CJC Open 6 (2024) 1513–1520

Original Article

Left Atrial Strain in Omicron-Type COVID-19 Patients

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ABSTRACT

Background: Information about left atrial (LA) 2-dimensional (2D) strain parameters in patients with the Omicron variant of COVID-19 is limited. The aim of this study is to evaluate LA strain (LAS) in COVID-19 patients with the Omicron variant and compare it to that of propensity-matched patients with the wild-type (WT) variant.

Methods: A total of 148 consecutive patients who were hospitalized with Omicron COVID-19 underwent an echocardiographic evaluation

RÉSUMÉ

Contexte : L'information sur les paramètres de déformation bidimensionnelle (2D) de l'oreillette gauche (OG) chez les patients atteints du variant Omicron de la COVID-19 est limitée. Le but de cette étude est d'évaluer la déformation de l'oreillette gauche (DOG) chez les patients atteints de la COVID-19 avec le variant Omicron et de la comparer à celle de patients appariés selon la propension ayant le variant de type sauvage (WT).

Multiple studies suggest that cardiac complications are prevalent in the wild-type (WT) variant of severe acute respiratory syndrome (SARS)-CoV-2 (COVID-19 Wuhan-hu-1), and are associated with increased mortality.[1,2] The fifth COVID-19 variant of concern—known as Omicron—had more changes in its spike protein relative to those of the WT virus.[3-5] Reports have suggested that admitted patients have less-severe lung disease.[3,4,6,7]

Previously, we described our experience in consecutive patients with WT COVID-19 assessed with left-ventricle (LV) and right-ventricle (RV) 2-dimensional (2D) speckle-tracking echocardiography (STE).[8,9] In a following report, we compared consecutive patients hospitalized with the Omicron variant to propensity-matched patients with the WT variant, using routine echocardiography.[10] We showed that patients with Omicron had a smaller RV size and a higher stroke-volume index, all related to their having a lower level of pulmonary vascular resistance.

Left-atrial (LA) 2D strain (LA 2D-STE) analysis is an echocardiographic method, based on LA myocardial deformation, to assess LA function, stiffness, and fibrous remodelling.[11] In this approach, the 3 phases (reservoir, conduit, contraction) of LA function are analyzed. Compared to routine echocardiography, the main advantages of measures of LA strain (LAS) are angle-independence, feasibility, and reproducibility.[12] LAS has been associated with adverse outcomes in several clinical settings, including ischemic stroke[13] and heart failure.[14]

In this study, we aim to both evaluate LA 2D-STE in patients with acute Omicron-type COVID-19 infection and compare these parameters to matched patients with the WT acute infection. In Omicron patients who had a previous echocardiogram within a year, we compared these 2D-STE parameters to those in historic echocardiography

Received for publication July 25, 2024. Accepted September 18, 2024.

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See page 1519 for disclosure information.

https://doi.org/10.1016/j.cjco.2024.09.006

within the first day after hospital admission and were compared to propensity-matched patients (1:1) with the WT variant. LA 2D speckle tracking echocardiography parameters included the following: LAS, reservoir (LASr); LAS, conduit (LAScd); LAS, contraction (LASct); and LASr to the ratio between early mitral inflow velocity/mitral annular early diastolic velocity (E/e'). The values for the parameters that occurred during acute Omicron-type infection were compared with those found on historic examinations in 36 patients.

Results: Compared to the matched WT cohort, patients with acute Omicron-type infection had similar LASr (31.3% ± 13.3% vs 33.0% ± 14.2%), LAScd (−18.7% ± 9.8% vs −18.6% ± 10.8%), and LASct (−12.5% ± 8.6% vs −13.6% ± 8.2%) values ($P > 0.2$ for all), but a higher E/e' ratio (11.8 ± 6 vs 10.1 ± 7; $P = 0.03$). Surprisingly, LASr (31.9% ± 13.7% vs 22.6% ± 13.9%; $P = 0.04$) and LAScd (−18.7% ± 9.7% vs −10.7% ± 6.6%; $P < 0.001$) improved in patients during acute infection. LASr, LAScd, and LASr/(E/e') were significantly associated with an increased risk of either in-hospital mortality, need for mechanical ventilation, or the combined event.

Conclusions: In hospitalized patients with an Omicron COVID-19 infection, LAS parameters are similar to those of matched patients with WT variant and are associated with mortality and respiratory deterioration. These abnormalities were recorded previously in the 36 patients with historical echocardiograms, suggesting that they are related to background cardiac disease.

