Corrected Minute Ventilation Is Associated With Mortality in ARDS Caused by COVID-19

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BACKGROUND: The ratio of dead space to tidal volume (V_D/V_T) is associated with mortality in patients with ARDS. Corrected minute ventilation ($\dot{V}_{E_{corr}}$) is a simple surrogate of dead space, but, despite its increasing use, its association with mortality has not been proven. The aim of our study was to assess the association between $\dot{V}_{E_{corr}}$ and hospital mortality. We also compared the strength of this association with that of estimated V_D/V_T and ventilatory ratio. METHODS: We performed a retrospective study with prospectively collected data. We evaluated 187 consecutive mechanically ventilated subjects with ARDS caused by novel coronavirus disease (COVID-19). The association between $\dot{V}_{E_{corr}}$ and hospital mortality was assessed in multivariable logistic models. The same was done for estimated V_D/V_T and ventilatory ratio. RESULTS: Mean ± SD $\dot{V}_{E_{corr}}$ was 11.8 ± 3.3 L/min in survivors and 14.5 ± 3.9 L/min in nonsurvivors ($P < .001$) and was independently associated with mortality (adjusted odds ratio 1.15, $P = .01$). The strength of association of $\dot{V}_{E_{corr}}$ with mortality was similar to that of V_D/V_T and ventilatory ratio. CONCLUSIONS: $\dot{V}_{E_{corr}}$ was independently associated with hospital mortality in subjects with ARDS caused by COVID-19. $\dot{V}_{E_{corr}}$ could be used at the patient's bedside for outcome prediction and severity stratification, due to the simplicity of its calculation. These findings need to be confirmed in subjects with ARDS without viral pneumonia and when lung-protective mechanical ventilation is not rigorously applied. *Key words: respiration; artificial; pneumonia; viral.* [Respir Care 2021;66(4):619–625. © 2021 Daedalus Enterprises]

Introduction

The ratio of dead space to tidal volume (V_D/V_T) is independently associated with mortality in patients with ARDS.[1-3] Measurement of V_D/V_T is challenging and impractical at the bedside, requiring volumetric capnography, indirect calorimetry, or Douglas bag technique to measure partial pressure of mean expired CO_2.[4] Alternatively, V_D/V_T can be estimated without a direct measurement of exhaled CO_2. This estimated V_D/V_T is correlated with measured V_D/V_T and is associated with outcome in patients with ARDS.[5-7] Ventilatory ratio, a surrogate measurement of V_D/V_T, is obtained by multiplying actual minute ventilation ($\dot{V}_E$) by P_{aCO_2} and dividing the result by the product of ideal $\dot{V}_E$ and ideal P_{aCO_2}. Ventilatory ratio is correlated with measured V_D/V_T and is associated with an increased risk of adverse outcomes in patients with ARDS, similar to V_D/V_T.[8] Corrected $\dot{V}_E$ ($\dot{V}_{E_{corr}}$) is another possible surrogate of V_D/V_T that is easier to calculate than ventilatory ratio.[9] $\dot{V}_{E_{corr}}$ is the $\dot{V}_E$ required to obtain the normal P_{aCO_2} value of 40 mm Hg.[10] $\dot{V}_{E_{corr}}$ was used as a surrogate measurement of dead space both during invasive mechanical ventilation in patients with ARDS and during the use of high-flow nasal cannula therapy in patients with hypoxemic respiratory failure.[11-14] Despite its increasing use, evidence supporting the use of $\dot{V}_{E_{corr}}$ to assess the severity of respiratory failure is lacking and its association with mortality has not been proven. The aim of our study was to assess

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Supplementary material related to this paper is available at http://www.rcjournal.com.

The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.08314

the association between $\dot{V}_{E_{corr}}$ as the simplest surrogate of V_D and hospital mortality in subjects with ARDS caused by COVID-19. Moreover, we compared the strength of this association with that of estimated V_D/V_T and ventilatory ratio.

Methods

This retrospective observational study of prospectively collected data was performed at the Poliambulanza Foundation Hospital of Brescia in Lombardy, Italy. All consecutive patients with laboratory-confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, referred to ICU between February 26 and April 29, 2020, were enrolled. Brescia's ethics committee approved the study and waived the need for informed consent due to the retrospective nature of the study. Subjects were eligible if they were ≥ 18 y old, had ARDS (per the Berlin Definition[9]) secondary to COVID-19, and received invasive mechanical ventilation. All subjects were managed according to our institution's protocol for lung-protective mechanical ventilation in ARDS (see the supplementary materials at http://www.rcjournal.com).

