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The dead space fraction as a prognostic death indicator in patients with ARDS: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Acute respiratory distress syndrome (ARDS) is a systemic disease with high morbidity and mortality. Dead space fraction (Vd/Vt) represents the volume of air that does not participate in gas exchange and accurately depicts the pathophysiology of ARDS due to ventilation and perfusion mismatch. In this study, we aim to conduct a systematic review and meta-analysis regarding its usefulness for predicting mortality.

MATERIALS AND METHODS: We performed a systematic literature search identifying comparative studies meeting the above criteria from four databases: MEDLINE, clinicaltrials.gov, CENTRAL, and Google Scholar. A statistical meta-analysis was conducted utilizing the "meta" package in R software, with the included studies assessed based on the Newcastle-Ottawa scale.

RESULTS: A total of twelve studies were included and data from over 1,700 patients was collected. Patients with higher levels of Vd/Vt were more likely to not survive with an OR=1.27 [95% CI (1.09, 1.48), I^2=93%, p<0.01]. In addition, non-survivors of ARDS had higher mean value levels of Vd/Vt than survivors with an MD=0.07 [95% CI (0.02, 0.11), I^2=82%, p<0.01]. Furthermore, a leave-one-out meta-analysis was performed in order to assess the effect of each individual study on the overall outcome, which led to the lowering of heterogeneity to 0.

CONCLUSIONS: The Vd/Vt ratio is an accurate index for determining the mortality of ARDS, reflecting the severity of the disease.

Key Words:
ARDS, Mortality, Vd/Vt, Dead space fraction.

Introduction

Acute respiratory distress syndrome (ARDS) is a major cause of admission and mortality in the intensive care unit (ICU)[1].

The volume of air that does not participate in gas exchange is called dead space (Vd/Vt). In ARDS, the pulmonary circulation is disturbed in various ways. Microthrombosis, endothelial injury, and right ventricular dysfunction are the major pathways. In addition, the application of positive end-expiratory pressure (PEEP) used in mechanical ventilation due to alveolar overdistension transforms the respiratory unit into the zone I West and reduces blood flow, thus increasing dead space.

In order to accurately calculate dead space ventilation in 1891, the Danish physiologist Christian Bohr[2] explained with simple equations that the dead space ventilation (or the fraction of the dead space to the breathing volume Vd/Vt) is $Vd/Vt = (FACO_2 - FECO_2)/FACO_2$, where $FACO_2$ = fraction of alveolar CO_2 and $FECO_2$ = fraction of expired CO_2. Another method[2] is indirect calorimetry (metabolic monitor), through which $FECO_2$ is usually determined after a few minutes of measurement. Bohr's formula is most often found in the form of replacing CO_2 fractions with partial pressures.

Furthermore, Enghoff[2] suggested replacing alveolar $PACO_2$ with arterial $PaCO_2$, since in an ideal lung these two values should be equal. However, many questions are raised as an ideal lung where V/Q=1 and alveolar-arterial difference (A-a gradient) = 0 does not exist.

The volumetric capnography method is currently used to measure exhaled CO_2 ($PeCO_2$) with special monitors [e.g., $NICO_2$® capnograph, Philips Respironics (Wallingford, CT, USA), CO_2-SMO® capnograph, Novametrix (Wallingford, CT, USA)][2].

It is important to highlight that measuring the end-expiratory pCO_2 value with a simple capnograph is practical, allowing for the substitution of $peCO_2$ with end-expiratory pCO_2.

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Frankenfield et al[3] proposed an alternative way of estimating dead space from the equation: VD/VT = 0.320 + 0.0106 ($PaCO_2$-$EtCO_2$) + 0.003 [respiratory rate or (RR)] + 0.0015 (age) using a simple capnograph. Finally, equations for indirect measurement of dead space have been proposed.

As early as 1976, Lamy et al[4] observed increased dead space values in patients with severe hypoxemia. Several years later, Gattinoni et al[5], studying the characteristics of patients with late ARDS, observed increased dead space values. Nuckton et al[6] in 2004 were the first to study Vd/Vt as a prognostic marker for ARDS and displayed an independent association between increased Vd/Vt in the first 24 h and mortality in patients with ARDS, thus inspiring many other research groups to study the Vd/Vt as a marker of mortality in ARDS.

