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ORIGINAL PAPER

Systematic lung ultrasound in Omicron-type vs. wild-type COVID-19

Ariel Banai[1†], Lior Lupu [1†], Aviel Shetrit[1], Aviram Hochstadt [1], Yael Lichter[2], Erez Levi[1], Yishay Szekely[1], Nadav Schellekes[3], Tammy Jacoby[1], David Zahler[1], Tamar Itach[1], Philippe Taieb[1], Sheizaf Gefen[1], Dana Viskin[1], Lia Shidlansik[1], Amos Adler[3], Ekaterina Levitsky[3], Ofer Havakuk[1], Shmuel Banai[1], Eihab Ghantous [1†], and Yan Topilsky [1*†]

[1]Department of Cardiology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Weizmann 6, Tel Aviv 6423919, Israel; [2]The Intensive Care Unit, Tel-Aviv Sourasky Medical Center and Sackler school of Medicine, Tel-Aviv University, Weizmann 6, Tel Aviv 6423919, Israel; and [3]Clinical Microbiology Laboratory, Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel-Aviv University, Weizmann 6, Tel Aviv 6423919, Israel

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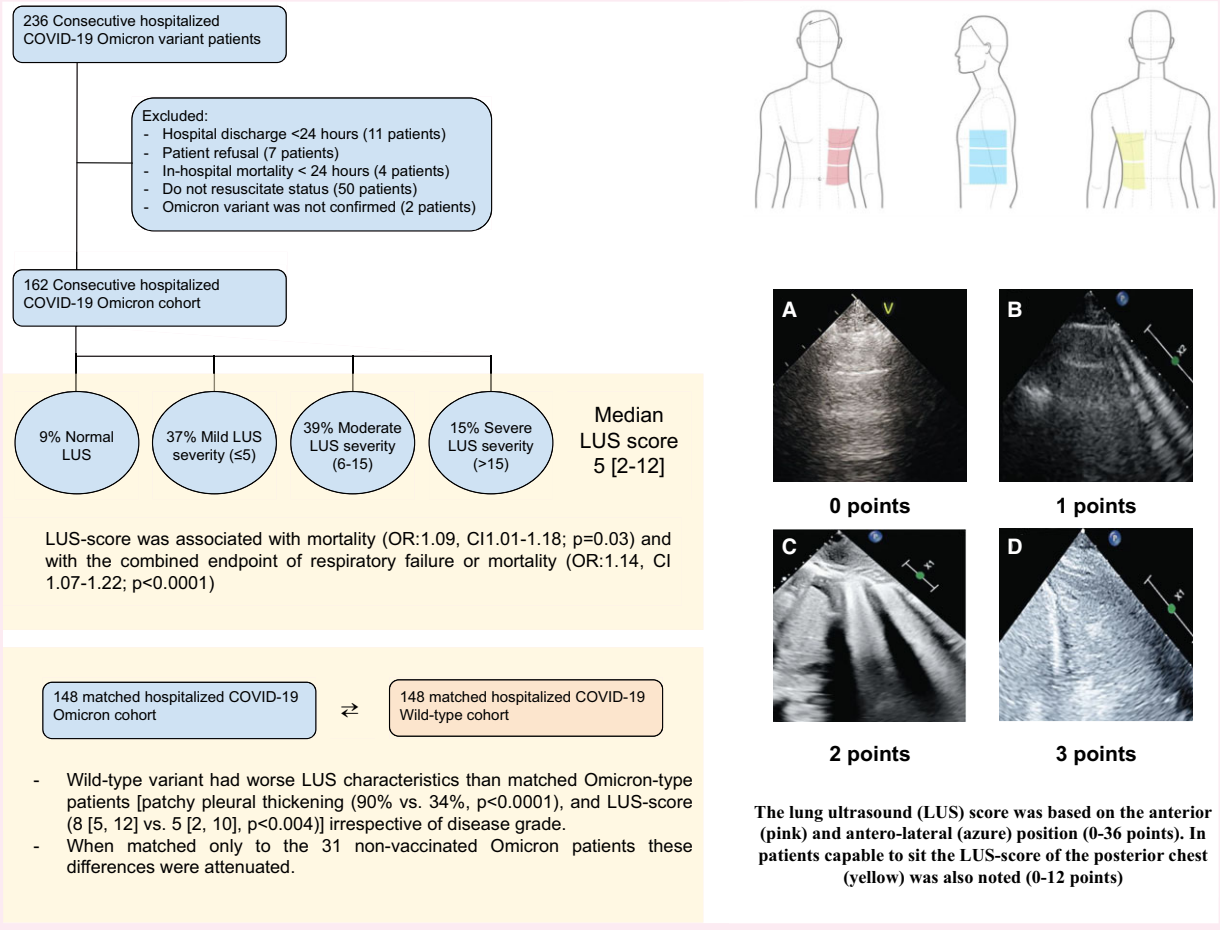
Aims Preliminary data suggested that patients with Omicron-type-Coronavirus-disease-2019 (COVID-19) have less severe lung disease compared with the wild-type-variant. We aimed to compare lung ultrasound (LUS) parameters in Omicron vs. wild-type COVID-19 and evaluate their prognostic implications.

