IJC Heart & Vasculature 43 (2022) 101150

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Association between right ventricular dysfunction and in-hospital mortality in surges of SARS-CoV-2 infection attributed to the Alpha, Delta, and Omicron variants

Alaa Mabrouk Salem Omar [a,b,1,*], Nolberto Hernandez [b,c,1], Diana Maria Ronderos Botero [b,d,1], Angel Delacruz [b,c], Sai Doppalapudi [b,c], Vikram Itare [b,c], Dongmin Shin [b,c], Jaydeep Mahasamudram [b,c], Neelanjana Pandey [b,c], Nishant Allena [b,c], Karan Sud [a,b], Sridhar Chilimuri [b,c], Jonathan N Bella [b,e]

[a] Department of Cardiology, Mount Sinai Morningside, New York, NY, USA
[b] Icahn School of Medicine at Mount Sinai, New York, NY, USA
[c] Department of Medicine, BronxCare Hospital Center, Bronx, NY, USA
[d] Division of Pulmonary and Critical Care Medicine, Department of Medicine, BronxCare Hospital Center, Bronx, NY, USA
[e] Department of Cardiology, BronxCare Hospital Center, Bronx, NY, USA

ARTICLE INFO

Keywords:
RV dysfunction
COVID-19
Mortality

ABSTRACT

Background: Right ventricular (RV) dysfunction in acute COVID-19 was reported to be associated with poor prognosis. We studied the association between parameters of RV dysfunction and in-hospital mortality during the surges caused by different SARS-CoV-2 variants.

Methods: In a retrospective single-center study, we enrolled 648 consecutive patients hospitalized with COVID-19 [66 (10 %) hospitalized during the alpha variant surge, 433 (67 %) during the delta variant surge, and 149 (23 %), during the omicron variant surge]. Patients were reported from a hospital with an underreported population of mostly African American and Hispanic patients. Patients were followed for a median of 11 days during which in-hospital death occurred in 155 (24 %) patients [Alpha wave: 25 (38 %), Delta Wave: 112 (26 %), Omicron wave: 18 (12 %), $p < 0.001$].

Results: RV dysfunction occurred in 210 patients (alpha: 32 %, 26 %, delta: 29 %, and omicron: 49 %, $p < 0.001$) and was associated with higher mortality across waves, however, independently predicted in-hospital mortality in the Alpha (HR = 5.1, 95 % CI: 2.06–12.5) and Delta surges (HR = 1.6, 95 % CI: 1.11–2.44), but not in the Omicron surge. When only patients with RV dysfunction were compared, the mortality risk was found to decrease significantly from the Alpha (HR = 13.6, 95 % CI: 3.31–56.3) to the delta (HR = 1.93, 95 % CI: 1.25–2.96) and to the Omicron waves (HR = 11, 95 % CI: 0.6–20.8).

Conclusions: RV dysfunction continues to occur in all strains of the SARS-CoV-2 virus, however, the mortality risk decreased from wave to wave likely due to evolution of better therapeutics, increase rate of vaccination, or viral mutations resulting in decrease virulence.

Registration number of clinical studies: BronxCare Hospital center institutional review board under the number 05 13 21 04.

* Corresponding author at: Department of Cardiology, Mount Sinai Morningside, New York, NY, USA.
E-mail address: alaamomar2016@gmail.com (A.M.S. Omar).
[1] Authors Contributed equally.

https://doi.org/10.1016/j.ijcha.2022.101150
Received 17 August 2022; Received in revised form 9 November 2022; Accepted 15 November 2022
Available online 17 November 2022

1. Introduction

1.1. Background

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is a global pandemic that caused significant morbidity and mortality worldwide overwhelming medical and financial capabilities of most institutions worldwide. COVID-19 reportedly carries significantly worse prognosis in patients who have comorbidities. Cardiovascular disease is considered in the center of attention of factors that increase the risk of mortality of COVID-19. Nevertheless, COVID-19 is reportedly fatal as well in patients who do not have risk factors[1]. Mechanisms behind fatality in these patients are not yet fully characterized however was thought to be related to variable contribution of thromboembolic and inflammatory processes. Echocardiography is an indispensable bedside tool that can be easily used for assessment of cardiac performance in COVID-19 patients [2]. Echocardiographic changes in the acute phase of the COVID-19 infection were reported early in the COVID-19 pandemic[3]. Specifically, parameters of RV dysfunction in the acute setting of the infection were reported to be independently associated with in-hospital mortality in the first wave of the pandemic[4–6], probably due to multifactorial RV strain due to thrombotic events, hypoxemic vasoconstriction, and direct myocardial damage. Reports have suggested variable virulence between different strains of the virus[7], however, the effect of the infection on RV functions and its effect on in-hospital outcomes during various waves contributed to different viral strains are not yet known.

We aimed to study and compare the association between parameters of RV function and in-hospital mortality during the surges of infections caused by the Alpha, Delta, and Omicron variants of the SARS-CoV-2 virus.

2. Methods

In a retrospective single-center study protocol, we enrolled consecutive patients (predominantly African American and Hispanic) hospitalized with COVID-19 infection at BronxCare Hospital Center, Bronx, New York, USA, who underwent clinically indicated echocardiograms. Our patients represent an underreported population of mostly African American and Hispanic patients. Patients were only included if they had a confirmed COVID-19 as a cause of hospital admission rather than an "incidental" COVID-19 finding that noticed in patients admitted for other causes. COVID-19 hospitalization trends and timeline in New York city were reviewed online from NYC health website (https://www1.nyc.gov/site/doh/covid/covid-19-data-totals.page) to define projected time intervals for wave surges of the viral infection attributed to the Alpha, Delta, and Omicron variants. Our patients were admitted sequentially during a period of the rise and peak of each of the infection surges attributed to different variants. The time interval during which patients were selected in our study whose infection was attributed to the Alpha variant was between March 2020 to July 2020, that during which patients were selected in our study whose infections was attributed to the delta variant was January 2021 to October 2021, and during which patients were selected in our study whose infections was attributed to the omicron variant was December 2021 to February 2022. Patients were included if they had an echocardiogram done and were excluded if they were<18 years of age or if they were pregnant women. Demographic, clinical, laboratory, and echocardiographic data were assessed, and the primary endpoint of the study was in-hospital mortality.

