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Evaluation of right ventricular function in patients with COVID-19 pneumonia after discharge with right ventricle early inflow-outflow index

COVID-19 pnömonili hastaların taburculuk sonrası sağ ventrikül fonksiyonunun sağ ventriküler erken giriş-çıkış indeksi ile ieğerlendirilmesi

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Abstract

Aim: The coronavirus disease 2019 (COVID-19) has been causing many cardiovascular complications. In patients with comorbidities, COVID-19 infection has a more severe course. Even with some patients who do not have comorbidities, severe infection and death may occur. In studies, many echocardiographic parameters were found to be impaired in patients with COVID-19 pneumonia. The right ventricle early inflow-outflow (RVEIO) index is a possible and indirect predictor of the severity of right ventricle dysfunction. The aim of our study is to evaluate the RVEIO index after discharge in patients with moderate-to-severe COVID-19 pneumonia without comorbidities.

Methods: The study was conducted prospectively in a single center. One month after discharge, echocardiography and biochemical tests were performed in 57 patients with moderate-to-severe COVID-19 pneumonia without comorbidities.

Results: Pulmonary artery diameter was found to be significantly larger in the severe group [1.9 (1.8-2) vs. 2 (1.9-2.1); p=0.014]. Pulmonary artery acceleration time [140.92±11.70 vs 114.58±12.03; p=0.001)] and RVOT VTI [23.48±1.96 vs 19.18±2.2; p <0.001] was significantly lower, while the RVEIO index was [2.51±0.54 vs 3.22±0.92; p<0.001] was found to be significantly higher in the severe group.

Conclusion: The long-term effects of COVID-19 infection are still unknown. Therefore, follow-up studies should be conducted. Echocardiography can be used in the follow-up of inpatients and discharged patients because of its easy accessibility and low cost. Long-term follow-up should be conducted for individuals who had a severe COVID-19 pneumonia and who do not have comorbidities. The RVEIO index may be used in the follow-ups.

Keywords: COVID-19, pneumonia, RVEIO index, right ventricle function, comorbidity.

Öz

Amaç: Koronavirüs hastalığı 2019 (COVID-19) birçok kardiyovaküler komplikasyona neden olmaktadır. Komorbiditesi olan hastalarda, COVID-19 enfeksiyonu daha ağır seyir etmektedir. Bazı hastaların komorbiditesi olmamasına rağmen, ağır enfeksiyon ve ölüm görülebilmektedir. Çalışmalarda COVID-19 pnömonili hastalarda, birçok ekokardiyografi parametresinin bozulduğu saptanmıştır. Sağ ventrikül erken giriş-çıkış (RVEIO) indeksi, sağ ventrikül disfonksiyonunun şiddetinin olası ve dolaylı bir belirtecidir. Çalışmamızın amacı, orta-ciddi COVID-19 pnömonili komorbiditesi olmayan hastalarda, taburculuk sonrası RVEIO indeksini değerlendirmektir.

Yöntemler: Çalışma tek merkezde, prospektif olarak yürütüldü. Taburculuktan bir ay sonra, komorbiditesi olmayan, 57 orta-ciddi COVID-19 pnömonili hastanın ekokardiyografisi ve biyokimyasal testleri yapıldı.

Bulgular: Pulmoner arter çapı ciddi grupta, anlamlı daha geniş saptandı [1,9 (1,8-2) ve 2 (1,9-2,1); p=0,014]. Pulmoner arter akselarasyon zamanı [140,92±11.70 ve 114,58±12,03; p=0,001)] ve RVOT VTI [23,48±1,96 ve 19,18±2,2; p <0,001] anlamlı daha düşük, RVEIO indeksi ise [2,51±0,54 ve 3,22±0,92; p<0,001] ciddi grupta anlamlı daha yüksek saptandı.

Sonuç: COVID-19 enfeksiyonunun uzun süreli etkilerini bilmiyoruz. Bu nedenle takip çalışmaları yapılmalıdır. Ekokardiyografi tetkiki kolay ulaşılabilir ve az maliyetli olması nedeniyle yatan hastalar ile taburcu edilen hastaların takiplerinde kullanılabilir. Özellikle hastalığı ciddi geçiren, komorbiditeleri olmayan bireylerin bile uzun dönem takipleri yapılmalıdır. Takiplerde RVEIO indeksi kullanılabilir.

Anahtar Kelimler: COVID-19, pnömoni, RVEIO indeksi, sağ ventrikül fonksiyonu, komorbidite.

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Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 spread from China to the whole world in December 2019. The World Health Organization declared a pandemic in March 2020. The infection infected millions of people, causing mortality and morbidity [1, 2].