Methods and results One hundred and sixty-two consecutive patients with Omicron-type-COVID-19 underwent LUS within 48 h of admission and were compared with propensity-matched wild-type patients (148 pairs). In the Omicron patients median, first and third quartiles of the LUS-score was 5 [2–12], and only 9% had normal LUS. The majority had either mild (≤5; 37%) or moderate (6–15; 39%), and 15% (≥15) had severe LUS-score. Thirty-six percent of patients had patchy pleural thickening (PPT). Factors associated with LUS-score in the Omicron patients included ischaemic-heart-disease, heart failure, renal-dysfunction, and C-reactive protein. Elevated left-filling pressure or right-sided pressures were associated with the LUS-score. Lung ultrasound-score was associated with mortality [odds ratio (OR): 1.09, 95% confidence interval (CI): 1.01–1.18; $P = 0.03$] and with the combined endpoint of mortality and respiratory failure (OR: 1.14, 95% CI: 1.07–1.22; $P < 0.0001$). Patients with the wild-type variant had worse LUS characteristics than the matched Omicron-type patients (PPT: 90 vs. 34%; $P < 0.0001$ and LUS-score: 8 [5, 12] vs. 5 [2, 10], $P = 0.004$), irrespective of disease severity. When matched only to the 31 non-vaccinated Omicron patients, these differences were attenuated.

Conclusion Lung ultrasound-score is abnormal in the majority of hospitalized Omicron-type patients. Patchy pleural thickening is less common than in matched wild-type patients, but the difference is diminished in the non-vaccinated Omicron patients. Nevertheless, even in this milder form of the disease, the LUS-score is associated with poor in-hospital outcomes.

* Corresponding author. E-mail: topilskyyan@gmail.com
† These authors contributed equally to this work.

Graphical Abstract



Keywords COVID-19 • lung ultrasound • risk stratification • clinical outcomes

Introduction

The main manifestation of the Coronavirus disease 2019 (COVID-19) is viral pneumonia, which may evolve to severe acute respiratory distress syndrome.[1,2] Bilateral lung infiltrates on computed tomography (CT) were considered the hallmark of disease in the wild-type COVID-19 variant.[3] The use of lung ultrasound (LUS) as a diagnostic tool, and for assessment of response to treatment as well as for follow-up, has become common practice in the early stages of the pandemic,[4–9] and findings were found to correlate with findings on high-resolution CT.[10,11] The fifth COVID-19 variant of concern, 'Omicron' (B.1.1.529 lineage), has a large number of changes in its spike protein relative to that of the original (wild-type) virus.[12–14] Within weeks, Omicron had been reported by over 100 countries, breaking COVID-19 infection records all over the world, including Israel.[15] Preliminary reports have suggested that the proportion of cases admitted to hospitals is lower compared with the earlier variants, and that those admitted have less severe lung disease, hinting that Omicron replicates less well in lung cells than other variants.[13,14,16,17] Yet, although the outbreak of Omicron COVID-19 infection started several months ago, systematic LUS evaluation of COVID-19 Omicron type patients has not been published. At the beginning of the COVID-19 pandemic, we performed prospective systematic LUS evaluation of the wild-type patients using a pre-defined comprehensive protocol in all consecutive patients admitted to our centre, irrespective of disease severity.[9,18] We, therefore, undertook this study in which we performed a complete similar LUS evaluation of consecutive Omicron COVID-19 patients requiring hospitalization to define the spectrum of LUS presentations in patients infected by this new variant and their prognostic effect, stratified by the severity of the disease. Furthermore, we compared the LUS parameters in the 'Omicron patients' with 148 propensity-matched paired patients with the wild-type variant. Last, to assess the impact of the Omicron variant in non-vaccinated patients, we compared the LUS parameters in the 31 non-vaccinated Omicron patients to propensity-matched 124 patients (1:4) with the wild-type variant (all were non-vaccinated).

Methods

The study population comprised two cohorts of patients with COVID-19 infection: (i) the recent 'Omicron cohort', including 162 consecutive hospitalized patients who had their COVID-19 diagnosis between 3 January 2022 to 25 January 2022, confirmed by a positive reverse-transcriptase–polymerase chain reaction assay for SARS-CoV-2 and whole-genome sequencing. (ii) The COVID-19 'wild-type cohort' includes 530 consecutive hospitalized patients who had their first SARS-CoV-2 infection between 21 March 2020 and 16 September 2020 with the original wild-type variant. Patient's

demographic data, comorbid conditions, physical examination, and laboratory findings were systematically recorded. Patient's disease severity defined as either mild, moderate, severe, or critical disease, was determined in accordance with the World Health Organization guidelines.[19] All patients underwent comprehensive LUS evaluation within 48 h of SARS-CoV-2 diagnosis as part of the predefined protocol. Clinical and imaging data were collected prospectively. Clinical endpoints were defined as either in-hospital death or in-hospital respiratory failure, defined as hypoxaemia necessitating either invasive mechanical ventilation or non-invasive ventilation [bi-level positive airway pressure or high flow inspiratory support (Vapotherm, Inc., Exeter, NH, USA)]. The combined endpoint included either in-hospital death or in-hospital respiratory failure. The Tel-Aviv Medical Center ethics committee approved the study and waived the requirement of informed consent for the echocardiographic assessment.

Whole-genome sequencing of SARS-CoV2 positive samples

Total nucleic acids were extracted from respiratory specimens. cDNA synthesis and enrichment were performed on the extracted total nucleic acids using Illumina COVIDSeq Test (Illumina, CA, USA). Amplicon libraries for viral genome sequencing were prepared using NovaSeq 6000 SP Reagent Kit v1.5 as instructed by the manufacturer's manual.

