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Right Ventricular Diastolic Dysfunction in Young Adults after Mild COVID-19

Mohamed Saber Hafez, Islam Bastawy, Heba Kamel*
Department of Cardiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
***Corresponding author:** Islam Bastawy, **Mobile:** (+20) 01288700196, **Email:** islambastawy@hotmail.com,
ORCID ID: 0000-0003-2838-7633

ABSTRACT

Background: Myocardial injury is neither limited to the acute Coronavirus disease 2019 nor moderate-to-severe cases.

Objectives: This study aimed to evaluate the relationship between right ventricular diastolic dysfunction and post-Coronavirus disease 2019 cardiovascular sequelae in young adults with mild disease.

Patients and Methods: This study recruited 150 young adults (between 18 and 30 years) who were classified into three equal groups: Group A included 50 patients who sustained cardiac symptoms 12 to 14 weeks following mild Coronavirus disease 2019. Group B included 50 patients who did not show cardiac symptoms 12 to 14 weeks following mild Coronavirus disease 2019. Group C included 50 gender-matched healthy subjects of similar ages without previous Coronavirus disease 2019. Each subject underwent a detailed transthoracic echocardiographic study to detect right ventricular diastolic dysfunction by measuring the tricuspid valve E/A ratio, tricuspid deceleration time, tricuspid E/e' ratio and tricuspid e'/a' ratio.

Results: Right ventricular diastolic dysfunction was higher in group A (80% versus 30% versus 0%, $p < 0.001$). Tricuspid valve e'/a' was lower in group A (0.86 ± 0.2 versus 1.08 ± 0.2 versus 1.44 ± 0.28, $p < 0.001$) while tricuspid valve E/ e' was higher (6.7 ± 1.1 versus 3.25 ± 3 versus 3.04 ± 0.36, $p < 0.001$). Post- Coronavirus disease 2019 patients with right ventricular diastolic dysfunction had a higher right ventricular basal diameter, higher right ventricular systolic pressure, lower right ventricular tricuspid annular plane systolic excursion, and lower fractional area change.

Conclusions: After recovery from mild Coronavirus disease 2019, some of young adults had right ventricular diastolic dysfunction, which was more prevalent in those with post- Coronavirus disease 2019 cardiac symptoms.

Keywords: COVID-19, Diastolic dysfunction, Echocardiography, Myocardial injury, Right ventricle, SARS CoV-2.

INTRODUCTION

Millions of people have become infected since the inception of the Coronavirus disease 2019 (COVID-19) pandemic [(1)]. Myocardial injury may occur during the acute COVID-19 and may persist after recovery due to the continuation of viral myocyte infection or persistence of the inflammatory process [(2)]. In addition, a persistent myocardial injury may imply post-COVID-19 cardiovascular sequelae [(3-4)]. However, their pathophysiological relationships have not been established yet, especially with heterogeneous age groups, co-morbidities, and disease severity among patients. Moreover, the incidence of myocardial injury is higher in hospitalized, elderly, and co-morbid patients [(5-6)]. Young adults (18–30 years old), representing nearly 20% of patients, primarily acquire a mild form of the disease but may experience myocardial injury due to mild COVID-19 [(5-8)]. In this age group, it is crucial to detect post-COVID-19 myocardial injury that may result in myocardial fibrosis, a potential risk factor for heart failure with preserved ejection fraction (HFPEF) [(9-10)]. The cornerstone for the diagnosis of post-COVID-19 myocardial injury is cardiac magnetic resonance imaging (CMR), which can detect it even in the absence of symptomatic post-COVID-19 cardiovascular sequelae [(2, 11)]. However, its cost and availability may be limiting factors as patients increase in number. Since the right ventricle (RV) is commonly affected by the COVID-19 [(12)]. This study aimed to use echocardiography as a screening tool to detect possible post-COVID-19 myocardial injury by evaluating RV diastolic dysfunction in young adults following mild infection and relating it to the post-COVID-19 cardiovascular sequelae.

PATIENTS AND METHODS

This prospective observational study recruited 150 young adults (aged between 18 and 30 years) between February and August 2021, divided into three equal groups. Group A included 50 patients who sustained cardiac symptoms 12 to 14 weeks following COVID-19 (defined as post-COVID-19 cardiovascular sequelae) [(9)], while group B included 50 patients who did not show cardiac symptoms 12 to 14 weeks following COVID-19. Both groups recruited only confirmed cases of COVID-19 who presented to Ain Shams University COVID-19 clinics. The included patients were tested positive for severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) real-time polymerase chain reaction after they had experienced typical symptoms (including fever, cough, anosmia, or diarrhea) [(13)]. Group C included 50 gender-matched healthy subjects of similar ages without a history of COVID-19 who underwent negative IgG and IgM ELISA assays for SARS-CoV-2.