Echocardiograms were performed according to a focused time efficient protocol, with appropriate use of personal protective equipment, and limited viral exposure time [8]. In addition to standard echocardiographic measurements, parameters of RV functions were obtained including basal diastolic RV diameter (RVDD) from a RV-focused apical view, and tricuspid annular plane systolic excursion (TAPSE) from the apical 4-chamber view. These measurements were confirmed with visual inspection. RV dysfunction was defined as RVDD $>$ 4.1 cm, TAPSE $<$ 1.7 cm, and/or tricuspid regurgitation velocity (TRV) $>$ 2.8 m/s.

2.1. Statistical analysis

Continuous parameters were expressed as mean $\pm$ SD and compared using Student's *t*-test or the Wilcoxon rank sum test, and categorical parameters were expressed as number (%) and were compared using chi-square test. Cox-regression models and Kaplan-Meier's survival curves were used to explore the associations of clinical and echocardiographic predictors of in-hospital mortality. The study protocol was approved by the institutional review board.

3. Results

The total study sample size was composed of 648 hospitalized patients with confirmed COVID-19 infection. Of these, 66 (10 %) patients [age: 63.5 $\pm$ 16.3 year, 23(35 %) women] were hospitalized during the wave attributed to the alpha variant, 433(67 %) patients [age: 66.4 $\pm$ 14.8 year, 187(43 %) women] were hospitalized during the wave attributed to the delta variant, and 149 (23 %) patients [age: 66.2 $\pm$ 15.8 year, 64 (43 %) women] were hospitalized during the wave attributed to the omicron variant. Of note, none of the patients in the alpha variant wave were vaccinated, 26 (6 %) patients in the delta variant wave were vaccinated, and 34 (23 %) patients in the omicron variant wave were vaccinated (13 partially vaccinated, 13 were fully vaccinated, and 8 were vaccinated and boosted). Table 1 summarizes the demographic, clinical, and laboratory differences between the three variants. In brief, there were no significant differences between infection attributed to the three waves regarding age, sex, or risk factors, however more patients in the omicron variant wave had history of congestive heart failure (CHF) and chronic kidney disease (CKD). The onset of symptoms to hospital presentation period was significantly longer in the wave attributed to the Alpha wave compared to the other waves. Furthermore, signature COVID-19 laboratory variables, including lymphocytic count, D-dimer, lactate dehydrogenase, and C-reactive protein were less severe from the alpha to delta to omicron waves with highest values in the Alpha wave and lower values in the omicron wave, except for creatinine level which was not statistically significantly different between waves. Regarding the therapeutics used, anticoagulation, tocilizumab, and antibiotics were used progressively less from the alpha to delta to omicron waves with their most frequent use in the alpha wave and least use in the omicron wave. Convalescent plasma was utilized more in delta variant wave while corticosteroids were utilized more in the delta variant followed by the omicron variant wave.

Patients were hospitalized for a median of 11 days, and there was no significant difference for follow-up time between groups. It was found that, overall, out of the 648 patients studied, 110 (17 %) patients were admitted to intensive care units, mechanical ventilation occurred in 166 (26 %) patients, and in-hospital death occurred in 155 (24 %) patients. Patients were less likely to be admitted to an intensive care unit from the alpha to the omicron waves [alpha wave = 32 (48 %) vs delta wave = 61 (14 %) vs omicron wave = 17 (11 %), all $p < 0.001$], as there was less likelihood of mechanical ventilation [alpha wave = 32 (48 %) vs delta wave: 106 (24 %) vs omicron wave: 28 (19 %), all $p < 0.001$], and less likelihood of in-hospital mortality [alpha wave = 25 (38 %) vs delta wave = 112 (26 %) vs omicron wave = 18 (12 %), $p < 0.001$].

3.1. Echocardiographic comparisons

Table 1 summarizes echocardiographic variables between different waves in our study. In brief, it was found that, for parameters of left ventricular (LV) function, there were no significant differences between waves regarding left ventricular mass index, left ventricular ejection fraction, Doppler-derived mitral velocity during early (E) and late

Table 1
Comparisons between different waves attributed to different virus strains.