Méthodes : Au total, 148 patients consécutifs, hospitalisés pour une COVID-19 avec variant Omicron ont subi une évaluation échocardiographique le premier jour de leur admission à l'hôpital et ont été comparés à des patients appariés selon la propension (1:1) avec la variante WT. Les paramètres de l'échocardiographie de suivi des marqueurs acoustiques en 2D de l'OG comprenaient les éléments d'évaluation de la DOG avec la fonction réservoir (DOGr); la fonction conduit (DOGcd); la fonction pompe/contraction (DOGct); ainsi que la DOGr au rapport entre la vitesse d'entrée mitrale précoce et la vitesse diastolique précoce annulaire mitrale (E/e'). Les valeurs des paramètres observées lors d'une infection aiguë de type Omicron ont été comparées à celles relevées lors d'examens antérieurs chez 36 patients.

Résultats : Par rapport à la cohorte WT appariée, les patients atteints d'une infection aiguë de type Omicron avaient des valeurs similaires de DOGr (31,3 % ± 13,3 % vs 33,0 % ± 14,2 %), DOGcd (-18,7 % ± 9,8 % vs -18,6 % ± 10,8 %) et DOGct (-12,5 % ± 8,6 % vs -13,6 % ± 8,2 %) ($p > 0,2$ pour tous), mais un rapport E/e' plus élevé (11,8 ± 6 vs 10,1 ± 7; $p = 0.03$). De façon surprenante, la fonction réservoir DOGr (31,9 % ± 13,7 % vs 22,6 % ± 13,9 %; $p = 0.04$) et la fonction conduit DOGcd (-18,7 % ± 9,7 % vs -10,7 % ± 6,6 %; $p < 0,001$) se sont améliorées chez les patients au cours d'une infection aiguë. Les paramètres DOGr, DOGcd et DOGr/(E/e') ont été significativement associés à un risque accru de mortalité hospitalière, de besoin de ventilation mécanique ou de l'événement combiné.

Conclusions : Chez les patients hospitalisés atteints de la COVID-19 avec une infection par Omicron, les paramètres de la DOG sont similaires à ceux des patients appariés avec le variant WT et sont associés à la mortalité et à la détérioration respiratoire. Ces anomalies ont été enregistrées précédemment chez les 36 patients ayant des échocardiogrammes antérieurs, ce qui suggère qu'elles sont liées à une maladie cardiaque sous-jacente.

examinations, to analyze whether LA function changes during acute infection. In addition, we compared 2D-STE during acute infection and recovery in patients who had a follow-up echocardiogram. Lastly, we assessed whether LA 2D-STE parameters recorded during acute infection are associated with in-hospital mortality and/or the need for mechanical ventilation in Omicron-variant patients.

Methods

The study population was comprised of 2 cohorts, both of which included consecutive, prospectively studied adult patients (aged ≥ 18 years) admitted to the Tel Aviv Medical Center, as follows: (i) the "Omicron wave cohort," including 236 consecutive patients who had their COVID-19 diagnosed between January 3, 2022 and January 25, 2022, confirmed by a reverse-transcriptase−polymerase chain reaction assay of SARS-CoV-2, and whole-genome sequencing; and (ii) the COVID-19 "WT cohort," including 530 consecutive patients who presented with their first SARS-CoV-2 infection, between March 21, 2020 and September 16, 2020, with the original WT variant. All patients' demographic data, comorbid conditions, physical examinations, and laboratory findings were recorded systematically. All patients who were included in the study underwent a comprehensive transthoracic echocardiogram within 24 hours of their SARS-CoV-2 diagnosis, as part of the step-by-step protocol. Clinical and imaging data were collected prospectively. Clinical endpoints were defined as experiencing either in-hospital mortality or in-hospital need for mechanical ventilation. Mechanical ventilation was defined as either invasive ventilation, or noninvasive ventilation (bi-level positive airway pressure [BIPAP] or high-flow inspiratory support [Vapotherm, Vaoptherm Inc, Exeter, NH], or both). The ethics committee of Tel Aviv Medical Center approved the study. The committee voided the requirement of obtaining informed consent for echocardiographic assessment. To evaluate for the presence of echocardiographic abnormalities in a controlled fashion, the echocardiographic characteristics in COVID-19 patients were compared with the reference values.[15]

Whole-genome sequencing of SARS-CoV2−positive samples

Total nucleic acids were extracted from respiratory specimens. Subsequently, complementary DNA synthesis and enrichment were performed using the extracted nucleic acids, using the Illumina COVIDSeq Test (Illumina, Cambridge, UK). Amplicon libraries of viral genome were sequenced with the NovaSeq 6000 SP Reagent Kit v1.5 (Illumina, Cambridge, UK), according to the manufacturer's manual. The libraries were sequenced on the Illumina NovaSeq platform (Illumina, Cambridge, UK), per manufacturer instructions.