Exclusion criteria: Patients with moderate or severe COVID-19 who required hospitalization, patients with more than one attack of COVID-19, and subjects who received any COVID-19 vaccination dosage. Also, obese patients with body mass index (BMI) above 30 kg/m^2 or those with chronic illnesses that may affect ventricular diastolic function. Chronic diseases included hypertension, diabetes mellitus, pulmonary

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hypertension, chronic kidney disease, ischemic heart disease, heart failure (HF), valvular heart disease, congenital heart disease, atrial fibrillation, and chronic obstructive pulmonary disease. In addition, patients with impaired ventricular systolic function dilated ventricular diameters and more than mild tricuspid regurgitation (TR) were excluded.

Ethical consent:

The study protocol was revised and approved by the Ethical Committee at Ain Shams University University and following declaration of Helsinki. All participants in the study signed an informed written consents. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All participants gave a comprehensive history to identify possible cardiac symptoms following COVID-19, such as chest pain, dyspnea, and palpitations. Detailed physical examination included blood pressure (BP), heart rate (HR) in beats per minute (bpm), BMI and oxygen saturation (using pulse oximetry). In addition, a twelve-lead surface electrocardiogram confirmed normal sinus rhythm in all participants.

Echocardiography: All patients were subjected to detailed transthoracic echocardiography by 2 experienced operators blinded to the study with accepted inter- and intra-observer variability using a Vivid E9 commercial ultrasound scanner (version BT11; GE Vingmed Ultrasound AS, Horten, Norway) with phased-array transducers (M5S-D).

Two-Dimensional Echocardiography and Motion-Mode: Echocardiographic scans were done on the left lateral decubitus. A two-dimensional (2D) assessment of the left ventricle (LV) was done in apical four-chamber and two-chamber views to exclude segmental wall motion abnormalities and valvular abnormality, aided by the color flow. In addition, pericardial effusion (if present) was analyzed regarding amount and location. The LV was assessed using motion-mode (M-mode) in the parasternal long-axis view to measure LV septal wall thickness in end-diastole (ED), LV posterior wall thickness in ED, and LV internal dimensions in ED and end-systole (ES) from which the ejection fraction (EF) was calculated. In the same parasternal view, aortic root diameter and left atrial diameter were measured.

Regarding the assessment of the RV, the basal diameter was measured in the apical four-chamber view in the ED. RV wall thickness was measured in the subcostal view in the ED. The tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode on the lateral tricuspid annulus. The RV fractional area change (FAC) was calculated after tracing the RV endocardial borders in ES and ED. The grade of TR was recorded using color flow. The Inferior vena cava (IVC) was visualized in the subcostal view, and its diameter was measured. Right atrial long axis diameter was measured in the apical four-chamber view.

Doppler Echocardiography

From the apical 4-chamber view, trans-mitral pulsed-wave (PW) Doppler at the mitral valve (MV) leaflet tips was used to measure the peak early diastolic filling wave (E-wave), the late diastolic filling wave (A-wave) velocities, the E/A ratio, and the deceleration time (DT) of early filling velocity. PW Doppler was then applied on the tricuspid valve (TV) to obtain the same measurements and on the pulmonary valve to obtain peak pulmonary valve velocity. These parameters were measured during quiet breathing in end-expiration. Finally, a continuous-wave (CW) Doppler was applied on the TV to calculate the RV systolic pressure (RVSP) after adding the estimated right atrial pressure according to the size and collapsibility of the IVC [(14-15)].

Tissue Doppler Echocardiography

Color-coded tissue Doppler imaging (TDI) was applied to a grey-scale apical 4-chamber view. PW Doppler was then applied to the lateral and medial aspects of the tricuspid annulus. Lateral and septal (a') and (e') wave velocities for diastolic RV myocardial relaxation were recorded. They were averaged to estimate the mean tricuspid E/e' and tricuspid e'/a' ratios. RV diastolic function was considered normal if the tricuspid E/A ratio was between 0.8 and 2.1, DT between 120 to 229 msec, average tricuspid E/e' less than 6, and e'/a' more than 1. RV diastolic dysfunction was defined as average E/e' more than 6 and e'/a' less than 1. According to the E/A ratio and DT, RV diastolic dysfunction was subdivided into grades I-III. Grade I RV diastolic dysfunction was defined as E/A ratio less than 0.8 and DT more than 229 msec, Grade II RV diastolic dysfunction was defined as E/A ratio between 0.8-2.1 with RV E/e' >6, while Grade III diastolic dysfunction was considered when E/A ratio was more than 2.1 and DT less than 120 msec [(14-15)].

Statistical Analysis: This study compared the symptomatic post-COVID-19, asymptomatic post-COVID-19, and control groups. The 25th version of the statistical package for social science (SPSS) was chosen for data analysis. Normality test was investigated using Kolmogorov-Smirnov test. Quantitative data with normal distribution were presented as mean ± standard deviation (SD), while median and interquartile range (IQR) was used for non-normally distributed ones. Qualitative data were presented as frequency and percentage. Kruskal-Wallis' test was used to compare the three groups, and Mann Whitney U test was used for subgroup analysis, while the Chi-square test was used for contingency tables. Finally, correlations were tested using the Spearman correlation coefficient test.

