Journal of the American Heart Association

ORIGINAL RESEARCH

Cardiologic Manifestations in Omicron-Type Versus Wild-Type COVID-19: A Systematic Echocardiographic Study

Eihab Ghantous, MD, MPH; Aviel Shetrit, MD; Aviram Hochstadt, MD, MPH; Ariel Banai, MD; Lior Lupu, MD, MBA; Erez Levi, MD; Yishay Szekely, MD; Nadav Schellekes, BMSc; Tammy Jacoby, MD; David Zahler, MD; Tamar Itach, MD; Philippe Taieb, MD; Sheizaf Gefen, MD; Dana Viskin, MD; Lia Shidlansik, MD; Amos Adler, MD; Ekaterina Levitsky, PhD; Ofer Havakuk, MD; Merav Ingbir, MD; Shmuel Banai, MD; Yan Topilsky, MD

BACKGROUND: Information about the cardiac manifestations of the Omicron variant of COVID-19 is limited. We performed a systematic prospective echocardiographic evaluation of consecutive patients hospitalized with the Omicron variant of COVID-19 infection and compared them with similarly recruited patients were propensity matched with the wild-type variant.

METHODS AND RESULTS: A total of 162 consecutive patients hospitalized with Omicron COVID-19 underwent complete echocardiographic evaluation within 24 hours of admission and were compared with propensity-matched patients with the wild-type variant (148 pairs). Echocardiography included left ventricular (LV) systolic and diastolic, right ventricular (RV), strain, and hemodynamic assessment. Echocardiographic parameters during acute infection were compared with historic exams in 62 patients with the Omicron variant and 19 patients with the wild-type variant who had a previous exam within 1 year. Of the patients, 85 (53%) had a normal echocardiogram. The most common cardiac pathology was RV dilatation and dysfunction (33%), followed by elevated LV filling pressure (E/e′ ≥14, 29%) and LV systolic dysfunction (ejection fraction <50%, 10%). Compared with the matched wild-type cohort, patients with Omicron had smaller RV end-systolic areas (9.3±4 versus 12.3±4 cm^2; P=0.0003), improved RV function (RV fractional-area change, 53.2%±10% versus 39.7%±13% [P<0.0001]; RV S′, 12.0±3 versus 10.7±3 cm/s [P=0.001]), and higher stroke volume index (35.6 versus 32.5 mL/m^2; P=0.004), all possibly related to lower mean pulmonary pressure (34.6±12 versus 41.1±14 mm Hg; P=0.0001) and the pulmonary vascular resistance index (P=0.0003). LV systolic or diastolic parameters were mostly similar to the wild-type variant-matched cohort apart from larger LV size. However, in patients who had a previous echocardiographic exam, these LV abnormalities were recorded before acute Omicron infection, but not in the wild-type cohort. Numerous echocardiographic parameters were associated with higher in-hospital mortality (LV ejection fraction, stroke volume index, E/e′, RV S′).

CONCLUSIONS: In patients with Omicron, RV function is impaired to a lower extent compared with the wild-type variant, possibly related to the attenuated pulmonary parenchymal and/or vascular disease. LV systolic and diastolic abnormalities are as common as in the wild-type variant but were usually recorded before acute infection and probably reflect background cardiac morbidity. Numerous LV and RV abnormalities are associated with adverse outcome in patients with Omicron.

Key Words: COVID-19 ■ echocardiography ■ Omicron ■ prognosis

Multiple reports suggest that cardiac complications are common in the wild-type SARS-CoV-2 (COVID-19 Wuhan-hu-1) variant and are associated with increased mortality.[1,2] At the beginning of the COVID-19 pandemic, we performed prospective systematic echocardiographic evaluation of patients with the wild-type variant using a predefined comprehensive echocardiographic protocol in all consecutive

Correspondence to: Yan Topilsky, MD, Department of Cardiology, Tel Aviv Medical Center, Weizmann 6, Tel Aviv 6423919, Israel. Email: topilskyyan@gmail.com

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027188

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Almost half of hospitalized patients with Omicron COVID-19 have normal echocardiographic examinations, one-third of the patients have right ventricular dysfunction, and fewer have left ventricular dysfunction.
- Numerous echocardiographic parameters were associated with higher in-hospital mortality (left ventricular ejection fraction, stroke volume index, E/e′, right ventricular S′) or need for mechanical ventilation or mortality (stroke volume index, E/e′, pulmonary vascular resistance).
- Compared with the wild-type-variant, patients with Omicron had smaller right ventricular size, improved right ventricular function, higher stroke volume index, and lower mean pulmonary pressure and pulmonary vascular resistance index; however, the prevalence of left ventricular systolic or diastolic dysfunction was similar to the matched patients with the wild-type-variant.

What Are the Clinical Implications?

- Echocardiography proved to be an important prognostic tool, predicting mortality and the need for mechanical ventilation, thus aiding in triaging admitted patients with Omicron.

patients admitted to our center, irrespective of severity of disease.[3] We showed that the most common cardiac manifestations are right ventricular (RV) dysfunction or dilatation, followed by left ventricular (LV) diastolic dysfunction, pericardial effusion, and systolic dysfunction.[3–7] The fifth COVID-19 variant of concern, Omicron (B.1.1.529 lineage), was first identified in South Africa on November 2021 and has a large number of changes in its spike protein relative to that of the wild-type virus.[8–10] Within weeks, Omicron had been reported by >100 countries, breaking COVID-19 infection records across Europe, North America, Africa, Australia, and Israel.[9] Preliminary reports have suggested that the proportion of cases admitted to hospitals is lower compared with earlier variants and that those admitted have less severe lung disease, hinting that Omicron replicates less well in lung cells than other variants.[8,9,11,12] Nevertheless, there is scarce literature on the effect of the Omicron variant on the heart of the affected patients. In the present study, we performed a complete prospectively predefined comprehensive echocardiographic evaluation of 162 consecutive patients with the COVID-19 Omicron variant of all disease grades requiring hospitalization, identical to the evaluation performed for the patients with the wild-type variant. We sought to determine the spectrum of cardiac manifestation, and their prognostic effect, stratified by the severity of disease. Furthermore, we compared the echocardiographic parameters in the patients with Omicron and the patients with the wild-type variant to historic echocardiographic exams, in 62 and 19 patients, respectively, who had a previous echocardiographic exam in our center within 1 year of acute Omicron infection. Lastly, we compared the cardiac involvement in the Omicron variant to 148 propensity-matched paired patients with the wild-type variant.

METHODS

The study population was composed of the following 2 cohorts of patients with COVID-19 infection: (1) the recent Omicron wave cohort that included 162 consecutive hospitalized patients who had their COVID-19 diagnosis between January 3, 2022, and January 25, 2022, confirmed by a positive reverse-transcriptase–polymerase chain reaction assay for SARS-CoV-2 and whole genome sequencing; and (2) the COVID-19 wild-type cohort that included 530 consecutive hospitalized patients who had their first SARS-CoV-2 infection between March 21, 2020, and September 16, 2020 with the wild-type variant. This “wild-type cohort” was used as control for the Omicron cohort. Both cohorts included consecutive prospectively studied adult patients (aged ≥18 years) admitted to the Tel Aviv Medical Center. All patients had demographic data, comorbid conditions, physical examinations, and laboratory findings systematically recorded. All patients underwent comprehensive transthoracic echocardiography within 48 hours of SARS-CoV-2 diagnosis as part of the predefined step-by-step protocol. Clinical and imaging data were collected prospectively. Clinical end points were defined as either in-hospital death or in-hospital respiratory deterioration. Respiratory deterioration was defined as acute new onset of hypoxemia requiring either invasive ventilation or noninvasive ventilation (bilevel positive airway pressure or high-flow inspiratory support (Vapotherm) or both). The ethics committee of the Tel Aviv Medical Center approved the study and voided the requirement of informed consent for the echocardiographic assessment. To evaluate for the presence of subtle echocardiographic abnormalities in a controlled fashion, we compared the echocardiographic characteristics in patients with COVID-19 with the reference values.[3] To assess the presence and severity of cardiac dysfunction related only to the virus, we analyzed the echocardiographic parameters in patients without cardiac disease (no ischemic heart disease or heart failure) and without cardiovascular risk factors (either hypertension, diabetes, or smoking) for the wild-type and Omicron variants. The data that support the findings of this

study are available from the corresponding author on reasonable request.

Whole Genome Sequencing of SARS-CoV-2–Positive Samples

Total nucleic acids were extracted from respiratory specimens. cDNA synthesis and enrichment were performed on the extracted total nucleic acids using the Illumina COVIDSeq Test. Amplicon libraries for viral genome sequencing using NovaSeq 6000 SP Reagent Kit version 1.5 were used as instructed by the manufacturer's manual. The library was sequenced on the Illumina NovaSeq platform according to the manufacturer's instructions.

