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Ventilatory Ratio at very high altitude in ARDS: A single-center longitudinal study

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Abstract

Background
Acute Respiratory Distress Syndrome (ARDS) is characterized by shunt-related hypoxemia and increased dead space (VD). Physiologic dead space reflects the severity of lung injury and is a prognostic factor in ARDS. The Ventilatory Ratio (VR) has emerged as an alternative measure of ventilatory efficiency, being a surrogate for dead space that is easily obtained at the patient's bedside.
Methods
Longitudinal, retrospective, cohort study. It was carried out at the Intensive Care Unit (ICU), El Alto Sur Hospital (4150 meters above sea level (m.a.s.l.), in 2021. The main objective was to determine the cut-off point on admission and fifth day of VR. The secondary outcomes were to establish mechanical ventilation and oxygenation parameters, VR on admission and fifth day stratified by survival, to evaluate the prognostic value of VR and associated factors for 90-day mortality.
Results
The area under the curve (AUC) was 0.7223 (95% CI: 0.6272 - 0.8174) among the surviving patients. The cut-off point at admission was 1.495, obtaining the best AUC of VR 2.06, on day 5. For patients with VR ≤2, the median survival was 25 days and a survival rate of 49% and VR > 2, the median survival was 18 days and a survival rate of 36.2%. Patients with VR > 2 on day 5 had a significantly lower 90-day survival compared to patients with VR ≤ 2 HR 1.52 (95% CI: 1.01-2.30; P = 0.043). VR and age were independent risk factors for mortality.
Conclusion
The value of ventilatory ratio stands out as a practical prognostic marker of ARDS at very high altitude, a value greater than 2 on day 5 and age were independently associated with higher mortality.

Keywords: Dead space, Ventilatory ratio, ARDS, Very high altitude.

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Introduction

Acute Respiratory Distress Syndrome (ARDS) is characterized by shunt-related hypoxemia and increased dead space (VD), the portion of tidal volume that does not contribute to gas exchange. Physiological dead space is a prognostic factor in ARDS. [1,2] It is calculated using the dead space fraction, which is the ratio of dead space to tidal volume (VD/VT). Normally this ratio is 30% since there is a physiological dead space, represented by the anatomical dead space and the alveolar dead space. [3]

The increase in the VD/VT fraction calculated using the Bohr-Enghoff equation [4] is a marker of the severity of the alteration of gas exchange and an independent predictor of mortality in ARDS, since it reflects the result of the Ventilation/Perfusion of the alveolar units caused by shock, overdistension of the uninjured lung, compromise of the vascular bed through endothelial damage or thrombosis. [5,6] Its rarely used, since it requires the measurement of the mixture of exhaled carbon dioxide ($PeCO_2$) and the simultaneous sampling of arterial blood to determine the arterial pressure of CO_2 ($PaCO_2$).

To calculate the dead space fraction (VD/VT), it is necessary to have a volumetric capnograph, which will measure the exhaled carbon dioxide as a function of the tidal volume, allowing the estimation of the dead space and alveolar ventilation in a dynamic and noninvasive way. [7,8] However, volumetric capnography gained greater popularity in the monitoring of gas exchange, but its usefulness continues to be debated. Another point to take into account is that not all intensive care services in our low-income setting have a capnograph, let alone a volumetric capnography.

There are mathematical formulas that, without counting on the direct measurement of exhaled carbon dioxide, have been able to correlate with the VD/VT measured by volumetric capnography in ARDS. [9] One formula is the Ventilatory Ratio (VR), which has emerged as an alternative measure, that is, a surrogate for ventilatory efficiency, and has been proposed as an alternative to assess risk in patients with respiratory failure. [10] The VR is a substitute for dead space that is easily obtained at the subject's bedside with arterial blood gas analysis and assessment of minute volume during invasive mechanical ventilation. The ventilatory ratio (VR) is calculated as (Measured minute volume (ml/min) × Measured $PaCO_2$ mmHg / Predicted weight (kg) × 100 × 37.5mmHg), the minute volume is obtained by multiplying respiratory rate by tidal volumen. 37.5 mmHg is the ideal $PaCO_2$, that is, the expected arterial pressure of carbon dioxide in normal lungs. At very high altitude, the ideal $PaCO_2$ value is modified, considering 27.9 mmHg as the ideal, [11] therefore, in the present study, this modification is made to the original formula proposed. The altitude is categorized according to the masl (meters above sea level) in: 1) intermediate altitude, 1,500-2,500 masl (no effects are felt during exercise) 2) high altitude, 2,500-3,500 masl (effects are felt during exercise) 3) very high altitude, 3,500-5,800 masl (effects are felt even at rest), and 4) extremely high altitude, > 5,800 masl (lifelong life would seem impossible). [12,13] Our study was conducted in the city of El Alto, which is located at 4,150 masl (very high altitude).

High VR values early after intubation have been shown to be associated with mortality in a large clinical trial and in observational ARDS cohorts, [14] and in another study where VR in intubated subjects with COVID-19 was a strong predictor of mortality. [15]

This main objective of the study is to determine the ventilatory ratio cut-off point on admission and on the fifth day, making a modification to the formula described; where the ideal $PaCO_2$ 37.5 mmHg is replaced by 27.9 mmHg at high altitude, being the ideal $PaCO_2$. The decision to take variables at different times of VR was a decision of the researcher, in order to know their behavior in a little-studied altitude region.

The secondary objectives were to establish mechanical ventilation and oxygenation parameters, including the ventilatory ratio at admission and fifth day stratified by survival, to evaluate the prognostic value of VR and associated mortality factors at 90 days, in mechanically ventilated subjects with ARDS at very high altitude.