$\dot{V}_{E_{corr}}$ was calculated as $(\dot{V}_{E_{corr}} \times P_{aCO_2})/40$ mm Hg, where 40 mm Hg is the ideal value of P_{aCO_2}.[9] Estimated V_D/V_T was calculated as $1 - \frac{(k \times \dot{V}_{CO_2})}{f \times V_T \times P_{aCO_2}}$, where k is a constant needed to convert gas concentration to partial pressure, $\dot{V}_{CO_2}$ is CO_2 production, and f is the breathing frequency. $\dot{V}_{CO_2}$ was calculated from resting energy expenditure (determined with the Harris Benedict equation) by the rearranged Weir equation (see the supplementary materials at http://www.rcjournal.com).[6] Ventilatory ratio was calculated as $\frac{\dot{V}_E \times P_{aCO_2}}{\text{predicted ideal } \dot{V}_E \times \text{ideal } P_{aCO_2}}$, where predicted ideal $\dot{V}_E$ is estimated as 0.1 L/kg and ideal P_{aCO_2} is the expected P_{aCO_2} in normal lungs if ventilated with the predicted $\dot{V}_E$. Ideal P_{aCO_2} for the ventilatory ratio calculation was set as 37.5 mm Hg as in previous works.[15] Predicted body weight was calculated as 50 + 0.91 (height in cm – 152.4) for male subjects and as 45.5 + 0.91 (height in cm – 152.4) for female subjects. All measurements were taken from data collected during the first 24 h of ICU stay, and the worst values were used for the current analysis.

The primary objective was to assess the independent association between $\dot{V}_{E_{corr}}$ and hospital mortality. The secondary objective was to assess the association between both estimated V_D/V_T and ventilatory ratio with hospital outcome.

Statistical Analysis

We planned to include in the analysis 180 subjects who had either been discharged from hospital or who had died (nonsurvivors). We estimated the need to observe 90 outcomes, therefore 9 variables could be included in the final model.[16]

Variables were described with mean ± SD or median (interquartile range) as appropriate, while factor variables were described as count (percentage). Data were compared between survivors and nonsurvivors at hospital discharge; the *t* test was used for numeric normally distributed variables, Wilcoxon-Mann-Whitney test was used for ordinal and non-normally distributed numerical variables, and the Fisher exact test was used for nominal variables.

The association between $\dot{V}_{E_{corr}}$ and hospital mortality was assessed with 2 different logistic models, which differed in the choice criteria of the covariates that were included to adjust the estimate. The first was the post hoc model, which adjusted the association between hospital mortality and $\dot{V}_{E_{corr}}$ for the following variables if they were significantly different ($P < .05$) in survivors and nonsurvivors: age, sex, body mass index, history of diabetes mellitus or arterial hypertension, organ dysfunction as assessed with the six fields of the Sequential Organ Failure Assessment (SOFA), PEEP, V_T/kg of predicted body weight, airway plateau pressure, driving pressure, respiratory system compliance. We planned to exclude P_{aO_2}/F_{IO_2}, P_{aO_2}, and F_{IO_2} from multiple analysis because they were already included in the SOFA respiratory subscore; P_{aCO_2} was excluded because it was used in the calculation of $\dot{V}_{E_{corr}}$. The second model was the a priori model, which was built starting from the initial logistic regression model with hospital mortality as a binary outcome and $\dot{V}_{E_{corr}}$ as the unique explanatory variable. The model was built in a stepwise fashion, with age and sex as a first step, then body mass index and the number of comorbidities, then the successive non-respiratory SOFA

QUICK LOOK

Current knowledge

The ratio of dead space to tidal volume (V_D/V_T) is strongly associated with hospital mortality in patients with ARDS. Using V_D/V_T can be impractical in daily practice because its measurement requires specific devices and its estimation requires calculation.

What this paper contributes to our knowledge

Corrected minute ventilation is a surrogate of V_D/V_T that is easy to calculate at the bedside. Similar to V_D/V_T, corrected minute ventilation was independently associated with hospital mortality in subjects with ARDS secondary to COVID-19. Therefore, corrected minute ventilation can be a reliable assessment of the dead space, which could be used for severity stratification or outcome prediction.