It is understandable that Vd/Vt reflects, to a satisfactory extent, the pathophysiology of ARDS. Following the study by Nuckton et al[6] there are many publications of primary observational studies in the international literature regarding the prognostic value of this index. However, to our knowledge, until now the prognostic value of dead space fraction regarding mortality has not been summarized.

In this systematic review and meta-analysis, we aim to conduct a thorough evaluation of all relevant studies to assess their effectiveness in predicting mortality. Our objective is to provide a comprehensive understanding of the available evidence on this important topic.

Materials and Methods

Protocols and Registration

The protocol of the present study has been registered in PROSPERO (CRD42023483851). This study was designed and executed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and protocols (**Supplementary Table I**)[7]. The eligibility criteria were established *a priori*.

Search Strategy

All studies presenting the dead space fraction to tidal volume as a mortality index were considered eligible for inclusion in the review. The selection of studies was done through three successive steps. First, the titles and abstracts of the articles in electronic format were screened. Following that, a full-text assessment of the studies that met the inclusion criteria was performed. Finally, the studies that were relevant to the aim and topic were included in the review. Three researchers (V.I., G.P.M., N.A.) both extracted in piloted forms the following data from the included studies: 1) name of the first author, 2) year of publication, 3) country and center where the study took place, 4) the type of study, 5) method of assessment of dead space and equation used, 6) ventilation parameters, mechanics and settings, 7) end result achieved. Three researchers (G.P.M., V.I., N.A.) independently extracted the data mentioned above from the included studies, and a fourth researcher (C.G.D.) independently verified them. The qualitative analysis was performed by three authors in conjunction (V.I., N.R., G.P.M.).

Inclusion/Exclusion Criteria

The following search algorithm was utilized by three blinded authors (V.I., G.P.M, N.A.) during the literature search: «(ARDS) OR (Acute Respiratory Distress Syndrome)) AND (Dead space fraction)) OR (AVDSF)) AND (mortality)» and the simplified algorithm: «dead space fraction AND ARDS AND prognostic value». This search formula was used as the aim of this systematic review in order to examine whether there is a relationship between ARDS patients with higher dead space fraction [or alveolar dead space fraction (AVDSF)] and mortality. Therefore, this algorithm was applied, and abstracts found were manually screened in order to assess whether they met the inclusion criteria for our systematic review. If, through this first screening process, abstracts met the inclusion criteria, they were sought for retrieval. Should there be inconclusive information from the abstract, full-text articles were retrieved.

The search term was utilized in the following databases: MEDLINE (1976-2023), Cochrane Central Register of Controlled Trials (CENTRAL) (2019-2023), and clinicaltrials.gov (2014-2023).

Regarding the "grey literature'' assessment, a thorough search was performed on the first ten pages of Google Scholar. In order to expand the search, we evaluated the sources of ten studies that were included in the study (snowball method). The last search date is April 4, 2023. Our analysis included solely English-language studies published over 20 years involving direct measurements of Vd/Vt in patients with ARDS and updates in mortality. Studies involving a pediatric population, indirect assessment of dead space, *in vitro* or *in vivo* animal studies, and studies not presenting mortality data in patients with ARDS

were not included in the review. Case studies (case reports), letters to the editor (letters to the editor), and reviews were excluded from this paper.

Methodological Quality Assessment

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the included studies. This scale applies to non-randomized observational studies. Studies are rated with stars (maximum number = 9) according to the choice of observation groups, the comparisons made within the groups, and the final results (outcome of interest)[8].

Certainty Assessment

Credibility of outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (ranging from very low to high). Examination of the quality of evidence was done through the following domains: study limitations, directness, consistency, precision, and publication bias[9].

