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Association of Ventilatory Ratio with Acute Cor Pulmonale and Mortality in COVID-19 ARDS: A Cohort Study

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Abstract

Purpose: An elevated ventilatory ratio (VR) and acute cor pulmonale (ACP) are associated with mortality in ARDS patients. The primary aim of this study was to assess the association between VR and ACP in patients with COVID-19-related ARDS (C-ARDS). The secondary objectives were to analyze the association between VR and ICU mortality, describe VR temporal behavior in survivors and non-survivors, and evaluate the association between VR and pulmonary embolism.

Materials and Methods: We studied a cohort of patients with C-ARDS. The VR was calculated using a validated formula. Echocardiography was used to diagnose ACP, and CT pulmonary angiography was performed to identify PE. To evaluate the associations between VR and ACP, mortality, and PE, a generalized logistic regression model was used.

Results: Of the 140 subjects, 60 (43%) had a VR < 2, while 80 (57%) had a VR ≥ 2. Patients with a VR ≥2 had a higher risk of developing ACP than those with a VR <2 (Odds Ratio (OR), 3.77; 95% CI: 1.30 - 8.72). The ICU mortality rate was 29%. Of the 40 patients who died, 30 (75%) had a VR ≥ 2. Mortality was significantly associated with VR ≥ 2 and driving pressure ≥ 15 cm H_2O. In non-survivor patients with a VR < 2 at ICU admission, a significant increase in VR was observed over the 7-day observation period. No significant association was observed between PE and VR ($p = .118$).

Conclusion: Elevated VR was associated with ACP in patients with C-ARDS. VR ≥ 2 combined with driving pressure ≥ 15 cm H_2O significantly improved the ability to identify patients at risk for ACP. Additionally, at ICU admission, elevated VR values and initially low values that increased over the first week were associated with higher ICU mortality.

Keywords

Acute Cor Pulmonale, Acute Respiratory Distress Syndrome, Ventilatory Ratio, COVID-19-associated ARDS

Background

Acute respiratory distress syndrome (ARDS) accounts for 10% of intensive care unit admissions, with mortality rates varying from 30% to 40% depending on severity.[1] A frequent complication among these patients is the development of acute cor pulmonale, which affects approximately 20% of patients[2,3] and increases the mortality rate of ARDS patients. Thus, the early diagnosis of acute cor pulmonale (ACP) is essential for implementing strategies to reduce stress on the right ventricle. Such strategies include the prone position, decreasing driving pressure, and lowering PEEP levels.[4] However, ACP diagnosis requires echocardiographic evaluation.

Several variables have been identified as contributors to ACP development. These include a partial pressure of

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carbon dioxide (Pa_{CO2}) exceeding 50 mm Hg,[5,6] a driving pressure (DP) above 18 cmH_2O, low respiratory system compliance (C_{RS}), and a ratio of partial pressure of oxygen in arterial blood (Pa_{O2}) to the fraction of inspiratory oxygen concentration (Fi_{O2}) (Pa_{O2}/Fi_{O2}) below 150 mm Hg.[6] Likewise, specific populations with ARDS, such as COVID-19-related ARDS (C-ARDS), exhibit significantly impaired pulmonary perfusion, which is likely caused by angiopathy and thrombosis.[7]

The ventilatory ratio (VR) is directly or indirectly associated with most variables that predict ACP.[8] As a result, higher VR values can enhance the ability to predict ACP compared with considering each variable individually in subjects with acute respiratory failure. Furthermore, elevated VR values have been linked to mortality in patients with classic ARDS; however, their behavior over time in those who develop these outcomes remains unclear.

Based on these observations, we hypothesized that elevated VR in patients with C-ARDS is associated with ACP and high mortality.

The primary aim of this study was to investigate the association between VR and ACP. The secondary objectives were to evaluate the temporal behavior of VR over time in survivors and non-survivors, to assess the association between VR and pulmonary embolism, and to explore the predictive capacity of VR for ACP.

Patients and Methods

This multicenter longitudinal cohort study was based on a previously published study[2] that included patients diagnosed with COVID-19. Patients were admitted to the ICUs of four university hospitals in Chile between April and July 2020. The original protocol was approved by the local ethics committee of each center, which waived the need for written informed consent (protocol ID: 200422002). The procedures were conducted in accordance with the ethical standards of the Institutional Committee on Human Experimentation and the Helsinki Declaration of 1975.

