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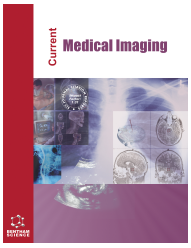

RESEARCH ARTICLE

Evaluation of the Atherogenic Effect of Covid-19 Pneumonia on Coronary and Carotid Arteries in Patients who Recovered from the Disease

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Abstract:

Background:

Acute inflammation induced by COVID-19 may lead to atherosclerotic plaque development or complicate existing plaque. In this study, we aimed to determine the atherogenic effect of COVID-19 pneumonia, confirmed by thoracic computed tomography, on coronary and carotid arteries in patients who recovered from the disease.

Methods:

Our study included patients who were diagnosed with COVID-19 in our hospital at least 1 year ago, recovered, and then underwent coronary CT angiography with suspected coronary artery disease. The aim was to evaluate the burden of atherosclerotic plaque in the coronary arteries of these patients who underwent coronary CT angiography.

Results:

Patients were assigned to 3 groups according to the results of the CT scan. Group 1 included patients in the control group with no history of COVID-19 (n=36), group 2 included those with mild to moderate pneumonia symptoms (n=43), and group 3 included those with severe pneumonia symptoms (n=29). The calcium scores were 23.25±36.8 in group 1, 27.65±33.4 in group 2, and 53.58±55.1 in group 3. The calcium score was found to be significantly higher in group 3 patients with severe pneumonia (group 1-2 p=0.885, group 1-3 p<0.05, group 2-3 p<0.05).

Conclusion:

Although there is no conclusive evidence of a relationship between COVID-19 and atherosclerosis, our study suggests a possible relationship between them. Since this relationship was found especially in cases with severe disease in our study, we believe that the treatment should focus on preventing excessive inflammatory response, and such patients should be under control in terms of coronary artery disease.

Keywords: COVID-19, Atherosclerosis, Coronary arteries, Carotid arteries, Coronary CT angiography.

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1. INTRODUCTION

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global health problem that can lead to viral pneumonia, sepsis, multiple organ failure, and even death [1, 2]. During the peak periods of the COVID-19 epidemic, there was a significant decrease in emergency department admissions and elective surgery cases due to the fear and anxiety experienced by most patients, which caused serious consequences for public health [2, 3]. The pathogenesis of COVID-19 is mainly characterized by inflammation triggered by viral entry *via* angiotensin-converting enzyme (ACE-2) receptors in the lung [4]. Pro-inflammatory cytokines resulting from stimulation have been linked to the severity and progression of infection [5]. Although ACE-2 is predominantly present in type 2 lung alveoli, it is also found in intestinal epithelium, cardiac cells, renal and vascular endothelial cells and cells in various tissues [6]. Pneumonia is the major clinical

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condition in COVID-19 patients, and acute respiratory distress syndrome (ARDS) is one of the complications with a very high mortality rate in patients with severe disease [7, 8]. Virus infection of alveolar epithelial cells triggers a host immune response, which induces the release of pro-inflammatory cytokines. This results in the development of various pathological conditions such as endothelial and epithelial cell damage, vascular leakage, hemorrhage, and pulmonary consolidation in the lungs [9]. In the case of hyperinflammation, overstimulation of the immune system and cytokine storm may lead to ARDS [10, 11]. Indeed, the cytokine storm is the underlying cause of tissue damage in all organs and has been implicated in complications such as sepsis and multiple organ failure.

In severe COVID-19 infection, clinical manifestations usually start with respiratory symptoms, but the cardiovascular system is also significantly affected and appears as an important complication of the virus. The most common complications are myocarditis, myocardial infarction, cardiomyopathies, heart failure and arrhythmias [12]. Occasionally, cardiac involvement may appear as the first symptom of the infection [13, 14]. Although not histologically proven, direct viral toxicity, endothelial damage, microvascular dysfunction, and susceptibility to thrombosis are possible pathophysiological mechanisms. The endothelium prevents thrombus formation by releasing nitric oxide and prostacyclin (PGI2). Metabolic, toxic or immunological events are known to cause endothelial dysfunction and predispose to atherosclerosis [15, 16]. However, some infectious agents may directly or indirectly cause endothelial damage, hypercoagulation, or local inflammation, leading to atherosclerotic plaque formation or further complicating the plaque [17 - 21]. Several studies have reported that infectious agents accelerate plaque formation and increase the risk of acute coronary syndrome [21, 22]. There are epidemiological studies on the atherogenic roles of many viral and bacterial infectious agents [23 - 25].

In this study, we aimed to determine the atherogenic effect of COVID-19 pneumonia, confirmed by chest computed tomography (CT) on coronary and carotid arteries in patients who recovered from the disease.

2. MATERIALS AND METHODS

2.1. Patient Selection

The study included patients who were diagnosed with COVID-19 at our hospital at least 1 year ago, recovered, and then underwent coronary CT angiography with suspected coronary artery disease. The demographic characteristics (age and sex), clinical data, and RT-PCR test results of the patients were retrospectively collected from the medical record system, the CT images were retrospectively scanned from the PACS system, and all images were recorded in the computerized database. Patients in the control group were selected from those who underwent coronary CT angiography for suspected coronary artery disease but had no known history of COVID-19 disease. The aim was to evaluate the burden of atherosclerotic plaque in the coronary arteries of these patients who had undergone coronary CT angiography. Patients with a known history of diseases such as hypertension, hyperlipidemia, diabetes, arrhythmia, and smokers were excluded from the study group. Written informed consent was subsequently obtained from the enrolled patients, and carotid intima-media thickness (CIMT) measurements were performed and recorded in our radiology department.

2.2. Thoracic CT Protocol and Image Analysis

Thoracic CT scan of all patients was performed with a 128-slice CT device (General Electric Revolution EVO, GE Medical Systems, Milwaukee, WI, USA). The examination area included the region from the apices of the lung to the costophrenic sinuses. All images were acquired during deep inspiration with the patients in the supine position. The CT acquisition protocol was as follows: tube voltage 120 kVP; mAs 40-70, pitch = 1.8, slice thickness = 2.5 mm. Chest CT images of all patients were evaluated retrospectively. On chest CT, ground-glass opacities, consolidations, or consolidations associated with ground-glass opacities in the lung parenchyma were interpreted as indicating the presence of involvement. The presence of additional findings such as reticular pattern, crazy-paving pattern, lymphadenopathy, halo sign, pleural and pericardial effusion, and vascular and bronchial enlargements were recorded. The severity of pneumonia was classified as mild (parenchymal involvement <25%), moderate (parenchymal involvement = 25-50%) and severe (parenchymal involvement >50%) pneumonia according to the extent of total lung volume involvement on chest CT [26, 27] (Fig. **1**).