Statistical Analysis

The statistical meta-analysis was performed by two blinded authors (C.G.D., G.P.M) in order to achieve a true effect using the "meta" package in R software[10], and the confidence intervals (CI) were set at 95%. Heterogeneity among the included studies was substantial, according to the Cochrane Handbook[11], and therefore, the Der Simonian-Laird random effect model[12] was utilized to calculate odds ratios (OR), mean values (MD), and 95% CI, with *p*-value set at 0.05. The second part of our meta-analysis included the exploration of mean values of Vd/Vt among survivors and non-survivors of early ARDS. As odds ratios are not normally distributed[13], we transformed them into logarithm odds ratios (logOR) in order to be able to meta-analyze them and then back-transform the final outcome into odds ratio (OR) for better interpretation of the results. Mean differences were meta-analyzed in order to showcase an overall trend from the dead space fraction regarding mortality in ARDS patients, while odds ratios were used to quantify the marker as a death indicator. The influence of each individual study on the overall outcome was explored through a leave-one-out meta-analysis; each study was consecutively omitted in order to evaluate its effect on the final estimate. Furthermore, prediction intervals for each comparison were calculated using the "meta" package in R.

Meta-regression analysis was not performed because, according to the Cochrane Handbook[11], at least 10 studies are required for this analysis to be robust. Last but not least, publication bias was examined visually through funnel plots created using the trim and fill method[14].

Results

Study Selection

In total, 177 studies were assessed for this systematic review. Following duplicate removal, a full-text review was conducted on 43 studies. 31 studies did not meet our inclusion criteria. This systematic review includes twelve studies[6,15-25], which met all the criteria we described. The flow diagram of the literature search and selection process is displayed in Figure 1.

Risk of Bias

The Newcastle-Ottawa Scale (NOS) was used for methodological quality assessment of the included studies, as shown in **Supplementary Table II** and Table I. One study[17] had a score of 4 stars, two studies[16,20] had a score of 5 stars, one[6] had a score of 6 stars, five studies[15,18,19,21,25] had a score of 7 stars. Finally, three studies[22-24] had a score of 8 stars.

Qualitative Analysis

Study characteristics are summarized in Table I.

Chronologically, the first prospective cohort study of Vd/Vt as a prognostic index was carried out in 2002 by Nuckton et al[6]. Of the 179 patients, the 75 who died had a difference in fraction [0.63±0.09 *vs.* 0.54±0.09 (p<0.001)] in comparison to those who survived, with an OR of 1.45 (1.15-1.83), p=0.002. In addition, they showed a small correlation of positive end-expiratory pressure (PEEP) with dead space (r=0.22, p=0.003) and Ppeak (r=0.27, p<0.001).

In 2004, Kallet et al[15] conducted a study involving 59 patients from the population of Nuckton et al[6]. The results showed a significant difference in dead space fraction between the diseased and survivor groups, with the survivor group consistently having a lower value. On day 6, the difference was particularly pronounced (0.66±0.09 *vs.* 0.51±0.08, p<0.001).

In 2007, a study with 42 subjects conducted by a group from the University of California[17] examined the association between early measurement of Vd/Vt and pulmonary artery systolic pressure with mortality. Among them, 15 patients with Vd/Vt values of 0.61±0.09 died, while 27 patients with Vd/Vt values of 0.53±0.10 survived (p=0.02).

