# Impaired Ventilation Is Not Independently Associated With 28-day Mortality in COVID-19 ARDS

**Luis Morales-Quinteros** ( luchomq2077@gmail.com )
Sagrat Cor University Hospital: Hospital Universitari Sagrat Cor https://orcid.org/0000-0002-8937-9824
**Ary Serpa Neto**
Australian and New Zealand Intensive Care Research Centre (ANZIC-RC)
**Antonio Artigas**
Universidad Autónoma de Barcelona: Universitat Autonoma de Barcelona
**Lluis Blanch**
Fundació Parc Taulí: Fundacio Parc Tauli
**Michela Botta**
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
**David A Kaufman**
NYU Langone Medical Center: NYU Langone Health
**Marcus J Schultz**
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
**Anissa Tsonas**
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
**Frederick Paulus**
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC
**Lieuwe D Bos**
Amsterdam UMC - Locatie AMC: Amsterdam UMC Locatie AMC

**Research**

**Keywords:** Acute respiratory distress syndrome, ARDS, Respiratory dead space, Dead space, Ventilatory ratio, COVID-19, Mortality, prognostication

**Posted Date:** January 21st, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-150970/v1

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

Writing committee: Luis Morales-Quinteros[1,2,3], Ary Serpa Neto[4,5,6,7], Antonio Artigas[2,3,8,9], Lluis Blanch[2,3,8,9], Michela Botta[4], David A. Kaufman[10], Marcus J. Schultz[4,11,12], Anissa Tsonas[4], Frederick Paulus[4], Lieuwe D. Bos[4].
On behalf of the PRoVENT-COVID study group.

[1]Intensive Care Unit, Hospital Universitari Sagrat Cor, Grupo Quironsalud, Barcelona, Spain.
[2]Universidad Autonoma de Barcelona, Barcelona, Spain.
[3]Institut d'Investigació i Innovació Parc Taulí I3PT, Sabadell, Spain
[4]Department of Intensive Care & Laboratory of Experimental Intensive Care and Anaesthesiology (L·E·I·C·A), Amsterdam UMC location AMC, Amsterdam, the Netherlands.
[5]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil
[6]Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia.
[7]Data Analytics Research & Evaluation (DARE) Centre, Austin Hospital and University of Melbourne, Melbourne, Australia
[8]Critical Care Center, Corporacion Sanitaria Universitaria Parc Taulí, Sabadell, Spain.
[9]CIBER Enfermedades Respiratorias (ISCiii), Madrid, Spain
[10]Division of Pulmonary, Critical Care, and Sleep Medicine, NYU School of Medicine, New York, New York, USA.
[11]Nuffield Department of Medicine, Oxford University, Oxford, UK.
[12]Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand.

Author's information: A complete list of members of the PRoVENT-COVID collaborative group is provided:
STEERING COMMITTEE: (in alphabetic order) A.G. Algera, L.S. Boers; L.D.J. Bos; M. Botta; J. Pillay, D.A. Dongelmans, M.W. Hollmann; J. Horn; F. Paulus; A. Serpa Neto; M.J. Schultz; A.M. Tsonas, A.P. Vlaar.
STUDY COORDINATORS: (in alphabetic order) M. Botta; A.M. Tsonas.
Investigators: (in alphabetic order): J.P. van Akkeren; A.G. Algera; C.K. Algoe; R.B. van Amstel; Artigas A; O.L. Baur; P. van de Berg; A.E. van den Berg; D.C.J.J. Bergmans; D.I. van den Bersselaar; F.A. Bertens; A.J.G.H. Bindels; M.M. de Boer; S. den Boer; L.S. Boers; M. Bogerd; L.D.J. Bos; M. Botta; J.S. Breel; H. de Bruin; S. de Bruin; C.L. Bruna; L.A. Buiteman–Kruizinga; O. Cremer; R.M. Determann; W. Dieperink; D.A. Dongelmans; H.S. Franke; M.S. Galek–Aldridge; M.J. de Graaff; L.A. Hagens; J.J. Haringman; S.T. van

