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Original Scientific Paper

EVALUATION OF PATIENTS WITH COVID-19 IN THE EARLY HYPOXEMIC STAGE AND PATIENTS WITH VIRAL RESPIRATORY TRACT INFECTION IN TERMS OF PULMONARY HYPERTENSION

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SUMMARY – Arterial hypoxemia occurs in many COVID-19 patients. Hypoxemia is one of the causes of pulmonary hypertension (PH). Main pulmonary artery dilatation and the main pulmonary artery diameter (mPAD) to ascending aorta diameter (AAD) ratio of ≥1 are significant findings regarding PH. In this study, COVID-19 patients and non-COVID-19 patients with viral respiratory tract infection were evaluated retrospectively in terms of PH. A total of 124 patients (71 male and 53 female), age range 18-85 years, were included in the study as case group and control group. Thoracic computed tomography (CT) images, blood and biochemical parameters, and demographic information were compared between the case group and control group. The normality of numerical variables was examined with Kolmogorov-Smirnov test and homogeneity of the variances with Levene's test. This is the first study researching the effect of early hypoxemic stage COVID-19 infection on development of PH. As a result, it was specified that COVID-19 infection had no effects on mPAD, whereas it had a positive effect on AAD and thus led to a decrease in the mPAD/AAD ratio. Through these values, which could be easily calculated from thoracic CT images, the changes caused by COVID-19 infection on vessel diameters were put forward.

Key words: *Ascending aorta; COVID-19; Pulmonary hypertension; Main pulmonary artery*

Introduction

The COVID-19 infection, which emerged in China in December 2019, spread in a short time and influenced the whole world. The coronavirus infection appears with common symptoms such as fever, cough, muscle pain and fatigue, and less commonly headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. Ground-glass opacity is observed in thoracic computed tomography (CT) images of patients with lung involvement depending on the course of the disease. While the vast majority of patients recover within 1-2 weeks, the disease may progress more severely in serious cases with respiratory distress or shortness of breath, and even result in death[1]. Even though many patients who present to hospitals with suspicion of coronavirus have apparent arterial hypoxemia, some patients may not be a notable respiratory problem. This condition, which emerges in those who caught

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the disease, is called 'silent hypoxemia' or 'happy hypoxemia'[2]. In the early hypoxemic stage, patients may have low oxygen levels without shortness of breath and without the use of accessory respiratory muscles[3]. Pulmonary hypertension (PH) is a pathophysiological disorder which can involve multiple clinical conditions and complicate most of the cardiovascular and respiratory diseases[4]. The prognosis of PH is poor; if PH is not detected and treated at an early stage, it may lead to progressive right ventricular failure along with a high mortality rate[5,6]. Vasoconstriction of pulmonary arteries is a significant factor in the pathogenesis of PH[7]. Clinically, PH is classified as PH associated with hypoxemia, pulmonary venous hypertension, chronic thromboembolic disease, pulmonary arterial hypertension, and PH shaped by the disorders directly affecting pulmonary vessels[8]. There are various methods to evaluate patients with suspected PH. Determination and evaluation of the increase in the diameter of main pulmonary artery are significant in the diagnosis of PH[9]. The ratio of the main pulmonary artery diameter (mPAD) to the ascending aorta diameter (AAD) is used in the diagnosis of PH[10].

In this study, it was aimed to retrospectively compare COVID-19 patients in the early hypoxemic stage with patients with viral respiratory tract infections and non-COVID-19 patients admitted to the hospital at least 2 years before the coronavirus pandemic (2018 and before) in terms of PH.

Subjects and Methods

A total of 124 patients (71 males and 53 females), age range 18-85 years, were included in the study as case group and control group. The case group included 62 patients (35 male and 27 female) in the early hypoxemic stage with positive COVID-19 polymerase chain reaction test result, and control group consisted of 62 non-COVID-19 patients (36 male and 26 female) with viral respiratory tract infection who had presented to our hospital at least 2 years before the coronavirus pandemic (2018 and before). First of all, white blood cell count (WBC), hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), platelet (PLT), neutrophil, lymphocyte, urea, creatine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP) and oxygen saturation (SpO_2) values of all patients in both groups were collected. Blood and biochemical parameters, demographic patient information, and thoracic CT images were obtained from hospital records. Ethical approval for the study was obtained from the Ethics Committee of Niğde Ömer Halisdemir University, decision number 05/07 dated June 1, 2020.