Bio-informatic analysis

Global phylogenetic placement was determined using the DRAGEN COVIDSeq v3.5.5 platform (Illumina, CA, USA). FASTA sequences were analyzed using the pipeline developed by the Israeli National Consortium for SARS-CoV-2 Sequencing.[20]

Lung ultrasound

We performed LUS on all patients with COVID-19 using a six-zone method for each lung, including a scan of the anterior, antero-lateral, and postero-lateral aspects of the thorax (*Figure 1A*). Examinations were performed by cardiologists with expertise in LUS recording and interpretation using the same equipment (CX 50, Philips Medical Systems, Bothell, WA, USA), with the same phased-array probe used for echocardiography. Each LUS lasted between 2 and 3 min, with the patient supine or semi-supine, omitting the need for position change during the examination. A point scoring system was employed for each region and ultrasound pattern: A-lines (normal reverberation artefacts of the pleural line that when accompanied by lung sliding correspond to normal aeration of the lung) were equal to 0 points; B-lines (shining lines vertical to the pleura line, arising from it and reaching the edge of the screen erasing A-lines, which represent reverberation artefact through oedematous interlobular septa or alveoli) were divided to B1 (separated ≤2 B-lines that correspond to moderate lung aeration loss) that was equal to 1 point, and B2 (≥3 separated, or coalescent B-lines that correspond to severe lung aeration loss) that was equal to 2 points; lung consolidation received 3 points. Thus, a LUS score of 0 was normal and 36 was the worst.[21] The LUS score was sub-categorized based on severity into none (0), Mild (1–5), Moderate (6–15), and Severe (16–36).[22] In 93 patients in the Omicron cohort that were able to cooperate to a change to the sitting position, we performed another LUS scan of the posterior chest in the paravertebral [2nd, 10th inter-costal (ICS)] lines. Thus, a posterior LUS score of 0 was normal and 12 was the worst. We also documented the presence of Pleural thickening and pleural effusions of each examination. Similar to our previous publications,[9,23] pleural thickening was qualitatively determined, indicating irregular pleural line either in cases of sub-pleural consolidations or in cases of B-lines accompanied by irregular pleural line. In accordance to present guidelines,[24] the following measures were undertaken to minimize the risk of inadvertent infection: (i) all studies were bedside studies performed at the designated COVID-19 internal ward units; (ii) all studies were performed with small dedicated scanners, because their disinfection is easier than that of larger machines with high-end ultrasound systems; and (iii) personal protection at the time of ultrasound recordings included airborne precautions comprising of N-95 respirator masks, gloves, head-covers, eye shields, and shoe covers.

Echocardiography

LV diameters and ejection fraction (LVEF) were calculated as recommended.[25] Measurements of mitral inflow and mitral septal and lateral annular velocities (*e'*) were measured in the apical four-chamber view.[26] Left atrial volume was calculated using the biplane area length method. Right ventricular (RV) function was evaluated by tricuspid annular plane systolic excursion and systolic tricuspid lateral annular velocity (RV S').[25,27] Non-invasive RV hemodynamic variables included pulmonic acceleration time (PAT), estimated right atrial (RA) pressure, and calculated mean pulmonary artery pressure (MPAP) based on the formula 48—(0.28 × PAT).[28]

Statistical analysis

Continuous normally distributed parameters were presented as mean ± standard deviation (SD) and compared using the Student's *t*-test. Non-normally distributed data were presented by median, 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's exact test. To analyze the association of the LUS score with clinical, and echocardiographic manifestations of patients we performed linear regression models with demographic, clinical, laboratory, and echocardiographic parameters of patients as independent variables and the LUS score as the dependent variable. Clinical or LUS variables affecting in-hospital mortality, respiratory failure or the combined endpoint defined as either one, were evaluated by univariable logistic regression. Association between the dependent and the independent variables was expressed as odds ratio (OR) with the corresponding 95% confidence interval (CI).

To compare the echocardiographic, clinical and laboratory parameters in patients with the Omicron variant to those with the original wild-type variant, the entire database of original COVID-19 patients ($N = 530$) was used, and patients with the Omicron variant were matched in a 1:1 ratio to patients in the original wild-type cohort. The propensity score was estimated using logistic regression with relevant variables entered the model (age, gender, disease grade, ischaemic heart disease, heart failure, chronic obstructive pulmonary disease, chronic renal failure, diabetes, hypertension, obesity, and body surface area), and then matching was performed using nearest neighbour 'greedy' with a 1:1 ratio between the Omicron and wild-type groups. To further decrease disparity in pairs, matching was restricted by a calliper of 0.2 of the SD of the propensity score, and exact matching was performed for clinical grade categories. Assessment of balance was performed by inspecting resulting standardized mean differences. A standardized mean difference of <0.1 was considered small. A matching process was performed for the 31 non-vaccinated Omicron patients, but with a 1:4 ratio between the Omicron and wild-type groups. Reported *P* values were two-tailed and considered statistically significant if <0.05. All data were analyzed with the JMP System software version 12.0 (SAS Institute, Inc, Cary, NC, USA).