2.3. Coronary CT Angiography Protocol and Image Analysis

To calculate the calcium load in all patients, the thoracic area from the region under the tracheal carina to the base of the heart was imaged without intravenous contrast administration. The imaging protocol for coronary calcium scoring was as follows: gantry rotation time 0.35 seconds, tube voltage 120 kV, 100 mAs, and slice thickness 2.5 mm. Patients were administered sublingual nitroglycerin spray (0.4 mg) 1-2 minutes prior to coronary CT angiography for its vasodilator effect on coronary arteries. Patients with a heart rate greater than 75 beats/min were given intravenous metoprolol tartrate. CT angiography scan was performed with a 128-slice CT device (General Electric Revolution EVO, GE Medical Systems, Milwaukee, WI, USA). The imaging protocol was performed with appropriately selected parameters of gantry rotation time of 0.35 seconds, tube voltage of 100-120 kilowatts, 250 milliamperes (mAs), and slice thickness of 0.625 millimeters. Images were acquired during a breath hold by scanning in a craniocaudal direction from the ascending aorta to the diaphragm. For coronary CT angiography, 1 mL/kg of contrast was administered intravenously using an automatic injector, followed by a 40 mL isotonic bolus at the same rate. The automatic peak enhancement intensity of the proximal descending aorta was +140 Hounsfield. Heart rate and electrocardiographic (ECG) tracings were recorded throughout the examination for segmental reconstruction. The resulting images were reconstructed to find the percentile with the least motion. While images of 75% of the R-R interval were automatically provided by the device, images of additional phases were manually determined in cases where this phase

was insufficiently formed. Reconstructed images were transferred to the workstation, and each coronary artery was evaluated on the workstation using axial images as well as reconstructed images generated using post-processing techniques of multi-planar reconstruction (MPR), maximum intensity projection (MIP), and 3D volume rendering (3D VRD) using appropriate software on the workstation. The total coronary artery calcium score (CACSc) of all patients was obtained by summing the calcium values from all coronary artery traces using the Agatston scoring system [28] (Fig. **2**).

2.4. Measurement of Carotid Intima-Media Thickness (CIMT)

To measure carotid intima-media thickness in the patients enrolled in the study, a Samsung RS80 EVO RDUS device (Samsung Medison Co., Ltd., Seoul, Korea) was used to perform a test using a linear probe with a frequency of 14 MHz. Examinations were performed in the supine position with the head extended and the neck at an angle of 30-40 degrees to the opposite side of the examination. All segments of both common carotid arteries were examined in grayscale in the transverse and longitudinal planes. CIMT was measured three times between the hyperechoic line facing the intima lumen in the segment 1 cm proximal to the bilateral common carotid artery bifurcation and the hyperechoic line formed by the media-adventitia deep in the media layer and the average of the values was calculated. Any thickening with a mean value greater than 1.5 mm was considered to be diffuse plaque and was not included in the study group (Fig. **3**).

2.5. Statistical Analysis

SPSS 18.0 software (Statistical Package for the Social Sciences, Chicago, IL) was used for data analysis. In the evaluation of study data, the Shapiro-Wilk test was used to test the normal distribution of continuous variables. The Mann-Whitney test and Student's t-test were used for pairwise independent group comparisons, and one-way ANOVA for comparisons of more than two groups, followed by TUKEY's test for differences between groups. The relationship between categorical variables was examined using Pearson's correlation coefficient. A significance level of $p<0.05$ was considered for statistical results.

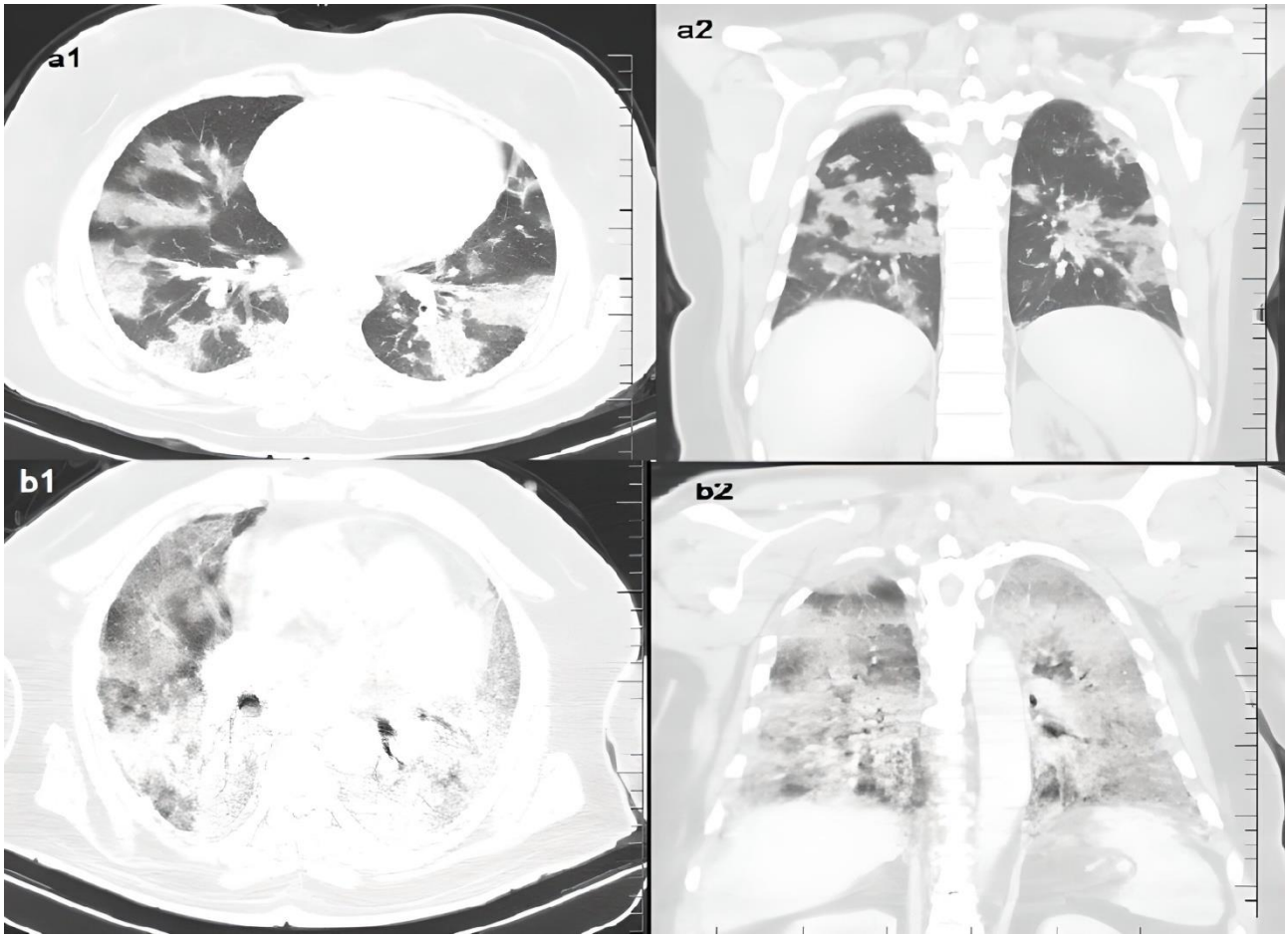

Fig. (1). Moderate pneumonia findings on transaxial (**a1**) and coronal (**a2**) thoracic CT: Consolidation associated with ground glass densities covering 25-50% of the total lung volume and "crazy-paving" pattern appearance. Severe pneumonia findings on transaxial (**b1**) and coronal (**b2**) thoracic CT: Ground glass densities covering more than 50% of the total lung volume, consolidations, septal thickening, and "crazy-paving" pattern appearance.