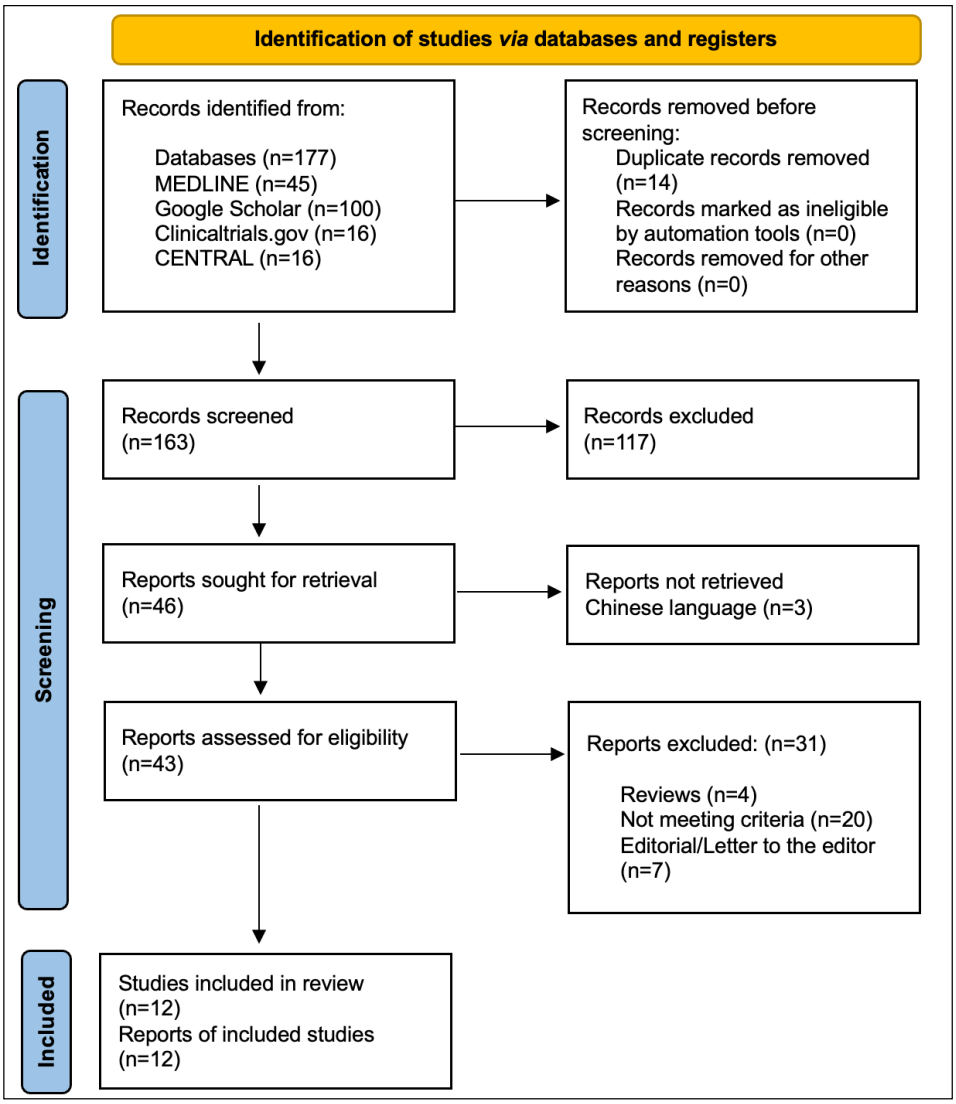

Figure 1. Flow diagram of the included studies.

Lucangelo et al[16] studied several parameters of volumetric capnography in 36 patients from two centers (Spain and Italy). The dead space fraction index had the best predictive value at 48 hours with a cut-off limit of 0.46 and area under the curve (AUC) of 0.75, sensitivity 63% and specificity 93%.

In another study conducted by Raurich et al[18] at a center in Spain, exhaled CO_2 levels were measured in 80 patients with early ARDS using a Douglas bag. The study found that on days 1 to 3, survivors had a Vd/Vt ratio of 0.53±0.11, while non-survivors had a ratio of 0.64±0.09 (p<0.001). The OR increased by 1.59 times for every 0.05 increase in Vd/Vt (95% CI 1.18-2.16, p<0.003). Additionally, 49 patients were reassessed throughout days 8 to 10, and in the survivors, the Vd/Vt ratio was lower compared to the diseased group (0.50±0.10 *vs.* 0.62±0.09, p<0.001). The OR was 2.87 (95% CI 1.36-6.04, p<0.005).

The group of Kallet et al[19] in 2014 obtained data from 126 patients with ARDS who participated in a phase III multicenter randomized trial analyzing the efficacy of albuterol. The Vd/Vt measurements on admission showed increased values in the deceased Vd/Vt=0.62±0.11 *vs.* 0.56±0.11, p=0.08, while a clearly greater difference is observed on day 1: 0.64±0.12 *vs.* 0.55±0.11, p=0.01 and on day 2: 0.67±0.12 *vs.* 0.56±0.11 p=0.004. Also, a statistically significant result was observed only on days 1 and 2 for both the unadjusted OR and the adjusted OR for ARDS etiology, PaO_2/FiO_2 (P/F), oxygenation index, and inotrope use. As a result, on day 1, the adjusted OR was calculated to be 6.84 (95% CI 1.62-28.84, p=0.01), and on day 2, OR=4.90 (95% CI 1.28-18.73 p=0.02). The study

group notes that the results are independent of albuterol use.

