients with less than 25% lung parenchyma involvement. Similarly, it was reported that lower FMD values were found in patients who had radiographic signs of pneumonia compared with those who did not.[14] This is another important finding showing that there is a relationship between the severity of the Covid-19 and low FMD values.

The present study has the following limitations. First, the small sample size obtained from a single center may make the generalizability of the observed results difficult. Second, an assessment of additional markers of endothelial dysfunction besides FMD, which could have supported the study results, was not performed. Biomarkers such as endothelin-1, endoglin, sE-selectin, thrombomodulin, soluble vascular cell adhesion molecule 1, and von Willebrand factor were measured in the previous study for detecting endothelial dysfunction in Covid-19 patients.[27] Third, FMD% of Covid-19 cases and non-Covid-19 controls were not compared in our study. Fourth, the absence of a long-term follow-up for patients who were discharged alive only allowed us to assess predictors of inhospital prognosis.

We conclude that severe Covid-19 patients presented endothelial dysfunction evaluated with FMD measurement and lower FMD% were associated with higher lung parenchyma involvement, ICU admission, and mortality in Covid-19. Therefore, the measurement of FMD in Covid-19 patients at hospital admission might facilitate our prognostic ability and possibly improve decision-making about treatment protocol.

Author contributions

Conceptualization: GG
Data curation: GG
Formal analysis: SD
Investigation: GG
Methodology: GG and SD
Project administration: GG
Resources: GG and SD
Supervision: SD
Visualization: SD
Writing—original draft: all authors
Writing—review and editing: SDt

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