der Heide; P.L.J. van der Heiden; N.F.L. Heijnen; S.J.P. Hiel; L.L. Hoeijmakers; L. Hol; M. W. Hollmann; M.E. Hoogendoorn; J. Horn; R. van der Horst; E.L.K. Ie; D. Ivanov; N.P. Juffermans; E. Kho; E.S. de Klerk; A.W.M.M Koopman-van Gemert; M. Koopmans; S. Kucukcelebi; M.A. Kuiper; D.W. de Lange; N. van Mourik; Morales-Quinteros L; S.G. Nijbroek; M. Onrust; E.A.N. Oostdijk; F. Paulus; C.J. Pennartz; J. Pillay; L. Pisani; I.M. Purmer; T.C.D. Rettig; J.P Roozeman; M.T.U. Schuijt; M.J. Schultz; A. Serpa Neto; M.E. Sleeswijk; M.R. Smit; P.E. Spronk; W. Stilma; A.C. Strang; A. M. Tsonas; P.R Tuinman; C.M.A. Valk; F.L. Veen-Schra; L.I. Veldhuis; P. van Velzen; W.H. van der Ven; A.P.J. Vlaar; P. van Vliet; P.H.J. van der Voort; L. van Welie; H.J.F.T. Wesselink; H.H. van der Wier-Lubbers; B. van Wijk; T. Winters; W.Y. Wong; A.R.H. van Zanten.

Word counts: 312 (abstract) and 3564 words (body of text)
References: 38 references
Inserts: 3 tables and 4 figures
Electronic supplement: 1 appendix

**Corresponding author:**
Luis Morales-Quinteros
Intensive Care Unit
Hospital Universitari Sagrat Cor, Grupo Quironsalud
Carrer de Viladomat, 288
08029 Barcelona, Spain
Email: luchomq2077@gmail.com

PRoVENT collaborative group e-mail: provent-covid@amsterdamumc.nl

**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 $PCO_2$ 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 $PCO_2$ 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[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[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[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)[13]:

$$\frac{V_D}{V_T} = 1 - \frac{\left(0.863 * \dot{V}CO_2\right)}{(RR * V_T * PaCO_2)} \; Eq.(1)$$

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 $CO_2$ production in mL/min estimated using the Eq. (2):

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

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)[13]:

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

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

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 $PCO_2$ ratio[14], and the formulas are described in the **Online Supplement**.

The secondary exposure of interest is the VR, calculated using the Eq. (4)[15]:

$$VR = \frac{\dot{V}_{E\ measured} * PaCO_{2\ measured}}{\dot{V}_{E\ predicted} * PaCO_{2\ predicted}}\ Eq.(4)$$

VR is the ventilatory ratio, $V_{E\ measured}$ is the measured minute ventilation in mL/min, $PaCO_{2\ measured}$ is the measured $PaCO_2$ in mmHg, $V_{E\ predicted}$ is the predicted minute ventilation in mL/min (calculated as 100 * predicted body weight)[15], and $PaCO_{2\ predicted}$ 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, $PaO_2/FiO_2$ 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)[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 $FiO_2$, had higher levels of lactate and creatinine, and lower levels of pH and end-tidal-to-arterial $PCO_2$.

*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 $PCO_2$ 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 Vd/Vt. 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 $P_{ET}CO2$. 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 $P_ECO_2$, 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 $P_{ET}CO_2/PaCO_2$ 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 $P_{ET}CO_2/PaCO_2$ 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[8]. 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[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[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[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[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 $V_D/V_T$ in patients with ARDS[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 $CO_2$ concentration versus the respective expired tidal volume of a single breath. Since volumetric capnography offers a more in-depth representation of the kinetics of $CO_2$ elimination per breath, the application of longitudinal or time-series models to analyze the effect of $CO_2$ 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

$FiO_2$: Fraction of Inspired Oxygen

HB: Harris-Benedict

ICU: Intensive Care Unit

IBW: Ideal Body Weight

IDI: Integrated Discrimination Improvement

MERS: Middle East respiratory syndrome

$PaCO_2$: Partial pressure of carbon dioxide in arterial blood

$P_ECO_2$: Expired partial pressure of carbon dioxide

PEEP: Positive End Expiratory Pressure

$PaO_2$: Partial pressure of oxygen in arterial blood

$PaO_2/FiO_2$: Arterial oxygen tension to fraction of inspired oxygen

PRoVENT-COVID: PRactice of VENTilation in Patients with Coronavirus Disease 2019

SARS: Severe Acute Respiratory Syndrome

$\dot{V}CO_2$: Carbon dioxide consumption

VR: Ventilatory ratio

$V_D/V_T$: 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.