Measurement of CT parameters

The Somatom Sensation 64 Siemens Medical Solutions (Siemens, Erlangen, Germany) machine was used for thoracic CT examination. The parameters used in thoracic CT examination were set at 5-mm slice thickness, 3-mm gap, 120 kV and 130 mAs, 0.5 s gantry rotation time. All the shots were carried out while the patient was lying in supine position, after taking a plan view from the lung apices to the diaphragm, by holding breath in deep inspiration, and without giving any intravenous contrast material. The images transferred to the workstation were evaluated by a radiologist in the Picture Archiving and Communication Systems (PACS) system, and the necessary measurements were performed. The mPAD, AAD and mPAD/AAD values were calculated from the CT images obtained (Fig. 1).

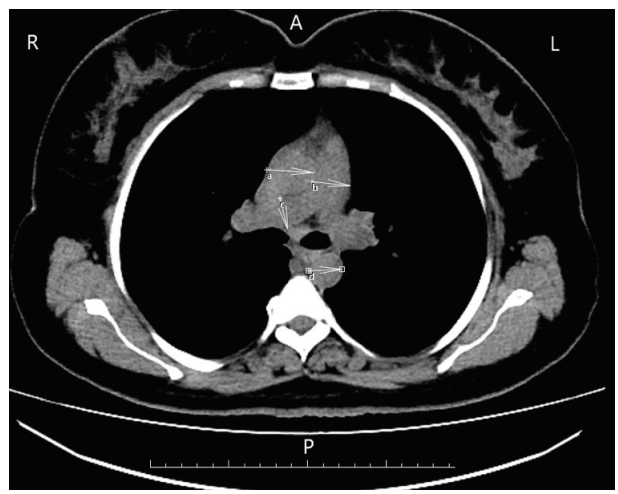

Fig. 1. Computed tomography image: (a) ascending aorta; (b) main pulmonary artery; (c) pulmonary artery; (d) descending aorta; A = anterior; P = posterior; R = right; L = left.

Statistical analysis

Statistical analyses were executed using SPSS 23.0 package software. Descriptive table of the data set was first demonstrated in the analysis. Numerical variables were summarized as mean ± standard deviation (SD), and median (minimum(min)-maximum(max)) values. Categorical variables were shown with numbers and percentages. The normality of numerical variables was

examined with the Kolmogorov-Smirnov test and the homogeneity of variances with Levene's test. Numerical variables between the two groups were examined by the t-test. The effect of COVID-19 on mPAD, AAD and mPAD/AAD variables was identified when age and gender were checked by using the most recent multiple linear regression analysis. The level of significance was set at $p<0.05$.

Results

There were 62 patients in the case group and 62 patients in the control group. As shown in Table 1, the mPAD and mPAD/AAD variables were observed to be slightly lower in the COVID-19 group. On the other hand, the AAD variable was lower in the control group. Still, gender and mean age of the patients in the COVID-19 and control groups were quite close to each other.

The mean age was 54.52±2.10 years in the case group and 55.24±2.08 years in the control group (Table 2). Considering p values (0.806 and 0.857), there was no significant difference between the COVID-19 and control groups according to age and gender. Even though the mPAD, AAD and mPAD/AAD values of COVID-19 patients differed from those in the control

