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Cardiac function in critically ill patients with severe COVID: A prospective cross-sectional study in mechanically ventilated patients

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ABSTRACT

Purpose: To evaluate cardiac function in mechanically ventilated patients with COVID-19.
Materials and methods: Prospective, cross-sectional multicenter study in four university-affiliated hospitals in Chile. All consecutive patients with COVID-19 ARDS requiring mechanical ventilation admitted between April and July 2020 were included. We performed systematic transthoracic echocardiography assessing right and left ventricular function within 24 h of intubation.
Results: 140 patients aged 57 ± 11, 29% female were included. Cardiac output was 5.1 L/min [IQR 4.5–6.2] and 86% of the patients required norepinephrine. ICU mortality was 29% (40 patients). Fifty-four patients (39%) exhibited right ventricle dilation out of whom 20 patients (14%) exhibited acute cor pulmonale (ACP). Eight out of the twenty patients with ACP exhibited pulmonary embolism (40%). Thirteen patients (9%) exhibited left ventricular systolic dysfunction (ejection fraction <45%). In the multivariate analysis acute cor pulmonale and PaO_2/FiO_2 ratio were independent predictors of ICU mortality.
Conclusions: Right ventricular dilation is highly prevalent in mechanically ventilated patients with COVID-19 ARDS. Acute cor pulmonale was associated with reduced pulmonary function and, in only 40% of patients, with co-existing pulmonary embolism. Acute cor pulmonale is an independent risk factor for ICU mortality.

1. Introduction

Several studies have shown evidence of cardiovascular alterations in SARS-COV-2 infections (COVID-19). First, increased troponin levels, associated with an increased mortality, were observed in a significant proportion of patients [1-3]. In addition, case reports of cardiogenic shock or fulminant myocarditis have been published [4,5]. Likewise, right ventricular dilation, acute cor pulmonale (ACP) and pulmonary embolism (PE) have also been reported [6-11].

Critical care echocardiography (CCE) has gained increasing acceptance as the preferred approach to study cardiac function in critically ill patients [12]. Since the start of the COVID-19 outbreak, many studies have described echocardiographic findings in these patients [6,8,13-16],

Abbreviations: A wave, Peak velocity in late diastole; ACP, Acute cor pulmonale; APACHE, Acute Physiology and Chronic Health Evaluation II; ARDS, Acute respiratory distress syndrome; CCE, Critical care echocardiography; COVID-19, Coronavirus disease of 2019; CT, Computed tomography; E wave, Peak velocity in early diastole; e' wave, Lateral mitral annulus velocity (early diastole); E/A ratio, Relation between early peak velocity wave and atrial velocity wave; E/e' ratio, Relation between early peak velocity wave and peak mitral annular myocardial velocity wave; IVC, Inferior vena cava; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow tract; MV, Mechanical ventilation; PE, Pulmonary embolism; PPV, Arterial pulse pressure variation; RV, Right ventricle; RVEDA/LVEDA ratio, Right over left ventricular end-diastolic area; s' wave, Mitral annular myocardial velocity; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOFA, Sequential Organ Failure Assessment; TAPSE, Tricuspid annular plane systolic excursion; TDI, Tissue Doppler Imaging; VTI, Velocity time integral.

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usually reporting low rates of left ventricular (LV) dysfunction and varying degrees of right ventricular (RV) dilation and ACP. The true prevalence of cardiac dysfunction is however difficult to address, as most of these studies included large numbers of patients with less severe disease and/or were retrospective series of echocardiographic studies performed at the discretion of the attending physician.

Additionally, limited data have been reported about cardiac function in relation to lung function and respiratory mechanics during mechanical ventilation. As these factors have been established in the classic Adult Respiratory Distress Syndrome (ARDS) related cardiac dysfunction [17] these might play a role in severe COVID-19 as well.

Therefore, our objective was to perform a cross-sectional systematic characterization of cardiac function in patients with severe COVID-19 using CCE within 24 h of the start of mechanical ventilation (MV). First, we aimed to determine the prevalence of RV and LV dysfunction in mechanically ventilated patients. Second, RV function was studied in relation to lung function, and hemodynamic parameters, and mortality. In addition, we measured the effect of ACP on the 1 year survival status in all patients.

2. Materials and methods

This prospective, multicenter study included patients with laboratory (PCR test) confirmed COVID-19 admitted between April and July 2020 to the ICU of four university-affiliated hospitals in Chile. The local ethics committee of each center approved the study and waived the need to provide written informed consent (protocol ID: 200422002).

2.1. The study population

All consecutive patients with COVID-19 requiring invasive MV were included in the study within 24 h of the start of MV. Patients under 18 years old, poor ultrasound window, severe valvulopathy, or a do-not-resuscitate status were excluded. Demographic data, Acute Physiology and Chronic Health Evaluation II (APACHE), Sequential Organ Failure Assessment (SOFA), respiratory system mechanics, hemodynamic variables, biomarkers and tissue perfusion parameters were recorded contemporaneously with the CCE examination. One year follow-up was assessed by telephone interview or using online death registry.

