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Determinants of endothelial dysfunction in noncritically ill hospitalized COVID-19 patients: A cross-sectional study

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Abstract

Objective: The aim of this study was to identify determinants of endothelial dysfunction in patients hospitalized with acute COVID-19.

Methods: A total of 109 hospitalized COVID-19 patients in noncritical status were cross-sectionally studied. Clinical data (age, sex, comorbidities, and medications) and BMI were assessed. Laboratory tests included serum hemoglobin, leukocytes, lymphocytes, platelets, C-reactive protein, ferritin, D-dimer, and creatinine. Physical status was evaluated using a handgrip dynamometer. Endothelial function was assessed noninvasively using the flow-mediated dilation (FMD) method.

Results: The sample average age was 51 years, 51% of patients were male, and the most frequent comorbidity was obesity (62%). Univariate analysis showed association of lower FMD with higher BMI, hypertension, use of oral antihypertensive, higher blood levels of creatinine, and larger baseline artery diameter. After adjusting for confounders, the multivariate analysis showed BMI (95% CI: −0.26 to −0.11; $p < 0.001$) as the major factor associated with FMD. Other factors associated with FMD were baseline artery diameter (95% CI: −1.77 to −0.29; $p = 0.007$) and blood levels of creatinine (95% CI: −1.99 to −0.16; $p = 0.022$).

Conclusions: Increased BMI was the major factor associated with endothelial dysfunction in noncritically hospitalized COVID-19 patients. This may explain one of the pathways in which obesity may increase the risk for severe COVID-19.

INTRODUCTION

COVID-19 is an infectious disease caused by SARS-CoV-2. Most cases of COVID-19 are mild, but 20% of the patients require hospitalization because of severe manifestations such as dyspnea and respiratory failure (1). Although COVID-19 is widely known for its respiratory symptoms as a result of viral pneumonia, the disease can also cause several extrapulmonary manifestations (2). In part, these manifestations result from systemic damage caused by the viral infection of multiple organs, including the brain, intestine, kidneys, heart, and blood vessels (3).

A strong theoretical rationale for multisystemic involvement is that COVID-19 is, in the end, an endothelial disease (4). Postmortem histological findings have already revealed that patients with severe COVID-19 have endothelial injury in multiple vascular beds of the lungs, kidney, and heart (5). As consequence, a dysfunctional endothelium has a negative impact on the control of hemostasis, fibrinolysis, vasomotion, inflammation, and vascular permeability (4). These conditions are also determinants for many complications of severe COVID-19, such as cardiovascular events (6), kidney injury (7), acute respiratory distress syndrome (8), and coagulation abnormalities (9).

In fact, there is an expert consensus stating that COVID-19 is associated with endothelial dysfunction, and this relationship is recognized as crucial for the pathogenesis and disease severity (4,10-12). However, during acute COVID-19, some clinical conditions may also interact to modulate endothelial damage. For example, aging, physical inactivity, and comorbidities (e.g., hypertension, diabetes, obesity), which are conditions associated with severe COVID-19 (12-13), are also independent risk factors for endothelial dysfunction (14). Other potential COVID-19-associated conditions include systemic hyperinflammation and procoagulant state, considered hallmarks of severe disease and which have the endothelium acting as an important regulator (15).

Therefore, even though risk factors for endothelial dysfunction are known in other non-COVID-19 conditions, little is known about associated factors during acute COVID-19. This knowledge is important for a better understanding of the effects of SARS-CoV-2 on endothelial biology and, more specifically, for identifying the susceptibility characteristics for endothelial dysfunction during COVID-19, with possible implications for targeted therapies. In this study, we aimed to identify the factors associated with endothelial dysfunction in patients hospitalized with acute COVID-19.

Study Importance

What is already known?

- ► Endothelial dysfunction is associated with COVID-19 and plays a central role in the pathogenesis, complications, and severity of disease.
- ► Even during viral infection, endothelial damage can be modulated by several clinical conditions such as comorbidities, physical status, inflammation, and coagulation.

What does this study add?

- ► Increased BMI was identified as the major factor associated with endothelial dysfunction in noncritically ill hospitalized COVID-19 patients.