Table 1. Descriptive table of COVID-19 patients and control patients

COVID-19 group					
	N	Mean	SD	Min	Max
mPAD (mm)	62	26.27	4.18	19.1	42.3
AAD (mm)	62	33.59	5.78	20.17	46.26
mPAD/AAD	62	0.79	0.12	0.55	1.09
Age (years)	62	54.52	16.56	18	84
Control group					
	N	Mean	SD	Min	Max
mPAD (mm)	62	26.67	4.41	19.33	41.38
AAD (mm)	62	32.22	4.21	24.17	42.62
mPAD/AAD	62	0.84	0.14	0.61	1.26
Age (years)	62	55.24	16.39	18	85

SD = standard deviation; mPAD = main pulmonary artery diameter; AAD = ascending aorta diameter

Table 2. Age and gender comparison of COVID-19 patients and control patients

	COVID-19 group	Control group	p
Age (years)	54.52±2.10	55.24±2.08	0.806
Female, n (%)	27 (43.55%)	26 (41.94%)	0.857
Male, n (%)	35 (56.45%)	36 (58.06%)	

Table 3. Comparison of two groups according to mPAD, AAD and mPAD/ADD

	COVID-19 group	Control group	Difference	p
SpO_2 (%) mPAD (mm)	93.44±2.64 26.27±0.53	94.84±2.22 26.67±0.55	-1.4 -0.399	0.002* 0.606
AAD (mm)	33.59±0.73	32.22±0.53	1.372	0.133
mPAD/ADD	0.79±0.016	0.84±0.01	-0.041	0.095

*Statistical significance set at the level of $p<0.05$; SpO_2 = oxygen saturation; mPAD = main pulmonary artery diameter; AAD = ascending aorta diameter

group, this difference did not depend on the age or gender variables (Table 2).

The mPAD/AAD values of the COVID-19 patients were lower than those in the control group, and the difference between them was statistically significant at the level of p=0.1, but not significant at the level of p=0.05. In other variables (mPAD and AAD), no statistically significant difference was detected. When we look at the SpO_2 parameter, the difference between the case and control groups was found to be statistically significant (p=0.002) (Table 3).

In Table 4, no effects of the COVID-19 infection were observed on the mPAD variable. However, it seems to have a positive effect on the AAD variable. In other words, the AAD value of COVID-19 patients was by 1.533 mm higher than in control group, which is statistically significant at the level of 0.05. In the last column, it is seen that the mPAD/AAD values of

Table 4. Multiple linear regression analysis between the groups

	mPAD	AAD	mPAD/AAD
COVID-19 group	-0.313	1.533**	-0.042*
p	(0.666)	(0.035)	(0.079)
Age	0.094***	0.191***	-0.0019**
p	(0.000)	(0.000)	(0.011)
Gender	1.073	1.346*	-0.0027
p	(0.149)	(0.069)	(0.909)
Invariant	20.832***	20.873***	0.941***
p	(0.000)	(0.000)	(0.000)
N	124	124	124
R-square	0.1365	0.3949	0.075

*, ** and *** indicate statistical significance at the levels of 0.1, 0.05 and 0.01, respectively; mPAD = main pulmonary artery diameter; AAD = ascending aorta diameter

Table 5. Comparison of blood and biochemical values between two groups

	COVID-19 group	Control group	Difference	p
WBC	6.92	9.45	-2.530***	<0.001
HB	13.38	13.79	-0.409	0.323
HCT	40.79	41.68	-0.891	0.429
MCV	86.99	87.26	-0.274	0.816
PLT	253.64	239.15	14.486	0.432
NE	4.68	6.67	-1.981***	0.005
LYM	1.59	2.77	-1.173*	0.076
Urea	29.76	38.85	-9.087**	0.019
Creatine	0.91	0.97	-0.049	0.732
AST	26.67	39.20	-12.535	0.188
ALT	28.07	33.11	-5.040	0.515
CRP	38.61	28.86	9.807	0.348

*,** and *** indicate statistical significance at the levels of 0.1, 0.05 and 0.01, respectively; WBC = white blood cell; HB = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; PLT = platelet; NE = neutrophil; LYM = lymphocyte; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein

COVID-19 patients were 0.042 lower than in control group patients. It was observed that the gender variable did not have a strong effect on the mPAD, AAD and mPAD/AAD variables, but had a positive effect only on AAD, and this was statistically significant at the level of 0.1. Regardless of the COVID-19 infection, the AAD values of men were by 1,346 mm higher than those of women. Considering the age variable, it is seen that age had a positive effect on mPAD and AAD. That is, as age increases, mPAD and AAD values also increase.

