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# Echocardiography and renin-aldosterone interplay as predictors of death in COVID-19

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Coronavirus disease 2019 (COVID-19) has spread worldwide and has resulted in millions of deaths mainly due to inappropriate systemic inflammatory reaction to SARS-CoV-2 and evolution to refractory hypoxemia leading to acute respiratory distress syndrome.<sup>1</sup> It has also been shown that cardiac injury, including biomarker increase (troponin, NT-proBNP), pulmonary embolism, alteration of ventricular function on echocardiography are associated with increased mortality.<sup>2, 3</sup> SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE2) receptor to enter cells and modulates the renin angiotensin aldosterone system (RAAS), a major factor of adverse cardiac remodeling.<sup>1</sup> The interplay between RAAS, systemic inflammation, lung and cardiac involvement in COVID-19 is unknown and was the purpose of the present work (NCT04320017; IRB-approval: CER-2020-14-JOCOVID). *The main objectives of this study were to delineate how these parameters were associated with each other's and identify among them, independent predictors of 30 days mortality.*

A total of 127 non-intensive care patients with COVID-19 (no inotropes or mechanical ventilation) were included consecutively between March 2020 and May 2020 in a French tertiary care hospital (Pitié-Salpêtrière Hospital, Paris, France). Upon admission, patients were **systematically** evaluated with a transthoracic echocardiography, performed as soon as possible completed by serial cardiac and inflammatory plasma biomarkers (troponin, NT-proBNP, C-reactive protein, lymphocyte count). COVID-19 infection was defined by at least one positive SARS-CoV-2 RT-PCR test (93%) or compatible thoracic scanner and symptoms during the first 2020 French pandemic wave. Thoracic scanners were performed to assess the magnitude of lung parenchymal involvement and to rule-out pulmonary embolism, as clinically indicated. Renin, aldosterone, ACE2 circulating levels were measured in a subgroup of patients due to the time-lag needed to set up these methods after the start of the pandemic. Severity of oxygen **(O<sub>2</sub>)** requirement at the time of echocardiography was defined by SpO<sub>2</sub>/FiO<sub>2</sub> with FiO<sub>2</sub> derived from nasal **O<sub>2</sub>** delivery (L/min). Past medical history of chronic heart or respiratory failure or of a thromboembolic event prior to COVID-19 event was assessed. New-onset venous thromboembolism and acute coronary syndrome concomitant to COVID-19 were prospectively collected. Normal echocardiographic values (left

and right ventricular dimensions and function, left ventricular filling pressures) were derived from the most recent guidelines.<sup>4,5</sup> All echocardiography were performed by the same trained operator (JES, Vivid S5, General-Electric); and analyzed by a blinded operator (NH). Intra-observer values of our core-lab for echocardiographic measurements have been detailed elsewhere.<sup>6,7</sup> Comparison between qualitative (n, %) and quantitative variables (medians, inter-quartile ranges) were performed by  $\chi^2$  and non-parametric tests (Wilcoxon: 2 groups, Kruskal-Wallis: 3 groups), respectively. Correlations between variables were computed by Spearman's test. P-values were adjusted for multiple testing's (Hochberg's) with adjusted- $p \leq 0.05$  deemed significant. Multivariable model (logistic regression, with and without imputation of missing data) was used to examine factors associated with death.

The clinico-demographic, biological, echocardiographic and thoracic scanner findings as a function of **02** need at the time of echocardiography (**classified into three groups: Ambient air, 02:0.5- 4.5L/min and 02 $\geq$ 5L/min**) and mortality 30 days after hospital admission are shown in the table. In this cohort (age=77[61-83]; 57% male), echocardiography were performed 3[2-5] days after hospital admission for COVID-19 and 47% (60/127) required **02** at the time of echocardiography, of which 27% (16/60) required  $\geq 5L/min$ . **02** requirement at the time of echocardiography was associated with older age ( $p \leq 0.01$ ), tachycardia ( $p \leq 0.01$ ), tachypnea ( $p \leq 0.001$ ), increased cardiac (troponin-T,  $p \leq 0.01$ ; NT-proBNP,  $p \leq 0.01$ ) and inflammatory biomarkers (CRP,  $p \leq 0.0001$ ), proportion of lung infiltration on scanner ( $p \leq 0.01$ ), and with 30-day mortality post-hospital admission ( $p \leq 0.0001$ ) (**Table**). Interestingly, echocardiographic surrogates of elevated LV filling pressures or LV systolic function were not associated with intensity of **02** requirement, nor mortality. Thirty-day total mortality (13/127, 10%) was also associated with tachycardia ( $p \leq 0.01$ ), increased cardiac (troponin-T,  $\leq 0.001$ ; NT-proBNP,  $p \leq 0.01$ ) and inflammatory biomarkers (CRP,  $\leq 0.001$ ), lymphopenia ( $p \leq 0.01$ ), higher plasma creatinine ( $p \leq 0.05$ ) and aldosterone levels ( $p \leq 0.01$ ) and right ventricular dysfunction (Tricuspid annular plane systolic excursion in M-mode,  $p \leq 0.05$ ; tissue-Doppler tricuspid annular systolic velocity,  $p \leq 0.05$ ; **Table**) in univariate analysis. In multivariable analysis with imputation of missing data (replacement by the mean), only aldosterone levels ( $\beta=0.8$ ,  $p=0.01$ ),

