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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.¹ 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.^{2, 3} 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.¹ 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 **(O2)** requirement at the time of echocardiography was defined by SpO₂/FiO₂ with FiO₂ derived from nasal **O2** 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.^{4,5} 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.^{6,7} Comparison between qualitative (n, %) and quantitative variables (medians, inter-quartile ranges) were performed by χ^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, ≤ 0.001 ; NT-proBNP, $p \leq 0.01$) and inflammatory biomarkers (CRP, ≤ 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 ₂ :0.5- 4.5L/min [n=44]	O ₂ ≥5L/min [n=16]	p-value unadjusted	Renin [n=50]	Aldo [n=62]	Alive [n=114]	Death [n=13]	p-value unadjusted
Demographics before COVID-19									
Age (years, median (IQR))	74(60-82) ^[67]	72(58-81) ^[44]	83(80-88) ^[16]	0.001*	0.22 ^[50]	-0.02 ^[62]	74(59-82) ^[114]	83(77-88) ^[13]	0.02
Gender (male, n, %)	(42, 63%) ^[67]	(22, 50%) ^[44]	(9, 56%) ^[16]	0.41	0.11 ^[50]	-0.02 ^[62]	(65, 57%) ^[114]	(8, 62%) ^[13]	0.99
Active tobacco user (n, %)	(22, 33%) ^[67]	(11, 25%) ^[44]	(4, 25%) ^[16]	0.62	0.13 ^[50]	-0.19 ^[62]	(37, 32%) ^[114]	(0, 0%) ^[13]	0.04
Hypertension (n, %)	(42, 63%) ^[67]	(25, 57%) ^[44]	(11, 69%) ^[16]	0.67	0.22 ^[50]	0.16 ^[62]	(70, 61%) ^[114]	(8, 62%) ^[13]	1
RAAS blockers use (n, %)	(27, 40%) ^[67]	(18, 41%) ^[44]	(7, 44%) ^[16]	0.97	0.40^{[50]*}	-0.06 ^[62]	(48, 42%) ^[114]	(4, 31%) ^[13]	0.62
Chronic diuretics (n, %)	(10, 15%) ^[67]	(6, 14%) ^[44]	(2, 12%) ^[16]	0.96	0.17 ^[50]	-0.08 ^[62]	(18, 16%) ^[114]	(0, 0%) ^[13]	0.26
Chronic corticosteroids (n, %)	(9, 13%) ^[67]	(5, 11%) ^[44]	(0, 0%) ^[16]	0.30	0.22 ^[50]	0.18 ^[62]	(13, 11%) ^[114]	(1, 7.7%) ^[13]	1
Ischemic cardiomyopathy (n, %)	(16, 24%) ^[67]	(8, 18%) ^[44]	(4, 25%) ^[16]	0.74	0.22 ^[50]	0.02 ^[62]	(23, 20%) ^[114]	(5, 38%) ^[13]	0.25
Known Heart failure (n, %)	(10, 15%) ^[67]	(5, 11%) ^[44]	(6, 38%) ^[16]	0.05	0.16 ^[50]	0.00 ^[62]	(18, 16%) ^[114]	(3, 23%) ^[13]	0.78
Thrombo-embolic disease history (n, %)	(10, 15%) ^[67]	(4, 9%) ^[44]	(1, 6%) ^[16]	0.49	0.08 ^[50]	-0.10 ^[62]	(14, 12%) ^[114]	(1, 7.7%) ^[13]	0.97
Chronic respiratory failure (n, %)	(3, 5%) ^[67]	(0, 0%) ^[44]	(2, 12%) ^[16]	0.08	-0.03 ^[50]	-0.13 ^[62]	(5, 4.4%) ^[114]	(0, 0%) ^[13]	0.99