Material and Methods

Observational, longitudinal, single-center, retrospective cohort study, 190 subjects were included. It was carried out in the Intensive Care Unit (ICU), Hospital el Alto Sur (4150 m.a.s.l.), between January and December 2021. The inclusion criteria were subjects with a diagnosis of ARDS due to COVID-19 on Invasive Mechanical Ventilation (IMV), subjects over 18 years of age. Exclusion criterio: subjects who had an unconfirmed COVID-19 infection, subjects who did not have data at the beginning for VR calculation or if they were admitted to the ICU with a diagnosis other than ARDS. Training and follow-up of the data collectors has been used as a method to minimize bias.

This study was reviewed and approved by the institution's ethics committee. Written informed consent was waived due to the retrospective nature of the study, the exemption granted by the committee.

Data collection

Data were collected from the clinical records, which include demographic data and daily monitoring of invasive mechanical ventilation of the subjects in the ICU. The data

extracted were those recorded on admission and on day 5 of IMV. ARDS was diagnosed according to the Berlin criterio. [16] At the time of recording ventilatory parameters and taking arterial blood gas samples, the subjects were on invasive mechanical ventilation and without spontaneous efforts for the entire 5 days, with continuous infusion of sedatives and neuromuscular blockers.

The subjects were ventilated with lung protection parameters. In volume-controlled mode, with a tidal volume between 6 and 8 ml/kg of predicted body weight. The respiratory rate was set according to the pH target (not less than 7.20).

For all subjects the following clinical and demographic variables have been recorded: age, gender, Body Mass Index (BMI), comorbidities, arterial blood gas analysis on admission, the relationship between arterial oxygen pressure (PaO_2) and the fraction of inspired oxygen (FiO_2), (P:F), ventilatory parameters, Acute Physiology And Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA), prone position. VR was calculated as [minute ventilation (ml/min) × $PaCO_2$ (mm Hg)] / (predicted body weight (kg) × 100 × 27.9] and was collected on admission and on day 5, use of corticosteroids and antivirals, acute kidney injury on admission, ventilator-associated pneumonia (VAP). Likewise, outcome variables related to days of stay in the ICU, days of invasive mechanical ventilation were considered.

Statistical analysis

The number and percentage of subjects were reported for categorical variables and the median with interquartile range (IQR) for continuous variables. Percentages were calculated excluding missing data. To compare categorical variables, the Chi-square test or Fisher's exact test was used. Continuous variables were compared using the Mann–Whitney U test, given the nonparametric nature of the data. To assess changes in clinical parameters between ICU admission and day 5, delta VR and tidal volume (VT) values were calculated for each subject, stratified by survival status.

A Receiver Operating Characteristic (ROC) curve for VR on day 5 was generated to assess its predictive capacity for mortality. The area under the curve (AUC) was calculated to determine the efficacy of the marker in predicting mortality. A cutoff point for VR was developed based on the ROC curve, as well as its sensitivity and specificity.

In addition, a survival analysis was performed using VR on day 5 as a predictor variable. The Hazard Ratio (HR) was calculated to assess the mortality risk associated with VR values greater than or equal to the established cut-off point. The 95% Confidence Interval was determined to provide a range of associated risk, and the discrimination capacity of the model was assessed.

Survival analysis using the Cox model allowed the identification of significant risk factors for mortality in patients. The significance level was set at 0.05 (two-sided), and all analyses were performed using R version 4.4.1.

Results

A total of 190 subjects were included in this study, of whom 109 (57.4%) subjects, died during their stay in the ICU. The population was predominantly male (62.6%). Demographic and clinical characteristics at admission are summarized in Table 1.

The mean age of all subjects was 54.13 years (IQR: 47-58 years). Survivors had a mean age of 47.84 years (IQR: 38-58 years), significantly younger than non-survivors, whose mean was 60 years (IQR: 52-67 years). This difference was statistically significant (P: 0.009).

Regarding age categories, significant differences in survival were observed. In the 18-35 age group, survivors accounted for 9%, while non-survivors accounted for only 3% ($P < 0.0001$). In the 36-45 age category, the difference was also significant, with 8% of survivors versus 4% of non-survivors (P 0.019). Subjects aged 46-60 years showed a notable discrepancy, with 19% in survivors and 25% in non-survivors (P 0.0007). The APACHE score showed a median score of 14.37 (IQR: 11-17) in all subjects, being significantly higher in non-survivors (median 15.61 and IQR: 12-18) compared to survivors (median 12.72 and IQR: 9.5-15) ($P < 0.0002$). The SOFA score also revealed relevant differences, although it did not reach statistical significance (P 0.051).

The median stay in the ICU was 20.46 days (IQR: 9-25 days). Survivors had a median stay of 25.58 days (IQR: 14-38 days), while non-survivors remained in the ICU for a median of 12 days (IQR: 8-19.5 days), this difference was statistically significant (P 0.002).

A significant prevalence of acute kidney injury was found, with 11% in survivors versus 20% in non-survivors (P 0.001). In addition, arterial blood gases on admission showed relevant differences: pH had a value of 7.4 (IQR: 7.31-7.45) in survivors and 7.35 (IQR: 7.22-7.425) in non-survivors (P 0.023), while $PaCO_2$ showed significant differences between the groups (P 0.004).

