



## SCIENTIFIC LETTER

### Acute *cor pulmonale* in patients with acute respiratory distress syndrome due to COVID-19



### *Cor pulmonale* agudo en pacientes con síndrome de distrés respiratorio agudo secundario a COVID-19

Dear Editor,

Disease due to by SARS-CoV-2 (COVID-19) is still a health problem around the world. Although most patients have suffered mild forms of the disease, the rate of acute respiratory distress syndrome (ARDS) has been unprecedented.<sup>1</sup> Despite the therapeutic advances made, mortality rate due to ARDS related COVID-19 in our setting sits at around 25%–40%.<sup>2</sup> There is evidence that right ventricular (RV) dysfunction in the form of pulmonary heart disease (PHD) is a factor associated with a higher mortality rate in non-COVID related ARDS.<sup>3</sup> Therefore, a PHD scoring system has been developed to guide the indication for echocardiography in these patients.<sup>4</sup> Also, RV dysfunction has been reported in patients with ARDS due to COVID-19.<sup>5</sup> However, data on the prevalence of PHD in these patients are scarce.

During the months of January 2021 through May 2021, we conducted an observational, prospective study at a tertiary center intensive care unit (ICU) to describe the incidence rate and predictors of PHD in patients with ARDS due to COVID-19 treated with invasive mechanical ventilation.

The study was approved by the clinical research ethics committee. All patients admitted to the ICU who needed invasive mechanical ventilation and had a PCR test diagnosis of SARS-CoV-2 infection were recruited prospectively. The diagnosis of ARDS was achieved according to the Berlin criteria.<sup>6</sup> The diagnosis of PHD was achieved on the transthoracic echocardiography performed within the first 3 days on mechanical ventilation, after visualization of a dilated RV on the 4-chamber view defined as a RV end-diastolic area/left ventricular end-diastolic area ratio >0.6 plus the presence of septal dyskinesia in the short axis parasternal view.<sup>7</sup>

The estimate of systolic pressure of both the pulmonary artery and the tricuspid annular plane systolic excursion was conducted following public recommendations.<sup>8</sup> Continuous variables were expressed as mean and 95% confidence interval or median (interquartile range) and compared using the Student *t* test or the Mann–Whitney *U* test when appropriate. Categorical variables were expressed as number and percentage and compared using the chi square test or Fisher's exact test. To assess the independent factors associated with the presence of PHD a multivariate logistic regression analysis was conducted with automated «backward» variable selection of all the variables that turned out significant in the bivariate analysis plus those described in similar trials.<sup>4</sup> The cut-off value was adapted to this study using Youden's index.

During the study period a total of 136 patients diagnosed with severe pneumonia due to COVID-19 were hospitalized. Eighteen of these patients were treated non-invasively with high-flow nasal cannulae. Eventually, 118 patients required invasive mechanical ventilation with the diagnosis of COVID-19-induced ARDS. A complete echocardiography study was conducted on 44 of these patients within the first 3 days on invasive mechanical ventilation. The patients' mean age was 66 years (63–69) with a SAPS II score within the first 24 h after admission of 32 (28–37); 75% were men. The rate of PHD was 18.2% (8/44, 95% confidence interval, 6%–30%). In patients with PHD admitted with more severity based on their SAPS II score (45 vs 30) no significant differences were found regarding population, analytical, ventilation or hemodynamic parameters (Table 1). No significant differences were found regarding the risk score of PHD between the PHD group and the non-PHD group. During the ICU stay, computed tomography scans were performed in a similar percentage of patients in both groups (62% vs 50%,  $P=0.701$ ). However, in patients in whom PHD was found, the computed tomography scan was performed early compared to the non-PHD subgroup (4 days vs 9 days,  $P<0.001$ ) (Table 1). No significant differences were seen regarding the days on mechanical ventilation, the ICU or the hospital stay. Patients with PHD had a higher mortality risk 90 days after ICU admission (RR, 6.82 [95%CI, 1.18–39.25]). In the multivariate analysis (Table 2) only SAPS scores >35 points and the presence of pulmonary thromboembolism were associated with PHD.