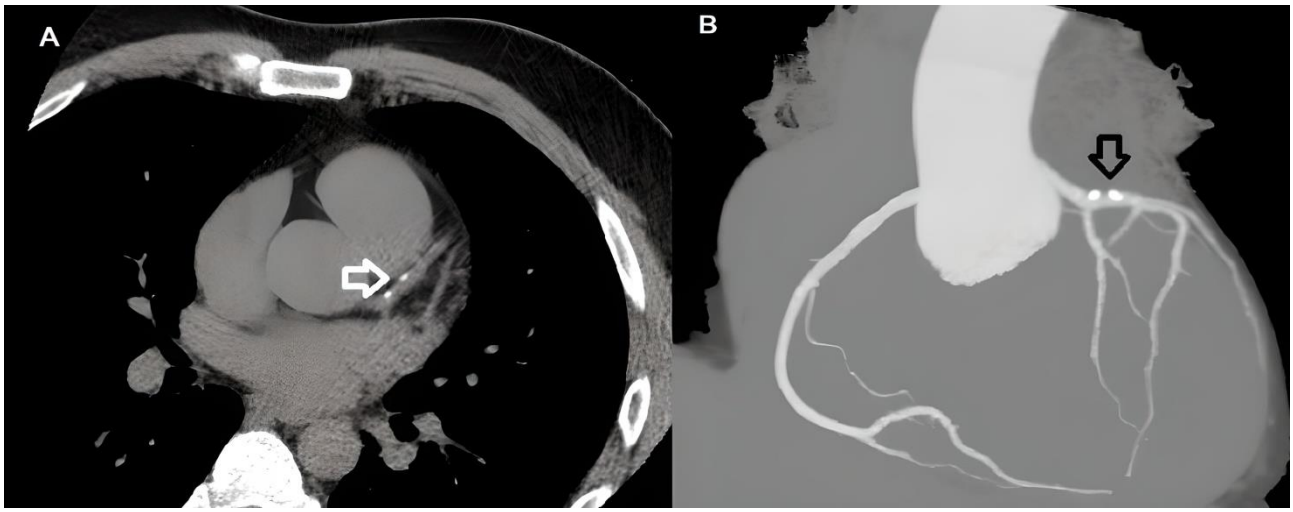

Fig. (2). CT images of coronary atherosclerotic plaques; arterial calcifications are seen in the left anterior descending coronary artery (LAD) on non-contrast axial CT (**A**) and MIP CT angiography (**B**) (arrows).

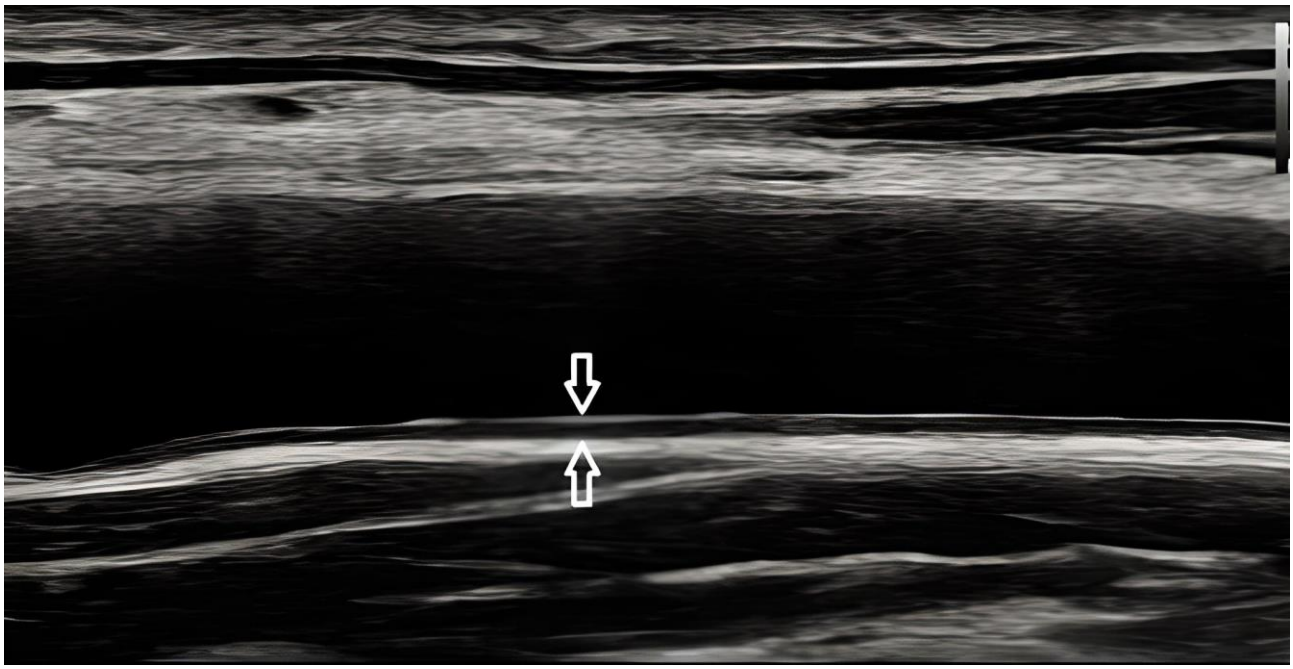

Fig. (3). Carotid artery intima-media thickness (CIMT) measurement was made between the hyperechoic line facing the lumen of the intima and the hyperechoic line formed by the media-adventitia deep in the media layer (arrows).

3. RESULTS

Of the 108 patients included in the study, 56.5% (n=61) were male and 43.5% (n=47) were female. The mean age of all patients was 50.5±7 years, ranging from 36 to 66 years. From the medical records of these patients, 72 (66.7%) had been hospitalized and treated for COVID-19 disease, and 36 (33.3%) had no history of COVID-19 and had undergone coronary CT angiography with suspected coronary artery disease, which constituted the control group. The mean age of the patients with a history of COVID-19 was 51.3±6.7 years, and that of the patients in the control group was 48.8±7.4 years. We found no statistically significant difference between the ages of the two groups (p=0.107). According to the Agatston classification of all patients included in the study, the calcium score was 0 in 44 (40.7%) patients, 1-10 in 15 (13.9%) patients, 11-100 in 40 (37.1%) patients, and 101-400 in 9 (8.3%) patients (Fig. **4**). None of the calcium scores were 400 or greater. The lowest and highest calcium scores measured were 0 and 156, respectively. According to the Agatston classification of the patient group with a history of COVID-19, the calcium score was 0 in 26 (36.1%) patients, 1-10 in 7 (9.7%) patients, 11-100

in 32 (44.4%) patients, 101-400 in 7 (9.7%) patients. In the control group, the calcium score was 0 in 18 (50%) patients, 1-10 in 8 (22.2%) patients, 11-100 in 8 (22.2%) patients, and 101-400 in 2 (5.6%) patients. In patients with a history of COVID-19, the CIMT values were 0.51±0.09 mm in patients with a calcium score of 0, 0.69±0.12 mm in patients with a calcium score of 1-10, 0.84±0.07 mm in patients with a calcium score of 11-100, and 0.94±0.05 mm in patients with a calcium score of 101-400. In the control group, it was 0.58±0.1 mm in patients with a calcium score of 0, 0.62±0.11 mm in patients with a calcium score of 1-10, 0.80±0.04mm in patients with a calcium score of 11-100, and 0.90±0.06mm in patients with a calcium score of 101-400. Pearson's correlation analysis showed a strong positive correlation between CACSc and CIMT values both in patients with a history of COVID-19 and in the control group ($r=0.766$, $p<0.01$ and $r=0.744$, $p<0.01$, respectively).