Bioinformatic analysis

Global phylogenetic placement was determined using the DRAGEN COVIDSeq v3.5.5 platform (Illumina). We analyzed FASTA sequences using the pipeline developed for SARS-CoV-2 sequencing by the Israeli National Consortium.[16]

Routine echocardiography

Echocardiography was performed in a standard manner, using the CX50 (Philips Medical Systems, Bothell, WA), by cardiologists with expertise in the recording and interpreting of echocardiographic examinations. The following measures were undertaken to lower the risk of inadvertent infection: (i) Echocardiographic studies were performed bedside at the designated COVID-19 internal department units; (ii) At the time of echocardiographic recordings, personal protection equipment included that for airborne precautions—N-95 masks, gowns, head covers, eye shields, gloves, and shoe covers. LV diameters and ejection fraction were measured as recommended.[17] Measurements of the mitral inflow included late diastolic filling (A-wave) and peak early filling (E-wave) velocities, the E/A ratio, and the deceleration time of early filling velocity. Early diastolic septal and lateral mitral annular velocities (e′) were measured in the apical 4-chamber view.[18] LA volume was calculated using the biplane area length method at end systole. The forward stroke volume was calculated using the LV outflow tract, with subsequent calculation of cardiac output and index. RV function was evaluated using the tricuspid annular plane systolic excursion and the systolic tricuspid lateral annular velocity, both measured in the apical 4-chamber view.[17,19]

2D STE

LA, LV, and RV strain analyses were performed using a fully automated 2D strain analytical software application (AutoStrain, Philips Medical Systems) from 2,3,4-chamber (for LA and LV) and RV focus (for RV) apical views.[20] The software automatically determined the LA, LV, and RV endocardial border, with a knowledge-based artificial intelligence algorithm, and produced speckle-tracking analysis through one complete cardiac cycle, by generating regional strain curves for LA, LV global, RV global, and free-wall longitudinal strain. The software provided the measurement of the average strain for the 3 major LA functions: reservoir (LASr); conduit (LAScd); and contractile (LASct) values. End diastole was used as the reference point for deformation analysis. If tracking of the LA, LV, or RV endocardium was unsatisfactory, manual adjustments were used to ensure optimal tracking. All measures were done blinded to patients' outcomes.

Statistical analysis

Continuous normally distributed parameters were presented as means ± standard deviations, and were compared using the Student *t* test. Normality was assessed using visual inspection of quantile−quantile plots and the Shapiro−Wilk test. Non-normally distributed data were presented as median, and 1st and 3rd quartiles, and were compared using the Wilcoxon rank-sum test. The χ^2 test, or Fisher's exact test, was used to compare categorical data between groups. To compare echocardiographic characteristics during acute infection to those in historic examinations, or examinations performed after recovery, a paired Student *t* test was used. To identify variables that significantly affect in-hospital mortality, or the combined outcome, we evaluated them using univariable logistic regression. To compare the echocardiographic, laboratory, and clinical parameters in patients with the Omicron variant to those in patients with the original WT variant, the database of original COVID-19 patients (N = 530) was used, and those with the Omicron variant were matched to patients in the original WT cohort in a 1:1 ratio. Logistic regression was used to estimate the propensity score, with all variables entered into the model. Afterward, matching was performed using nearest-neighbour matching (ie, matching the 2 closest propensity-score pairs) in a 1:1 ratio between the Omicron and WT groups. To decrease the disparity in the pairs, the matching was restricted by a caliper width of 0.7 of the standard deviation of the propensity score. Inspection of resulting standardized mean differences was used for assessment of balance. A standard mean difference < 0.2 was considered small. The predefined matching baseline parameters were age, gender, grade of disease, body mass index, and history of ischemic heart disease. The process produced groups with balanced comorbidities. Statistical significance was considered to be present if P values were < 0.05. In the case of multiple pairwise comparisons, a false discovery rate correction was used to adjust the P value. All data were analyzed using version 12.0 of JMP software (SAS Institute, Cary, NC). All authors participated in collecting and analyzing the data, designing the study, and drafting and revising the manuscript.