	Alpha (n = 66)	Delta (n = 433)	Omicron (n = 149)	p-value	No in-hospital mortality (n = 493)	in-hospital mortality (n = 155)	p-value
Age, years	63.5 ± 16.3	66.4 ± 14.8	66.2 ± 15.8	0.347	66.2 ± 15	65.7 ± 15	0.720
Women, n(%)	23(35)	187(43)	64(43)	0.344	201(41)	73(47)	0.135
Hypertension, n(%)	44(67)	333(77)	118(79)	0.06	382(77)	113(73)	0.270
Diabetes millitus, n(%)	34(52)	218(50)	76(51)	0.993	249(51)	79(51)	0.870
Asthma, n(%)	6(9)	79(18)	33(22)	0.071	89(18)	29(19)	0.830
Chronic obstructive pulmonary disease, n(%)	8(12)	60(14)	23(15)	0.805	77(16)	14(9)	0.04
Congestive heart failure, n(%)	10(15)	50(12)	53(36)	<0.001	86(17)	27(17)	0.983
Coronary artery disease, n(%)	11(17)	57(13)	24(16)	0.627	72(15)	20(13)	0.607
Chronic kidney disease, n(%)	7(11)	60(14)	36(24)	0.007	86(17)	17(11)	0.057
Symptom onset to presentation time, days	6 ± 5.5	2.9 ± 5	3.8 ± 4.7	<0.001*$	3.5 ± 5.1	3.2 ± 5	0.643
Laboratory values							
Neutrophile count, 10^3/uL	8 ± 4.5	6.3 ± 4.5	6.1 ± 3.9	0.01*$	6 ± 3.9	7.7 ± 5.6	<0.001
Lymphocyte count, 10^3/uL	0.9 ± 0.7	1.3 ± 1.6	1.3 ± 1.5	0.145	1.24 ± 1.3	1.2 ± 2	0.731
D-dimer, ng/ml	4813 ± 10530	1941 ± 5719	1475 ± 4189	0.001*$	1925 ± 5730	2830 ± 7452	0.124
Lactate dehydrogenase, U/L	640 ± 434	509 ± 424	395 ± 267	<0.001*$#	465 ± 213	599 ± 587	<0.001
C-reactive protein, mg/L	185 ± 176	99 ± 179	72 ± 83	<0.001*$	85.1 ± 110	168 ± 255	<0.001
Creatinine, mg/dL	1.51 ± 1.17	1.96 ± 2.24	1.88 ± 2.49	0.314	1.8 ± 2	2.2 ± 2.7	0.052
Medications used							
Convalescent plasma, n(%)	1(2)	165(38)	3(2)	<0.001	124(25)	45(29)	0.337
Therapeutic anticoagulation, n(%)	48(73)	234(54)	40(27)	<0.001	212(43)	110(71)	<0.001
Steroids, n(%)	2(3)	328(76)	82(55)	<0.001	303(61)	109(70)	0.046
Tocilizumab, n(%)	24(36)	99(23)	26(17)	0.007	102(21)	47(30)	0.013
Antibiotics, n(%)	53(80)	298(69)	70(47)	<0.001	304(62)	117(75)	0.002
In-hospital death, n(%)	25(38)	99(23)	18(12)	<0.001	–	–	
Mechanical ventilation, n(%)	32(48)	106(24)	28(19)	<0.001	66(13)	100(65)	<0.001
Intensive care unit, n(%)	32(48)	61(14)	17(11)	<0.001	13(3)	97(63)	<0.001
Hospitalization time, n(%)	16.6 ± 15	13.8 ± 11	12.9 ± 10.4	0.091	13.1 ± 11.4	16.6 ± 11	0.001
Echocardiography							
Left atrial volume index (ml/m2)	30.1 ± 15.5	30.1 ± 13	35 ± 15	0.004 #	31.5±±14	31.1 ± 14.5	0.774
Left ventricular mass index, g/m^2	112.1 ± 37.9	113.1 ± 32.9	117.5 ± 36.8	0.379	114.3 ± 35	113.5 ± 33	0.817
Ejection fraction, (%)	55.7 ± 13.9	59.5 ± 13.9	56.9 ± 16.6	0.055	59.5 ± 14	55.1 ± 17	0.002
Mitral early diastolic (E)-wave velocity, cm/s	0.8 ± 0.27	0.76 ± 0.3	0.78 ± 0.3	0.656	77 ± 27	77 ± 39	0.901
Mitral late diastolic (A)-wave velocity, cm/s	0.73 ± 0.38	0.83 ± 0.34	0.83 ± 0.26	0.085	87 ± 23	94 ± 41	0.043
Septal mitral annular e' velocity, cm/s	6.3 ± 2	6.5 ± 2.7	5.7 ± 2	0.043	6 ± 2.4	6 ± 2.7	0.208
E/A ratio	1.19 ± 0.9	0.99 ± 0.58	1.01 ± 0.63	0.078	1.01 ± 0.55	1.04 ± 0.83	0.566
E/e' ratio	13.9 ± 7.3	12.3 ± 6	14.8 ± 6.4	0.004#	13.8 ± 8.7	13 ± 6.9	0.337
Right atrial area, cm^2	16.9 ± 6.7	14.1 ± 7	16.9 ± 7.1	<0.001*#	14.7 ± 7	16.2 ± 7.1	0.042
Right ventricular basal dimension, cm	3.85 ± 0.863	3.6 ± 0.44	3.55 ± 0.4	0.006*$	1.98 ± 1.8	2.7 ± 1.9	<0.001
Tricuspid regurgitation velocity, m/s	2.95 ± 0.6	2.81 ± 0.59	2.75 ± 0.6	0.120	2.75 ± 0.58	3 ± 0.6	<0.001
Pulmonary artery systolic pressure, mmHg	44.3 ± 17.4	43.6 ± 13.4	40.1 ± 14.3	0.065	41.2 ± 14	14.8 ± 15	<0.001
Right ventricular dimension > 4.1 cm, n(%)	15(23)	40(9)	18(12)	0.001	42(9)	31(20)	<0.001
Tricuspid regurgitation velocity > 2.8 m/s, n (%)	34(52)	175(40)	66(44)	0.697	188(38)	87(56)	<0.001
TAPSE < 1.7 cm, n(%)	12(18)	14(3)	15(10)	<0.001	18(4)	23(15)	<0.001
RV dysfunction, n(%)	17(26)	120(28)	73(49)	<0.001	136(28)	74(48)	<0.001

*p < 0.05 between alpha and delta, $, p < 0.05 between alpha and Omicron, #, p < 0.05 between delta and omicron.

diastole (A) and the mitral E/A ratio. Patients in the omicron variant wave had larger left atrial volume index, lower tissue Doppler-derived septal mitral annular velocity (e'), and higher E/e' ratio. On the other hand, for parameters of RV functions, right atrial area was larger in the alpha and omicron variant waves while RV basal diameter was progressively smaller from the alpha to delta to omicron variant waves. There were no statistically significant differences between patients regarding tricuspid regurgitation velocity (TRV). In addition, RV diameter > 4.1 cm and tricuspid annular systolic excursion (TAPSE) < 1.7 cm were more frequent in the Alpha wave, while TRV > 2.8 was not different between waves. RV dysfunction according to our study definition occurred in 210 patients out of the 648 studied patients (32 %). The highest frequency of RV dysfunction occurred in the omicron wave [alpha: 17(26 %), delta: 120(28 %), omicron: 73(49 %), p < 0.001].

3.2. Comparisons for subgroups classified based on RV function

Comparisons between waves in the absence of RV dysfunction: Among patients who did not have RV dysfunction, there were no significant differences between waves regarding age, sex, risk factors, or comorbidities (Table 2). The time interval from symptoms onset to hospital presentation was longer in the alpha variant compared to the other waves. In this group, the signature COVID-19 laboratory variables, including D-dimer, lactate dehydrogenase, and C-reactive protein were progressively lower in the alpha to delta to omicron waves with highest values in the alpha wave and lowest values in the omicron wave. The use of anticoagulation, tocilizumab and antibiotics decreased from the alpha to delta to micron waves with the most frequent use in the alpha wave and the least in the omicron wave, while steroids and convalescent plasma were more frequently used in the delta wave. Admission to ICU, need for mechanical ventilation and in-hospital death decreased from the alpha to delta to omicron waves with the most frequent in the alpha wave and the least in the omicron wave.

Regarding echocardiographic variables, parameters of LV function were not different between groups. However, despite the lack of RV dysfunction in this subgroup according to the definition used in our study, worse values for RV basal dimension and RA area were noted in the alpha and omicron waves.

Table 2
Comparisons between waves after classification based on presence or absence of RV dysfunction.