Patients were divided into 3 groups according to their chest CT findings. Group 1 included control patients with no history of COVID-19 (n=36), group 2 included patients with mild to moderate pneumonia symptoms (n=43), and group 3 included patients with severe pneumonia symptoms (n=29). The calcium scores were 23.25±36.8 in group 1, 27.65±33.4 in group 2, and 53.58±55.1 in group 3. The ANOVA test was used to test whether there was a significant difference in CACSc values between the groups, and a significant difference was found between the groups as a result of the test ($p<0.05$). Tukey's test was used to determine the direction of the difference, and according to the test result, the calcium score was found to be significantly higher in group 3 patients with severe pneumonia (group 1-2 $p=0.885$, group 1-3 $p<0.05$, group 2-3 $p<0.05$) (Table **1** and Fig. **5**). The mean CIMT values were 0.65±0.13 mm in group 1, 0.67±0.12 mm in group 2, and 0.78±0.20 mm in group 3. A significant difference in the mean CIMT values between the groups was found by the ANOVA test, and Tukey's test showed that the mean CIMT values in group 3 were significantly higher than the other two groups (group 1-2 $p=0.759$, group 1-3 $p<0.05$, group 2-3 $p<0.05$) (Table **1** and Fig. **6**).

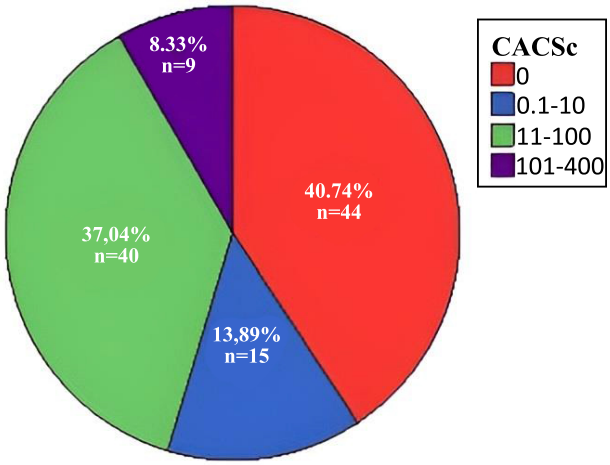

Fig. (4). Coronary CT angiography calcium score distribution according to Agatston classification of all patients included in the study.

Table 1. Coronary artery calcium score (CACSc) values and carotid artery intima-media thickness (CIMT) measurements of groups 1, 2 and 3.

-	Group 1 (n = 36)	Group 2 (n = 43)	Group 3 (n =29)	p
CACSc mean ± SD Group 1 *vs* 2 Group 1 *vs* 3 Group 2 *vs* 3	23.25±36.8	27.65±33.4	53.58±55.1	< 0.05[a] 0,885 [b] < 0.05[b] < 0.05[b]
CIMT (mm) mean ± SD Group 1 *vs* 2 Group 1 *vs* 3 Group 2 *vs* 3	0.65±0.13	0.67±0.12	0.78±0,20	< 0.05[a] 0,759 [b] < 0.05[b] < 0.05[b]

Note:[a]p < 0.05 was considered statistically significant (one-way ANOVA).

[b]p < 0.05 was considered statistically significant (one-way ANOVA with a post hoc Tukey test).

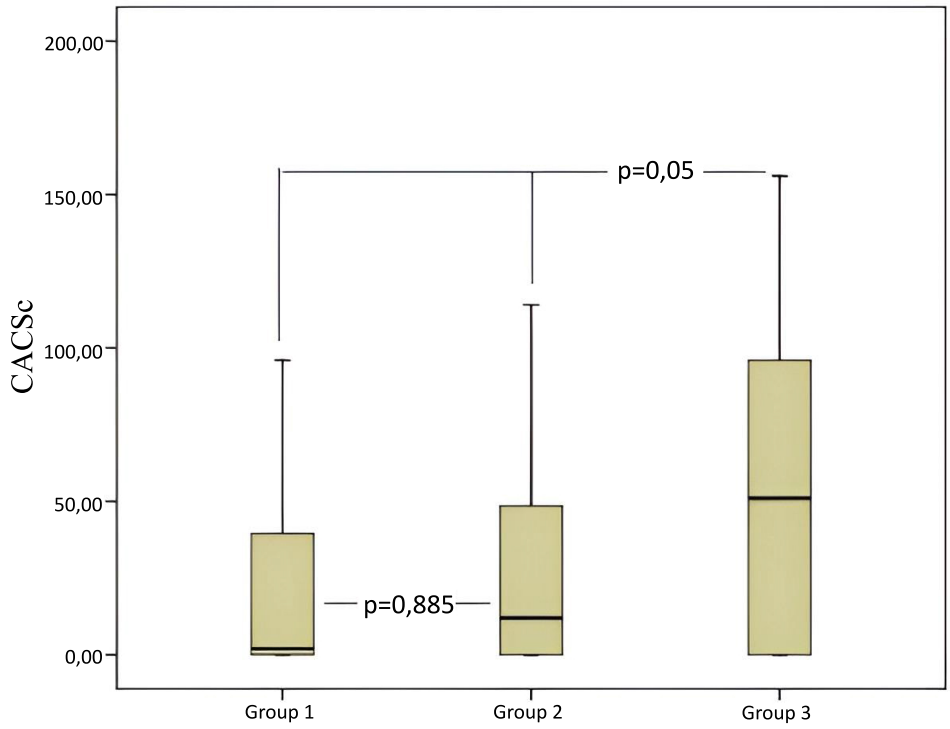

Fig. (5). Comparison of apparent coronary artery calcium score (CACSc) values for each group. The horizontal lines within each box represent the mean values. The horizontal lines inside each box represent the mean values while the bottom and top rows of each box represent the minimum and maximum values respectively.