Inclusion Criteria

- Patients with COVID-19-related ARDS (C-ARDS), according the Berlin definition
- Mechanical ventilation less than 24 h
- Aged older than 18 years
- Deep sedation, RASS −5

Exclusion Criteria

- Inadequate echocardiographic acoustic window
- Severe valvular heart disease
- Patients with end-of-life care
- Requirement for extracorporeal membrane oxygenation

This study included three time points for the data collection. Time I, corresponded to the first 24 h of mechanical ventilation, while Time II and Time III were on the third and seventh days, respectively. Respiratory mechanics and arterial blood gas levels were recorded at times I, II, and III. Echocardiography was performed within the first 24 h of mechanical ventilation (Time I).

Mechanical Ventilation

The respiratory signals of pressure, volume, flow, and RR were acquired directly from the ventilator. The driving pressure was determined as the plateau pressure at the end of the inspiration cycle minus the total PEEP ($PEEP_{TOT}$ = external PEEP + intrinsic PEEP), and C_{RS} was calculated as V_T/driving pressure. Minute ventilation ($\dot{V}E$) was calculated using the following formula: $V_T \times$ respiratory rate. $\dot{V}E$ was normalized to the predicted body weight (PBW).

Ventilatory Ratio (VR)

The VR was calculated using the following formula:

$$(\dot{V}E\ (\text{mL min}^{-1}) \times Pa_{CO2}\ (\text{mm Hg}))/(PBW \times 100 \times 37.5).$$[8]

$\dot{V}E$ is the product of V_T and respiratory rate, Pa_{CO2} is the partial pressure of CO_2 obtained from arterial blood samples, PBW corresponds to the predicted body weight, and 37.5 mm Hg is the ideal Pa_{CO2}. The minute ventilation of 100 mL min^{-1} kg^{-1} used in this formula was extracted from population nomograms derived from anesthetic practices to calculate the predicted value.[9] Given the narrow range of Pa_{CO2} values in healthy individuals, a value close to the mean was selected to represent the predicted Pa_{CO2}. Likewise, subjects were categorized as having "low VR" if their VR was below two and "high VR" if they were ≥ 2.[10]

Echocardiography

Transthoracic echocardiography (TTE) was performed in all subjects within the first 24 h of mechanical ventilation. In all cases, TTE was performed immediately after obtaining an arterial blood gas sample to assess Pa_{CO2} and Pa_{O2} levels. TTE examinations were performed by experienced, board-certified operators. Three clinical ultrasound devices were used for image acquisition (GE Medical Systems, Milwaukee, WI, USA; Philips CX 50; Philips Healthcare, DA Best, The Netherlands; and Mindray M9 Bio-Medical Electronics Co., Shenzhen, China). TTE evaluation was performed according to a predefined protocol following international recommendations,[11] which included an assessment of the left and right ventricular end-diastolic areas (LVEDA and RVEDA, respectively) using an apical 4-chamber view. RVEDA/LVEDA ratios were calculated from these measurements. Our study defined ACP as right ventricular dilation, characterized by an RVEDA/LVEDA ratio greater than 0.6, accompanied by paradoxical septum motion. Right ventricular systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE).[11,12]

Arterial Blood Gases

Arterial blood gases were measured with simultaneous recording of mechanical ventilation parameters. At all centers, Pa_{CO2} and partial pressure of arterial oxygen (Pa_{O2}) were analyzed using arterial blood samples (GEM® PREMIER™ 4000; Instrumentation Laboratory, Lexington, USA).

Computed Tomography (CT) Pulmonary Angiography

CT pulmonary angiography was performed within 24 h of being connected to mechanical ventilation according to the clinical suspicion of pulmonary embolism.

Endpoints

- Primary Endpoint

To assess the association of VR with ACP

- Secondary endpoints

To analyze the association between VR and ICU mortality.
To describe VR behaviors over time in survivors and non-survivors.

To analyze the association between VR and pulmonary embolism.