The median P:F on admission was 71 mmHg (IQR: 55-93 mmHg) in all subjects. Survivors had a median P:F of 77.9 mmHg (IQR: 56 - 92 mmHg), whereas nonsurvivors had a median of 70 mmHg (IQR: 55 - 93 mmHg). No significant difference was observed between the groups (P 0.924). On

day 5, the median P:F increased to 96.5 mmHg (IQR: 66.5 - 135 mmHg). Survivors had a median P:F of 123 mmHg (IQR: 88 - 165 mmHg), in contrast to nonsurvivors, who had a P:F of 79 mmHg (IQR: 57 - 109 mmHg). This difference was statistically significant (P < 0.001), indicating better respiratory function in survivors.

Finally, in relation to the ventilatory ratio on the fifth day, survivors had a median of 2.23 (IQR: 1.86 - 2.87), while non-survivors had a median of 1.97 (IQR: 1.615 - 2.715), this difference being significant (P 0.002).

The difference in Ventilatory Ratio (VR) between survivors and non-survivors was assessed by calculating the delta VR between the day of ICU admission and the fifth day. The Wilcoxon test showed a P-value of 0.231 Δ VR between the groups. The bootstrap analysis yielded a median difference (Δ VR) of 0.19, with a 95% CI of [-0.04, 0.31], suggesting a non-significant difference between both groups. Regarding descriptive statistics, for survivors, the median VR on admission was 1.90 (IQR: 1.49 - 2.49) and on the fifth day it was 1.96 (IQR: 1.53 - 2.24). In non-survivors, the median was 1.97 (IQR: 1.62 - 2.70) on admission and 2.23 (IQR: 1.86 - 2.87) on day 5 (Figure 1-A).

In regards to the the difference in tidal volume (Δ VT) between surviving and non-surviving patients. The Wilcoxon test showed a P value of 0.510, indicating that there was no statistically significant difference in Δ VT between the groups. For non-survivors, a Δ VT of 0 [0, 10] was observed, whereas in survivors the Δ VT was 0 [-20, 20]. Descriptive statistics showed that on admission, the median tidal volume was 380 mL (Q1: 350, Q3: 400) in survivors and 380 mL (Q1: 350, Q3: 408) in non-survivors. On day 5, the median tidal volume remained at 380 mL (Q1: 350, Q3: 400) for survivors and 380 mL (Q1: 350, Q3: 407) for non-survivors (Figure 1-B).

In regards to the difference in P:F ratio between survivors and non-survivors. The Wilcoxon test revealed a P value of 0.001, indicating a highly significant difference in P:F ratio between the two groups. Regarding descriptive statistics, the median P:F ratio on admission was 74 mmHg (Q1: 57, Q3: 108) in survivors and 95 mmHg (Q1: 68, Q3: 130) in non-survivors. By day 5, the median P:F ratio was 69 mmHg (Q1: 53, Q3: 94) in survivors and 77 mmHg (Q1: 61, Q3: 116) in non-survivors (Figure 1-C).

Multivariate logistic regression analysis shows the evaluation of the relationship between several independent variables and the probability of a given event (in this case, the survival of subjects in the ICU). P values less than 0.05 indicate that the results are statistically significant. A positive coefficient indicates a higher probability of survival, while a negative coefficient suggests a higher risk of mortality. The ROC curve obtained for the regression model shows an area under the curve (AUC) of 0.873, with a 95% CI 0.825 - 0.921 (estimated using the DeLong method). This AUC value indicates that the model has a strong discriminative ability to differentiate between surviving and non-surviving patients (Table 2).

The ROC curve for VR on the first day is observed, showing an area under the curve (AUC) of 0.540 and an optimal cut-off point of 1.495 (95% CI: 0.259 - 0.853) (Figure 2-A).

The area under the ROC curve was calculated to evaluate the predictive value of VR on the fifth day. The area under the ROC curve for VR showed a non-statistically significant predictive marker of mortality (AUC: 0.660 and 95% CI: 0.582 - 0.737). The cut-off value for VR on day 5 was 2.045 with a sensitivity of 59.3% and specificity of 68.8% (Figure 2-B).

The ROC curve to assess the predictive capacity of VR parameter on day 5 in subjects younger than 60 years. The analysis included a total of 66 controls (surviving patients) and 52 cases (non-surviving patients). The area under the curve (AUC) was 0.7223 (95% CI: 0.627 - 0.817), indicating a moderate ability to discriminate between patients who survived. When evaluating the sensitivity and specificity at the best cut-off point, a threshold of 2.06 was found, with a sensitivity of 71.15% and a specificity of 66.67% (Figure 2-C).

The survival analysis using a Cox regression model evaluated several clinical variables in relation to mortality in ICU patients. The model included a total of 190 subjects, with 109 mortality events recorded.

Age was a significant factor in the risk of mortality, with a Hazard Ratio (HR) of 1.035 (95% CI: 1.018 - 1.052) and a P value of < 0.001. This indicates that for each additional year of age, the risk of mortality increases by 3.5%, highlighting the importance of age as a critical predictor in this population. Another relevant finding was the effect of acute kidney injury. The HR for patients without this condition was 0.486 (95% CI: 0.32 - 0.737) with a P value of 0.001. This suggests that subjects without acute kidney injury have a 51.4% lower risk of mortality compared to those with this condition, highlighting the severity of renal injury on the prognosis of patients (Table 3).