Bioinformatic Analysis

Global phylogenetic placement was determined using the DRAGEN COVIDSeq version 3.5.5 platform (Illumina). FASTA sequences were analyzed using the pipeline developed by the Israeli National Consortium for SARS-CoV-2 Sequencing.[13]

Echocardiography

Echocardiography was performed in a standard manner using the same small, dedicated scanners (CX 50, Philips Medical Systems, Bothell, WA) by cardiologists with expertise in echocardiographic recording and interpretation. The following measures were undertaken to minimize the risk of inadvertent infection: (1) all echocardiographic studies were bedside studies performed at the designated COVID-19 internal ward units and (2) personal protection at the time of echocardiographic recordings included airborne precautions composed of N-95 respirator masks, gowns, gloves, head covers, eye shields, and shoe covers. Left ventricle diameters and LV ejection fraction (LVEF) were measured as recommended.[14] Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling (A wave) velocities, the E/A ratio, and deceleration time of early filling velocity. Early diastolic mitral septal and lateral annular velocities (e') were measured in the apical 4-chamber view.[15] Left atrial volume was calculated using the biplane area length method at end systole. Forward stroke volume was calculated from the LV outflow tract with subsequent calculation of cardiac output and index.

Right Ventricle Assessment

From RV-focused 4-chamber views encompassing the entire RV, end-systolic and end-diastolic RV areas and the tricuspid annulus were measured. Apart from qualitative grading, RV function was evaluated by tricuspid annular plane systolic excursion, systolic tricuspid lateral annular velocity (RV S′) measured in the apical 4-chamber view, and RV fractional area change.[14,16] Noninvasive RV hemodynamic variables included pulmonic acceleration time, estimated right atrial pressure, mean pulmonary artery pressure, pulmonary vascular resistance index, and RV stroke work. Mean pulmonary artery pressure was calculated based on the formula 48 – (0.28 × pulmonic acceleration time). Pulmonary vascular resistance index was calculated based on the formula (9– [0.07 × pulmonic acceleration time]) ×80. RV stroke work was calculated based on the formula 0.0136 × (stroke volume × [mean pulmonary artery pressure – right atrial pressure]).[6] Dilated RV was defined by comparing RV end-diastolic area index to sex-related reference values.[14] The cutoff used was RV end-diastolic area index >12.6 cm^2/m^2 for men and >11.5 cm^2/m^2 for women.

Two-Dimensional Speckle-Tracking Echocardiography

Speckle-tracking analysis was performed in accordance with the Consensus Document of the European Association of Cardiovascular Imaging/American Society of Echocardiography/Industry Task Force to Standardize RV and LV myocardial deformation imaging.[14,17] All speckle-tracking echocardiography analyses were performed offline. Peak RV free wall and global 4-chamber longitudinal and peak LV global longitudinal strain were obtained using grayscale images of apical views of 1 heart cycle. Analyses were done using commercial feature-tracking software (2-dimensional Cardiac Performance Analysis TomTec Imaging Systems, Unterschleissheim, Germany).

Statistical Analysis

Continuous normally distributed parameters were presented as mean±SD and compared using the Student *t* test. Normality was assessed using the Shapiro–Wilk test and visual inspection of quantile–quantile plots. Non-normally distributed data were presented by median and first and third quartiles and compared using the Wilcoxon rank sum test. Categorical data were compared between groups using the χ^2 test or Fisher exact test. To compare echocardiographic parameters during acute infection to historic exams, a paired *t* test was used. To identify variables that significantly affected in-hospital mortality, or the combined outcome, we evaluated them using univariable logistic regression. All variables with a significant relationship were entered into a multivariable logistic regression including age. The predictive ability of the echocardiographic parameters in patients with and without the Omicron variants was assessed using an interaction term. To compare the echocardiographic, clinical, and laboratory parameters in patients with the Omicron variant with those with the wild-type variant, the entire database of patients with wild-type COVID-19

(N=530) was used, and patients with the Omicron variant were matched in a 1:1 ratio to patients in the wild-type cohort. The propensity score was estimated using logistic regression with all variables entered into the model, and then matching was performed using nearest neighbor (ie, matching 2 closest propensity score pairs) with a 1:1 ratio between the Omicron and wild-type groups. To further decrease disparity in pairs, matching was restricted by a caliper of 0.7 of the SD of the propensity score. Assessment of balance was performed by inspecting resulting standardized mean differences. A standard mean difference of <0.2 was considered small.

The predefined baseline matching parameters were age, sex, body mass index, grade of disease, and history of ischemic heart disease. The selection process produced groups with balanced comorbidities. *P* values of <0.05 were considered to indicate statistical significance. All data were analyzed with the JMP System software version 12.0 (SAS Institute, Inc, Cary, NC).

RESULTS

Clinical data were collected in 236 consecutive patients hospitalized with the COVID-19 Omicron variant. A total of 72 patients were excluded because they did not undergo echocardiographic assessment. The reasons for not performing the echocardiogram were the following: hospital discharge ≤24 hours (11 patients), patient refusal (7 patients), death shortly after hospitalization (4 patients), and "do not resuscitate" status (50 patients). In 2 patients, the Omicron variant was not confirmed. Thus, the study group included 162 patients with the COVID-19 Omicron variant who underwent echocardiographic evaluation (aged 71.9±17 years; 62% men). At the time of baseline echocardiographic evaluation, patients were stratified to 91 patients with mild disease (no radiographic evidence of lower respiratory tract disease by x-ray film), 15 patients with moderate COVID-19 (radiographic evidence of lower respiratory tract disease and PO_2 saturation ≥94% in room air), and severe disease in 51 patients (oxygen saturation <94% at room air). A total of 5 patients were in critical condition at presentation (need for mechanical ventilation). Table 1 shows the baseline characteristics and echocardiographic assessments of all patients stratified by disease grade. The most common comorbidity was hypertension (53%), followed by diabetes (38%) and ischemic heart disease (24%). The majority of patients (125 [77%]) were vaccinated at least once, and all with the BNT162b2 vaccine (Pfizer–BioNTech). Baseline echocardiographic characteristics of patients with Omicron COVID-19 compared with reference values[3] are shown in Table S1. The most common echocardiographic pattern (33%) was RV dilatation (either RV end-diastolic or end-systolic area above normal range) with or without dysfunction (either abnormal RV S′, tricuspid annular plane systolic excursion, or RV fractional area change), followed by elevated filling pressure (E/e′ ≥14, 29%), and systolic dysfunction (LVEF <50%, 10%). The remaining 85 (53%) patients had a normal echocardiogram. Analyzing vaccination status as can be seen in Table S2 shows that vaccination/prior infection status (either ≥1 vaccine or any prior COVID-19 infection) did not impact the infection severity (with the exception of higher CRP [C-reactive protein] and rate of atrial fibrillation in nonvaccinated patients) and the severity of RV abnormalities. Of note, nonvaccinated patients were slightly younger, which may have skewed the data in their favor.

Comparison With the Historic Echocardiographic Exams in the Patients With Omicron

To assess if pathologic LV, RV, and Doppler parameters in the Omicron cohort are related to the acute infection, we compared them in 62 patients to historic echocardiographic exams within 1 year (218 [48, 355] days - median [IQR]). The results of these comparisons are shown in Table 2 and in Figure 1. No significant changes occurred during acute disease, including LV systolic and most LV diastolic parameters, and there was no change in RV size, function, or right-sided hemodynamics (*P*>0.2 for all). The only exception was a decrease in the A wave velocity during acute infection. In 7/9 (78%) of the patients with low LVEF during acute Omicron infection who had a previous echocardiographic exam, low LVEF had already been recorded. In 15/22 (68%) of the patients with elevated left-filling pressure who had a previous echocardiographic exam, E/e′ ≥14 had already been recorded. In 14/16 (88%) of the patients with RV dilatation or dysfunction who had a previous echocardiographic exam, RV dilatation or dysfunction had already been recorded.

Comparison With the Wild-Type COVID-19 Cohort

Matching produced 148 pairs of patients with Omicron and the wild-type COVID-19 variant, with an overall nonsignificant difference between group's clinical characteristics (*P*>0.2 for all). Patients with the wild-type variant had higher troponin, D-dimers, and CRP than the matched patients with Omicron. Characteristics of both groups, stratified to clinical, LV, RV, and Doppler characteristics, are presented in Table 3 and Figure 2. Patients with the wild-type variant had smaller LV, but no difference in LVEF, compared with patients in the Omicron-variant matched cohort. Patients with the wild-type variant had larger RV, poorer RV function, lower stroke volume index and cardiac index, lower E wave velocity, higher estimated mean pulmonary artery pressure, and higher pulmonary vascular resistance compared with patients in the Omicron-variant matched cohort. In the wild-type cohort, 83% of

Table 1. Baseline Clinical and Echocardiographic Characteristics of Hospitalized Patients With Omicron Stratified by Severity of Disease