Results

Clinical data were collected in 236 consecutive patients hospitalized with the COVID-19 Omicron variant. Seventy-two patients were excluded because they did not undergo echocardiographic assessment due to hospital discharge ≤24 h (11 patients), patient refusal (7 patient), death shortly after hospitalization (4 patients), and a 'Do Not Resuscitate/Intubate' status (50 patients). In two patients the Omicron variant was not confirmed. Thus, the study group included 162 COVID-19 Omicron variant patients (aged 71.9 ± 17 years, 62% male). Patients were stratified to 91 patients (56%) with mild disease, 15 patients (10%) with moderate COVID-19, 51 (31%) with severe disease, and 5 (3%) in critical condition at presentation. *Table 1* shows the

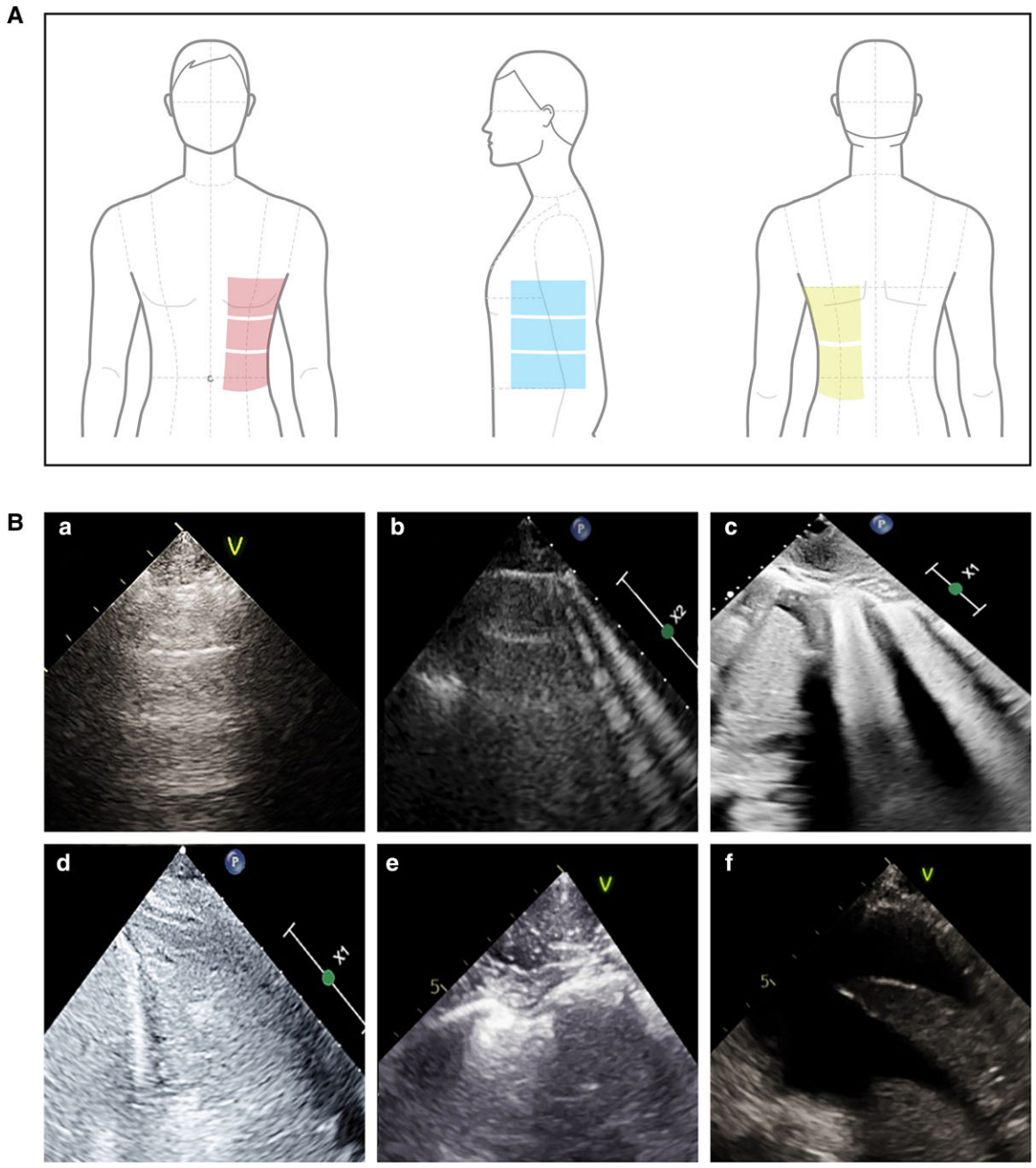


Figure 1 Lung ultrasound points and examples of different patterns of lung ultrasound findings. (*A*) Probe positions in the anterior and antero-lateral positions (left and middle), and in the postero-lateral positions (right). (*B*) The different patterns of US findings and scoring (a) A-lines, normal reverberation artifacts of the pleural line that correspond to normal aeration of the lung. Lung ultrasound score (LUS) equals zero. (b) Separated two fine B-lines that represent reverberation artefact through mildly oedematous interlobular septa or alveoli that correspond to moderate aeration lost. LUS score equals one. (c) Multiple coalescent B-lines that correspond to severe lung aeration loss. LUS score equals two. (d) Lung consolidation (liver is on the left side of the picture, the consolidated lung on the right, and between them the dense line of the diaphragm) that correspond to complete aeration loss. LUS score equals three (e) Patchy pleural thickening. Compare to the fine plural line in picture a. (f) Pleural effusion with lower lobe passive lung atelectasis within.

