Journal of Intensive Medicine 4 (2024) 187–193

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Prognostic value of time-varying dead space estimates in mechanically ventilated patients with acute respiratory distress syndrome

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ARTICLE INFO

Managing Editor: Jingling Bao/ Zhiyu Wang

Keywords:
Acute respiratory distress syndrome
Mechanical ventilation
Dead space
28-day mortality

ABSTRACT

Background: The dead space fraction (V_D/V_T) has proven to be a powerful predictor of higher mortality in acute respiratory distress syndrome (ARDS). However, its measurement relies on expired carbon dioxide, limiting its widespread application in clinical practice. Several estimates employing routine variables have been found to be reliable substitutes for direct measurement of V_D/V_T. In this study, we evaluated the prognostic value of these dead space estimates obtained in the first 7 days following the initiation of ventilation.

Methods: This retrospective observational study was conducted using data from the Chinese database in intensive care (CDIC). Eligible participants were adult ARDS patients receiving invasive mechanical ventilation while in the intensive care unit between 1st January 2014 and 31st March 2021. We collected data during the first 7 days of ventilation to calculate various dead space estimates, including ventilatory ratio (VR), corrected minute ventilation ($\dot{V}_{Ecorr}$), V_D/V_T (Harris–Benedict), V_D/V_T (Siddiki estimate), and V_D/V_T (Penn State estimate) longitudinally. A time-dependent Cox model was used to handle these time-varying estimates.

Results: A total of 392 patients (median age 66 [interquartile range: 55–77] years, median SOFA score 9 [interquartile range: 7–12]) were finally included in our analysis, among whom 132 (33.7%) patients died within 28 days of admission. VR (hazard ratio [HR]=1.04 per 0.1 increase, 95% confidence interval [CI]: 1.01 to 1.06; P=0.013), $\dot{V}_{Ecorr}$ (HR=1.08 per 1 increase, 95% CI: 1.04 to 1.12; $P < 0.001$), V_D/V_T (Harris–Benedict) (HR=1.25 per 0.1 increase, 95% CI: 1.06 to 1.47; P=0.006), and V_D/V_T (Penn State estimate) (HR=1.22 per 0.1 increase, 95% CI: 1.04 to 1.44; P=0.017) remained significant after adjustment, while V_D/V_T (Siddiki estimate) (HR=1.10 per 0.1 increase, 95% CI: 1.00 to 1.20; P=0.058) did not. Given a large number of negative values, V_D/V_T (Siddiki estimate) and V_D/V_T (Penn State estimate) were not recommended as reliable substitutes. Long-term exposure to VR >1.3, $\dot{V}_{Ecorr}$ >7.53, and V_D/V_T (Harris–Benedict) >0.59 was independently associated with an increased risk of mortality in ARDS patients. These findings were validated in the fluid and catheter treatment trial (FACTT) database.

Conclusions: In cases where V_D/V_T cannot be measured directly, early time-varying estimates of V_D/V_T such as VR, $\dot{V}_{Ecorr}$, and V_D/V_T (Harris–Benedict) can be considered for predicting mortality in ARDS patients, offering a rapid bedside application.

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening respiratory failure characterized by the loss of aerated lung tissues and increased lung stiffness, resulting in ventilation and perfusion abnormality that eventually leads to hypoxemia and impaired carbon dioxide (CO_2) clearance.[1] Despite advances in treatment,[2] reported hospital mortality rates for ARDS still range from 34.6% to 46.1%.[3] Poor prognosis in ARDS patients undergoing mechanical ventilation often manifests as worsening gas exchange.[4]

Gas exchange in ARDS comprises oxygenation and ventilation. Oxygenation is often quantified by the ratio of arterial oxy-

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https://doi.org/10.1016/j.jointm.2023.08.002
Received 9 June 2023; Received in revised form 9 August 2023; Accepted 10 August 2023
Available online 9 October 2023

gen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and is widely used in clinical practice to stratify ARDS into mild (PaO_2/FiO_2 201–300), moderate (PaO_2/FiO_2 101–200), and severe (PaO_2/FiO_2 < 100) categories.[1] However, there is conflicting evidence regarding the validity of this severity measure.[5] Ventilation, on the other hand, can be assessed through pulmonary dead space, which measures the portion of wasted ventilation, a composite of all causes of ventilation–perfusion heterogeneity.[6] Assessing dead space may be a more reliable predictor of ARDS outcomes than oxygenation.[7]