Statistical Analysis

The Kolmogorov–Smirnov test was used to evaluate data normality. Continuous variables are presented as mean ± standard deviation or median and interquartile range. Univariate analysis was performed to identify the associations with ACP. To examine the association between VR and ACP, binomial logistic regression was employed using a generalized linear model (GLM) approach. Additional covariates were included in the logistic regression model to assess independent effects of the primary variable of interest.[5] In addition, a logistic regression model was used to predict the likelihood of ACP. Continuous variables were expressed as mean ± standard deviation (SD). VR was assessed in each patient at multiple time points over a 7-day period in the overall population as well as in survivors and non-survivors. Independent sample t-tests were used to compare VR between survivors and non-survivors. Additionally, repeated-measures ANOVA was performed to analyze the VR changes over time within each group (survivors and non-survivors). Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive power of clinical variables for diagnosing ACP. This analysis included calculation of the area under the curve (AUC), which provided a measure of the overall accuracy of the diagnostic test. The Youden's index was used to determine the most effective diagnostic threshold. Additionally, the VR threshold for predicting ACP was examined. For categorical variables, the chi-squared test was used. Kaplan-Meier curve analysis was used to compare survival between patients with VR < 2 and those with VR ≥ 2 plus ACP. Statistical significance was set at $p < .05$. All analyses were performed using the R for Statistical Computing 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 175 patients with C-ARDS were screened, and 140 who met the inclusion criteria within the first day of being connected to mechanical ventilation were included in the study (Table 1). Thirteen patients were excluded because of the inability to perform transthoracic echocardiography within the first 24 h of admission, an additional 22 patients were excluded due to inadequate echocardiographic image quality (n = 16), receiving end-of-life care (n = 4), and severe aortic regurgitation (n = 2). A total of 140 patients were included; 80 (57%) patients exhibited a VR ≥2, and 60 (43%) patients had a VR < 2 on day one of mechanical ventilation. The ICU mortality rate in this cohort was 29% (n = 40). Among patients with a VR ≥2, the ICU mortality rate was 37.5% (30/80), whereas in those with a VR <2 was 16.7% (10/60) ($p = .012$). The mechanical ventilation settings closely adhered to lung-protective ventilation strategies. The baseline patient characteristics are shown in Table 1.

Association of VR with ACP

Twenty patients (14%) presented with ACP within the first 24 h of being connected to mechanical ventilation. Patients with a VR ≥2 had a higher risk of developing ACP than those with a VR < 2 (Odds Ratio (OR), 3.77; 95% CI: 1.30 - 8.72; $p = 0.017$). The optimal cutoff point of VR for predicting ACP was 2, with a 13% probability of ACP. As VR increased progressively, the probability of ACP increased logarithmically, as shown in Figure 1. When VR was ≥ 2 and driving pressure was ≥ 15 cm H_2O, the ACP probability was 29%. The ACP probability increased logarithmically with increasing DP; at a DP of 16 cm H_2O, the ACP probability increased to 41%, and at a DP of 18 cm H_2O, it increased to approximately 60%, as shown in Figure 1C-D.

Table 2 presents the results of the univariate analysis of dichotomous variables and ACP. Additionally, the table includes a multivariate logistic regression model of VR ≥ 2 adjusted for both continuous and dichotomous variables that have recognized associations with ACP.[3,6] Table 3 presents the area under the curve (AUC) analysis assessing the ability of ventilatory and cardiac variables to discriminate ACP.

Additionally, patients with a $Pa_{CO2} \geq 50$ mm Hg had a higher risk of developing ACP than those with a $Pa_{CO2} < 50$ mm Hg (Odds Ratio, 4.38; 95% CI: 1.50 - 13.95; $p = .002$). The

Table 1. The Baseline Characteristics of all the Patients and Those with VR < 2 and VR ≥ 2.

	All patients (n = 140)	VR < 2 (n = 60)	VR ≥ 2 (n = 80)
Age (years)	57 ± 11	56 ± 13	58 ± 10
Male / Female gender (%)	71 / 29	73 /27	70 / 30
APACHE II	14 [10–18]	14 [10–17]	13 [10–19]
Mechanical ventilation			
Tidal volume (mL)	380 [350–420]	400 [360–420]	380 [340–420]
Tidal volume (mL/kg/PBW)	6.0 [5.5–6.5]	6.1 [5.4–6.7]	6.0 [5.3–6.5]
Respiratory rate (bpm)	26 [24–30]	26 [22–28]	28 [26–30]
Minute ventilation (mL min^{-1} Kg^{-1})	157 [143–175]	149 [138–164]	164[152–179]*
PEEP (cm H_2O)	10 [10–1 2]	10 [8–12]	10 [9–12]
Plateau pressure (cm H_2O)	22 [20–24]	22 [20–24]	22 [20–25]
C_{RS} (mL cm H_2O^{-1})	33 [26–40]	35 [29–41]	31 [24–38]
Driving pressure (cm H_2O)	11 [10–13]	9 [8–11]	12 [10–14] *
Arterial blood gases			
P_{aO2}/F_{IO2} ratio (mm Hg)	155 [107–177]	177 [144–207]	142 [115–189]*
P_{aCO2} (mm Hg)	42 [39–55]	39 [34–42]	51 [40–60]*
Echocardiography			
ACP (n/total), (%)	20/140 (14%)	5/60 (8%)	15/80 (19%)*
RVEDA/LVEDA ratio	0.6 [0.5–0.7]	0.57 [0.5–0.68]	0.61 [0.46–0.78]
TAPSE, mm	20 [18–23]	22 [19–24]	19 [16–22]

Continuous data are expressed as medians [25th–75th percentiles]. Categorical variables were expressed as numbers. *Significant differences between groups (P < 0.05). APACHE II = Acute Physiology and Chronic Health Evaluation; ICU = Intensive Care Unit; PEEP = Positive end-expiratory pressure; CRS = Compliance of respiratory system; ACP = Acute Cor Pulmonale; RVEDA/LVEDA = Left and Right ventricular end-diastolic area; TAPSE = tricuspid annular plane systolic excursion.