Competing Interests: Dr Bos receives funding from the Dutch lung foundation (longfonds), from the Innovative Medicine Initiative and from Amsterdam UMC via the AUMC fellowship. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Funding: This article did not receive sponsorship for publication

Author contributions:

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.

Acknowledgements: Not applicable

**REFERENCES**


1. Wu Z, McGoonan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-1242.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia inWuhan, China. *JAMA*. 2020;323:1061-1069.
3. Liu X, Liu X, Xu Y, et al. Ventilatory Ratio in Hypercapnic Mechanically Ventilated Patients with COVID-19 Associated ARDS. *Am J Respir Crit Care Med*. 2020;201:1297-1299.
4. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med*. 2002;346:1281-1286.
5. Kallet RH, Zhuo H, Liu KD, et al. The association between physiologic dead-space fraction and mortality in subjects with ARDS enrolled in a prospective multi-center clinical trial. *Respir Care.* 2014;59:1611-1618.
6. Beitler JR, Thompson BT, Matthay MA, et al. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. *Crit Care Med*. 2015;43:1026-1035.
7. Sinha P, Calfee CS, Beitler JR, et al. Physiologic Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med*. 2019;199:333-341.
8. Morales-Quinteros L, Schultz MJ, Bringué J, et al. Estimated dead space fraction

and the ventilatory ratio are associated with mortality in early ARDS. *Ann Intensive Care*. 2019;9:128.

9. Schenck EJ, Hoffman K, Goyal P, et al. Respiratory Mechanics and Gas Exchange in COVID-19 Associated Respiratory Failure. *Ann Am Thorac Soc*. 2020;17:1158-1161.
10. Boers NS, Botta M, Tsonas AM, et al. Practice of Ventilation in Patients with Novel Coronavirus Disease (PRoVENT-COVID): rationale and protocol for a national multicenter observational study in The Netherlands. *Ann Transl Med. 2020*;8:1251.
11. Paulus F. PRoVENT-COVID. In: https://sites.google.com/view/provent-covid/provent-covid?authuser=0. Accessed 12 Jan 2021.
12. Prokop M, van Everdingen W, van Rees Vellinga T, et. al. CO-RADS - A categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. *Radiology*. 2020;296:E97-E104.
13. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. *Proc Natl Acad Sci U S A*. 1918;4:370-373.
14. Kallet RH, Lipnick MS. END-TIDAL-TO-ARTERIAL PCO2 RATIO AS SIGNIFIER FOR PHYSIOLOGIC DEADSPACE RATIO AND OXYGENATION DYSFUNCTION IN ACUTE RESPIRATORY DISTRESS SYNDROME. *Respir Care*. 2020;Jul 7:respcare. 08061. Online ahead of print.
15. Sinha P, Fauvel NJ, Singh S, et al. Ventilatory ratio: a simple bedside measure of ventilation. *Br J Anaesth*. 2009;102:692-697.
16. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-

project.org/.

17. Siddiki H, Kojicic M, Li G, Yilmaz M, et al. Bedside quantification of dead-space fraction using routine clinical data in patients with acute lung injury: secondary analysis of two prospective trials. *Crit Care*. 2010;14:R141.
18. Beitler JR, Thompson BT, Matthay MA, et al. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. *Crit Care Med*. 2015;43:1026-1035.
19. Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! *Intensive Care Med*. 2011;37:735-746.
20. Mosing M, Kutter AP, Iff S, et al. The effects of cardiac output and pulmonary arterial hypertension on volumetric capnography derived-variables during normoxia and hypoxia. *J Clin Monit Comput*. 2015;29:187-196.
21. Suarez-Sipmann, Bohm S, Tusman G. Volumetric capnography: the time has come. *Curr Opin Crit Care*. 2014;20:333-339.
22. Lucangelo U, Bernabè F, Vatua S, et al. Prognostic value of different dead space indices in mechanically ventilated patients with acute lung injury and ARDS. *Chest*. 2008;133:62-71.
23. Kallet RH, Alonso JA, Pittet JF, et al. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. *Respir Care*. 2004;49:1008-1014.
24. Kallet RH, Zhuo H, Ho K, Lipnick MS, et al. Lung Injury Etiology and Other Factors Influencing the Relationship Between Dead-Space Fraction and Mortality in ARDS. *Respir Care*. 2017;62:1241-1248.
25. Raurich JM, Vilar M, Colomar A, et al. Prognostic value of the pulmonary dead-

space fraction during the early and intermediate phases of acute respiratory distress syndrome. *Respir Care*. 2010;55:282-287.