Results

Clinical data were collected in 236 consecutive patients hospitalized with the COVID-19 Omicron variant. A total of 72 patients were excluded for the following reasons: they had not undergone an echocardiographic assessment (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, no confirmation of the Omicron variant occurred. Another 14 patients were excluded from the study because echocardiographic images were inadequate for conducting LA STE analysis. Thus, the study group included 148 patients with an Omicron-type COVID-19 infection who underwent LAS analysis (mean age, 71.6 ± 17 years; 60% male). At the time of baseline echocardiographic assessment, patients were stratified as follows: 81 patients with mild disease (chest X ray with no radiographic evidence of lower respiratory tract disease); 14 patients with moderate COVID-19 (chest X ray with evidence of lower respiratory tract disease, and oxygen saturation ≥ 94% in room air); 48 patients with severe disease (oxygen saturation < 94% in room air); and 5 patients with critical disease at presentation (need for mechanical ventilation or vasopressors). Table 1 shows the baseline characteristics, routine echocardiographic assessments, and 2D-STE assessments of all patients, stratified by disease grade. The majority of patients (78%) were vaccinated at least one time, all with the BNT162b2 vaccine (Pfizer [New York, NY]−BioNTech [Mainz, Germany]).

Table 1. Baseline characteristics in Omicron-type patients, stratified by severity of disease

Variables	All (N = 152)	Mild/Moderate (n = 96)	Severe/Critical (n = 56)	*P*
Clinical characteristics				
Age, y	71.8 ± 17	70.5 ± 18	74.5 ± 14	0.11
Male gender	93 (61)	56 (58)	37 (66)	0.34
Body mass index	26.7 ± 5	26.7 ± 5	26.8 ± 5	0.96
Ischemic heart disease	37 (24)	21 (22)	16 (29)	0.32
Stroke	25 (16)	17 (18)	8 (15)	0.61
Chronic kidney disease	31 (20)	19 (20)	12 (22)	0.76
COPD	9 (6)	4 (4)	5 (9)	0.22
Other lung disease	6 (4)	4 (4)	2 (4)	0.87
Diabetes mellitus	58 (38)	43 (45)	15 (27)	0.03
Hypertension	80 (53)	52 (54)	28 (51)	0.69
Vaccinated	118 (78)	74 (77)	44 (78)	0.27
Temperature, ° C	37.1 ± 0.7	37.2 ± 0.7	37.1 ± 0.8	0.37
O_2 saturation, %	94.1 ± 5	95.6 ± 4	91.5 ± 3	< 0.0001
Heart rate, beats/min	84.0 ± 20	82.3 ± 21	85.3 ± 18	0.53
Systolic blood pressure, mm Hg	131.8 ± 24	134.3 ± 24	127.6 ± 23	0.09
Diastolic blood pressure, mm Hg	70.9 ± 15	71.0 ± 14	70.6 ± 15	0.87
Hemoglobin, g/dL	12.2 ± 2	12.0 ± 2	12.4 ± 2	0.24
White blood cells, $10^3/\mu L$	7.3 [4.8, 13.7]	6.7 [4.5, 9.8]	8.3 [6.1, 10.4]	0.02
Blood urea nitrogen, mg/dL	24.6 ± 21	23.2 ± 15	27.3 ± 28	0.32
Creatinine, mg/dL	1.30 ± 1.2	1.25 ± 1.1	1.39 ± 1.3	0.49
C-reactive protein, mg/L	39 [12, 119]	25 [7, 73]	66 [24, 166]	0.0004
D-dimer, mg/L	2.9 ± 5.8	1.9 ± 2.2	4.4 ± 8.4	0.09
Troponin-I, ng/L	14 [5, 62]	13 [4, 61]	19 [7, 63]	0.14
Brain natriuretic peptide*	202 [53, 743]	119 [41, 458]	378 [70, 1068]	0.04
Bilateral infiltrate	40 (26)	14 (14)	26 (47)	< 0.0001
Routine echocardiography				
LVEF, %	55.5 ± 9	56.7 ± 7	55.7 ± 8	0.46
LA volume, mL	34.1 ± 14	67.2 ± 29	32.7 ± 11	0.28
TAPSE, cm	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.4	0.93
RV S′, cm/s	12.0 ± 3	11.8 ± 3	12.8 ± 4	0.18
Stroke volume, mL	35.6 ± 10	67.5 ± 19	65.1 ± 18	0.47
E/A ratio	1.19 ± 0.6	1.15 ± 0.6	1.16 ± 0.6	0.95
E/e′ average ratio	12.3 ± 6	11.5 ± 5	13.3 ± 7	0.09
Pulmonic flow acceleration time, msec	91.6 ± 24	95.7 ± 24	82.3 ± 18	0.0004
Strain, as measured by speckle tracking echocardiography, %				
Global longitudinal	−17.8 ± 5.1	−18.0 ± 4.8	−17.2 ± 5.5	0.55
LA reservoir	31.1 ± 13.7	30.8 ± 13.9	31.3 ± 13.5	0.81
LA conduit	−18.7 ± 9.7	−18.5 ± 9.5	−18.9 ± 10.0	0.80
LA contraction	−12.3 ± 9.6	−12.3 ± 9.9	−12.2 ± 9.3	0.97
RV free-wall	−20.9 ± 7.4	−21.1 ± 7.6	−20.3 ± 7.2	0.85
RV global 4C	−17.2 ± 4.7	−17.7 ± 4.3	−16.2 ± 5.3	0.3