Variables	All, N=162	Mild/moderate, n=106	Severe/critical, n=56	*P* value
Clinical characteristics				
Age, y, mean±SD	71.9±17	70.3±18	74.8±14	0.08
Male sex, n (%)	100 (62)	60 (63)	40 (42)	0.45
BMI, mean±SD	26.6±5	26.5±5	26.8±5	0.72
BSA, mean±SD	1.85±0.2	1.85±0.2	1.85±0.2	0.89
Ischemic heart disease, n (%)	39 (24)	22 (21)	17 (30)	0.21
Stroke, n (%)	28 (17)	18 (17)	10 (18)	0.94
Chronic kidney disease, n (%)	32 (20)	17 (16)	15 (27)	0.10
COPD, n (%)	9 (6)	4 (4)	5 (9)	0.19
Other lung disease, n (%)	11 (7)	5 (5)	6 (10)	0.17
Any lung disease, n (%)	20 (12)	9 (8)	11 (20)	0.04
Diabetes, n (%)	62 (38)	45 (43)	17 (29)	0.10
Hypertension, n (%)	86 (53)	56 (53)	30 (53)	0.93
Vaccinated, n (%)	125 (77)	79 (75)	46 (83)	0.27
Temperature, °C, mean±SD	37.3±0.7	37.3±0.8	37.3±0.5	0.75
O_2 saturation, %, mean±SD	93.0±5	94.9±4	88.5±4	<0.0001
Heart rate, beats/min, mean±SD	88.6±22	87.5±23	91.0±19	0.49
SBP, mm Hg, mean±SD	131.3±24	131.0±25	131.7±23	0.90
DBP, mm Hg, mean±SD	72.9±15	71.9±15	75.2±15	0.40
Hemoglobin, g/dL, mean±SD	12.1±2	12.2±2	12.1±2	0.85
White blood cells, $10^3/\mu L$, median [quartiles]	7.1 (4.8, 9.9)	6.8 (4.7, 10.2)	8 (5.3, 9.4)	0.49
Platelets, $10^3/\mu L$, mean±SD	192.6±82	194.0±80	189.3±90	0.83
Blood urea nitrogen, mg/dL, mean±SD	25.8±24	22.0±11	34.8±40	0.07
Creatinine, mg/dL, mean±SD	1.25±1.1	1.14±0.9	1.53±1.5	0.12
C-reactive protein, mg/L, median (quartiles)	40 (13, 117)	27 (7, 74)	65 (25, 146)	0.002
D-dimer, mg/L, mean±SD	2.6±4.7	2.1±2.5	3.5±7.0	0.30
Troponin-I, ng/L, median (quartiles)	14 (5, 64)	11 (4, 64)	19 (8, 65)	0.10
Brain natriuretic peptide, median (quartiles)*	165 (55, 770)	108 (36, 422)	378 (93, 1068)	0.05
Bilateral infiltrate, n (%)	40 (25)	15 (14)	25 (45)	<0.0001
Atrial fibrillation, n (%)	19 (12)	16 (15)	3 (5)	0.07
ST/T wave changes, n (%)	43 (27)	30 (28)	13 (23)	0.48
Echocardiography				
Global longitudinal strain, mean±SD	–17.8±5.1	–18.0±4.8	–17.2±5.5	0.55
LVEF, %	55.5±9	56.5±7	54.8±8	0.23
LVEDD, mm, mean±SD	45.6±8	46.1±6	45.4±9	0.56
LVESD, mm, mean±SD	30.8±7	30.4±7	31.0±7	0.64
LAVI, mL/m^2, mean±SD	34.1±14	35.3±15	32.7±11	0.28
RV free wall strain, mean±SD	–20.9±7.4	–21.1±7.6	–20.3±7.2	0.57
RV global 4C strain, mean±SD	–17.2±4.7	–17.7±4.3	–16.2±5.3	0.10
RVEDA index, cm^2/m^2, mean±SD	10.8±4	11.1±4	10.4±4	0.44
RVESA index, cm^2/m^2, mean±SD	4.9±2	5.3±2	4.5±2	0.10
RVFAC, %, mean±SD	55.5±10	51.8±10	55.6±10	0.13
TAPSE, cm, mean±SD	2.2±0.5	2.2±0.5	2.2±0.4	0.97
RV S′, cm/s, mean±SD	12.0±3	11.8±3	12.4±4	0.25
SVI, mL/m^2, mean±SD	35.6±10	36.4±11	34.1±8	0.18

(*Continued*)

Table 1. Continued

Variables	All, N=162	Mild/moderate, n=106	Severe/critical, n=56	*P* value
CI, L/min per m^2, mean±SD	2.7±0.8	2.7±0.9	2.7±0.6	0.95
E wave velocity, cm/s, mean±SD	78.6±23	75.4±21	82.3±27	0.09
A wave velocity, cm/s, mean±SD	69.7±22	70.7±22	72.3±22	0.69
E/A ratio, mean±SD	1.19±0.6	1.13±0.6	1.15±0.6	0.87
e′ septal, cm/s, mean±SD	6.5±2	6.6±2	6.1±2	0.15
e′ lateral, cm/s, mean±SD	8.0±3	8.2±3	7.6±3	0.23
E/e′ average ratio, mean±SD	12.3±6	11.6±5	14.0±7	0.02
RAP, mm Hg, mean±SD	7.9±4	7.6±4	8.6±4	0.24
SPAP, mm Hg, mean±SD*	37.5±12	35.1±9	42.0±14	0.02
PAT, msec, mean±SD	91.6±24	97.2±23	81.0±19	0.0001
PAT<90 msec, %	47	34	70	0.0002
Global, segmental, or normal systolic function, %	Global, 21 Segmental, 10 Normal, 69	Global, 20 Segmental, 10 Normal, 70	Global, 20 Segmental, 12 Normal, 68	0.94
Pericardial fluid, %	13	10	18	0.17

4C indicates 4-chamber; BMI, body mass index; BSA, body surface area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PAT, pulmonic acceleration time; RAP, right atrial pressure; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; SVI, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

*Assessed only in 36 patients.

patients had at least 1 abnormal RV-related parameter compared with only 48% in the matched Omicron cohort (*P*<0.0001). Table S3 shows the main echocardiographic findings in the matched Omicron and wild-type cohort categorized by COVID-19 severity (mild/moderate versus severe and critical). As can be seen, patients with the wild-type variant had larger RV, poorer RV function, and higher pulmonary vascular resistance compared with patients in the Omicron-variant matched cohort irrespective of grade of disease. Interestingly, patients with Omicron and severe disease had higher E/e′ than matched patients with the wild-type variant.From 148 pairs of patients with Omicron and the wild-type COVID-19 who underwent routine echocardiographic evaluation, subsequent offline speckle-tracking echocardiography evaluation was feasible in 85 (57%) and 135 (91%) patients for the left ventricle and right ventricle in the Omicron cohort and in 93 (63%) and 115 (78%) patients for the left ventricle and right ventricle in the wild-type cohort, respectively. In the Omicron cohort, patients with poorer clinical grade levels had similar left ventricular global longitudinal strain, right ventricular global longitudinal strain, and right ventricular free wall longitudinal strain (*P*>0.1 for all; Table 1). Surprisingly, as shown in Table 2, patients with Omicron-type acute infection and a preceding echocardiographic exam showed improvement in left ventricular global longitudinal strain during acute infection, but no difference in right ventricular global longitudinal strain and right ventricular free wall longitudinal strain compared with the evaluation performed before the acute phase of the disease. Neither left ventricular global longitudinal strain nor right ventricular global longitudinal strain and right ventricular free wall longitudinal strain were associated with mortality (Table 4).

A total of 36 (24%) patients with Omicron were treated with COVID-19–targeted therapy (6 baricitinib, 4 molnupiravir, 1 casirivimab and imdevimab, 23 nirmatrelvir and ritonavir, and 13 remdesevir). None of the patients with the wild-type infection were treated with COVID-19–targeted therapy. COVID-19–targeted therapy was not associated with mortality in the univariate analysis (Table 4).

When adjusted for age and COVID-19–related therapies, tricuspid annular plane systolic excursion (odds ratio [OR], 0.12 [0.3–0.5]; *P*=0.02), but not stroke volume index (OR, 0.21 [0.02–2.5]; *P*=0.2), was associated with mortality. As with the patients with the Omicron variant, in the matched patients with the wild-type variant, we compared the echocardiographic parameters of the acute infection to a historic echocardiogram from the past year (Table S4) and found that patients with acute wild-type infection had a marked decrease in LV end-diastolic diameter, A wave velocity, E/e′, stroke volume, and RV S′, concomitant with an increase in RV end-diastolic area, right atrium pressure, and shortening of pulmonic acceleration time.

Patients with acute wild-type infection and no cardiac disease or cardiovascular risk factors, compared with matched patients with acute Omicron-type infection, had smaller LV size, smaller left atrium volume index and lower E wave velocity, E/e′, stroke volume index, and RV S′, concomitant with a slight increase in RV end-diastolic area and shortening of pulmonic acceleration time (Table S5).