VR on day 5 showed a HR of 1.335 (95% CI: 1.118 - 1.595) and a P value of 0.001. This finding implies that an increase in VR is associated with a 33.5% increase in mortality risk, suggesting that higher ventilation might be linked to worse outcomes. Regarding the P:F ratio, the results were conclusive. Subjects with a P:F ratio between 60 and 119 mmHg had a HR of 0.264 (95% CI: 0.164 -

0.423) and a P value of < 0.001, indicating that these subjects have a 73.6% lower risk of mortality compared to those with lower P:F ratios. Similarly, those with a P:F ratio of 119 to 179 mmHg had a HR of 0.214 (95% CI: 0.115 - 0.398) and a P value of < 0.001, indicating a 78.6% lower risk of mortality. In contrast, categorization of the P:F ratio for values greater than 179 mmHg showed a HR of 0.269 (95% CI: 0.11 - 0.655) with a P value of 0.004, suggesting that these subjects also have a significantly lower risk of mortality (Table 3).

The HR showed that subjects with a VR value on day 5 greater than or equal to 2 have approximately 1,529 (95% CI: 1.013 – 2.306) times higher risk of not surviving compared to those with values less than 2. The results of the survival analysis revealed significant differences between the groups categorized by the ventilatory ratio. For subjects with a ventilatory ratio less than 2, the median survival was 25 days. In contrast, patients with a ventilatory ratio greater than or equal to 2 had a median survival of 18 days (Figure 3).

Table 1 Clinical and Demographic characteristics of patients with ICU survival outcomes. Categorical variables are expressed as numbers (percentages) and continuous variables are expressed as medians (interquartile range). P values marked in bold indicate numbers that are statistically significant

Variable	All patients	Survivors	Non-survivors	P value
Age (years)	54.13 (47-58)	47.84 (38-58)	60 (52-67)	**0.009**
Sex, male	119 (63%)	49 (26%)	70 (37%)	0.6
Age, categories				
18-35	22 (12%)	17 (9%)	5 (3%)	**< 0.001**
36 - 45	23 (12%)	15 (8%)	8 (4%)	**0.019**
46 - 60	84 (44%)	36 (19%)	48 (25%)	**< 0.001**
61 - 70	44 (23%)	9 (5%)	35 (19%)	0.96
71+	17 (9%)	4 (2%)	13 (7%)	0.10
Body Mass Index (BMI) Kg/m2	30.131 (27 – 32.25)	29.75 (27 – 32.25)	30.41 (26.85 - 33)	0.14
Comorbidities				
Two or more comorbidities	80 (42%)	29 (15%)	51 (27%)	0.13
High blood pressure	57 (30%)	23 (12%)	34 (18%)	0.68
Diabetes	20 (11%)	9 (5%)	11 (6%)	0.82
Multiple Sclerosis	2 (1%)	1 (1%)	1 (1%)	0.83
Erythrocytosis	15 (8%)	6 (3%)	9 (5%)	0.83
Rheumatoid arthritis	1 (1%)	0 (0%)	1 (1%)	0.39
Asthma or COPD	4 (2%)	0 (0%)	4 (2%)	0.08
Obesity	83 (44%)	32 (17%)	51 (27%)	0.32
Ventilator days	17.88 (8 - 22.25)	14 (8 – 29.5)	12 (8 - 19)	0.09
ICU LOS	20.46 (9 - 25)	18 (14 - 38)	12 (8 - 19.5)	**< 0.001**
APACHE score	14.37 (11 - 17)	12.72 (9.5 - 15)	15.61 (12 - 18)	**< 0.001**
SOFA score	5.97 (5-6)	5.48 (5 - 6)	6.33 (5 - 7)	0.051
Acute kidney injury	49 (26%)	11 (6%)	38 (20%)	**0.001**
Corticosteroids, dexamethasone	73 (39%)	32 (17%)	41 (22%)	0.08
Corticosteroids, hydrocortisone	17 (9%)	6 (3%)	11 (6%)	0.52
Corticosteroids, methylprednisone	98 (52%)	41 (22%)	57 (30%)	**< 0.001**
Antiviral, remdesivir	75 (40%)	33 (17%)	42 (22%)	0.76
Arterial blood gases on admission to ICU, El Alto City (4150 masl) Pb = 453 mmHg				
P:F (mmHg)	71 (55 - 93)	77.9 (56 - 92)	70 (55 - 93)	0.92
P:F < 60 mmHg	72 (37.89%)	33 (17.37%)	39 (20.53%)	0.49
P:F 61 - <119 mmHg	96 (50.53%)	39 (20.53%)	57 (30%)	0.57
P:F 119 - 179 mmHg	22 (11.58%)	9 (4.74%)	13 (6.84%)	0.31