The gold standard for assessing dead space is the Enghoff modification of the Bohr equation (the ratio of physiologic dead space to tidal volume, V_D/V_T).[8] V_D/V_T has proven useful in evaluating disease progression and the risk of death in ARDS patients.[9] However, V_D/V_T is not readily applicable as a stratifying variable for ARDS in clinical practice due to the need for volumetric capnography, Douglas bag, or indirect calorimetry techniques for measurement.[10]

In recent years, several estimates, such as the ventilatory ratio (VR), corrected minute ventilation ($\dot{V}_{Ecorr}$), V_D/V_T (Harris–Benedict), V_D/V_T (Siddiki estimate), and V_D/V_T (Penn State estimate), have been proposed as surrogate indices of impaired ventilation. These estimates use routine data and do not require the direct measurement of mean exhaled CO_2 partial pressure at the bedside.[1,11–14] Previous studies have shown that these estimates correlate well with V_D/V_T and have independent predictive values in ARDS patients.[15,16]

Nevertheless, the association between time-varying dead space estimates and mortality remains largely unknown. In light of this, we hypothesized that long-term exposure to high dead space estimates has predictive value for mortality in ARDS patients over time.

Methods

Study design and participants

This single-center retrospective observational study was conducted in the mixed intensive care unit (ICU) of a tertiary teaching hospital (Department of Critical Care Medicine, Zhongda Hospital affiliated with Southeast University) in China. Informed consent was waived due to the observational nature of our study, and we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for study conduct.

Participants included consecutive adult patients with ARDS receiving mechanical ventilation for more than 24 h in the ICU between 1st January 2014 and 31st March 2021. The Berlin Definition was used to determine the diagnosis of ARDS after experienced critical care physicians and radiologists reviewed the patient's medical history, blood gas data, positive end-expiratory pressure (PEEP) levels, and imaging tests, including chest X-ray or computed tomography scans. Patients who met any of the following criteria were excluded: (1) received extracorporeal membrane oxygenation treatment, (2) had a concurrent diagnosis of tuberculosis or chronic obstructive pulmonary disease, and (3) had incomplete data necessary for calculating dead space estimates. External validation of the conclusions was performed using the fluid and catheter treatment trial (FACTT) database in ARDSnet.

Data collection and formulas

Demographics, anthropometrics, scores, premorbid diseases, vital signs, and laboratory indices were collected on the first day of ventilation. Respiratory parameters such as tidal volume (VT), respiratory rate (RR), and arterial partial pressure of CO_2 ($PaCO_2$) were recorded at the first measurement after ventilation and then continuously collected at 7 a.m. over the subsequent 6 days, until extubation, discharge, or death. The treatments administered during ICU duration were also recorded. Mortality at 28 days after admission was the primary outcome assessed in our study.

Five different approaches for estimating V_D/V_T were proposed for a rapid bedside application:

(1) VR

According to Sinha et al.,[11] VR was defined according to the following formula:

$$VR = \frac{V_{Emeasured} \times PaCO_{2measured}}{V_{Epredicted} \times PaCO_{2predicted}},$$

where $V_{Emeasured}$ represents the measured minute ventilation, equal to RR (breaths per min) × VT (mL). $V_{Epredicted}$ is calculated as 100 × predicted body weight (PBW, kg) in mL/min. $PaCO_{2measured}$ and $PaCO_{2predicted}$ are measured and predicted $PaCO_2$ in mmHg, with the latter determined as 37.5 mmHg. Thus, VR was estimated using this equation:

$$VR = \frac{RR \times VT \times PaCO_2}{PBW \times 100 \times 37.5}.$$

(2) Corrected minute ventilation ($\dot{V}_{Ecorr}$)

$\dot{V}_{Ecorr}$ is an easier surrogate of V_D/V_T, representing the minute ventilation ($\dot{V}_E$) required to obtain the ideal value of $PaCO_2$.[17] The formula is as follows:

$$\dot{V}_{Ecorr} = \frac{\dot{V}_E \times PaCO_2}{40\ mmHg},$$

where 40 mmHg represents the normal value of $PaCO_2$.