RESULTS

Baseline Characteristics

Baseline characteristics among the three groups are presented in **Table (1).** Regarding group A symptoms, 56% of patients had palpitations, 28% had chest pain

and 22% had dyspnea. The mean age was 24.13 ± 3.71 years and patients were gender-matched in the three groups. There was no significant difference between the three groups regarding age, BMI, smoking, and systolic blood pressure (SBP) when group A was compared to the other groups. However, group A had a significantly higher HR than group B and C (100 ± 20 bpm versus 88 ± 6 bpm versus 85 ± 7 bpm respectively, p < 0.001).

Table (1): Comparing the baseline characteristics between the three study groups

	Symptomatic COVID-19 [A]		**Asymptomatic COVID-19 [B]**		**Control [C]**		**Kruskal-Wallis's test**	**A vs B^**	**A vs C^**	**B vs C^**
	Median / Frequency	**IQR / %**	**Median / Frequency**	**IQR / %**	**Median / Frequency**	**IQR / %**	**p**	**p**	**p**	**p**
Age[τ] (years) *(mean/SD)*	24.22	3.68	24.30	3.88	23.88	3.65	0.837			
Gender *(Male)* □	25	50%	25	50%	25	50%	1			
Smoking □	15	30%	15	30%	16	32%	0.969			
BMI[τ] (kg/m2) *(mean/SD)*	22	2.1	22.50	7.0	23	4.0	0.062			
SBP (mmHg)	120	10	110	10	12٠	10	0.319			
Heart rate(bpm)	100	20	88	6	85	7	**<0.001***	**<0.001***	**<0.001***	**0.001***
O2_sat. (%)	97	1	96	1	95.5	2	**0.004***	**0.003***	**0.007***	0.497
Duration of acute infection (days) *(mean/SD)*	7	2.24	6.9	2.22			**0.82**			
Palpitations □	28	56%								
Dyspnea □	11	22%								
Chest pain □	14	28%								

BMI: body mass index, O2 sat: oxygen saturation, SBP: systolic blood pressure. [A] Symptomatic COVID-19, [B] Asymptomatic COVID-19, [C] Control ^ Mann Whitney U test is used □ Chi test is used [τ] T test is used
*p value is significant if <0.05

Echocardiography

Two-D, M mode, PW and TDI echocardiographic examination findings among the three groups presented in **Table (2)**. LV diastolic dysfunction was higher in groups A and B (22% versus 10% versus 0%, p= 0.002). The MV average E/e' was significantly higher in group A than in group C (5.68 ± 1.45 versus 5 ± 0.5, p 0.005).

The RV diastolic dysfunction was significantly higher in group A (80% versus 30% versus 0%, p < 0.001). Regarding the RV diastolic dysfunction in group A, 34 patients (68%) had impaired relaxation and 6 patients (12%) had pseudo-normal patterns. In group B 15 patients (30%) had RV diastolic dysfunction exclusively impaired relaxation pattern.

Regarding RV diastolic function parameters, TV E/A was significantly lower in group A (0.7 ± 0.14 versus 1.28 ± 0.48 versus 1.26 ± 0.12, p <0.001). Also, TV e'/a' was significantly lower in group A (0.86 ± 0.2 versus 1.08 ± 0.2 versus 1.44 ± 0.28, p <0.001) while TV E/ e' was significantly higher in group A (6.7±1.1 versus 3.25±3 versus 3.04 ± 0.36, p < 0.001).

Additionally, RV basal diameter was significantly higher in group A (36 ± 4 versus 32 ± ٧ versus 35 ± 9 mm, p < 0.001) and RVSP was significantly higher in group A (25 ± ٥ versus 23 ± 3 versus 23 ± 6 mmHg, p 0.001). At the same time, RV TAPSE was significantly lower in group A (22 ± 4 versus 23±7 versus 25±5 mm, p =0.001) and RV FAC was significantly lower in group A (42±5 versus 48 ± 5 versus 48 ± 4%, p < 0.001). Pericardial effusion was present exclusively in group A patients (56% versus 0% versus 0%, p value <0.001).