baseline characteristics and LUS assessments of all patients and stratified by disease grade. The majority of Omicron patients [131 (81%)] were vaccinated at least once. The number of vaccinations per person (median, and 25th and 75th percentiles) was 3 [2, 3], all with the BNT162b2 vaccine (Pfizer–BioNTech). Bilateral infiltration was the most common chest X-ray manifestation. Fifteen (9%) of the patients had normal LUS (A-lines accompanied by lung sliding in all zones). Sixty patients (37%), 63 patients (39%), and 24 (15%) had mild (LUS ≤ 5), moderate (6–15), and severe (≥ 15) LUS scores, respectively. Fifty-eight (36%) patients had patchy pleural thickening in at least one

Table 1 Baseline characteristics in the Omicron type patients, stratified by disease grade

Variables	All N = 162	Mild/moderate N = 106	Severe/critical N = 56	P value
Lung ultrasound				
Pleural effusion right, *n* (%)	8 (5)	1 (1)	7 (12)	0.002
Pleural effusion left, *n* (%)	5 (3)	1 (1)	4 (7)	0.03
Any Pleural effusion, *n* (%)	9 (6)	1 (1)	8 (14)	0.0005
Pleural thickening, *n* (%)	58 (36)	30 (28)	28 (49)	0.009
Posterior lung ultrasound score, median [IQR]	3 [1, 6]	2.5 [0, 4]	4.5 [3.5, 6.7]	0.001
Lung ultrasound score, median [IQR]	5 [2, 12]	4 [1, 7]	10 [2.5, 16]	0.0002
Chest X-ray				
Lobar infiltration, *n* (%)	15 (9)	8 (8)	7 (12)	0.30
Bilateral infiltration, *n* (%)	50 (31)	16 (15)	34 (61)	<0.0001
Pleural effusion, *n* (%)	22 (13)	8 (8)	14 (25)	0.002
Hilar congestion, *n* (%)	39 (24)	17 (16)	22 (39)	0.0009
Clinical characteristics				
Age (years), mean ± SD	71.9 ± 17	70.3 ± 18	74.8 ± 14	0.08
Male gender, *n* (%)	100 (62)	60 (63)	40 (42)	0.45
Body mass index, mean ± SD	26.6 ± 5	26.5 ± 5	26.8 ± 5	0.72
Body surface area, mean ± SD	1.85 ± 0.2	1.85 ± 0.2	1.85 ± 0.2	0.89
Ischaemic 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
Heart failure, *n* (%)	33 (20)	19 (18)	14(25)	0.30
Chronic obstructive pulmonary disease, *n* (%)	9 (6)	4 (4)	5 (9)	0.19
Interstitial lung disease, *n* (%)	7 (4)	5 (5)	2 (4)	0.71
Any lung disease, *n* (%)	20 (12)	9 (8)	11 (20)	0.04
Diabetes mellitus, *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
Systolic blood pressure (mmHg), mean ± SD	131.3 ± 24	131.0 ± 25	131.7 ± 23	0.90
Diastolic blood pressure (mmHg), mean ± SD	72.9 ± 15	71.9 ± 15	75.2 ± 15	0.40
Haemoglobin (g/dL), mean ± SD	12.1 ± 2	12.2 ± 2	12.1 ± 2	0.85
White blood cells, (10^3/μL), median [IQR]	7.1 [4.8, 9.9]	6.8 [4.7, 10.2]	8 [5.3, 9.4]	0.49
Platelets (10^3/μL), 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 [IQR]	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 [IQR]	14 [5, 64]	11 [4, 64]	19 [8, 65]	0.10
Brain natriuretic peptide, median [IQR]	165 [55, 770]	108 [36, 422]	378 [93, 1068]	0.05
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				
LVEF (%)	55.5 ± 9	56.5 ± 7	54.8 ± 8	0.23
Left atrial volume index (mL/m^2), mean ± SD	34.1 ± 14	35.3 ± 15	32.7 ± 11	0.28
TAPSE (cm), mean ± SD	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.4	0.97

Continued

Table 1 Continued

Variables	All N = 162	Mild/moderate N = 106	Severe/critical N = 56	P value
RV S′ (cm/s), mean ± SD	12.0 ± 3	11.8 ± 3	12.4 ± 4	0.25
Stroke volume index (mL/m^2), mean ± SD	35.6 ± 10	36.4 ± 11	34.1 ± 8	0.18
Cardiac index (L/min/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/*e*′ average ratio, mean ± SD	12.3 ± 6	11.6 ± 5	14.0 ± 7	0.02
Right atrial pressure (mmHg), mean ± SD	7.9 ± 4	7.6 ± 4	8.6 ± 4	0.24
Mean pulmonary artery pressure (mmHg), mean ± SD	35.1 ± 12	32.4 ± 12	40.3 ± 10	<0.0001
Systolic pulmonary artery pressure (mmHg), mean ± SD	37.7 ± 11	35.5 ± 9	42.0 ± 13	0.04

Abbreviations: IQR, interquartile range; SD, standard deviation; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle.