Values are mean ± standard deviation, n (%), or median [quartiles], unless otherwise indicated.

COPD, chronic obstructive pulmonary disease; E/A ratio, early to late diastolic transmitral flow velocity; E/e′ ratio, E, peak early diastolic flow velocity/e′, mitral annulus early diastolic velocity; LA, left atrial; LVEF, left ventricular ejection fraction; RV, right ventricular; S', tissue Doppler systolic wave; TAPSE, tricuspid annular plane systolic excursion; 4C, 4-chamber.

*Assessed in only 36 patients.

Baseline 2D-STE data for Omicron COVID-19 patients, compared to reference values,[21] were abnormal in 66%, 62%, and 66%, for LASr, LAScd, and LASct, respectively.

Comparison to the historic echocardiographic examinations

To assess whether pathologic 2D-STE LA parameters in the Omicron cohort were related to the acute infection, we compared them to those of all 36 patients who had a previous echocardiogram within 1 year (median 218 days [IQR 48, 355]), and 2D-STE evaluation for LA. The results of these comparisons are presented in Table 2 and Figure 1. Surprisingly, LASr and LAScd increased (improved) in most patients during acute infection, whereas no significant changes occurred during acute disease for the LASct or the LASr to the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'). 2D-STE parameters in historic examinations of Omicron COVID-19 patients, as compared to reference values, were abnormal in 81%, 92%, and 67% for LASr, LAScd, and LASct, respectively.

Comparison to the recovery echocardiographic examinations

By June 2023, a total of 13 patients of the Omicron cohort with 2D-STE analysis had undergone a follow-up transthoracic echocardiographic examination (at 288 days [62, 394]) after the echocardiographic examination during acute infection. In the follow-up echocardiogram, the mean LASr, LAScd, and LASct were, respectively, as follows: 27.3% ± 17% vs 30.7% ± 17%, $P = 0.4$; −17.9% ± 10% vs −22.2% ± 11%, $P = 0.16$; and −9.4% ± 9% vs −8.4% ± 11%, $P = 0.7$.

Table 2. Echocardiographic characteristics, before, compared to during, acute Omicron COVID-19 infection

Strain, %	Pre-Omicron	During acute infection	*P*, paired Student *t* test
Speckle tracking echocardiography			
Global longitudinal (n = 21)	−13.3 ± 7.0	−17.8 ± 5.1	0.012
LA reservoir (n = 36)	22.6 ± 13.9	31.9 ± 13.7	0.04
LA conduit (n = 36)	−10.7 ± 6.6	−18.7 ± 9.7	< 0.0001
LA contraction (n = 36)	−11.8 ± 10.0	−12.2 ± 9.6	0.75
LA reservoir / E/e' (n = 33)	2.5 ± 2.2	2.7 ± 2.1	0.57
RV free-wall (n = 35)	−20.2 ± 7.7	20.9 ± 7.4	0.85
RV global 4C (n = 35)	−15.9 ± 5.8	−17.2 ± 4.7	0.39

E/e', peak early diastolic flow velocity/mitral annulus early diastolic velocity; LA, left atrium; RV, right ventricle; 4C, 4-chamber.

Comparison to the WT COVID-19 cohort

Matching produced 134 pairs of patients with the Omicron and the WT COVID-19 variants, with no significant difference between the groups' clinical characteristics ($P > 0.2$ for all). Characteristics of both groups, stratified to clinical, routine, and 2D-STE parameters, are presented in Table 3 and Figure 2. Patients with the Omicron variant had a higher E/e' ratio, suggesting the presence of a higher LA filling pressure, compared to that in patients in the WT variant—matched cohort. The most important finding is that no significant differences were seen in LA 2D-STE parameters for the Omicron vs the matched WT patients.