$02 \geq 5L/min$  ( $\beta=0.5$ ,  $p=0.05$  vs. ambient air), CRP ( $\beta=0.9$ ,  $p=0.002$ ), and NT-proBNP ( $\beta=0.5$ ,  $p=0.01$ ) remained associated with 30-day mortality. Results were similar for association between aldosterone level and 30-day mortality in multivariable analysis in non-imputed data ( $\beta=0.73$ ,  $p=0.03$ ). The association between RAAS and echocardiographic cardiac alteration is displayed in the **Table**. Renin levels were **moderately correlated** with RAAS blockers intake with 24hours ( $r=0.41$ ) and surrogate of volume overload including increased NT-proBNP ( $r=0.4$ ), and more marginally left atrial volume ( $r=0.32$ ), and pericardial effusions ( $r=0.33$ ) but not 30-day mortality nor severity of **02** requirement (**Table**). Aldosterone levels were only associated with 30-day mortality, but not with any other echocardiographic or biological variables.

**Our results show that right ventricular dysfunction in COVID-19 is independent from RAAS pathways alterations.** Circulating aldosterone levels emerged as a novel potential predictor of COVID-19 mortality after adjustment on echocardiographic findings, cardiac biomarkers, systemic inflammation and extension of pulmonary lesions. **Further prospective large-scale studies are needed to further confirm this exploratory result and evaluate any therapeutic potential for drugs altering aldosterone pathways in COVID-19. Indeed, the main limitations of our study are the relatively limited sample size and the fact that aldosterone could only be evaluated in a subset of it.**

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Table. Clinico-demographic, biological, echocardiographic and thoracic scanner findings as a function of oxygen need at the time of echocardiography and 30-day mortality after hospital admission for COVID-19 in 127 patients. Association between aldosterone and renin circulating levels and these latter parameters.