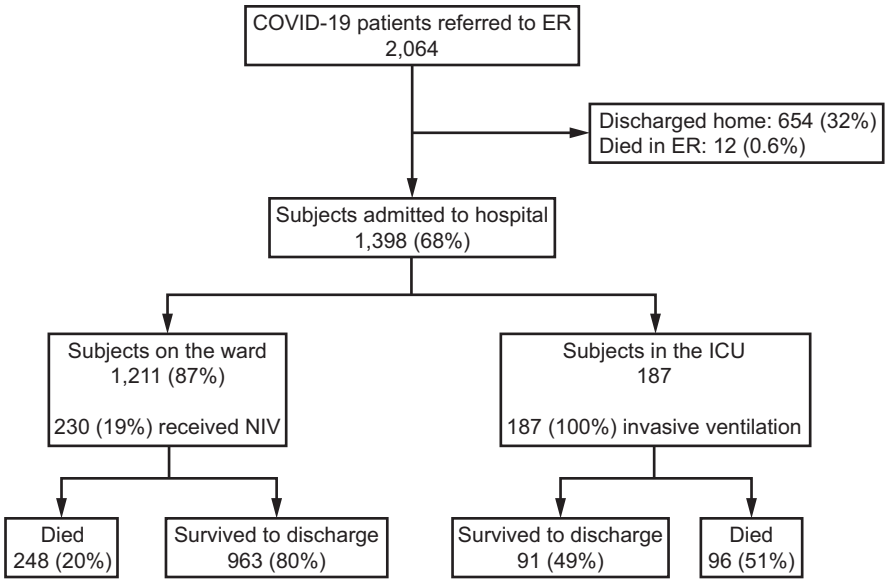

Fig. 1. Flow chart. ER = emergency room; NIV = noninvasive ventilation.

scores, then P_{aO_2}/F_{IO_2}, and finally the respiratory system compliance. At every step, the likelihood ratio test was used to assess if the more complex model fitted the data better than the simpler one. If this was true, the additional parameters were added to the more complex model in the following step, otherwise they were added to the simpler model. Residual multicollinearity in the regression models was assessed with the variance inflation factor (VIF). Variables with VIF > 5 were removed one by one from the model, beginning from the covariate with the highest VIF. The associations between hospital mortality and estimated V_D/V_T, and between hospital mortality and ventilatory ratio, were assessed with a process similar to that described above for $\dot{V}_{E_{corr}}$. The post hoc and a priori models with $\dot{V}_{E_{corr}}$, estimated V_D/V_T and ventilatory ratio, were compared in terms of second-order Akaike Information Criteria (AICc), assessing the δ AICs and the evidence ratio (see the supplementary materials at http://www.rcjournal.com).[17-19] Linearity assumption was assessed by plotting the independent variable versus predicted logit for each final model described.

Cases with missing data were excluded from analysis. Statistical analyses were performed with R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 2,064 patients were referred to the emergency department of our hospital, of whom 187 were admitted to the ICU with respiratory failure secondary to SARS-CoV-2 infection (Fig. 1). The characteristics of ICU survivors and nonsurvivors are shown in Table 1. Subjects who died were more frequently male, older, with more days of noninvasive ventilation before ICU admission, and more severe organ dysfunctions (apart from

Table 1. Clinical Characteristics of Subjects With COVID-19

	Alive ($n = 91$)	Died ($n = 96$)	P
Subjects	91 (49)	96 (51)	
Sex			.035
Female	26 (29)	15 (16)	
Male	65 (71)	81 (84)	
Age, y	63 (56–69)	68 (64–72)	< .001
Body mass index, kg/m^2	28.0 (25.0–3.5)	28.00 (26.0–31.0)	.58
Hypertension	19 (21)	22 (23)	.86
Diabetes	10 (11)	13 (14)	.66
Length of hospital stay before ICU admission, d	2.5 (0.0–6.0)	3.00 (0.0–6.0)	.68
Duration of NIV before ICU admission, d	0.0 (0.0–2.0)	1.0 (0.0–4.0)	.02
SOFA score	6 (5–7)	8 (5–9)	.001
Respiratory score	3 (3–4)	4 (3–4)	.003
Coagulation score	0 (0–0)	0 (0–0)	.27
Liver score	0 (0–0)	0 (0–0)	.84
Cardiovascular score	1 (1–3)	1 (1–4)	.007
Neurological score	0 (0–0)	0 (0–0)	.030
Renal score	0 (0–1)	1 (0–2)	.004
SAPS II score	34 (30–40)	39 (35–47)	< .001
Length of hospital stay, d	32.0 (22.8–43.2)	14.5 (8.8–23.0)	< .001
Length of ICU stay, d	22.0 (11.0–31.0)	9.0 (4.8–17.2)	< .001

