Impaired ventilation is not independently associated with 28-day mortality in COVID-19 ARDS

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ABSTRACT

**Background:** Surrogates for impaired ventilation such as estimated dead-space fractions and the ventilatory ratio have been shown to be independently associated with an increased risk of mortality in the acute respiratory distress syndrome and small case series of COVID-19 related ARDS.

**Methods:** Secondary analysis from the PRoVENT-COVID study. The PRoVENT-COVID is a national, multicentre, retrospective observational study done at 22 intensive care units in the Netherlands. Consecutive patients aged at least 18 years were eligible for participation if they had received invasive ventilation for COVID-19 at a participating ICU during the first month of the national outbreak in the Netherlands. The aim was to quantify the dynamics and determine the prognostic value of surrogate markers of impaired ventilation patients with COVID-19 related ARDS.

**Results:** 927 consecutive patients admitted with COVID-19 related ARDS were included in this study. Surrogates of impaired ventilation such as the estimated dead space fraction (by Harris-Benedict and direct method) and ventilatory ratio were significantly higher in non-survivors than survivors at baseline and during the following days of mechanical ventilation (p <0.001). The end-tidal-to-arterial PCO₂ ratio was lower in non-survivors than in survivors (p<0.001). As ARDS severity increased, mortality increased with successive tertiles of dead space fraction by Harris-Benedict and by direct estimation, and for the VR. The same trend was observed with decreased levels in the tertiles for the end-tidal-to-arterial PCO₂ ratio. After adjustment for a base risk model that included chronic comorbidities and ventilation- and oxygenation-parameters, none of the surrogates of
impaired ventilation measured at the start of ventilation or the following days were significantly associated with 28-day mortality.

**Conclusions:** There is significant impairment of ventilation in the early course of COVID-19 related ARDS but quantification of this impairment does not add prognostic information when added to a baseline risk-model.

**Key Words:** Acute respiratory distress syndrome, ARDS, Respiratory dead space, Dead space, Ventilatory ratio, COVID-19, Mortality, prognostication.
BACKGROUND

Since the outbreak of coronavirus disease 2019 (COVID-19) in the City of Wuhan, Hubei Province, China, caused by the transmission of the novel coronavirus SARS-CoV-2, millions of individuals have been infected and more than one million have died. Severe disease requiring admission to intensive care unit (ICU) occurs in approximately 5% of infections\(^1\), and the most common reason for admission is respiratory failure requiring high-level support. Among these patients, two-thirds meet the criteria for the acute respiratory distress syndrome (ARDS)\(^2\).

Patients with COVID-19 pneumonia that meets criteria for ARDS usually present with a high respiratory drive and minute ventilation, potentially due to hypercapnia and an increased dead space fraction \((V_D/V_T)^3\). In patients with ARDS, an elevated \(V_D/V_T\) is a predictor of death and is one of the few lung-specific physiological variables independently associated with mortality\(^4,5\). Methods for estimating \(V_D/V_T\) do not require quantitative assessment of exhaled carbon dioxide, are less complicated to perform, and easier to calculate at the bedside\(^6\). In recent years, the ventilatory ratio (VR) was proposed as an easily acquired bedside index of impaired ventilation that can be computed using routinely measured respiratory variables\(^7\). In patients with ARDS, the VR correlates well with \(V_D/V_T\)\(^7\) and may function as a surrogate marker for impaired ventilation\(^8\).

At least two independent groups have described series of patients with COVID-19 related ARDS who may have inefficient CO\(_2\) removal due to increased physiologic dead space\(^3,9\). However, no published study has assessed the impact of estimated \(V_D/V_T\) and VR on mortality in a large cohort of COVID-19 patients undergoing invasive ventilation. Therefore, we aimed to assess the association between markers of impaired ventilation, such as estimated \(V_D/V_T\) and VR with 28-day mortality in patients undergoing invasive
ventilation because of COVID-19 ARDS. We hypothesized that these markers of impaired ventilation are independently associated with 28-day mortality.
Methods