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital Status at D30 of admission for COVID-19		
	Ambient air [n=67]	O <sub>2</sub> :0.5- 4.5L/min [n=44]	O <sub>2</sub> ≥5L/min [n=16]	p-value unadjusted	Renin [n=50]	Aldo [n=62]	Alive [n=114]	Death [n=13]	p-value unadjusted
<b>Demographics before COVID-19</b>									
Age (years, median (IQR))	74(60-82) <sup>[67]</sup>	72(58-81) <sup>[44]</sup>	83(80-88) <sup>[16]</sup>	<b>0.001*</b>	0.22 <sup>[50]</sup>	-0.02 <sup>[62]</sup>	74(59-82) <sup>[114]</sup>	83(77-88) <sup>[13]</sup>	<b>0.02</b>
Gender (male, n, %)	(42, 63%) <sup>[67]</sup>	(22, 50%) <sup>[44]</sup>	(9, 56%) <sup>[16]</sup>	0.41	0.11 <sup>[50]</sup>	-0.02 <sup>[62]</sup>	(65, 57%) <sup>[114]</sup>	(8, 62%) <sup>[13]</sup>	0.99
Active tobacco user (n, %)	(22, 33%) <sup>[67]</sup>	(11, 25%) <sup>[44]</sup>	(4, 25%) <sup>[16]</sup>	0.62	0.13 <sup>[50]</sup>	-0.19 <sup>[62]</sup>	(37, 32%) <sup>[114]</sup>	(0, 0%) <sup>[13]</sup>	<b>0.04</b>
Hypertension (n, %)	(42, 63%) <sup>[67]</sup>	(25, 57%) <sup>[44]</sup>	(11, 69%) <sup>[16]</sup>	0.67	0.22 <sup>[50]</sup>	0.16 <sup>[62]</sup>	(70, 61%) <sup>[114]</sup>	(8, 62%) <sup>[13]</sup>	1
RAAS blockers use (n, %)	(27, 40%) <sup>[67]</sup>	(18, 41%) <sup>[44]</sup>	(7, 44%) <sup>[16]</sup>	0.97	<b>0.40<sup>[50]*</sup></b>	-0.06 <sup>[62]</sup>	(48, 42%) <sup>[114]</sup>	(4, 31%) <sup>[13]</sup>	0.62
Chronic diuretics (n, %)	(10, 15%) <sup>[67]</sup>	(6, 14%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.96	0.17 <sup>[50]</sup>	-0.08 <sup>[62]</sup>	(18, 16%) <sup>[114]</sup>	(0, 0%) <sup>[13]</sup>	0.26
Chronic corticosteroids (n, %)	(9, 13%) <sup>[67]</sup>	(5, 11%) <sup>[44]</sup>	(0, 0%) <sup>[16]</sup>	0.30	0.22 <sup>[50]</sup>	0.18 <sup>[62]</sup>	(13, 11%) <sup>[114]</sup>	(1, 7.7%) <sup>[13]</sup>	1
Ischemic cardiomyopathy (n, %)	(16, 24%) <sup>[67]</sup>	(8, 18%) <sup>[44]</sup>	(4, 25%) <sup>[16]</sup>	0.74	0.22 <sup>[50]</sup>	0.02 <sup>[62]</sup>	(23, 20%) <sup>[114]</sup>	(5, 38%) <sup>[13]</sup>	0.25
Known Heart failure (n, %)	(10, 15%) <sup>[67]</sup>	(5, 11%) <sup>[44]</sup>	(6, 38%) <sup>[16]</sup>	<b>0.05</b>	0.16 <sup>[50]</sup>	0.00 <sup>[62]</sup>	(18, 16%) <sup>[114]</sup>	(3, 23%) <sup>[13]</sup>	0.78
Thrombo-embolic disease history (n, %)	(10, 15%) <sup>[67]</sup>	(4, 9%) <sup>[44]</sup>	(1, 6%) <sup>[16]</sup>	0.49	0.08 <sup>[50]</sup>	-0.10 <sup>[62]</sup>	(14, 12%) <sup>[114]</sup>	(1, 7.7%) <sup>[13]</sup>	0.97
Chronic respiratory failure (n, %)	(3, 5%) <sup>[67]</sup>	(0, 0%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.08	-0.03 <sup>[50]</sup>	-0.13 <sup>[62]</sup>	(5, 4.4%) <sup>[114]</sup>	(0, 0%) <sup>[13]</sup>	0.99
<b>COVID-19 features during hospital stay</b>									
Acute coronary syndrome (n, %)	(2, 3%) <sup>[67]</sup>	(1, 2%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.17	0.20 <sup>[50]</sup>	-0.04 <sup>[62]</sup>	(4, 4%) <sup>[114]</sup>	(1, 8%) <sup>[13]</sup>	1
Acute venous thrombo-embolism (n, %)	(4, 6%) <sup>[67]</sup>	(2, 5%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.53	-0.18 <sup>[50]</sup>	0.18 <sup>[62]</sup>	(6, 5%) <sup>[114]</sup>	(2, 15%) <sup>[13]</sup>	0.41