2.2. Echocardiography

Transthoracic echocardiography was performed by a medical operator trained in accordance with CCE guidelines [12] all studies were recorded and interpreted off-line by the medical operator and subsequently supervised by the principal investigator of each center (DV, PM, RP and NM). Echocardiographic measurements were obtained with a Vivid I echocardiography system (GE Medical Systems, Milwaukee, WI, USA), Philips CX 50 (Philips Healthcare, DA Best, The Netherlands), and Mindray M9 (Bio-Medical Electronics Co., Shenzhen, China), as used in each center. Patients were managed with lung protective ventilation strategies throughout their treatment. Adequate sedation was guaranteed during the echocardiographic evaluation. Measurements were acquired at end-expiration and averaged over three consecutive cardiac cycles [18,19]. Patients in prone position were placed in the swimmer position as previously described [20], which was frequently used during the COVID-19 pandemic [21,22].

LV systolic function was assessed by the left ventricular ejection fraction (LVEF), as measured with Simpson's modified rule. Based on LVEF patients were categorized in hyperkinetic (LVEF >60%), normokinetic (LVEF between 45% and 60%) and hypokinetic (LVEF <45%) [23]. Cardiac output (CO) was calculated from the LV outflow tract (LVOT) [24]. The diameter of the LVOT was taken from the long parasternal view when it was available in supine position. Pulsed wave Doppler samples were obtained at the LVOT from the apical view and the average of three measurements of velocity time integral (VTI) was calculated. The stroke volume (SV) was calculated as the product of the LVOT area and the VTI. The CO was calculated as the product of SV and heart rate. Peak mitral annular myocardial velocity wave (s') was recorded at the level of the lateral mitral annulus using Tissue Doppler Imaging (TDI) [25].

Left ventricular diastolic function was assessed by mitral inflow pulsed wave Doppler, to measure early peak velocity (E) and atrial velocity (A). The early diastolic peak velocity (e') of the lateral mitral annulus was also measured with TDI. From these variables E/A and E/e' ratios were calculated [19].

Left and right ventricular end-diastolic area (LVEDA and RVEDA) were measured from an apical 4-chamber view and RVEDA/LVEDA ratio was calculated. ACP was defined as RV dilation (RVEDA/LVEDA ratio > 0.6) associated with a paradoxical septum motion [26,27]. RV systolic function was assessed by the tricuspid annular plane systolic excursion (TAPSE) and peak tricuspid annular myocardial velocity wave (s') was recorded using TDI from an apical 4-chamber view [28,29].

Systolic pulmonary artery pressure (SPAP) was obtained from tricuspid regurgitation (TR) in those patients in whom it was present. TR was aligned with continuous wave Doppler; maximal velocity of the TR was recorded, and the TR pressure gradient was calculated using the simplified Bernoulli equation (TRPGmax). SPAP was calculated (SPAP = TRPGmax + CVP) [30].

2.3. Hemodynamic assessment

Hemodynamic variables and vasopressor support were recorded during the CCE examination. Maximum and minimum inferior vena cava (IVC) diameter were measured. Fluid responsiveness was assessed by either the respiratory variations of inferior vena cava (IVC) [31], or by the arterial pulse pressure variation (PPV) [32]. Increased LV filling pressure was defined as an E/e' ratio > 15 [33]. Tissue perfusion was assessed by capillary refill time (CRT) and lactate levels [34].

High-sensitive Troponin T and D-Dimer concentrations were measured simultaneously with echocardiographic assessment.

Computed tomography (CT) pulmonary angiography was performed in all patients with ACP and on clinical indication in the remaining patients.

2.4. Statistical analysis

Normality was tested by Kolmogorov-Smirnov test. The continuous data is presented as mean ± standard deviation or as median and interquartile ranges, depending on the data distribution. Comparisons among groups were analyzed by Friedman test and between groups with Wilcoxon rank-sum test. Categorical variables were compared through chi square test. Pearson or Spearman correlation was performed according to data distribution.

To identify independent predictors for mortality and ACP, a multivariate regression analysis was carried out including all variables of interest in a univariate analysis (p value <0.05) and forward stepwise selection method was used to determine the final logistic regression model. Youden index was used to estimate the best cutoff point regarding sensitivity and specificity of continuous variables. Final logistic models were assessed by Hosmer and Lemeshow test and ROC analyses were performed. Kaplan-Meier curve was performed to compare survival among patients with and without ACP. Statistical analysis was performed with SPSS (version 22.0, IBM SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

3. Results

Of the 175 screened patients, 140 (age 57 ± 11 yr, 29% female) were included in the study (Fig. 1). Severity of disease on admission was: APACHE II 14 [IQR 10–18] and SOFA 7 [4-8]. The main comorbidities

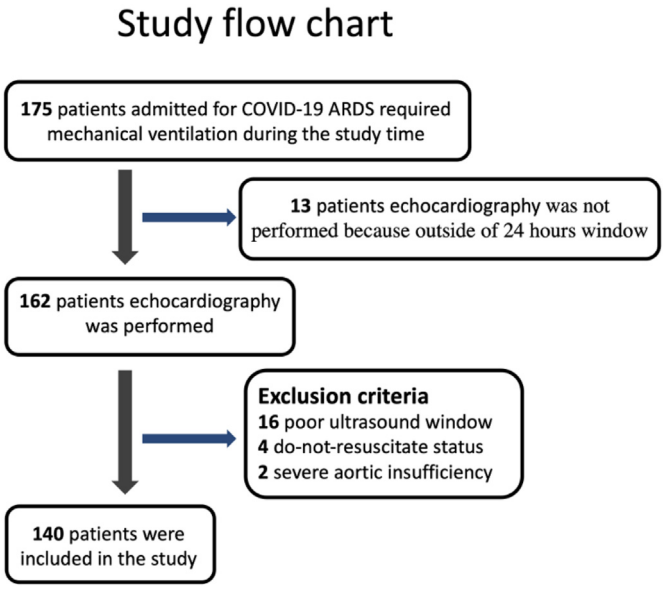

Fig. 1. Study flow chart

were diabetes mellitus, obesity and hypertension. Demographic and clinical characteristics on ICU admission are shown in Table 1.