Data are presented n (%), mean (SD), or median [interquartile range]. $P \leq .05$ was considered statistically significant.
NIV = noninvasive ventilation
SOFA = Sequential Organ Failure Assessment
SAPS = Simplified Acute Physiology Score

Table 2. Mechanical Ventilation and Respiratory Physiology Characteristics

	Alive ($n = 91$)	Died ($n = 96$)	P
V_T per kg predicted body weight, mL/kg	5.8 (5.5–6.3)	5.8 (5.5–6.2)	.77
Breathing frequency, breaths/min	23 (2)	23 (3)	.95
$\dot{V}_E$, L/min	9.0 (1.3)	9.0 (1.3)	.67
PEEP, cm H_2O	11 (3)	12 (3)	.09
F_{IO_2}	0.6 (0.2)	0.7 (0.2)	< .001
pH	7.33 (0.09)	7.24 (0.11)	< .001
P_{aCO_2}, mm Hg	52 (13)	64 (15)	< .001
P_{aO_2}, mm Hg	80 (70–96)	80 (70–95)	.75
P_{aO_2}/F_{IO_2}	150 (51)	124 (41)	< .001
Driving pressure, cm H_2O	11 (3)	11 (3)	.21
Respiratory system compliance, mL/cm H_2O	39 (11)	37 (11)	.56
$\dot{V}_{E_{corr}}$, L/min	11.8 (3.3)	14.5 (3.9)	< .001
V_D/V_T	0.62 (0.10)	0.69 (0.08)	< .001
Ventilatory ratio	1.87 (1.52–2.15)	2.27 (1.85–2.75)	< .001

Data are shown as mean (SD) or median (interquartile range). $P \leq .05$ was considered statistically significant.
VT = tidal volume
$\dot{V}_E$ = minute ventilation
$\dot{V}_{E_{corr}}$ = corrected minute ventilation
V_D/V_T = ratio of dead space to tidal volume

coagulative and hepatic dysfunctions) than survivors. Arterial hypertension and diabetes mellitus were not associated with hospital mortality. Nonsurvivors had a longer stay in ICU and in the hospital than survivors.

Data regarding mechanical ventilation and respiratory physiology are shown in Table 2. All subjects were subjected to the same mechanical ventilation protocol, so the ventilatory settings were similar in survivors and nonsurvivors except for F_{IO_2}. The F_{IO_2} needed to obtain the same oxygenation target was higher in nonsurvivors than in survivors. Nonsurvivors had similar respiratory system compliance but higher $\dot{V}_{E_{corr}}$ than survivors. Likewise, estimated V_D/V_T and ventilatory ratio were higher in nonsurvivors. This is explained by the strong correlation among $\dot{V}_{E_{corr}}$, estimated V_D/V_T, and ventilatory ratio, with all the correlation coefficients being significantly different from 0 ($r > 0.8$ and $P < .001$ for each relationship).

The comparisons between all the evaluated a priori models are shown in the supplementary materials (available at http://www.rcjournal.com). The best model was the one adjusted for age, sex, number of comorbidities, body mass index, and P_{aO_2}/F_{IO_2} for all 3 estimates of V_D. Table 3 shows the adjusted odds ratios of $\dot{V}_{E_{corr}}$, V_D/V_T, and ventilatory ratio for hospital mortality. All 3 estimates of V_D were independently associated with hospital mortality when assessed in both the post hoc model and in the a priori model. The adjusted odds ratios in the post hoc and a priori models were very similar. The AICc comparisons among the models are shown in Table 4 (for an in-depth explanation of Akaike Information Criteria, see the supplementary materials at http://www.rcjournal.com). The a priori models had AICc lower than the post hoc models, and the best model used ventilatory ratio as an assessment of V_D. Nonetheless, a priori models using $\dot{V}_{E_{corr}}$ and V_D/V_T can be considered equivalent to the best model, as assessed with δ AICc and evidence ratio. Conversely, all post hoc models showed a consistent loss of information when compared with the best model. The final model included 162 (87%) complete cases. Sensitivity analysis with imputed missing values gave the same results as the analysis with complete cases.