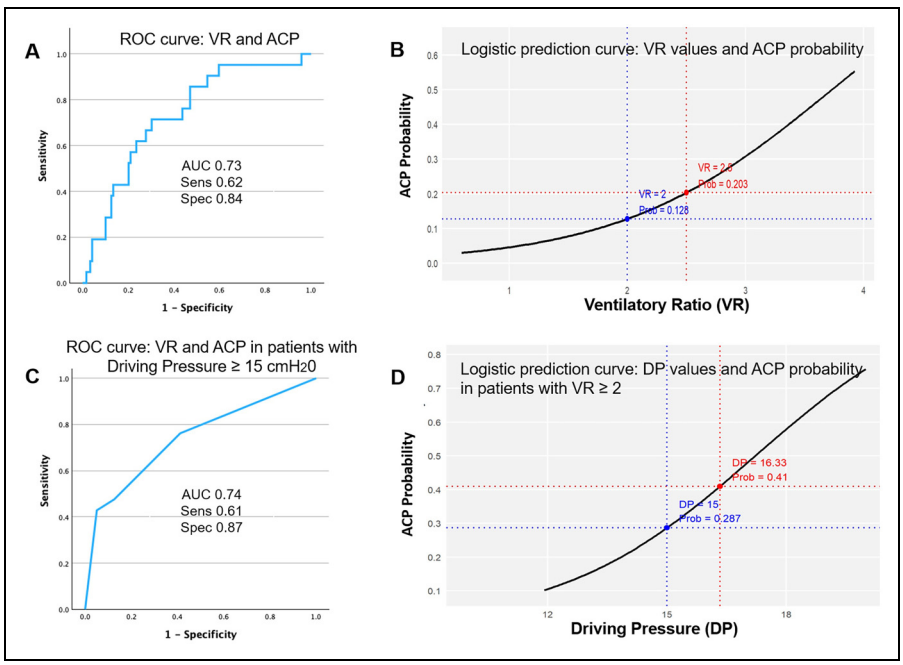


Figure 1. Receiver Operating Characteristic Curves and Scatter Plots. the Ability of VR Alone and VR Together with Driving Pressure to Discriminate ACP and Identify the Cutoff Point for the Probability of ACP Occurrence. Legend: A: ROC Curve of the Ventilatory Ratio to Predict ACP. B: Logistic Prediction Curve of VR for Predicting ACP and Assessment of Different VR Cutoff Values. C: ROC VR ≥2 and Driving Pressure ≥ 15 cmH2O. D: Logistic Prediction Curve for VR ≥ 2 and Driving Pressure for ACP, and Different Driving Pressure cut-off Values.

optimal cutoff point of Pa_{CO2} for predicting ACP was 50.5 mm Hg with 15% ACP probability (e-Figure 4a).

When Pa_{CO2} was ≥ 50 and the driving pressure was ≥ 15 cm H_2O, the ACP probability was 22%. This probability increased linearly with increasing DP (e-Figure 4b).

Association of VR with ICU Mortality

In this cohort of 140 C-ARDS patients, the ICU mortality rate was 29%. Of the 40 patients who died, 30 (75%) had a VR ≥ 2 and 10 (25%) had a VR < 2 (p = .012). Mortality was

Table 2. Analysis of the Association Between Study Variables and Acute cor Pulmonale.

