Original article

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The effect of coronavirus disease 2019 pneumonia on myocardial ischemia detected by single-photon emission computed tomography myocardial perfusion imaging

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Objective **We aimed to examine the effects of COVID-19 pneumonia on cardiac ischemia detected by myocardial perfusion imaging with single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) in patients presenting with chest pain and shortness of breath after recovery from COVID-19.**

Materials and method **Patients with a history of COVID-19 confirmed by reverse transcriptase-PCR test who underwent SPECT-MPI for the evaluation of ischemia with the complaints of chest pain and shortness of breath were screened for this study. Patients who underwent thorax CT during the acute period of the COVID-19 were included. Patients with and without pneumonia were determined based on computed tomographic criteria. The patients with a summed stress score of at least 4 on SPECT-MPI were considered to have abnormal MPI in terms of ischemia.**

Results **A total of 266 patients were included in the study. Sixty-five (24%) patients had ischemia findings on SPECT-MPI. Thorax CT showed pneumonia in 152 (57%) patients, and the patients were divided into two groups as pneumonia and nonpneumonia. Abnormal SPECT-MPI scores, which represented myocardial ischemia, were higher in the pneumonia group. Multivariate logistic regression analyses showed that the presence of hyperlipidemia and pneumonia on CT increased the risk of ischemia on SPECT-MPI (OR, 2.08; 95% CI, 1.08–3.99; *P*-value = 0.029; and OR, 2.90; 95% CI, 1.52–5.54; *P*-value = 0.001, respectively).**

Conclusion **COVID-19 pneumonia was identified as an independent predictor of ischemia on SPECT-MPI. Symptoms including chest pain and shortness of breath in patients who have had COVID-19 pneumonia may be attributed to coronary ischemia. *Nucl Med Commun* 43: 756–762**

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Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a significant cause of morbidity and mortality worldwide [1]. Along with the escalating number of cases, concerns about long-term sequelae are also growing in patients recuperating from COVID-19 [2]. Cardiovascular complications including myocarditis, acute coronary syndrome, thromboembolic events, and arrhythmia may develop in the acute period of COVID-19 [3]. Cardiovascular damage may be directly associated with cardiac and endothelial damage by the virus, or it may occur secondary to cytokine storm, hypercoagulability, and hypoxia [4]. Cardiovascular symptoms such as chest pain, shortness of breath, palpitations, and postural orthostatic tachycardia may be observed in patients recovering from COVID-19. The persistence of these complaints for more than 3 months is defined as chronic or prolonged COVID-19 [5]. Maestrini *et al*. [6] found that 47.5% of patients had persistent symptoms, with fatigue (14.2%) being the most common complaint, followed by dyspnea (10.8%), palpitations (4.2%), and chest pain (1.7%) during the 1-year follow-up of patients who recovered from COVID-19. Another study found that symptoms persisted in 77.1% of 96 patients after 1 year of follow-up, and the most common complaints were decreased exercise capacity, fatigue, and shortness of breath, in decreasing order [7].

Coronary microvascular dysfunction (CMD) during COVID-19 may arise due to various causes including renin-angiotensin system (RAAS) dysregulation,

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endothelial damage, and microthrombi [8]. Persistent chest pain after recovery from COVID-19 has been linked to CMD demonstrated using adenosine stress cardiac myocardial MRI [9]. There is inadequate data on the role of myocardial perfusion scintigraphy in evaluating myocardial ischemia in patients who develop pneumonia during COVID-19. In this study, we aimed to examine the correlation between previous COVID-19 pneumonia and myocardial ischemia using single-photon emission computed tomography (CT) myocardial perfusion imaging (SPECT-MPI) in patients presenting with chest pain, shortness of breath, or both after recovery from COVID-19.