In the table, it is seen that COVID-19 patients had lower values than patients in the control group in terms of WBC, Neutrophil (NE), Urea and Lymphocyte (LYM) parameters. When we look at the p values statistically, it was revealed that WBC and NE were statistically significant at 0.01, the Urea value at 0.05 and the LYM value at 0.1 (Table 5).

Discussion

In this retrospective study, we investigated whether there was a difference between the two groups in terms of development of PH using thoracic CT examinations in patients with COVID-19 at the early hypoxemic stage and non-COVID-19 patients with viral respiratory tract infection. Patients were divided in two groups with similar age and gender distribution. This is the first study researching the effect of the early hypoxemic stage COVID-19 infection on the development of PH. In the light of the results of the study, it was found that the COVID-19 infection had no effects on the mPAD value, whereas it had a positive effect on the AAD value and thus led to a decrease in the mPAD/AAD ratio.

In the initial period of the COVID-19 infection, areas with ground-glass density were observed in lung parenchyma in bilateral and multilobar localization, in peripheral lung areas or in the connected areas, frequently involving the middle and lower lobes on thoracic CT[11,12]. Particularly in elderly patients, it was observed that consolidation accompanied the areas with ground-glass density[13,14]. As the disease progressed, the crazy paving pattern emerged with the addition of thickening in interlobular septal structures to the areas with ground-glass density[12,13]. Moreover, bronchiectasis and pleural thickening were the findings observed in later stage of the disease. Pleural effusion, lymphadenopathy, cavitation, halo sign and pneumothorax were rare signs that indicated progression[11,12]. It should be remembered that the findings observed on thoracic CT in the COVID-19 infection have bilateral, peripheral and basal localization, and are nonspecific findings such as atypical pneumonia or organized pneumonia, and they may be observed in other viral pneumonias[12,13].

An abnormal increase in pressure in pulmonary circulation is defined as PH[4,7]. In this case, the mean pulmonary artery pressure is higher than 25 mm Hg, and pulmonary capillary wedge pressure is 18 mm Hg and above. The mean pulmonary artery pressure can be determined by inserting a catheter or noninvasively *via* echocardiography[4]. Clinically, the term "pulmonary hypertension" is used to include both pulmonary arterial and pulmonary venous hypertension. The prognosis of PH is poor; if not detected and treated at an early stage, it can cause progressive right ventricular failure and result in mortality[4,7].

In thoracic CT examination, mediastinal window, and evaluation of the mediastinal main vascular structures, detection of dilatation in the mPAD (mPAD greater than 29 mm), the mPAD/AAD ratio ≥1, and presence of calcification in pulmonary arteries, especially in chronic patients, are important findings in respect of PH[6,15-20]. In thoracic CT examination of the lung parenchyma, an apparent increase in the diameter of the central pulmonary arteries adjacent to the central bronchi, a decrease and interruption in the diameter of pulmonary arteries as the peripheral parts of the lung are reached, and presence of mosaic perfusion are important findings in terms of PH[4,15]. The term 'mosaic perfusion' refers to peripherally located air trapping areas with low attenuation and presence of hyperattenuation areas adjacent to these areas. The increase in the diameter of peripheral pulmonary arteries in the hyperattenuated areas and sudden interruption in hypoattenuated areas are the characteristics of mosaic perfusion[4,15,16].

Among the patients included in our study, mPAD was found to be bigger than 29 mm in 15 patients in the case group and 14 patients in the control group (Table 1). Furthermore, the mPAD/AAD ratio was found to be ≥1 in 6 patients in the case group and 15 patients in the control group (Table 1). No calcification was observed in the main pulmonary artery in any patient included in our study. In the examination of the lung parenchyma in both case and control groups, there were no findings that might indicate PH.