In a study published in 2014[20], an alternative way of estimating dead space was used in 26 patients from the equation of Frankenfield et al[3] VD/VT=0.320+0.0106 ($PaCO_2$-$EtCO_2$) + 0.003 (RR) + 0.0015 (age) using a simple capnograph. In the last available measurements (final/last available time point calculation) of VD/VT (equation of FrankenfIeld et al[3]), there was a clear difference between those who survived (VD/VT=0.56) and those who did not survive (VD/VT=0.71). After Bonferroni correction, a statistically significant difference between survivors and diseased was observed on days 6 to 9: 0.553 (0.436-0.642) *vs.* 0.797 (0.668-0.926) p=0.0016.

The same approach was used in a center in China a few years later[21]. In 46 patients, both the VD/VT index with the equation of Frankenfield et al[3], and the Vd/Vt index by means of volumetric capnography were measured in the first six days after intubation. A statistically significant difference in Vd/Vt values between survivors and non-survivors was seen on day 5, where Vd/Vt=0.45±0.04 *vs.* 0.41±0.06, (p=0.008) and on day 6, where Vd/Vt=0.47±0.05 *vs.* 0.40±0.03, (p=0.008). A similar difference was observed in VD/VT (Equation of FrankenfIeld et al[3]) on day 4. The panel showed that the equation of FrankenfIeld et al[3] is a superior prognostic indicator which offers a more reliable measurement at day 4, with an AUC of the ROC curve of 0.974±0.093 *vs.* 0.701±0.023 (95% CI 0.857-0.999 *vs.* 0.525-0.841, p=0.0024).

The group of Kallet et al[22] in 2017, in a retrospective study of 685 patients, provided data regarding the severity and cause of ARDS and Vd/Vt. Severe ARDS had higher mortality and higher Vd/Vt than mild and moderate ARDS. Also, overall, in the deceased group, the Vd/Vt ratio was higher (0.68±0.11) compared to the non-deceased group (0.60±0.11) (p<0.001). In relation to other prognostic indicators, such as driving pressure, oxygenation index, and age, a superiority of Vd/Vt is observed with an adjusted OR=1.22 (95% CI 1.11-1.35, p<0.001).

In 2018, data from a subgroup of the patients from the study mentioned above were published[23]. After first excluding those with sepsis, 86 patients with moderate ARDS of unusual causes were studied. A statistically significant effect between deceased and survivors was observed in median Vd/Vt 0.66 (0.57 to 0.78) *vs.* 0.59 (0.51 to 0.68), p=0.012. No statistically significant differences were observed in all parameters between the different causes, pulmonary and extrapulmonary. ARDS patients displayed a higher fraction, which is attributed to liver failure, potentially due to the pathophysiology of the disease.

Lecompte-Osorio et al[24] took data from 124 patients from three ARDS patient databases and studied the End Tidal CO_2 ($EtCO_2$)-$PaCO_2$ index as a predictor of mortality. They also measured the Vd/Vt index by substituting the mean exhaled CO_2 with $EtCO_2$ in the well-known Enghoff equation. The research team then conducted a retrospective study with 302 patients from the University of Chicago center to verify the observations. Analyzing the databases in a multivariate analysis, it emerged that the $EtCO_2$-$PaCO_2$ index, as well as the Vd/Vt, remained statistically significant for the prognosis of mortality. The $EtCO_2$-$PaCO_2$ index from the ARDS network population had OR=1.10 (95% CI 1.00-1.21 p=0.047), and from the University of Chicago OR=1.03 (95% CI 1.01-1.06 p=0.031). Similar results were displayed for modified Vd/Vt, where from the ARDS network population, an OR=1.05 (95% CI 1.00-1.10, p=0.024) was calculated. The University of Chicago also calculated an OR=1.02 (95% CI 1.01-1.090, p=0.003).

The last publication was by the research group of Graf et al[25] in 2022, which included 60 patients with COVID-19 ARDS. Forty-two percent (42%) of patients had Vd/Vt >0.57. The median Vd/Vt was calculated to be 0.58 (0.51-0.65) for non-survivors *vs.* 0.51 (0.44-0.58) for survivors (p=0.015) in survivors.