Materials and method

Patients who presented to the cardiology outpatient clinic of our hospital with complaints of chest pain, shortness of breath, or both after recovery from acute COVID-19 and underwent SPECT-MPI between 1 January 2021 and 1 November 2021 were screened for this single-center retrospective study. Patients with a history of critical coronary stenosis, previous coronary revascularization, severe valvular diseases, hypertrophic cardiomyopathy, cardiac failure, and those who could not achieve an optimal MPI were excluded. After exclusion, a total of 266 patients were included in the analyses, 152 of whom had COVID-19 pneumonia on thorax CT. Presence of prior COVID-19 infection was confirmed using a reverse transcriptase-PCR test at the time of initial presentation with COVID symptoms. Presence of more than 50% stenosis in any coronary artery in patients who underwent coronary angiography was defined as critical stenosis. Left ventricular ejection fraction (%) was measured by the Simpson method or visual assessment. Patients' demographic characteristics, comorbidities, laboratory parameters, and coronary angiography results were collected from the electronic medical records of the hospital and the national electronic medical registry system.

Myocardial perfusion imaging

The 2-day stress-rest protocol was performed on all patients. The stress protocol was applied as pharmacological stress according to the recommendation of the European Association of Nuclear Medicine within the scope of COVID-19 measures. Before the stress study, all patients were asked to interrupt taking dipyridamole and xanthine derivatives 24 h in advance, and tea and coffee 12 h in advance. A 6-min infusion of adenosine at 140 μg/kg/min was administered to all patients with a technetium-99m-methoxyisobutylisonitrile (Tc-99m) MIBI bolus injection of 11 MBq/kg at the third minute of the infusion [10]. The adverse reactions regressed with the discontinuation of the infusion in patients who experienced side effects, and no patient needed an aminophylline infusion. On the next day, the same dose of Tc-99m MIBI bolus injection was administered for the rest imaging. In order to enhance hepatobiliary clearance, patients were given fatty foods like milk and chocolate 15 min after the radiopharmaceutical injection. In addition, gastric distension was ensured with carbonated drinks. SPECT images were acquired with 60 projections at the 9th–13th seconds in every 3° projection using the Step & Shoot method to have an anterior orbit from a 180° 64 × 64 matrices by scanning the area between the 45° right anterior oblique and 45° left posterior oblique projections in L-mode (angle of 90° between collimators) with a low-energy ultrahigh-resolution collimator in the supine position using the GE Orbita NM 640 SPECT-CT instrument (GE Healthcare, Milwaukee, Wisconsin, USA) 30–45 min after injection for stress images and 45–60 min for rest images. Then, low-dose CT (140 keV, 2.5 mAs) images were acquired from the thorax for attenuation correction.

Evaluation of images

All images were processed using the Myovation Evolution Software (OSEM with 12 iterations, 10 subsets) on the Xeleris 2.0 (Xeleris, GE Healthcare, Haifa, Israel) workstation. Motion artifacts, if any, were corrected with the motion correction program. CT images and myocardial perfusion images were automatically recorrected using filtered back projection and Butterworth filter (0.4 order 10) after the reconstruction of images by manual overlapping. The reconstructed images with QGS/QPS software (Xeleris, Cedars-Sinai Medical Center, Los Angeles, California, USA) were assessed by a consensus of two experienced nuclear medicine specialists without any clinical information other than the sex, height, and weight of the patients. Myocardial perfusion was assessed using the standard 17-segment myocardial modeling, a visual semiquantitative method [11]. Perfusion was evaluated on a 5-point scale in each segment: 0: normal, 1: mildly reduced, 2: moderately reduced, 3: severely reduced, and 4: absent uptake. After scoring all segments, the summed stress score (SSS), which is the sum of all scores from 17 segments, the summed rest score (SRS), and the summed difference score, which was calculated by subtracting the SSS from the SRS and indicates ischemia, were computed for stress and rest images individually. An SSS of at least 4 was considered abnormal perfusion for MPI. The total perfusion deficit (TPD) was calculated based on both the extent and severity of ischemia and a TPD of at least 10% was considered as abnormal myocardium [12].