	No RV dysfunction				RV Dysfunction			
	Alpha (n = 49)	Delta (n = 313)	Omicron (n = 69)	p-value	Alpha (n = 17)	Delta (n = 120)	Omicron (n = 73)	p-value
Age, years	62.2 ± 15.8	65.8 ± 15.1	65 ± 16.3	0.347	67.1 ± 17.8	65.9 ± 15	68.2 ± 15.2	0.586
Women, n(%)	29(59)	121(39)	41(59)	0.772	3(18)	50(42)	43(59)	0.140
Hypertension, n(%)	33(67)	178(57)	52(75)	0.09	11(65)	92(77)	60(82)	0.284
Diabetes millitus, n(%)	26(53)	115(37)	32(46)	0.651	8(47)	61(51)	39(53)	0.894
Asthma, n(%)	4(8)	47(15)	17(24)	0.07	2(12)	20(17)	12(16)	0.858
Chronic obstructive pulmonary disease, n (%)	6(12)	24(8)	9(13)	0.896	2(12)	24 (20) §	12(16)	0.596
Congestive heart failure, n(%)	6(12)	28(9)	15(22)	0163	4(24)	12(10)	34(47) §	<0.001
Coronary artery disease, n(%)	7(14)	28(9)	9(13)	0.960	4(24)	14(12)	15(21)	0.195
Chronic kidney disease, n(%)	7(14)	33(11)	14(20)	0.551	0(0)	16(13)	22(30)	0.022
Symptom onset to presentation time, days	6.12 ± 5.8	3.52 ± 5.6	4.1 ± 5.3	0.045*	5.63 ± 4.2	2.3 ± 4.2	3.6 ± 4.3	0.027
Laboratory values								
Neutrophile count, 10^3/uL	7.97 ± 4.4	6.32 ± 4.1	6.04 ± 3.9	0.025*$	7.95 ± 4.9	6.95 ± 6.2	6.18 ± 3.8	0.363
Lymphocyte count, 10^3/uL	0.91 ± 0.8	1.21 ± 1.24	1.13 ± 0.67	0.222	0.75 ± 0.36	1.4 ± 2.2	1.42 ± 2	0.452
D-dimer, ng/ml	2858 ± 6983	1690 ± 4358	1023 ± 2402	0.001*$#	10217 ± 15942 §	2511 ± 5322	1823 ± 5322	0.001*$
Lactate dehydrogenase, U/L	631 ± 422	483 ± 286	392 ± 235	0.001*$	664 ± 478	588 ± 653	398 ± 299	0.045#
C-reactive protein, mg/L	195 ± 194	102 ± 192	57 ± 77	0.002*$	157.7 ± 114	97.4 ± 91	85 ± 86	0.016*$
Creatinine, mg/dL	1.33 ± 0.774	1.96 ± 2.277	1.4 ± 1.35	0.01#	2.03 ± 1.8 §	1.83 ± 2.1	2.38 ± 3.2 §	0.348
Medications used								
Convalescent plasma, n(%)	1(2)	85(27)	0(0)	<0.001	0(0)	41(34)	3(4)	<0.001
Therapeutic anticoagulation, n(%)	35(71)	128(41)	15(22)	<0.001	13(76)	71(59)	24(33)	<0.001
Steroids, n(%)	2(4)	166(53)	31(45)	<0.001	0(0)	100 (83) §	49(67) §	<0.001
Tocilizumab, n(%)	20(41)	43(14)	6(9)	<0.001	4(24)	38(32) §	19(26) §	0.615
Antibiotics, n(%)	39(80)	152(49)	34(49)	0.002	14(82)	88(73)	36(49)	0.001
In-hospital death, n(%)	14(29)	49(16)	4(6)	0.003	11(65) §	50(42) §	13(16) §	<0.001
Mechanical ventilation, n(%)	23(47)	51(16)	6(9)	<0.001	10(59)	38(32)	21(29)	0.057
Intensive care unit, n(%)	23(47)	30(10)	7(10)	<0.001	10(59)	26(22) §	8(11)	<0.001
Hospitalization time, n(%)	18.4 ± 16.7	14.3 ± 11	10.8 ± 8.7	0.002*$	11.5 ± 5.9	15.8 ± 12.2	15.5 ± 11.6 §	0.349
Echocardiography								
Left atrial volume index (ml/m^2)	28.7 ± 13.9	28.8 ± 11.9	32.3 ± 11.5	0.135	33.8 ± 19	32.8 ± 15.3 §	37.3 ± 17.1	0.223
Left ventricular mass index, g/m^2	109.3 ± 31.5	110.8 ± 31	102.3 ± 30	0.135	120 ± 52	119 ± 34 §	131.5 ± 37.2 §	0.076
Ejection fraction, (%)	57.6 ± 12.8	60.9 ± 13	60.3 ± 11.3	0.258	50.1 ± 15.8	57 ± 16 §	54.1 ± 19.6 §	0.213
Mitral early diastolic (E)-wave velocity, cm/s	78.8 ± 27.3	76 ± 29.2	73 ± 20.7	0.544	83.4 ± 26.8	78 ± 338.2	81.7 ± 30.5	0.701
Mitral late diastolic (A)-wave velocity, cm/s	87 ± 29.1	91 ± 26.7	85 ± 22.8	0.339	89 ± 16.8	89 ± 36.7	90 ± 22.3	0.989
Septal mitral annular e' velocity, cm/s	6.5 ± 2.1	6.4 ± 2.4	6 ± 2	0.470	5.9 ± 1.9	6.5 ± 3.2	5.4 ± 1.9	0.09
E/A ratio	0.9 ± 0.35	0.87 ± 0.36	0.91 ± 0.33	0.693	0.91 ± 0.36	0.92 ± 0.46	0.9 ± 0.4	0.988
E/e' ratio	12.5 ± 5	12.7 ± 6.1	13.6 ± 6.04	0.572	16 ± 8.5	12 ± 5.8	16.6 ± 6.6 §	<0.001*#
Right atrial area, cm^2	15.1 ± 5.8	12.7 ± 6.5	14.9 ± 3.7	0.014*	21.5 ± 6.7 §	16.9. ± 7.2 §	18.5 ± 8.6 §	0.07
Right ventricular basal dimension, cm	3.29 ± 0.5	3.4 ± 0.2	3.41 ± 0.2	0.02*	4.68 ± 0.57 §	3.8 ± 0.56 §	3.69 ± 49 §	<0.001*$
Tricuspid regurgitation velocity, m/s	2.82 ± 0.5	2.65 ± 0.65	2.29 ± 0.5	<0.001 $#	3.3 ± 0.704 §	3.06 ± 0.35 §	3.1 ± 0.4 §	0.066
Pulmonary artery systolic pressure, mmHg	40.6 ± 13.9	40.2 ± 14.1	28.5 ± 10	<0.001 $#	54.4 ± 22.2 §	48.7 ± 10.2 §	47.3 ± 11.6 §	0.106
Right ventricular dimension > 4.1 cm, n(%)	0(0)	0(0)	0(0)	–	15(88)	40(33)	18(25)	<0.001
Tricuspid regurgitation velocity > 2.8 m/s, n (%)	0(0)	0(0)	0(0)	–	12(71)	102(85)	66(90)	0.033
TAPSE < 1.7 cm, n(%)	0(0)	0(0)	0(0)	–	12(71)	14(12)	15(21)	<0.001

*p < 0.05 between alpha and delta, $, p < 0.05 between alpha and Omicron, #, p < 0.05 between delta and omicron.
§p < 0.05 between corresponding values in patients without RV dysfunction versus patients with RV dysfunction.