The following three methods for estimating V_D/V_T are based on the alveolar ventilation equation[18]:

$$PaCO_2 = \frac{\dot{V}CO_2 \times 0.863}{\dot{V}A},$$

where $\dot{V}CO_2$ represents the production of CO_2 in mL/min, and $\dot{V}A$ is alveolar ventilation defined as V_T minus V_D. Taking V_D/V_T into consideration, a new equation was generated:

$$\frac{V_D}{V_T} = 1 - \frac{\dot{V}CO_2 \times 0.863}{RR \times VT \times PaCO_2},$$

In this rearranged equation, $\dot{V}CO_2$ is the only variable without routine measurement, which can be estimated from the predicted resting energy expenditure equation (REE) using the Weir equation,[19] where the respiratory quotient (RQ) is a constant assumed to be 0.8:

$$\dot{V}CO_2 = \frac{REE}{\left(\frac{5.616}{RQ} + 1.584\right)} = \frac{REE}{8.604}.$$

An unadjusted Harris–Benedict estimate and two modified equations are constructed for predicting REE.

(3) V_D/V_T (Harris–Benedict)

This is the unadjusted Harris–Benedict estimate of V_D/V_T[12] using the original gender-specific Harris–Benedict formula for estimating REE_{HB}, with weight in kilograms, height in centimeters, and age in years:

$$REE_{HB} = \begin{cases} 66.473 + 13.752 \times \text{Weight} + 5.003 \times \text{Height} - 6.755 \times \text{age}, & \text{Males} \\ 655.096 + 9.563 \times \text{Weight} + 1.850 \times \text{Height} - 4.676 \times \text{age}, & \text{Females} \end{cases}$$

Since the Harris–Benedict equation was reported to have a weak correlation with REE in severely ill patients,[20] two modified equations were then generated.

(4) V_D/V_T (Siddiki estimate)

It is common for critically ill patients to encounter hypermetabolic conditions. Thus, Siddiki et al.[13] modified the Harris–Benedict formula based on hypermetabolic factors (*hf*) to predict $REE_{Siddiki}$:

$$REE_{Siddiki} = REE_{HB} \times hf,$$

where *hf* is the highest value selected from potential values of 1.6 for severe infection, 1.35 for major trauma, 1.2 for minor surgery, and 1.13 per ˚C above 37 ˚C.

(5) V_D/V_T (Penn State estimate)

This is another formula derived to estimate REE specifically for critically ill patients by Frankenfield.[14] First, the Mifflin-St. Jeor equation[21] was applied to estimate REE in a healthy state:

$$REE_{MSJ} = \begin{cases} 10 \times \text{Weight} + 6.25 \times \text{Height} - 5 \times \text{age} + 5, & \text{Males} \\ 10 \times \text{Weight} + 6.25 \times \text{Height} - 5 \times \text{age} - 161, & \text{Females} \end{cases}$$

Then, body mass index (BMI), RR, VT (liters), and T_{max} (maximum temperature in ˚C of the day) were incorporated to generate the Penn State estimate for a critically ill state:

$$REE_{PS} = \begin{cases} 0.96 \times REE_{MSJ} + 31 \times RR \times VT + 167 \times T_{max} - 6212, & \text{BMI} < 30\ \text{kg/m}^2 \\ 0.71 \times REE_{MSJ} + 64 \times RR \times VT + 85 \times T_{max} - 3085, & \text{BMI} \geq 30\ \text{kg/m}^2 \end{cases}$$

Statistical analysis

Descriptive data are presented as median (interquartile range [IQR]) or means ± standard deviations for continuous variables and absolute numbers (percentages) for categorical variables. We used the non-parametric Mann–Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables to compare differences between groups.

Daily dead space estimates were regarded as time-varying variables to avoid potential time-related confounding. Imputation was performed by multiple imputation chain equations using the "MICE" package in R to include more patients. We employed the time-dependent Cox model[22] to investigate the association between these time-varying estimates and 28-day mortality, providing results in terms of *P*-values, hazard ratios, and their corresponding 95% confidence intervals (CIs). Univariate Cox regression was employed to evaluate the unadjusted association between each dead space estimate and mortality. Based on prior knowledge, baseline variables known to impact prognosis, including the Acute Physiology and Chronic Health Evaluation (APACHE) score, PEEP, PaO_2/FiO_2 ratio, driving pressure, and compliance of the respiratory system, were fully adjusted in the multivariate analysis to avoid potential covariate effects. Associations between dead space estimates and mortality were assessed using restricted cubic splines with five knots. All analyses were conducted using R version 4.1.2 (R Core Team 2021, Vienna, Austria). $P < 0.05$ (two-tailed) was set to indicate statistical significance.