Acquisition of thorax computed tomography images and technical parameters

All examinations were performed using 16- and 64-channel multislice CT scanners [Emotion 16, Somatom Sensation 64 (Siemens Healthineers, Erlangen, Germany)]. CT scans were performed in the supine position at the end of deep inspiration without administering a contrast agent. A standard dose or low-dose setting was used with automatic dosing control to have a CT acquisition protocol of 120 kV, 80 mA, and a slice thickness of

1 mm. Coronal images were obtained by reconstructing the axial images over a slice thickness of 1.5 mm. Window settings for lung parenchyma (window level 600 HU and window width 1500 HU) and mediastinum (window level 40 HU and window width 350 HU) were selected, and shootings were performed. Thorax CT scans were evaluated for parameters associated with COVID-19 disease in the lung parenchyma including ground glass densities, consolidation, nodular densities, cobblestone appearance, reticulation, subpleural band, interlobular septal thickening, halo and reverse halo signs, enlarged vessel sign at the lesion level, bronchi wall changes, and traction bronchiectasis. Cases with thorax CT findings evaluated in the typical COVID-19 category based on the Expert Consensus Statement of the American College of Radiology and the Radiological Society of North America (RSNA) were considered positive for the radiological findings of COVID-19, whereas those in the atypical category and without infection findings according to the RSNA guidelines were considered negative for the radiological findings of COVID-19 [13]. As per this classification system, cases in the indeterminate group were excluded from the study. The study was approved by the local ethics committee of the institution (approval no: 2022/20). The study protocol is in concordance with the Declaration of Helsinki.

Statistical analysis

The data were analyzed using SPSS-24 (Statistical Package for Social Science for Windows; IBM Corporation, Armonk, New York, USA) package program. Histogram and Shapiro-Wilks tests were used to verify the normality of data. Continuous variables were presented as a median and interquartile range (IQR) (25–75%) owing to their nonnormal distribution. Categorical variables were expressed as percentages. Continuous variables were compared using Mann–Whitney U test, whereas categorical variables were compared using the Chi-square test or Fisher's exact test. We selected predictive candidate variables that have known or plausible associations with ischemia in SPECT-MPI. These variables (age, sex, hypertension, diabetes, hyperlipidemia, smoking, white blood cell count, creatinine, hemoglobin, C-reactive protein, and pneumonia in thorax CT) were used in regression analyses. Univariable and multivariable logistic regression analyses were performed to determine the predictors of ischemia in SPECT-MPI. Variables with a *P*-value of <0.200 in univariable analyses were included in the model for multivariable analysis. A *P*-value of <0.05 was considered statistically significant in all statistical analyses.

Results

A total of 266 patients were included in the study. The median age in the study group was 57 years (IQR, 50–64 years), and 79 (30%) were male. All patients were symptomatic during the acute COVID-19 period and underwent thorax CT. CT revealed COVID-19 pneumonia in 152 (57%) of the patients. Patients were divided into two groups: pneumonia and nonpneumonia. The time from COVID-19 diagnosis to MPI was 154 days (IQR, 81–224). Among these patients, 65 (24%) had ischemia findings on SPECT-MPI (Fig. 1). Coronary angiography was performed in 54 patients, and 11 had at least 50% stenosis (Fig. 2).

There was no statistically significant difference between the groups in terms of age, sex, diabetes, hypertension, hyperlipidemia, and smoking. The SSS and abnormal SPECT-MPI scores in terms of ischemia were higher in the pneumonia group (*P*-values were 0.002 and 0.017, respectively). Demographic, clinical, and laboratory characteristics of the study population are presented in Table 1.