Table (2): Echocardiographic comparison between the three study groups

		Symptomatic COVID-19 [A]		Asymptomatic COVID-19 [B]		Control [C]		Kruskal - Wallis's test	A vs B^	A vs C^	B vs C^
		Median / Frequency	IQR / %	Median / Frequency	IQR / %	Median / Frequency	IQR / %	p	p	p	p
LA diameter(mm)		34	5	30.5	2	29	4	**<0.001***	**<0.001***	**<0.001***	**0.015***
IVS(mm)		8	2	8	2	8	2	0.412			
PW(mm)		8	2	8	1	8	1.3	0.167			
LVEDD(mm)		45	5	48	6	48	3	**0.004***	**0.013***	**0.001***	0.759
LVESD(mm)		27	6	29	3	28.5	9	0.05			
EF(%)		70	8	68	5	69	4	0.213			
Mitral E/A		1.1	0.35	1.1	0.63	1.1	0.2	0.128			
Mitral DT(ms)		149	35	153	54	169	35	**<0.001***	0.898	**<0.001***	**<0.001***
Mitral E/e' lateral		5.55	1.47	5	1	5	1.25	**0.039***	0.356	**0.011***	0.116
Mitral E/e' septal		5.85	1.5	5	1	5	2	**0.03***	0.076	**0.010***	0.432
Average E/e'		5.68	1.45	5.5	1	5	0.5	**0.023***	0.183	**0.005***	0.191
LV diastolic dysfunction (impaired relaxation) □		11	22%	5	10%	0	0%	**0.002***	0.102	**<0.001***	**0.022***
RA diameter(mm)		38	4	38	4	37	2	0.128			
RV basal diameter(mm)		36	4	32	7	35	9	**<0.001***	**<0.001***	**0.001***	0.140
RV wall thickness(mm)		3	0.72	4	1	3	1	**<0.001***	**<0.001***	**0.001***	0.073
RVTAPSE(mm)		22	4	23	7	25	5	**0.001***	**<0.001***	**0.002***	0.516
RVFAC(%)		42	5	48	5	48	4	**<0.001***	**<0.001***	**<0.001***	0.636
RVSP(mmhg)		25	5	23	3	23	6	**<0.001***	**0.001***	**<0.001***	**0.012***
IVC diameter(mm)		14	2	13	2	13	2	**0.044***	**0.028***	**0.033***	0.800
Pulmonary valve peak velocity(m/s)		1.25	0.2	1.2	0.1	1.2	0.2	**<0.001***	**0.004***	**0.001***	0.377
Pericardial effusion □		28	56%	0	0%	0	0%	**<0.001***	**<0.001***	**<0.001***	
Tricuspid E(cm/s)		39	14	35	7	42.5	2	**<0.001***	0.201	**0.002***	**<0.001***
Tricuspid A(cm/s)		50	13	45	7	34	3	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Tricuspid E/A		0.7	0.14	1.28	0.48	1.26	0.12	**<0.001***	**<0.001***	**<0.001***	٠.374
Tricuspid DT(ms)		235.5	67	245.5	129	247	19	**<0.001***	0.360	**0.001***	**<0.001***
Tricuspid e' (cm/s)		5.85	2.93	14	8.60	14	2	**<0.001***	**<0.001***	**<0.001***	٠.200
Tricuspid a'(cm/s)		6.8	1.28	12	6.6	10	2	**<0.001***	**<0.001***	**<0.001***	**٠.002***
Tricuspid e'/a'		0.86	0.2	1.08	0.2	1.44	0.28	**<0.001***	**<0.001***	**<0.001***	**<0.001***
TV E/e'		6.70	1.1	3.25	3	3.04	0.36	**<0.001***	**<0.001***	**<0.001***	**<0.001***
RV diastolic dysfunction □		40	80%	15	30%	0	0%	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Type of RV diastolic dysfunction □	Normal	10	20%	35	70%	50	100%	**<0.001***	**<0.001***	**<0.001***	**<0.001***
	Impaired relaxation	34	68%	15	30%	0	0%				
	Pseudo normal	6	12%	0	0%	0	0%				

A: late diastolic filling, DT: deceleration time, E: early diastolic filling, EF : ejection fraction, FAC: fractional area change, IVC: inferior vena cavea, IVS: interventricular septum, LA: left atrial, LV: left ventricle, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, PW: posterior wall, RA: right atrial, RV : right ventricle, RVSP: right ventricular systolic pressure, TAPSE: trans annular plane systolic excursion.

[A] Symptomatic COVID-19, [B] Asymptomatic COVID-19, [C] Control ^ Mann Whitney U test is used □ Chi test is used

*p value is significant if <0.05

RV diastolic dysfunction in the Post-COVID-19 Group

Table (3) the baseline characteristics in subgroup analysis comparing the RV diastolic function in the 100 post-COVID-19 patients and dividing them into two groups, one with normal RV diastolic function and the other with RV diastolic dysfunction. There was a statistical difference between the two groups regarding age, which was significantly lower in the RV diastolic dysfunction group (25.89 ± 3.11 years versus 22.93 ± 3.75 years, p < 0.001). Also, smoking was significantly lower in the RV diastolic dysfunction group (21.8% versus 40%, p 0.048) while HR was significantly higher in the RV diastolic dysfunction group (100 ± 18 bpm versus 88 ± 8 bpm with normal RV diastolic function, p < 0.001).

The RV diastolic dysfunction group had more incidence of palpitations (50.9% versus 0%, p <0.001) and chest pain (21.8% versus 4.4%, P 0.013). However, it showed lower incidence of dyspnea (5.5% versus 17.8%, p= 0.05).