At time of echocardiographic measurement, 65 (46%) patients were in prone position. PaO2/FiO2 ratio was 155 [IQR 107–177] and MV settings adhered closely to lung protective ventilation strategies: tidal volume 6.0 [IQR 5.5–6.5] ml/kg/predicted body weight, plateau pressure 22 [IQR 20–24] cmH2O and driving pressure 11 [IQR 10–13] cmH2O. Other respiratory system parameters are shown in Table 2. Cardiac output was 5.1 [IQR 4.5–6.2] L/min and 86% of the patients required norepinephrine to maintain mean arterial pressure at >65 mmHg using a median dose of 0.05 μg/kg/min [IQR 0.03–0.14]. Perfusion markers were normal in most patients; lactate levels were 1.7 mmol/L [IQR 1.2–2.1] and the Pv-aCO_2 gradient was 6 [4-8]. Thirty-six patients (26%) were fluid responsive according to the parameters used, whereas seven patients (5%) had evidence of increased LV filling pressure. Veno-venous extracorporeal membrane oxygenation (vvECMO) was not used in any of the patients. Extra corporeal carbon dioxide removal (Novalung) was used in one non-survivor.

3.1. Right ventricular function

Fifty-four patients (39%) had RV dilation, out of whom twenty patients (14%) met criteria for ACP. Patients with RV dilation without ACP showed preserved right ventricular function as assessed by TAPSE (22 mm [IQR 19–24]) and TDI Tricuspid s' wave (13 cm/s [IQR 11–16]) similar to the patients with normal RV. However, the maximum IVC diameter in these patients was increased compared to patients with normal RV (21 mm [IQR 20–24] vs. 19 [IQR 17–22] $p = 0.005$, respectively). In addition, RV dilation was not associated with abnormal hemodynamics, tissue perfusion or respiratory system parameters (Table 2). A comprehensive comparison between patients with normal RV and with RV dilation without and with ACP is shown in Tables 2 and 3.

Patients with ACP showed more severe lung disease, as reflected by lower compliance, higher driving pressure and the presence of respiratory acidosis associated with higher APACHE II and SOFA score on admission when compared to patients with RV dilatation (Table 1). Patients with ACP had a significant decrease in RV systolic function when compared to patient with dilatation only, TAPSE (16 mm [IQR 13–20] vs 22 [IQR 19–24], $p = 0.001$ respectively). Furthermore, patients with ACP required more norepinephrine, had higher heart rate and lower stroke volume, prolonged capillary refill time and higher lactate levels associated with a higher prevalence of LV systolic dysfunction (30%) and troponin levels (Table 2). We measured the pressure gradients across the tricuspid and pulmonary valves from tricuspid regurgitation (TRV) in 37 patients. On 65% of patients with ACP showed a SPAP of 49 mmHg [IQR 43–55] whereas in 20% of patients without ACP showed a SPAP of 35 mmHg [IQR 28–38], $p = 0.001$). Predictors of ACP are shown in Table S3.

3.2. Left ventricular function

Seventy-nine patients (56%) had hyperkinetic LVEF, forty-eight patients (35%) had normal LVEF and thirteen patients (9%) exhibited LV systolic dysfunction (LVEF <45%). Patients with LV systolic dysfunction

Table 1
Demographic and clinical characteristics among patients with normal right ventricle, right ventricle dilation without ACP and ACP.

	All $n = 140$	Normal RV $n = 86$	RV dilation $n = 34$	ACP $n = 20$
Age, y.o.	57 ± 11	56 ± 12	58 ± 11	57 ± 11
Sex, male (%)	99 (71)	61 (71)	26 (77)	12 (60)
APACHE II score	14 [10–18]	11 [10–15]	15 [11—20]	22 [11–25]*
SOFA score on ICU admission	7 [4–8]	6 [4–8]	7 [6–9]	8 [5–9]*
SOFA score at time of echocardiography	7 [5–8]	6 [5–8]	8 [6–10]	8 [7–10]*
Charlson comorbidity index	2 [1–3]	2 [1–2]	3 [2–3]	2 [1–3]
Comorbidities				
Myocardial infarction	3 (2)	3 (3)	0	0 (0)
Chronic heart failure	5 (4)	4 (4)	0	1 (5)
COPD or Asthma	10 (7)	8 (9)	2 (6)	0 (0)
Diabetes mellitus	36 (26)	15 (17)	12 (35)	9 (45)*
Chronic kidney disease	7 (5)	1 (1)	3 (9)	3 (15)
Arterial hypertension	66 (47)	34 (40)	20 (59)	12 (60)
Obesity	59 (42)	40 (47)	8 (24)	11 (50)*
Outcomes				
Mechanical ventilation days	13 [8–18]	14 [8–19]	12 [9–16]	10 [7–17]
ICU length of stay, days	16 [11—23]	17 [11–24]	16 [12—22]	13 [7–21]
Hospital length of stay, days	26 [19–40]	25 [18–40]	30 [20–47]	23 [14–27]
ICU mortality	40 (29)	23 (27)	3 (9)	14 (70)
Total hospital mortality	44 (31)	25 (29)	3 (9)	16 (80)
One year mortality	45 (32)	26 (30)	3 (9)	16 (80)