Association between 2D-STE echocardiographic parameters and outcome

In the Omicron cohort, 8 patients died in-hospital (5.4%), 13 (8.7%) needed in-hospital mechanical (invasive or noninvasive) ventilation, and 15 (10.1%) had a clinical combined in-hospital event. The results of the univariate analyses for mortality, mechanical ventilation, and the combined event are shown in Table 4. The 2D-STE parameters that were significantly associated with a higher risk of either mechanical ventilation, in-hospital mortality, or the combined event, were the LASr, the LAScd, and the LASr/(E/e') ratio.

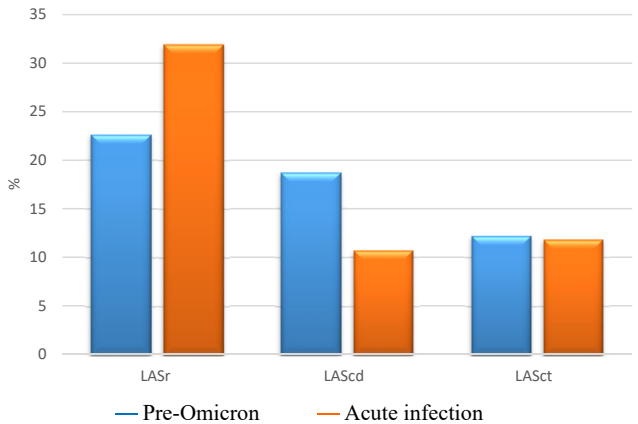

Figure 1. Comparison of 2-dimensional- speckle tracking echocardiography left atrial parameters during infection with Omicron, compared to those from the historic echocardiographic examinationss. Left atrial strain (LAS), reservoir (LASr), LAS, conduit (LAScd), and LAS contraction (LASct) are represented by blue box plots (before acute infection) and orange box plots (during acute infection). Note that LASr and LAScd improved during the period of acute infection, whereas no significant changes occurred for LASct, during the period of acute disease.

Table 3. Baseline clinical and echocardiographic characteristics of hospitalized Omicron patients vs those of matched wild-type COVID-19 patients

Variables	Original N = 134	Omicron N = 134	*P*
Clinical characteristics			
Age, y	71.1 ± 16	71.9 ± 17	0.67
Male gender	78 (58)	83 (62)	0.40
Severity grade			0.96
Mild	72 (54)	69 (51)	
Moderate	12 (9)	13 (10)	
Severe	44 (32)	46 (34)	
Critical	6 (5)	6 (5)	
Body surface area	1.82 ± 0.2	1.83 ± 0.2	0.46
Ischemic heart disease	31 (23)	36 (27)	0.48
Diabetes mellitus	46 (34)	50 (37)	0.26
Stroke	17 (13)	21 (16)	0.48
Chronic kidney disease	23 (17)	27 (20)	0.53
Hypertension	85 (63)	70 (52)	0.06
COPD	13 (10)	9 (7)	0.37
Temperature, °C	37.5 ± 0.8	37.4 ± 0.8	0.47
O_2 saturation, %	91.9 ± 10	92.9 ± 5	0.29
Heart rate, beats/min	85.3 ± 15	89.2 ± 22	0.17
Systolic blood pressure, mm Hg	137.2 ± 22	132.2 ± 26	0.15
Diastolic blood pressure, mm Hg	75.2 ± 12	72.9 ± 15	0.25
Routine echocardiography			
LVEF, %	52.4 ± 16	55.3 ± 10	0.08
LV end-diastolic diameter, mm	40.8 ± 13	45.3 ± 8	0.0008
LV end-systolic diameter, mm	25.9 ± 11	30.2 ± 8	0.0004
Stroke volume index, mL/m^2	31.1 ± 12	34.2 ± 13	0.04
LA volume index, mL/m^2	32.4 ± 18	33.6 ± 15	0.55
TAPSE, cm	2.01 ± 0.8	2.12 ± 0.6	0.19
RV S', cm/s	10.0 ± 4	10.7 ± 5	0.16
E/A ratio	0.9 ± 0.6	1.0 ± 0.7	0.20
E/e' average ratio	10.1 ± 7	11.8 ± 6	0.03
Pulmonic flow acceleration time, msec	71.3 ± 38	80.0 ± 37	0.06
Strain, as measured by speckle tracking echocardiography, %			
Global longitudinal	−17.1 ± 3.6	−17.9 ± 5.1	0.55
LA reservoir	33.0 ± 14.2	31.3 ± 13.3	0.45
LA conduit	−18.6 ± 10.8	−18.7 ± 9.8	0.93
LA contraction	−13.6 ± 8.2	−12.5 ± 8.6	0.75
LA reservoir / E/e'	3.9 ± 2.6	3.3 ± 2.1	0.06
RV free-wall	−20.4 ± 9.8	−20.7 ± 7.7	0.85
RV global 4C	−17.3 ± 5.9	−17.1 ± 4.8	0.67

Values are mean ± standard deviation, or n (%), unless otherwise indicated.