How might these results change the direction of research or the focus of clinical practice?

- ► Our findings add practical evidence suggesting another important mechanism by which obesity increases the risk for severe COVID-19.
- ► Vascular dysfunction should be considered an important therapeutic target in patients with COVID-19, especially when obesity coexists.

METHODS

Study design

This is an observational, cross-sectional, double-center study including patients hospitalized with suspected COVID-19 at the Bauru State Hospital and the Holy House of São Carlos (São Paulo, Brazil) from July 2020 to February 2021. All patients were assessed in a hospital ward setting within 72 hours of admission. Inclusion criteria were as follows: 1) patients of both sexes and aged over 18 years; 2) laboratory-confirmed COVID-19 diagnosis, with SARS-CoV-2 detected by reverse transcriptase-polymerase chain reaction (RT-PCR) test; 3) stable hemodynamics with no use of vasoactive drugs; and 4) Glasgow Coma Scale score of 15 and breathing spontaneously. Exclusion criteria was COVID-19 diagnosis not confirmed. All study procedures were approved by the Research Ethics Committee at the São Paulo State University (CAAE: 32134720.4.1001.5398) and the Federal University of São Carlos (CAAE: 38936620.5.0000.5504).

Clinical assessment

A bedside clinical anamnesis and physical examination were performed to obtain demographic characteristics, detailed history of disease with time since first symptoms, smoking habit, comorbidities, body weight and height, and use of oxygen therapy. BMI was calculated as weight in kilograms divided by height in meters squared, and patients were classified into underweight (BMI < 18.5), normal weight (BMI = 18.5-24.9), overweight (BMI = 25.0-29.9), and obesity (BMI ≥ 30.0) (16). Current smokers were defined as patients who were smoking at the time of study or who had stopped smoking during the last month prior to the study. Vital signs such as body temperature, blood pressure (BP), heart rate, respiratory rate, and

pulse oxygen saturation (SpO_2) were assessed at rest. Medications in use were obtained from the electronic patient record.

Laboratory tests

Complete blood count was used to assess serum hemoglobin, leukocytes, lymphocytes, and platelets. Inflammation and coagulation profile were evaluated by serum levels of C-reactive protein (CRP), ferritin, and D-dimer. COVID-19-associated hyperinflammatory syndrome (COV-HI) was characterized as a CRP concentration greater than 150 mg/L or a ferritin concentration greater than 1,500 mg/dL (17). Blood creatinine were analyzed as a marker of kidney function. All laboratory data were obtained at hospital admission.

Endothelial function

The endothelium-dependent function was assessed using the noninvasive and standardized method of flow-mediated dilation (FMD) (18). Before measurement, patients rested in supine position for at least 10 minutes, and a BP cuff was positioned on their forearm. An ultrasound device (SonoSite M-Turbo, FUJIFILM) was used to evaluate blood flow velocity and brachial artery diameter, which were recorded continuously for 1 minute pre-cuff inflation and 3 minutes post-cuff release during hyperemia. All assessments were performed by an experienced operator with more than 100 scans/y, which is suggested to maintain competency with the FMD method (19). In order to ensure accurate FMD measures, we respected the recommendations for technique execution and data acquisition (19). Doppler blood flow and artery diameter analyses in B-mode video images were performed using an edge-detection and wall tracking software (Brachial Analyzer for Research, Medical Imaging Applications). The endothelial function was determined by the following formula: FMD (percentage) = ([peak diameter − baseline diameter]/baseline diameter) × 100 (18).

Physical status

After FMD measurement, physical status was assessed by grip strength, which was evaluated using a Jamar hydraulic dynamometer (Performance Health). In order to perform the measurement, the patient was positioned seated, with the elbow flexed at 90 degrees and the wrist in neutral. At least three measures were performed for each hand, and the greater of the two averaged values was recorded for the final grip strength value (20).