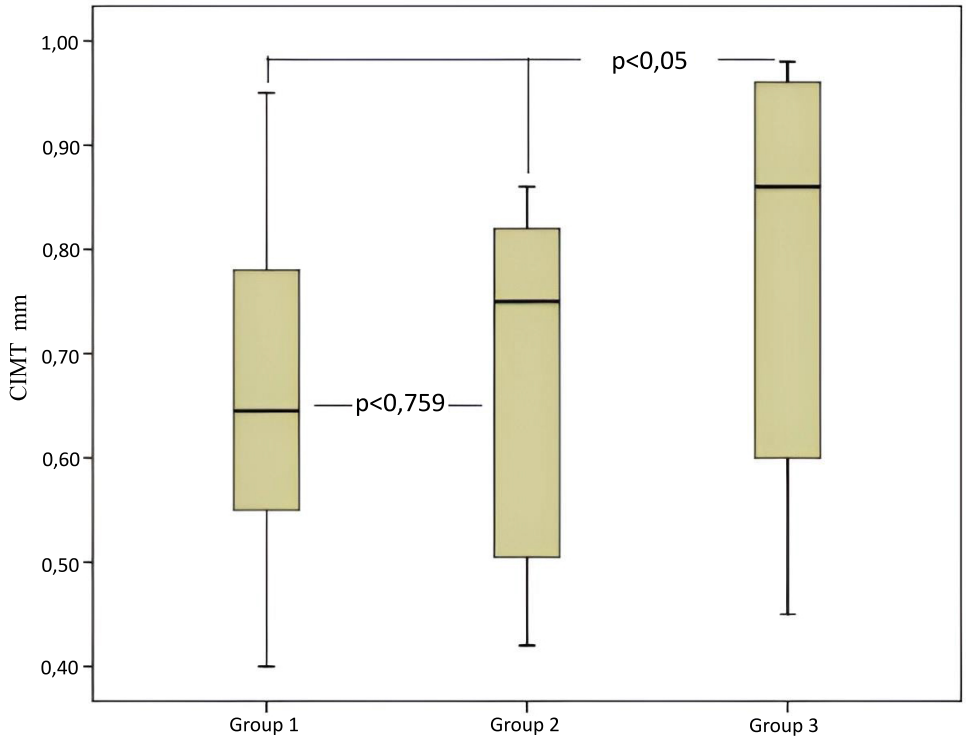

Fig. (6). Comparison of apparent carotid artery intima-media thickness (CIMT) measurements for each group. The horizontal lines within each box represent the mean values. The horizontal lines inside each box represent the mean values while the bottom and top rows of each box represent the minimum and maximum values respectively.

4. DISCUSSION

Acute inflammation caused by COVID-19 disease may cause the development of atherosclerotic plaque or complicate the existing plaque [29, 30]. Cardiac involvement is an important complication of the coronavirus disease. The receptor protein ACE2 receptor, which is used by the SARS-CoV-2 virus to attach to alveolar epithelial cells, is also commonly found in myocytes and vascular endothelial cells [31]. Therefore, cardiac damage caused by COVID-19 infection could theoretically be caused by endothelial activation mediated by ACE2 receptors. Endotheliitis, induced by infection, is linked to increased levels of circulating proinflammatory cytokines (IL-6, IL-2R, TNF-α) and chemokines (MCP-1) that are released by dysfunctional endothelial cells [32]. However, the uptake and degradation of ACE2 receptors into the cell during virus entry also affects the renin-angiotensin system (RAS), causing an increase in angiotensin II (Ang-II). Research suggests that Ang-II contributes to endothelial dysfunction, oxidative stress, and an increase in Ca^{2+} concentration in endothelial cells by activating calmodulin. This process is reported to contribute to the development of atherosclerosis [33]. In addition, cardiac complications such as myocardial infarction, heart failure, or arrhythmias have been reported to be common in patients with pneumonia [34]. Therefore, it is possible that the cardiac outcomes of COVID-19 are related to both the direct cardiac effects of infection and the severity of pulmonary involvement. As a result of viral replication, pro-inflammatory cytokines are released that can cause cellular damage in the epithelium and endothelium, and these pro-inflammatory cytokines recruit neutrophils and monocytes to the site of infection to activate other pro-inflammatory cytokines and chemokines. Conditions such as endothelial and smooth muscle cell proliferation and activation, activated macrophages and hypercoagulation as a result of inflammation are the factors that prepare the atherosclerotic ground during COVID-19 [35].

Usually, the demonstration of coronary artery calcifications provides evidence of coronary artery disease (CAD) and the presence of atheromatous plaques at the localized sites. However, the relationship between plaque calcification and plaque severity, risk, and luminal stenosis is weak. Because atherosclerotic plaques have a polyphasic progression, individuals with diffuse coronary calcification but no significant luminal stenosis may be seen, whereas individuals without calcification or with a low total calcium score may have high-risk, active atherosclerotic plaques [36, 37]. However, apart from these extreme cases, many studies have shown that a positive calcium score is indicative of the presence of coronary artery disease and provides information about the risk of developing a major coronary event in proportion to the score [36, 38, 39].

Atherosclerosis is the most common underlying cause of the worldwide epidemic of coronary heart disease. In addition to known risk factors, infectious agents have been shown to cause endothelial dysfunction, inflammation, and atherosclerosis [40, 41]. Several studies have shown that the inflammatory response in the plaque develops as a result of an immune process due to high levels of acute phase proteins in coronary artery disease (CAD) and that T lymphocytes and macrophages are detected in atherosclerotic lesions [22, 42, 43]. Especially in recent years, several studies have shown that infectious agents and acute phase reactants both directly cause the development of atherosclerosis and indirectly contribute to the progression of atherosclerosis [18, 20]. Epidemiologic studies have focused on the atherogenic role of infectious agents such as Chlamydia pneumoniae (C. pneumoniae), cytomegalovirus (CMV), herpes simplex virus (HSV), Helicobacter pylori, influenza A virus, human immunodeficiency virus (HIV), and hepatitis B and C viruses [23 - 25, 44, 45].

C. pneumoniae has been detected in human atherosclerotic lesions using various techniques such as electron microscopy, immunohistochemistry, and PCR [35, 45]. In addition, an increased frequency of C. pneumoniae has been found in atherosclerotic lesions compared to normal vessels [46]. There are several studies showing that C. pneumoniae initiates or increases atherosclerotic lesions in animal experiments [47 - 50]. Raza-Ahmad *et al*. detected HSV antigens in coronary artery biopsy samples taken during bypass grafting [51]. Patel *et al*. found that the frequency of H. pylori infection was higher in patients with coronary atherosclerosis [52]. Lo *et al*. reported an increased incidence of coronary atherosclerosis in HIV-positive men compared to healthy individuals [53]. Paton *et al*. found atherosclerotic changes causing significant stenosis in the coronary arteries of eight HIV-positive young men (23-32 years) with no known coronary risk factors at autopsy [54]. Animal studies have shown that atherosclerosis develops after exposure to P. gingivalis and that vaccination against this pathogen can halt or even improve the progression of atherosclerosis [55, 56]. Streptococcus pneumoniae is another pathogen that has been found to be associated with atherosclerosis, and it has been reported that there is a significant reduction in the rate of myocardial infarction in cases followed up after pneumococcal vaccination [57, 58]. In a meta-analysis study conducted by Hessami *et al*., they found that the prevalence of cardiovascular complications was higher in hospitalized symptomatic COVID-19 patients [59]. Pillarisetti *et al*. reported that the mortality risk in COVID-19 patients who developed cardiac complications was significantly higher than in the group of patients who did not develop cardiac complications [60]. In our study, we found increased coronary CTA calcium scores in the group of patients who had severe pneumonia due to COVID-19 and recovered, compared with the other two groups. The fact that there was no significant difference in the patient group with mild to moderate pneumonia compared to the control group suggests that high levels of pro-inflammatory cytokines may have contributed to plaque formation.