Table (3): Baseline characteristics in post-COVID-19 groups

		Normal RV diastolic function (No.=45)		**RV diastolic dysfunction (No.=55)**		**Mann Whitney U test**
		Median / Frequency	**IQR / %**	**Median / Frequency**	**IQR / %**	**p**
Age *(years) (mean/SD)*		25.89	3.11	22.93	3.75	**<0.001***
Gender (male) □		22	48.9%	28	50.9%	0.841
Group □	**Symptomatic COVID-19**	10	22.2%	40	72.7%	**<0.001***
	Asymptomatic COVID-19	35	77.8%	15	27.3%	
Palpitations □		0	0%	28	50.9%	**<0.001***
Dyspnea □		8	17.8%	3	5.5%	0.05
Chest pain □		2	4.4%	12	21.8%	**0.013***
Smoking □		18	40%	12	21.8%	**0.048***
BM (kg/m2) *(mean/SD)*		22.03	3.68	22.60	2.43	0.375
Heart rate(bpm)		88	8	100	18	**<0.001***
SBP(mmHg)		120	10	120	10	**0.503**
O2_sat.(%)		96	2	96	1	0.364

BMI: body mass index, O2 sat: oxygen saturation, SBP: systolic blood pressure □ *Chi test is used* τ *T test is used*
**p value is significant if <0.05*

Table (4) showed the echocardiography findings between the two groups. In the group of patients who had RV diastolic dysfunction, there was a statistical difference in the LV diastolic dysfunction (29.1% versus 0%, p<0.001). Also, MV average E/e' was significantly higher in the RV diastolic dysfunction group (5.75 ± 1.6 versus 5.5 ± 0.55, p= 0.028). Most of the patients with RV diastolic dysfunction had impaired relaxation type (89.1%). The TV E/A was significantly lower in RV diastolic dysfunction group (0.7 ± 0.14 versus 1.31 ± 0.14, p<0.001). Also, TV e'/a' was significantly lower in the RV diastolic dysfunction (0.84 ± 0.15 versus 1.16 ± 0.18, p <0.001) while TV E/e' was significantly higher in the RV diastolic dysfunction group (6.7 ± 0.9 versus 3.21 ±0.31, p <0.001).

Table (4): Echocardiographic examination in post-COVID-19 groups

	Normal RV function (No.=45)		**RV diastolic dysfunction (No.=55)**		**Mann Whitney U test**
	Median / Frequency	**IQR / %**	**Median / Frequency**	**IQR / %**	**p**
LA diameter(mm)	31	3	33	6	0.008*
IVS(mm)	8	2	8	2	**0.037***
PW(mm)	8	2	8	1.0	0.604
LVEDD(mm)	48	7	46	5	0.983
LVESD(mm)	29	4	29	6	0.556
EF(%)	69	5	68	6	0.407
Mitral E/A	1.20	0.5	1	0.4	**0.001***
Mitral DT(ms)	156	19	131	50	**0.001***
Mitral E/e' lateral	5	1.1	5.5	1.4	**0**.051
Mitral E/e' septal	5	1.15	6	1.70	**0.004***
Average E/e'	5.5	0.55	5.75	1.6	**0.028***
LV diastolic dysfunction (impaired) □	0	0%	16	29.1%	**<0.001***
RA diameter(mm)	36	3	39	3	**<0.001***
RV basal diameter(mm)	30	7.0	36	3	**<0.001***
RV wall thickness(mm)	3	1	3.2	1.2	0.809
RVTAPSE(mm)	24	7	22	3	**<0.001***
RVFAC(%)	48	5	42	5	**<0.001***
RVSP(mmhg)	23	3	25	5	**0.025***
IVC diameter(mm)	13	2	14	2	**0.029***
Pulmonary valve peak velocity(m/s)	1.2	0.19	1.2	0.2	0.868
Pericardial effusion □	0	0%	28	50.9%	**<0.001***
Tricuspid E(cm/s)	35	4	40	12	0.074
Tricuspid A(cm/s)	45	2	47	16	0.616
Tricuspid E/A	1.31	0.14	0.7	0.14	**<0.001***
Tricuspid DT(ms)	246	4	233	137	·.110
Tricuspid e' (cm/s)	14	1.5	5.3	1.6	**<0.001***
Tricuspid a'(cm/s)	12	2	6.30	1.4	**<0.001***
Tricuspid e'/ a'	1.16	0.18	0.84	0.15	**<0.001***
TV E/e'	3.21	0.31	6.7	0.9	**<0.001***

A: late diastolic filling, DT: deceleration time, E: early diastolic filling, EF : ejection fraction, FAC: fractional area change, IVC: inferior vena cavea, IVS: interventricular septum, LA: left atrial, LV: left ventricle, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, PW: posterior wall, RA: right atrial, RV : right ventricle, RVSP: right ventricular systolic pressure, TAPSE: trans annular plane systolic excursion,.

□ *Chi test is used* **p value is significant if <0.05*

The RV basal diameter was significantly higher in the RV diastolic dysfunction group (36 ± 3 mm versus 30 ± 7mm, p<0.001). In addition, RVSP was significantly higher in the RV diastolic dysfunction group (25 ± 5 versus 23 ± 3mmHg, p= 0.025). At the same time, RV TAPSE was significantly lower in the RV diastolic dysfunction group (22 ± 3 mm versus 24 ± 7 mm, p<0.001) and RV FAC was significantly lower in the RV diastolic dysfunction group (42 ± 5 versus 48 ± 5%, p<0.001). Pericardial effusion was present exclusively in the RV diastolic dysfunction group (50.9% versus 0%, p<0.001). The flow chart of the study is presented in **Figure (1).**