26. Tomashefski JF Jr, Davies P, Boggis C, et al. The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol 1983*. 1983;112:112-126.
27. Chang JC. Hemostasis based on a novel “two-path unifying theory” and classification of hemostatic disorders. *Blood Coagul Fibrinolysis*. 2018;29:573-584.
28. Chang JC. Thrombogenesis and thrombotic disorders based on “two-path unifying theory of hemostasis”: philosophical, physiological and phenotypical interpretation. *Blood Coagul Fibrinolysis*. 2018;29:585-595.
29. Chang JC. Acute Respiratory Distress Syndrome as an Organ Phenotype of Vascular Microthrombotic Disease: Based on Hemostatic Theory and Endothelial Molecular Pathogenesis. *Clin Appl Thromb*. 2019;25:1-20.
30. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*. 2020;173:268-277.
31. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417-1418.
32. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128.
33. Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. . *Am J Respir Crit Care Med*. 2020;202:690-699.
34. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury

and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1-13.

35. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol*. 2013;11:836-848.

36. Franks TJ, Chong PY, Chui P, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. *Hum Pathol*. 2003;34:743-748.

37. Hariri LP, North CM, Shih AR, et al. Lung histopathology in COVID-19 as compared to SARS and H1N1 influenza : A systematic Review. *Chest*. 2021;159: 73-84.

38. Liu KD, Levitt J, Zhuo H, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. *Am J Respir Crit Care Med*. 2008;178:618-623.

