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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-Salpétrière 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 **(02)** requirement at the time of echocardiography was defined by Sp02/Fi02 with Fi02 derived from nasal **02** 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≤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≥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 ≥5L/min. **02** requirement at the time of echocardiography was associated with older age (p≤0.01), tachycardia (p≤0.01), tachypnea (p≤0.001), increased cardiac (troponin-T, p≤0.01; NT-proBNP, p≤0.01) and inflammatory biomarkers (CRP, p≤0.0001), proportion of lung infiltration on scanner (p≤0.01), and with 30-day mortality post-hospital admission (p≤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≤0.01), increased cardiac (troponin-T, ≤0.001; NT-proBNP, p p≤0.01) and inflammatory biomarkers (CRP, ≤0.001), lymphopenia (p≤0.01), higher plasma creatinine (p≤0.05) and aldosterone levels (p≤0.01) and right ventricular dysfunction (Tricuspid annular plane systolic excursion in M-mode, p≤0.05; tissue-Doppler tricuspid annular systolic velocity, p≤0.05; **Table**) in univariate analysis. In multivariable analysis with imputation of missing data (replacement by the mean), only aldosterone levels (β=0.8, p=0.01), 02≥5L/min (β=0.5, p=0.05 vs. ambient air), CRP (β=0.9, p=0.002), and NT-proBNP (β=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 (β=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]	0^2:0.5-4.5L/min [n=44]	0^2≥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
$Sp0_2$ - 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***
0_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***
$Sp0_2/Fi0_2$ (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/m²,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/m² (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/m², 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/m² 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/m², 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/m² 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/m², 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/m² (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; SpO_2/FiO_2: oxygen saturation to fraction of inspired oxygen ratio (FiO_2=0.21+0.03*O_2 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.