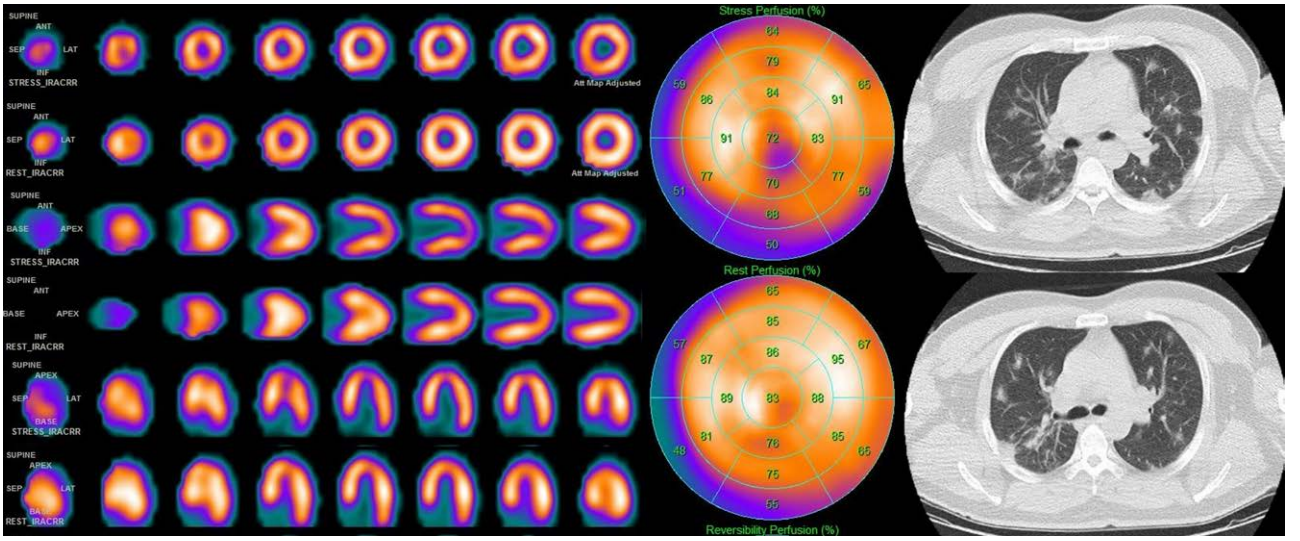
Pneumonia and hyperlipidemia were found to be predictors of ischemia in the univariable logistic regression analysis ($P = 0.012$ and $P = 0.002$, respectively). In the multivariate logistic regression analysis performed with parameters with a *P*-value of <0.200 in the univariant analysis, it was observed that the presence of hyperlipidemia and pneumonia significantly increased the risk of ischemia in SPECT-MPI [odds ratio (OR), 2.08; 95% confidence interval (CI), 1.08–3.99; *P*-value = 0.029, and OR, 2.90; 95% CI, 1.52–5.54; *P*-value = 0.001, respectively] (Table 2).

Discussion

To the best of our knowledge, this is the first study assessing the impact of COVID-19 pneumonia (detected by thorax CT) on myocardial ischemia (detected by SPECT-MPI) in patients with a history of COVID-19 and presented with chest pain, shortness of breath, or both after recovery. In our study, abnormal SPECT-MPI scores were higher in the pneumonia group, reflecting higher rate of ischemia. Furthermore, multivariate logistic regression analysis revealed that the presence of pneumonia and hyperlipidemia augmented the risk of ischemia on SPECT-MPI.

COVID-19, which remains a significant cause of morbidity and mortality around the world, has been found to cause cardiovascular effects in the acute period of the disease as well as an increase in the risk of cardiovascular events in the postacute period. A study showed that the risk of developing myocardial infarction, stroke, heart failure, and arrhythmia increased three-fold in patients recovering from the disease [14]. SARS-CoV-2 can directly cause infection by binding to the transmembrane angiotensin-converting enzyme 2 (ACE2) receptor on the surface of vascular endothelial cells. Therefore, it may result in both endothelial dysfunction and myocardial inflammation/infarction due to atherosclerotic plaque instability and increased vascular inflammation

