Evaluation of the cardio-ankle vascular index in COVID-19 patients

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SUMMARY

OBJECTIVE: This study aimed to investigate the relationship and prognostic significance of cardio-ankle vascular index, which is a measure of arterial stiffness that can lead to endothelial dysfunction and poor cardiovascular issues in COVID-19 patients, with COVID-19.

METHODS: The study included 115 patients, of which 65 patients in the case group with Real time reversetranscription-polymerasechainreaction test positive and diagnosed for COVID-19 and 50 volunteers in the control group. Patients with COVID-19 were classified as moderate/severe or mild COVID-19 in the subgroup analysis based on the severity of the disease. We investigated the relationship between cardio-ankle vascular index and COVID-19 by using the VaSera VS-1000 device to automatically measure each patient's cardio-ankle vascular index and ankle-brachial pressure index.

RESULTS: The mean age of participants included in the study was 65.7 ± 10.7 years. Patients and volunteers were statistically similar in terms of age, gender, comorbidities, Charlson comorbidity index scores, and body mass index values ($p > 0.05$). The right-cardio-ankle vascular index value was 9.6 ± 2.4 in the case group and 8.5 ± 1.1 in the control group ($p = 0.004$). The left-cardio-ankle vascular index value was 9.4 ± 2.7 in the case group and 8.5 ± 1.2 in the control group ($p = 0.01$). The right-cardio-ankle vascular index value was 10.8 ± 3.4 in the moderate/severe disease group and 8.8 ± 0.9 in the mild disease group ($p = 0.008$). The left-cardio-ankle vascular index value was 10.7 ± 3.6 in the moderate/severe disease group and 8.5 ± 1.5 in the mild disease group ($p < 0.001$). The right-cardio-ankle vascular index and left-cardio-ankle vascular index values were found to be significantly higher in COVID-19 patients in our study. When receiver operating characteristic analysis was performed to distinguish moderate/severe COVID-19 patients from mild patients, right-cardio-ankle vascular index was area under the curve 0.757 (0.630–0.884), and left-cardio-ankle vascular index was area under the curve 0.782 (0.661–0.902).

CONCLUSION: The right-cardio-ankle vascular index and left-cardio-ankle vascular index values increased in COVID-19 patients in our study, and this was thought to be prognostically significant.

KEYWORDS: COVID-19. Arterial stiffness. Cardio ankle vascular index. Endothelium.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a disease with a high mortality rate and a proclivity for multiple organ failure by wreaking havoc on various organ systems, particularly the lungs, heart, brain, kidney, and vascular system¹. Endothelial dysfunction is critical in the pathogenesis of the disease. The endothelium, which is located at the key interface between blood and tissues, acts as a portal that operates white blood cells to enter tissues to fight invaders, microbes, or viruses, and to help repair injury and heal wounds². Normal endothelium has a pattern of anticoagulant, antithrombotic, and profibrinolytic properties and has a basis dynamically regulated to maintain a balance between properties supporting and inhibiting thrombus deposition. Furthermore, the endothelial cell has a variety of defense mechanisms reducing local oxidative stress. This balance is disrupted when stimulated by proinflammatory cytokines, bacterial endotoxins, neutrophil

extracellular traps (NETs), and similar molecules. NADPH oxidases producing superoxide anions that contribute to oxidative stress are activated³. As a result of all of these circumstances, inappropriate or excessive production of cytokines, such as IL-1 α and IL-1 β , IL-6, and TNF- α , results in a situation named “a cytokine storm.” Endothelial damage and associated complications occur as a result. Coronavirus disease 2019 (COVID-19) is a disease with irregular endothelial function, and the severity of the disease is closely related to this endothelial dysfunction². Although COVID-19 is initiated by the impact of pneumocytes and alveolar macrophages, impaired endothelial function contributes to the ongoing destruction of SARS-CoV-2 in the lung. Impaired endothelial barrier function results in protein and fluid accumulation in the alveolar space and impaired blood oxygenation. The resulting cytokine storm causes capillary leakage and exacerbation of the adult respiratory syndrome (ARDS) originated from COVID-19^{4,5}. The most serious problems with this

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disease are lung and cardiovascular anomalies^{6,7}. Increased arterial stiffness, which is a vascular functional abnormality, has been shown to be an independent risk factor for cardiovascular disease⁸. Both structural and functional abnormalities can cause arterial stiffness⁹. Viral infections can cause functional vascular damage, such as increased arterial stiffness, which is reversible at the beginning of its course¹⁰. Thrombotic microangiopathy and endothelial dysfunction generalized with pulmonary embolism and venous thromboembolism in patients infected with COVID-19 have been especially demonstrated in autopsy studies¹¹. Endothelial dysfunction and associated arterial stiffness may cause adverse cardiovascular issues in COVID-19 patients. This study aimed to measure the functional change in arterial stiffness that may cause endothelial dysfunction and adverse cardiovascular issues in COVID-19 patients and to determine the prognostic significance of this situation.