Overall 30 days mortality (n, %)	(2, 3%) <sup>[67]</sup>	(4, 9%) <sup>[44]</sup>	(7, 44%) <sup>[16]</sup>	<b>≤0.0001*</b>	0.18 <sup>[50]</sup>	<b>0.40<sup>[62]*</sup></b>	Not Applicable		
<b>Clinical variables at the time of echocardiography</b>									
Corporeal Surface (m <sup>2</sup> , median (IQR))	1.8(1.7-2) <sup>[67]</sup>	1.8(1.7-2) <sup>[44]</sup>	1.7(1.5-1.8) <sup>[16]</sup>	0.07	-0.11 <sup>[50]</sup>	-0.01 <sup>[62]</sup>	1.8(1.7-2) <sup>[114]</sup>	1.8(1.5-1.9) <sup>[13]</sup>	0.12
Sinus rhythm (n, %)	(58, 87%) <sup>[67]</sup>	(42, 95%) <sup>[44]</sup>	(11, 73%) <sup>[15]</sup>	0.06	0.00 <sup>[50]</sup>	-0.04 <sup>[62]</sup>	(101, 89%) <sup>[114]</sup>	(10, 83%) <sup>[12]</sup>	0.95
Heart rate (bpm, median (IQR))	78(68-84) <sup>[67]</sup>	86(74-93) <sup>[44]</sup>	92(78-100) <sup>[16]</sup>	<b>0.001*</b>	0.00 <sup>[50]</sup>	0.11 <sup>[62]</sup>	80(70-90) <sup>[114]</sup>	92(86-110) <sup>[13]</sup>	<b>0.002*</b>
Systolic blood pressure (mmHg, median (IQR))	120 (110-130) <sup>[65]</sup>	130 (110-130) <sup>[44]</sup>	130 (110-140) <sup>[16]</sup>	0.29	-0.14 <sup>[49]</sup>	-0.03 <sup>[61]</sup>	120 (110-130) <sup>[112]</sup>	140(110-150) <sup>[13]</sup>	0.29
Diastolic blood pressure(mmHg, median(IQR))	66(60-72) <sup>[65]</sup>	74(61-82) <sup>[44]</sup>	70(60-80) <sup>[16]</sup>	0.24	-0.25 <sup>[49]</sup>	0.06 <sup>[61]</sup>	68(60-79) <sup>[112]</sup>	71(66-82) <sup>[13]</sup>	0.3
SpO <sub>2</sub> - oxygen saturation (% , median (IQR))	97(95-99) <sup>[65]</sup>	96(95-99) <sup>[44]</sup>	92(89-95) <sup>[16]</sup>	<b>≤0.0001*</b>	0.09 <sup>[49]</sup>	-0.15 <sup>[61]</sup>	97(95-99) <sup>[112]</sup>	93(90-95) <sup>[13]</sup>	<b>≤0.0001*</b>
O <sub>2</sub> (L/min, median (IQR))	0(0-0) <sup>[65]</sup>	2(1-3) <sup>[44]</sup>	15(7-15) <sup>[16]</sup>	<b>≤0.0001*</b>	-0.02 <sup>[49]</sup>	0.06 <sup>[62]</sup>	0(0-2) <sup>[114]</sup>	15(1-15) <sup>[13]</sup>	<b>≤0.0001*</b>
SpO <sub>2</sub> /FiO <sub>2</sub> (median (IQR))	460(450-470) <sup>[66]</sup>	350(320-390) <sup>[44]</sup>	140(140-230) <sup>[16]</sup>	<b>≤0.0001*</b>	0.08 <sup>[49]</sup>	-0.07 <sup>[61]</sup>	450(350-460) <sup>[112]</sup>	150(140-390) <sup>[13]</sup>	<b>≤0.0001*</b>
Respiratory rate (median (IQR))	20(18-24) <sup>[62]</sup>	24(20-26) <sup>[44]</sup>	28(24-31) <sup>[16]</sup>	<b>≤0.0001*</b>	0.02 <sup>[49]</sup>	0.00 <sup>[61]</sup>	22(18-24) <sup>[110]</sup>	25(20-30) <sup>[12]</sup>	0.1
Diuretics use within 48h (n, %)	(11, 16%) <sup>[67]</sup>	(9, 20%) <sup>[44]</sup>	(3, 19%) <sup>[16]</sup>	0.86	0.20 <sup>[50]</sup>	0.01 <sup>[62]</sup>	(21, 18%) <sup>[114]</sup>	(2, 15%) <sup>[13]</sup>	1
RAAS blockers use within 48h (n, %)	(20, 30%) <sup>[67]</sup>	(12, 27%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.37	<b>0.41<sup>[50]*</sup></b>	-0.01 <sup>[62]</sup>	(31, 27%) <sup>[114]</sup>	(3, 23%) <sup>[13]</sup>	1
<b>Biological variables at the closest time of echocardiography</b>									
NT-proBNP (µg/L, median (IQR))	0.3(0.1-0.7) <sup>[60]</sup>	0.4(0.1-1.1) <sup>[40]</sup>	3.2(2.1-13) <sup>[15]</sup>	<b>≤0.0001*</b>	<b>0.31<sup>[50]</sup></b>	-0.10 <sup>[62]</sup>	0.3(0.1-0.9) <sup>[103]</sup>	4(1.6-15) <sup>[12]</sup>	<b>0.0003*</b>