In the study population—representative of 38% of the patients on invasive mechanical ventilation—the rate of PHD

**Table 1** Main differences between patient with COVID-19-induced acute respiratory distress syndrome with or without pulmonary heart disease.

	N	All (N = 44)	Without PHD (N = 36)	With PHD (N = 8)	P
Age (years)	44	66 (63–69)	65 (62–69)	70 (63–77)	0.276
Sex (men)	44	33 (75%)	26 (72%)	7 (87.5%)	0.656
SAPS II 24 h after admission	41	32 (28–37)	30 (26–34)	45 (29–61)	0.005
Days with symptoms before ICU admission	44	10 (9–11)	10 (9–11)	9 (5–12)	0.272
<b>Comorbidities</b>					
Arterial hypertension	44	24 (55%)	19 (53%)	5 (62%)	0.710
Diabetes mellitus	44	14 (32%)	11 (31%)	3 (37%)	0.695
Heart failure	44	2 (5%)	2 (6%)	0	1
COPD	44	5 (11%)	4 (11%)	1 (12%)	1
Chronic kidney disease	44	3 (7%)	3 (8%)	0	1
<b>Ventilation patterns during TTE</b>					
TV (mL/kg)	44	5.9 (5.6–6.1)	5.9 (5.6–6.1)	6 (5–7)	0.712
RR (cycles/min)	44	24 (23–25)	24 (23–25)	23 (20–27)	0.552
PEEP (cmH <sub>2</sub> O)	44	13 (12–13)	13 (12–13)	12 (10–15)	0.538
Plateau pressure (cmH <sub>2</sub> O)	44	23 (23–24)	23 (23–24)	24 (22–25)	0.799
DP (cmH <sub>2</sub> O)	44	11 (10–12)	11 (10–12)	12 (9–15)	0.379
Compliance (mL/cmH <sub>2</sub> O)	44	36 (33–40)	37 (33–40)	34 (21–46)	0.484
Prone the day of the TTE	44	35 (79%)	29 (80%)	6 (75%)	1
<b>Hemodynamic parameters during TTE</b>					
SAP (mmHg)	44	114 (110–119)	115 (110–120)	112 (97–126)	0.558
DAP (mmHg)	44	61 (58–64)	61 (60–65)	60 (54–66)	0.677
HR (beats/min)	44	83 (78–87)	82 (77–86)	89 (76–102)	0.198
Shock	44	19 (43%)	15 (43%)	4 (50%)	1
TAPSE (mm)	44	19 (16–21)	20 (19–21)	15 (12–18)	0.005
PASP (mmHg)	24	38 (34–43)	34 (28–40)	44 (41–46)	0.034
<b>Analytical data during TTE</b>					
PaO <sub>2</sub> /FiO <sub>2</sub>	44	180 (157–204)	186 (159–212)	155 (90–220)	0.336
PaCO <sub>2</sub> (mmHg)	44	46 (40–52)	46 (40–53)	45 (37–53)	0.843
pH	44	7.38 (7.36–7.40)	7.38 (7.36–7.40)	7.34 (7.29–7.39)	0.085
hs-TnT (ng/L)	38	11 [8–17]	10 [7–14]	37 [16–282]	0.137
NT-proBNP (ng/L)	31	301 [133–759]	271 [129–271]	980 [274–2705]	0.227
D-dimer (ng/mL)	44	1516 [880–3336]	1349 [827–2487]	2214 [1384–9211]	0.802
<b>Diagnostic procedures</b>					
ACP risk score	44	2 (1–2)	2 (1–2)	2 (1–3)	0.593
Day of echocardiogram	44	1 (1–2)	1 (1–2)	1 (1–2)	0.738
Thoracic CT scan	44	23 (52%)	18 (50%)	5 (62%)	0.701
Day of thoracic CT scan	23	8 (1–9)	9 (8–10)	4 (3–6)	<0.001
Diagnosis of PTE	44	9 (20.5%)	5 (13.9%)	4 (50%)	0.042
<b>Data on patient progression</b>					
Days on IMV	44	17 (12–22)	16 (11–21)	23 (3–45)	0.336
ICU stay	44	20 (15–25)	19 (14–24)	22 (3–42)	0.627
Hospital stay (days)	44	30 (23–37)	31 (23–39)	26 (6–45)	0.620
90-day mortality rate	44	17 (38%)	11 (31%)	6 (75%)	0.04