Study design and oversight

PRoVENT–COVID is an investigator–initiated, multicenter, observational cohort study undertaken at 22 ICUs in the Netherlands. The study protocol including the statistical analysis plan are available\(^\text{10}\). The approved protocol is available in Supplement 1. A statistical analysis plan for the current analysis was written before assessing the database, and is available online\(^\text{11}\). Study sites were recruited through direct contact by members of the steering committee of PRoVENT–COVID. The institutional review boards of the participating centers approved the study protocol, and need for patient informed consent was waived. Study coordinators contacted the local doctors, trained data collectors to assist the local doctors, and monitored the study according to the International Conference on Harmonization Good Clinical Practice–guidelines. Integrity and timely completion of data collection was ensured by the study coordinators.

Patients

Consecutive patients ≥ 18 years were eligible for participation in PRoVENT–COVID if they were admitted to one of the participating ICUs and had received invasive ventilation for COVID–19 ARDS. COVID-19 infection was defined by a confirmed reverse transcriptase-polymerase chain reaction (RT-PCR), or highly suspected based on presence of typical abnormalities on chest computer tomography (CT) images\(^\text{12}\). PRoVENT–COVID had no exclusion criteria, but for the current analysis we excluded patients transferred from a non–participating hospital who had been receiving invasive ventilation for more than 2 calendar days, patients without complete data to calculate the \(V_D/V_T\) or VR in the first day of ventilation, and patients with no data about 28-day mortality.
Data collection

Demographics and data regarding premorbid diseases and medication were collected at baseline. In the first hour of invasive ventilation and every 8 hours thereafter, at fixed time points in the first 4 calendar days, ventilator settings and parameters were collected. In the present study, the first day of ventilation is called ‘at start of ventilation’.

Data definition and exposure

The primary exposure of interest was the $V_D/V_T$ calculated using the Harris-Benedict formula as described in Eq. (1)\textsuperscript{13}:

$$\frac{V_D}{V_T} = 1 - \frac{(0.863 \times \dot{V}CO_2)}{(RR \times V_T \times PaCO_2)} \text{ Eq. (1)}$$

RR is the respiratory rate in breaths per minute, $V_T$ the tidal volume in liters, $PaCO_2$ the partial pressure of carbon dioxide in mmHg, and $VCO_2$ the CO\textsubscript{2} production in mL/min estimated using the Eq. (2):

$$\dot{V}CO_2 = \frac{REE_{HB}}{(5.616 \times RQ) + 1.584} \text{ Eq. (2)}$$

RQ is the respiratory quotient, assumed to be 0.8, and $REE_{HB}$ is the rest energy expenditure calculated by the unadjusted Harris-Benedict estimate using the Eq. (3)\textsuperscript{13}:

$$\text{Males}: REE_{HB} = 66.473 + (13.752 \times \text{weight}) + (5.003 \times \text{height}) - (6.755 \times \text{age}) \text{ Eq. (3)}$$

$$\text{Females}: REE_{HB} = 655.096 + (9.563 \times \text{weight}) + (1.850 \times \text{height}) - (4.676 \times \text{age}) \text{ Eq. (3)}$$

Weight is in kilograms, height is in centimeters and age in years.

In addition, two additional estimations of $V_D/V_T$ were done considering a direct estimation and the end-tidal-to-arterial PCO\textsubscript{2} ratio\textsuperscript{14}, and the formulas are described in the Online Supplement.

The secondary exposure of interest is the VR, calculated using the Eq. (4)\textsuperscript{15}:
VR = \frac{V_E \text{ measured} \times PaCO_2 \text{ measured}}{V_E \text{ predicted} \times PaCO_2 \text{ predicted}} \quad \text{Eq. (4)}

VR is the ventilatory ratio, $V_E \text{ measured}$ is the measured minute ventilation in mL/min, $PaCO_2 \text{ measured}$ is the measured PaCO$_2$ in mmHg, $V_E \text{ predicted}$ is the predicted minute ventilation in mL/min (calculated as 100 * predicted body weight)$^{15}$, and $PaCO_2 \text{ predicted}$ is the predicted PaCO$_2$ determined as 37.5 mmHg.