METHODS

The study was a prospective case-control study conducted at Trabzon Vakfıkebir State Hospital from October 2020 to April 2021. The study included a total of 115 participants whose COVID-19 status was known. While the case group included 65 people who tested positive for COVID-19 rtRT-PCR, the control group included 50 people who tested negative for COVID-19 rtRT-PCR and had similar demographic features. COVID-19 patients were divided into two groups based on the severity of the disease. Patients with fever, shortness of breath, or a severe cough were classified as having moderate/severe COVID-19, while those who did not have these symptoms were classified as having mild COVID-19. People with known peripheral artery disease, glomerular filtration rate (eGFR) less than 30 ml/min, or malignancy were not included in the study. Baseline characteristics and clinical histories, values of systolic and diastolic blood pressure, urea, creatinine, eGFR at admission, serum lipid profile, body mass index (BMI), cardio-ankle vascular index (CAVI), and ankle-brachial pressure index (ABPI) examinations of all participants were performed. CAVI and ABPI were measured using the VaSera VS-1000 (Fukuda-Denshi Company Ltd., Tokyo, Japan), which is a portable machine.

The study protocol was designed in accordance with the principles of the Declaration of Helsinki, and the approval (no: 23618724/2021/22) of the ethics committee was obtained.

Statistical analysis

All variables in the study were subjected to descriptive statistical analysis. The Kolmogorov-Smirnov test was used to determine

the conformity of data obtained by measures to the normal distribution. Student's t-test was used for data that conform to the normal distribution, and the Mann-Whitney U test was used for data that did not conform to the normal distribution. In the analysis of categorical variables, the chi-square test was used. The data obtained by measurements were expressed as mean±standard deviation. The data obtained by scoring were expressed by numbers (%). The sensitivity and specificity of the statistically significant variables were calculated using the receiver operating characteristic (ROC) curve analysis. $p < 0.05$ was accepted as statistically significant.

RESULTS

The study included 65 COVID-19 patients in the case group and 50 volunteers in the control group. Volunteers are people who have tested negative for the COVID-19 rtRT-PCR test and have no other disease symptoms. Patients with COVID-19 were aged 67 ± 12.3 years, and the volunteers were aged 64.5 ± 9.2 years ($p = 0.213$). Patients and volunteers were statistically similar in terms of age, gender, comorbidities, Charlson comorbidity index (CMI) scores, and BMI values ($p > 0.05$). Systolic blood pressure, one of the hemodynamic parameters, was 127.5 ± 19.8 in the case group and 140.8 ± 24.7 in the control group ($p = 0.002$). Both groups had similar diastolic blood pressure ($p = 0.174$). The R-CAVI value was 9.62.4 in the case group and 8.51.1 in the control group ($p = 0.004$). The L-CAVI value was 9.4 ± 2.7 in the case group and 8.5 ± 1.2 in the control group ($p = 0.01$). The R-ABI and L-ABI values in both groups were similar ($p > 0.05$). Demographic characteristics, laboratory findings, hemodynamic parameters, and arterial stiffness measurements of patients and volunteers are presented in Table 1.

In our internal evaluation of COVID-19 patients, 25 patients were classified as having moderate/severe disease and were hospitalized, while 40 patients were classified as having mild disease and were treated as outpatients. In the analysis between both groups, gender and age were statistically similar. Hypertension was more common among patients in the moderate/severe disease group ($p = 0.004$). The R-CAVI value was 10.8 ± 3.4 in the moderate/severe disease group and 8.8 ± 0.9 in the mild disease group ($p = 0.008$). The L-CAVI value was 10.7 ± 3.6 in the moderate/severe disease group and 8.5 ± 1.5 in the mild disease group ($p < 0.001$). The R-ABI and L-ABI values in both groups were similar ($p > 0.05$). Demographic characteristics, laboratory findings, hemodynamic parameters, and arterial stiffness measurements of the patients in moderate/severe and mild COVID-19 disease groups are presented in Table 2.

Table 1. Analysis of demographic, clinical, and laboratory findings of case and control groups.

	COVID-19 n=65	Control n=50	p-value
Age (years)	66.9±12.3	64.5±9.2	0.213
Gender (female) n (%)	34 (52.3)	19 (38.0)	0.127
BMI (kg/m ²)	27.7±3.6	27.9±3.8	0.804
Systolic BP, mmHg	127.4±19.8	140.8±24.7	0.002
Diastolic BP, mmHg	77.9±11.6	80.6±13.9	0.174
CAD, n (%)	12 (18.5)	17 (34.0)	0.057
Hypertension, n (%)	32 (49.2)	33 (66.0)	0.072
Diabetes mellitus, n (%)	6 (24)	14 (28)	0.926
CMI scores	3.3±1.9	3.6±1.6	0.354
right-cardio-ankle vascular index	9.6±2.4	8.5±1.1	0.004
left-cardio-ankle vascular index	9.4±2.7	8.5±1.2	0.01
right-ankle-brachial index	1.04±0.14	1.04±0.10	0.886
left-ankle-brachial index	1.06±0.26	1.04±0.09	0.984

CAD: coronary artery disease; CMI: Charlson comorbidity index; BMI: body mass index. Bold values are determined as statistically significant.