COPD, chronic obstructive pulmonary disease; E/A, ratio, early to late diastolic transmitral flow velocity; E/e', peak early diastolic flow velocity/mitral annulus early diastolic velocity; LV, left ventricular; LVEF, LV ejection fraction; LA, left atrium; RV, right ventricle; S', tissue Doppler systolic wave; TAPSE, tricuspid annular plane systolic excursion; 4C, 4-chamber.

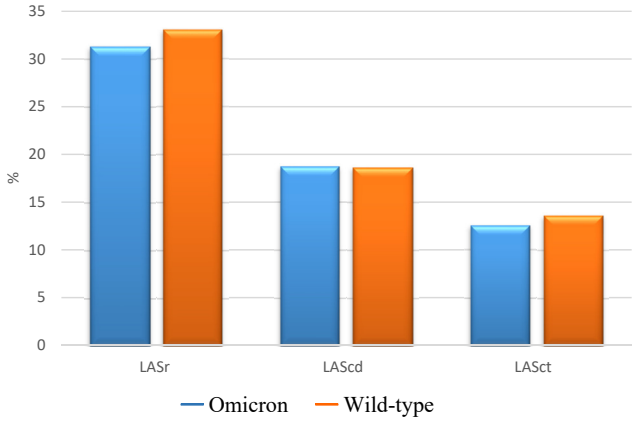

Figure 2. Comparison of 2-dimensional speckle tracking echocardiography left atrial parameters during infection with Omicron to those of the wild-type COVID-19 cohort. Left atrial strain (LAS), reservoir (LASr), LAS, conduit (LAScd), and LAS contraction (LASct) are represented by blue box plots (Omicron-type) and orange box plots (wild-type). Note that no significant differences occurred in LASr, LAScd, and LASct between the COVID-19 strains during the period of acute infection.

Discussion

This study emphasizes the importance of STE analyses in evaluating myocardial function in patients with Omicron COVID-19 infection. Our main findings are as follows: (i) In hospitalized patients with Omicron COVID-19 infection, LAS parameters at admission are abnormal in a large proportion of patients. (ii) The prevalence of LA 2D-STE abnormalities in hospitalized Omicron patients is similar to that in matched WT-variant patients. (iii) In the majority of Omicron patients who had a previous echocardiographic examination, these abnormalities have already been recorded before the acute infection. (iv) In Omicron patients who had a follow-up echocardiographic examination, LAS parameters did not change. (v) LASr and LAScd increased in most patients during acute infection, compared to the levels in historic examinations. (vi) LAS parameters at admission are predictors of mortality and respiratory deterioration in patients with COVID-19 infection.

LA mechanical function has proven its value in recent years in several clinical settings.[22,23] 2D-STE LA measurements were found to be related to LV end-diastolic pressure, whereas the LASr to E/e' ratio is correlated to invasively measured LA compliance.[24] LASr and the LASr to E/e' ratio were found to hold independent prognostic value in patients with heart failure.[25] Nevertheless, the potential interplay between LAS parameters and patients with acute COVID-19 infection rarely was investigated. Researchers in France evaluated LAS in 79 patients with severe COVID-19 pneumonia, and they found that it is associated with the occurrence of atrial fibrillation. However, the cohort included only patients with severe disease, and recruitment was conducted during 2020, and thus did not include the current Omicron strains. Furthermore, the small number of patients precluded performance of outcome analyses.[26]

Strain assessment of patients with either the WT or the Omicron variants in our study involved routine studies performed in all consecutive patients with COVID-19, irrespective of clinical indication or severity of disease, to assess a homogeneous unselected patient population. In our study, abnormal LAS appeared in approximately two thirds of patients with the Omicron-type variant, and it was the most common 2D-STE pathology. The prevalence of abnormal LAS was similar to that of the matched WT patients. An important finding to note is that in the majority of patients with abnormal LAS, and a previous echocardiographic examination, similar abnormalities were recorded in the examination that occurred prior to the current admission, suggesting that in most Omicron patients, LA dysfunction is associated with background cardiac disease, and acute infection does not cause significant additive LA injury. The surprising finding that, in a large proportion of patients with acute Omicron COVID 19 infection, LASr and LAScd actually were increased during acute infection is probably