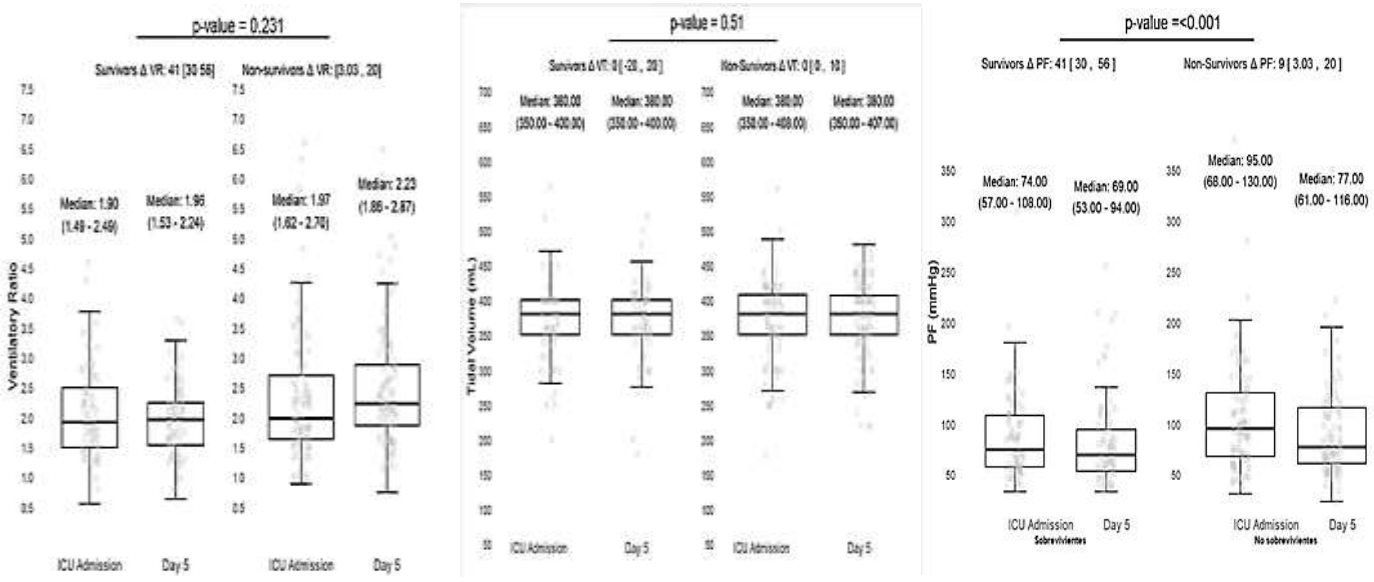
pH	7.341 (7.26 - 7.45)	7.4 (7.31 - 7.45)	7.35 (7.22 – 7.425)	**0.023**
$PaCO_2$, mmHg	38.807 (28.925 - 41.5)	34 (28 - 41.5)	38 (29.5 – 48.85)	**0.004**
Lactate, mmol/L	2.464 (1.6 - 2.65)	2.1 (1.5 - 2.65)	2.2 (1.7 - 2.85)	0.85
SPO_2 %	87 (82 - 94)	89 (84 - 92)	90 (81 - 95)	0.78
Ventilatory parameters and pulmonary mechanics on admission				
Tidal volume (mL)	380 (350 - 400)	380 (350 - 400)	380 (350 - 400)	0.19
Minute volume (Lpm)	8.9 (7.6 - 10)	9 (7.8 - 10.55)	8,8 (7.2 – 9.8)	0.12
Respiratory rate, bpm	25.052 (22 - 28)	25 (22 - 28)	24 (21.5 - 28)	0.50
PEEP (cmH_2O)	10.39 (10 - 12)	10 (10 - 12)	10 (10 - 12)	0.52
FIO_2 %	98 (81.25 - 100)	96 (80 - 100)	98 (90 - 100)	0.10
Ventilatory Mode, CMV-VC	130 (69%)	64 (34%)	66 (35%)	**0.01**
Prone	177 (94%)	68 (36%)	109 (58%)	**< 0.001**
Ventilatory Ratio	2.201 (1.5875 – 2.59)	1.9 (1.49 - 2.49)	1.97 (1.615 - 2.715)	0.13
Arterial blood gases on the 5th day in STI, El Alto City (4150 masl) Pb = 453 mmHg				
P:F (mmHg)	96.5 (66.5 - 135)	123 (88 - 165)	79 (57 - 109)	**< 0.001**
P:F < 60 mmHg	35 (18.42%)	4 (2.11%)	31 (16.32%)	**< 0.001**
P:F 60 - <119 mmHg	89 (46.84%)	33 (17.37%)	56 (29.47%)	0.15
P:F 119 - 179 mmHg	47 (24.74%)	31 (16.32%)	16 (8.42%)	**< 0.001**
P:F > 179 mmHg	19 (10%)	13 (6.84%)	6 (3.16%)	**0.017**
$PaCO_2$ mmHg	35 (29 - 45)	35 (29 - 38)	39 (32 - 50)	**0.005**
Ventilatory parameters and pulmonary mechanics on day 5				
Tidal volume (mL)	380 (350 - 400)	380 (350 - 400)	380 (360-410)	**0.005**
Minute volume (Lpm)	9.149 (7.6 – 10.5)	8.8 (7.7 - 10)	9.1 (7.6 – 10.8)	0.38
Respiratory rate, bpm	25.121 (21 - 30)	22 (20 - 26)	26 (22 - 30)	**0.001**
PEEP (cmH_2O)	9.58 (8 - 10)	10 (8 - 10)	10 (9-12)	**0.003**
FiO_2%	72.32 (53.75 - 95)	65.79 (45 - 85)	77.17 (60 - 98)	**< 0.001**
Ventilatory mode (CMV-VC)	108 (57%)	50 (26%)	58 (31%)	0.24
Ventilatory Ratio	2.30 (1.647 – 2.64)	1.96 (1.53 – 2.24)	2.23 (1.86 - 2.87)	**< 0.001**
Ventilator Associated Pneumonia (VAP)	135 (71.1%)	57 (30%)	78 (41.1%)	0.86

Table 2. Multivariate logistic regression: variables independently associated with mortality

Variable	**Coefficient**	**Standard Error**	**P value**
Intercept	-0.995	1.138	0.382
Age (years)	0.073	0.016	**<0.001**
Days of stay in ICU	-0.042	0.012	**0.001**
Acute kidney injury	-1.143	0.487	**0.019**
P: F 5th day: 60 < 119 mmHg	-1.520	0.693	**0.028**
P: F 5th day: 119 - 179 mmHg	-2.692	0.750	**< 0.001**
P: F 5th day: > 179 mmHg	-3.005	0.860	**< 0.001**
P: F 1st day: ≤ 119 mmHg	0.588	0.435	0.177
P: F 1st day: ≤ 179 mmHg	0.469	0.695	0.500
VR 5th day >2	0.973	0.397	**0.014**