The lungs are the target organ of the virus. Asymptomatic infection in patients with COVID-19 can cause severe respiratory failure, dysfunction in other organs, primarily the heart and it can even lead to death. Mortality is higher in patients with cardiac involvement. Male gender, coronary artery disease, advanced age, hypertension, diabetes, obesity, lung disease affect mortality and morbidity. The virus can cause severe pneumonia and death in some patients, even in those who do not have comorbidity [3-5].

COVID-19 infection may cause cardiovascular complications such as myocarditis, heart failure, sudden death, acute myocardial infarction, cardiogenic shock, arrhythmia, venous thromboembolism. It causes these effects directly and indirectly [6-8]. Studies have shown that right ventricle afterload increases and right ventricle contractility decreases. It has been reported that pulmonary artery systolic pressure, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC) and right ventricular (RV) strain are impaired and associated with mortality [9, 10].

COVID-19 has been found to cause subclinical myocardial dysfunction even in mildly symptomatic patients [11,12]. Despite regular vaccination, the spread of the virus has not been stopped. The long-term effects of the virus are still unknown. A follow-up study of patients recovering from SARS infection has found an increased risk of cardiovascular disease [13]. For this reason, follow-up studies should be performed on patients with especially severe-critical COVID-19 infection. Echocardiography can be used in these studies because of its easy accessibility and low cost.

The RVEIO Index is a possible and indirect predictor of the severity of tricuspid regurgitation and right ventricle dysfunction in pulmonary embolism [14]. In a recent study of intensive care patients, the RVEIO index has been found to be high in severe patients [15]. Studies on the RVEIO index should be performed on discharged patients. In our study, the RVEIO index was evaluated in after-discharge echocardiograms of patients with moderate-severe COVID-19 pneumonia without comorbidities.

Material and methods

Study Population

The study was conducted prospectively in a single centre between 15 May 2020 and 30 July 2020. The clinical and radiological definition of the World Health Organization was used to diagnose patients with COVID-19 pneumonia [16]. Echocardiography and biochemical tests were performed 1 month after discharge on 31 severe and 26 moderate COVID-19 pneumonia patients without comorbidities. The COVID PCR tests of the patients were positive at admission and the PCR tests performed after discharge were negative. Patients with severe COVID-19 had one of the three criteria: I-Respiratory distress and respiratory rate greater than 30 per minute; II-Fingertip blood oxygen saturation at rest <93%; III-Partial arterial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2) <300 mmHg. Patients who did not undergo invasive mechanical ventilation were included in the study.

Patients over the age of 18 without comorbidity were included in the study. Coronary artery disease, hypertension, heart failure, left bundle branch and right block, atrial fibrillation, patients under 18 years of age, moderate-severe valve pathology, diabetes mellitus, anemia, thyroid dysfunction, chronic renal failure, pulmonary hypertension, invasive mechanical ventilation, patients with a history of pulmonary embolism, cancer, rheumatic valve disease, chronic lung disease, BMI > 30 kg/m2 and myocarditis during hospitalization, acute coronary syndrome and patients with poor echogenicity were excluded from the study.

Echocardiographic examinations

Transthoracic echocardiographies of the patients were performed and recorded with the EPIQ 7C ultrasound system (Philips Medical Systems, Andover, Massachusetts). Two independent observers analysed the images. Two-dimensional, M-mode transthoracic, tissue Doppler echocardiographies were performed in accordance with the guidelines of the American and European Society of Echocardiography [17,18]. Left ventricle end-diastolic (LVEDD) and end-systolic diameter (LVESD), interventricular septum (IVS), posterior wall (PW) and left atrium (LA) diameters were measured from the parasternal long axis. Right ventricular (RV) diastolic diameter, RV diastolic area, RV systolic area were obtained from RV-focused apical 4-chamber view. RVFAC was calculated from right ventricular area measurements. Mitral and tricuspid early diastolic and late diastolic maximal flow velocities were determined from the apical 4-chamber view using pulse wave (PW) Doppler. Left ventricular ejection fraction (LVEF) was calculated by the Teicholz method. Pulmonary artery systolic pressure was calculated from the tricuspid regurgitation jet using Bernoulli's equation. Estimated pulmonary artery systolic pressure (PAPs) was calculated by adding 5-10 mmHg to these values according to the width of the inferior vena cava. Intermittent flow spectral mode was used for tissue Doppler imaging. Systolic, early and late diastolic tissue velocities were measured by taking tissue Doppler images from the apical 4-chamber view of the mitral and tricuspid lateral annulus. TAPSEs were measured using the M mode. Pulmonary artery acceleration time was measured with PW Doppler just proximal to the pulmonary valve annulus. RV outflow velocity time interval (VTI) was traced from the pulse-wave Doppler recording at the RV outflow tract (RVOT) on the parasternal short-axis view (Figure 1). The RVEIO index was calculated using the equation described in Figure 2.