Table 4. Outcome analysis of predictors of clinical events

Parameter	OR, combined	OR, mechanical ventilation	OR, mortality	*P*, combined	*P*, mechanical	*P*, mortality
Age, y	1.06 (1.01−1.10)	1.01 (0.98−1.05)	1.07 (1.007−1.13)	0.005	0.34	0.008
Gender male	1.11 (0.40−3.0)	0.66 (0.23−1.93)	0.98 (0.27−3.5)	0.84	0.46	0.98
Troponin-I, ng/L	1.002 (0.99−1.005)	1.0002 (0.99−1.0005)	1.002 (1.002-1.006)	0.15	0.05	0.02
Strain, %						
Global longitudinal	1.04 (0.91−1.20)	1.06 (0.92−1.23)	1.12 (0.91−1.38)	0.53	0.39	0.30
LA reservoir	0.95 (0.92−0.99)	0.94 (0.90−0.98)	0.95 (0.91−1.00)	0.03	0.007	0.06
LA conduit	1.08 (1.01−1.16)	1.09 (1.01−1.19)	1.09 (1.00−1.19)	0.02	0.02	0.04
LA contraction	1.02 (0.97−1.07)	1.03 (0.98−1.09)	1.02 (0.96−1.08)	0.37	0.15	0.54
LA reservoir / E/e'	0.66 (0.48−0.91)	0.60 (0.41−0.87)	0.69 (0.47−0.99)	0.004	0.002	0.05
RV free wall	1.02 (0.96−1.09)	1.03 (0.96−1.09)	1.04 (0.97−1.12)	0.47	0.40	0.23
RV global 4C	1.07 (0.96−1.19)	1.10 (0.99−1.23)	1.12 (0.99−1.28)	0.20	0.09	0.08

E/e', peak early diastolic flow velocity/mitral annulus early diastolic velocity; LA, left atrial; ; OR, odds ratio; RV, right ventricle; 4C, 4-chamber.

related to the heightened adrenergic tone and the hyperdynamic circulation, which commonly are seen in acute WT and Omicron COVID-19 infection.[10,27]

An important finding is that the LASr and the LASr-to-E/e' ratio were associated with excess events in Omicron patients. Our results suggest the presence of an association between LA dysfunction and stiffness, and the prognosis of COVID-19, possibly due to loss of the buffering effect of LA compliance on the hemodynamic effects of acute infection. Thus, identifying LA function and compliance in patients with the Omicron variant seems to be important to improve risk stratification. The interplay between LAS and COVID-19 highlights the usefulness of assessing LA function by strain analysis in this population, to enhance the clinical decision-making process. The introduction of the new, fully automated, 2D strain analytical software makes our findings applicable in routine practice, to help in deciding on treatment strategies.

Study limitations

This single-centre study included only hospitalized patients. Only a minority of patients with the Omicron COVID-19 variant are admitted to the hospital, which leads to overestimation of the prevalence of LA functional pathology in these patients. Outcome analyses should be interpreted with caution, owing to the small number of patients and events, and possible underpowering. Furthermore, the lowness of the number of events precluded multivariate outcome analysis. We believe that our results should encourage exploration of the issue of routine use of LAS analysis as a predictor of clinical deterioration in Omicron COVID-19 patients in larger series. Pre— and post—COVID-19 echocardiograms were evaluated in only a minority of patients; thus, the prevalence levels of the findings that have preceded, or followed, COVID-19 infection are unclear.

Conclusions

Our prospective analysis of consecutive patients with Omicron-type COVID-19 infection is the first to evaluate comprehensive 2D-STE LAS analyses in these patients, and to show that it is linked with outcome. LAS is a sensitive measure of LA compliance and function, and it appears to not decline, and even to improve, during acute Omicron-type COVID-19 infection.

Acknowledgements

The authors thank the Israeli National Consortium for the sequencing of SARS-CoV-2 and the Public Health Services in the Ministry of Health for the SARS-CoV-2 sequencing data.

Ethics Statement

The ethics committee of Tel Aviv Medical Center approved the study. The committee voided the requirement of informed consent for echocardiographic assessment.

Patient Consent

The authors confirm that patient consent is not applicable to this article. The ethics committee of Tel Aviv Medical Center have approved the study and voided the requirement of consent for the echocardiographic assessment.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

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