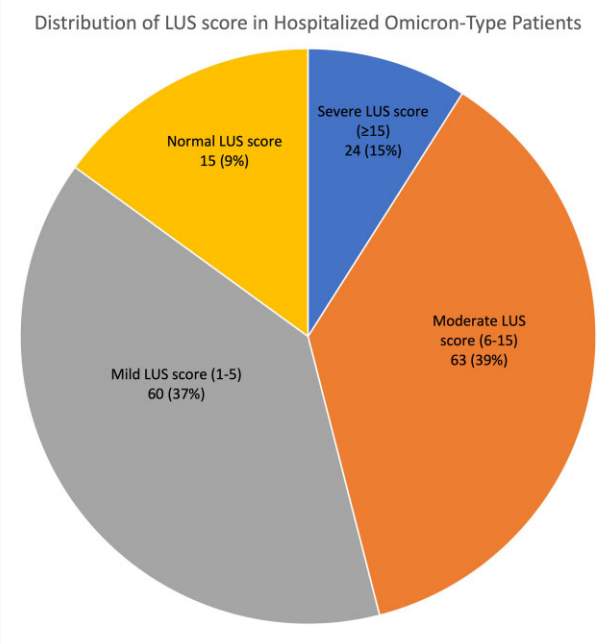


Figure 2 Distribution of LUS grades in hospitalized patients with COVID-19 Omicron type.

zone. Pleural effusion was rare in LUS as well ($n = 9$, 6%). The median total LUS score was 5 [2–12]. Distribution of LUS score grades is shown in *Figure 2*.

Association of LUS score with demographic, clinical, and echocardiographic parameters

Supplementary data online, *Table S1* shows the associations between demographic, clinical, and echocardiographic parameters to the LUS score. Factors associated with the LUS score included ischaemic heart disease, heart failure, O_2 saturation, renal dysfunction, and C-reactive protein (CRP). Age, gender, and all other co-morbidities were not associated with the LUS score. Multiple echocardiographic parameters were associated with poor LUS score, all related to either elevated left filling pressure (*E*/*e*′ ratio, E wave velocity), or elevated right sided pressures (high RA pressure, MPAP, and low stroke volume). The only parameters associated with the LUS score in the adjusted analysis were CRP, O_2 saturation, and *E*/*e*′ ratio.

Lung ultrasound score of patients with concomitant heart failure was higher than those without heart failure (10 [1, 17] vs. 4.5 [2, 8.2]; $P = 0.01$); however, no difference was noted between patients with and without interstitial lung disease and COPD (5 [1, 24] vs. 5 [2, 10]; $P = 0.76$ and 6.5 [4.5, 6.5] vs. 5 [1.2, 11]; $P = 0.28$; respectively).

Association between LUS parameters and outcome

There were 14 deaths during hospitalization (8.6%). Higher total LUS score at baseline was significantly associated with increased mortality (OR: 1.09, 95% CI: 1.008–1.18; $P = 0.03$, *Table 2*). Respiratory failure occurred in 15 patients (9%) during hospitalization, with 4 patients (2%) requiring invasive ventilation and 11 patients (7%) requiring non-invasive ventilation. The combined endpoint of in hospital mortality or respiratory failure occurred in 19 patients (12%). A higher total LUS score was significantly associated with the combined endpoint (OR: 1.14, 95% CI:1.07–1.22; $P < 0.0001$, *Table 2*).

Comparison to the wild-type COVID-19 cohort

Baseline characteristics of both groups, stratified to clinical, LUS, chest X-ray, and echocardiographic characteristics are presented in Supplementary data online, *Tables S2–S4* and *Figure 3*. Patients with the wild-type variant had much worse LUS characteristics than the matched Omicron type patients, as reflected in higher prevalence of pleural thickening (90 vs. 34%, $P < 0.0001$) and higher LUS score (8 [5–12] vs. 5 [2–10], $P = 0.004$).

Supplementary data online, *Table S4* shows the main LUS, chest X-ray, and echocardiographic findings in the matched Omicron and wild-type cohort categorized by COVID-19 severity (mild/moderate vs. severe/critical). Interestingly, patients with Omicron and severe disease had a higher prevalence of hilar congestion, and higher *E*/*e*′ than matched patients with the wild-type variant. Matching produced 31 non-vaccinated patients with Omicron and 124 non-vaccinated patients with the wild-type COVID-19 variant. Characteristics of both groups, stratified to clinical, LUS, chest X-ray, and echocardiographic characteristics are presented in Supplementary data online, *Table S5*. Interestingly,

Table 2 Association of LUS, clinical and echocardiographic parameters with outcomes in Omicron type patients