All variables were calculated three times per day and the values were aggregated as the mean in the respective day. Primary analyses focused on the values obtained in the day of start of ventilation.

Outcomes

The outcome assessed in this study was death at 28 days, defined as the mortality 28 days after the start of ventilation. Other clinical outcomes are reported only to describe the cohort but were not used to test their association with the exposures described above.

Statistical analysis

The amount of missing data was low for most of the variables (eTable 1 in Online Supplement). Continuous variables are presented as medians (quartile 25% - quartile 75%) and categorical variables as numbers and percentages. Descriptive data is presented according to the 28-day status (non-survivors vs. survivors), and the two groups were compared using Wilcoxon rank–sum test for continuous variables, and Fisher exact tests for categorical variables.

Trends in markers of impaired ventilation were presented in boxplots between survivors and non-survivors over the first 4 calendar days. The direction of effect over time of the variables was assessed with mixed–effect linear models with center and patients treated as random effect to account for clustering and repeated measurements, and with
28-day vital status (alive/dead), time (as a continuous variable), and an interaction of 28-day vital status and time as fixed effect. Overall $P$ values from this analysis represent the overall difference among groups over time and $P$ values from interaction represent a statistical assessment of whether the trend over time differed among the groups. All daily measurements of variables (three times a day) were aggregated as the mean per day. In addition, to compare variables at each day, the day variable was entered as a categorical variable in the model described above, and the $P$ value for the daily difference was extracted using pairwise comparisons after Bonferroni correction.

We examined the risk of death for each tertile of the lung-specific physiological variables was used to evaluate whether the predictive ability of each variable varied by level. In addition, a simple stratification creating two groups according to the median of the variables was also assessed. The comparison of the two groups was presented in Kaplan-Meier curves and compared using Log-rank tests.

Univariable mixed-effect generalized linear models considering a binomial distribution and with center as random effect were used to estimate the unadjusted effect of each variable on 28-day mortality. A multivariable mixed-effect generalized linear model considering a binomial distribution and with center as random effect were used to test the association of each of the exposures described above with 28-day mortality. A list of candidate confounders was determined a priori, and based on clinical relevance rather than statistical significance. The following baseline variables (measured at baseline or within 1 hour after intubation or ICU admission with ventilation) were considered in the models: age, gender, body mass index, $\text{PaO}_2/\text{FiO}_2$ ratio, plasma creatinine, hypertension, diabetes, use of angiotensin converting enzyme inhibitors, use of angiotensin II receptor blockers, use of a vasopressor or an inotropic drug, fluid balance, pH, mean arterial
pressure, heart rate, respiratory system compliance, and PEEP. Multicollinearity was assessed through the analysis of the variance inflation factors, and the final model was assessed for discrimination using c-statistics, and for calibration using the Brier-Score.

In addition to the odds ratio (OR) and its 95% confidence interval, the predictive accuracy of the lung-specific physiological variables was measured by the area under the receiver operating characteristics curve (AUC-ROC). Also, to estimate whether these variables improved predictive accuracy on top of that of the base model described above, the net reclassification improvement (NRI) and the integrated discrimination index (IDI) were assessed.

For the primary analysis, covariates with less than 3% of missing were imputed by the median value of the overall cohort. Since respiratory compliance was missing in 8.2% of the patients (eTable 1 in Online Supplement), an additional sensitivity analysis considering multiple imputation for all missing variables was conducted (described in details in Online Supplement).