Table 2. Echocardiographic Characteristics Before Compared With During Acute Omicron COVID-19 Infection

Variables	Pre-Omicron, N=61	Acute infection, N=61	*P* value paired *t* test
LVEF, %, mean±SD	56.2±9	54.9±8	0.08
Global longitudinal strain (N=21), mean±SD	−13.3±7.0	−17.8±5.1	0.004
LVEDD, mm, mean±SD	46.9±7	46.7±7	0.79
LVESD, mm, mean±SD	30.9±8	31.2±8	0.69
Stroke volume, mL, mean±SD	67.8±18	64.1±20	0.14
Cardiac output, L/m^2, mean±SD	4.9±1.2	4.9±1.4	0.80
LA volume, mL, mean±SD	71.7±26	76.2±29	0.43
E wave, cm/sec, mean±SD	79.4±26	80.1±24	0.86
A wave, cm/sec, mean±SD	82.7±23	72.3±25	0.0009
E/A ratio, mean±SD	1.03±0.6	1.22±0.8	0.20
E/e′ average, mean±SD	13.5±6	14.1±6	0.35
PAT, msec, mean±SD	88.5±25	83.5±21	0.33
SPAP, mm Hg, mean±SD	45.1±13	40.1±10	0.11
RA pressure, mm Hg, mean±SD	8.2±5	11.4±9	0.08
RV free wall strain, N=35, mean±SD	−20.2±7.7	20.9±7.4	0.76
RV global 4C strain, N=35, mean±SD	−15.9±5.8	−17.2±4.7	0.26
RVEDA, cm^2, mean±SD	19.0±6	19.9±8	0.56
RVESA, (cm^2), mean±SD	9.7±4	9.7±6	0.93
RVFAC, (%), mean±SD	51.3±8	51.8±10	0.81
TAPSE, (mm), mean±SD	20.2±5	21.7±5	0.44
Pulsed RV S′, cm/s, mean±SD	11.3±3	11.7±3	0.42

4C indicates 4-chamber; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PAT, pulmonic acceleration time; RA, right atrium; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.

Association Between Echocardiographic Parameters and Outcome

In the matched cohort, 11 and 30 patients with the COVID-19 Omicron and wild-type variants, respectively, died in the hospital (*P*=0.001). In the matched cohort, 14 and 38 patients with the Omicron and wild-type variants, respectively, needed in-hospital mechanical (invasive or noninvasive) ventilation (*P*=0.0002). In the matched cohort, 19 and 45 patients with the Omicron and wild-type variants, respectively, had a clinical combined in-hospital event (*P*=0.0002). Results of the univariate analyses for mortality are shown in Table 4. Results of the univariate analyses for the combined event are shown in Table S6. The echocardiographic parameters significantly associated with a higher risk of either in-hospital mortality or the combined event in the wild-type variant were all RV related and included RV S′, tricuspid annular plane systolic excursion, right atrial pressure, and pulmonic acceleration time (Table 4). However, in the Omicron-variant cohort, in addition to RV-related parameters, LVEF, stroke volume index, cardiac index, and E/e′ were also associated with outcome. Interestingly, the impact of E/e and stroke volume index on outcome were restricted to the patients with Omicron in the interaction analysis (*P* values 0.04 and 0.02, respectively). When adjusted for age and COVID-19–related therapies, RV-related parameters and stroke volume index were still associated with outcome (Table 4 and Table S5).

DISCUSSION

This is the first systematic echocardiographic study of nonselected hospitalized patients with Omicron-variant COVID-19 requiring hospitalization. Of the hospitalized patients with Omicron-type COVID-19 acute infection, 53% have normal echocardiography at presentation. The most common echocardiographic pathology was RV dilatation with or without dysfunction (33%), followed by elevated left-filling pressure (29%), and systolic dysfunction (10%). The prevalence of LV systolic or diastolic dysfunction was similar to the wild-type variant cohort.[3] However, in difference with the patients with the wild-type variant who had a previous echocardiographic exam in which acute infection resulted in lower left-filling pressure, LV size, and stroke volume, these LV abnormalities have already been recorded before in the patients with acute Omicron infection. Compared with matched patients with the wild-type variant, patients with the Omicron variant had larger LV size, smaller RV, better RV function, and higher stroke volume, all related to lower pulmonary pressure and pulmonary vascular resistance. Numerous LV and RV echocardiographic parameters are associated with in-hospital mortality and the need for mechanical ventilation in patients with the Omicron variant.

Patients with acute wild-type infection and no cardiac disease or cardiovascular risk factors had echocardiographic LV and RV parameters, suggesting that acute wild-type infection causes acute elevation of RV afterload, resulting in lower left-filling pressure and stroke volume. However, in a similar group of patients with acute Omicron-type infection, these changes were not recorded.

RV Dysfunction

We have previously shown that RV hemodynamics and function are poor in a large proportion of patients assessed during the early acute phase of infection with

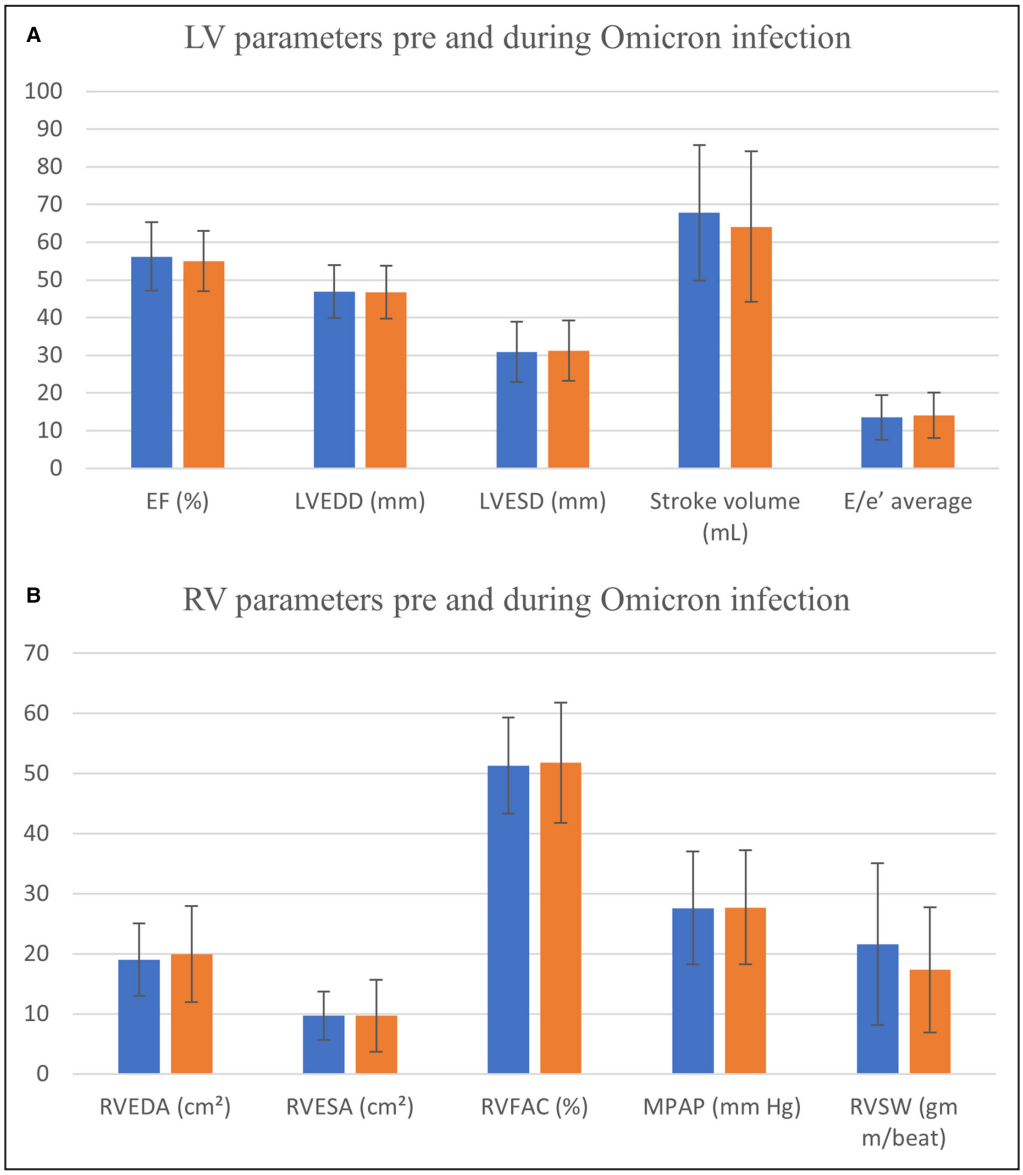

Figure 1. Echocardiographic parameters before and during acute Omicron COVID-19 infection. **A**, Left ventricle–related parameters. Blue boxes denote pre-Omicron parameters. Orange boxes denote parameters during acute infection. **B**, Right ventricle–related parameters. Orange boxes denote pre-omicron parameters. Blue boxes denote parameters during acute infection. EF indicates ejection fraction; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MPAP, mean pulmonary artery pressure (mm Hg); RV, right ventricular; RVEDA, right ventricular end-diastolic area (cm^2); RVESA, right ventricular end-systolic area (cm^2); RVFAC, right ventricular fractional area change (percentage); and RVSW, right ventricular stroke work ([gm m]/beat).

the wild-type COVID-19 variant.[3–7] We have also shown that these RV abnormalities are strongly related to elevated pulmonary vascular resistance,[6] outcome,[6] and worse COVID-19–related lung injury.[5] There are many conditions that can precipitate acute RV failure or increase pulmonary vascular resistance. These include primary RV injury related to infection or cytokine storm, pulmonary embolism, hypoxic pulmonary vasoconstriction, decrease in lung volume, bacterial superinfection, elevated left atrial pressure, or a combination. In the wild-type cohort, patients with higher pulmonary resistance and RV dysfunction were older, had more comorbidities, and most important had worse lung disease, lower oxygen saturation, and higher left-filling pressure.[6] Those data suggested that elevated pulmonary vascular resistance in the wild-type cohort is multifactorial and related to parenchymal lung disease, pulmonary vascular disease, and elevated left atrial pressure, all leading to RV dysfunction. In the present Omicron cohort, RV dilatation and dysfunction are