Comparisons between waves in the presence of RV dysfunction: Among patients who had RV dysfunction, there were no significant differences between waves regarding age, sex, risk factors, or comorbidities, apart from more CHF and CKD in the Omicron wave. The time interval from symptoms onset to hospital presentation was longer in the alpha variant compared to the other waves. In this subgroup, the signature COVID-19 laboratory variables, including D-dimer, lactate dehydrogenase, and C-reactive protein were progressively getting lower from the alpha to delta to omicron waves with highest values in the alpha wave and lowest values in the omicron wave while lymphocytic count and creatinine levels were not different between waves. The use of anticoagulation and antibiotics decreased from the alpha to delta to omicron waves with the most frequent use in the alpha wave and the least in the omicron wave, while steroids and convalescent plasma were more frequently used in the wave attributed to the delta wave while tocilizumab use was not different between groups. Admission to ICU and in-hospital death in this subgroup progressively decreased in the alpha to delta to omicron waves while need for mechanical ventilation was not different.

Considering echocardiographic variables, parameters of LV function were not different between groups except for mitral E/e' ratio which was higher in the alpha and the omicron waves compared to the delta waves. On the other hand, parameters of RV function were progressively better from the alpha to delta to omicron waves.

3.3. Predictor of in-hospital mortality

Cox-regression analysis derived univariable echocardiographic predictors of in-hospital mortality in each wave can be found summarized in Table 3. In the wave attributed to the alpha variant, the predictors of in-hospital mortality were ejection fraction, RV dimension, TRV, TAPSE < 1.7 cm, and RV dysfunction. In the wave attributed to the delta variant, the predictors of in-hospital mortality were e' velocity, TAPSE < 1.7 cm, and RV dysfunction. In the wave attributed to the omicron variant, no echocardiographic parameters were predictive of in-hospital mortality. After adjustment for clinical and laboratory co-variates (age, sex, hypertension, diabetes mellitus, D-dimer levels, mechanical ventilation, and use of anticoagulation, tocilizumab, antibiotics, steroids, and convalescent plasma), the independent echocardiographic predictors for in-hospital mortality persisted in the alpha and delta variant, and the lack of predictors also persisted for the omicron variant.

Kaplan Meir curves (Fig. 1) revealed that patients with RV dysfunction had higher risks of in-hospital mortality in all waves compared to patients without RV dysfunction. However, when the analysis was done only in patients without RV dysfunction, no differences in in-hospital mortality was detected between waves, while when the analysis was done only for patients with RV dysfunction, it was found that the mortality risk decreased significant from the alpha to the delta and to the omicron waves, with the highest risk in the alpha wave and the lowest risk was found in the omicron wave, while the delta wave carried a relative intermediate risk. Furthermore, compared to the alpha wave, the hazard ratio of in-hospital mortality in the delta wave was 0.4 (95 % CI: 0.2 to 0.77, p = 0.007), and the compared to the alpha wave, the hazard ratio of in-hospital mortality in the omicron wave was 0.178 (95 % CI: 0.08 to 0.4, p < 0.001). After controlling for covariates (age, sex, hypertension, diabetes mellitus, D-dimer levels, mechanical ventilation, and use of anticoagulation, tocilizumab, antibiotics, steroids, and convalescent plasma), the independent risk in-hospital death was attenuated in the delta wave (HR: 0.72, 95 % CI: 0.234 to 2.21, p = 0.563) but remained significant for the omicron wave (HR: 0.29, 95 % CI: 0.09 to 0.96, p = 0.045).

Finally, in the omicron wave, RV dysfunction was associated with mortality in unvaccinated patients (adjusted HR: 4.48, 95 % CI: 1.02 to 19.6, Fig. 2).

4. Discussion

Parameters of right ventricular dysfunction have been associated with worse in-hospital outcomes in the rise of the COVID-19 pandemic. To the best of our knowledge, there is lack in appropriate studies concerned with comparison of the occurrence and prognostic ability of RV dysfunction as well as other echocardiographic parameters of cardiac functions across the wave surges of the disease attributed to different variants.

Our study showed that, RV dysfunction as defined by RV dilation, depressed TAPSE or increased RV systolic pressure continued to occur in all waves attributed to different strains of the SARS-CoV-2. Despite that mortality continues to occur in all waves, the independent mortality risk associated with RV dysfunction among patients decreased as time progress through the different waves. Furthermore, our study also suggests that the decreasing mortality risk associated with RV dysfunction seems to persist despite adjustment for covariates.

We have previously reported that RV dysfunction continued to occur in the latest reported surge of COVID that was thought to be attributed to the omicron variant and was still associated with mortality [9]. Early in the COVID-19 pandemic, echocardiographic studies showed that RV dysfunction is a common finding in patients with COVID-19 and is associated with poor prognosis [4–6]. In particular, studies showed that elevated RV systolic pressure, dilated RV dimension, and diminished RV longitudinal function as suggested by TAPSE are independently associated with in-hospital mortality during the first wave of the pandemic [10]. Multivariable analysis revealed that parameters of RV dysfunction were the only factors significantly and independently associated with more severe symptoms [11] and in-hospital mortality [5]. Furthermore, RV dysfunction remained the main echocardiographic predictor of mortality despite controlling for covariates and when compared to non-COVID-19 matched controls [12].