Apart from thoracic CT, cardiac CT, Cine cardiac magnetic resonance imaging (MRI) in which ventricular volumes are evaluated, late contrast MRI obtained 10 minutes after the injection of the intravenous contrast agent are also used radiologically to diagnose PH but they were kept out of the scope of the study owing to the nature of COVID-19 infection, emergency conditions, and the retrospective nature of the study[4,6,15]. One of the causes of PH is hypoxemia[4,15,16]. Some patients have arterial hypoxemia in the early stage of the COVID-19 infection but there may not be a significant respiratory problem; this condition is called 'silent hypoxemia' or 'happy hypoxemia'[7,17,20]. Even though there is increasing knowledge about the epidemiology, pathogenicity and clinical characteristics of the COVID-19 infection during the pandemic period, information on the PH pathophysiology is relatively limited. This limitation may be linked with the wide variety in the PH etiology[4,15]. In our case group consisting of patients infected with COVID-19, the mPAD value higher than 29 mm and mPAD/AAD ratio of ≥1 were expected, which would be consistent with PH but the COVID-19 infection did not have any effect on the mPAD value, whereas it was observed that it had a positive effect on the AAD value and therefore caused a decrease in the mPAD/AAD ratio. Besides, although we did not detect it in our patient group, tachycardia identified in patients infected with COVID-19 may cause an increase in AAD in the long run[21,22].

In relation to the physiological characteristics of the lung, host factors and pathogen microorganism density, it was relatively well preserved in the early stages of the COVID-19 infection[17,23]. There was no increase in airway resistance or dead space ventilation, especially since fibrosis did not develop in the lung in this period[2,17]. However, sudden and rapid respiratory decompensation may occur in later stages of the disease, particularly in patients who develop acute respiratory distress syndrome (ARDS). In this case, mechanical ventilation support and patient evaluation under intensive care conditions may be taken into consideration[2,24,25]. In our study, we assume that PH, which is explained by the mPAD value higher than 29 mm and mPAD/AAD ratio of ≥1, had not yet occurred since thorax CT examinations of patients diagnosed with COVID-19 were carried out in the happy hypoxemic period of the disease. The mean SpO_2 value was measured as 93.44 in the case group, and this value was statistically significantly lower when compared with 94.84 which was recorded in our control group. This result shows that SpO_2 started to drop in COVID-19 patients in the happy hypoxemic period. However, the value of 93.44 confirms the happy hypoxemic period, as the clinical effects of hypoxemia were not observed, and the patient did not complain of this situation[2].

None of the patients included in our study needed mechanical ventilation and none was evaluated in intensive care conditions. Additionally, none of the patients included in our study died due to the COVID-19 infection.

With aging, there is an increase in both mPAD and AAD values, but the increase in the AAD value is more prominent. Accordingly, the mPAD/AAD ratio drops with aging[18,26]. Similarly, in our study, an increase in the mPAD and AAD values and a decrease in the mPAD/AAD ratio were detected with aging (Table 4). The mPAD and AAD values were higher in men than in women; however, the mPAD/AAD ratio was found to be higher in women than in men. In our study, it was revealed that gender had no effects on the mPAD value and mPAD/AAD ratio. However, in our study, it was found that the AAD value was higher in men, which is consistent with the literature (Tables 2 and 4).

Lymphopenia is observed in 40%-91.6% of COVID-19 patients and can be used as a prognostic factor for COVID-19 infection[27]. However, we did not detect lymphopenia in the patients included in our study. We think that this may have been due to the fact that the lymphocyte levels of patients included in our study group were checked at the time of admission to the emergency department, that is, at the early hypoxemic stage.