Table 3. Baseline Clinical and Echocardiographic Characteristics of Hospitalized Omicron Versus Matched Wild-Type COVID-19 Variants

Variables	Wild type	Omicron	*P* value
Clinical characteristics			
Age, y, mean±SD	71.0±16	71.4±17	0.78
Male sex, n (%)	89 (60)	94 (63)	0.55
Severity grade, n (%)			1.0
Mild	80 (54)	80 (54)	
Moderate	14 (10)	14 (10)	
Severe	47 (31)	47 (31)	
Critical	7 (5)	7 (5)	
BSA, mean±SD	1.82±0.2	1.84±0.2	0.57
Ischemic heart disease, n (%)	34 (23)	38 (25)	0.59
Diabetes, n (%)	48 (32)	55 (37)	0.40
Stroke, n (%)	18 (12)	24 (16)	0.31
Chronic kidney disease, n (%)	24 (16)	29 (19)	0.45
Hypertension, n (%)	94 (63)	87 (59)	0.40
COPD, n (%)	14 (9)	10 (7)	0.39
Other lung disease, n (%)	6 (4)	10 (7)	0.30
Lung disease, n (%)	20 (14)	20 (14)	1.0
Temperature, °C, mean±SD	37.5±0.8	37.4±0.8	0.47
O_2 saturation, %, mean±SD	91.9±10	92.9±5	0.29
Heart rate, beats/min, mean±SD	85.3±15	89.2±22	0.17
SBP, mm Hg, mean±SD	137.2±22	132.2±26	0.15
DBP, mm Hg, mean±SD	75.2±12	72.9±15	0.25
Hemoglobin, g/dL, mean±SD	12.9±2	12.2±2	0.004
White blood cells, 10^3/μL, mean±SD	7.6±3	10.0±21	0.21
Platelets, 10^3/μL, mean±SD	201.6±90	199.2±93	0.82
Blood urea nitrogen, mg/dL, mean±SD	23.6±21	25.6±22	0.42
Creatinine, mg/dL, mean±SD	1.19±1.2	1.3±1.2	0.52
C-reactive protein, mg/L, median [quartiles]	76 [24, 145]	38 [11, 117]	0.001
D-dimer, mg/L, median [quartiles]	0.9 [0.5, 1.8]	0.2 [0, 1.1]	<0.0001
Troponin-I, ng/L, median [quartiles]	11 [5, 25]	5 [0, 21]	0.0003
Bilateral infiltrate, n (%)	66 (45)	28 (19)	<0.0001
Pleural effusion, n (%)	7 (5)	11 (7)	0.33
Lobar infiltrate, n (%)	24 (16)	9 (6)	0.005
Atrial fibrillation, n (%)	7 (5)	8 (5)	0.81
ST/T wave changes, n (%)	17 (11)	20 (13)	0.59
Echocardiography			
LV and LA parameters			
Global longitudinal strain, mean±SD	−17.1±3.6	−17.9±5.1	0.38
LVEF, %, mean±SD	56.8±7	56.1±7	0.40
Abnormal LVEF, n (%)	15 (10)	15 (10)	1.0
LVEDD, mm, mean±SD	43.5±7	45.9±7	0.005
LVESD, mm, mean±SD	27.6±8	30.5±7	0.004
LA volume, mL, mean±SD	63.0±29	64.0±28	0.75
LAVI, mL/m^2, mean±SD	34.6±16	34.6±14	0.99
RV parameters			
RV free wall strain, mean±SD	−20.4±9.8	−20.7±7.7	0.85
RV global 4C strain, mean±SD	−17.3±5.9	−17.1±4.8	0.67
RVEDA, cm^2, mean±SD	21.1±5	19.8±6	0.17
RVEDA index, cm^2/m^2, mean±SD	11.4±2	11.0±4	0.32
RVESA, cm^2, mean±SD	12.3±4	9.3±4	0.0006
RVESA index, cm^2/m^2, mean±SD	6.9±2	5.0±2	<0.0001
RVFAC, %, mean±SD	39.7±13	53.2±10	<0.0001
Abnormal RVFAC, (%)	61 (41)	4 (3)	<0.0001
TAPSE, cm, mean±SD	2.15±0.5	2.18±0.4	0.66
Abnormal TAPSE, (%)	34 (23)	24 (16)	0.15
RV S′, cm/s, mean±SD	10.7±3	12.0±3	0.001
Abnormal RV S′	54 (36)	47 (31)	0.41
Abnormal RV function/size	123 (83)	71 (48)	<0.0001
Doppler and hemodynamic parameters			
Stroke volume, mL, mean±SD	58.9±19	65.6±19	0.004
SVI, mL/m^2, mean±SD	32.5±10	35.6±10	0.009
Abnormal SVI, (%)	100 (68)	74 (50)	0.002
Cardiac output, L/min, mean±SD	4.5±1.5	5.0±1.6	0.008
CI, L/min per m^2, mean±SD	2.5±0.8	2.7±0.8	0.01
Abnormal CI, n (%)	86 (58)	68 (46)	0.03
E wave velocity, cm/s, mean±SD	67.5±25	77.8±24	0.0006
A wave velocity, cm/s, mean±SD	66.7±19	70.4±21	0.16
E/A ratio, mean±SD	1.00±0.5	1.16±0.6	0.02
e′ septal, cm/s, mean±SD	6.2±2	6.3±2	0.51
e′ lateral, cm/s, mean±SD	7.7±3	8.0±3	0.47
E/e′ average ratio, mean±SD	11.0±6	12.3±6	0.08
Abnormal E/e′, n (%)	37 (25)	41 (28)	0.59
RAP, mm Hg, mean±SD*	8.2±4	8.7±7	0.53
Abnormal RAP*, n (%)	64 (48)	46 (42)	0.33
SPAP, mm Hg, mean±SD*	37.8±13	37.5±11	0.91
Abnormal SPAP, n (%)*	12 (38)	28 (39)	0.85
PAT, msec, mean±SD	80.4±26	91.9±23	0.0003

(*Continued*)

(*Continued*)

Table 3. Continued

Variables	Wild type	Omicron	*P* value
Abnormal PAT, n (%)	90 (61)	52 (35)	<0.0001
MPAP, mm Hg, mean±SD	41.1±14	34.6±12	0.0001
PVR index, dynes x sec/ cm^5 per m^2	269±144	205±132	0.0003
RVSW, gm m/beat, mean±SD	25.4±11	23.2±13	0.20

4C indicates 4-chamber; BSA, body surface area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; LA, left atrium; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MPAP, mean pulmonary artery pressure; PAT, pulmonic acceleration time; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; RVSW, right ventricular stroke work; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; SVI, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

*RV size/function was qualitatively assessed using multiple acoustic windows. Abnormal RV size/function was defined as RV size/dysfunction ≥mild, abnormal LVEF (<50%), abnormal TAPSE (<17 mm), abnormal S′ (<9.5 cm/sec), and abnormal RV fractional area change (<35%).

less pronounced compared with the matched patients with the wild-type variant. Because the patients were matched for comorbidities and age, the difference in RV parameters is most probably related to either lesser inflammatory response, lung parenchymal or vascular injury, better left atrial pressure, or a combined effect of these conditions. Based on our data, it seems that the major mechanism is indeed lesser lung injury, inflammatory response (suggested by lower CRP), and vascular disease (suggested by lower D-dimers). There was no difference in parameters related to left-filling pressure (E/e′, left atrium volume index) between these cohorts. In fact, there was a trend for higher left-filling pressure in the Omicron cohort, reaching clinical significance in the patients with severe infection, possibly attributed to improved RV function and volume delivery to the left atrium. There was also no difference in RV stroke work between the cohorts. Thus, it is unlikely that the lower rate of RV dysfunction observed in the Omicron cohort is related to lower LV filling pressure or attenuated primary RV injury. On the other side, all parameters related to pulmonary vascular resistance (mean pulmonary artery pressure, pulmonary vascular resistance) or lung parenchymal injury (higher prevalence of either bilateral, or lobar lung infiltrates, in chest x-ray film) were better in the patients with Omicron compared with the matched patients with the wild-type variant, suggesting that this milder lung injury is the main mechanism for attenuated RV dysfunction compared with the wild-type variant. The reasons for the milder lung injury in admitted patients during the Omicron pandemic are not known but are likely to be attributed to either a less virulent virus, higher immunity from prior COVID-19 infections, vaccinations, or combination.[8,9,11,12,18] Indeed, in the present cohort, 77% of patients were vaccinated at least once (25 patients up to 4 times) compared with none in the wild-type cohort. This suggests a possible role for vaccination or improved immunity attributed to a previous infection in reducing lung and consequential RV injury. Unfortunately, the vaccinated patients in our Omicron cohort were much older and had more comorbidities compared with unvaccinated patients, thus it was impossible to assess the isolated role of vaccination versus innate virus virulence in our study. A recent tissue-based study showed that the Omicron variant infects the cells of the bronchus faster, but cells of the lung slower than previous strains.[18,19] This may at least partially account for the less severe lung disease and improved RV function in the patients with Omicron.