All continuous variables were entered after standardization to improve convergence of the models, and the odds ratio (OR) represents the increase in one standard deviation of the variable. All analyses were conducted in R v.4.0.2 (R Foundation, Vienna, Austria)\textsuperscript{16} and significance level was set at 0.05.
RESULTS

Study population

From March 1, 2020, through June 1, 2020, 31 ICUs were invited for participation in PRoVENT–COVID, and 22 met inclusion criteria. A total of 1340 individuals were screened. A total of 218 were not enrolled; 62 did not have COVID–19 related ARDS, 150 never received invasive ventilation, and 6 for other reasons (eFigure 1 in Online Supplement). Of the enrolled 927 patients, 259 (28.7%) were non-survivors and 661 (71.3%) were survivors at day 28. Demographics characteristics are presented in Table 1. Non-survivors were older, more often males, had a greater severity of ARDS and higher creatinine level at admission, more frequent presented co-existing disorders like hypertension, diabetes and chronic obstructive pulmonary disease, and more often were using systemic steroids, metformin, beta-blockers and statins at home. Ventilatory variables in the first day of ventilation and general clinical outcomes are shown in eTables 2 and 3 in Online Supplement. Non-survivors received higher FiO₂, had higher levels of lactate and creatinine, and lower levels of pH and end-tidal-to-arterial PCO₂.

Markers of impaired ventilation

The dynamic change of markers of impaired ventilation over the first four days of ventilation as shown in Table 2 and Figure 1. V_D/V_T calculated using the Harris-Benedict formula was higher in non-survivors and increased more during the first four days compared to survivors. Similar trend was found with the direct V_D/V_T calculation. While VR was also higher in non-survivors, especially after day 2, the end-tidal-to-arterial PCO₂ ratio was lower.

Mortality by tertiles of each variable is reported in Figure 2. Tertiles were calculated separately for each variable and each day, to account for potential differences in scaling
and measurements. Mortality increased with successive tertiles of dead space fraction by Harris-Benedict and by direct estimation, and of ventilatory ratio, and decreased with successive tertiles of end-tidal-to-arterial PCO$_2$ ratio.

Mortality over the first 28 days was higher in patients in the high group of dead space fraction by Harris Benedict (16.4% vs. 12.3%; $p = 0.003$), but similar in the groups considering the dead space fraction by direct estimation (15.4% vs. 13.3%; $p = 0.100$), and the ventilatory ratio (15.5% vs. 13.2%; $p = 0.080$) (Figure 3). When assessing the end-tidal-to-arterial PCO$_2$ ratio, 28-day mortality was lower in the highest tertile group (10.7% vs. 17.1%; $p < 0.001$).

**Predictive accuracy of markers of impaired ventilation**

The unadjusted impact of each marker of impaired ventilation is shown in eTable 4 in Online Supplement. Estimated dead space fraction (by HB and direct method) and end-tidal-to-arterial PCO$_2$ ratio were associated with 28-day mortality at the start of mechanical ventilation. Twenty-four hours after this, dead space fraction by Harris-Benedict, and end-tidal-to-arterial PCO$_2$ ratio were associated with 28-day mortality. The final multivariable base risk model is shown in eTable 5 and in the Online Supplement. No problems were found due to multicollinearity or linearity assumption (eTables 6 and 7 in Online Supplement).

After adjustment for the base risk model, none of the markers of impaired ventilation measured at the start of ventilation or the following day was significantly associated with 28-day mortality (Table 3). The inclusion of these variables did not improve the AUC-ROC compared to the base model (Figure 4). The addition of dead space fraction by direct estimation at start of ventilation, and of end-tidal-to-arterial PCO$_2$ ratio at start of ventilation
or day 1 slightly improved the predictive accuracy of the base model in terms of IDI (Table 3).

*Sensitivity analysis*

Results after multiple imputation were similar to the primary analysis (eTables 8 and 8, and eFigures 2 and 3 in Online Supplement).
DISCUSSION

The findings of this multicenter, observational cohort study of COVID-19 related ARDS patients showed that surrogate markers for impaired ventilation and increased $V_D/V_T$ increased over the first days of invasive ventilation and were significantly higher in non-survivors than survivors. However, none of these indices was independently associated with mortality when corrected for potential confounders. Therefore, impaired ventilation, and, tentatively, increased dead space fraction, seems to be a marker for disease severity rather than an independent predictor of outcome.