Continuous data were expressed as mean ± SD or median [25th–75th percentiles]. Categorical variables expressed as number. * represent significant difference between groups ($p < 0.05$). APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; ICU = Intensive Care Unit; COPD = chronic obstructive pulmonary disease; ACP = Acute Cor Pulmonale.

Table 2
Respiratory system parameters and inflammatory biomarkers among patients with normal right ventricle, right ventricle dilation without ACP and ACP.

	All n = 140	Normal RV n = 86	RV dilation n = 34	ACP n = 20	p value
Mechanical ventilation					
Tidal volume, ml	380 [350–420]	380 [340–420]	400 [355–430]	370 [320–420]	0.321
Tidal volume, ml/Kg	6.0 [5.5–6.5]	6.0 [5.5–6.5]	6.3 [5.8–6.9]	6.0 [5.0–6.8]	0.210
Peak airway pressure, cmH_2O	29 [26–31]	28 [26–31]	29 [26–32]	31 [27–35]	0.204
Plateau pressure, cmH_2O	22 [20–24]	22 [20–24]	22 [20–24]	22 [21–25]	0.559
Mean airway pressure, cmH_2O	15 [14–17]	15 [14–17]	15 [14–17]	15 [13–18]	0.938
PEEP, cmH_2O	10 [10−12]	10 [9–12]	10 [8–12]	10 [8–10]	0.178
Driving pressure, cmH_2O	11 [10−13]	11 [10–12]	12 [10–14]	14 [11–15]*	**0.014**
RS compliance, ml/cmH_2O	33 [26–40]	35 [27–40]	32 [26–42]	28 [20–37]*	0.060
Respiratory rate	26 [24–30]	26 [24–28]	26 [24–29]	29 [26–32]*	**0.020**
Inspiratory oxygen fraction	0.5 [0.4–0.7]	0.5 [0.4–0.6]	0.45 [0.4–0.7]	0.70 [0.45–0.80]	0.079
PaO_2/FiO_2 ratio	155 [107–177]	155 [107–173]	158 [112−200]	156 [83–174]	0.403
Neuromuscular Blockers, n(%)	108 (77)	65 (76)	25 (74)	18 (95)	0.262
Prone position, n(%)	65 (46)	40 (47)	14 (41)	11 (55)	0.616
Acid base state					
pH	7.33 [7.24–7.38]	7.33 [7.26–7.38]	7.35 [7.24–7.40]	7.24 [7.18–7.32]*	**0.007**
PCO_2, mmHg	43 [39–56]	43 [39–53]	45 [38–57]	55 [43–65]*	**0.034**
PO_2, mmHg	79 [70–90]	78 [70–95]	80 [78–88]	75 [64–87]	0.273
Bicarbonate, mEq/l	23 [21–26]	23 [21–25]	24 [21–26]	23 [21–25]	0.590
Base excess	−3.5 [−6.4- -0.3]	−3.8 [−6.3- -1.0]	−2.0 [−6.7–1.9]	−4.2 [−10.8 – −0.4]	0.334
Ferritin, ng/ml	1548 [520–2518]	1515 [391–2502]	1787 [899–2451]	883 [322–2984]	0.722
LDH, U/L	588 [458–752]	544 [428–734]	622 [521–746]	625 [491–988]	0.223
D-Dimer, ng/ml	1576 [977–5893]	1154 [864–3962]	2308 [725–6635]	7477 [3476–37,543]*	**0.001**
White blood cells x1000	11.8 [7.8–15.2]	10.3 [7.5–13.9]	12.9 [8.7–21.2]	14.1 [10.1–19.0]*	**0.041**
CRP, mg/dL	24.7 [12.3–35.5]	21.7 [11.6–34.6]	25.1 [12.2–40.0]	31.9 [18.1–39.6]	0.213

Continuous data were expressed mean ± SD or median [25th–75th percentiles]. Categorical variables expressed as number (percentage). * represent significant difference between patients with ACP and RV dilation ($p < 0.05$). PEEP = positive end-expiratory pressure; RS = respiratory system; LDH = lactate dehydrogenase; CRP = C-reactive protein.

were more tachycardic, had decreased pulse pressure, received higher norepinephrine doses and had higher troponin levels (Table S1, S2). In addition, both LV systolic dysfunction and ACP were present in six patients (4%), this finding was related to higher severity of the disease (Table S1, S2). We cannot rule out wall motion abnormalities as these were not assessed in the echocardiography study.