An association between carotid intima-media thickness and cardiovascular disease has been reported [61]. Salonen *et al*. found that the risk of CAD increased with increasing CIMT in middle-aged men [62]. In a study by Demircan *et al*., carotid intima-media thickness was found to be higher in patients with coronary artery disease *versus* the control group [61]. Takashi *et al*. found that atherosclerotic changes in the carotid artery were more frequent in patients with coronary artery disease *versus* the control group [63]. Adams *et al*. found a positive

correlation between CIMT and the extent of coronary artery atherosclerosis [64]. Similarly, in our study, we found a strong positive correlation between carotid intima-media thickness and coronary calcium score. Several studies suggest that infectious agents may affect carotid intima-media thickness and predispose to the risk of atherosclerosis [65, 66]. Doğan and Özdemir reported that carotid intima-media thickness increased significantly in patients with a history of COVID-19 compared to the control group [67]. In our study, we found higher carotid intima-media thickness in the group of patients with severe pneumonia compared with the other two groups.

CONCLUSION

Although there is no conclusive evidence of an association between COVID-19 and atherosclerosis, our study suggests a possible relationship. However, it is clear that further studies are needed to establish a definite relationship. Since this relationship was found especially in cases with severe disease in our study, we believe that treatment should focus on preventing excessive inflammatory response, and such patients should be under control in terms of coronary artery disease.

LIMITATIONS

There were several limitations in our study. First, due to the small number of patients, our findings need to be supported by studies with a larger patient population. Second, the patient groups included in the study were selected cases with clinically suspected coronary artery disease, and the values do not reflect the normal population as they do not include the normal population. Third, since the pre-study coronary calcium scores and carotid artery intima-media thickness measurement values of the subjects included in the study are unknown, long-term observation and prospective studies are warranted to confirm the atherogenic effect of COVID-19.

AUTHORS' CONTRIBUTIONS

Semih Sağlık: concept, design, supervision, data collection, literature search, writing manuscript, critical review, analysis and interpretation, and resources.

Necip Nas: concept, design, data collection, analysis, literature review, manuscript writing, critical review, resources, materials and editing.

LIST OF ABBREVIATIONS

ACE-2	=	Angiotensin-converting enzyme
ARDS	=	Acute respiratory distress syndrome
C. pneumoniae	=	*Chlamydia pneumoniae*
CACSc	=	Coronary artery calcium score
CAD	=	Coronary artery disease
CIMT	=	Carotid intima-media thickness
CMV	=	Cytomegalovirus
COVID-19	=	Coronavirus disease
CT	=	Computed tomography
CTA	=	Computed Tomography Angiography
HIV	=	Human immunodeficiency virus
HSV	=	Herpes simplex virus
LAD	=	Descending coronary artery
MIP	=	Maximum intensity projection
MPR	=	Multi-planar reconstruction
PCR	=	Polymerase Chain Reaction

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics Committee Approval was obtained from the Siirt University Non-Invasive Ethics Committee (Date: 20.03.2023, Decision No: 66115).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the study participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Data information can be obtained from the author upon request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Zhu N, Zhang D, Wang W, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382(8): 727-33. [http://dx.doi.org/10.1056/NEJMoa2001017] [PMID: 31978945]

[2] Mulita F, Vailas M, Tchabashvili L, *et al.* The impact of the COVID-19 outbreak on emergency surgery: A Greek emergency department experience. Prz Gastroenterol 2021; 16(1): 95. [http://dx.doi.org/10.5114/pg.2021.104739] [PMID: 33986894]

[3] Mulita F, Sotiropoulou M, Vailas M. A multifaceted virus. Non-reducible and strangulated effects of COVID-19. J Trauma Acute Care Surg 2021; 91(1): e34. [http://dx.doi.org/10.1097/TA.0000000000003219] [PMID: 33797481]

[4] Jin Y, Yang H, Ji W, *et al.* Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020; 12(4): 372. [http://dx.doi.org/10.3390/v12040372] [PMID: 32230900]

[5] Bello R, Chin V, Abd Rachman IM, *et al.* The role, involvement and function(s) of interleukin-35 and interleukin-37 in disease pathogenesis. Int J Mol Sci 2018; 19(4): 1149. [http://dx.doi.org/10.3390/ijms19041149] [PMID: 29641433]

[6] Ortiz ME, Thurman A, Pezzulo AA, *et al.* Heterogeneous expression of the SARS-Coronavirus-2 receptor ACE2 in the human respiratory tract. EBioMedicine 2020; 60: 102976. [http://dx.doi.org/10.1016/j.ebiom.2020.102976] [PMID: 32971472]

[7] Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): A clinical update. Front Med 2020; 14(2): 126-35. [http://dx.doi.org/10.1007/s11684-020-0767-8] [PMID: 32240462]

[8] Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in wuhan, China. JAMA 2020; 323(11): 1061-9. [http://dx.doi.org/10.1001/jama.2020.1585] [PMID: 32031570]

[9] Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, *et al.* Respiratory function in patients post-infection by COVID-19: A systematic review and meta-analysis. Pulmonology 2021; 27(4): 328-37. [http://dx.doi.org/10.1016/j.pulmoe.2020.10.013] [PMID: 33262076]

[10] Montenegro F, Unigarro L, Paredes G, *et al.* Acute respiratory distress syndrome (ARDS) caused by the novel coronavirus disease (COVID-19): A practical comprehensive literature review. Expert Rev Respir Med 2021; 15(2): 183-95. [http://dx.doi.org/10.1080/17476348.2020.1820329] [PMID: 32902367]

[11] Garg S, Garg M, Prabhakar N, Malhotra P, Agarwal R. Unraveling the mystery of Covid-19 cytokine storm: From skin to organ systems. Dermatol Ther 2020; 33(6): e13859. [http://dx.doi.org/10.1111/dth.13859] [PMID: 32559324]

[12] Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Cooper Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation 2020; 141(23): 1903-14. [http://dx.doi.org/10.1161/CIRCULATIONAHA.120.047349] [PMID: 32297796]

[13] Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J 2021; 42(2): 206-6. [http://dx.doi.org/10.1093/eurheartj/ehaa190] [PMID: 32176300]

[14] Inciardi RM, Lupi L, Zaccone G, *et al.* Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5(7): 819-24. [http://dx.doi.org/10.1001/jamacardio.2020.1096] [PMID: 32219357]

[15] Milutinović A, Šuput D, Zorc-Pleskovič R. Pathogenesis of atherosclerosis in the tunica intima, media, and adventitia of coronary arteries: An updated review. Bosn J Basic Med Sci 2020; 20(1): 21-30. [PMID: 31465719]

[16] Libby P. Inflammation in atherosclerosis—no longer a theory. Clin Chem 2021; 67(1): 131-42. [http://dx.doi.org/10.1093/clinchem/hvaa275] [PMID: 33393629]