Despite the potential clinical value, $V_D/V_T$ is not routinely measured in daily critical care practice. One possible barrier is the requirement of volumetric capnography (or other techniques of analyzing exhaled gas) to measure $V_d/V_t$. Surrogate measures for estimating $V_D/V_T$ are more frequently utilized and a wide array of these surrogates were included in this study\(^{17,18}\). VR is a recently validated index that is appealing because it is simple to calculate using readily available measurements; it compares arterial carbon dioxide tension ($PaCO_2$) and minute ventilation to corresponding “ideal” and “predicted” values as a stand-in for $V_D/V_T$$^{15}$. The VR was shown to be high in patients with COVID-19 related ARDS\(^3,9\) and is known to show moderate correlation with $V_D/V_T$ by volumetric capnography\(^7\). This index has been validated in controlled modes of mechanical ventilation because the VR depends on the carbon dioxide production $(\dot{V}CO_2)\(^{7,15}\). Any changes in the latter will have significant changes in its value. Recently, the end-tidal-to-arterial $PCO_2$ ratio ($P_{ET}CO_2/PaCO_2$) has been described as another surrogate for $V_D/V_T$ in ARDS patients\(^{14}\). Each of these surrogates has particular limitations and they should be seen as complementary: if all point in the same direction, this likely reflects impaired ventilation. For example, in the presence of increased intrapulmonary shunt (as in ARDS
patients), rising PaCO\(_2\) coincides with decreasing \(P_{ETCO2}\). Both shunt and low cardiac output states are known determinants of \(V_D/V_T\). In the case of shunt, the increase in venous admixture will elevate the PaCO\(_2\) increasing dead space fraction\(^{19}\). This contribution is of special importance when \(V_D/V_T\) is high, where physiologic dead space can be contaminated by the large shunt fractions present in any type of ARDS. In low cardiac output states, a decrease in pulmonary blood flow leads to a reduced alveolar CO\(_2\) delivery decreasing \(P_{E}CO_2\), thereby increasing \(V_D/V_T\)\(^{20}\). In both cases, impaired ventilation indices would capture these phenomena and is hard to know each part's relative contribution in practice. Taken together, dead space indices reflect impaired outgassing of CO\(_2\) because of abnormal ventilation-perfusion matching giving a good global index of a lung’s gas exchange efficiency\(^{21,22}\).

Surrogate measures of impaired ventilation were significantly increased in non-survivors in the first four days of mechanical ventilation compared to survivors. This is line with previous studies in all patients with ARDS (not only those with COVID19), in which dead space (\(V_D/V_T\)) was elevated during the first week after start of invasive ventilation\(^4,23\). We also validated the association between ventilation impairment and outcome that was previously observed in patients with ARDS due to other causes than COVID-19\(^4,23\). However, in our study the investigated surrogates did not add predictive value to a model that included other known predictors for 28-day mortality, with the possible exception of \(P_{ETCO2}/PaCO2\) at the start and at day 1 of ventilation. This contrasts with several studies in ARDS that showed increased dead space ventilation to be a robust and independent predictor of mortality risk\(^4,23–25\). Decreasing \(P_{ETCO2}/PaCO2\) was also independently associated with mortality risk in one study\(^{14}\). Yet, our findings are in line with a previous report in which we assessed the added value of markers of impaired ventilation during the
first days of mechanical ventilation in non-COVID-19 related ARDS. Taken together, the data suggest that markers of impaired ventilation reflect disease severity but are not independent predictors of outcome, irrespective of the cause of ARDS.