Results

Enrollment and characteristics of patients

In the CDIC cohort, a total of 392 patients met the inclusion and exclusion criteria and were finally included in the analyses (Figure 1). The median APACHE II score was 22 [17–29], and the median PaO_2/FiO_2 ratio was 166 (IQR: 127 – 213) mmHg. Pneumonia was the leading cause of ARDS, accounting for 73.2% of cases. The 28-day all-cause mortality rate was 33.7%. Table 1 presents a comparison of characteristics between survivors and non-survivors. For the FACTT database, out of 1000 patients, 346 had complete data to calculate VR, $\dot{V}_{Ecorr}$, and V_D/V_T (Harris–Benedict) after excluding patients with extracorporeal membrane oxygenation and chronic obstructive pulmonary disease. After imputation, data from 929 patients in the FACTT database were reanalyzed, which was chosen as the validation cohort. Detailed information is provided in Supplementary Tables 1 and 2.

Time-varying exposure to dead space estimates

The percentages of patients still requiring mechanical ventilation in the subsequent 6 days were as follows: 392 (100%), 373 (95.2%), 329 (83.9%), 297 (75.8%), 276 (70.4%), and 248 (63.3%), due to various reasons such as death, discharge, or extubation. Figure 2 illustrates overall changes in these dead space estimates during the first 7 days after ventilation. None of these estimates showed significant differences on the first day of ventilation. However, values for these estimates were generally higher in deceased patients than in survivors. Detailed information regarding time-varying differences between survivors and non-survivors is shown in Supplementary Figure 1. It is important to mention that some individuals exhibited negative values for V_D/V_T (Siddiki estimate) and V_D/V_T (Penn State estimate).

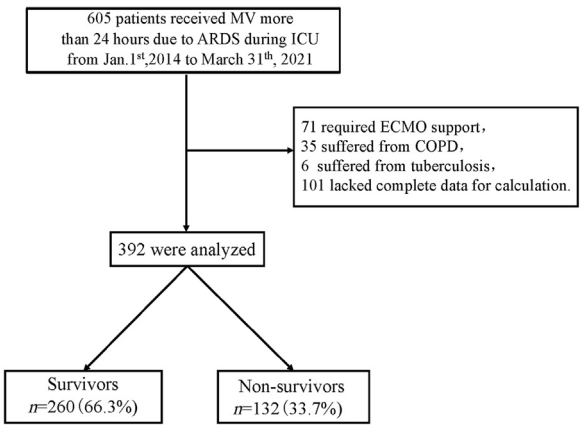

Figure 1. Flowchart of patient screening and enrollment. A total of 392 patients were included for analysis until hospital discharge or death.
ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; MV: Mechanical ventilation.

Table 1
Characteristics of patients on the first day of ventilation with stratification by 28-day mortality.