ACP, acute cor pulmonale risk score; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DAP, diastolic arterial pressure; DP, driving pressure; HR, heart rate; hs-TnT, high-sensitivity troponin T; ICU, intensive care unit; IMV, invasive mechanical ventilation; N, number of patients with data; PASP, pulmonary artery systolic pressure; PEEP, positive end-expiratory pressure; PTE, pulmonary thromboembolism; RR, respiratory rate; SAP, systolic arterial pressure; SAPS II, Simplified Acute Physiology Score II; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; TV, tidal volume.

was similar compared to that already published regarding patients with non-COVID-19-induced ARDS (19%–25%).<sup>3</sup> However, our data show that the pathophysiological mechanism here is different. In patients with non-COVID-19-induced ARDS, PHD is linked to factors associated with pulmonary mechanics (driving pressure) and gas exchange (hypoxemia and hypercapnia).<sup>4</sup> In this study, in patients with

COVID-19-induced ARDS, the main mechanism was associated with the presence of thromboembolic phenomena in pulmonary blood vessels. In this sense, our results are consistent with a study recently published.<sup>9</sup> Although the study conducted by Cavaleiro et al. reported on a rate of PHD in the COVID-19 population (38%) that is higher compared to that described in the non-COVID-19 population,

**Table 2** Bivariate and multivariate analyses of parameters associated with the presence of pulmonary heart disease in patients with acute respiratory distress syndrome due to COVID-19.

	N	Bivariate analysis	Multivariate analysis
Driving pressure > 11 cmH <sub>2</sub> O	44	1.49 (0.31–7.19); <i>P</i> =0.71	Variable not preserved
PaO <sub>2</sub> /FiO <sub>2</sub> < 122	44	4.14 (0.83–20.79); <i>P</i> =0.09	Variable not preserved
PaCO <sub>2</sub> > 45 mmHg	44	1.57 (0.34–7.33); <i>P</i> =0.69	Variable not preserved
SAPS II > 35	41	7.50 (1.21–46.51); <i>P</i> =0.03	7.06 (1.19–52.11); <i>P</i> =0.04
Diagnosis of PTE	44	6.20 (1.16–33.17); <i>P</i> =0.04	8.76 (1.17–65.58); <i>P</i> =0.03

Data are presented as OR [95% confidence interval]. The multivariate model showed good calibration based on the goodness of fit test adjusted according to the Hosmer–Lemeshow test (*P*=0.981).

N, number of patients with data; SAPS II, Simplified Acute Physiology Score II; PTE, pulmonary thromboembolism.

it also reveals that the main factor associated with the presence of PHD in COVID-19-induced ARDS is the coexistence of pulmonary thromboembolism. In patients with COVID-19 admitted to the ICU with ARDS, the coexistence of endothelial inflammation, systemic alterations of coagulation, and local phenomena in pulmonary capillaries due to deep hypoxemia increases the rate of pulmonary thromboembolisms compared to that of patients with ARDS due to non-COVID related viral pneumonias.<sup>10</sup>

In conclusion, in patients with COVID-19-induced ARDS the coexistence of PHD is mainly associated with the presence of pulmonary thromboembolic phenomena. In these patients the finding of PHD should trigger the use of computed tomography scans to rule out the presence of pulmonary thromboembolism. These findings should be confirmed in larger studies.

**Authors/collaborators**

LZ, and JCS designed the study, collected data, analyzed data and drafted the manuscript. MFO, EMM, and AS collected data. JAS analyzed data and drafted the manuscript.

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