Statistical analysis

Data with normal distribution are reported as mean (SD), whereas data with nonnormal distribution are presented as median (25-75 interquartile range). Categorical variables are shown as absolute frequency (percentage). First, univariate analysis was used to investigate relationships between FMD and underlying clinical conditions. Control variables with a $p < 0.20$ in the univariate analyses were incorporated into the multivariate model using the stepwise forward method, and those with a $p < 0.05$ in the final model were considered to be significantly associated with the outcome (FMD) (21). In order to avoid multicollinearity, a variance inflation factor < 5 was considered to include variables in the model (22). The final model was adjusted for age, sex, comorbidities, physical status, hyperinflammatory syndrome, and D-dimer blood level. All statistical tests were performed in Stata 15 software (StataCorp).

RESULTS

A total of 132 patients were evaluated, of which, 11 were excluded after COVID-19 diagnosis was not confirmed, and 12 were excluded because of missing data. Therefore, 109 COVID-19 patients were included in the final analysis (Table 1). Average age of studied population was 51 years, and 51% of the patients were male. The most frequent comorbidity was obesity (62%), followed by hypertension (47%) and diabetes (17%). No patient was underweight (BMI < 18.5). The average time since first symptoms was 12 days, and the six most frequent COVID-19-related symptoms were cough (88%), dyspnea (87%), fever (84%), fatigue (73%), myalgia (70%), and headache (62%). Vital signs showed suboptimal control of heart rate (80 [15] beats/min), systolic BP (124 [15] mmHg), diastolic BP (77 [12] mmHg), body temperature (36.3 [0.7]), and respiratory rate (22 [5] breaths/min). Most patients were using supplemental oxygen (72%) to maintain SpO_2 93% [4%]. All patients were using prophylactic anticoagulant, and most were using antibiotic (91%), corticosteroid (87%), and oral antihypertensive (51%) medications.

Univariate regression analysis showed an association between lower FMD and higher BMI, hypertension diagnosis, use of oral antihypertensive, higher blood levels of creatinine, and larger baseline artery diameter (Table 2). After adjusting for potential confounders, the multivariate analysis showed that only BMI ($\beta = -0.19$; 95% CI: −0.26 to −0.11; $p < 0.001$), baseline artery diameter ($\beta = -1.03$; 95% CI: −1.77 to −0.29; $p = 0.007$), and blood levels of creatinine ($\beta = -1.07$; 95% CI: −1.99 to −0.16, $p = 0.022$) were associated with FMD ($R^2 = 0.33$, adjusted $R^2 = 0.26$, $p < 0.001$; Table 3).

DISCUSSION

The present study investigated the determinants of endothelial dysfunction in noncritically ill patients hospitalized due to COVID-19. As the main finding, we found a cross-sectional association between endothelial dysfunction assessed by FMD and higher BMI in patients hospitalized during acute COVID-19. Analysis of possible underlying factors revealed that larger baseline artery diameter and elevated blood levels of creatinine were also associated with lower FMD.

TABLE 1 General characteristics and vascular measures of COVID-19 patients

	Total ($n = 109$)
General characteristics	
Age (y)	51.3 ± 12.8
Male sex, *n* (%)	55 (51)
BMI (kg/m^2)	32.6 ± 6.8
Normal weight, *n* (%)	14 (12)
Overweight, *n* (%)	28 (26)
Obesity, *n* (%)	67 (62)
Current smoker, *n* (%)	10 (9)
Hypertension, *n* (%)	51 (47)
Diabetes, *n* (%)	19 (17)
Asthma, *n* (%)	8 (7)
Heart failure, *n* (%)	7 (6)
Days of symptoms (d)	12 ± 4
Cough, *n* (%)	96 (88)
Dyspnea, *n* (%)	95 (87)
Fever, *n* (%)	92 (84)
Heart rate (beats/min)	80 ± 15
Systolic BP (mm Hg)	124 ± 15
Diastolic BP (mm Hg)	77 ± 12
Temperature (°C)	36.3 ± 0.7
Respiratory rate (breaths/min)	22 ± 5
SpO_2 (%)	93 ± 4
Oxygen therapy, *n* (%)	78 (72)
Grip strength (kgf)	30.8 ± 11.0
Antibiotic, *n* (%)	99 (91)
Corticosteroid, *n* (%)	95 (87)
Oral antihypertensive, *n* (%)	56 (51)
β-blocker, *n* (%)	13 (12)
Bronchodilator, *n* (%)	38 (35)
CRP (mg/L)	66.4 (34.5-131.2)
Ferritin (ng/mL)	738 (396-1,463)
COV-HI, *n* (%)	33 (30)
D-dimer (mg/L)	2.5 ± 6.4
Creatinine (mg/dL)	0.9 ± 0.5
Hemoglobin (g/dL)	13.7 ± 1.6
Leukocytes (10^3/mm^3)	8.4 ± 4.0
Lymphocytes (%)	13.4 ± 7.2
Platelets (10^3/mm^3)	249.1 ± 73.4
Vascular measures	
Baseline artery diameter (mm)	4.41 ± 0.78
Baseline blood flow (cm/s)	20.0 ± 6.9
Hyperemic blood flow (cm/s)	50.3 ± 16.4
FMD (mm)	0.24 ± 0.10
FMD (%)	5.48 ± 2.53