Fig. 1



Myocardial perfusion scintigraphy performed for evaluating chest pain in a 39-years-old male patient with a recent history of COVID-19 showed findings consistent with ischemia in the apical and mid-sections of the anterior wall and the apical inferior wall. Coronary angiography showed no narrowing of the coronary arteries. Bilateral diffuse ground glass opacities, consistent with COVID-19 pneumonia, were observed on the thorax CT of the patient performed in the acute disease period. CT, computed tomography; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

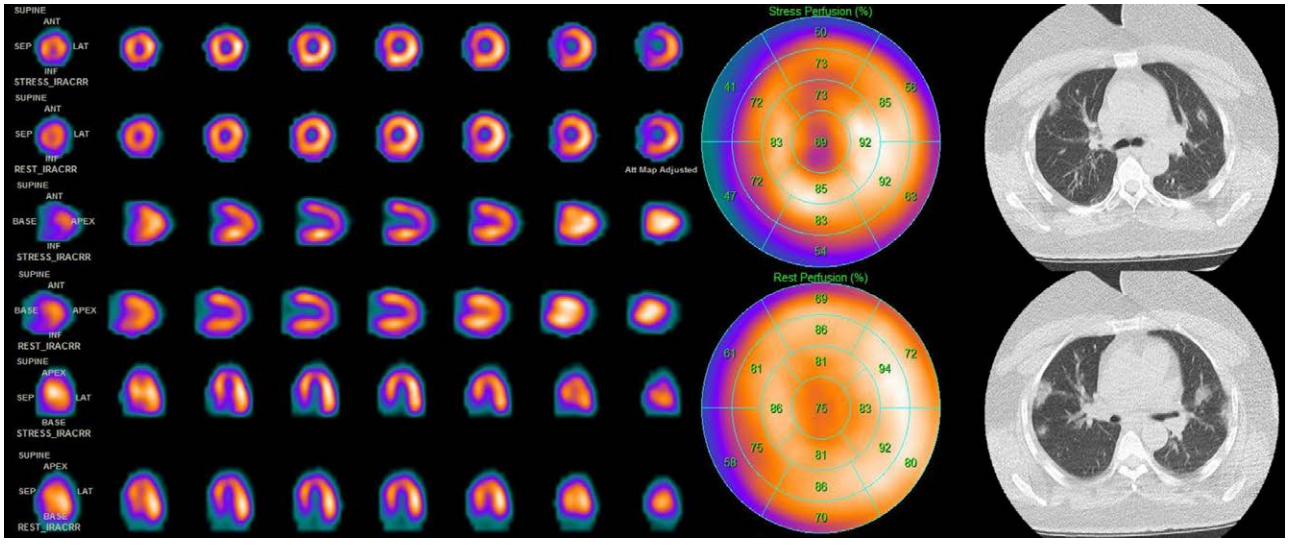


Fig. 2

A 55-year-old female patient with a history of COVID pneumonia 9 months ago was evaluated by myocardial perfusion scintigraphy for chest pain. In MPI images, ischemia was observed in the apex, mid and apical sections of the anterior wall. In coronary angiography, 50% stenosis was observed in the proximal LAD. No stenosis was observed in RCA and LCX. Bilateral diffuse ground glass opacities, consistent with COVID-19 pneumonia, were observed on the thorax CT of the patient performed in the acute disease period. CT, computed tomography.

and microthrombi [15,16]. In addition to direct endothelial damage, it leads to CMD and further worsens the endothelial damage because of an exaggerated autoimmune response and excessively released proinflammatory cytokines [17]. Indeed, circulating biomarkers showing endothelial dysfunction and damage have been demonstrated to increase in COVID-19 in correlation with the severity of the disease [18,19]. Under normal conditions, in cases of inflammation, there is endothelium-dependent dilation and constriction of coronary