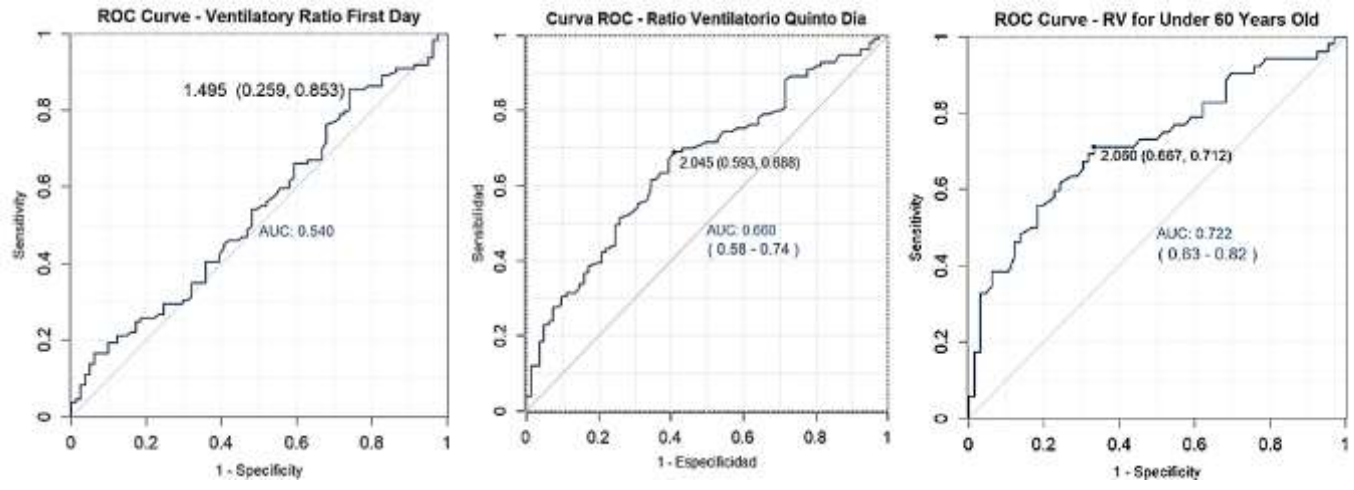
Table 3. COX regression: forest plot of variables independently associated with mortality. HR: Hazard ratio, CI: Confidence Interval

Variable	HR (CI 95%)	P value
Age	1.035 (1.018 – 1.052)	**< 0.001**
Acute kidney injury	0.486 (0.32 – 0.737)	**0.001**
P:F 5th day: 60 < 119 mmHg	0.264 (0.164 – 0.423)	**< 0.001**
P:F 5th day: 119 - 179 mmHg	0.214 (0.115 – 0.398)	**< 0.001**
P:F 5th day: > 179 mmHg	0.269 (0.11 – 0.655)	**0.004**
VR 5th day: > 2	1.335 (1.118 – 1.595)	**0.001**



1-A 1-B 1-C

Figure 1: Box and Whisker plot comparison between admission and day 5 of Ventilatory Ratio (VR) (1-A), Tidal Volume (1-B), and PaO_2:FiO_2 ratio (1-C) between survivors and non-survivors



2-A 2-B 2-C

Figure 2: ROC curve to predict mortality cut-off point according to Ventilatory Ratio on the fifth day