LV Function

Numerous reports showed that patients infected with the wild-type strain have prevalent LV abnormalities in echocardiography[3,7] or by cardiac magnetic resonance imaging.[20] LV dysfunction was attributed to either direct myocardial viral invasion, endothelial injury, or the "cytokine storm" in these patients with wild-type COVID-19.[1,21] Interestingly, LV involvement was described even in the absence of severe lung disease.[1,2,7,22] Echocardiographic assessment of patients with either the wild-type or Omicron variant in our study involved routine studies in all consecutive patients with COVID-19 infection, irrespective of severity of disease or clinical indication, to assess a homogeneous unselected patient population. LVEF and E/e′ were mostly in the normal range in the Omicron hospitalized cohort; however, the prevalence of abnormal ejection fraction or E/e′ were similar to the matched patients with the wild-type variant. Importantly, in the majority of patients with abnormal LV systolic function, or elevated filling, and a previous echocardiographic exam, similar abnormalities were recorded in the exam before the current admission, suggesting that in most patients with Omicron, LV dysfunction is related to background cardiac disease and that acute infection does not cause significant additive LV injury. However, it is important to note that assessment of LV function by routine echocardiography may underestimate LV injury, and acute injury may be more common once more advanced imaging methods, such as cardiac magnetic resonance imaging, or LV speckle tracking analysis are used.[7] Importantly, even if just representing background cardiac morbidity, parameters of LV systolic and diastolic dysfunction were associated with excess events in patients with the Omicron variant. Thus, it seems to be important to identify LV function in patients with the Omicron variant for better risk

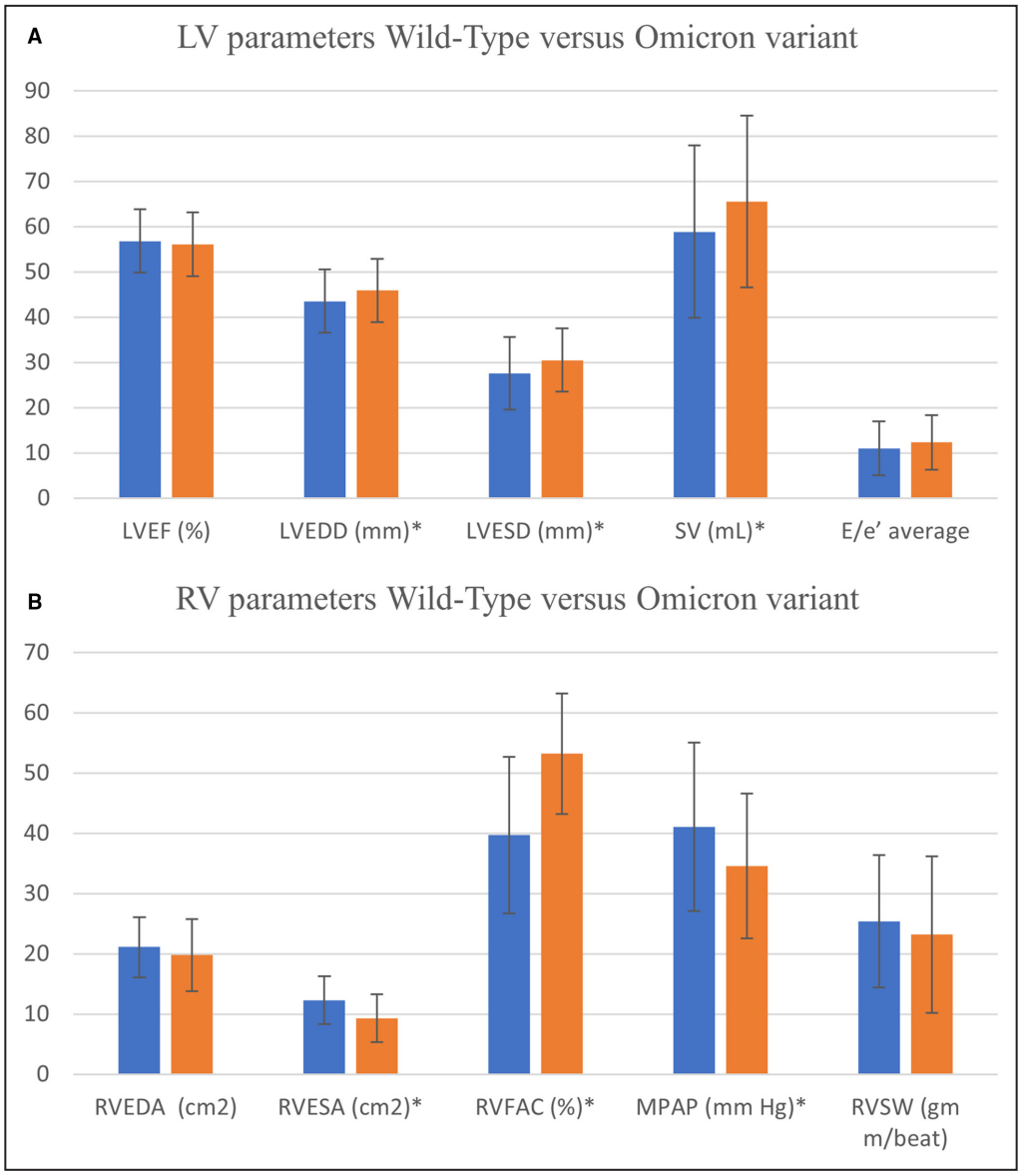

Figure 2. Echocardiographic parameters during acute wild-type vs Omicron COVID-19 infection. **A**, Left ventricle–related parameters. Blue boxes denote wild-type variant parameters during acute infection. Orange boxes denote Omicron variant parameters during acute infection. **B**, Right ventricle–related parameters. Blue boxes denote wild-type variant parameters during acute infection. Orange boxes denote Omicron variant parameters during acute infection. LV indicates left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MPAP, mean pulmonary artery pressure (mm Hg); RV, right ventricular; RVEDA, right ventricular end-diastolic area (cm^2); RVESA, right ventricular end-systolic area (cm^2); RVFAC, right ventricular fractional area change (percentage); RVSW, right ventricular stroke work ([gm m]/beat); and SV, stroke volume. *Denotes *P* value <0.05.

stratification, and possibly, in future studies, to assess LV function by these more advanced and sensitive technologies.

In the patients with Omicron-type infection, there were no significant differences in LV/RV functional parameters between patients with severe versus mild/moderate infection, incongruent with our assumption that lesser RV alterations in Omicron may be related to milder lung injury. Severe/critical infection can affect LV/RV in 2 "opposite" directions. It can decrease function by increasing RV afterload, decreasing LV preload, or by direct injury to the myocardium. However, it can improve contraction by increasing the adrenergic tone. In patients infected with the wild-type strain, the marked alterations in RV afterload, LV preload, and possible myocardial injury resulted in worsening

Table 4. Outcome Analysis of Echocardiographic Prediction of Clinical Events

Parameter	Odds ratio mortality Omicron (95% CI)	Odds ratio mortality wild type (95% CI)	*P* interaction mortality
Age	1.07 (1.007–1.13); *P*=0.008	1.09 (1.04–1.14); *P*<0.0001	0.60
Sex	0.98 (0.27–3.5); *P*=0.98	1.007 (0.44–2.28); *P*=0.98	0.89
COVID-19 therapies	0.83 (1.17–4.1); *P*=0.82	NA	
Troponin-I	1.002 (1.002–1.006); *P*=0.02	1.004 (1.0006–1.008); *P*=0.003	0.02
Global longitudinal strain	1.06 (0.92–1.23); *P*=0.39	0.85 (0.72–0.99); *P*=0.03	0.05
LVEF	0.94 (0.89–0.99); *P*=0.04	0.98 (0.92–1.04); *P*=0.45	0.40
SVI	0.89 (0.81–0.97); *P*=0.004	0.98 (0.94–1.02); *P*=0.38	0.04
CI	0.32 (0.11–0.98); *P*=0.02	0.92 (0.54–1.56); *P*=0.75	0.08
E/e′	1.12 (1.04–1.23); *P*=0.006	1.05 (0.98–1.12); *P*=0.14	0.19
LAVI	1.001 (0.96–1.04); *P*=0.93	1.01 (0.98–1.03); *P*=0.47	0.77
RV free wall strain	1.04 (0.97–1.12); *P*=0.4	0.91 (0.76–1.01); *P*=0.10	0.11
RV global 4C strain	1.12 (0.99–1.28); *P*=0.09	0.89 (0.77–1.02); *P*=0.09	0.40
TAPSE	0.46 (0.21–1.03); *P*=0.07	0.50 (0.31–0.81); *P*=0.005	0.88
RV S″	0.87 (0.78–0.98); *P*=0.03	0.89 (0.82–0.98); *P*=0.02	0.76
RA pressure	1.03 (0.96–1.1); *P*=0.33	1.10 (0.99–1.21); *P*=0.06	0.29
PAT	0.98 (0.95–1.00); *P*=0.055	0.98 (0.96–0.99); *P*=0.03	0.92
PVR index	1.003 (0.99–1.007); *P*=0.1	1.003 (1.001–1.007); *P*=0.03	0.92

4C indicates 4-chamber; CI, cardiac index ; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; NA, not assessed; PAT, pulmonic acceleration time; PVR, pulmonic vascular resistance; RA, right atrium; RV, right ventricular; SVI, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

LV/RV functional parameters in patients with severe/critical disease.[5,6,23,24] However, in the Omicron cohort, with lesser alteration in loading conditions, possibly the increase in adrenergic tone "tilted" the functional LV/RV parameters in the opposite direction. Furthermore, another possible hypothesis is that in patients with Omicron infection, RV/LV dysfunction are mostly related to background disease and less to the acute infection.