Thus, RV dysfunction is a hallmark cardiac involvement in hospitalized COVID-19 patients with high mortality risk. This may be related to the fact that the RV is more susceptible to lung injury than the LV. Considering that COVID-19 shows initial pulmonary tropism, there is a specific affinity towards RV dysfunction with any resultant increase in pulmonary vascular resistance [13]. The suggested pulmonary-RV related pathological mechanisms include COVID-19 associated acute respiratory distress syndrome (ARDS), which is reported to occur in 19.6 to 31 % of these patients [14–16]. Other mechanisms include pulmonary embolism that was sought to have a special increased risk in COVID-19 due to virus-induced endothelial injury, vascular inflammation, and prolonged hospitalization related immobilization causing hypercoagulable state[1]. Viral related and cytokine storm related myocardial injury as well as hypoxia induced vasoconstriction and myocarditis can also partly accounts for RV dysfunction especially in later stages of the disease [17].

Table 3
Predictors of in-hospital mortality.

	Alpha			Delta			Omicron		
	HR	P	95 % CI	HR	P	95 % CI	HR	P	95 % CI
Left atrial volume index, ml/m^2	0.99	0.851	0.96 to 1.03	1	0.495	0.99 to 1.02	1.01	0.347	0.98 to 1.05
Ejection fraction, %	0.97	0.022	0.94 to 0.97	0.99	0.067	0.98 to 1	0.98	0.148	0.96 to 1.01
Mitral early diastolic (E)-wave velocity, cm/s	0.94	0.947	0.16 to 5.5	1.34	0.257	0.81 to 2.22	2.77	0.322	0.37 to 20.9
Septal mitral annular e' velocity, cm/s	1.04	0.743	0.83 to 1.29	0.91	0.049	0.84 to 1	1.05	0.756	0.76 to 1.46
E/A ratio	1.34	0.135	0.91 to 1.97	1.1	0.691	0.76 to 1.5	1.74	0.157	0.81 to 3.7
E/e' ratio	0.99	0.816	0.92 to 1.07	1.01	0.685	0.97 to 1.1	1.03	0.539	0.94 to 1.1
Right ventricular basal dimension, cm	2.2	0.019	1.14 to 4.2	1.14	0.625	0.68 to 1.9	1.26	0.708	0.38 to 4.22
Tricuspid regurgitation velocity, m/s	2.8	0.009	1.29 to 6	1.1	0.722	0.66 to 1.82	1.9	0.149	0.79 to 4.95
Right ventricular dimension > 4.1 cm, n(%)	3.66	0.019	1.23 to 10.8	1.4	0.218	0.82 to 2.39	1.7	0.400	0.49 to 6
Tricuspid regurgitation velocity > 2.8 m/s, n(%)	2.4	0.106	0.83 to 7.1	1.33	0.286	0.79 to 2.23	1.97	0.294	0.56 to 7
TAPSE < 1.7 cm, n(%)	3.6	0.01	1.36 to 9.4	3.7	<0.001	1.8 to 7.87	2.6	0.071	0.92 to 7.6
Right ventricular dysfunction, n (%)	5.1	<0.001	2.06 to 12.5	1.6	0.014	1.11 to 2.44	2.1	0.21	0.67 to 6.4
Right ventricular dimension > 4.1 cm, n (%)*	87	0.004	4.2 to 1797	1.35	0.332	0.74 to 2.47	1.37	0.722	0.24 to 7.69
Tricuspid regurgitation velocity > 2.8 m/s, n (%)*	4.2	0.08	0.84 to 20.9	1.33	0.302	0.57 to 1.91	178	0.05	0.99 to 3187
TAPSE < 1.7 cm, n(%)*	89	0.001	7 to 1294	2.85	0.037	1.07 to 7.6	6.4	0.114	0.64 to 63.6
Right ventricular dysfunction, n (%)*	13.6	<0.001	3.31 to 56.3	1.93	0.003	1.25 to 2.96	11	0.107	0.6 to 20.8

*controlled for age, sex, hypertension, diabetes mellitus, D-dimer levels, need for mechanical ventilation, and medications (anticoagulation, tocilizumab, antibiotics, steroids, convalescent plasma).