Characteristics	All patients (*n*=392)	Survivors (*n*=260)	Non-survivors (*n*=132)	*P*-value
Age (years)	66 (55, 77)	65 (53, 75)	69 (60, 79)	0.002
Male	277 (70.7)	184 (70.8)	93 (70.5)	1.000
Height (cm)	170 (160, 172)	170 (160, 172)	170 (160, 172)	0.849
Weight (kg)	70 (60, 75)	70 (60, 75)	65 (60, 70)	0.012
SOFA score	9 (7, 12)	9 (6, 11)	11 (8, 13)	<0.001
APACHE II score	22 (17, 29)	21 (15, 25)	26 (20, 32)	<0.001
Source of ARDS				0.490
Pneumonia	287 (73.2)	187 (71.9)	100 (75.8)	
Non-pneumonia	105 (26.8)	73 (28.1)	32 (24.2)	
Severity of ARDS				0.037
Mild	122 (31.1)	90 (34.6)	32 (24.2)	
Moderate	215 (54.8)	140 (53.8)	75 (56.8)	
Severe	55 (14.0)	30 (11.5)	25 (18.9)	
Vital signs				
MAP (mmHg)	91 (83, 104)	93 (85, 107)	88 (81, 97)	<0.001
Temperature (°C)	37.8 ± 1.0	37.8 ± 0.9	37.6 ± 1.1	0.031
Heart rate (beats/min)	98 (95, 99)	98 (95, 99)	99 (96, 132)	0.012
Parameters of mechanical ventilation				
RR (breaths/min)	20 (16, 25)	20 (16, 24)	22 (18, 26)	0.009
VT (mL/kg PBW)	6.9 (6.0, 8.0)	6.9 (6.0, 7.9)	6.9 (6.0, 8.1)	0.612
Minute ventilation (L/min)	8.6 (6.8, 10.9)	8.4 (6.7, 10.4)	9.0 (7.2, 11.8)	0.033
PEEP (cmH_2O)	8 (5, 10)	8 (5, 10)	8 (6, 10)	0.889
Ppeak (cmH_2O)	20 (17, 23)	20 (17, 22)	20 (18, 24)	0.075
Driving pressure (cmH_2O)	12 (9, 15)	11 (9, 14)	13 (10, 15)	0.021
Compliance (mL/cmH_2O)	36.3 (28.1, 49.6)	37.7 (28.3, 51.2)	35.3 (25.9, 45.7)	0.158
PaO_2 (mmHg)	84.9 (71.5, 101.5)	85.3 (71.5, 103.7)	83.5 (71.6, 100.6)	0.790
$PaCO_2$ (mmHg)	34.2 (28.8, 40.1)	34.4 (29.8, 39.3)	33.4 (27.4, 41.6)	0.352
PaO_2/FiO_2 (mmHg)	166 (127, 213)	174 (134, 222)	155 (111, 199)	0.013
Laboratory findings				
Arterial pH	7.39 (7.32, 7.44)	7.39 (7.34, 7.44)	7.38 (7.29, 7.43)	0.037
Bicarbonate (mmol/L)	20.9 (17.9, 24.0)	21.2 (18.7, 24.1)	19.8 (17.1, 22.9)	0.009
Lactate (mmol/L)	1.9 (1.3, 3.0)	1.8 (1.2, 2.6)	2.3 (1.5, 3.7)	<0.001
Serum creatinine (mmol/L)	101 (69, 157)	96 (67, 147)	110 (76, 203)	0.021
Interventions during the first 7 days				
Fluid balance (mL)	920 (−621, 3336)	472 (−787, 2906)	1734 (333, 3519)	0.002
NMB	38 (9.7)	21 (8.1)	17 (12.9)	0.181
Recruitment maneuver	106 (27.2)	69 (26.7)	37 (28.0)	0.881
Prone position	82 (20.9)	47 (18.1)	35 (26.5)	0.070

Data are expressed as *n* (%) and median (interquartile range) or mean±standard deviation.
APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute respiratory distress syndrome; MAP: Mean arterial blood pressure; NMB: Neuromuscular blocking drugs; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PaO_2: Partial pressure of arterial oxygen; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; pH: Potential of hydrogen; Ppeak: Peak inspiratory pressure; RR: Respiratory rate; SOFA: Sequential organ failure assessment score; VT: Tidal volume.

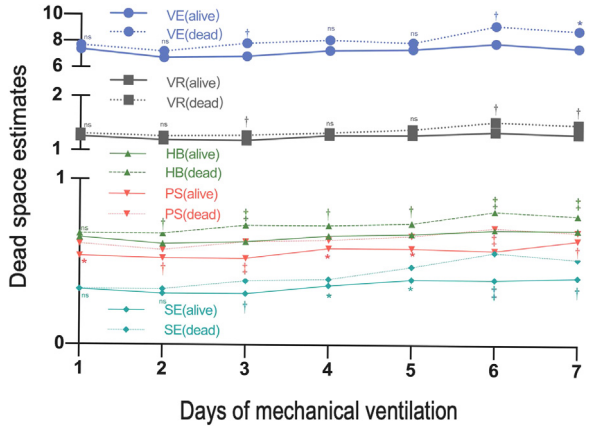

Figure 2. Trajectories of dead space estimates over the first 7 days of ventilation. The solid line represents patients who survived on the 28th day of admission (*n*=260 [66.3%]), and the dotted one represents those who died (*n*=132 [33.7%]). Dots depict the median values of these dead space estimates. $^{*}P < 0.05$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.001$.
HB: V_D/V_T (Harris–Benedict); PS: V_D/V_T (Penn State estimate); SE: V_D/V_T (Siddiki estimate); V_D/V_T: The ratio of physiologic dead space to tidal volume; VE: Corrected minute ventilation; VR: Ventilatory Ratio.