In the current study in patients with COVID-19 related ARDS, impaired ventilation was already present in the first days of invasive ventilation. The studied surrogates for $V_D/V_T$ further increased during the first days of invasive ventilation, especially in patients who did not survive. Possible mechanisms include endothelial abnormalities with injury to the capillaries by thrombotic and inflammatory mechanisms and obstruction of pulmonary blood flow leading to altered ventilation-perfusion relationships. In patients with ARDS, a disordered pulmonary ventilation/perfusion ratio results from endothelial injury, microvascular plugging with cellular aggregates and thrombi, with disordered pulmonary blood flow, leading to increased $V_D/V_T^{26}$. Altered hemostasis and thrombosis are postulated to be a key element of ARDS, with the endothelium playing a key role. Endothelial injury activates inflammatory and microthrombotic pathways in which hemostasis initiates thrombogenesis and promotes microthrombogenesis, leading to vascular microthrombotic state$^{27–29}$. Endothelial infection and activation and disorders of the microvasculature have been described in the pathogenesis of COVID-19. Autopsy findings include pulmonary vascular microthrombi$^{30}$ in addition to diffuse alveolar damage. Examination of lung tissue reveals direct viral infection of the pulmonary vascular endothelium and disordered microvascular organization$^{31–33}$ as well as inflammation and complement-mediated endothelial injury$^{34}$. Although the endothelium may play a critical role in the pathogenesis of COVID-related ARDS, other features have been shown as well, such diffuse alveolar damage associated with injury to the alveolar lining, exudative pulmonary edema, and hyaline membrane formation. These pathologic changes are very
similar to those observed in ARDS caused by different pathogens and insults, including pneumonia-initiated SARS and MERS\textsuperscript{35–37}.

The strengths of this study include the size of the multi-center cohort, careful data collection and with few missing data, the pre-specified analysis plan, and the evaluation of multiple surrogates for impaired ventilation. The central limitation of this study is that we did not quantify dead space ventilation directly by volumetric capnography or another technique. This was not possible in the setting of a pandemic, where the critical care systems were overwhelmed with patients. A second limitation is the observational nature of the study. Therefore, this study does not provide insight into potential mechanisms that may contribute to the association between high dead space surrogates and mortality in COVID-19 related ARDS patients. Another important aspect to take into account is the aspect of the instrumental dead space. Use of heated humidifiers of HMEs is heterogeneous in the clinical practice, and different HMEs have different dead space volumes. Instrumental dead space may significantly affect the total dead space, mainly when using low tidal volume ventilation. We did not register the type of system humidification device in our study.

For the estimated $V_D/V_T$ computed by the Harris-Benedict formula, we assumed an RQ of 0.8 for VCO$_2$ calculation based on a previous study\textsuperscript{18}. Although the RQ may vary among ARDS patients, a recently previous work showed a good correlation between the VR (which also depends on the VCO$_2$) and the measured dead space by volumetric capnography\textsuperscript{7}.

The results of this study imply that surrogate markers of ventilation are not independently associated with mortality and the observed effect sizes were remarkably similar to those observed in non-COVID-19 related ARDS with similar methodology. This contrasts
several reports that have hypothesized that profound endothelial injury and coagulopathy may be central mediators of lung injury in COVID-19\textsuperscript{33}. We acknowledge that we did not measure these processes in this study, but we do provide evidence that COVID-19 related ARDS appears to be similar to non-COVID ARDS with respect to Vd/Vt. This implies that dead space and its estimates should be understood as a readily available marker of ARDS severity. Whether a high dead space identifies an enriched patient population with a higher prevalence of vascular injury, and who might benefit from treatments aimed at restoring normal pulmonary perfusion is unknown. Previous data suggest that some drugs with anticoagulant properties may decrease Vd/Vt in patients with ARDS\textsuperscript{38}, making this an attractive hypothesis to consider.

At the moment no data exists on the measurement of physiologic dead space in COVID-19 related ARDS by integrating volumetric capnography plots of eliminated CO\textsubscript{2} concentration versus the respective expired tidal volume of a single breath. Since volumetric capnography offers a more in-depth representation of the kinetics of CO\textsubscript{2} elimination per breath, the application of longitudinal or time-series models to analyze the effect of CO\textsubscript{2} elimination impairment on outcome warrants further research.