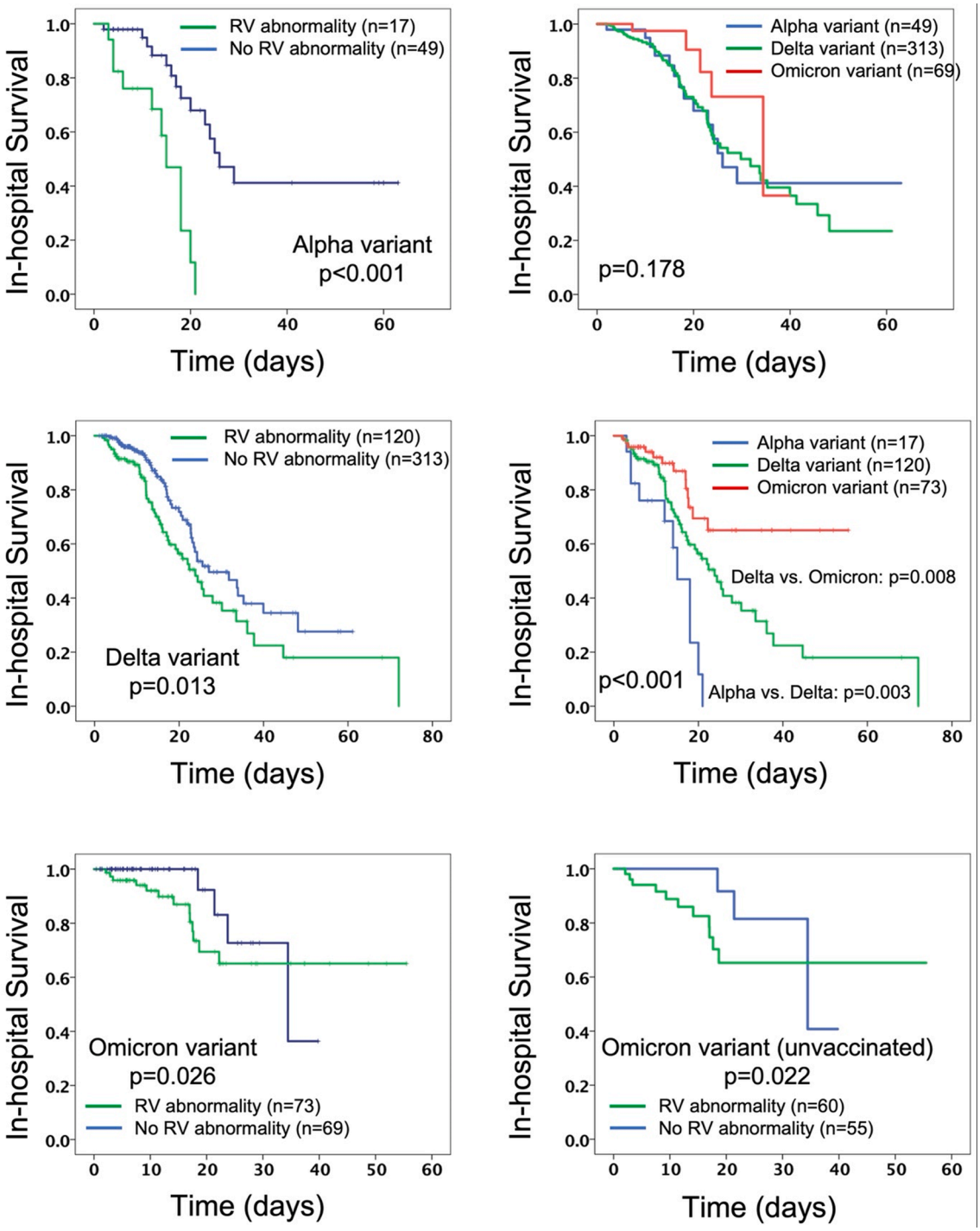

Fig. 1. Relationship of RV dysfunction to in-hospital morality in waves attributed to different variants of SARS-CoV-2 virus. Upper left panel, Kaplan-Myer curve showing worse in-hospital mortality during the wave attributed to the Alpha variant in patients with compared to patients without right ventricular (RV) dysfunction (defined as RV basal diastolic dimension > 4.1 cm or tricuspid annular systolic excursion < 1.5). Middle left panel, Kaplan-Myer curve showing worse in-hospital mortality during the wave attributed to the Delta variant in patients with compared to patients without right ventricular (RV) dysfunction. Lower left panel, Kaplan-Myer curve showing worse in-hospital mortality during the wave attributed to the Omicron variant in patients with compared to patients without right ventricular (RV) dysfunction. Upper right panel, Kaplan-Myer curve in patients without right ventricular (RV) dysfunction showing no differences in risk of in-hospital mortality between waves attributed to the Alpha, Delta and Omicron variants. Middle right panel, Kaplan-Myer curve in patients with right ventricular (RV) dysfunction showing attenuation of risk of in-hospital mortality from the wave attributed to the Alpha variant through that attributed to the Delta variant and towards that attributed to the Omicron variant. Lower right panel, Kaplan-Myer curve in unvaccinated patients during the wave attributed to the omicron variant showing that RV dysfunction is associated with elevated risk of in-hospital mortality.

Cardiac injury is reported in COVID-19 across waves attributed to different waves including the omicron variant [18] which was associated with coronary thromboembolism, myocardial inflammation, stress-induced cardiomyopathy, pericardial injury and RV dysfunction. However, lack of echocardiographic predictors of mortality aside from RV dysfunction coupled with difficulty in obtaining echocardiography in such patients due to a potential increased risk of transmission lead to a decrease in usability of echocardiography in the acute phase of COVID.

Our study shows that RV dysfunction remains prevalent among hospitalized patients with COVID-19 across variant surges [9,18]. In fact, RV dysfunction in our study seemed to be more prevalent in the omicron wave than that in prior waves, as similarly recently reported [19]. However, despite so, the association of RV dysfunction with mortality was attenuated compared to prior waves. This is an important aspect that distinguishes the omicron wave associated RV dysfunction suggesting a probable different pathological behavior of the virus or a significant effect of vaccination. The later explanation can be supported by the fact that RV dysfunction remained an independent predictor of mortality in the omicron wave in unvaccinated patients. While our study was not powered to detect larger differences in the laboratory and clinical aspects of COVID-19 across variant waves, it suggests gross differences between the waves compared to the initial wave that may be attributed to evolution of therapeutics, increase rate of vaccination, or the reported viral mutation that cause milder clinical presentation yet higher infectivity. All the aforementioned observations may partially explain the attenuation of the risk of mortality associated with the development of RV dysfunction. The fact that the attenuation of mortality risk persisted in patients with RV dysfunction from one viral variant to the other despite controlling for clinical variables related to the baseline status of the patients (age, sex, risk factors), laboratory parameters suggestive of the pathological effect of the virus (D-dimer), parameters suggestive of severity (mechanical ventilation) and commonly used medications, suggested that there is a fundamental change in viral virulence related to the mutations associated with the suggested variants, however further clinical and histopathological studies are needed to test this hypothesis.

4.1. Study limitations

This is a small single center retrospective study in a specific high-risk population composed of underreported racial groups. Larger multi-center studies should be done to confirm our findings. Due to the retrospective nature of the study, our data relies on wave classifications and associations with suspected variants and there were no molecular studies to confirm the variants involved. However, the various surges attributed to different viral variants were identified by the NY Department of Health as the dominant variants during the specified time period. In our study, complete state of vaccination was only reported in the surge that was attributed to the omicron variant and was not completely reported in the surge attributed to the delta variant, however the effects noted in our study are expected to occur partially because of vaccination status and suggests an expected well reported protective mechanisms of the vaccines. Nevertheless, further studies should take into consideration vaccination status and adjust for its effect. In our study, the baseline status of RV dysfunction as well as RV functions by follow-up echocardiograms are not known, which makes it unclear whether the RV dysfunction observed in our study is directly linked to COVID-19 infection. As such, it is not possible to deduce whether RV dysfunction occurred denovo as a result of COVID-19 infection or that COVID-19 infection exacerbated a pre-existing RV dysfunction effect. Accordingly, future studies should take a longitudinal follow-up of echocardiographic measures of RV dysfunction into consideration. RV dysfunction in our study was defined based on limited parameters that were shown in literature to be associated with outcomes in COVID-19 patients especially during the wave associated with the alpha variant [20]. As such, more comprehensive assessment of RV function may have changed the prevalence of RV dysfunction in our study and its association with in-hospital mortality. The study was concerned with short-term in-hospital outcomes. However, cardiopulmonary testing suggests chronic involvement in patients with long COVID syndrome and further studies should report long term effects in patients with RV dysfunction. Finally, our study was comprised of predominantly African-American and Hispanic patients. While this may be considered a limitation, we consider this a strength as these patients have been disproportionately affected by the COVID pandemic and have been grossly underrepresented in clinical studies.

5. Conclusion

To the best of our knowledge, this is the first report concerned with comparison of RV dysfunction and its prognostic associations in patients with COVID-19 in different waves speculated to be related to different mutant variants of the virus. Our study indicates that RV dysfunction as defined by RV dilation, depressed RV longitudinal function, or increased RV systolic pressure continued to occur across waves and across strains of the SARS-CoV-2 virus and however association with mortality continues to be attenuated with time from one wave to the other.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

There are no funding associated with this manuscript.