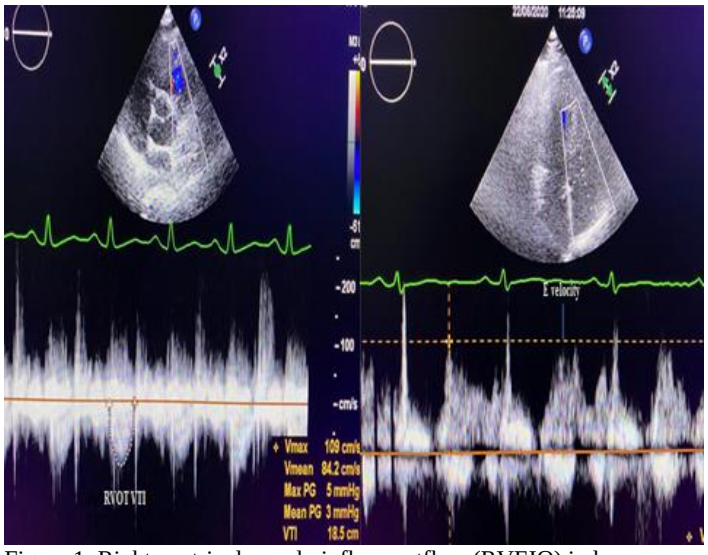

Figure 1: Right ventricular early inflow-outflow (RVEIO) index parameters.

RVEIO Index= E velocity/RVOT VTI

Figure 2: Equation of RVEIO index.

Statistical Analysis

All data was analysed using SPSS (Statistical Package for Social Sciences) software version 26.0. Student-t test was used for data showing normal distribution and Mann Whitney-U test was used for data not showing normal distribution. Paired sample-t test was used for the comparison of the parameters within the group and the chi-square test was used for the comparison of the qualitative data. Mean±standard deviation was used for descriptive parameters. The results were evaluated at the 95% confidence interval. A p value of <0.05 was accepted to indicate statistical significance.

Results

A total of 57 patients, 45 of whom were male, were included in the study. The mean age of the severe group was higher [43.26±10.31 vs. 49.29±10.86; p=0.037]. Six patients in the severe group and one patient in the moderate group were hospitalized in the intensive care unit [p=0.018]. The duration of hospital stay was longer in the severe group than in the moderate group [8.80±4.51 vs. 14.13±7.14; p=0.002]. Other clinical, demographic characteristics and laboratory findings were similar in the two groups. Table 1 shows the clinical, demographic characteristics and laboratory findings of the patients.

Table 1. Clinical, demographic and laboratory characteristics of the study population.

	Moderate Pneumonia (n=26)	Severe Pneumonia (n=31)	p value
Age, years	43.26±10.31	49.29±10.86	0.037
Gender (male), *n*	20 (76.9)	25 (80.6)	0.731
BMI, kg/m^2	27.48±2.15	27.22±2.18	0.7
Tobacco exposure, n	1 (3.8)	1 (3.2)	0.946
SBP, mmHg	118±10.32	115±8.11	0.12
DBP, mmHg	74.73±6.02	72.58±7.28	0.22
Heart Rate, beats/min	88.69±15.01	90.38±12.62	0.64
Oxygen Saturation %	98 (96-98)	97 (96-98)	0.380
ICU stay, n	1 (3.8)	6 (19.4)	0.018
Total time of stay, days	8.80±4.51	14.13±7.14	0.002
WBC	4609±732	4315±726	0.135
Lymphocyte, count	2218±746	1981±593	0.21
Hemoglobin, g/dL	14.07±1.36	13.80±1.26	0.44
Platelet, count	222538±65831	193354±72446	0.11
CRP, mg/dL	0.55±0.4	0.36±1	0.39
LDH, U/L	222±66.76	231±52.74	0.64

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, ICU: intensive care unit.

The patients were treated according to the national COVID-19 treatment guidelines. While hydroxychloroquine, favipravir and antibiotics were included in the medical treatment, there was no intensive steroid treatment. Hydroxychloroquine was given to 8 patients, hydroxychloroquine and azithromycin to 49 patients, favipravir to 41 patients and tocilizumab to 6 patients. Only 4 of the patients received intravenous steroid therapy. All patients were given sc heparin and pulmonary embolism was not detected in any of the patients. All patients received oxygen therapy. Invasive mechanical ventilation was not applied to the patients hospitalized in the intensive care unit.