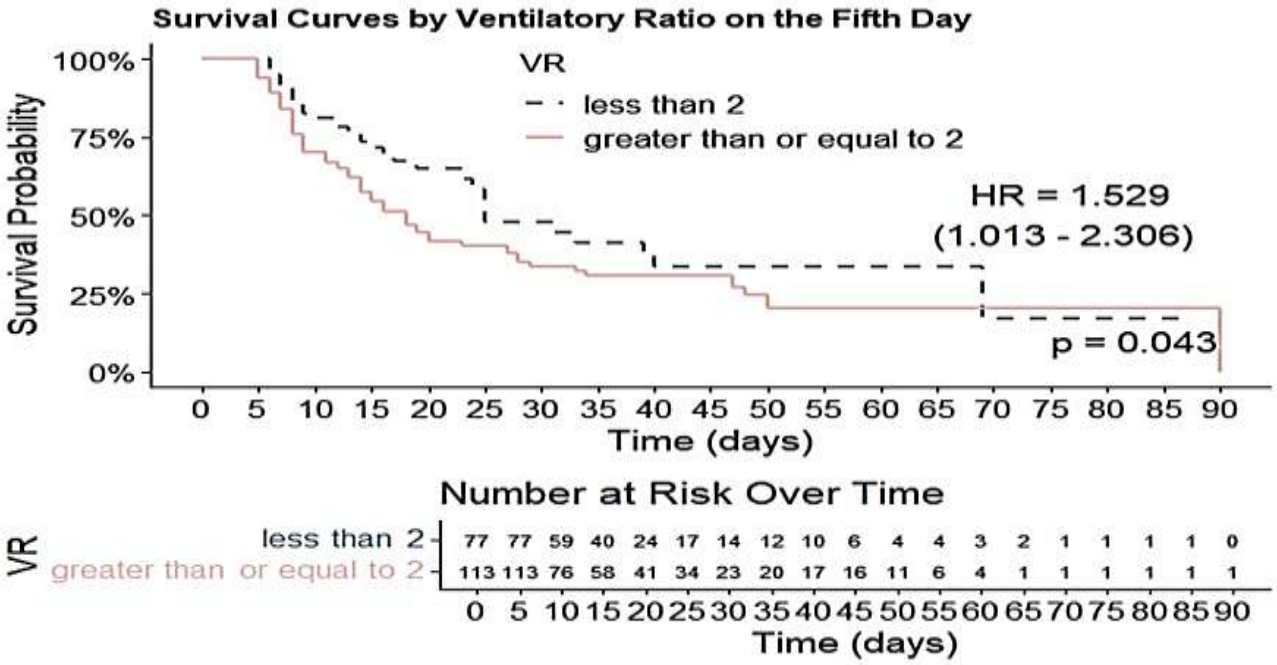


Figure 3: Survival curve by Ventilatory Ratio on the fifth day

Discussion

In this analysis, the results of the study can be summarized as follows: This is a homogeneous cohort of subjects with COVID-19 ARDS, who required orotracheal intubation and invasive mechanical ventilation upon admission to the ICU. The in-hospital mortality of these subjects in the pandemic was 57.4%. This is the first time that VR has been investigated at very high altitude, a simple method at the bedside of the subject with ARDS. [1] The cut-off point for VR on admission was 1.495 (95% CI: 0.259 - 0.853), showing an area under the curve (AUC) of 0.540. The cut-off value for VR on the fifth day was 2.045, with a sensitivity of 59.3% and a specificity of 68.8%. The area under the ROC curve for the Ventilatory Ratio showed a non-

statistically significant predictive marker of mortality (AUC: 0.660 and 95% CI: 0.582 - 0.737). The predictive capacity of the VR parameter has been evaluated on the fifth day in subjects under 60 years of age; when evaluating the sensitivity and specificity at the best cut-off point, a threshold of 2.06 was found, with a sensitivity of 71.15% and a specificity of 66.67%. The area under the curve (AUC) was 0.722 (95% CI: 0.627 - 0.817), indicating a moderate capacity to discriminate between subjects who survived. [2] Parameters of mechanical ventilation, oxygenation and ventilatory ratio stratified by survival have been established. The VR between survivors and non-survivors, calculating the delta VR between the day of ICU admission and day 5 suggests a non-significant difference between the two groups. For survivors, the median VR on admission was 1.90 (IQR: 1.49 - 2.49) and on day 5 it was 1.96 (IQR: 1.53 - 2.24). In non-survivors, the median was 1.97 (IQR: 1.62 - 2.70) on admission and 2.23 (IQR: 1.86 - 2.87) on day 5. The P:F ratio, stratified by high altitude barometric pressure to define mild, moderate, and severe ARDS, [17] between survivors and non-survivors, revealed a P value of 0.001, indicating a highly significant difference in the P:F ratio between the two groups. The median P:F ratio on admission was 74 mmHg in survivors and 95 mmHg in non-survivors. On day 5, the median P:F ratio was 69 mmHg in survivors and 77 mmHg in non-survivors.

The results of the survival analysis revealed significant differences between groups categorized by ventilatory ratio. For subjects with a ventilatory ratio less than 2, the median survival was 25 days. In contrast, subjects with a ventilatory ratio greater than or equal to 2 had a median survival of 18 days. A P value of 0.043 was obtained, which is statistically significant. This means that the predictor VR on day 5 less than 2 has a significant relationship with survival. The HR means that patients with a VR value on day 5 greater than or equal to 2 have approximately 1.529 (95% CI: 1.013 - 2.306) times the risk of not surviving compared with those with values less than 2. VR on day 5 greater than or equal to 2 was independently associated with 90-day mortality, even after controlling for other prognostic variables. Age, P:F ratio on day 5, and increasing ventilatory ratio were found to be independent factors associated with 90-day in-hospital mortality.

VR was proposed by Sinha in 2009, calculated as a ratio comparing actual and predicted values of minute ventilation and $PaCO_2$. [10] It was considered to reflect the combined effect of dead space and shunt on CO_2 removal in ARDS, where there is likely to be a high ventilation-perfusion mismatch. For our study, a modification was made to the VR calculation, adjusting $PaCO_2$ to altitude, in this case to the population of the city of El Alto (4150 m asl). [11,18] Therefore, for healthy residents at high altitude, the ideal $PaCO_2$ is 27.9 mmHg, these levels are lower, due to increased CO_2 removal secondary to compensatory hyperventilation. At altitude, acute hypocapnia causes individuals to be alkalotic, whereas during chronic hypocapnia, such as that experienced with prolonged stays at altitude, the kidneys compensate for respiratory alkalosis with relative metabolic acidosis, returning blood pH to normal values. [19,20] This hypothesis appears to be untrue, since no compensation for acid-base imbalances reaches a normal pH; however, at altitude, serum pH is perfectly normal, which indicates that the high-altitude inhabitant is not compensated, much less in respiratory alkalosis, but adapted with a very specific physiology and conditioned to live at altitude, with a total lung capacity even greater than that of sea-level inhabitants. [21]

In this study, during the ROC analysis, we determined a cut-off value for VR at admission of 1.495; however, these results showed a non-statistically significant predictive marker of mortality. In a cohort of 927 patients, no association was found between VR on day 1 and 30-day mortality. [22] To achieve a sensitivity of > 71.15%, a VR cutoff value of 2.06 was identified at high altitude, indicating a moderate ability to discriminate between survivors and non survivors. In 2019, a physiological analysis demonstrated that VR correlates well with dead space fraction in subjects with ARDS, and higher values > 2 are associated with increased risk of adverse outcomes, [14] making VR promising as a simple bedside marker assessing impaired ventilation in ARDS.