Table 3. Adjusted Odds Ratio of $\dot{V}_{E_{corr}}$, V_D/V_T, and Ventilatory Ratio for Hospital Mortality

	Post Hoc Model		A Priori Model	
	Adjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio (95% CI)	P
$\dot{V}_{E_{corr}}$	1.15 (1.03–1.30)	.01	1.14 (1.02–1.29)	.03
V_D/V_T	1.05 (1.01–1.09)	.01	1.06 (1.01–1.11)	.01
Ventilatory ratio	2.67 (1.37–5.45)	.005	2.56 (1.3–5.3)	.009

For V_D/V_T, increments of 0.01 were evaluated. $P \leq .05$ was considered statistically significant.
$\dot{V}_{E_{corr}}$ = corrected minute ventilation
V_D/V_T = ratio of dead space to tidal volume

Discussion

The main finding of the study was the independent relationship between $\dot{V}_{E_{corr}}$ and hospital mortality in subjects with ARDS caused by COVID-19. Moreover, our results

Table 4. Comparison of Models Associating Hospital Mortality With Dead-Space Ventilation Estimates

	Model	k	AICc	δ AICc	AICc Weight	Evidence Ratio
Ventilatory ratio	a priori	7	183.8	0.0	0.48	1.0
V_D/V_T	a priori	7	184.9	1.1	0.28	1.7
$\dot{V}_{E_{corr}}$	a priori	7	186.1	2.2	0.16	3.0
Ventilatory ratio	post hoc	9	188.6	4.8	0.04	10.8
V_D/V_T	post hoc	9	190.2	6.4	0.02	24.2
$\dot{V}_{E_{corr}}$	post hoc	9	191.0	7.1	0.01	35.6

AICc = second order Aikake Information Criteria
V_D/V_T = ratio of dead space to tidal volume
$\dot{V}_{E_{corr}}$ = corrected minute ventilation

indicate that the known association between hospital mortality and both estimated V_D/V_T and ventilatory ratio is also true in the presence of ARDS secondary to COVID-19.

The impact of dead space on mortality in subjects with ARDS was first described in 2002 and confirmed in successive papers.[1-3] In these studies, the Enghoff modification of the Bohr equation was used (see the supplementary materials at http://www.rcjournal.com). The Enghoff approach calculates physiological dead space, which is the sum of anatomical and alveolar dead space and is particularly appropriate for describing gas exchange in disease because it is sensitive to intrapulmonary shunt, diffusion impairment, and alveolar ventilation-perfusion ratio heterogeneity.[20] The increase of V_D/V_T in patients with ARDS has a well-recognized pathophysiological background, and it is the mechanism by which hypercapnia and respiratory acidosis develop when protective ventilation with a low tidal volume is maintained in the presence of an increase in P_{aCO_2}.

The origin of high physiologic dead space in ARDS is intriguing and deserves an in-depth explanation. In ARDS, lung injury is associated with local (as opposed to systemic) increased activation of procoagulant processes. Since the 1980s, it has been well recognized that diffuse pulmonary endothelial injury is present in the early phase of ARDS, and that it is associated with macro- and microthrombi (consisting of fibrin and red and white cell clots) that can be embolic, formed in situ, or both.[21] The local formation of microthrombi may increase the mechanical obstruction of pulmonary blood flow.[22] This might suggest that the basis of the high V_D/V_T in ARDS could be explained by the relevant contribution of regions with high ventilation-perfusion ratio in pulmonary circulation. However, the multiple inert gas elimination technique demonstrated the minor role of high ventilation-perfusion ratio regions in patients with ARDS despite severe elevations in the physiological V_D/V_T measurement.[20,23] Therefore, intrapulmonary shunt plays a major role in explaining the increase of physiological V_D/V_T, along with increased ventilation-perfusion ratio.[20]