Data are expressed as mean ± SD, median (interquartile range 25%-75%), or absolute frequency (percentage).

Abbreviations: BP, blood pressure; COV-HI, COVID-19-associated hyperinflammatory syndrome; CRP, C-reactive protein; FMD, flow-mediated dilation; SpO_2, pulse oxygen saturation.

TABLE 2 Univariate regression analysis of factors potentially associated with endothelial dysfunction measured by FMD (percentage) in COVID-19 patients

	β Coefficient	95% CI	*p* value
Age (y)	−0.01	−0.04 to −0.03	0.719
Male sex (yes/no)	−0.33	−1.29 to 0.63	0.498
BMI (kg/m^2)	−0.15	−0.21 to −0.08	<0.001
Current smoker (yes/no)	−0.51	−2.18 to 1.15	0.544
Hypertension (yes/no)	−1.23	−2.13 to −0.32	0.008
Diabetes (yes/no)	−0.41	−1.68 to 0.86	0.522
Days of symptoms (d)	0.04	−0.09 to 0.17	0.558
Heart rate (beats/min)	−0.02	−0.05 to 0.01	0.114
Systolic BP (mm Hg)	−0.02	−0.05 to 0.01	0.168
Diastolic BP (mm Hg)	−0.01	−0.05 to 0.03	0.599
SpO_2 (%)	0.01	−0.12 to −0.14	0.859
Oxygen therapy (yes/no)	−0.38	−1.45 to 0.68	0.474
Grip strength (kgf)	−0.01	−0.04 to 0.04	0.947
Antibiotic (yes/no)	0.19	−1.48 to 1.86	0.819
Corticosteroid (yes/no)	−0.31	−1.76 to 1.12	0.666
Oral antihypertensive (yes/no)	−1.08	−2.02 to 0.13	0.025
β-blocker (yes/no)	−1.03	−2.51 to 0.44	0.169
Bronchodilator (yes/no)	−0.17	−1.19 to 0.83	0.729
COV-HI (yes/no)	−0.29	−1.34 to 0.76	0.585
D-dimer (mg/L)	0.11	−1.11 to 1.33	0.860
Creatinine (mg/dL)	−1.00	−1.94 to −0.06	0.036
Hemoglobin (g/dL)	−0.13	−0.42 to 0.16	0.380
Leukocytes (10^3/mm^3)	0.01	0.00 to 0.01	0.385
Lymphocytes (%)	−0.02	−0.09 to 0.04	0.434
Platelets (10^3/mm^3)	0.00	0.00 to 0.00	0.385
Baseline artery diameter (mm)	−0.95	−1.54 to −0,35	0.002

Abbreviations: BP, blood pressure; COV-HI, COVID-19-associated hyperinflammatory syndrome; FMD, flow-mediated dilation; SpO_2, pulse oxygen saturation.

Previous studies have reported that, in patients with COVID-19, obesity has been associated with poor outcomes such as increased disease severity, hospitalization, intensive care unit admission, need for invasive mechanical ventilation, and mortality (23). In our study, obesity was the most prevalent comorbidity (62%), followed by hypertension (47%) and diabetes (17%). Other observational studies with hospitalized COVID-19 patients have also found a high prevalence of obesity, with rates of 61%, 48%, and 42%, respectively (24-26). These findings tend to confirm that patients with obesity are more prone to severe COVID-19, with a consequent need for hospital admission.