[17] Huang CY, Shih CM, Tsao NW, *et al.* GroEL1, from Chlamydia pneumoniae, induces vascular adhesion molecule 1 expression by p37(AUF1) in endothelial cells and hypercholesterolemic rabbit. PLoS One 2012; 7(8): e42808. [http://dx.doi.org/10.1371/journal.pone.0042808] [PMID: 22900050]

[18] Lebedeva A, Maryukhnich E, Grivel JC, Vasilieva E, Margolis L, Shpektor A. Productive cytomegalovirus infection is associated with impaired endothelial function in ST-elevation myocardial infarction. Am J Med 2020; 133(1): 133-42. [http://dx.doi.org/10.1016/j.amjmed.2019.06.021] [PMID: 31295440]

[19] Montarello NJ, Nguyen MT, Wong DT, Nicholls SJ, Psaltis PJ. Inflammation in coronary atherosclerosis and its therapeutic implications. Cardiovasc Drugs Ther 2020; 36(2): 347-62. [PMID: 33170943]

[20] Bachmaier K, Le J, Penninger JM. "Catching heart disease": Antigenic mimicry and bacterial infections. Nat Med 2000; 6(8): 841-2. [http://dx.doi.org/10.1038/78561] [PMID: 10932199]

[21] Ielapi N, Caprino F, Malizia B, *et al.* Infection, infectious agents and vascular disease. Rev Recent Clin Trials 2021; 16(3): 262-71. [http://dx.doi.org/10.2174/1574887116666210325124045] [PMID: 33823769]

[22] Peterson E, Lo KB, DeJoy R, *et al.* The relationship between coronary artery disease and clinical outcomes in COVID-19: A single-center retrospective analysis. Coron Artery Dis 2021; 32(5): 367-71. [http://dx.doi.org/10.1097/MCA.0000000000000934] [PMID: 32732512]

[23] Kumar S, Kashyap B, Kumar S, Kapoor S. Diagnostic utility of serology and polymerase chain reaction for detection of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* in paediatric community-acquired lower respiratory tract infections. Indian J Med Microbiol 2020; 38(2): 152-6. [http://dx.doi.org/10.4103/ijmm.IJMM_20_145] [PMID: 32883927]

[24] Zhu W, Liu S. The role of human cytomegalovirus in atherosclerosis: A systematic review. Acta Biochim Biophys Sin 2020; 52(4): 339-53. [http://dx.doi.org/10.1093/abbs/gmaa005] [PMID: 32253424]

[25] Tong L, Wang BB, Li FH, Lv SP, Pan FF, Dong XJ. An updated meta-analysis of the relationship between Helicobacter pylori infection and the risk of coronary heart disease. Front Cardiovasc Med 2022; 9: 794445. [http://dx.doi.org/10.3389/fcvm.2022.794445] [PMID: 35571162]

[26] Colombi D, Bodini FC, Petrini M, *et al.* Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology 2020; 296(2): E86-96. [http://dx.doi.org/10.1148/radiol.2020201433] [PMID: 32301647]

[27] Choi H, Qi X, Yoon SH, *et al.* Extension of coronavirus disease 2019 on chest CT and implications for chest radiographic interpretation. Radiol Cardiothorac Imaging 2020; 2(2): e200107. [http://dx.doi.org/10.1148/ryct.2020200107] [PMID: 33778565]

[28] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15(4): 827-32. [http://dx.doi.org/10.1016/0735-1097(90)90282-T] [PMID: 2407762]

[29] Lazcano U, Cuadrado-Godia E, Grau M, *et al.* Increased COVID-19 mortality in people with previous cerebrovascular disease: A population-based cohort study. Stroke 2022; 53(4): 1276-84. [http://dx.doi.org/10.1161/STROKEAHA.121.036257] [PMID: 34781706]

[30] Naeini MB, Sahebi M, Nikbakht F, *et al.* A meta-meta-analysis: Evaluation of meta-analyses published in the effectiveness of cardiovascular comorbidities on the severity of COVID-19. Obes Med 2021; 22: 100323. [http://dx.doi.org/10.1016/j.obmed.2021.100323] [PMID: 33521379]

[31] Gheblawi M, Wang K, Viveiros A, *et al.* Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20th anniversary of the discovery of ACE2. Circ Res 2020; 126(10): 1456-74. [http://dx.doi.org/10.1161/CIRCRESAHA.120.317015] [PMID: 32264791]

[32] Grzegorowska O, Lorkowski J. Possible correlations between atherosclerosis, acute coronary syndromes and COVID-19. J Clin Med 2020; 9(11): 3746. [http://dx.doi.org/10.3390/jcm9113746] [PMID: 33233333]

[33] Ziegler T, Abdel Rahman F, Jurisch V, Kupatt C. Atherosclerosis and the capillary network; pathophysiology and potential therapeutic strategies. Cells 2019; 9(1): 50. [http://dx.doi.org/10.3390/cells9010050] [PMID: 31878229]

[34] Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: A descriptive study. Medicine 2007; 86(2): 103-11. [http://dx.doi.org/10.1097/MD.0b013e3180421c16] [PMID: 17435590]

[35] Libby P, Simon DI. Inflammation and thrombosis. Circulation 2001; 103(13): 1718-20. [http://dx.doi.org/10.1161/01.CIR.103.13.1718] [PMID: 11282900]

[36] Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: Mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 2005; 46(5): 807-14. [http://dx.doi.org/10.1016/j.jacc.2005.05.049] [PMID: 16139129]

[37] Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: The St. Francis Heart Study. J Am Coll Cardiol 2005; 46(1): 158-65. [http://dx.doi.org/10.1016/j.jacc.2005.02.088] [PMID: 15992651]

[38] Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003; 228(3): 826-33. [http://dx.doi.org/10.1148/radiol.2283021006] [PMID: 12869688]

[39] Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: A systematic review and meta-analysis. Arch Intern Med 2004; 164(12): 1285-92. [http://dx.doi.org/10.1001/archinte.164.12.1285] [PMID: 15226161]

[40] Thom DH, Grayston JT, Siscovick DS, Wang SP, Weiss NS, Daling JR. Association of prior infection with Chlamydia pneumoniae and angiographically demonstrated coronary artery disease. JAMA 1992; 268(1): 68-72.