Prognostic value of dead space estimates

In univariate time-dependent Cox regression analysis, all the dead space estimates were associated with an increased risk of 28-day mortality (Table 2). After adjusting for predefined covariates, only VR, $\dot{V}_{Ecorr}$, V_D/V_T (Harris–Benedict), and V_D/V_T (Penn State estimate) remained statistically significant. Each unit increase in these estimates was associated with a 4% (HR=1.04 per 0.1 increase, 95% CI: 1.01 to 1.06; *P*=0.013), 8% (HR=1.08 per 1 increase, 95% CI: 1.04 to 1.12; $P < 0.001$), 25% (HR=1.25 per 0.1 increase, 95% CI: 1.06 to 1.47; *P*=0.006), and 22% (HR=1.22 per 0.1 increase, 95% CI: 1.04 to 1.44; *P*=0.017) higher risk of death, respectively, over this timeframe. Comparable results were observed in the FACTT database (Table 3), and these findings remained consistent even after imputation (Supplementary Table 3).

The relationships between these dead space estimates and mortality are depicted in Figure 3. Linear associations were identified for VR, $\dot{V}_{Ecorr}$, and V_D/V_T (Penn State estimate). Long-term exposure to VR >1.30, $\dot{V}_{Ecorr}$ >7.53, V_D/V_T (Harris–Benedict) >0.59, V_D/V_T (Siddiki estimate) >0.45, and V_D/V_T (Penn State estimate) >0.59 during the early stages of venti-

Table 2
Cox model using time-varying dead space estimates in CDIC.

Dead space estimates	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
VR*	1.05 (1.03 to 1.07)	<0.001	1.04 (1.01 to 1.06)	0.013
Corrected minute ventilation	1.08 (1.05 to 1.12)	<0.001	1.08 (1.04 to 1.12)	<0.001
V_D/V_T (Harris to Benedict)*	1.33 (1.16 to 1.52)	<0.001	1.25 (1.06 to 1.47)	0.006
V_D/V_T (Siddiki estimate)*	1.14 (1.06 to 1.24)	0.001	1.10 (1.00 to 1.20)	0.058
V_D/V_T (Penn State estimate)*	1.31 (1.14 to 1.50)	<0.001	1.22 (1.04 to 1.44)	0.017

* Per 0.1 increase. Corrected for the following covariates: APACHE II, PaO_2/FiO_2, PEEP, driving pressure, and compliance.
APACHE II: Acute Physiology and Chronic Health Evaluation II; CDIC: Chinese Database in Intensive Care; CI: Confidence interval; HR: Hazard ratio; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP: Positive end-expiratory pressure; VR: Ventilatory ratio.

Table 3
Cox model using time-varying dead space estimates in FACTT.

Dead space estimates	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
VR*	1.04 (1.03 to 1.06)	<0.001	1.04 (1.02 to 1.06)	<0.001
Corrected minute ventilation	1.07 (1.05 to 1.10)	<0.001	1.06 (1.03 to 1.09)	<0.001
V_D/V_T (Harris–Benedict)*	1.50 (1.24 to 1.82)	<0.001	1.51 (1.18 to 1.94)	0.001

* Per 0.1 increase. Corrected for the following covariates: APACHE III, PaO_2/FiO_2, PEEP, driving pressure, and compliance.
APACHE III: Acute Physiology and Chronic Health Evaluation III; CI: Confidence interval; FACTT: Fluid and Catheter Treatment Trial; HR: Hazard ratio; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP: Positive end-expiratory pressure; VR: Ventilatory ratio.