Twenty-seven patients (19%) showed LV or RV dysfunction. Eighty-two patients (59%) had evidence of diastolic dysfunction: Grade I in sixty-six (47%), Grade II in sixteen patients (12%) and no patient exhibited grade III. Both LV systolic and diastolic dysfunction were not independently associated with mortality (Table S4).

3.3. Biomarkers

A positive correlation was observed between the RVEDA/LVEDA ratio and Troponin levels ($r = 0.36$, $p = 0.001$). Increased troponin levels (>14 pg/mL) were present in 56% of the patients with a negative correlation between LVEF and troponin levels ($r = -0.31$, $p = 0.002$).

D-dimers were significantly increased in patients with ACP compared to the other patients (Table 2).

Multivariate analysis identified pulmonary embolism and respiratory system compliance ≤25 ml/cmH_2O as independent predictors of ACP (Table S3).

On 91 patients CT pulmonary angiography was performed: On 57% of the patients (49/86) with normal RV, 65% of patients (22/34) with RV dilation without ACP, and in all patients with ACP. Prevalence of PE was: 14% (7/49) in patients with normal RV, 18% (4/22) in patients with RV dilation without ACP and 40% (8/20) in patients with ACP.

3.4. Mortality

A total of 44 patients (31%) died, of whom 40 died during ICU stay. Patients with ACP had the highest ICU mortality (70% vs 22%, $p = 0.01$, Table 1). Only one patient died during the one-year follow-up (Fig. 2. Kaplan-Meier curve). In the multivariate analysis ACP and PaO_2/FiO_2 were independent predictors of mortality (ROC 0.81 95% CI 0.73–0.89) (Table S4).

4. Discussion

The main findings of our study were that RV dilation and ACP are more prevalent than LV dysfunction in patients requiring mechanical ventilation due to severe COVID-19. The presence of ACP was associated with parameters of poorer lung function and pulmonary embolism in 40% of the patients. ACP, in contrast to RV dilation only, was an independent risk factor for ICU mortality. Additional mortality between hospital discharge and 1-year follow-up was negligible.

Acute cor pulmonale in the context of classic ARDS is seen in 22% - 50% of the patients and has been associated with increased mortality [35]. However, Evrard et al. [10] found a lower prevalence of ACP in COVID-19 ARDS when compared to classic ARDS (17% vs 48%, respectively). Similar to Evrard et al. [10] and our results (14%), Huang et al. [16] reported a comparable low prevalence of ACP (17,4%) in the largest study to date (667 patients) in COVID-19 patients. Nonetheless, a confounding factor is that most of the studies in COVID-19 ARDS are retrospective series of echocardiographic assessment due to clinical indication, hence the reported prevalence of ACP could be higher. Our study is the first cross sectional view that could explain the slightly lower prevalence of ACP (14%). Nevertheless, when ACP is present the prognosis is worse [16]. In addition, this lower prevalence of ACP in COVID-19 ARDS could be related to differences in lung function as indicated by the significantly higher respiratory system compliance, and lower driving pressure than found in patients with classic ARDS at least during the early stages of the disease.

Several risk factors for developing ACP in patients with classic ARDS [27] have been identified: pneumonia as a cause of pulmonary ARDS, driving pressure ≥ 18 cm H2O, PaCO2 ≥ 48 mmHg, and PaO2/FiO2 ratio < 150. In our study, patients with ACP exhibited worse respiratory mechanics, as reflected by markedly lower respiratory system compliance, higher driving pressure, and respiratory acidosis (Table 2). Likewise, in our population driving pressure ≥ 18 cm H2O, PaCO2 ≥ 48 mmHg were associated with ACP. Nevertheless, the ACP risk score showed a poor discriminative ability to predict ACP (AUC 0.66 [95%CI 0.47–0.85]) due to the fact that PaO2/FiO2 ratio was not associated with ACP (Table S3). Nevertheless, our patients with ACP had higher

Table 3
Hemodynamic and echocardiography parameters among patients with normal right ventricle, right ventricle dilation without ACP and ACP.