<b>NT-proBNP</b> >0.45µg/L if <50years; >0.9µg/L if 50-75years; >1.8µg/L if >75years (n, %)	(12, 20%) <sup>[59]</sup>	(11, 28%) <sup>[40]</sup>	(11, 73%) <sup>[15]</sup>	<b>0.0003*</b>	<b>0.40</b> <sup>[50]*</sup>	-0.10 <sup>[62]</sup>	(26, 25%) <sup>[102]</sup>	(8, 67%) <sup>[13]</sup>	<b>0.009</b>
<b>Troponin-T</b> (ng/L, median (IQR))	14(7-33) <sup>[60]</sup>	18(9-29) <sup>[41]</sup>	44(22-95) <sup>[16]</sup>	<b>0.003*</b>	<b>0.45</b> <sup>[50]*</sup>	0.05 <sup>[62]</sup>	15(8-29) <sup>[105]</sup>	78(40-100) <sup>[12]</sup>	<b>0.0002*</b>
<b>Troponin-T</b> >14 ng/L (n, %)	(29, 48%) <sup>[60]</sup>	(24, 59%) <sup>[41]</sup>	(16, 100%) <sup>[16]</sup>	<b>0.0009*</b>	<b>0.34</b> <sup>[50]</sup>	0.02 <sup>[62]</sup>	(58, 55%) <sup>[105]</sup>	(11, 92%) <sup>[12]</sup>	<b>0.04</b>
<b>C-reactive Protein</b> (mg/L, median (IQR))	23(7-64) <sup>[67]</sup>	79(45-120) <sup>[44]</sup>	100(57-150) <sup>[16]</sup>	<b>≤0.0001*</b>	-0.03 <sup>[50]</sup>	-0.01 <sup>[62]</sup>	49(14-87) <sup>[114]</sup>	130(64-280) <sup>[13]</sup>	<b>0.0002*</b>
<b>C-reactive Protein</b> >5 mg/L (n, %)	(54, 81%) <sup>[67]</sup>	(43, 98%) <sup>[44]</sup>	(16, 100%) <sup>[16]</sup>	<b>0.006*</b>	0.04 <sup>[50]</sup>	-0.08 <sup>[62]</sup>	(100,88%) <sup>[114]</sup>	(13,100%) <sup>[13]</sup>	0.38
<b>Lymphocyte count</b> (x10 <sup>9</sup> /L, median (IQR))	1.2(0.8-1.6) <sup>[67]</sup>	0.9(0.7-1.3) <sup>[44]</sup>	0.7(0.5-1.0) <sup>[16]</sup>	<b>0.01</b>	-0.13 <sup>[50]</sup>	-0.02 <sup>[62]</sup>	1.1(0.8-1.5) <sup>[114]</sup>	0.6(0.4-0.8) <sup>[13]</sup>	<b>0.0006*</b>
<b>Lymphocyte count</b> <1.5 x10 <sup>9</sup> /L (n, %)	(47, 70%) <sup>[67]</sup>	(37, 84%) <sup>[44]</sup>	(15, 94%) <sup>[16]</sup>	0.06	-0.05 <sup>[50]</sup>	0.00 <sup>[62]</sup>	(86, 75%) <sup>[114]</sup>	(13,100%) <sup>[13]</sup>	0.10
<b>D-dimers</b> (µg/mL, median (IQR))	0.7(0.5-1.6) <sup>[38]</sup>	0.8(0.6-1.1) <sup>[25]</sup>	1.5(1.1-1.6) <sup>[6]</sup>	0.24	0.02 <sup>[48]</sup>	-0.09 <sup>[58]</sup>	0.9(0.6-1.6) <sup>[65]</sup>	1(0.5-1.6) <sup>[4]</sup>	0.94
<b>D-dimers</b> >0.5 µg/mL (n, %)	(28, 74%) <sup>[38]</sup>	(22, 88%) <sup>[25]</sup>	(6, 100%) <sup>[6]</sup>	0.17	0.15 <sup>[48]</sup>	-0.03 <sup>[58]</sup>	(53, 82%) <sup>[65]</sup>	(3, 75%) <sup>[4]</sup>	1
<b>Renin</b> (pg/mL, median (IQR))	9.4(5.3-14) <sup>[28]</sup>	5.5(1-18) <sup>[17]</sup>	19(7.3-41) <sup>[7]</sup>	0.32	Not Applicable		8.7(3.4-16) <sup>[47]</sup>	19(13-130) <sup>[3]</sup>	0.23
<b>Aldosterone</b> (pg/mL, median (IQR))	29(18-39) <sup>[35]</sup>	31(14-67) <sup>[20]</sup>	43(19-84) <sup>[7]</sup>	0.66			29(17-43) <sup>[57]</sup>	98(71-110) <sup>[5]</sup>	<b>0.002*</b>
<b>ACE-2</b> (pg/mL, median (IQR))	1.8(1.4-2.8) <sup>[23]</sup>	1.5(0.9-3.4) <sup>[11]</sup>	1.4(1.3-1.5) <sup>[2]</sup>	0.42	0.08 <sup>[30]</sup>	0.23 <sup>[36]</sup>	1.7(1.3-3.1) <sup>[35]</sup>	1.6 <sup>[1]</sup>	0.89
<b>Creatinine Clearance</b> (ml/min/m <sup>2</sup> , median(IQR))	79(63-96) <sup>[67]</sup>	74(56-88) <sup>[44]</sup>	100(80-150) <sup>[16]</sup>	<b>0.02</b>	<b>0.37</b> <sup>[50]</sup>	-0.08 <sup>[62]</sup>	76(61-94) <sup>[114]</sup>	110(82-160) <sup>[13]</sup>	<b>0.01*</b>
<b>Creatinine Clearance</b> <60 ml/min/m <sup>2</sup> (n, %)	(14, 21%) <sup>[67]</sup>	(13, 30%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.33	<b>-0.32</b> <sup>[50]</sup>	-0.12 <sup>[62]</sup>	(28, 25%) <sup>[114]</sup>	(1, 8%) <sup>[13]</sup>	0.31
<b>Echocardiographic findings</b>									
<b>LVEF</b> (%), (median (IQR))	63(59-68) <sup>[67]</sup>	64(62-68) <sup>[44]</sup>	59(58-70) <sup>[16]</sup>	0.23	-0.13 <sup>[50]</sup>	0.00 <sup>[62]</sup>	63(60-69) <sup>[114]</sup>	58(55-63) <sup>[13]</sup>	<b>0.03</b>
<b>LVEF</b> <52% for male; <54% for female (n, %)	(7, 10%) <sup>[67]</sup>	(0, 0%) <sup>[44]</sup>	(1, 6.2%) <sup>[16]</sup>	0.09	<b>0.32</b> <sup>[50]</sup>	0.00 <sup>[62]</sup>	(7, 6.1%) <sup>[114]</sup>	(1, 7.7%) <sup>[13]</sup>	1
<b>LV Strain</b> (-%), (median (IQR))	17(14-19) <sup>[60]</sup>	18(14-20) <sup>[36]</sup>	16(16-20) <sup>[9]</sup>	0.74	<b>-0.49</b> <sup>[38]*</sup>	0.10 <sup>[48]</sup>	18(14-20) <sup>[114]</sup>	16(16-20) <sup>[9]</sup>	0.96