COVID-19 features during hospital stay									
Acute coronary syndrome (n, %)	(2, 3%) ^[67]	(1, 2%) ^[44]	(2, 12%) ^[16]	0.17	0.20 ^[50]	-0.04 ^[62]	(4, 4%) ^[114]	(1, 8%) ^[13]	1
Acute venous thrombo-embolism (n, %)	(4, 6%) ^[67]	(2, 5%) ^[44]	(2, 12%) ^[16]	0.53	-0.18 ^[50]	0.18 ^[62]	(6, 5%) ^[114]	(2, 15%) ^[13]	0.41
Overall 30 days mortality (n, %)	(2, 3%) ^[67]	(4, 9%) ^[44]	(7, 44%) ^[16]	≤0.0001*	0.18 ^[50]	0.40^{[62]*}	Not Applicable		
Clinical variables at the time of echocardiography									
Corporeal Surface (m ² , median (IQR))	1.8(1.7-2) ^[67]	1.8(1.7-2) ^[44]	1.7(1.5-1.8) ^[16]	0.07	-0.11 ^[50]	-0.01 ^[62]	1.8(1.7-2) ^[114]	1.8(1.5-1.9) ^[13]	0.12
Sinus rhythm (n, %)	(58, 87%) ^[67]	(42, 95%) ^[44]	(11, 73%) ^[15]	0.06	0.00 ^[50]	-0.04 ^[62]	(101, 89%) ^[114]	(10, 83%) ^[12]	0.95
Heart rate (bpm, median (IQR))	78(68-84) ^[67]	86(74-93) ^[44]	92(78-100) ^[16]	0.001*	0.00 ^[50]	0.11 ^[62]	80(70-90) ^[114]	92(86-110) ^[13]	0.002*
Systolic blood pressure (mmHg, median (IQR))	120 (110-130) ^[65]	130 (110-130) ^[44]	130 (110-140) ^[16]	0.29	-0.14 ^[49]	-0.03 ^[61]	120 (110-130) ^[112]	140(110-150) ^[13]	0.29
Diastolic blood pressure(mmHg, median(IQR))	66(60-72) ^[65]	74(61-82) ^[44]	70(60-80) ^[16]	0.24	-0.25 ^[49]	0.06 ^[61]	68(60-79) ^[112]	71(66-82) ^[13]	0.3
SpO ₂ - oxygen saturation (% , median (IQR))	97(95-99) ^[65]	96(95-99) ^[44]	92(89-95) ^[16]	≤0.0001*	0.09 ^[49]	-0.15 ^[61]	97(95-99) ^[112]	93(90-95) ^[13]	≤0.0001*
O ₂ (L/min, median (IQR))	0(0-0) ^[65]	2(1-3) ^[44]	15(7-15) ^[16]	≤0.0001*	-0.02 ^[49]	0.06 ^[62]	0(0-2) ^[114]	15(1-15) ^[13]	≤0.0001*
SpO ₂ /FiO ₂ (median (IQR))	460(450-470) ^[66]	350(320-390) ^[44]	140(140-230) ^[16]	≤0.0001*	0.08 ^[49]	-0.07 ^[61]	450(350-460) ^[112]	150(140-390) ^[13]	≤0.0001*
Respiratory rate (median (IQR))	20(18-24) ^[62]	24(20-26) ^[44]	28(24-31) ^[16]	≤0.0001*	0.02 ^[49]	0.00 ^[61]	22(18-24) ^[110]	25(20-30) ^[12]	0.1
Diuretics use within 48h (n, %)	(11, 16%) ^[67]	(9, 20%) ^[44]	(3, 19%) ^[16]	0.86	0.20 ^[50]	0.01 ^[62]	(21, 18%) ^[114]	(2, 15%) ^[13]	1
RAAS blockers use within 48h (n, %)	(20, 30%) ^[67]	(12, 27%) ^[44]	(2, 12%) ^[16]	0.37	0.41^{[50]*}	-0.01 ^[62]	(31, 27%) ^[114]	(3, 23%) ^[13]	1
Biological variables at the closest time of echocardiography									
NT-proBNP (µg/L, median (IQR))	0.3(0.1-0.7) ^[60]	0.4(0.1-1.1) ^[40]	3.2(2.1-13) ^[15]	≤0.0001*	0.31^[50]	-0.10 ^[62]	0.3(0.1-0.9) ^[103]	4(1.6-15) ^[12]	0.0003*