**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

# Figures

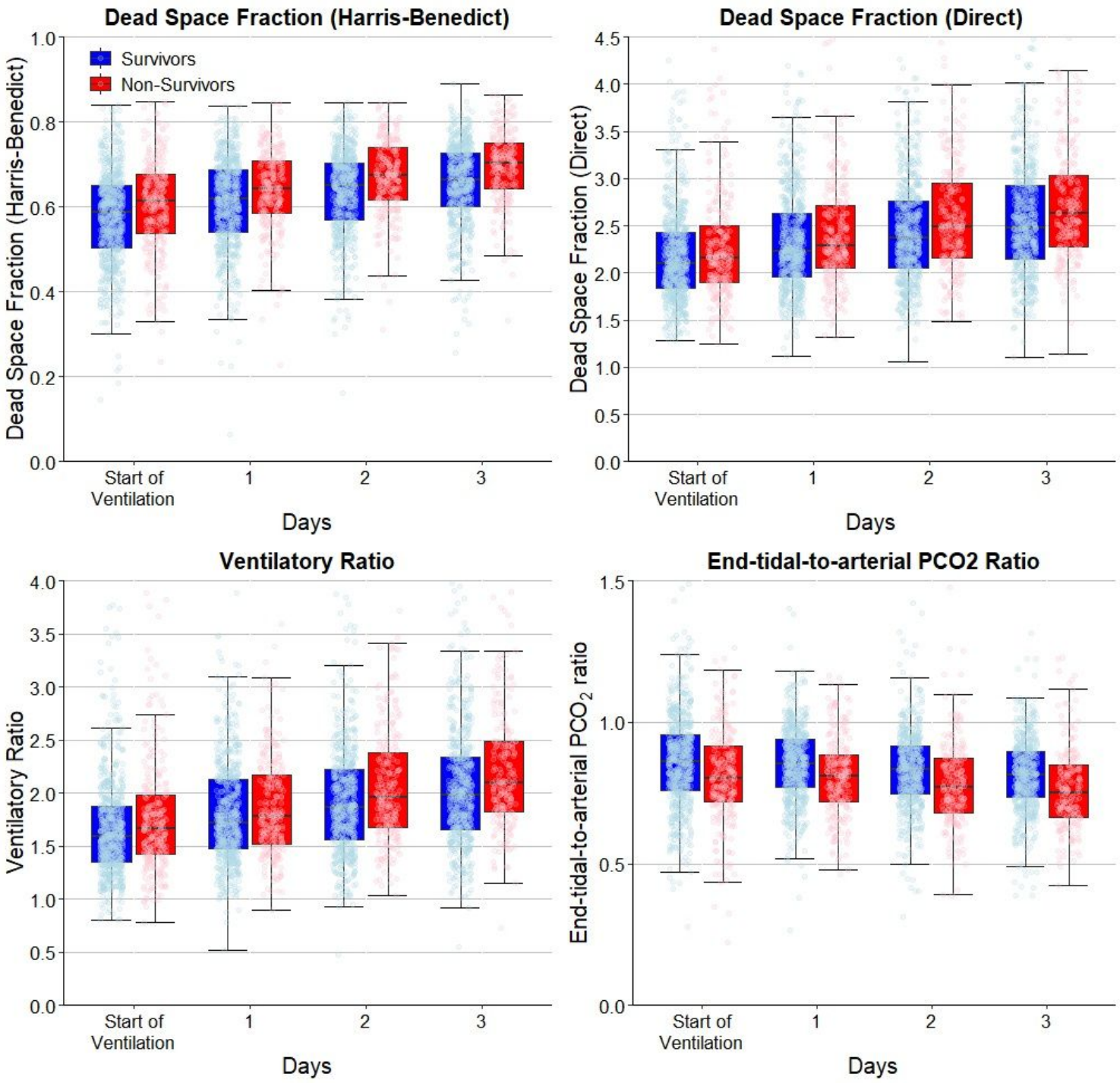
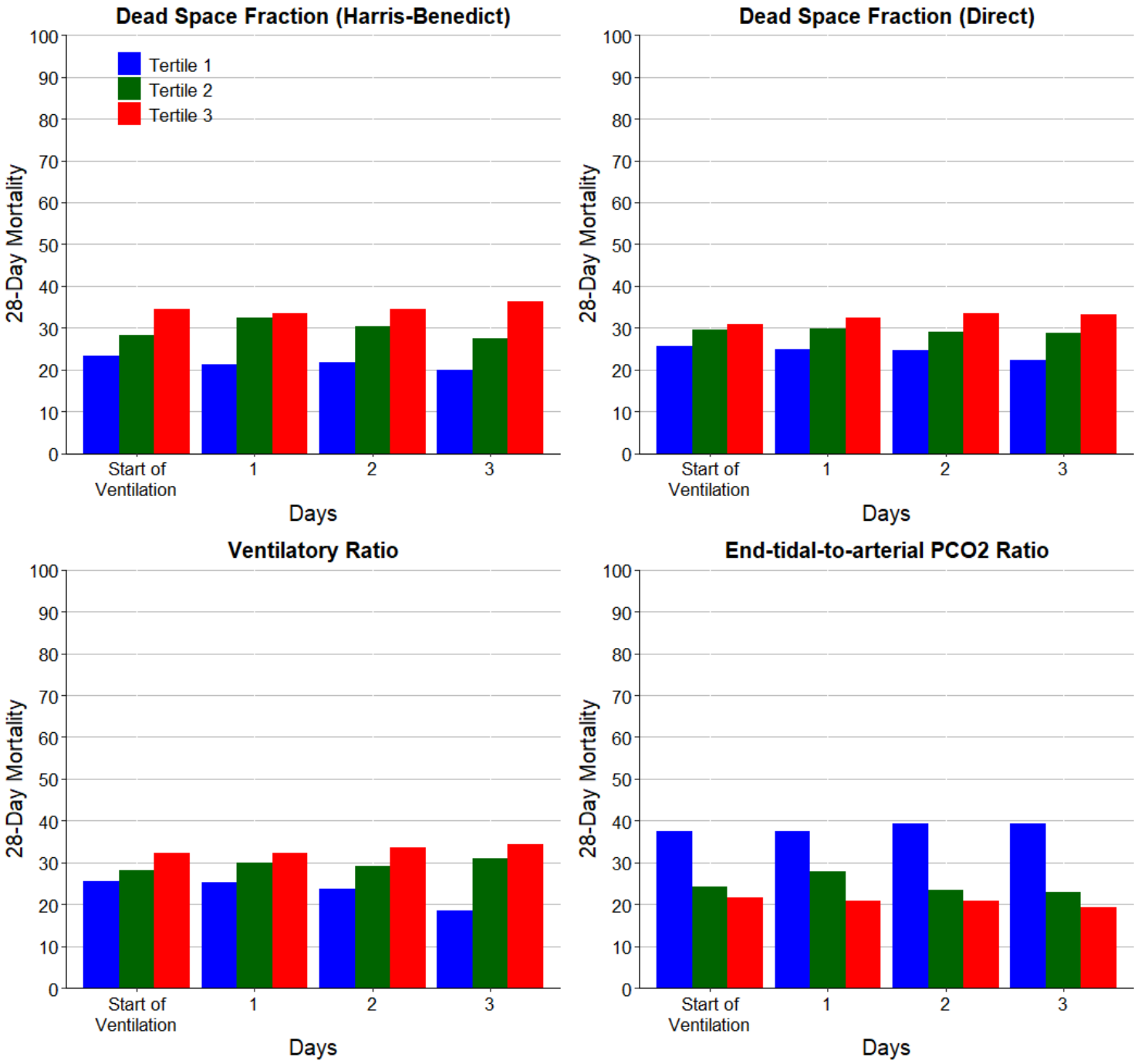