	All n = 140	Normal RV n = 86	RV dilation n = 34	ACP n = 20	p value
Macro-hemodynamic parameters					
SBP, mmHg	117 [104–131]	123 [107–137]	114 [103−130]	105 [98–123]	**0.030**
DBP, mmHg	61 [55–70]	61 [55–70]	63 [55–72]	61 [55–65]	0.620
MAP, mmHg	79 [73–92]	79 [73–94]	79 [73–92]	77 [70–85]	0.568
NE, mcg/kg/min	0.05 [0.03–0.14]	0.05 [0.03–0.12]	0.04 [0.01–0.08]	0.20 [0.05–0.30]*	**0.004**
HR, beats/min	80 [67–100]	75 [64–97]	83 [64–95]	106 [90–119]*	**0.001**
CVP, mmHg	8 [5–11]	9 [5–11]	10 [6–12]	10 [6–11]	0.303
Fluid balance, ml	179 [−403–1050]	57 [−440–859]	325 [−229–1172]	547 [−307–1384]	0.391
Tissue perfusion parameters					
Pv-aCO2 gap, mmHg	6 [4–8]	6 [4–8]	5 [4–8]	6 [5–11]	0.394
Central Venous Saturation, %	77 [70–82]	77 [70–82]	78 [73–82]	66 [57–76]	0.113
Capillary Refill Time, *sec*	2 [2–3]	2 [1–3]	3 [2–3]	3 [2–3]	**0.006**
Lactate, mmol/l	1.9 [1.4–2.5]	1.8 [1.3–2.3]	2.1 [1.5–2.7]	2.5 [2.0–3.7]	**0.001**
Predictors of fluid responsiveness					
Maximum IVC diameter, mm	20 [17–22]	19 [17–22]	21 [20–24]#	22 [19–23]	**0.005**
Minimum IVC diameter, mm	18 [15–21]	17 [13−20]	18[15–22]	19 [17–22]	**0.009**
IVC distensibility index, %	10 [5–22]	9.5 [5.1–23.2]	10.5 [5.6–24.1]	11 [8–21]	0.784
Pulse Pressure Variation, %	4 [3–5]	4 [2–5]	4 [3–5]	5 [5–7]	0.116
CO and LV function					
Cardiac output, L/min	5.1 [4.5–6.2]	5.1 [4.6–6.2]	4.7 [3.7–6.3]	4.9 [4.7–5.7]	0.357
Cardiac index, L/min/m^2	2.6 [2.3–3.2]	2.7 [2.3–3.3]	2.5 [1.8–3.4]	2.5 [2.3–2.8]	0.297
Left Ventricular Ejection Fraction, %	62 [53–67]	63 [55–68]	62 [54–67]	51 [44–71]	0.286
LV Ejection Fraction <45, (%)	13 (10)	5 (6)	2 (6)	6 (30)	**0.003**
LVOT VTI, cm	20 [16–24]	21 [17–24]	18 [16–21] #	16 [14–20]	**0.001**
Stroke Volume, ml	63 [52–79]	68 [56–82]	59 [50–73]	52 [45–61]	**0.001**
MAPSE, mm	15 [13–17]	16 [14–17]	15 [12–17]	13 [11–16]	**0.021**
Mitral TDI s' wave, cm/s	12 [10–14]	12 [9–14]	12 [10–14]	15 [11–18]	**0.018**
Right ventricle function					
TAPSE, mm	20 [18–23]	21 [18–23]	22 [19–24]	16 [13–20]*	**0.001**
Tricuspid TDI s' wave, cm/s	13 [11–16]	13 [11–16]	13 [11–16]	13 [9–14]	0.463
Right end diastolic area, cm^2	14 [11–18]	13 [10–17]	14 [11–16]	17 [14–21]	**0.001**
Left end diastolic area, cm^2	23 [19–32]	25 [21–34]	23 [18–34]	18 [14–21]	**0.001**
RVEDA/LVEDA ratio	0.6 [0.5–0.7]	0.5 [0.4–0.5]	0.7 [0.7–0.8] #	0.9 [0.8–1.2]	**0.001**
SPAP, mmHg	38 [30–48]	32 [28–37]	36 [29–44]	49 [43–55]*	**0.001**
Thorax CT angiography, %	91 (65)	49 (57)	22 (65)	20 (100)	**0.001**
Pulmonary embolims, %	19 (14)	7 (14)	4 (18)	8 (40)	**0.001**
Diastolic function					
Doppler Trans-mitral E wave, cm/s	65 [54–79]	68 [60–81]	62 [49–70] #	53 [40–76]	**0.014**
Doppler Trans-mitral A wave, cm/s	62 [48–74]	62 [48–73]	58 [49–69]	66 [37–78]	0.671
E/A ratio	1.0 [0.8–1.3]	1.1 [0.8–1.4]	0.9 [0.8–1.3]	0.9 [0.7–1.2]	0.147
Mitral TDI e' wave, cm/s	10.0 [8.0–12.0]	10.0 [8–12.1]	10.0 [8.2–12.1]	10.4 [8–12]	0.852
E/e' ratio	6.5 [5.3–7.9]	6.8 [5.6–8.4]	5.8 [4.5–7.4] #	5.4 [3.9–7.8]	**0.019**
Cardiac biomarker					
Troponin T, pg/ml	19 [8–42]	13 [7–3]	24 [8–105]	43 [24–253]	**0.001**

Continuous data were expressed as median [25th–75th percentiles]. Categorical variables expressed as number (percentage). # represent significant difference between patients with RV dilation and normal RV ($p < 0.05$). * represent significant difference between patients with ACP and RV dilation ($p < 0.05$). SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = median arterial pressure; NE = norepinephrine; HR = heart rate; CVP = central venous pressure; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; MAPSE = mitral annular plane systolic excursion; LVOT = left ventricular outflow tract; VTI = velocity time integral; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; RVEDA/LVEDA ratio = right ventricle end diastolic area/left ventricle end diastolic area ratio; SPAP = systolic pulmonary arterial pressure; ACP = acute cor pulmonale; E/A ratio = E wave/A wave ratio; E/e' ratio = E wave/tissue Doppler image e' wave ratio; IVC = inferior vena cava.