Univariate analysis	Odds ratio (CI 95%)	*P*- value
VR ≥ 2	3.77 (1.30-8.72)	0.017
P_{aCO2} > 6.6 KPa (> 50 mm Hg)	4.38 (1.50-13.95)	0.002
Minute ventilation ($\dot{V}E$) ≥ 200 mL min^{-1} Kg^{-1}	2.29 (0.35-6.77)	0.215
Driving pressure ≥ 15 cm H_20	6.18 (2.08-12.07)	< 0.001
P_{aO2}/F_{IO2} < 20 KPa (< 150 mm Hg)	5.01 (1.61-18.73)	< 0.001
C_{RS} < 30 mL cm H_2O^{-1}	2.87 (1.01-8.71)	0.030
TAPSE < 17 mm	11.50 (3.69-28.51)	< 0.001
Pulmonary embolism	3.27 (1.08-9.87)	0.035
VR ≥ 2 Multivariable Logistic Regression Analysis	Odds ratio (CI 95%)	*P*- value
VR ≥ 2	3.66 (1.29-11.39)	0.001
Driving pressure	1.37 (1.14-1.69)	0.002
VR ≥ 2	3.49 (1.26-9.78)	0.016
C_{RS}	0.93 (0.87-0.99)	0.030
VR ≥ 2	3.54 (1.21-11.33)	0.025
TAPSE	0.77 (0.67-0.88)	0.001
VR ≥ 2 Adjusted to dichotomies variables	Odds ratio (CI 95%)	*P*- value
VR ≥ 2	4.02 (1.44-12.40)	0.010
Driving pressure ≥ 15 cm H_20	5.05 (1.74-14.71)	0.002
VR ≥ 2	3.66 (1.31-11.29)	0.016
C_{RS} < 30 mL cm H_2O^{-1}	2.19 (0.80-6.26)	0.131
VR ≥ 2	4.20 (1.48-13.17)	0.009
TAPSE < 17 mm	6.48 (2.17-19.76)	0.001
VR ≥ 2	3.28 (1.09-9.88)	0.035
Pulmonary embolism	2.70 (0.85-8.53)	0.089

Legend: VR, ventilatory ratio; PaCO2: Partial pressure of carbon dioxide; PaO2/FIO2: Ratio of partial pressure of oxygen in arterial blood (PaO2) to the fraction of inspiratory oxygen concentration (FIO2); CRS, compliance of the respiratory system; TAPSE, tricuspid annular plane systolic excursion. The results were expressed as odds ratios. Statistical significance was set at p < .05.

significantly higher in patients with a VR ≥ 2, with an OR of 3.00 (95% CI: 1.33-6.78, p = .008). Patients were monitored over a 7-day period (eTable 1-2) (Figure 2A). In patients who did not survive and initially presented with VR ≥ 2, these values remained stable over the 7-day observation period (p = .572) (Figure 2A). In patients who did not survive and initially presented with a VR < 2, a significant increase in VR was observed over the 7-day observation period (p = .037). Between Time I and Time II, the VR increased by 0.28 units (+17.73%). This was followed by an additional increase of 0.22 units (+11.58%) between Time II and Time III. When comparing Time I to Time III, the cumulative increase in VR reached 0.51 units (+31.7%), as showed in Figure 2B.

Among the patients who survived, those who initially presented with a VR ≥ 2 exhibited a significant reduction in VR during the first week, −0.44 units (−17%) and −0.30 units (−10%) at Time II and Time III compared to Time I, respectively (p = .034). In contrast, patients who initially presented with VR < 2 at Time I showed no significant change in VR during the first week (p = .067) (Figure 2C).

The VR value used to construct the survival curves corresponded to the measurements obtained during the first 24 h of mechanical ventilation. The 180-day global mortality rate was 32% (n = 45). The survival probability of patients with a VR ≥ 2 was notably lower than that of patients with a VR < 2, at a follow-up period of 180 days. The chances of survival were significantly lower for patients with a VR ≥ 2 and ACP than for those who had a VR < 2 and did not have ACP (Figure 3A–3B). The overall clinical outcomes based on ventilatory ratios of ≥2 and <2 are shown in eTable 3. Non-survivors exhibited significantly higher driving pressures, respiratory rates, and $PaCO_2$ levels, along with a lower PaO_2/FiO_2 ratio and a trend toward reduced respiratory compliance at ICU admission (e-Table 4).

Association Between VR and Pulmonary Embolism (PE)

In 86 patients, CT angiography was performed within the first 24 h of ICU admission. PE was diagnosed in 19 (22%) patients: 12 with VR ≥ 2 and seven with VR < 2; no significant association was observed between PE and VR (p = .118). However, PE was associated with ACP (p = .035). Additionally, VR ≥ 2 was independently associated with ACP after adjusting for PE (Table 2).

Discussion

In mechanically ventilated patients with COVID-19-related ARDS, an elevated ventilatory ratio (VR ≥2) within the first 24 h was independently associated with the development of

Table 3. Area Under the Curve (AUC) Analysis to Evaluate the Capacity of Ventilatory and Cardiac Variables to Discriminate ACP.