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

Peak tricuspid regurgitation velocity >2.8m/sec (n, %)	(7, 12%) ^[58]	(5, 15%) ^[33]	(5, 33%) ^[15]	0.13	0.08 ^[50]	0.13 ^[53]	(15, 16%) ^[95]	(2, 18%) ^[11]	1
Normal LV filling pressure (n, %)⁴	(57, 88%) ^[65]	(39, 91%) ^[43]	(13, 81%) ^[16]	0.61	0.17 ^[49]	0.06 ^[61]	(97, 87%) ^[111]	(12, 92%) ^[13]	0.95
RV basal diameter (mm, median (IQR))	30(27-34) ^[64]	28(27-30) ^[40]	30(27-33) ^[13]	0.15	0.09 ^[49]	-0.18 ^[61]	30(27-33) ^[105]	28(27-30) ^[12]	0.21
RVED/LVED (median (IQR))	0.76(0.73-0.83) ^[67]	0.78(0.71-0.82) ^[42]	0.78(0.74-0.82) ^[15]	0.92	0.21 ^[48]	0.02 ^[60]	0.77(0.72-0.82) ^[112]	0.8(0.78-0.84) ^[12]	0.14
RV dilatation with RV basal diameter >41mm or RVED/LVED>1 (n, %)	(3, 4.5%) ^[67]	(2, 4.5%) ^[44]	(3, 19%) ^[16]	0.09	0.17 ^[50]	-0.06 ^[62]	(7, 6.1%) ^[114]	(1, 7.7%) ^[13]	1
TAPSE (mm, median (IQR))	22(19-24) ^[64]	21(20-23) ^[43]	18(15-22) ^[16]	0.05	-0.12 ^[50]	-0.14 ^[61]	22(19-24) ^[111]	18(15-20) ^[12]	0.01*
TAPSE <17mm (n, %)	(8, 12%) ^[64]	(4, 9.3%) ^[43]	(5, 31%) ^[16]	0.09	0.06 ^[50]	-0.17 ^[61]	(13, 12%) ^[111]	(4, 33%) ^[12]	0.1
Tricuspid s' (cm/s, median (IQR))	11(10-13) ^[67]	12(10-13) ^[44]	11(7-12) ^[16]	0.24	0.02 ^[50]	-0.17 ^[62]	12(10-13) ^[114]	10(7-12) ^[13]	0.07
Tricuspid s' < 9.5 cm/s (n, %)	(11, 16%) ^[67]	(5, 11%) ^[44]	(6, 38%) ^[16]	0.06	0.08 ^[50]	0.23 ^[62]	(16, 14%) ^[114]	(6, 46%) ^[13]	0.01*
Pericardial effusion (n, %)	(23, 34%) ^[67]	(14, 32%) ^[44]	(5, 31%) ^[16]	0.95	-0.06 ^[50]	0.11 ^[62]	(38, 33%) ^[114]	(4, 31%) ^[13]	1
Pericardial effusion ≥10 mm (n, %)	(3, 4.5%) ^[67]	(1, 2.3%) ^[44]	(1, 6.2%) ^[16]	0.74	0.33 ^[50]	0.07 ^[62]	(4, 3.5%) ^[114]	(1, 7.7%) ^[13]	1
Thoracic scanner findings at the closest time to echocardiography^{¶¶}									
Proportion of lung parenchyma affected[§] (median (IQR))	2(1-2.5) ^[51]	3(2-4) ^[37]	2(1-4) ^[13]	0.002*	0.11 ^[44]	0.12 ^[56]	2(1-3) ^[91]	2.5(1-3.8) ^[10]	0.71
Pulmonary artery diameter (mm, median (IQR))	26(25-29) ^[51]	26(25-28) ^[37]	26(25-30) ^[13]	0.40	-0.02 ^[44]	0.05 ^[56]	26(25-29) ^[91]	26(25-28) ^[10]	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; SpO₂/FiO₂: oxygen saturation to fraction of inspired oxygen ratio (FiO₂=0.21+0.03*O₂ in L/min); TAPSE: Tricuspid annular plane systolic excursion

[§] 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%)

[¶] 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.

^{¶¶} 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 χ^2 tests, respectively. Correlations (rho) were performed by spearman's test. ^[N] 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.