There are some hypotheses on the mechanisms underpinning the association between obesity and severe COVID-19. This higher risk has been suggested to be due to chronic inflammation, impairment of respiratory function and pulmonary perfusion, critical care

TABLE 3 Multiple linear regression to identify factors associated with endothelial dysfunction measured by FMD (percentage) in COVID-19 patients

	β Coefficient	95% CI	*p* value
BMI (kg/m^2)	−0.19	−0.26 to −0.11	<0.001
Baseline artery diameter (mm)	−1.03	−1.77 to −0.29	0.007
Creatinine (mg/dL)	−1.07	−1.99 to −0.16	0.022

$R^2 = 0.33$; adjusted $R^2 = 0.26$. Model adjusted by age, sex, hypertension, diabetes, grip strength, COVID-19-associated hyperinflammatory syndrome, and levels of D-dimer.

Abbreviation: FMD, flow-mediated dilation.

management difficulties, immune dysfunction, and metabolic and cardiovascular complications (27). In our study, we showed that people with obesity and/or a higher BMI had a worse endothelial function during acute COVID-19. In practice, this finding corroborates previous speculation that has suggested that endothelial dysfunction may explain, at least in part, one of the mechanisms by which obesity increases the risk for severe COVID-19 (28).

From a pathological point of view, the entry of SARS-CoV-2 into the human cell is dependent on the angiotensin-2 converting enzyme (ACE-2), which functions as a receptor and binding site for viral S protein (3). Although ACE-2 is present in different human cells, including type II pneumocytes and endothelial cells, this protein is more prominently expressed in subcutaneous and visceral adipose tissue (29). Because of this, there is a theoretical framework that suggests a high SARS-CoV-2 tropism for adipocytes, making the adipose tissue a kind of reservoir for viral spread, with increased viral shedding (30). Interestingly, this hypothesis of high viremia in patients with obesity is supported by a previous study on patients hospitalized due to COVID-19, in which it was observed that individuals with obesity had longer length of positive oropharyngeal and/or nasal swab tests, suggesting a delayed viral clearance and a prolonged SARS-COV-2 shedding (31). This condition presumably predisposes patients with obesity to a massive virus exposure. Consequently, this would increase the possibility of direct infection to endothelial cells, leading to systemic endotheliitis and endothelial dysfunction (5).

Translating these findings into clinical practice, it is important to highlight prior knowledge that a 1% decrease in FMD is associated with a 9% increase in the risk of cardiovascular events (32). As our study revealed a β coefficient of −0.19 in the association between BMI and FMD, this means that for each additional unit (kilograms per meters squared) in BMI, a 0.19% decrease in FMD is expected. In a practical context, when two COVID-19 patients, one with normal weight (BMI of 20) and the other with obesity (BMI of 30), are compared, the latter tends to have a 1.9% lower FMD. This could also be speculated as an elevated cardiovascular risk of more than 17%. Interestingly, our results may support other larger population studies in which an increased risk for vascular events was observed among hospitalized COVID-19 patients with obesity. For example, in a retrospective study on 7,606 patients hospitalized with COVID-19, the presence of obesity was found to be associated not only with an increased risk of in-hospital death, but also with a high risk of venous thromboembolism (33). Similar evidence was found in a retrospective cohort of 609 patients hospitalized for COVID-19, in which class I and III subgroups of patients with obesity had significantly higher risk-adjusted odds of venous thromboembolism compared with patients without obesity (34).