Surprisingly, the results of stratification by survival showed an association between the delta of the P:F ratio in oxygenation as a factor associated with higher mortality. The increase in oxygenation from day 1 to day 5 seemed to have a higher survival rate in regions at very high altitude. Our hypothesis is that in regions at very high altitude, the P:F ratio could have a very important role in monitoring oxygenation. In a similar cohort study at altitude, the P:F ratio was not a factor associated with mortality [23] and in another study in Spain, no association was found with mortality. [24]

Ventilatory parameters such as the delta of tidal volume did not vary significantly. The delta ventilatory ratio, although it showed an increase from the day of admission to day 5, between surviving and non-surviving subjects, did not vary significantly. On admission to the ICU, we found some demographic variables associated with higher mortality, such as age, days of stay in the ICU, APACHE II score, acute kidney injury, corticosteroids, $PaCO_2$, prone position, and ventilatory mode. These parameters reflect a more vulnerable population in which COVID-19 has a worse outcome. Studies confirm that age is a poor prognostic factor in ventilated subjects. [23]

Acute kidney injury on admission to the ICU was associated with in-hospital mortality; similar studies show that increased creatinine was associated with mortality. [24] The changes found in serum creatinine levels reflect organ failure in subjects with severe COVID; kidney failure may occur due to direct kidney injury[25]. In our study, parameters such as tidal volume, P:F ratio, respiratory rate, PEEP, FIO_2, and VR were statistically significant on day 5. Similar to our study, a multicenter study in COVID-19 patients by Torres and colleagues found that age, delta VR, delta serum creatinine, delta platelet count on day three were predictors of mortality, however the delta P:F was not. [24]

We found an association between VR less than 2 and a higher 90-day survival in a very high altitude region, such as the city of El Alto. In the Monteiro study, [25] subjects with VR > 2 (median) on day 1 had a significantly lower 90 day survival compared to subjects with VR ≤ 2 (HR 1.36, 95% CI 1.10 - 1.69). VR on day 1 was significantly associated with 28-day mortality (OR = 1.40, 95% CI (1.15-1.72). [26] Previous studies in COVID-19 a direct association between VR and 28-day mortality. [22-24]

However, an elevated VR > 2 on day 5 may be a more generalizable predictor of mortality, as it might be independent of the severity of the initial disease and, therefore, could be a good marker. We did not find an association between VR on admission and mortality at 90 days, comparing with previous works that also did not find statistically significant results at day 1. [24] We evaluated the change between day 1 and day 5 of VR, finding that the increase in this value above 2.06 on day 5 was associated with a higher risk of mortality at 90 days, this finding can be explained by the deterioration of lung mechanics and severe inflammation during the course of the disease.

Our study indicates that a ventilatory ratio (VR) cutoff of 2, even after adjusting for the effects of altitude on $PaCO_2$, is consistent with the findings of Parada et al. [23] They also found a VR greater than 2 to be associated with mortality in their study, which was conducted in Bogotá, Colombia, a high-altitude city (2625 meters above sea

level). Their VR calculation used a target $PaCO_2$ of 37.5 mmHg. These findings suggest that the VR cutoff point remains consistent at altitude, without the need for modification as compared to sea level.

Altitude medicine is a compelling field, and it's essential that we develop our own understanding of medical practices at high altitude, rather than relying solely on research conducted primarily in seal level regions. El Alto and La Paz are among the world's most populous cities above 3000 meters, making them exceptional locations for research on mechanical ventilation. We believe it is crucial to establish our own data-driven norms for this population. Specifically, incorporating typical high-altitude $PaCO_2$ values into the Van Slyke equation [27] is preferable. This approach helps avoid misdiagnosis in the estimated 200 million healthy individuals living above 2500 meters. These considerations are vital for accurate acid-base management in ICUs at very high altitudes. [27]

The findings of this study confirm the hypothesis that VR could be used also at high altitude as a useful prognostic marker of impaired ventilation at the bedside. However, the results must be interpreted in light of several limitations. First, its retrospective design inherently exposes it to potential biases and limitations associated with data analysis. Second, the relatively small sample size of the study may limit the generalizability of its findings. Implementing a prospective study design with a larger patient cohort would improve the validity and reliability of the results. Furthermore, the inclusion of data from only one hospital, which may differ, introduces the possibility of hospital-specific biases. Additionally, our study was conducted in COVID-19 subjects so the results might not be valid for other etiologies of acute respiratory failure.

The strengths of the study include the design of a cohort study, the first at very high altitude, evaluating ventilatory and oxygenation parameters where correction and classification were performed according to ARDS barometric pressure, to calculate the P:F ratio and $PaCO_2$; and the multivariate Cox analysis determined risk factors for mortality. The results of this study have implications for clinical practice, since they demonstrate that VR measurement is a tool that can be added to other respiratory mechanics parameters such as driving pressure, plateau pressure, and mechanical power, for the prognosis of subjects with ARDS, thanks to its simple formula that can be applied at the subject's bedside to estimate the dead space fraction.

Conclusions

Ventilatory Ratio is a valuable prognostic marker for ARDS at very high altitude, with a VR greater than 2 is significantly associated with increased 90-day ICU mortality. Higher day 5 VR, age, P/F ratio, and acute kidney injury were independent risk factors for in-hospital mortality. While these findings offer a simple bedside tool for assessing ARDS outcomes and prognosis, larger prospective and interventional studies are needed to further elucidate the impact of VR at high altitude.

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