[http://dx.doi.org/10.1001/jama.1992.03490010070032] [PMID: 1608116]

[41] Zhu J, Shearer GM, Norman JE, *et al.* Host response to cytomegalovirus infection as a determinant of susceptibility to coronary artery disease: Sex-based differences in inflammation and type of immune response. Circulation 2000; 102(20): 2491-6. [http://dx.doi.org/10.1161/01.CIR.102.20.2491] [PMID: 11076822]

[42] de Boer OJ, van der Wal AC, Becker AE. Atherosclerosis, inflammation, and infection. J Pathol 2000; 190(3): 237-43. [http://dx.doi.org/10.1002/(SICI)1096-9896(200002)190:3<237::AID-PATH541>3.0.CO;2-N] [PMID: 10685058]

[43] Rosenfeld ME, Campbell LA. Pathogens and atherosclerosis: Update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. J Thromb Haemost 2011; 106(5): 858-67. [PMID: 22012133]

[44] Ji YN, An L, Zhan P, Chen XH. Cytomegalovirus infection and coronary heart disease risk: A meta-analysis. Mol Biol Rep 2012; 39(6): 6537-46. [http://dx.doi.org/10.1007/s11033-012-1482-6] [PMID: 22311014]

[45] Jackson LA, Campbell LA, Kuo CC, Rodriguez DI, Lee A, Grayston JT. Isolation of Chlamydia pneumoniae from a carotid endarterectomy specimen. J Infect Dis 1997; 176(1): 292-5. [http://dx.doi.org/10.1086/517270] [PMID: 9207386]

[46] Kuo CC, Grayston JT, Campbell LA, Goo YA, Wissler RW, Benditt EP. Chlamydia pneumoniae (TWAR) in coronary arteries of young adults (15-34 years old). Proc Natl Acad Sci 1995; 92(15): 6911-4. [http://dx.doi.org/10.1073/pnas.92.15.6911] [PMID: 7624342]

[47] Hu H, Pierce GN, Zhong G. The atherogenic effects of chlamydia are dependent on serum cholesterol and specific to Chlamydia pneumoniae. J Clin Invest 1999; 103(5): 747-53. [http://dx.doi.org/10.1172/JCI4582] [PMID: 10074493]

[48] Moazed TC, Campbell LA, Rosenfeld ME, Grayston JT, Kuo C. Chlamydia pneumoniae infection accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. J Infect Dis 1999; 180(1): 238-41. [http://dx.doi.org/10.1086/314855] [PMID: 10353889]

[49] Laitinen K, Laurila A, Pyhälä L, Leinonen M, Saikku P. Chlamydia pneumoniae infection induces inflammatory changes in the aortas of rabbits. Infect Immun 1997; 65(11): 4832-5. [http://dx.doi.org/10.1128/iai.65.11.4832-4835.1997] [PMID: 9353072]

[50] Muhlestein JB, Anderson JL, Hammond EH, *et al.* Infection with Chlamydia pneumoniae accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model. Circulation 1998; 97(7): 633-6. [http://dx.doi.org/10.1161/01.CIR.97.7.633] [PMID: 9495296]

[51] Raza-Ahmad A, Klassen GA, Murphy DA, *et al.* Evidence of type 2 herpes simplex infection in human coronary arteries at the time of coronary artery bypass surgery. Can J Cardiol 1995; 11(11): 1025-9. [PMID: 8542544]

[52] Patel P, Mendall MA, Khulusi S, *et al.* Salivary antibodies to Hellcobacter pylori: Screening dyspeptic patients before endoscopy. Lancet 1994; 344(8921): 511-2. [http://dx.doi.org/10.1016/S0140-6736(94)91899-6] [PMID: 7802777]

[53] Lo J, Abbara S, Shturman L, *et al.* Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. AIDS 2010; 24(2): 243-53. [http://dx.doi.org/10.1097/QAD.0b013e328333ea9e] [PMID: 19996940]

[54] Paton P, Tabib A, Loire R, Tete R. Coronary artery lesions and human immunodeficiency virus infection. Res Virol 1993; 144(3): 225-31. [http://dx.doi.org/10.1016/S0923-2516(06)80033-6] [PMID: 8356344]

[55] Miyamoto T, Yumoto H, Takahashi Y, Davey M, Gibson FC III, Genco CA. Pathogen-accelerated atherosclerosis occurs early after exposure and can be prevented *via* immunization. Infect Immun 2006; 74(2): 1376-80. [http://dx.doi.org/10.1128/IAI.74.2.1376-1380.2006] [PMID: 16428788]

[56] Koizumi Y, Kurita-Ochiai T, Oguchi S, Yamamoto M. Nasal immunization with Porphyromonas gingivalis outer membrane protein decreases *P. gingivalis*-induced atherosclerosis and inflammation in spontaneously hyperlipidemic mice. Infect Immun 2008; 76(7): 2958-65. [http://dx.doi.org/10.1128/IAI.01572-07] [PMID: 18426881]

[57] Caligiuri G, Khallou-Laschet J, Vandaele M, *et al.* Phosphorylcholine-targeting immunization reduces atherosclerosis. J Am Coll Cardiol 2007; 50(6): 540-6. [http://dx.doi.org/10.1016/j.jacc.2006.11.054] [PMID: 17678738]

[58] Frostegård J. Low level natural antibodies against phosphorylcholine: A novel risk marker and potential mechanism in atherosclerosis and cardiovascular disease. Clin Immunol 2010; 134(1): 47-54. [http://dx.doi.org/10.1016/j.clim.2009.08.013] [PMID: 19748321]

[59] Hessami A, Shamshirian A, Heydari K, *et al.* Cardiovascular diseases burden in COVID-19: Systematic review and meta-analysis. Am J Emerg Med 2021; 46: 382-91. [http://dx.doi.org/10.1016/j.ajem.2020.10.022] [PMID: 33268238]

[60] Pillarisetti J, Cheema MS, Haloot J, *et al.* Cardiac complications of COVID-19: Incidence and outcomes. Indian Heart J 2022; 74(3): 170-7. [http://dx.doi.org/10.1016/j.ihj.2022.04.008] [PMID: 35490848]

[61] Demircan Ş, Tekin A, Tekin G, *et al.* Comparison of carotid intima-media thickness in patients with stable angina pectoris *versus* patients with acute coronary syndrome. Am J Cardiol 2005; 96(5): 643-4. [http://dx.doi.org/10.1016/j.amjcard.2005.04.035] [PMID: 16125486]

[62] Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991; 11(5): 1245-9. [http://dx.doi.org/10.1161/01.ATV.11.5.1245] [PMID: 1911709]

[63] Takashi W, Tsutomu F, Kentaro F. Ultrasonic correlates of common carotid atherosclerosis in patients with coronary artery disease. Angiology 2002; 53(2): 177-83. [http://dx.doi.org/10.1177/000331970205300208] [PMID: 11952108]

[64] Adams MR, Nakagomi A, Keech A, *et al.* Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. Circulation 1995; 92(8): 2127-34. [http://dx.doi.org/10.1161/01.CIR.92.8.2127] [PMID: 7554192]

[65] Sorlie PD, Adam E, Melnick SL, *et al.* Cytomegalovirus/herpesvirus and carotid atherosclerosis: The aric study. J Med Virol 1994; 42(1): 33-7. [http://dx.doi.org/10.1002/jmv.1890420107] [PMID: 8308517]

[66] Chiu B, Viira E, Tucker W, Fong IW. Chlamydia pneumoniae, cytomegalovirus, and herpes simplex virus in atherosclerosis of the carotid artery. Circulation 1997; 96(7): 2144-8. [http://dx.doi.org/10.1161/01.CIR.96.7.2144] [PMID: 9337182]

[67] Doğan Y, Turunç Özdemir A. Assessment of carotid intima-media thickness in COVID-19 survivors. Int J Cardiovasc Acad 2023; 9(1): 16-9. [http://dx.doi.org/10.4274/ijca.57966]