Parameter	OR (95% CI) for respiratory failure	OR (95% CI) for mortality	OR (95% CI) for the combined endpoint
Clinical characteristics			
Age, years	1.02 (0.98–1.06); $P = 0.21$	1.06 (1.007–1.13); $P = 0.03$	1.03 (1.001–1.08); $P = 0.04$
Gender male	0.60 (0.20–1.80); $P = 0.36$	1.11 (0.31–3.95); $P = 0.87$	0.84 (0.32–2.24); $P = 0.74$
O_2 saturation (%)	0.84 (0.74–0.96); $P = 0.007$	0.80 (0.95–1.24); $P = 0.01$	0.82 (0.73–0.93); $P = 0.002$
Heart rate (beats/min)	1.02 (0.99–1.05); $P = 0.19$	1.009 (0.97–1.05); $P = 0.63$	1.01 (0.98–1.04); $P = 0.39$
Systolic blood pressure (mmHg)	0.97 (0.95–1.003); $P = 0.07$	0.93 (0.89–0.98); $P = 0.003$	0.97 (0.95–1.006); $P = 0.10$
Diastolic blood pressure (mmHg)	0.97 (0.93–1.02); $P = 0.22$	0.90 (0.83–0.97); $P = 0.003$	0.97 (0.93–1.02); $P = 0.26$
Disease grade (mild/moderate vs. severe/critical)	14.1 (3.05–66.0); $P < 0.0001$	9.95 (2.07 47.8); $P = 0.0008$	9.32 (2.92–29.7); $P < 0.0001$
Lung ultrasound			
Pleural effusion	3.9 (0.71–21.4); $P = 0.15$	2.02 (0.22–18.1); $P = 0.52$	2.64 (0.49–14.2); $P = 0.29$
Pleural thickening	2.6 (0.87–8.0); $P = 0.08$	1.55 (0.45–5.3); $P = 0.48$	2.22 (0.85–5.8); $P = 0.10$
Lung ultrasound score	1.15 (1.07–1.24); $P = 0.0002$	1.09 (1.008–1.18); $P = 0.03$	1.14 (1.07–1.22); $P < 0.0001$
Lung ultrasound score posterior	1.02 (0.76–1.37); $P = 0.89$	1.33 (0.78–2.26); $P = 0.28$	1.09 (0.84–1.42); $P = 0.42$
Chest X-ray			
Lobar infiltration	2.9 (0.1–1.9); $P = 0.26$	2.65 (0.26–26.7); $P = 0.44$	5.06 (1.06–24.2); $P = 0.04$
Bilateral infiltration	12 (2.4–60.8); $P = 0.0006$	10.9 (1.16–102); $P = 0.02$	7.87 (1.92–32.3); $P = 0.002$
Pleural effusion	3.3 (0.74–15.0); $P = 0.11$	4.96 (0.74–33.1); $P = 0.12$	2.88 (0.66–12.7); $P = 0.18$
Hilar congestion	1.7 (0.15–2.3); $P = 0.45$	3.66 (0.57–23.1); $P = 0.16$	2.18 (0.61–7.8); $P = 0.23$
Echocardiography			
LVEF (%)	0.97 (0.92–1.03); $P = 0.32$	0.95 (0.91–1.005); $P = 0.07$	0.97 (0.93–1.02); $P = 0.24$
E/e' ratio	1.13 (1.04–1.22); $P = 0.003$	1.13 (1.04–1.23) ;$P = 0.004$	1.13 (1.06–1.22); $P = 0.0005$
Left atrial volume (mL)	0.99 (0.97–1.02); $P = 0.66$	0.99 (0.97–1.02); $P = 0.86$	0.99 (0.97–1.01); $P = 0.61$
TAPSE (cm)	0.39 (0.11–1.38); $P = 0.13$	0.08 (0.02–0.38); $P = 0.0006$	0.25 (0.08–0.79); $P = 0.01$
RV S' (cm/s)	0.78 (0.63–0.98); $P = 0.02$	0.62 (0.47–0.82); $P < 0.0001$	0.75 (0.62–0.91); $P = 0.002$
Right atrial pressure (mmHg)	1.009 (0.93–1.09); $P = 0.82$	1.03 (0.97–1.10); $P = 0.34$	1.02 (0.96–1.09); $P = 0.41$
Mean pulmonary artery pressure (mmHg)	1.07 (1.01–1.13); $P = 0.008$	1.03 (0.98–1.09); $P = 0.17$	1.06 (1.01–1.10); $P = 0.01$
Systolic pulmonary artery pressure (mmHg)	1.03 (0.95–1.11); $P = 0.37$	1.05 (0.98–1.13); $P = 0.18$	1.04 (0.98–1.10); $P = 0.25$

Abbreviation: OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

the differences in LUS characteristics between the patients with the wild-type variant and Omicron-type became all non-significant once matching was performed for only the non-vaccinated patients.

Discussion

The results of our study showed that: (i) elevated LUS score was associated with ischaemic heart disease, heart failure, O_2 saturation, renal dysfunction, CRP, and either high left filling pressure or elevated right sided pressures, but not with age, or other co-morbidities; (ii) LUS demonstrated fewer abnormalities in patients with the Omicron variant than the wild-type variant, a difference which was no longer evident when comparing unvaccinated patients; and (iii) high LUS score at presentation is associated with a higher risk for in-hospital mortality and respiratory failure.

Ultra-sonographic features of COVID-19 Omicron-type

The majority of patients demonstrated abnormal LUS findings of some degree, a score pointing to visible lung involvement in most degrees of illness, even in those with normal chest X-ray and normal ambient O_2 saturation. Nevertheless, the LUS score, the prevalence of pleural thickening, and the hallmark of lung injury in the wild-type strain[9,29,30] were lower in the Omicron-type patients, suggesting that Omicron-type presents with lesser lung injury compared with the wild-type variant. Importantly, the LUS score was associated with echocardiographic signs of elevated filling pressures and concomitant heart failure. Possible mechanisms for these associations are that these patients actually had heart failure with congestion, and COVID-19 was just an 'innocent' bystander, or that oedematous interlobular septa or alveoli due to high post-capillary pressure play a larger role in the new variant. The answers to these intriguing questions will require prospective studies using invasive hemodynamic assessment. Nevertheless, our preliminary analysis in the small group of non-vaccinated Omicron patients, showed attenuation of the differences between the Omicron and wild-type cohorts, suggesting that the lesser lung injury in the Omicron patients may be explained at least in part by their vaccination status.