Despite its increasing use as V_D/V_T surrogate, $\dot{V}_{E_{corr}}$ failed to show an independent association with mortality in subjects with ARDS in 2 previous works, which include the ARDS Berlin definition[9,24] and a study by Sinha et al.[15] Nonetheless, we think that the results of our study can still be consistent with the findings of these works. The panel of experts who concurred on the Berlin ARDS definition assessed $\dot{V}_{E_{corr}}$ as a binomial variable with a threshold of 10 L/min. This value was considered to correspond approximately to a V_D/V_T of 0.5, which was supposed to be associated with increased mortality. Actually, subsequent studies showed that the threshold of V_D/V_T for mortality prediction was 0.6–0.7.[5,7,15] In our analysis, the estimated V_D/V_T was consistent with these values, and $\dot{V}_{E_{corr}}$ was substantially higher (on average 11.8 L/min and 14.5 L/min in survivors and nonsurvivors, respectively) than the threshold of 10 L/min chosen when the diagnostic criteria of ARDS were defined. Therefore, we believe that the approach used for the Berlin definition cannot give information about $\dot{V}_{E_{corr}}$ as a continuous variable. In the study from Sinha and colleagues,[15] mechanical ventilation was set differently between survivors and nonsurvivors, with higher driving pressures and $\dot{V}_E$ used in nonsurvivors compared to survivors, to obtain a substantial normocapnia. Conversely, in our subjects, all ventilatory variables were similar between survivors and nonsurvivors. Therefore, it is possible that $\dot{V}_{E_{corr}}$ is associated with hospital mortality when protective ventilation is prioritized over P_{aCO_2} control. At this time there is no definitive evidence on the best approach to use, even if guidelines and recommendations for patients with ARDS suggest limiting V_T, driving pressure, and breathing frequency so as to prevent the risk of ventilator-induced lung injury.[25]

Data about the association between estimated V_D/V_T and mortality are conflicting. The independent association between the 2 parameters was reported in 2 large studies involving subjects with ARDS,[5,6] but it was not confirmed in a post hoc analysis of the Molecular Diagnosis and Risk Stratification of Sepsis project.[7] Our data support the association between estimated V_D/V_T and mortality, endorsing its use for severity stratification in patients with ARDS. Nevertheless, prospective ad hoc designed studies are warranted to reach a conclusion.

Unlike $\dot{V}_{E_{corr}}$ and estimated V_D/V_T, all previous studies and our own data support the use of ventilatory ratio as an estimate of dead space that is independently associated with mortality.[7,15] We estimated an adjusted odds ratio that was twice as high as what was previously reported,[7-15] but this could be explained by the difference in patient characteristics and hospital mortality, as our subjects were

diagnosed with ARDS secondary to COVID-19. Ventilatory ratio, as a surrogate for dead space, appears to be sufficiently strong to overcome the presence of confounders, such as different causes of ARDS and different protocols of protective ventilation.

This study has some limitations. First, it is a retrospective analysis of prospectively collected data. Second, it is a single-center study, and the findings might be valid only for centers with a similar ventilatory strategy. Third, $\dot{V}_E$, P_{aCO_2}, and $\dot{V}_{CO_2}$ are strictly related. Diet and sedation affect $\dot{V}_{CO_2}$ and must be taken into account to interpret the study results. All subjects were fasting, and most of them were sedated on the first day of mechanical ventilation. Therefore, the findings of our study cannot be automatically applied to nonsedated patients receiving supplemental feeding or nutrition. Lastly, data were collected only in subjects with ARDS secondary to COVID-19. Nevertheless, these findings appear generalizable to other patients with COVID-19. Our data indicate that age, sex, and history of arterial hypertension and diabetes mellitus in our cohort were similar to what was reported in previous work.[26-34] Respiratory system compliance, driving pressure, plateau pressure, and PEEP in our subjects were similar to what was previously reported in subjects with COVID-19.[35]

COVID-19 gives a homogeneous pattern of ARDS, while non-COVID-19 ARDS is usually secondary to many different pulmonary or extrapulmonary diseases.[9] Therefore, the relationship between $\dot{V}_{E_{corr}}$ and outcome should be verified in subjects with ARDS not secondary to viral pneumonia.

Conclusions

The association between $\dot{V}_{E_{corr}}$ and hospital mortality could make $\dot{V}_{E_{corr}}$ useful in clinical practice for outcome prediction and severity stratification of patients with ARDS. In the context of protective ventilation in patients with ARDS, more exhaustive calculations (eg, estimated V_D/V_T and ventilatory ratio) do not present advantages over $\dot{V}_{E_{corr}}$. Further studies are needed to confirm these findings in subjects with ARDS without viral pneumonia and to assess whether ventilatory ratio could be more reliable than $\dot{V}_{E_{corr}}$ when different protocols of mechanical ventilation are applied.

ACKNOWLEDGMENTS

The authors thank the clinical staff who treated the patients in Poliambulanza Foundation Hospital. They thank Dr Marco Marri for helping with data collection.

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