PaO2/FiO2 ratio compared to patients with classic ARDS and ACP [27] (148 ± 53 vs 106 ± 4, respectively). Interestingly Huang et al. [16] also found no association between PaO2/FiO2 ratio and ACP in COVID-ARDS even though their patients exhibited lower PaO2/FiO2 ratio (118 [IQR 86–167]). These data suggest that COVID-19 might be associated with a blunted hypoxic pulmonary vasoconstriction [36,37]. These physiological variables could increase the risk for developing ACP by increasing pulmonary vascular tone and thus RV afterload [35] that was present in our ACP patients without PE (60%). The right ventricle is sensitive to afterload increases, it is adapted to a low-pressure circulation and an increase in pulmonary vascular tone in COVID-19 ARDS has been proposed as one of several factors involved in the development of ACP [38]. Also, in our study, patients with ACP showed a significant increase in SPAP, underscoring the potential role of pulmonary vascular tone in the development of ACP in both classic and COVID-19 ARDS.

RV dilatation is a functional adaptation to maintain cardiac output by Frank-Starling mechanism, but if decompensating factors persist the RV dilates to produce a negative diastolic interaction due to ventricular competition for the space within the non-compliant pericardium, leading to RV dilation associated with a paradoxical septum motion (ACP), decreased LV filling and stroke volume, and finally shock [39]. In our study we also found that patients with ACP had significantly lower LV filling pressures, as assessed by the Trans-mitral E wave and E/e´ ratio, and a lower stroke volume. Moreover, these patients exhibited severe hemodynamic compromise reflected by hypotension, high NE doses, tachycardia, and impaired tissue perfusion reflected by prolonged capillary refill time and increased lactate levels.

Tricuspid annular plane systolic excursion (TAPSE) has been used to assess RV systolic function in critically ill patients [29], although there is no clear consensus on its use in the critical care setting [40]. Recently,

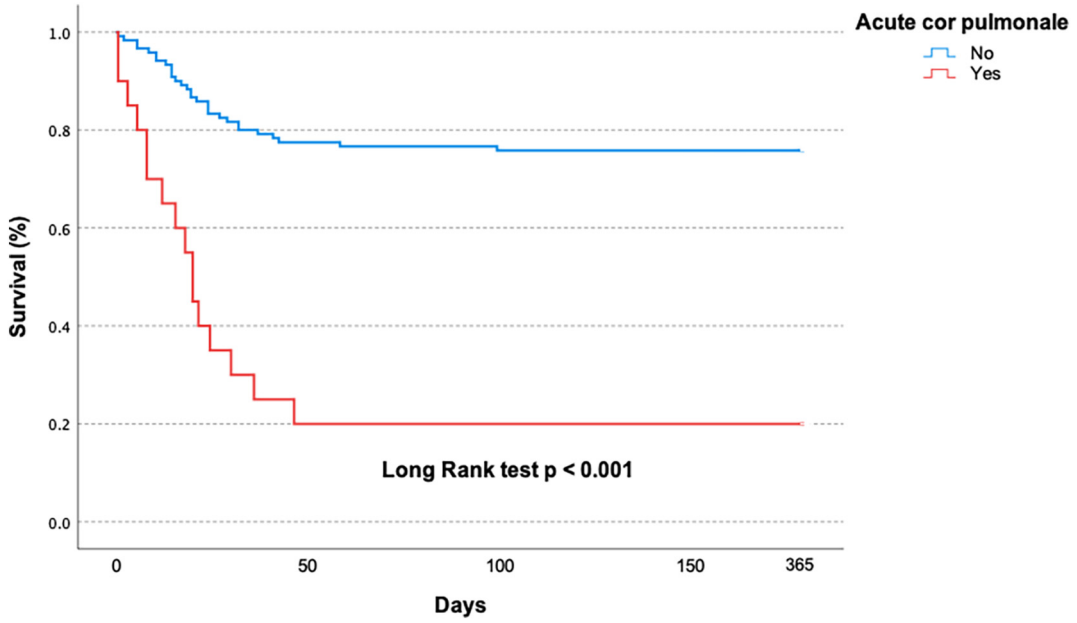

Fig. 2. Kaplan Meier 1-year survival analysis in patients with and without acute cor pulmonale

Chotalia et al. [15]. in a retrospective study of 172 patients with COVID-19 ARDS, found that 51% had RV systolic impairment where this condition by itself was not associated with mortality. We found that RV systolic function assessed by TAPSE was normal in both patients with normal and dilated RV whereas, in patients with ACP TAPSE was significantly impaired. We believe that this could reflect the fact that in the ACP patients all compensatory mechanisms had been exhausted. As in the study of Chotalia et al. [15] RV systolic impairment by itself was not associated with mortality.