**Figure 1**

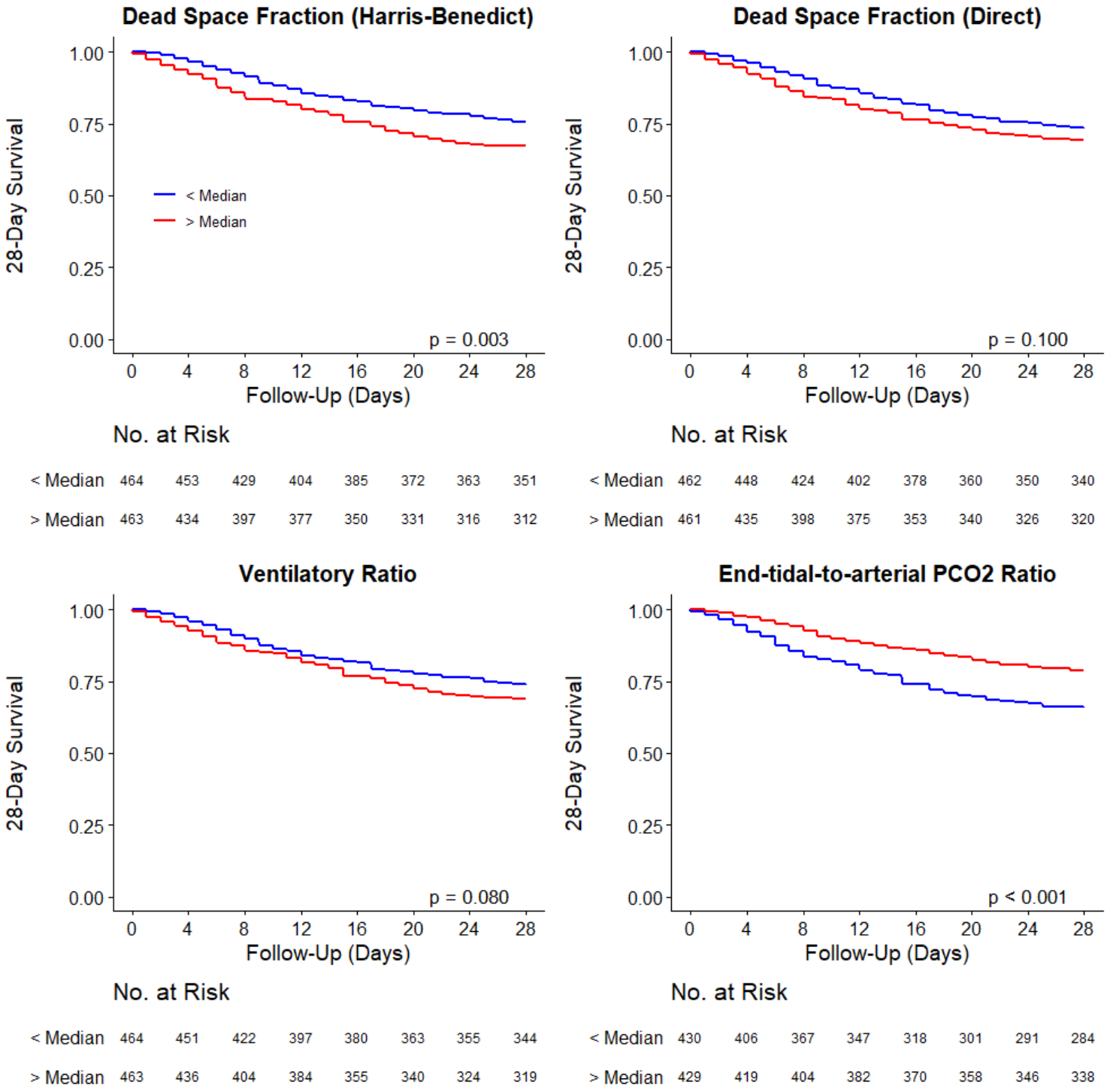
Lung-Specific Physiological Variables Over the First Four Days of Ventilation Jitter boxplot of lung-specific physiological variables over the first four days of ventilation.