Table 2. Analysis of demographic, clinical, and laboratory findings of patients according to the severity of COVID-19.

	COVID-19 inpatient n=25	COVID-19 outpatient n=40	p-value
Age	70.7±13.1	64.7±11.2	0.051
Gender (female) n (%)	16 (64)	18 (45)	0.136
BMI (kg/m ²)	28.4±4.1	27.3±3.2	0.226
Systolic BP, mmHg	124.4±20.2	129.4±19.6	0.174
Diastolic BP, mmHg	76.0±8.7	79.1±13.0	0.245
CAD, n (%)	7 (28)	5 (12.5)	0.188
Hypertension, n (%)	18 (72)	14 (35)	0.004
Diabetes mellitus, n (%)	6 (24)	6 (15)	0.363
CMI scores	4.2±2.1	2.8±1.6	0.003
right-cardio-ankle vascular index	10.8±3.4	8.8±0.9	0.008
left-cardio-ankle vascular index	10.7±3.6	8.5±1.5	<0.001
right-ankle-brachial index	1.0±0.16	1.06±0.11	0.162
left-ankle-brachial index	1.06±0.4	1.05±0.1	0.225

CAD: coronary artery disease; CMI: Charlson comorbidity index; BMI: body mass index. Bold values are determined as statistically significant.

When the ROC analysis was performed to distinguish moderate/severe COVID-19 patients from patients with mild disease, AUC 0.757 (0.630–0.884) at cutoff point >8.75 for R-CAVI had 76% sensitivity and 56% specificity, and AUC 0.782 (0.661–0.902) at cutoff point >8.5 for L-CAVI had 88% sensitivity and 58% specificity (Figure 1).

DISCUSSION

Under physiological conditions, the endothelium has a structure that prevents mononuclear cell adhesion at the blood–tissue interface. Inflammation caused by allowing white blood cells to enter tissues in order to fight microbial agents and aid in the healing of damaged tissues activates endothelial cells that cause the loss of vascular integrity, allows increased expression of adhesion molecules (such as VCAM-1 and ICAM-1), and allows endothelial cells to participate in the inflammatory response¹². Increased expression of adhesion molecules stimulates the adhesion and migration of monocytes to the vessel wall, where these

Figure 1. Receiver operating characteristic curve demonstrating the prognostic value of right-cardio-ankle vascular index and left-cardio-ankle vascular index in COVID-19 patients with moderate/severe and mild disease.

cells further differentiate into macrophages, increasing vasculitis. Continuous endothelial cell activation results in subsequent endothelial dysfunction, which is the first step in atherogenesis and contributes to the development of distinct clinical features that characterize later stages of vascular disease¹³. While coronaviruses are known to cause endothelial dysfunction, it is remarkable that COVID-19 causes endothelial dysfunction in such a short period of time, and this situation is associated with prognosis. Researchers in New York City observed a seven-fold increase in large vessel strokes in patients younger than 50 years old during the 2-week period from March 23 to April 7, 2020, compared with a 2-week period over the previous 12 years¹⁴. This study aimed to assess the functional change in arterial stiffness, which is commonly associated with endothelial dysfunction in COVID-19 patients, and to determine the prognostic significance of this condition. The presence of nitric oxide primarily regulates arterial stiffness, and CAVI, an indicator of arterial stiffness, somehow measures endothelial cell function¹⁵. In our study, R-CAVI and L-CAVI values were found to be significantly higher in the analysis between the case and control groups, as well as between moderate/severe patients and mild patients,

and the level of endothelial dysfunction was associated with the clinical status of the patients. The AUC value was determined by ROC curve analysis to be 0.757 for R-CAVI and 0.782 for L-CAVI, and the area under the quite high curve was located. The high sensitivity rates at the determined cutoff points also demonstrate the usefulness of the CAVI measurements.

CONCLUSIONS

The findings of the study lead us to believe that both R-CAVI and L-CAVI values can be used as prognostic indicators in COVID-19 patients. Given the global impact of the pandemic, well-designed large-scale clinical studies are required to convert this knowledge into clinical practice.

AUTHORS' CONTRIBUTIONS

EA: Conceptualization, Writing – original draft, Writing – review & editing. **AK:** Data curation, Formal Analysis, Writing – review & editing. **GY:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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