COVID-19 predisposes patients to thromboembolic events. Studies in COVID-19 patients using CT pulmonary angiography have shown that up to 25% may develop PE [41]. Cavaleiro et al. [11] in 117 COVID-ARDS patients MV found a higher prevalence of ACP (38%) which was only independently associated with PE (16%). However, fifty-eight patients were excluded because they had no available CCE. Therefore, assuming these patients had no clinical indication (and thus likely no suspicion of ACP) we could speculate that the actual prevalence of ACP in this population was likely much lower (25%) and thus similar to previous reports [41]. Moreover, in patients with ACP despite the presence of moderate hypoxia (PaO2/FiO2 ratio129 [IQR 91–189]), respiratory system compliance was mildly decreased (37 [IQR 29–44]) while driving pressure remained protective (12 [IQR [10-14]) in the presence of an almost normal PaCO2. These findings suggest that ACP has a higher prevalence and is more frequently related to pulmonary embolism in COVID ARDS when compared to classic ARDS [11]. Likewise, in our study, patients with ACP also showed higher rate of PE (40%), and PE was independently associated with ACP. Nonetheless, parameters of respiratory system mechanics, respiratory acidosis and hemodynamic impairment also were associated with ACP. These differences compared to our findings could be explained by the fact that our patients were more severely ill and had more lung damage when compared to Cavaleiro et al. [11]. Furthermore, RS compliance ≤25 ml/cmH_2O was independently associated with the presence of ACP. We performed CT pulmonary angiography on 65% of the patients with RV dilatation without ACP where a CT angiogram was clinically indicated only four patients (18%) showed PE. All PE diagnosed in patients with ACP were segmental or subsegmental and none of these patients had a history of chronic RV dysfunction due to COPD or asthma. PE can precipitate the development of ACP due to a sudden increase in RV afterload secondary to pulmonary artery occlusion, and its effect depends on the thrombus size, the extent of occlusion and baseline cardiopulmonary status [42]. Furthermore, autopsy and detailed angiographic studies from patients with COVID-19 have shown a high presence of widespread microvascular thrombosis with occlusion of alveolar capillaries [43,44]. However, we do not know the real impact of microvascular thrombosis in the development of RV dilation or ACP in our patients.

We found a high prevalence of RV dilation, which is consistent with previous reports on COVID-19 ARDS. In a prospective study, Szekely et al. [6] found RV dilation in 39% of hospitalized COVID-19 patients, even though only 10 patients had ARDS requiring mechanical ventilation. In our study we observed no differences in respiratory system mechanics or lung function between patients with and without RV dilation. This may explain why we found the same prevalence of RV dilation as Szekely et al. [6] even though all our patients required MV. In addition, we showed that stroke volume, NE doses and tissue perfusion were similar in patients with and without RV dilation whereas these variables were significantly abnormal in patients with ACP. This reinforces the hypothesis that RV dilatation could be a functional adaptation to maintain cardiac output by the Frank-Starling mechanism and does not necessarily imply a worse prognosis.

The diagnosis of ACP during the first 24 h of mechanical ventilation was an independent predictor of ICU mortality even after adjustment for severity scores, respiratory system mechanical variables, PaCO2 and PaO_2/FiO_2 ratio. In the multivariate analysis ACP and poor oxygenation (PaO_2/FiO_2 ratio) were independent predictors of ICU mortality.

Recently, RV protective measures have been proposed in the management of ACP in patients with classic ARDS, such as protective ventilation strategies, prone position, and extracorporeal CO2 removal [39]. In our study, PaCO2 ≥ 48 mmHg, pH ≤ 7.30, RS compliance ≤25 ml/cmH_2O were associated with the presence of ACP. We were unable to demonstrate a possible protective effect of prone positioning on the RV as we did not supine the patients to repeat the CCE. However, we found no difference in the proportion of right ventricular dysfunction between patients in prone and supine position. Nevertheless, this underscores the relevance of timely CCE for detection of ACP, and application of protective measures when indicated.

The prevalence of LV systolic dysfunction in the present study was low and similar to previous studies in hospitalized COVID-19 patients [6-10]. Most of our patients had a normal or hyperkinetic LV function,

requiring only a low dose of norepinephrine due to sedation. Most patients had negative fluid responsiveness predictors with perfusion markers being normal in most cases. The patients with LV dysfunction did not show LV dilation while the estimated LV filling pressure was normal. This suggests an acute secondary injury as also indicated by the significantly higher Troponin levels in our patients a finding also reported by others [1-3]. We cannot report on wall motion abnormalities as these were not recorded in the study. These findings were similar to the data from Huang et al. [16] study although the prevalence of LV dysfunction in their cohort was higher. This could be related, as discussed earlier, to the retrospective nature of that study.

The present study has several limitations. First, CT pulmonary angiography was only performed on patients with clinical suspicion of PE that included all patients with ACP. Thus, we do not know the true prevalence of PE and its impact on RV in the whole study population. Second, systolic pulmonary artery pressure could not be estimated in every patient without ACP. Third, CCE examinations were performed in the prone position in 46% of our patients, thus ACP could be underestimated. However, our findings reflect a real scenario of critically ill patients on mechanical ventilation. In addition, this was a prospective cohort study in all patients with 1-year follow-up. CCE was performed regardless of the clinical judgment of the attending team and so true prevalence in this population could be assessed. The study was performed in 4 centers, including public and private hospitals, reflecting a heterogeneous population. Finally, to our knowledge this is the largest prospective study in critically ill COVID-19 ARDS patients requiring mechanical ventilation.

5. Conclusions

Right ventricular dilation is highly prevalent in mechanically ventilated patients with COVID-19 ARDS. Acute cor pulmonale was associated with reduced pulmonary function and, in only 40% of patients, with co-existing pulmonary embolism. Acute cor pulmonale is an independent risk factor for ICU mortality.

Authors' contributions

DV and PM designed and led the study. DV, PM, RP, NM, EP, DU, FM, DE, CA, JM, AG, MR, JR and JA participated in the recruitment of patients. DV, PM, JA, GH, AB, MS and JB contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154166.

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