AUC analysis (continuous variables)	AUC (Std. error)	95% Confidence Interval	
VR	0.73 (0.67– 0.79)	0.62	0.84
P_{aCO2}	0.71 (0.65-0.77)	0.59	0.82
Driving pressure	0.74 (0.68-0.80)	0.62	0.86
P_{aO2}/F_{IO2}	0.69 (0.63-0.75)	0.57	0.81
C_{RS}	0.71 (0.64-0.78)	0.57	0.84
TAPSE	0.79 (0.74-0.84)	0.57	0.89
AUC analysis (categorical variables)	AUC (Std. error)	95% Confidence Interval	
VR ≥ 2	0.68 (0.61-0.74)	0.55	0.81
P_{aCO2} ≥ 50 mm Hg	0.67 (0.60-0.74)	0.54	0.80
Driving pressure ≥ 15 cm H_2O	0.67 (0.59-0.74)	0.53	0.81
C_{RS} < 30 mL cm H_2O^{-1}	0.63 (0.56-0.70)	0.50	0.78
Pulmonary embolism	0.64 (0.57-0.71)	0.50	0.79
Combined analysis (AUC)	AUC (Std. error)	95% Confidence Interval	
VR ≥ 2 + Driving pressure ≥ 15 cm H_20	0.74 (0.68-0.81)	0.61	0.87
P_{aCO2} ≥ 50 mm Hg + Driving pressure ≥ 15 cm H_20	0.73 (0.66-0.80)	0.60	0.86
VR + Driving pressure	0.79 (0.73-0.84)	0.68	0.89
P_{aCO2} + Driving pressure	0.77 (0.71-0.83)	0.65	0.88

VR: Ventilatory ratio; P_{aCO2}: Partial pressure of carbon dioxide; P_{aO2}/F_{IO2}: The ratio of partial pressure of oxygen in arterial blood (P_{aO2}) to the fraction of inspiratory oxygen concentration (F_{IO2}); C_{RS}: compliance of the respiratory system; TAPSE: tricuspid annular plane systolic excursión; AUC: area under the curve; Sens: sensitivity.

acute cor pulmonale (ACP) and increased ICU mortality. Furthermore, combining VR with driving pressure (≥15 cmH_2O) significantly improved the ability to predict ACP. Importantly, the worsening trajectories of VR during the first week also identified patients with a higher risk of death, even if their initial values were normal.

Our study revealed that 57% of the patients had a VR ≥ 2. This prevalence is comparable to the 49% reported in patients with classic ARDS.[10] In our cohort, however, 75% of ICU deaths occurred in patients with VR ≥2, in contrast to the 60% reported by Sinha et al[8] among deceased patients. This discrepancy in mortality may reflect differences in the populations studied; while our cohort included only patients with COVID-19-related ARDS, Sinha et al evaluated heterogeneous ARDS etiologies. Importantly, our findings revealed a marked increase in mortality among patients with both VR ≥2 and ACP, highlighting the critical impact of ARDS etiology and the hemodynamic consequences of mechanical ventilation on right ventricular function in severe respiratory failure.

Our investigation revealed an ACP prevalence of 14% among patients with C-ARDS, which is notably lower than the 36% reported by Beyls *et al*[13%] and 38% by Cavaleiro *et al*.[13] However, it surpasses the rates identified in the research conducted by McCall *et al* and Jozwiak et al, who reported ACP prevalence rates of 6% and 2%, respectively.[14,15] Although the cause of ACP in patients with ARDS is not completely clear, it is associated with multiple factors, including ventilator settings. Interestingly, in the era of protective ventilation, the prevalence of ACP has significantly decreased compared to the period before this practice was adopted, when the prevalence reached 60% of patients.[16] Despite this reduction, it is essential to emphasize that ACP continues to be a frequent issue in patients with ARDS.

In a multivariable analysis conducted by Metkonso *et al*, three predictors of ACP in patients with classic ARDS were identified: driving pressure ≥18 cmH_2O, P_{aO2}/F_{IO2} ratio <150 mm Hg, and Pa_{CO2} ≥ 48 mm Hg.[6] Our results align with the findings of the present study, demonstrating consistency across boards. We also observed an association between elevated Pa_{CO2} and ACP development. The association between these factors and ACP onset has been elucidated through multiple pathophysiological pathways. Elevated Pa_{CO2} levels lead to pulmonary vasoconstriction,[17] increasing the afterload on the right ventricle, potentially leading to its failure.[18,19]

It is important to consider that Pa_{CO2} is one of the most critical variables in the VR formula, and has been included as a substitute for alveolar CO_2 pressure ($PACO_2$) to calculate ventilatory efficiency. However, by integrating Pa_{CO2} into its formula, VR provides only a global estimate of ventilation-perfusion mismatch and does not distinguish the underlying mechanisms contributing to impaired gas exchange, such as increased venous admixture or physiological dead space.[20,21] Therefore, it does not provide a detailed differentiation of the specific mechanisms that affect gas exchange, and does not entirely clarify whether its increase is due to ventilatory inefficiency.[10] Furthermore, minute ventilation ($\dot{V}E$), another component of VR, depends on tidal volume and respiratory rate, both of which influence driving pressure and, by extension, lung stress and strain.[22,23] In this study, the association between VR and ACP persisted even after adjusting for elevated driving pressure and low respiratory system compliance.