Table 1 Demographic characteristics and clinical and laboratory findings of the patients

Variables	Total ($n = 266$)	Pneumonia ($n = 152$)	Nonpneumonia ($n = 114$)	*P*-value
Age, (years)	57 (50–64)	58 (50–66)	55 (50–63)	0.084
Male sex, *n* (%)	79 (30)	42 (28)	37 (32)	0.394
Hypertension, *n* (%)	137 (52)	84 (55)	53 (46)	0.157
Abnormal MPS, *n* (%)	65 (24)	48 (32)	17 (15)	**0.002**
Total perfusion defect, *n* (%)	33 (12)	23 (15)	10 (9)	0.165
SSS	0 (0–3)	0 (0–4)	0 (0–1)	**0.017**
Time fromCOVID-19diagnosis to SPECT-MPI (day)	154 (81–224)	162 (85–230)	148 (80–210)	0.172
Diabetes, *n* (%)	80 (30)	50 (33)	30 (26)	0.247
Smoking, *n* (%)	65 (24)	37 (24)	28 (25)	0.984
Hyperlipidemia, *n* (%)	63 (24)	36 (24)	27 (24)	0.995
Ejection fraction (%)	60 (60–61)	60 (60–61)	60 (60–62)	0.322
Creatinine, mg/dl	0.77(0.68–0.90)	0.78(0.69–0.91)	0.76 (0.68–0.89)	0.716
Total cholesterol, mg/dl	190 (170–221)	189 (165–219)	197 (175–221)	0.244
HDL-cholesterol, mg/dl	45 (38–54)	44 (37–54)	46 (39–55)	0.370
LDL-cholesterol, mg/dl	112 (91–133)	111 (89–130)	116 (95–137)	0.184
Triglyceride, mg/dl	170 (124–228)	180 (137–228)	155 (105–226)	0.056
Hemoglobin, g/dl	13.5(12.5–14.7)	13.4(12.5–14.8)	13.7 (12.5–14.7)	0502
White blood cell count, 10^3/µl	7.71 (6.56–9.00)	7.80 (6.62–8.90)	7.65 (6.51–9.10)	0.819
Platelet, count, 10^3/µl	271 (217–317)	273 (224–315)	271 (217–317)	0.365
CRP, mg/dl	2 (2–6)	3 (2–7)	2 (2–5)	0.330

Bold characters used to indicate statistical significance.
Continuous variables are presented given as median (interquartile range) and categorical variables were expressed as number.
CRP, C-reactive protein; MPS, myocardial perfusion scintigraphy; SPECT-MPI, single-photon emission computed tomography myocardial perfusion imaging; SSS, summed stress score.

Table 2 Univariable and multivariable logistic regression analyses for determining the predictors of ischemia in single-photon emission computed tomography myocardial perfusion imaging

	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)	0.99	0.96–1.01	0.364	ND	ND	ND
Sex (male)	1.18	0.64–2.15	0.597	ND	ND	ND
Hypertension	0.82	0.47–1.43	0.480	ND	ND	ND
Diabetes	1.66	0.92–2.99	0.092	1.70	0.89–3.24	0.109
Hyperlipidemia	2.20	1.19–4.08	0.012	2.08	1.08–3.99	0.029
Smoking	1.68	0.91–3.12	0.100	1.94	0.97–3.86	0.060
Creatinine (mg/dl)	0.98	0.90–1.06	0.565	ND	ND	ND
White blood cell (10^3/µl)	1.11	0.97–1.28	0.140	1.11	0.96–1.29	0.175
CRP (mg/l)	1.01	0.96–1.07	0.641	ND	ND	ND
Hemoglobin (g/dl)	1.00	0.84–1.19	0.984	ND	ND	ND
Pneumonia	2.63	1.42–4.89	0.002	2.90	1.52–5.54	0.001

CI, confidence interval; CRP, C-reactive protein, ND, no data; OR, odds ratio.