Quantitative Synthesis

A total of 5 studies reported odds ratios regarding our outcome of interest Vd/Vt as a predictor of mortality in early ARDS and were included in the meta-analysis[6,18,19,22,24], one of which included data regarding two separate populations[24]. The analysis regarding Vd/Vt as an indicator of mortality (Figure 2) led to a statistically significant association of this marker with death with a pooled OR equal to 1.27 [95% CI (1.09, 1.48), I^2=93%, p<0.01]. Furthermore, 7 studies[6,15-19,22] were included in the meta-analysis regarding the mean difference in which non-survivors within the populations given from the included studies had a higher Vd/Vt than survivors (Figure 3) with an MD=0.07 [95% CI (0.02, 0.11), I^2=82%, p<0.01].

Leave-One-Out Meta-Analysis

In order to estimate the effect of each included study on the overall outcome, a leave-one-out

Table I. Study characteristics.

Author and year	Country of origin	NOS scale	Study design	Method used to calculate dead space + time of measurement	Ventilation parameters	Etiology of ARDS-severity	Outcome
Nuckton et al[6] 2002 (N=179)	San Francisco, CA, USA - two centers	******	Prospective cohort	-Metabolic monitor (Deltarac) -Bohr-Enghoff equation -Measurement of Vd/Vt at 10.9±7.4 hours after diagnosis of ARDS	-Vt 10±1.4 ml/kg IBW -PEEP 8.8±3.4 -Position and sedation used: not described	-Multiple (sepsis, aspiration, pneumonia, trauma, overdose, fat emboli, or idiopathic) -Moderate (ALI patients) and severe ARDS -SAPS II = 47±17	A total of 104 patients survived and 75 died. There was a difference in the fraction [0.63±0.09 *vs.* 0.54±0.09 (p<0.001), OR 1.45 (1.15-1.83, p=0.002)]. Poor correlation of PEEP with Vd/Vt and no correlation with mortality was found.
Kallet et al[15] 2004 (N=59)	San Francisco, CA, USA - two centers	*******	Prospective cohort	-Metabolic monitor (Deltarac) -Bohr-Enghoff equation -Measurements of Vd/Vt at 24 hours and at days 2, 3 and 6	-Vt 10±1 ml/kg IBW -PEEP 8.8±3.4 -Position and sedation used: not described	-Sepsis, aspiration, pneumonia, trauma, transfusion related -Moderate (ALI patients) and severe ARDS -APACHE II = 21.6±6.0	A subgroup of patients was utilized from the study of Nuckton et al[6]. At the 24-hour mark, a notable difference in measurements was identified, with results showing 0.64±0.09 in one group compared to 0.53±0.09 in another (p<0.05). This difference suggests an early indication of the disease's impact. Furthermore, a more pronounced disparity emerged after 6 days, where values reached 0.66±0.09 and 0.51±0.08 (p<0.001). This significant change clearly illustrates the disease's progression over time, highlighting the evolving nature of the condition. A cut-off was proposed at 0.55. A poor correlation of PEEP and Vt was found with Vd/Vt.
Cepkova et al[17] 2007 (N=42)	San Francisco, CA, USA - one center	****	Prospective cohort	-Volumetric capnography (NOVAMETRIX-NICO) -Bohr-Enghoff equation -Measurement at ICU admission	-Vt 7±1.3 ml/kg IBW -PEEP 9.7±3.6 -Position and sedation used: not described	-Pneumonia, aspiration, sepsis, transfusion related -Moderate (ALI patients) and severe ARDS -APACHE II = 21±7.0	In a study measuring Vd/Vt in 39 patients, 15 patients died while 27 survived. The Vd/Vt values were 0.61±0.09 for those who died and 0.53±0.10 for those who survived (p=0.02). In addition, measurement of mean systolic pressure of pulmonary artery was not associated with mortality.
Lucangelo et al[16] 2008 (N=36)	Italy and Spain - two centers	*****	Prospective cohort	-Volumetric capnography (NOVAMETRIX CO_2SMO+) -Bohr-Enghoff equation -Measurements were conducted at 30 min-12 h-24 h-48 h following ICU admission	-Vt 6-8 ml/kg IBW -PEEP 8-10 cm H_2O -Position: not described -Sedation used: Midazolam	-Post-operative respiratory failure, pneumonia, sepsis, lung contusion. -Moderate (ALI patients) and severe ARDS -SAPS II = 44 (41-53)	Vd/Vt and a new index, the VAE/Vt ratio, representing the ratio of alveolar exhaled CO_2 to tidal volume, were studied. The Vd/Vt index had the best predictive value at 48 hours with a cut-off limit of 0.46 and AUC of 0.75, sensitivity 63% and specificity 93%. In addition, admission VAE/Vt and 48 h VAE/Vt showcased AUC 0.83, sensitivity 73% and specificity 93%.
Raurich et al[18] 2010 (N=80)	Spain - one center	*******	Prospective cohort	-Exhaled gas volume collection for five minutes in Douglas bag. Analysis of mixed exhaled PCO_2. -Bohr-Enghoff equation -Measurements at 1 to 3 days from the initiation of ARDS. -In 49 of 80 a new measurement at days 7 to 10	-Aim Pplat <33 cm H_2O Vt 7.9±2.6 ml/kg IBW -PEEP 10±3.6 cm H_2O -Position and sedation used: not described	-Pneumonia, sepsis, aspiration, trauma -Moderate and severe ARDS -SAPS II = 45±16	Early measurements of the volume distribution ratio (Vd/Vt) in the survivor group showed values of 0.53±0.11 compared to 0.64±0.09 in the non-survivor group (p<0.001). For each 0.05 increase in Vd/Vt, the odds ratio (OR) was 1.59 [95% confidence interval (CI) 1.18-2.16, p<0.003]. The area under the receiver operating characteristic (AUC to ROC) curve was 0.78 (95% CI 0.67-0.86), with a cut-off value of 0.58. Measurements taken between days 7 and 10 revealed values of 0.50±0.10 in the survivor group compared to 0.62±0.09 (p<0.001). For this period, the OR increased to 2.87 (95% CI 1.36-6.04, p<0.005), with an AUC to ROC curve of 0.80 (95% CI 0.66-0.90), and a cut-off value of 0.62.