On the other hand, even in the absence of SARS-CoV-2 infection, obesity is a condition often associated with endothelial dysfunction. Possible underlying mechanisms are diverse and include insulin resistance, increased free fatty acids, oxidative stress, and low grade of chronic inflammatory state (35). However, during the active phase of COVID-19, there is a hypothesis suggesting that patients with obesity have an amplified inflammatory state in a phenomenon already known as "cytokine storm" (36). In our study, although the patients had high median levels of CRP and ferritin, we did not find a relationship between the hyperinflammatory syndrome (COV-HI) and the degree of endothelial dysfunction. However, some concerns must be raised. First, laboratory tests were obtained early on in hospital admission and were not temporally accurate with FMD assessments. As FMD assessment was performed within 72 hours after admission, the patient's inflammatory status may have changed, especially after administration of corticosteroid treatment (87% were receiving). Furthermore, even though CRP is an inflammatory marker widely used in clinical practice, there is no perfect association or linear temporal response with other pro-inflammatory mediators such as interleukin 6 and procalcitonin (37), which also have a negative influence on endothelial function.

Another finding of our study was the association between endothelial dysfunction and increased blood levels of creatinine. This may suggest a possible role of endothelial damage in the development of renal dysfunction, although at an early or mild stage, because the mean creatinine levels were in normal range. According to a recent meta-analysis, 28% of patients hospitalized due to COVID-19 develop acute kidney injury (AKI) (38). The mechanisms of COVID-19-associated AKI are multifactorial but possibly include coagulopathy, complement activation, and endothelial dysfunction (39). Histological postmortem findings have revealed that COVID-19 patients have endothelial damage in several extrapulmonary vascular beds, including the renal microcirculation (5,40). This renal endothelial injury, consequently, may result in impaired control of renal arteriolar tone, especially by reducing the bioavailability of nitric oxide, which favors a state of sustained vasoconstriction and leads to hypoperfusion and prerenal azotemia (7). Up to now, in addition to evidence from postmortem analyses, few studies, to our knowledge, have verified the relationship between endothelial damage and renal dysfunction in COVID-19 patients. Henry et al. (41) prospectively studied patients hospitalized due to COVID-19 and observed a positive association between the development of AKI and circulating levels of angiopoietin-2, which is a cytokine associated with endothelial inflammation and vascular hyperpermeability. These results, in addition to those observed in our study, point to the impairment of endothelial function as one of the possible pathways for the development of renal dysfunction in COVID-19.

Finally, our study has some limitations. First, the cross-sectional design is not able to provide a cause-and-effect relationship between the studied variables. Second, the sampling carried out in only two hospitals showed particular characteristics of the population, which may limit extrapolations to other health care settings. However, an important condition is that, until the end of data collection, there was no record of circulation of viral variants in the participating hospitals. This excludes the possibility of distinct physiological responses as a result of infection with different SARS-CoV-2 strains. In addition, all patients were in the condition of primary infection and were not vaccinated, ruling out the chance of previous immunological contact with the viral antigen. Third, we used only the FMD method to assess endothelial function. Although FMD is validated and widely used in clinical practice, mainly because it is a noninvasive method, we believe that it would be interesting to use other complementary biomarkers in order to obtain a more detailed profile of the endothelial function. As a fourth limitation, we consider the lack of further investigation of the inflammatory profile. Although not routinely applied in clinical practice, the quantification of pro-inflammatory cytokines, including interleukin-6, could contribute to a better understanding of the role of the COVID-19-associated cytokine storm in endothelial dysfunction. The fifth and last limitation was that we did not assess nitroglycerin-mediated vascular dilation, which can be used to quantify maximal vascular dilation independently of endothelium. Therefore, we were unable to determine whether vasodilation was impaired only because of the inability of endothelial cells to release nitric oxide but also by a loss in arterial smooth-muscle cell integrity.

CONCLUSION

Increased BMI was identified as a major factor associated with endothelial dysfunction in noncritically ill hospitalized COVID-19 patients. This finding may explain, at least partially, one of the pathways in which obesity may increase the risk for the development of severe COVID-19. Future studies should assess whether COVID-19 patients with obesity might benefit from a more intense therapeutic strategy to attenuate endothelial dysfunction.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

ADH, APV, BM, EGC, and RGM designed this study. ADH, APV, SNL, VTA, NSS, and GYOO carried out the data collection. ADH, ABS, PCR, and TSA worked on data analysis and statistical analysis. ADH, EGC, and RGM wrote the manuscript, and all authors revised and approved the final version.

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