Limitations

This single-center study included only hospitalized patients with COVID-19. The fact that only a minority of patients with Omicron COVID-19 are admitted to the hospital leads to an overestimation of the severity of echocardiographic pathology in these patients. A total of 72 patients (30.7%) were excluded from analysis, and the majority of them had "Do Not Resuscitate/Intubate" orders and received only palliative care. This limitation might create an opposite bias, resulting in an underestimation of cardiac manifestations in patients with Omicron COVID-19. Using small, dedicated scanners set aside in each COVID-19–designated ward is acceptable when performing echocardiography but resulted in a low rate of accurate assessment of mean or peak pulmonary artery pressure by the pulmonic valve regurgitation or tricuspid valve regurgitation method. Outcome analyses in our study should be interpreted with caution because of the small number of patients, small number of events, and possible underpower. We believe that our results should serve as incentive to explore the issue of echocardiographic predictors of clinical deterioration in patients with Omicron COVID-19 in larger series. There were no significant differences between vaccinated/prior infected and nonvaccinated patients with Omicron in terms of RV abnormalities. However, because of the small number of patients and the younger age of the nonvaccinated group, small differences between the groups cannot be excluded. Pre–COVID-19 echocardiograms were evaluated only in 62 of the 162 patients with Omicron, thus our hypothesis on possible lesser changes in cardiac function is limited by selection bias.

CONCLUSIONS

We describe the first large cohort of echocardiographic studies in hospitalized patients with Omicron COVID-19. More than half of the patients had normal echocardiography. The most frequent abnormality was RV dilation with or without dysfunction, possibly related to pulmonary parenchymal or vascular disease. However, the frequency of RV dilation with or without dysfunction was lower in the patients with Omicron compared with matched patients with the wild-type COVID-19 variant, possibly because of a lesser inflammatory response, parenchymal, and possibly vascular lung injury, all leading to lower RV afterload. Among patients with abnormal echocardiogram at presentation, systolic LV or elevated LV filling pressure were observed in 10% and 29% of

patients, respectively, but similar to the prevalence in the matched patients with wild-type COVID-19. However, in a minority of patients who had a previous echocardiographic exam, these LV abnormalities have already been recorded before acute Omicron infection, as opposed to the patients with the wild-type variant, suggesting that LV disturbances in hospitalized patients with Omicron may reflect background cardiac morbidity in a large proportion of patients. Importantly, numerous RV and LV echocardiographic parameters are associated with poor outcome in hospitalized patients with Omicron.

ARTICLE INFORMATION

Received November 4, 2022; accepted December 6, 2022.

Affiliations

Department of Cardiology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine (E.G., A.S., A.H., A.B., L.L., E.L., Y.S., T.J., D.Z., T.I., P.T., S.G., D.V., L.S., O.H., S.B., Y.T.)Tel Aviv Sourasky Medical Center and Sackler School of Medicine (N.S.)Clinical Microbiology Laboratory, Tel Aviv Sourasky Medical Center and Sackler School of Medicine (A.A., E.L.) and Department of Internal Medicine J, Tel Aviv Sourasky Medical Center and Sackler School of Medicine (M.I.).

Acknowledgments

We thank the Israeli National Consortium for SARS-CoV-2 Sequencing and the Public Health Services, Ministry of Health for the SARS-CoV-2 sequencing data.

Ghantous, Shetrit, Hochstadt, Banai, Lupu, Levi, Szekely, Schellekes, Jacoby, Zahler, Itach, Taieb, Gefen, Viskin, Shidlansik, Adler, Levitsky, Havakuk, Ingbir, Banai, and Topilsky participated in designing the study, collecting and analyzing data, and drafting and revising the article.

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Tables S1–S6

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SUPPLEMENTAL MATERIAL

Table S1.

Variables	COVID-19 patients (N=162)	Normal values	Threshold Deviating N (%)
LVEF (%), mean ± SD	55.5±9	M 62±5 F 64±5	50 16 (9.8)
LVEDD (mm), mean ± SD	45.6±8	M 50.2±4.1 F 45.0±3.6	M <42; F<37.8 27 (16.6)
LVESD (mm), mean ± SD	30.8±7	M 32.4±3.7 F 28.2±3.3	M <25; F<21.6 18 (11)
SVI (mL/m²), mean ± SD	35.6±10	33-47	≥35 73 (45)
CI (Lmin/m²/), mean ± SD	2.7±0.8	2.5-4	<2.5 68 (42)
LAVI (mL/m²), mean ± SD	34.1±14	M 25.1±7 F 24.5±6.4	≤34 71 (44)
E/e' average, mean ± SD	12.3±6	6.8+2.1	>14 47 (29)
PAT (msec), mean ± SD	91.3±23	137±24	<100 98 (60)
RVEDA (cm²), mean ± SD	19.7±6	M 17±3.5 F 14±3	M>24; F>20 34 (21)
RVESA (cm²), mean ± SD	9.1±4	M 9±3 F 7±2	M>15; F>11 13 (8)

RVEDA Index (cm^2/m^2), mean ± SD	10.8±4	M 8.8±1.9 F 8.0±1.7	M>12.6; F>11.5 40 (25)
RVESA Index (cm^2/m^2), mean ± SD	4.9±2	M 4.7±1.3 F 4.0±1.2	M>7.4; F>6.4 3 (5)
RVFAC (%), mean ± SD	55.5±10	49±7 <35	<35 6 (3.5)
TAPSE (cm), mean ± SD	2.2±0.5	2.4±0.35	<1.7 1.8 (11)
RV S' (cm/s), mean ± SD	12.0±3	14.1±2.3	<9.5 34 (21)

CI, cardiac index; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricle ejection fraction; LVESD, left ventricular end-systolic diameter; PAT, pulmonic acceleration time; RV, right ventricle; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.

Table S2.

Variables	Vaccinated/ previous infection 128	Non vaccinated 34	P-value
Age (years), mean ± SD	72.8±16	66.2±	0.08
Male sex, n (%)	82 (64)	19 (56)	0.38
Blood urea nitrogen (mg/dL), mean ± SD	24.3±16	26.9±33	0.66
Creatinine (mg/dL), mean ± SD	1.24±1.1	1.24±1.2	0.98
C-reactive protein (mg/L), median [quartiles]	30 [10, 93]	66 [29, 144]	0.02
D-dimer (mg/L), mean ± SD	2.1±3	4.4±9	0.80
Troponin-I (ng/L), median [quartiles]	14.5 [5, 55]	12.4 [4, 197]	0.89
Brain natriuretic peptide, median [quartiles]*	240 [70, 752]	150 [51, 2108]	0.86
Bilateral infiltrate, n (%)	29 (23)	11 (32)	0.24
Atrial fibrillation, n (%)	11 (8)	8 (23)	0.01
ST/T wave changes, n (%)	34 (27)	10 (30)	0.73
Echocardiography			
LVEF (%)	55.4±8	57.9±6	0.06
LVEDD (mm), mean ± SD	46.3±6	44.3±6	0.13
LVESD (mm), mean ± SD	31.0±6	29.2±7	0.20
LAVI (mL/m2), mean ± SD	35.2±14	33.2±14	0.47
RVEDA index (cm2/m2), mean ± SD	11.0±3	10.3±4	0.48
RVESA index (cm2/m2), mean ± SD	5.1±2	4.7±2	0.53
RVFAC (%), mean ± SD	52.6±9	56.9±8	0.11
TAPSE (cm), mean ± SD	2.2±0.5	2.2±0.6	0.87
RV S' (cm/s), mean ± SD	12.0±3.4	11.8±3.4	0.70
SVI (mL/m2), mean ± SD	35.7±10	35.6±12	0.98
CI (L/min/m^2), mean ± SD	2.7±0.8	2.8±0.9	0.68
E wave velocity (cm/s), mean ± SD	77.8±24	76.7±22	0.78
A wave velocity (cm/s), mean ± SD	71.5±22	68.7±19	0.51
E/A ratio	1.12±0.4	1.2±0.7	0.48
e' septal (cm/s), mean ± SD	6.2±1.8	6.5±2.5	0.53

e' lateral (cm/s), mean ± SD	7.7±2.7	8.6±2.9	0.09
E/e' average ratio, mean ± SD	12.5±6	11.8±7	0.58
RAP (mmHg), mean ± SD	8.9±7	7.3±4	0.15
SPAP (mmHg)*, mean ± SD	37.5±12	38.3±11	0.81
PAT (msec), mean ± SD	90.9±24	91.6±25	0.89

CI, cardiac index; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PAT, pulmonic acceleration time; RAP, right atrial pressure; RV, right ventricle; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.