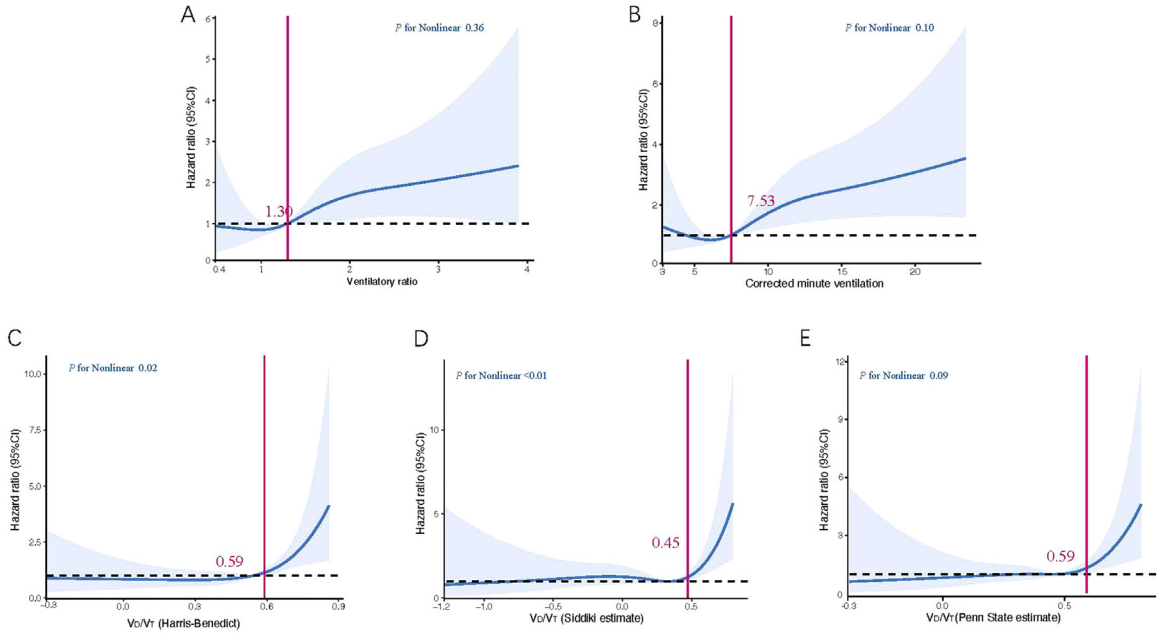

Figure 3. Associations of time-varying dead space estimates with 28-day mortality after admission. A: VR and mortality. B: Corrected minute ventilation and mortality. C: V_D/V_T (Harris–Benedict) and mortality. D: V_D/V_T (Siddiki estimate) and mortality. E: V_D/V_T (Penn State estimate) and mortality. Hazard ratios are indicated by solid lines in blue, and 95% CIs by shaded areas. Significant cut-offs are shown in pink solid lines. All models were adjusted for PaO_2/FiO_2, PEEP, driving pressure, and compliance of the respiratory system.
CIs: Confidence intervals; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP: Positive end-expiratory pressure; V_D/V_T: The ratio of physiologic dead space to tidal volume; VR: Ventilatory Ratio.

lation were all independently associated with an increased risk of death.

Discussion

This study primarily focused on investigating the relationship between time-varying dead space estimates and mortality of ARDS patients receiving mechanical ventilation. We investigated the temporal trends of these dead space estimates during the first week after ventilation. The main findings of our study can be summarized as follows: (1) Dynamic changes in estimated dead space measures among ARDS patients should be taken more seriously than focusing solely on baseline values. (2) After adjusting for confounding factors, long-term exposure to elevated VR, $\dot{V}_{Ecorr}$, and V_D/V_T (Harris–Benedict) emerged as independent predictors of increased mortality.

Recent studies have indicated that the strategy of classifying ARDS only according to the severity of hypoxemia did not

achieve the desired effect.[5,23] Instead, inefficient ventilation, represented by V_D/V_T, has been identified as a potentially superior predictor of outcomes.[7] V_D/V_T has demonstrated predictive validity for mortality even within the first 10 days after the onset of ARDS.[24] ARDS is characterized by high shunt and low cardiac output states, which can be reflected well by elevated V_D/V_T.[25] In addition, we may need to set high minute ventilation to compensate for increased dead space, leading to ventilation-associated lung injury due to high mechanical power.[26] Therefore, it is essential to incorporate V_D/V_T into clinical practice. Since the measurement of V_D/V_T is limited in practice, reliable alternative methods for rapid bedside application are needed.

Several studies have sought to identify reliable methods for estimating V_D/V_T at the bedside. Sinha et al.[11] proposed VR as a promising bedside index of V_D/V_T in 2009, demonstrating a correlation coefficient of 0.66, which was later found to be a significant predictor of mortality,[15] especially on day 2.[27] The ARDS Berlin Definition Task Force introduced $\dot{V}_{Ecorr}$ as a replacement for V_D/V_T,[1] showing a high correlation with V_D/V_T (r>0.8). However, its predictive value has remained controversial.[1,28] Additionally, three estimates that account for metabolism have been proposed. Beitler et al.[16] confirmed their correlation with V_D/V_T and validated their respective predictive value. Among these estimates, V_D/V_T (Harris–Benedict) yielded the best performance, consistent with our findings.