Echocardiographic data of the two groups are summarized in Table 2. The EF of both groups was within normal limits but the EF of the severe group was found to be significantly lower compared to the moderate group [65.96±2.63 vs 64.36±2.59; p=0.027]. The apicobasal length of the right atrium was significantly higher in the severe group [3.61±0.22 vs 3.78±0.27; p=0.017]. The pulmonary artery was found to be significantly larger in the severe group [1.9 (1.8-2) vs 2 (1.9-2.1); p=0.014]. Pulmonary artery acceleration time [140.92±11.70 vs 114.58±12.03; p=0.001)] and RVOT VTI [23.48±1.96 vs 19.18±2.2; p <0.001] was significantly lower. The RVEIO index was [2.51±0.54 vs 3.22±0.92; p<0.001] was significantly higher in the severe group.

Table 2. Echocardiographic characteristics of the study population.

	Moderate Pneumonia (n=26)	Severe Pneumonia (n=31)	p value
LVEDD, cm	4.85±0.28	4.85±0.33	0.985
LVESD, cm	3.0 (2.7-3.1)	3.0 (2.8-3.1)	0.534
LA, cm	3.65±0.19	3.61±0.15	0.517
IVS, cm	1.1±0.1	1.1±0.2	0.935
PW, cm	0.9±0.1	1±0.1	0.517
LVEF %	65.96±2.63	64.36±2.59	0.027
Mitral E, cm/s	77.43±11.1	73.13±16.7	0.268
Mitral A, cm/s	70.91±15.71	69.95±14.97	0.814
Mitral DT, ms	220 (211-230)	211 (201-236)	0.072
Mitral tdi E`, cm/s	14.55±3.02	16.34±13.63	0.514
Mitral tdi A`, cm/s	13.21±3.32	13.74±2.58	0.504
Mitral tdi S, cm/s	13.1±2.06	12.82±1.82	0.541
RA Mediolateral, cm	3.31±0.18	3.42±0.27	0.065
RA Apicobasal, cm	3.61±0.22	3.78±0.27	0.017
RA area, mm2	11.70±2.24	11.08±3.26	0.400
RV EDD bazal, cm	2.5 (2.47-2.6)	2.5 (2.4-2.6)	0.762
RV ED area, mm2	19.19±3.51	19.81±3.24	0.491
RV ES area, mm2	10.66±2.14	10.97±2.71	0.628
RVFAC %	45.11±7.36	42.78±7.08	0.235
TAPSE, cm	2.29±0.23	2.26±0.26	0.248
Tricuspid E, cm/s	58.77±12.81	60.61±13.01	0.593
Tricuspid A, cm/s	56.39±14.74	60.55±17.58	0.343
Tricuspid tdi E`, cm/s	14.96±2.58	14.38±3.78	0.493
Tricuspid tdi A`, cm/s	13.95 (12.2-15.67)	14.7 (12.3-17.2)	0.619
Tricuspid tdi S, cm/s	14.34±2.11	14.15±1.39	0.69
PAPs, mmHg	22.57±7.3	22.25±7.91	0.875
Pulmonary artery, cm	1.9 (1.8-2)	2 (1.9-2.1)	0.014
RVOT VTI, cm	23.48±1.96	19.18±2.22	<0.001
PAAT, ms	140.92±11.70	114.58±12.03	0.001
RVEIO index	2.51±0.54	3.22±0.92	<0.001

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: left atrial, IVS: interventricular septum, PW: posterior Wall, LVEF: left ventricular ejection fraction, RA: right atrial area, RV EDD: right ventricular end-diastolic diameter, RVFAC: right ventricular fractional area change, TAPSE: tricuspid annular plane systolic excursion, tdi: tissue Doppler imaging, PAPs: systolic pulmonary artery pressure, RVOT VTI: Right ventricular outflow tract velocity time integral, PAAT: Pulmonary Artery Acceleration Time, RVEIO: right ventricle early inflow-outflow.

Discussion

Our study consisted of patients without comorbidities who were hospitalized for moderate-severe COVID-19 pneumonia in the first wave of the pandemic. In echocardiography performed one month after discharge, we found the RVEIO index to be significantly higher in the severe group than the moderate group. We argue that this parameter can be used especially in the follow-up of patients who had severe or critical COVID-19 pneumonia.

SARS-CoV-2 causes RV damage by increasing RV afterlode and decreasing RV contractility due to acute respiratory distress syndrome, pulmonary vascular thrombosis, direct viral myocardial damage, hypoxia, inflammatory response and autoimmune damage [19].