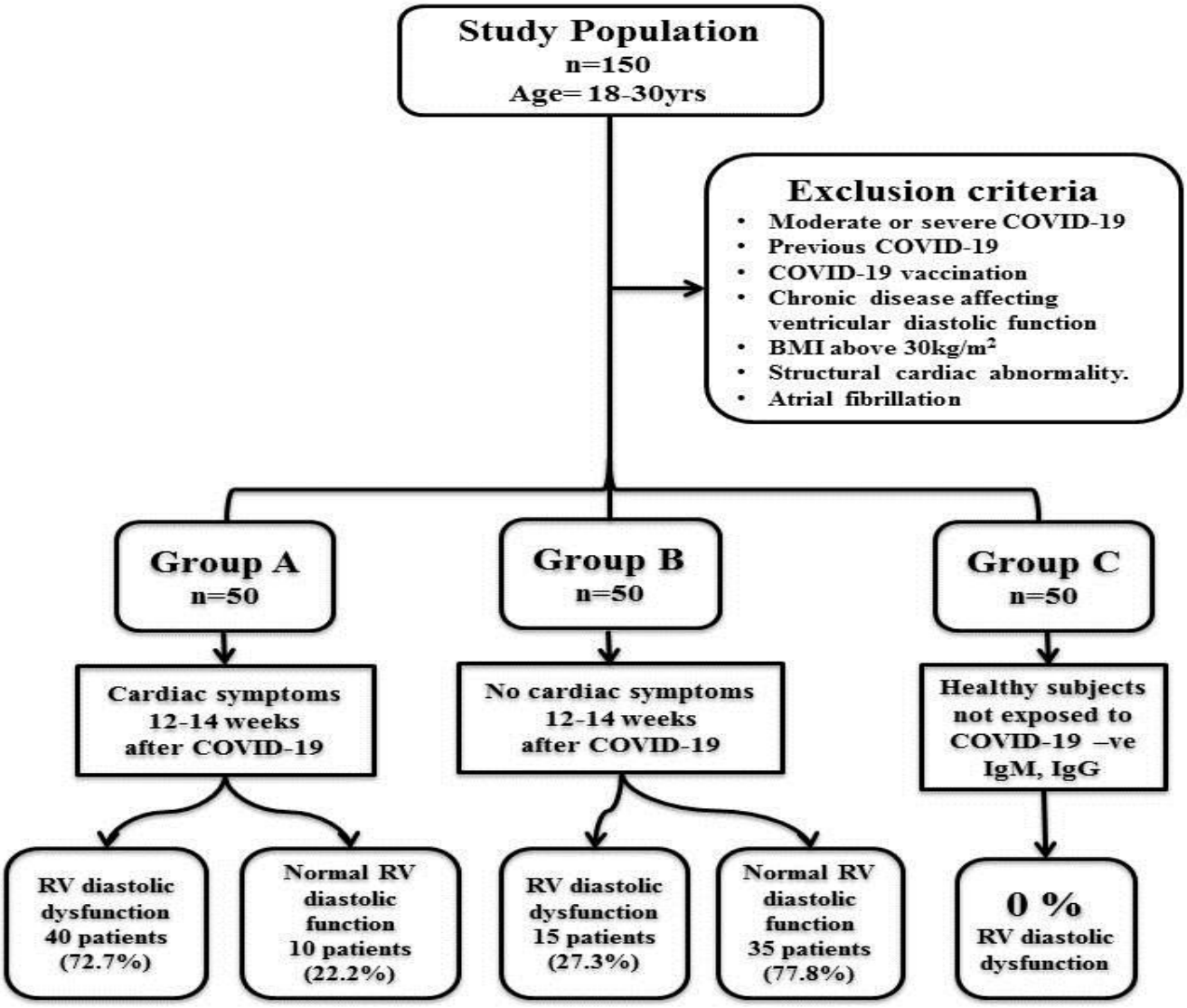

Figure (1): Flow chart of the study

BMI: body mass index, COVID -19: Coronavirus disease 2019, RV: right ventricle

In post-COVID-19 patients, the correlation between TV E/A, TV e'/a', TV E/e', and RV basal diameter, TAPSE, RV FAC and RVSP were evaluated by Spearman correlation analysis. Regarding TV E/A and TV e'/a', there was a significant positive correlation with TAPSE and RV FAC and a significant negative correlation with RV basal diameter and RVSP. While as regards TV E/e' there was a significant positive correlation with RV basal diameter and RVSP and a significant negative correlation with TAPSE and RV FAC as shown in table (5).

Table (5): Correlation between TV diastolic function parameters and right ventricular measurements

		RV basal diameter(mm)	TAPSE (mm)	RVFAC (%)	RVSP (mmhg)
Tricuspid E/A	Spearman Correlation	**-0.574***	**0.408***	**0.588***	**-0.316***
	p	**<0.001**	**<0.001**	**<0.001**	**0.001**
Tricuspid e'/a' prime	Spearman Correlation	**-0.522**	**0.410**	**0.511**	**-0.304**
	p	**<0.001**	**<0.001**	**<0.001**	**0.002***
TV E/e' prime	Spearman Correlation	**0.574**	**-0.369**	**-0.523**	**0.214**
	p	**<0.001**	**<0.001**	**<0.001**	**0.032***

RA: right atrial, RV: right ventricle, RVSP: right ventricular systolic pressure, TAPSE: trans annular plane systolic excursion.