<b>LV Strain</b> below -20% (n, %)	(49, 82%) <sup>[60]</sup>	(26, 72%) <sup>[36]</sup>	(6, 67%) <sup>[9]</sup>	0.42	0.16 <sup>[38]</sup>	-0.04 <sup>[48]</sup>	(75, 78%) <sup>[96]</sup>	(6, 67%) <sup>[9]</sup>	0.71
<b>LVIDd</b> (mm/m <sup>2</sup> , median (IQR))	27(24-29) <sup>[67]</sup>	26(24-29) <sup>[44]</sup>	28(24-30) <sup>[16]</sup>	0.89	<b>0.27</b> <sup>[50]</sup>	-0.22 <sup>[62]</sup>	27(24-29) <sup>[114]</sup>	27(25-29) <sup>[13]</sup>	0.26
<b>LVIDd</b> >30mm/m <sup>2</sup> male; >31 female (n, %)	(9, 13%) <sup>[67]</sup>	(7, 16%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.92	0.23 <sup>[50]</sup>	-0.02 <sup>[62]</sup>	(16, 14%) <sup>[114]</sup>	(2, 15%) <sup>[13]</sup>	1
<b>LV mass</b> (g/m <sup>2</sup> , median (IQR))	88(72-100) <sup>[67]</sup>	80(64-110) <sup>[44]</sup>	88(77-100) <sup>[16]</sup>	0.77	0.18 <sup>[50]</sup>	-0.13 <sup>[62]</sup>	84(70-100) <sup>[114]</sup>	95(88-110) <sup>[13]</sup>	0.26
<b>LV mass</b> >115g/m <sup>2</sup> male; >95 female (n, %)	(20, 30%) <sup>[67]</sup>	(10, 23%) <sup>[44]</sup>	(2, 12%) <sup>[16]</sup>	0.32	0.07 <sup>[50]</sup>	-0.17 <sup>[62]</sup>	(29, 25%) <sup>[114]</sup>	(3, 23%) <sup>[13]</sup>	1
<b>LV RWT</b> (median (IQR))	0.4 (0.35-0.43) <sup>[67]</sup>	0.4 (0.36-0.42) <sup>[44]</sup>	0.42 (0.4-0.47) <sup>[16]</sup>	<b>0.02</b>	-0.10 <sup>[50]</sup>	<b>0.31</b> <sup>[62]</sup>	0.4(0.36-0.43) <sup>[114]</sup>	0.42(0.4-0.44) <sup>[13]</sup>	<b>0.05</b>
<b>LV RWT</b> >0.42 (n, %)	(19, 28%) <sup>[67]</sup>	(9, 20%) <sup>[44]</sup>	(7, 44%) <sup>[16]</sup>	0.20	-0.03 <sup>[50]</sup>	<b>0.31</b> <sup>[62]</sup>	(30, 26%) <sup>[114]</sup>	(5, 38%) <sup>[13]</sup>	0.55
<b>E</b> (m/s, median (IQR))	63(54-74) <sup>[67]</sup>	64(54-78) <sup>[44]</sup>	62(48-69) <sup>[16]</sup>	0.66	-0.04 <sup>[50]</sup>	-0.15 <sup>[62]</sup>	63(55-77) <sup>[114]</sup>	54(42-68) <sup>[13]</sup>	0.1
<b>E/A ratio</b> (median (IQR))	0.8(0.7-1.1) <sup>[57]</sup>	0.8(0.7-0.9) <sup>[40]</sup>	0.7(0.6-0.8) <sup>[12]</sup>	0.13	-0.15 <sup>[44]</sup>	-0.12 <sup>[54]</sup>	0.8(0.7-1) <sup>[98]</sup>	0.7(0.6-0.8) <sup>[11]</sup>	0.32
<b>Septal e'</b> (cm/s, median (IQR))	6.6(5-9) <sup>[65]</sup>	7(5-8) <sup>[43]</sup>	5.5(4.5-5.8) <sup>[16]</sup>	0.10	-0.16 <sup>[50]</sup>	-0.16 <sup>[62]</sup>	6(5-8) <sup>[111]</sup>	5.6(5-7) <sup>[13]</sup>	0.52
<b>Septal e'</b> <7 cm/s (n, %)	(33, 51%) <sup>[65]</sup>	(21, 49%) <sup>[43]</sup>	(13, 81%) <sup>[16]</sup>	0.06	0.20 <sup>[50]</sup>	0.15 <sup>[62]</sup>	(60, 54%) <sup>[114]</sup>	(7, 54%) <sup>[13]</sup>	1
<b>Lateral e'</b> (cm/s, median (IQR))	8(7-11) <sup>[65]</sup>	8.5(7-10) <sup>[44]</sup>	8.2(5.9-9) <sup>[16]</sup>	0.47	-0.16 <sup>[50]</sup>	-0.13 <sup>[62]</sup>	8.3(7-10) <sup>[112]</sup>	8.5(7-9) <sup>[13]</sup>	0.44
<b>Lateral e'</b> <10 cm/s (n, %)	(41, 63%) <sup>[65]</sup>	(29, 66%) <sup>[44]</sup>	(13, 81%) <sup>[16]</sup>	0.39	0.09 <sup>[50]</sup>	0.18 <sup>[62]</sup>	(72, 64%) <sup>[112]</sup>	(11, 85%) <sup>[13]</sup>	0.25
<b>E/e'</b> (average septal/medial) (median (IQR))	8.4(6.8-11) <sup>[64]</sup>	8.9(7.2-11) <sup>[42]</sup>	9.4(7.9-11) <sup>[16]</sup>	0.79	0.10 <sup>[49]</sup>	-0.09 <sup>[61]</sup>	8.7(6.9-11) <sup>[109]</sup>	8.6(5.7-10) <sup>[13]</sup>	0.49
<b>E/e'</b> >14 (average septal/medial), (n,%)	(7, 11%) <sup>[64]</sup>	(5, 12%) <sup>[42]</sup>	(2, 12%) <sup>[16]</sup>	0.98	0.20 <sup>[49]</sup>	0.06 <sup>[61]</sup>	(13, 12%) <sup>[109]</sup>	(1, 7.7%) <sup>[13]</sup>	1
<b>Left atrium volume</b> (ml/m <sup>2</sup> , median (IQR))	33(23-45) <sup>[67]</sup>	32(26-41) <sup>[43]</sup>	33(24-49) <sup>[16]</sup>	0.81	0.13 <sup>[49]</sup>	-0.06 <sup>[61]</sup>	32(24-44) <sup>[113]</sup>	35(28-51) <sup>[13]</sup>	0.25
<b>Left atrium volume</b> >34 ml/m <sup>2</sup> (n, %)	(29, 43%) <sup>[67]</sup>	(18, 42%) <sup>[43]</sup>	(7, 44%) <sup>[16]</sup>	0.99	<b>0.32</b> <sup>[49]</sup>	-0.06 <sup>[61]</sup>	(46, 41%) <sup>[114]</sup>	(8, 62%) <sup>[13]</sup>	0.25
<b>Peak tricuspid regurgitation velocity</b> (m/sec, median (IQR))	2.3(2.2-2.6) <sup>[58]</sup>	2.4(2.2-2.5) <sup>[33]</sup>	2.7(2.4-3) <sup>[15]</sup>	<b>0.04</b>	0.02 <sup>[50]</sup>	0.07 <sup>[53]</sup>	2.4(2.2-2.6) <sup>[95]</sup>	2.5(2.3-2.7) <sup>[11]</sup>	0.33