LUS findings in relation to disease severity

With worsening disease, more pleural thickening and higher LUS scores were recorded in line with data published on the wild-type variant.[9,23] This suggests that in patients with the Omicron-type, the mechanism of

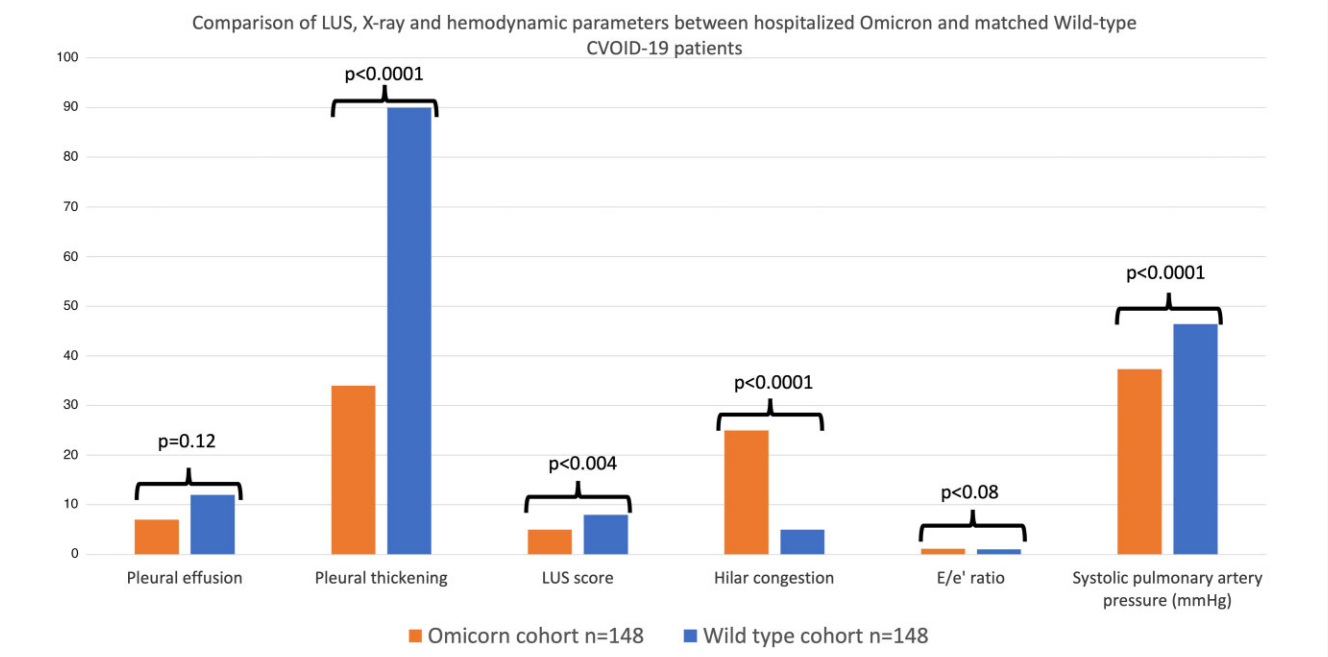


Figure 3 LUS, chest X-ray, and hemodynamic parameters during acute wild-type vs. Omicron-type COVID-19 infection. For each parameter, the left and right columns respresent the Omicron-type and the wild-type variants, respectively. LUS: Lung ultrasound.

desaturation may be different than in the wild-type variant, with less parenchymal and sub-pleural injury and possibly larger influence of background lung, or cardiac disease, or interlobular, or alveolar oedema related to elevated post-capillary pressure.

LUS as a predictive tool of clinical course and outcome

Higher LUS score, but not pleural thickening was associated with respiratory failure, mortality, and the combination of both. None of the deceased patients had a normal LUS. This is in concordance with previously described evidence in patients with the wild-type variant.[9,31,32] Just like in the wild-type variant,[9] the peripheral distribution of lung infiltrates makes LUS a reliable imaging study and may reduce the number of chest X-rays, or CT scans performed,[33,34] with their associated risks of radiation and iodinated contrast exposure.[18] Our study identified patients without any pleural thickening or B-lines, who did not experience respiratory failure or death, showing the ability of a straightforward baseline LUS to predict a good clinical outcome and serve as a mean of triage, especially in case of widespread infection and emergency room overcrowding. It may serve as an adjunct in hospitalized patients' discharge decisions.

Limitations

The fact that only a minority of patients diagnosed with COVID-19 infection in Israel are admitted to the hospital probably led to an overestimation of the severity of LUS in COVID-19 infection. Seventy-two patients were excluded, some due to Do Not Resuscitate/Intubate orders. This fact may create an opposite bias resulting in underestimation of LUS severity in patients with COVID-19 Omicron-type infection. Using phased-array transducers is acceptable when performing LUS, but its low frequency and high penetrance can compromise pleural evaluation. Nevertheless, placing the focus at the pleura level enabled a reasonable assessment of the pleural line. There are several LUS protocols and scoring schemes. Nevertheless, we elected to perform a similar protocol to the one we used in our wild-type cohort to avoid bias. Lastly, the number of adverse clinical events was relatively low, thus, to avoid overfitting and spurious results, we could not perform comprehensive multivariable analysis for associates of such events. Outcome analyses and data on non-vaccinated Omicron patients in our study should be interpreted with caution due to the small number of patients and possible under-power.

Conclusions and clinical implications

In patients with COVID-19 Omicron-type, LUS abnormalities are less common compared with the matched patients with the wild-type variant, partially related to their vaccination status. Nevertheless, even in this milder form of lung disease, LUS rapidly identifies pulmonary involvement and provides risk stratification, as well as prediction of need for mechanical ventilation and mortality, above clinical and routine radiographic assessment.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Data will be available upon request from the authors.

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