Table continued

Table I *(Continued)*. Study characteristics.

Author and year	Country of origin	NOS scale	Study design	Method used to calculate dead space + time of measurement	Ventilation parameters	Etiology of ARDS-severity	Outcome
Kallet et al[19] 2014 (N=99)	Multicenter study - ARDS network	*******	Prospective cohort	-Volumetric capnography (NOVAMETRIX-NICO) -Bohr-Enghoff equation -Measurement at 4 hours, in 80 of 99 patients on the 1st day and in 56 of 80 on the second day	-Vt 6-8 ml/kg IBW -PEEP 9.7±3.4 (day 0) -Position: semi-recumbent -Sedation used: not described	-Pneumonia, sepsis, aspiration, trauma and other -Mild, moderate and severe ARDS -APACHE III = 91.8±27.7	Increased values of Vd/Vt were observed among the non-survivors at different time points: at 4 hours, the values were 0.62±0.11 for non-survivors compared to 0.56±0.11 for survivors (p=0.08); on day 1, the values were 0.64±0.12 for non-survivors *vs*. 0.55±0.11 for survivors (p=0.01); and on day 2, the values were 0.67±0.12 for non-survivors compared to 0.56±0.11 for survivors (p=0.004). The adjusted odds ratio (OR) at 4 hours was 1.73 (95% CI 0.82-3.63, p=0.15). The odds ratio was statistically significant on day 1, with an OR of 6.84 (95% CI 1.62-28.84, p=0.01). On day 2, the OR was 4.90 (95% CI 1.28 - 18.73, p=0.02).
Vender et al[20] 2014 (N=26)	USA - one center	*****	Prospective cohort	-Capnography -Equation from Frankenfield et al[3]: VD/VT= 0.320 + 0.0106 ($PaCO_2$-$EtCO_2$) + 0.003 (RR) +0.0015 (age) -Daily measurements from the first day of intubation up to the 9th day	N/A	-Patients with cystic fibrosis, acute bacterial pneumonia and ARDS -ARDS severity not described -Severity of disease classification not described	A significant difference was observed after the Bonferoni correction between survivors and non-survivors; 0.553 (0.436-0.642) *vs*. 0.797 (0.668-0.926), p=0.0016.
Zhang et al[21] 2016 (N=46)	China - one center	*******	Prospective cohort	-Volumetric capnography (Drager Medical, Germany) -Bohr-Enghoff and Frankenfield[3] equations. -Daily measurements of Vd/Vt and VD/VT for 6 days from the first day of stabilization of the patient post intubation	-Protective mechanical ventilation with low Vt PEEP adjustment (moderate to high), so that PaO_2 >60 mmHg -Position: not described -Muscle sedation provided in some patients	-Pneumonia, sepsis, aspiration, trauma and other -Mild, moderate and severe ARDS -APACHE III = 25±0.5 (survivors) and 28±0.4 (non-survivors)	The values of Vd/Vt did not differ between survivors and non-survivors during the first four days. However, on the fifth day, the values were 0.45±0.04 for survivors compared to 0.41±0.06 for non-survivors (p=0.008). On the sixth day, the values were 0.47±0.05 for survivors and 0.40±0.03 for non-survivors (p=0.008). Additionally, the VD/VT values began to show significant differences between the two groups starting from the fourth day. The VD/VT marker proves to be a better prognostic indicator from the fourth day onward. The area under the curve (AUC) of the ROC analysis for VD/VT and Vd/Vt on the fourth day was 0.974±0.093 *vs*. 0.701±0.023 (95% CI: 0.857-0.999 *vs*. 0.525-0.841, p=0.0024). There was no observed correlation with the increase in PEEP.
Kallet et al[22] 2017 (N=685)	USA - one center	********	Retrospective observational	-Volumetric capnography (NOVAMETRIX- NICO) -Bohr-Enghoff equation -Ninety seven percent of measurements were made on the day ARDS onset. Additional measurements within 48 hours	-Vt 6-8 ml/kg IBW -PEEP: 7-15 cm H_2O -Position: Semi-recumbent -Sedation used: Not described	-Pneumonia, sepsis, aspiration, trauma and other -Pulmonary etiologies were much more common than non-pulmonary etiologies. -Mild, moderate and severe ARDS -APACHE III = 21.6±7.8 (survivors) and 29.2±8.8 (non-survivors)	Vd/Vt values were lower in non-pulmonary etiologies of ARDS, but not difference in mortality was observed. However, overall difference between survivors and non-survivors was 0.68±0.11 *vs*. 0.60±0.11 (p<0.001), Vd/Vt OR=1.22 (95% CI 1.11-1.35, p<0.001). Difference between mild and severe ARDS was observed.