In terms of the pros and cons of these five estimates, they are all fairly simple to calculate and generally available in clinical settings. Taking shunt into account, they are not so much a reflection of dead space as a reflection of ventilation–perfusion ratio imbalance,[10] which aligns with the pathophysiological characteristics of ARDS.[29] Calculation based on indirect estimates of VCO_2 was their main disadvantage, which can be easily influenced by various factors.[30] Moreover, they cannot reflect focal ventilation–perfusion ratio imbalance.

There are also several other alternatives of V_D/V_T that were not researched in our study. One such alternative is the arterial to end-tidal CO_2 difference ($P(a-ET)CO_2$) ,[31] which has been proven to be a reliable substitute for V_D/V_T and independently associated with increased mortality in ARDS patients. Gattinoni et al.[32] proposed the end-tidal to arterial PCO_2 ratio ($PETCO_2/PCO_2$) as a measure of gas exchange efficiency, which was found to be negatively correlated with V_D/V_T.[33] Frankenfield et al.[34] derived V_D/V_T (Frankenfield) using stepwise regression analysis, with the final equation being $0.320 + 0.0106 \times P(a-ET)CO_2 + 0.003 \times RR + 0.0015 \times age$. This estimate has been validated as an unbiased and precise method for estimating V_D/V_T. However, neither of these alternatives is routinely available at the bedside, requiring the measurement of end-tidal CO_2.

Our study builds upon and provides more detailed insights into previous reports. We found that the time-varying performance of these estimates outperformed that of baseline values, probably because it reflected the response to ventilator settings.[35] Similar to Beitler's findings,[16] our study observed negative values in V_D/V_T (Penn State estimate) and V_D/V_T (Siddiki estimate), which tend to overestimate metabolic effects. As a result, these estimates were not our preferred recommendation for lack of clinical interpretability. When the necessary equipment is unavailable, incorporating these estimates into clinical practice may still aid in prognostic identification and potentially promote the optimization of ventilator settings, particularly in the context of this heterogeneous syndrome.

Our study had some limitations. First, we compared the confirmed substitutes of V_D/V_T based on previous studies alone. The accuracy of these estimates in predicting V_D/V_T cannot be evaluated because V_D/V_T was not measured in our study. Second, the observational nature of our study means that our conclusions are more indicative of correlations rather than causality. Third, our medical center adhered to protocolized low tidal volume lung-protective ventilation strategies,[36] which may have controlled some factors that can affect dead space.[37] This could potentially limit the generalizability of our findings to other hospital settings. This also explains why dead space estimates in our study were generally lower than those in the FACTT database. Therefore, large prospective studies are necessary to further validate our conclusions.

Conclusions

When V_D/V_T cannot be measured directly, early time-varying estimates of V_D/V_T, such as VR, $\dot{V}_{Ecorr}$, and V_D/V_T (Harris–Benedict) holds promise for predicting mortality in ARDS patients. Long-term exposure to VR >1.30, $\dot{V}_{Ecorr}$ >7.53, and V_D/V_T (Harris–Benedict) >0.59 during the initial stages of ventilation independently correlates with an increased risk of mortality among ARDS patients.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

Lianlian Jiang: Data curation, Formal analysis, Visualization, Writing – original draft. **Hui Chen:** Methodology, Software. **Jianfeng Xie:** Project administration, Writing – review & editing. **Ling Liu:** Validation. **Yi Yang:** Conceptualization, Funding acquisition, Supervision.

Acknowledgments

Not applicable.

Funding

This work was supported by the Key Technologies Research and Development Program (Grant numbers: 2022YFC2504400 and 2021YFC2500804) and the Jiangsu Provincial Key Research and Development Program (Grant number: BE2022854).

Ethics Statement

This study was approved by the Research Ethics Commission of Zhongda Hospital Southeast University. For ARDSNet trials, all data were approved by the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC, https://biolincc.nhlbi.nih.gov).

Data Availability

The dataset supporting the conclusions of this article is available upon reasonable request and with approval from the Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University. The datasets of ARDSNets are available at https://biolincc.nhlbi.nih.gov (the BioLINCC website).

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jointm.2023.08.002.

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