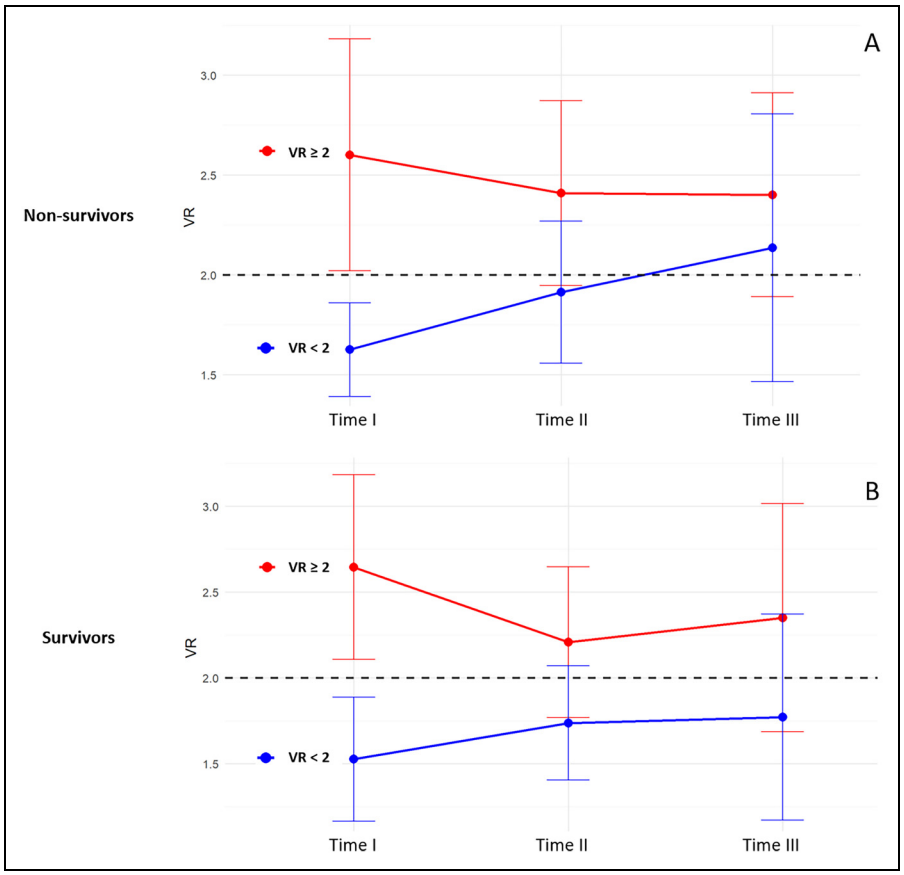


Figure 2. VR behavior during seven days of evaluation in survivors and non-survivors. Legend: A: VR change in non-survivors; B: VR change in survivors. The black dashed line represents the VR ≥2 cutoff point. Time I was the first 24 h after patients were included in the study. Time II was registered at third day. Time III was registered at seventh day.

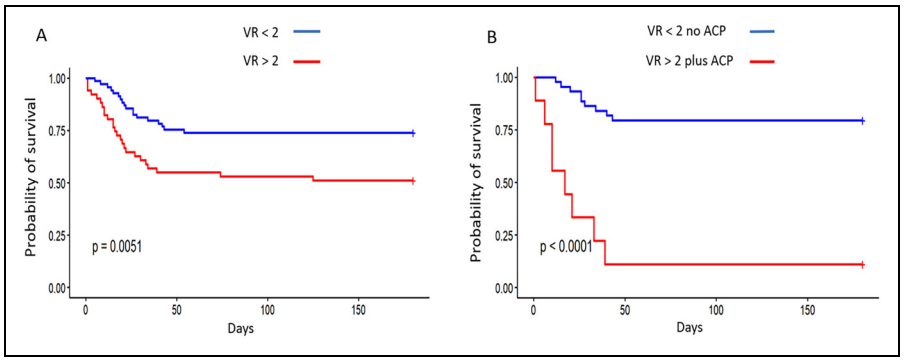


Figure 3. Probability of Survival 180 Days After C-ARDS in Patients with VR ≥2 and ACP. Legend: 3A: Kaplan-Meier 180 Days Survival Analysis of Patients with and Without VR ≥2. 3B: Kaplan-Meier Survival Analysis at 180 Days in Patients with and Without VR ≥2 Plus ACP.