References

[1] D.M. Ronderos Botero, A.M.S. Omar, H.K. Sun, N. Mantri, K. Fortuzi, Y. Choi, M. Adrish, M. Nicu, J.N. Bella, S. Chilimuri, COVID-19 in the Healthy Patient Population: Demographic and Clinical Phenotypic Characterization and Predictors of In-Hospital Outcomes, Arterioscler Thromb. Vasc. Biol. 40 (2020) 2764–2775.

[2] Y. Li, L. Fang, S. Zhu, Y. Xie, B. Wang, L. He, D. Zhang, Y. Zhang, H. Yuan, C. Wu, H. Li, W. Sun, Y. Zhang, M. Li, L. Cui, Y. Cai, J. Wang, Y. Yang, Q. Lv, L. Zhang, A. M. Johri, M. Xie, Echocardiographic Characteristics and Outcome in Patients With COVID-19 Infection and Underlying Cardiovascular Disease, Front. Cardiovasc. Med. 8 (2021), 642973.

[3] H.M. Mahmoud-Elsayed, W.E. Moody, W.M. Bradlow, A.M. Khan-Kheil, J. Senior, L.E. Hudsmith, R.P. Steeds, Echocardiographic Findings in Patients With COVID-19 Pneumonia, Can. J. Cardiol. 36 (2020) 1203–1207.

[4] Omar A, De La Cruz Tejada A, Ronderos D, Hernandez N, Miranda J, Rehmani A, Nicu M, Chilimuri S and Bella Jonathan N. Echocardiography derived predictors of worse outcomes in the acute phase of covid-19 patients compared to matched controls. J. Am. College Cardiol., 2021; 77: 3168-3168.

[5] E. Argulian, K. Sud, B. Vogel, C. Bohra, V.P. Garg, S. Talebi, S. Lerakis, J. Narula, Right Ventricular Dilation in Hospitalized Patients With COVID-19 Infection, JACC Cardiovasc. Imag. 13 (2020) 2459–2461.

[6] J. Kim, A. Volodarskiy, R. Sultana, M.P. Pollie, B. Yum, L. Nambiar, R. Tafreshi, H. W. Mitlak, A. RoyChoudhury, E.M. Horn, I. Hriljac, N. Narula, S. Kim, L. Ndhlovu, P. Goyal, M.M. Safford, L. Shaw, R.B. Devereux, J.W. Weinsaft, Prognostic Utility of Right Ventricular Remodeling Over Conventional Risk Stratification in Patients With COVID-19, J. Am. Coll. Cardiol. 76 (2020) 1965–1977.

[7] S.P. Otto, T. Day, J. Arino, C. Colijn, J. Dushoff, M. Li, S. Mechai, G. Van Domselaar, J. Wu, D.J.D. Earn, N.H. Ogden, The origins and potential future of SARS-CoV-2 variants of concern in the evolving COVID-19 pandemic, Curr. Biol. 31 (2021) R918–R929.

[8] J.N. Kirkpatrick, C. Mitchell, C. Taub, S. Kort, J. Hung, M. Swaminathan, ASE Statement on Protection of Patients and Echocardiography Service Providers During the 2019 Novel Coronavirus Outbreak: Endorsed by the American College of Cardiology, J Am Coll Cardiol 75 (2020) 3078–3084.

[9] Salem Omar A, Alam L, Talebi S, Garc ıa-Sastre A, Narula J and Argulian E. Right Ventricular Abnormality in Patients Hospitalized With COVID-19 Infection During Omicron Variant Surge. American Journal of Cardiology 2022.

[10] Y. Li, H. Li, S. Zhu, Y. Xie, B. Wang, L. He, D. Zhang, Y. Zhang, H. Yuan, C. Wu, W. Sun, Y. Zhang, M. Li, L. Cui, Y. Cai, J. Wang, Y. Yang, Q. Lv, L. Zhang, M. Xie, Prognostic Value of Right Ventricular Longitudinal Strain in Patients With COVID-19, JACC Cardiovasc Imaging 13 (2020) 2287–2299.

[11] M.R. Dweck, A. Bularga, R.T. Hahn, R. Bing, K.K. Lee, A.R. Chapman, A. White, G. D. Salvo, L.E. Sade, K. Pearce, D.E. Newby, B.A. Popescu, E. Donal, B. Cosyns, T. Edvardsen, N.L. Mills, K. Haugaa, Global evaluation of echocardiography in patients with COVID-19, Eur Heart J Cardiovasc Imaging 21 (2020) 949–958.

[12] Omar A, Tejada ADLC, Ronderos D, Hernandez N, Miranda J, Rehmani A, Nicu M, Chilimuri S and Bella JN. ECHOCARDIOGRAPHY DERIVED PREDICTORS OF WORSE OUTCOMES IN THE ACUTE PHASE OF COVID-19 PATIENTS COMPARED

TO MATCHED CONTROLS. Journal of the American College of Cardiology 2021; 77: 3168-3168.

[13] X. Repesse, C. Charron, A. Vieillard-Baron, Right ventricular failure in acute lung injury and acute respiratory distress syndrome, Minerva Anestesiol. 78 (2012) 941–948.

[14] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395 (2020) 497–506.

[15] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062.

[16] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 323 (2020) 1061–1069.

[17] R.M. Inciardi, L. Lupi, G. Zaccone, L. Italia, M. Raffo, D. Tomasoni, D.S. Cani, M. Cerini, D. Farina, E. Gavazzi, R. Maroldi, M. Adamo, E. Ammirati, G. Sinagra, C. M. Lombardi, M. Metra, Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) 819–824.

[18] L. Alam, A.M.S. Omar, S. Talebi, J. Narula, E. Argulian, Echocardiographic Findings in Patients With COVID-19 With Myocardial Injury During the Omicron Variant Surge, Am. J. Cardiol. (2022).

[19] A. Salem Omar, L. Alam, S. Talebi, A. Garcıa-Sastre, J. Narula, E. Argulian, Right Ventricular Abnormality in Patients Hospitalized With COVID-19 Infection During Omicron Variant Surge, Am. J. Cardiol. (2022).

[20] B. Corica, A.M. Marra, S. Basili, R. Cangemi, A. Cittadini, M. Proietti, G.F. Romiti, Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis, Sci. Rep. 11 (2021) 17774.