<b>Peak tricuspid regurgitation velocity &gt;2.8m/sec (n, %)</b>	(7, 12%) <sup>[58]</sup>	(5, 15%) <sup>[33]</sup>	(5, 33%) <sup>[15]</sup>	0.13	0.08 <sup>[50]</sup>	0.13 <sup>[53]</sup>	(15, 16%) <sup>[95]</sup>	(2, 18%) <sup>[11]</sup>	1
<b>Normal LV filling pressure (n, %)<sup>4</sup></b>	(57, 88%) <sup>[65]</sup>	(39, 91%) <sup>[43]</sup>	(13, 81%) <sup>[16]</sup>	0.61	0.17 <sup>[49]</sup>	0.06 <sup>[61]</sup>	(97, 87%) <sup>[111]</sup>	(12, 92%) <sup>[13]</sup>	0.95
<b>RV basal diameter (mm, median (IQR))</b>	30(27-34) <sup>[64]</sup>	28(27-30) <sup>[40]</sup>	30(27-33) <sup>[13]</sup>	0.15	0.09 <sup>[49]</sup>	-0.18 <sup>[61]</sup>	30(27-33) <sup>[105]</sup>	28(27-30) <sup>[12]</sup>	0.21
<b>RVED/LVED (median (IQR))</b>	0.76(0.73-0.83) <sup>[67]</sup>	0.78(0.71-0.82) <sup>[42]</sup>	0.78(0.74-0.82) <sup>[15]</sup>	0.92	0.21 <sup>[48]</sup>	0.02 <sup>[60]</sup>	0.77(0.72-0.82) <sup>[112]</sup>	0.8(0.78-0.84) <sup>[12]</sup>	0.14
<b>RV dilatation with RV basal diameter &gt;41mm or RVED/LVED&gt;1 (n, %)</b>	(3, 4.5%) <sup>[67]</sup>	(2, 4.5%) <sup>[44]</sup>	(3, 19%) <sup>[16]</sup>	0.09	0.17 <sup>[50]</sup>	-0.06 <sup>[62]</sup>	(7, 6.1%) <sup>[114]</sup>	(1, 7.7%) <sup>[13]</sup>	1
<b>TAPSE (mm, median (IQR))</b>	22(19-24) <sup>[64]</sup>	21(20-23) <sup>[43]</sup>	18(15-22) <sup>[16]</sup>	<b>0.05</b>	-0.12 <sup>[50]</sup>	-0.14 <sup>[61]</sup>	22(19-24) <sup>[111]</sup>	18(15-20) <sup>[12]</sup>	<b>0.01*</b>
<b>TAPSE &lt;17mm (n, %)</b>	(8, 12%) <sup>[64]</sup>	(4, 9.3%) <sup>[43]</sup>	(5, 31%) <sup>[16]</sup>	0.09	0.06 <sup>[50]</sup>	-0.17 <sup>[61]</sup>	(13, 12%) <sup>[111]</sup>	(4, 33%) <sup>[12]</sup>	0.1
<b>Tricuspid s' (cm/s, median (IQR))</b>	11(10-13) <sup>[67]</sup>	12(10-13) <sup>[44]</sup>	11(7-12) <sup>[16]</sup>	0.24	0.02 <sup>[50]</sup>	-0.17 <sup>[62]</sup>	12(10-13) <sup>[114]</sup>	10(7-12) <sup>[13]</sup>	0.07
<b>Tricuspid s' &lt; 9.5 cm/s (n, %)</b>	(11, 16%) <sup>[67]</sup>	(5, 11%) <sup>[44]</sup>	(6, 38%) <sup>[16]</sup>	0.06	0.08 <sup>[50]</sup>	0.23 <sup>[62]</sup>	(16, 14%) <sup>[114]</sup>	(6, 46%) <sup>[13]</sup>	<b>0.01*</b>
<b>Pericardial effusion (n, %)</b>	(23, 34%) <sup>[67]</sup>	(14, 32%) <sup>[44]</sup>	(5, 31%) <sup>[16]</sup>	0.95	-0.06 <sup>[50]</sup>	0.11 <sup>[62]</sup>	(38, 33%) <sup>[114]</sup>	(4, 31%) <sup>[13]</sup>	1
<b>Pericardial effusion ≥10 mm (n, %)</b>	(3, 4.5%) <sup>[67]</sup>	(1, 2.3%) <sup>[44]</sup>	(1, 6.2%) <sup>[16]</sup>	0.74	<b>0.33</b> <sup>[50]</sup>	0.07 <sup>[62]</sup>	(4, 3.5%) <sup>[114]</sup>	(1, 7.7%) <sup>[13]</sup>	1
<b>Thoracic scanner findings at the closest time to echocardiography<sup>¶¶</sup></b>									
<b>Proportion of lung parenchyma affected<sup>§</sup> (median (IQR))</b>	2(1-2.5) <sup>[51]</sup>	3(2-4) <sup>[37]</sup>	2(1-4) <sup>[13]</sup>	<b>0.002*</b>	0.11 <sup>[44]</sup>	0.12 <sup>[56]</sup>	2(1-3) <sup>[91]</sup>	2.5(1-3.8) <sup>[10]</sup>	0.71
<b>Pulmonary artery diameter (mm, median (IQR))</b>	26(25-29) <sup>[51]</sup>	26(25-28) <sup>[37]</sup>	26(25-30) <sup>[13]</sup>	0.40	-0.02 <sup>[44]</sup>	0.05 <sup>[56]</sup>	26(25-29) <sup>[91]</sup>	26(25-28) <sup>[10]</sup>	0.73