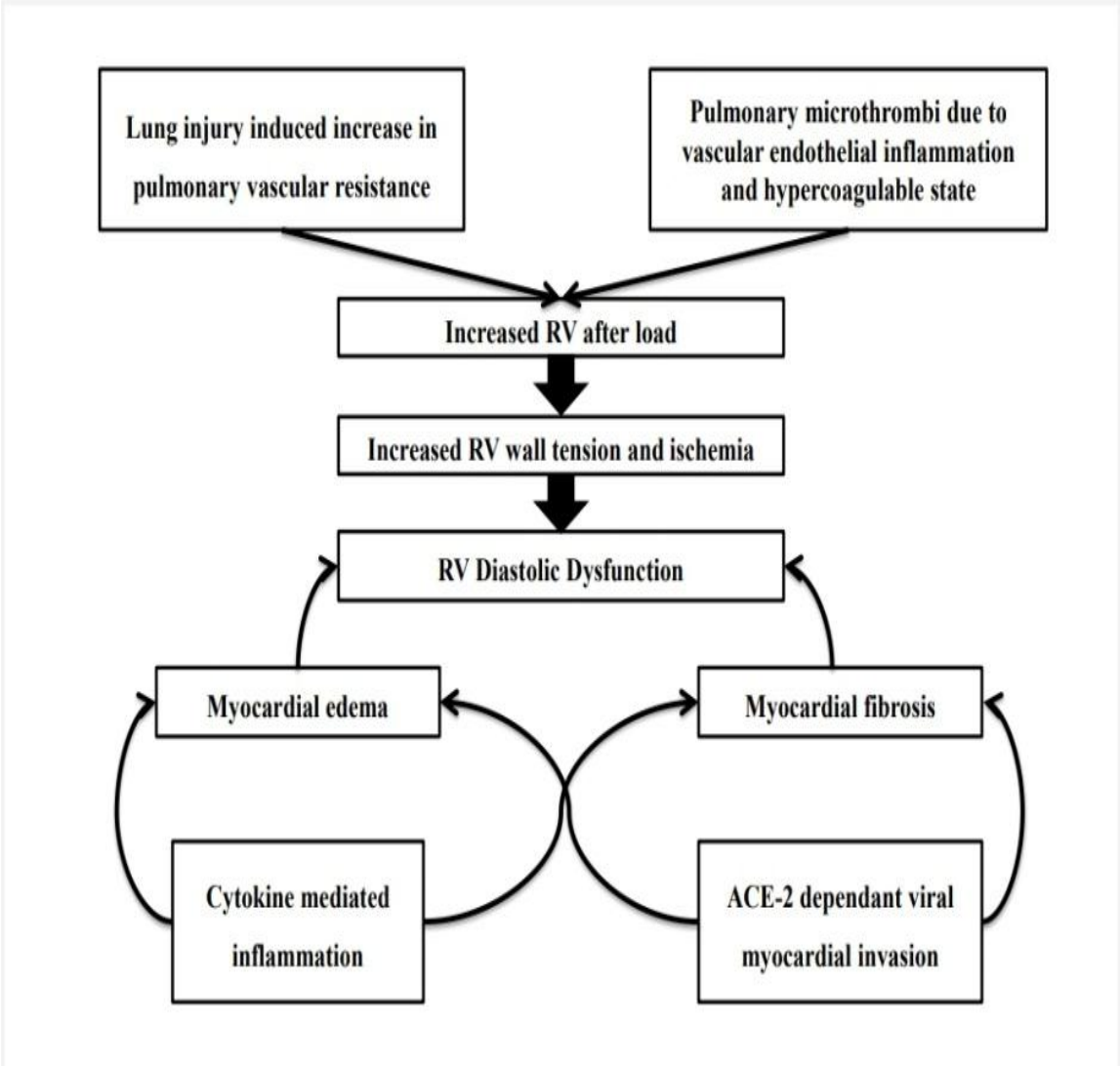

Figure (2): The potential mechanisms of RV diastolic dysfunction following mild COVID-19
ACE: angiotensin converting enzyme, RV: right ventricle

DISCUSSION

Echocardiography is a cornerstone in diagnosing COVID-19 myocardial injury, either during acute infection or after recovery [2, 12, and 16]. The most common presentations of this myocardial injury are RV dilatation or systolic dysfunction [12], which occur more frequently in hospitalized, elderly, and co-morbid patients [2, 5-6, 17]. Most of the studies that evaluated myocardial injury after recovery from COVID-19 have focused on moderate-to-severe cases. However, mild COVID-19 is less studied [17]. Although the RV is the primary target for COVID-19 myocardial injury, there is a lack of data on RV diastolic functions after recovery in the current literature.