The right ventricle is more prone to disruption than the left ventricle. Studies have shown that decreased RV longitudinal strain (LS) is a strong predictor of mortality in patients with COVID-19 despite having normal LV EF [20, 21].

Studies in hospitalized and discharged patients have shown an increase in pulmonary artery pressure, decrease in TAPSE and RVFAC, decrease in tricuspid tdi S and deterioration in left and right ventricle strain parameters [20-22]. Therefore, studies showing right ventricle dysfunction and looking at the RVEIO index should be performed on discharged patients.

In a 12-year follow-up study of patients with SARS infection, cardiovascular problems were found in 44%, impaired glucose metabolism in 60% and dysregulated lipid metabolism in 68% [13]. In SARS-CoV-2 virus, we may see these complications in more patients in the coming years, as it resembles SARS virus and spreads more rapidly. In addition, in community-acquired pneumonia, the risk of active cardiovascular disease has been found to be increased several years after hospitalization [23,24].

It is known that viral infections can lead to pulmonary hypertension [25, 26]. Studies have shown that the pulmonary vascular effects of COVID-19 infection resemble the pathology of pulmonary hypertension [27,28]. In COVID-19 pneumonia, unlike other pneumonias, vascular thickening has been detected [29–32]. Therefore, patients with COVID-19 pneumonia may develop more pulmonary hypertension over time unlike other viral infections.

Karagodin et al. [33] found that the echocardiographic parameters of the patients in the first wave of the pandemic were significantly more abnormal than those of the patients in the second wave. LV and RV global LS, RV free wall strain, RV basal diameter were statistically found to be significantly lower in patients in the first wave compared to the patients in the second wave and RV basal diameter was statistically higher. They commented that the reason for this is the effect of new treatment methods and the increasing awareness of COVID-19 patients. Our patients were also treated with the treatment protocol in the first wave of the pandemic and did not receive intensive steroids.

The RVEIO index is a new parameter that has proved to be useful in determining the severity of tricuspid regurgitation and evaluating RV dysfunction in pulmonary embolism [14, 15]. The main cause of RV failure in COVID-19 pneumonia is tho ught to be an increase in pulmonary vascular resistance (PVR). The increase in RA pressure in response to increased PVR causes an increase in E-wave velocity on echocardiography. The reduction in RVOT VTI is the result of impaired RV systolic function due to increased PVR. RVEIO index is calculated from these two parameters. Parameters indicating RV dysfunction may not deteriorate simultaneously. RV functions can be maintained despite an increase in RV afterload up to a critical threshold. An increase in the RVEIO index may indicate RV adaptation at this stage. Kahyaoğlu et al. [15] showed that the RVEIO index can provide information about the severity of pneumonia in patients hospitalized in the intensive care unit due to COVID-19. They found an increase in the RVEIO index in the severe patient group compared to the non-serious group [15]. In our study, we found the RVEIO index to be significantly higher in the severe group one month after discharge than in the moderate group.

In the study of Mostafavi et al., it was stated that the RVEIO index in hospitalized patients was not an index showing RV dysfunction and mortality in patients with COVID-19 [34]. In BJ Kimura's article, Kahyaoglu's study was criticized while the necessity of conducting studies on the RVEIO index was highlighted [35]. Our study is a follow-up study that has shown that the RVEIO index can be used especially in the controls of patients with severe-critical COVID-19 pneumonia.

Despite all the precautions taken, COVID-19 infection continues to infect millions of people around the world. It appears that some patients have been infected with COVID-19 several times even if they have more than one vaccine. In follow-up studies, subclinical myocardial dysfunction has been shown even in patients with mild infection. With the cumulative effect of recurrent infections, further damage may occur to the heart of patients. In studies, disturbances were detected in strain echocardiography of patients. In our country, strain echocardiography program is not available in every clinic. Therefore, we can use echocardiographic parameters such as the RVEIO index in the follow-up of patients.

As the limitations of the study, since most of the hospitalized patients with COVID-19 pneumonia had comorbidities, the number of patients in our study was small. If the number of patients were greater, statistically more significant results could be obtained. Most of the patients did not have baseline echocardiograms. If they had baseline echocardiograms, we could compare it to echocardiograms done one month after discharge.

In conclusion, since the long-term effects of COVID-19 infection are unknown, follow-up studies are essential. In particular, even patients who had serious or critical COVID-19 infection but do not have comorbidities should be checked for a long time at certain periods. Echocardiography, an easily accessible and noninvasive imaging method, can be used in these controls. We think that the RVEIO index will be useful in the follow-up of patients.

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