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

Joe-Elie Salem, Nadjib Hammoudi, Bruno Pinna, Stephane Ederhy, Antonin Lamazière, Charlotte Fenioux, Alban Redheuil, Pierre Salem, Claire Ribet, Omar Hamwy, et al.

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

Joe-Elie Salem, MD, PhD[1]; Nadjib Hammoudi, MD, PhD[2]; Bruno Pinna, MD[1]; Stephane Ederhy, MD[3]; Antonin Lamazière, Pharm D, PhD[4]; Charlotte Fenioux, MD[1]; Alban Redheuil, MD, PhD[5]; Pierre Salem, MD[1]; Claire Ribet[1]; Omar Hamwy[1]; Anne-Geneviève Marcelin MD, PhD[7]; Sonia Burrel, MD[7]; Christian Funck-Brentano, MD, PhD[1]; Gilles Montalescot, MD, PhD[3]; Jean-Marc Lacorte, MD, PhD[8]; Estelle Gandjbakhch, MD, PhD[2]; Olivier Benveniste, MD, PhD[9]; David Saadoun, MD, PhD[9]; Yves Allenbach, MD, PhD[9]; Samia Boussouar, MD[5]; Edi Prifti, PhD[10]; Patrice Cacoub MD, PhD[9]

[1] Sorbonne Université, INSERM CIC-1901, APHP.Sorbonne, Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris, France

[2] Department of Cardiology, Sorbonne Université, APHP, Pitié-Salpêtrière Hospital, Paris, France

[3] Department of Cardiology, Sorbonne Université, APHP, Saint-Antoine Hospital, Paris, France

[4] Department of Clinical Metabolomics, Sorbonne Université, APHP, Saint-Antoine Hospital, Paris, France

[5] Department of Radiology, Sorbonne Université, APHP, Pitié-Salpêtrière Hospital, Paris, France

[6] Department of Biology, Sorbonne Université, APHP, Pitié-Salpêtrière Hospital, Paris, France

[7] Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), AP-HP, Hôpital Pitié-Salpêtrière, Service de Virologie, Paris, France

[8] Sorbonne University, INSERM, Research unit on cardiovascular and metabolic disease UMR ICAN, Department of endocrine and oncological biochemistry, AP-HP, Hôpital Pitié Salpêtrière, F-75013 Paris, France

[9] Department of internal medicine, Sorbonne Université, APHP, Pitié-Salpêtrière Hospital, Paris, France

[10] IRD, Sorbonne University, UMMISCO, 32 Avenue Henri Varagnat, F-93143 Bondy, France

Corresponding: Joe-Elie Salem, MD, PhD, Department of Clinical Pharmacology, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne Université, INSERM, CIC-1901, Paris, France. Email: joe-elie.salem@aphp.fr

Word count: 858 words

Table: 1

Funding: None

Acknowledgments: We thank Pr Xavier Girerd for his help in reviewing this manuscript.

Disclosures: None related to this manuscript

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.**

REFERENCES

1. Chung MK, Zidar DA, Bristow MR, Cameron SJ, Chan T, Harding CV, 3rd, Kwon DH, Singh T, Tilton JC, Tsai EJ, Tucker NR, Barnard J and Loscalzo J. COVID-19 and Cardiovascular Disease: From Bench to Bedside. *Circ Res*. 2021;128:1214-1236.
2. Lavie CJ, Sanchis-Gomar F and Lippi G. Cardiac Injury in COVID-19-Echoing Prognostication. *J Am Coll Cardiol*. 2020;76:2056-2059.
3. Mancia G, Rea F, Ludergnani M, Apolone G and Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med*. 2020;382:2431-2440.
4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA and Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.
5. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1-39 e14.
6. Salem JE, Laveau F, Ceccaldi A, Funck-Brentano C, Hulot JS, Mameri A, Barthelemy O, Helft G, Feuvre CL, Isnard R and Hammoudi N. Impact of negative inotropic drugs on accuracy of diastolic stress echocardiography for evaluation of left ventricular filling pressure. *Sci Rep*. 2017;7:9537.
7. Salem JE, Nguyen LS, Hammoudi N, Preud'homme G, Hulot JS, Leban M, Funck-Brentano C, Touraine P, Isnard R, Bachelot A and Group CS. Complex Association of Sex Hormones on Left Ventricular Systolic Function: Insight into Sexual Dimorphism. *J Am Soc Echocardiogr*. 2018;31:231-240 e1.

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.