**CONCLUSION**

Surrogate markers for impaired ventilation are abnormal at the start of invasive ventilation in patients with COVID-19 related ARDS and worsen during consequent days. Ventilation impairment seems to be more extensive in non-survivors than in survivors, but they do not yield prognostic information when added to a baseline risk model. In the absence of bedside capnography, surrogates of impaired ventilation may serve as an important tool
to assess the severity of COVID-19 related ARDS along with other variables such as oxygenation abnormalities and respiratory mechanics.
LIST OF ABBREVIATIONS

ARDS: Acute Respiratory Distress Syndrome
AUROCC: Area Under the Receiver Operating Characteristic Curve
COVID-19: Coronavirus disease 2019
FiO₂: Fraction of Inspired Oxygen
HB: Harris-Benedict
ICU: Intensive Care Unit
IBW: Ideal Body Weight
IDI: Integrated Discrimination Improvement
MERS: Middle East respiratory syndrome
PaCO₂: Partial pressure of carbon dioxide in arterial blood
PₑCO₂: Expired partial pressure of carbon dioxide
PEEP: Positive End Expiratory Pressure
PaO₂: Partial pressure of oxygen in arterial blood
PaO₂/FiO₂: Arterial oxygen tension to fraction of inspired oxygen
PRoVENT-COVID: PRactice of VENTilation in Patients with Coronavirus Disease 2019
SARS: Severe Acute Respiratory Syndrome
VCO₂: Carbon dioxide consumption
VR: Ventilatory ratio
Vₑ/Vₜ: Dead space fraction
DECLARATIONS

Ethics Approval and Consent to Participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and supporting materials section: Morales-Quinteros, Bos and Serpa Neto had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; the members of the Steering Committee for PRoVENT–COVID Collaborative Group vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

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LMQ, LDB, AA, ASN, MJS and FP, carried out the concept and design.

LMQ, LDB and ASN carried out the statistical analysis.

FP and MJS obtained funding for the present study.

LDB and ASN carried out the supervision the manuscript.

MB, AT participated in the coordination of the study.

All authors contributed in the acquisition, analysis, interpretation of data and drafting of the manuscript.

All authors contributed on the critical revision of the manuscript for important intellectual content.

All authors read and approved the final manuscript.
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FIGURE LEGENDS

Figure 1 - Lung-Specific Physiological Variables Over the First Four Days of Ventilation

Jitter boxplot of lung-specific physiological variables over the first four days of ventilation.

Figure 2 - 28-Day Mortality According to Tertiles of Lung-Specific Physiological Variables Over the First Four Days of Ventilation

(A) tertiles are < 0.54, 0.54 - 0.64 and > 0.64 for start of ventilation, < 0.58, 0.58 - 0.67, > 0.67 for day 1, < 0.62, 0.62 - 0.69, > 0.69 for day 2, and < 0.64, 0.64 - 0.71, > 0.71 for day 3; (B) tertiles are < 1.94, 1.94 - 2.32 and > 2.32 for start of ventilation, < 2.09, 2.09 - 2.47, > 2.47 for day 1, < 2.19, 2.19 - 2.65, > 2.65 for day 2, and < 2.31, 2.31 - 2.80, > 2.80 for day 3; (C) tertiles are < 1.45, 1.45 - 1.80 and > 1.80 for start of ventilation, < 1.57, 1.57 - 1.98, > 1.98 for day 1, < 1.71, 1.71 - 2.13, > 2.13 for day 2, and < 1.80, 1.20 - 2.26, > 2.26 for day 3; and (D) tertiles are < 0.77, 0.77 - 0.91 and > 0.91 for start of ventilation, < 0.79, 0.79 - 0.90, > 0.90 for day 1, < 0.76, 0.76 - 0.87, > 0.87 for day 2, and < 0.74, 0.74 - 0.85, > 0.85 for day 3.

Figure 3 - 28-Day Survival According to Lung-Specific Physiological Variables Measured at the Start of Ventilation

Groups were created according to the median of the variables at start of ventilation; \( p \) values from Log-rank tests

Figure 4 - Receiver-Operating Characteristics Curve of the Base Model and With the Inclusion of Lung-Specific Physiological Variables
Additional material is provided in the Online Supplement:

- File name: Online supplement
- File format: .pdf
- Title: Impaired ventilation is not associated with 28-day mortality in COVID-19 ARDS
- Description of data: methods, tables and figure