## 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

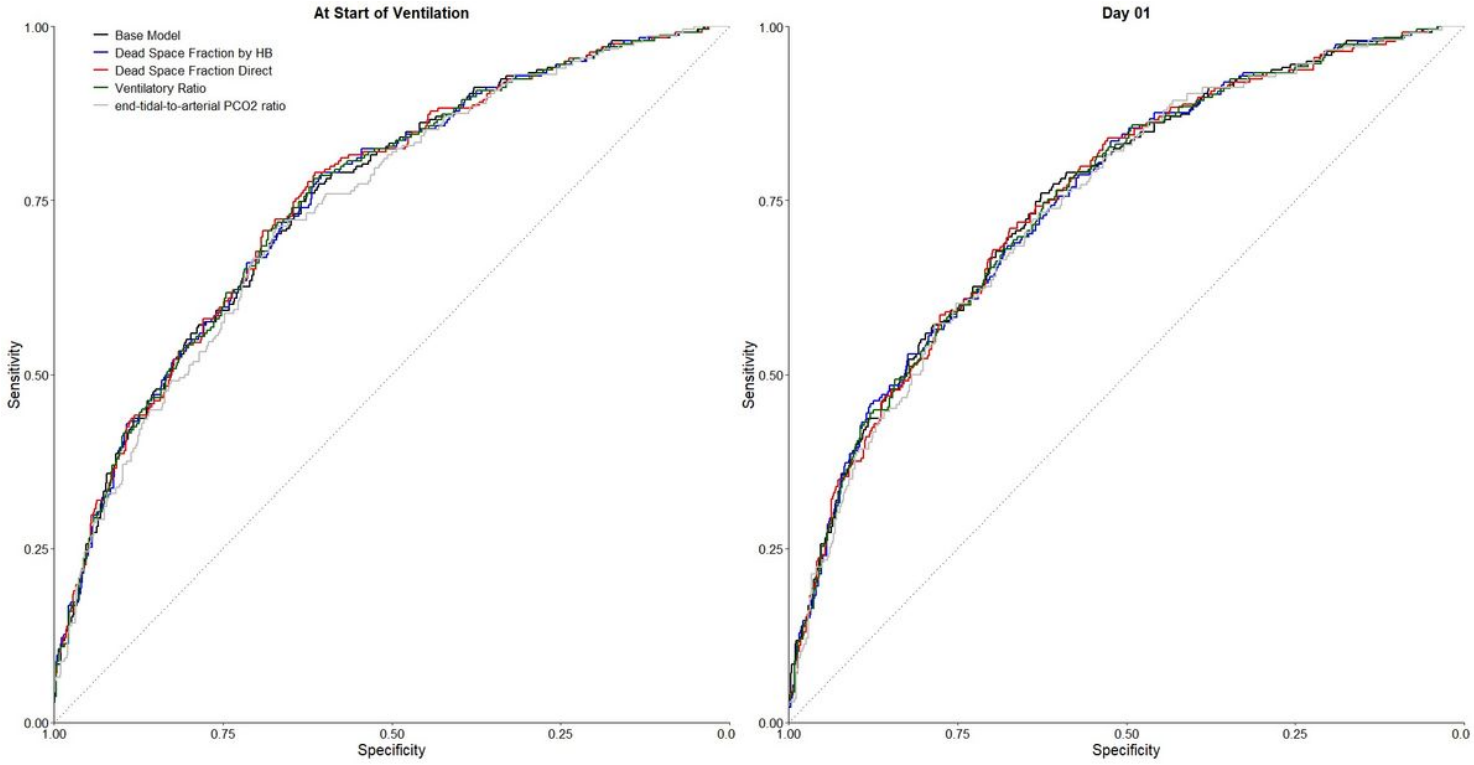



**Figure 4**

Receiver-Operating Characteristics Curve of the Base Model and With the Inclusion of Lung-Specific Physiological Variables

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- OnlineSupplement.pdf
- Table1.docx
- Table2.docx
- Table3.docx