Although neutrophil and leukocyte values are found to be normal in COVID-19 patients in the early hypoxemic stage, an increase in these values can be observed especially in advanced COVID-19 patients with ARDS[1,23,26]. In our study, these parameters were found to be lower in the case group compared to the control group. The patients in our control group did not have COVID-19 infection and presented to the emergency department with different respiratory symptoms. We think that the low levels of neutrophils and leukocytes in our case group may have been due to the fact that they were examined in the early hypoxemic stage on presentation to the emergency department. This suggests that there may not be an increase

in the levels of these parameters in COVID-19 patients in the early hypoxemic phase.

The limitations of our study were that the control group consisted of patients who had presented to Niğde Ömer Halisdemir Training and Research Hospital in 2018 and before with various respiratory system complaints. Moreover, the fact that CT examination was performed in isolated conditions and in limited periods for patients infected with COVID-19 under pandemic conditions limited performance of different CT examination methods such as cardiac CT and high-resolution CT. In the patients included in the study, it was preferred not to use contrast material during the examination because the nephrotoxic effect could not always be determined quickly and completely in emergency conditions, and it increased the costs and contact rate between the patient and the healthcare personnel. It was attempted to overcome this limitation *via* evaluation of all thoracic CTs by the same radiologist. Despite some limitations, our study has contributed to the current literature since it aimed to detect changes in the mediastinal vascular structures that might be significant in terms of PH at an early stage in patients infected with COVID-19.

Conclusion

In conclusion, mPAD and AAD values and mPAD/AAD ratios of the patients infected with COVID-19 were compared with the control group in our study. Through these values, which could be easily calculated from thoracic CT images, the changes caused by COVID-19 infection on the vessels were put forward. In this way, it was tried to determine the possible effect of COVID-19 infection on the pathophysiology of PH. PH is not frequently encountered in patients in the early hypoxemic period in the early stage of COVID-19 infection, probably because pulmonary vasoconstriction and sufficient intrapulmonary shunts do not develop. There is a need for new studies with a higher number of cases, including early and late stage diagnosis and follow-up stages in which pulmonary artery pressure measurements can be performed, and cardiac echocardiography, cardiac CT and cardiac MRI examinations are also carried out.

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Sažetak

PROCJENA STANJA BOLESNIKA S COVID-19 U RANOJ FAZI HIPOKSEMIJE I BOLESNIKA S VIRUSNOM INFEKCIJOM DIŠNIH PUTOVA U PLUĆNOJ HIPERTENZIJI

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Arterijska hipoksemija javlja se u mnogih bolesnika oboljelih od COVID-19. Hipoksemija je jedan od uzroka plućne hipertenzije. Dilatacija glavne plućne arterije i omjer promjera glavne plućne arterije (mPAD) i promjera uzlazne aorte (AAD) od ≥1 značajni su nalazi u pogledu plućne hipertenzije. U ovoj studiji bolesnici s COVID-19 i osobe koje nisu oboljele od COVID-19, ali s virusnom infekcijom respiracijskog trakta procijenjeni su retrospektivno u smislu plućne hipertenzije. U istraživanje su uključene ukupno 124 osobe (71 muškarac i 53 žene) u dobi od 18 do 85 godina podijeljene u ispitnu skupinu i kontrolnu skupinu. Uspoređene su snimke kompjutorizirane tomografije (CT) prsnog koša, krvni i biokemijski parametri te demografski podaci bolesnika između ispitne i kontrolne skupine. Normalnost numeričkih varijabla ispitana je Kolmogorov-Smirnovljevim testom, a homogenost varijanca Levenovim testom. Ovo je prva studija koja istražuje učinak infekcije COVID-19 u ranoj hipoksemiji na razvoj plućne hipertenzije. Kao rezultat navodi se da infekcija COVID-19 nije imala utjecaja na mPAD, dok je imala pozitivan učinak na AAD i time dovela do smanjenja omjera mPAD/AAD. Kroz ove vrijednosti koje se lako mogu izračunati iz CT snimaka prsnog koša istaknute su promjene uzrokovane infekcijom COVID-19 na promjerima žila.

Ključne riječi: *Uzlazna aorta; COVID-19; Plućna hipertenzija; Glavna plućna arterija*