arterioles per myocardial oxygen supply and demand. The coronary microvascular circulatory disorder may arise due to excessive cytokine release, thrombotic microvascular obstruction, and disruption of signaling pathways in smooth muscle cells and endothelium [20]. However, RAAS dysregulation, which contributes to the pathophysiology of CMD, acts by reducing the conversion of angiotensin II (AII) to angiotensin 1–7, with the SARS-CoV-2 virus downregulating ACE2 activity in myocardial and endothelial cells. This reduced activity increases the dominance of the RAAS pathway caused by AII activation, resulting in vasoconstriction, fibrosis, hypertrophy, and the release of reactive oxygen radicals [21]. These pathophysiological changes in the acute period of COVID-19 may have long-term implications for coronary microvascular circulation, even if active inflammation resolves. As autoregulation and modulation of coronary blood flow are impaired in response to different stimuli (such as physical exercise) in CMD, exertional dyspnea and chest pain may be observed [22]. Studies have found that symptoms such as shortness of breath, chest pain, and fatigue may occur after recovery from COVID-19 [23]. A meta-analysis evaluating the cardiac sequelae of 52 906 patients, in which the median time from diagnosis to recovery from COVID-19 was 48 days, showed that 25% of the patients experienced chest pain, 36% had shortness of breath, 15% had pericardial effusion, 40% had diastolic dysfunction on echocardiography, and 10% had late gadolinium enhancement on cardiac MRI [24]. These studies demonstrate that patients recovering from COVID-19 may develop cardiovascular symptoms at a significant rate, even after a long time.

SPECT-MPI is the basic imaging method for coronary ischemia and risk assessment. In an invasive study of CMD by Djaïleb *et al.* [25], it was observed that SPECT-MPI ischemia could be employed as a prognostic factor for microvascular dysfunction and serious cardiac events

in patients without obstructive coronary artery disease. A post-COVID study concluded that persistent chest pain might be due to microvascular dysfunction on adenosine stress cardiac MRI examination [9]. Rovas *et al.* [18] evaluated patients with dyspnea and post-COVID fatigue syndrome following recovery from COVID-19 and found that the myocardial perfusion reserve was significantly lower on cardiac MRI in the COVID group compared with healthy controls. In our study, the rate of abnormal MPI was significantly higher in the pneumonia group (32%), and we found that the presence of pneumonia in acute period of COVID-19 is a predictor of ischemia on SPECT-MPI. The severity of pneumonia in COVID-19 patients has been found to be associated with cytokine storm, and a higher rate of inflammatory cytokines (IL-1β, IL-6, and IL-8), macrophages, and neutrophils were detected in the bronchoalveolar lavage fluids of patients with severe symptoms than those with mild symptoms [26,27]. Given all these pathophysiological mechanisms, we believe that the presence of pneumonia during the acute period of COVID-19 produces a greater inflammatory response and, therefore, leads to CMD via vascular endothelial damage. This may cause the rates of ischemia on SPECT-MPI to be higher in the pneumonia group.

Chest pain and shortness of breath can be observed in the postacute period of patients with a history of COVID-19. These complaints may be more common in patients with pneumonia, and coronary ischemia may be due to CMD resulting from COVID-19 pneumonia in cases with non-critical epicardial coronary arteries and ischemia detected on SPECT-MPI.

Limitations

One of the most important limitations of this study is that it is a retrospective study with a relatively small number of patients. Another limitation is that family history, which is one of the most important risk factors for coronary ischemia, cannot be included in the regression analysis because the related data was not available for all patients. Also, we could not conduct an invasive assessment of microvascular dysfunction because of the retrospective nature of the study and difficulties in invasive assessment.

Conclusion

In our study, COVID-19 pneumonia was identified as an independent predictor of ischemia on SPECT-MPI. Therefore, symptoms including chest pain and shortness of breath in patients who have had COVID-19 pneumonia may be attributed to coronary ischemia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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