Healthy, non-obese young adults usually have normal RV diastolic function [18]. However, the key finding in the current study was the evident RV diastolic dysfunction in young adults 12-14 weeks after recovery from mild COVID-19. Figure (2) showed the potential pathophysiological mechanisms of myocardial injury that may lead to myocardial fibrosis, ischemia, and edema, explaining this diastolic dysfunction. They include direct viral cellular entry through the myocardial angiotensin-converting enzyme-2 receptor, inflammatory mediator induced cardiotoxicity, myocardial ischemia, endothelial inflammation, and micro-pulmonary thrombosis [6, 9, 19-20]. As the RV is a load-dependent chamber, it is susceptible to increased pulmonary arterial pressure that occurs with COVID-19 lung injury and pulmonary thrombosis. This finding corresponds with CMR studies after COVID-19 recovery, showing elevated native T1 and late gadolinium enhancement (LGE) suggestive of myocardial fibrosis or elevated T2 suggestive of ongoing myocardial edema and inflammation [21-23]. In addition, a study on young asymptomatic athletes following mild COVID-19 showed evidence of myocarditis in 15% (50% of them also had pericardial effusion), while nearly one-third had LGE [24].

In this study, RV diastolic dysfunction was more common in symptomatic patients. The most encountered symptom was the sense of palpitations due to higher HR that could be attributed to post-COVID-19 induced sympathetic stimulation [25]. Sub-group analysis of the post-COVID-19 patients showed that RV diastolic dysfunction was less related to dyspnea, which may be explained by decreased

functional capacity as a part of post-COVID-19 chronic fatigue syndrome rather than myocardial injury [26]. A possible explanation for the more RV diastolic dysfunction in symptomatic patients is a continuous inflammatory state that could be supported by a localized rim of pericardial effusion in nearly half of the patients. This theory is supported by some CMR studies that showed a tendency toward more elevation in T2 in symptomatic patients after recovery [27]. In another study, 84% of positive CMR patients were symptomatic, compared to only half of the patients with negative CMR [28]. In addition, although LV diastolic dysfunction was more in post-COVID-19 patients, previous studies [12, 29] showed concomitant RV diastolic dysfunction that could be explained by ventricular interdependence [30]. Previous studies on mild COVID-19 cases showed that RV diameters and systolic function were usually within the normal range despite evidence of myocardial injury [16-17]. However, they correlated significantly with parameters of RV diastolic dysfunction in this study.

The clinical importance of the current study is that it sheds light on the value of RV diastolic dysfunction evaluation by echocardiography after recovery of mild COVID-19 as evidence of RV myocardial injury. These patients are at an increased future risk of HFPEF [10]. Also, RV diastolic dysfunction may be considered an early predictor of RV systolic dysfunction, an independent predictor of adverse outcomes and mortality in post-COVID-19 patients [31].

Due to the high cost of CMR, screening for RV diastolic dysfunction using echocardiography could be done before referral to CMR, which is the gold standard for diagnosis of COVID-19 myocardial injury [32]. However, one of the limitations is to identify RV diastolic dysfunction based on tricuspid E/A ratio, which is challenging in the presence of increased HR. Instead, its diagnosis should rely on TDI, which denotes intrinsic RV diastolic dysfunction independent of HR [14, 33].

LIMITATION OF THE STUDY

This study aimed to relate RV diastolic dysfunction to post-COVID-19 cardiovascular sequelae. It excluded patients with moderate or severe RV dilatation as they have a higher risk of RV dilatation and systolic dysfunction. Unavailable laboratory data during the acute infection prevented correlation to RV diastolic dysfunction. CMR imaging was not done to correlate RV diastolic dysfunction with positive CMR findings.

Due to the lack of CMR studies, subtle pathologies that may affect RV diastolic function, such as arrhythmogenic right ventricular cardiomyopathy, were not addressed [34]. In addition, computed tomography (CT) of the chest to assess lung parenchymal injury following COVID-19 or CT pulmonary angiography to exclude pulmonary embolism as potential etiologies for symptoms or RV diastolic dysfunction was not done. However, only mild COVID-19 cases were included [2, 35]. No follow-up was done for those with post-COVID-19 cardiac symptoms to assess if RV diastolic dysfunction is reversible after the resolution of symptoms.

CONCLUSIONS

After recovery from mild COVID-19 in young adults, echocardiography showed a prevalent RV diastolic dysfunction that is possibly related to post-COVID-19 myocardial injury. This prevalence was higher in post-COVID-19 patients with ongoing cardiac symptoms, especially palpitations and chest pain, suggesting more myocardial injury related to ongoing myocardial inflammation. Among post-COVID-19 patients, those with RV diastolic dysfunction had higher RV basal diameters, higher RVSP, lower TAPSE, and lower FAC despite being within the normal range, suggesting that RV diastolic dysfunction is a predictor of subtle RV systolic dysfunction.

HIGHLIGHTS

- Prevalent RV diastolic dysfunction by echocardiography is possibly related to post-COVID-19 myocardial injury.
- RV diastolic dysfunction is higher in post-COVID-19 patients with ongoing cardiac symptoms suggesting more myocardial injury.
- RV diastolic dysfunction maybe a predictor of subtle RV systolic dysfunction.

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