Table S3.

Variables	Wild-type Mild/Moderate N=94	Omicron Mild/Moderate N=94	P value paired T test	Wild-type Severe/Critical N=54	Omicron Severe/Critical N=54	P value paired T test
LVEF (%), mean ± SD	57.2±5	56.5±7	0.51	56.1±8	55.3±8	0.60
LVEDD (mm), mean ± SD	42.8±7	46.1±7	0.002	44.6±8	45.5±7	0.53
LVESD (mm), mean ± SD	26.8±8	30.2±8	0.006	28.9±9	31.0±6	0.21
Stroke volume (mL), mean ± SD	58.1±17	66.5±19	0.004	60.1±17	64.1±19	0.27
Cardiac output (L/m²), mean ± SD	4.4±1.6	4.9±1.7	0.03	4.7±1.3	5.1±1.4	0.14
LA volume (mL), mean ± SD	58.6±23	66.8±31	0.04	70.6±35	59.4±21	0.06

E wave (cm/sec), mean ± SD	68.9±27	75.9±22	0.06	65.0±23	81.1±27	0.002
A wave (cm/sec), mean ± SD	66.9±21	69.7±21	0.40	66.3±17	71.7±23	0.22
E/A ratio, mean ± SD	1.04±0.5	1.17±0.6	0.14	0.94±0.4	1.14±0.6	0.08
E/e' average, mean ± SD	11.4±7	11.6±5	0.90	10.1±4	13.4±7	0.005
PAT (msec), mean ± SD	85.5±29	97.2±25	0.008	72.6±17	82.4±19	0.009
SPAP (mmHg), mean ± SD *	38.7±14	35.5±10	0.37	36.7±13	41.3±14	0.30
RAP (mmHg), mean ± SD *	8.2±3	8.9±8	0.56	8.3±4	8.4±4	0.83
RVEDA (cm^2), mean ± SD	21.1±5	20.2±7	0.47	21.0±5	19.2±5	0.18
RVESA (cm^2), mean ± SD	12.1±4	10.0±5	0.06	13.1±5	8.2±2	0.006
RVFAC (%), mean ± SD	41.4±13	51.0±9	0.004	34.2±13	56.5±9	<0.0001

TAPSE (mm), mean ± SD	2.15±0.5	2.15±0.5	0.92	2.16±0.6	2.23±0.4	0.56
RV S' (cm/s), mean ± SD	10.4±2	11.6±3	0.008	11.2±3	12.6±4	0.03
MPAP (mmHg), mean ± SD	38.5±15	31.9±12	0.004	44.9±10	39.5±10	0.01
PVR index (dynes*s/cm5/ m2), mean ± SD	240±164	175±136	0.009	313±95	258±106	0.009
RVSW (gm m/beat), mean ± SD	22.8±10	20.6±13	0.30	29.2±11	27.7±12	0.56

* Assessed only in 36 patients.

LA, left atrium; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter; MPAP, mean pulmonary artery pressure; PAT, pulmonic acceleration time; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSW, right ventricle stroke work; RV, right ventricle; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

Table S4. Echocardiographic characteristics before compared to during acute wild-type COVID-19 infection.

Variables	Pre-Wild type N=19	Acute Infection N=19	P value paired T test
LVEF (%), mean ± SD	54.7±5	54.1±6	0.63
LVEDD (mm), mean ± SD	48.9±7	43.8±6	0.0003
LVESD (mm), mean ± SD	29.4±5	29.6±6	0.86
Stroke volume (mL), mean ± SD	73.9±18	57.4±18	0.01
Cardiac output (L/m²), mean ± SD	4.7±1.6	4.2±2.9	0.39
LA volume (mL), mean ± SD	63.9±21	62.2±25	0.80
E wave (cm/sec), mean ± SD	70.7±19	62.4±21	0.08
A wave (cm/sec), mean ± SD	82.3±20	68.9±19	0.006
E/A ratio, mean ± SD	0.91±0.3	0.94±0.4	0.62
E/e' average, mean ± SD	13.2±8	10.4±5	0.05
PAT (msec), mean ± SD	111.3±18	87.6±27	0.01

RAP (mmHg), mean ± SD	5.3±1.1	7.7±3	0.01
RVEDA (cm²), mean ± SD	15.7±4	20.8±5	0.0001
RVESA (cm²), mean ± SD	10.4±3	12.2±4	0.26
RVFAC (%), mean ± SD	36.9±7	42.2±12	0.17
TAPSE (mm), mean ± SD	2.2±0.4	2.1±0.7	0.39
RV S' (cm/s), mean ± SD	11.5±2	10.2±2	0.05

LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, ejection fraction; LVESD, left ventricular end-systolic diameter; PAT, pulmonic acceleration time; RAP, right atrial pressure; RV, right ventricle; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

Table S5.

Variables	Omicron 37	Wild-type 43	P-value
Age, years	62.5±19	60.2±17	0.56
Sex, male (%)	14 (38)	16 (37)	0.96
BSA, mean ± SD	1.86±0.2	1.87±0.2	0.75
LVEF (%)	57.4±5	57.8±5	0.74
LVEDD (mm), mean ± SD	45.8±6	42.4±7	0.02
LVESD (mm), mean ± SD	30.5±6	27.4±6	0.03
LAVI (mL/m2), mean ± SD	31.2±11	27.8±9	0.04
RVEDA (cm2), mean ± SD	18.7±3	19.9±4	0.19
RVESA (cm2), mean ± SD	9.2±4	11.4±3	0.10
RVFAC (%), mean ± SD	52.9±9	46.9±12	0.10
TAPSE (cm), mean ± SD	2.4±0.4	2.4±0.5	0.48
RV S' (cm/s), mean ± SD	13.2±3.3	11.6±2.2	0.01
SVI (mL/m2), mean ± SD	37.7±12	34.3±9	0.08
CI (L/min/m^2), mean ± SD	2.8±0.8	2.6±0.7	0.15
E wave velocity (cm/s), mean ± SD	74.5±19	61.5±14	0.001
A wave velocity (cm/s), mean ± SD	63.7±16	58.7±13	0.08
E/A ratio	1.2±0.5	1.1±0.5	0.19
e' septal (cm/s), mean ± SD	7.5±2.1	6.9±2.0	0.13
e' lateral (cm/s), mean ± SD	9.5±2.9	9.1±2.9	0.57
E/e' average ratio, mean ± SD	9.5±3	8.1±2	0.02
RAP (mmHg), mean ± SD	6.3±4	6.3±2	0.89
PAT (msec), mean ± SD	92.6±22	85.9±20	0.09

BSA, body surface area; CI, cardiac index; LAVI, left atrial volume index; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter; PAT, pulmonic acceleration time; RAP, right atrial pressure; RV, right ventricle; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.

Table S6.

Parameter	Odds Ratio Combined Omicron	Odds Ratio Combined Wild-type	P Interaction combined
Age	1.06 (1.01- 1.10); p=0.005	1.04 (1.02- 1.07); p=0.0001	0.71
Sex, male	1.11 (0.40- 3.0); p=0.84	0.99 (0.48- 2.1); p=0.98	0.91
Troponin-I	1.002 (0.99- 1.005);p =0.15	1.004 (1.0004- 1.008); p=0.004	0.02
COVID therapies	0.58 (0.20- 1.65); p=0.32	NA	
LVEF	0.95 (0.90- 1.01); p=0.13	1.00 (0.95-1.06); p= 0.83	0.36
SVI	0.93 (0.88- 0.99); p=0.02*	0.98 (0.94- 1.02); p=0.40	0.13
CI	0.50 (0.24- 1.09); p=0.06	0.94 (0.60- 1.49); p=0.82	0.15
E/e’	1.12 (1.05- 1.21); p=0.001	1.01 (0.95- 1.08); p=0.58	0.02
LAVI	0.98 (0.95- 1.03); p=0.58	1.008 (0.98- 1.03); p=0.47	0.91
TAPSE	0.52 (0.26- 1.01); p=0.06	0.58 (0.37- 0.92); p=0.02	0.78
RV S’	0.82 (0.73- 0.90); p<0.001*	0.93 (0.86- 1.02); p=0.14	0.03
RAP	1.02 (0.95- 1.08); p=0.59	1.12 (1.02- 1.23); p=0.01	0.07
PAT	0.96 (0.94- 0.99); p=0.01*	0.98 (0.96- 0.99); p=0.03	0.35
PVR index	1.005 (1.001- 1.01); p=0.01*	1.003 (1.002- 1.006); p=0.02	0.35

CI, cardiac index; COVID, coronavirus disease; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; PAT, pulmonic acceleration time; PVR, pulmonic vascular resistance; RAP, right atrial pressure; RV, right ventricle; SPAP, systolic pulmonary artery pressure; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.