Clinically, relying solely on $PaCO_2$ may overlook patients who maintain normocapnia at the expense of excessive ventilatory effort, whereas VR can uncover latent inefficiency that contributes to increased right ventricular afterload. This distinction underscores the value of VR as a robust and dynamic predictor of ACP in severe lung compromise in patients with C-ARDS.

Our study identified a ventilatory ratio (VR) threshold of 2 as the optimal cut-off for predicting acute cor pulmonale (ACP), corresponding to an ACP probability of 13%, which likely reflects the low prevalence of ACP in the cohort.[24] Notably, the probability of ACP increased exponentially as the VR values rose above this threshold, suggesting a nonlinear relationship between ventilatory inefficiency and right ventricular dysfunction. Importantly, the predictive power of VR was significantly enhanced when combined with elevated driving pressure (DP). While a VR ≥2 alone was associated with modest predictive accuracy, the ACP probability increased to 29% when DP was also ≥15 cmH_2O. This interaction between VR

and DP suggests a synergistic effect in augmenting right ventricular afterload. The logarithmic increase in ACP probability observed with increasing DP values reaching 41% at 16 cmH_2O and approximately 60% at 18 cmH_2O highlights the pivotal role of mechanical stress in the pathogenesis of ACP.[25]

Another mechanism that may contribute to the increased dead space and RV afterload is pulmonary thromboembolism (PE). In our cohort, PE was associated with ACP in the univariate analysis; however, this association was no longer significant in the multivariate models after adjusting for VR ≥ 2. This suggests that VR may act as integrative markers that capture the cumulative burden of pulmonary vascular dysfunction that affects the right ventricle.

Finally, an elevated VR > 2 has been associated with the need for mechanical ventilation,[26] and its increase by day 3 is linked to higher mortality in COVID-19 patients admitted to the ICU.[27] Furthermore, each unit increase in VR was associated with a 5% increase in the ICU mortality risk.[26] Although VR ≥ 2 was independently associated with ACP and mortality, temporal evolution may offer superior prognostic insight. Among non-survivors with initially normal VR values, progressive increases over seven days were observed, indicating worsening gas exchange and potentially delayed pathophysiological decompensation. In contrast, survivors with elevated baseline values showed a more favorable decline. These trends suggest that serial VR monitoring may outperform static measurements in anticipation of clinical deterioration. This observation opens the door to potential interventional strategies, modulation of ventilatory efficiency through protective ventilation strategies, early proning, improved RV coupling, and mitigation of progression to ACP. Whether these changes can alter outcomes remains an open question that warrants prospective evaluation.

Limitations

This study has several limitations that should be highlighted. Although significant differences were identified in the main outcomes of this study, the wide variability in the confidence intervals indicates the need to increase the sample size to improve the precision of these findings and mitigate the impact of potential random errors that could have affected the results. Second, our study included only COVID-19 patients, which limits the generalizability of the data to other ARDS etiologies. Finally, owing to the nature of the study design, it was impossible to determine whether VR preceded ACP in the first 24 h.

Conclusions

In patients with COVID-19 related ARDS, an elevated ventilatory ratio (VR ≥ 2) within the first 24 h of mechanical ventilation was independently associated with the development of acute cor pulmonale. The predictive value of VR was notably enhanced when combined with elevated driving pressure, underscoring the interaction between ventilatory inefficiency and mechanical stress on the right ventricle. Furthermore, both elevated and rising VR values during the first week were associated with increased ICU mortality, even in patients with initially normal values.

Abbreviations

VR	Ventilatory ratio
ACP	Acute cor pulmonale
ARDS	Acute respiratory distress syndrome
C-ARDS	COVID-19-associated ARDS
ICU	Intensive care unit
PBW	predicted body weight
P_{aCO2}	Partial arterial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
RV	Right ventricular
RVEDA	Right ventricular end-diastolic area
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography

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Authors' Contributions

MB, RB, and EDV: conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, data curation, interpretation of data, validation, writing - original draft, and writing - review and editing.

RP, JM, EP, DU, FM, DE, CA, EK, and GB: data interpretation, investigation, supervision, resources, validation, writing, review, and editing.

RB: Statistical analysis

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Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no conflicts of interest.

Declaration of Conflicting Interests

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Data Statement

The data underlying this article will be shared upon reasonable request by the corresponding author.

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Supplemental Material

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