# 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 $\chi^2$ 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≤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 $\chi^2$ 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.