**Abbreviations:** A: late diastolic trans-mitral flow velocity; aldo: aldosterone; bpm: beats per minute; E/e': early diastolic trans-mitral flow velocity to tissue-Doppler mitral annular early diastolic velocity; IQR: interquartile-range; L/min: liters/minute; LV(ED)/(EF): left ventricle (end-diastolic dimension)/(ejection fraction); LVIDd: LV internal dimension in diastole; m/sec: meter per second; n: numbers; RAAS: renin-angiotensin-aldosterone system; RT-PCR: Reverse transcription polymerase chain reaction; RV(ED): right ventricle (end-diastolic dimension); RWT: relative wall thickness; s': tissue-Doppler tricuspid annular systolic velocity; SpO<sub>2</sub>/FiO<sub>2</sub>: oxygen saturation to fraction of inspired oxygen ratio (FiO<sub>2</sub>=0.21+0.03\*O<sub>2</sub> in L/min); TAPSE: Tricuspid annular plane systolic excursion

<sup>§</sup> Six levels scaling for lung parenchyma involvement secondary to COVID-19 (0: none; 1: <10%, 2: 10-25%, 3: 25-50%, 4: 50-75%; 5: >75%)

<sup>¶</sup> The median (IQR) time between echocardiography and circulating levels of NT-proBNP, troponin-T, c-reactive Protein, lymphocyte count, D-dimers, renin, aldosterone, ACE-2 and creatinine clearance was 1[0-1] days, 1[0-1], 1[0-1], 1[0-1], 1[0-3], 2[1-2], 2[1-2], 2[1-2], 2[1-2] days, respectively.

<sup>¶¶</sup> The median (IQR) time between echocardiography and thoracic was 3[2-7]days

**Statistics:** Quantitative and qualitative variables were compared using Wilcoxon's (2 groups) or Kruskal-Wallis (3 groups) and  $\chi^2$  tests, respectively. Correlations (rho) were performed by spearman's test. <sup>[N]</sup> represent the number of evaluations available. P-values were adjusted for multiple testing's (Benjamini Hochberg's method) with significant adjusted-p≤0.05 value in bold, underlined in yellow and marked with \*; and unadjusted-p≤0.05 value just in bold.