Table continued

Table I *(Continued)*. Study characteristics.

Author and year	Country of origin	NOS scale	Study design	Method used to calculate dead space + time of measurement	Ventilation parameters	Etiology of ARDS-severity	Outcome
Kallet et al[23] 2018 (N=86)	USA - one center	********	Prospective cohort	-Volumetric capnography (NOVAMETRIX-NICO) -Bohr-Enghoff equation -Measurements made 24 hours after the onset of ARDS	-Vt 6-8 ml/kg IBW -PEEP: 7-15 cm H_2O -Position: Semi-recumbent -Sedation used: not described	-Data from a subgroup of the patients from the study mentioned above[22] -Patients with ARDS of unusual etiology such as inhalation injury, drug toxicity, pancreatitis, hepatic failure and idiopathic. Patients with sepsis were excluded. -Moderate ARDS -Overall severity of disease classification not provided	Vd/Vt values had a statistically significant difference between non-survivors and survivors [0.66 (0.57 to 0.78) *vs.* 0.59 (0.51 to 0.68), *p*=0.012]. A statistically significant difference in respiratory mechanics between various etiologies was not observed. Higher Vd/Vt values were observed in patients with ARDS and hepatic encephalopathy due to the pathophysiology of the disease.
Lecompte-Osorio et al[24] 2021 (N=426)	USA - University of Chicago (N=302) and ARDS network (N=124)	********	Retrospective observational	-Capnography -Simplified Enghoff equation, replacing mean expired CO_2 with end-tidal CO_2. -Measurements were made on the first day of ARDS diagnosis	-Vt: 5.8-7.2 ml/kg IBW -PEEP: not described -Position and sedation used: not described	-ARDS etiology not described -Moderate and severe ARDS -APACHE III (ARDS network patients) = 90 (72-113) -APACHE II (University of Chicago) = 29 (23-36)	Patients from the ARDS network were included in the study to examine the $PaCO_2$-$PetCO_2$/$PaCO_2$ ratio as a prognostic marker, and a cohort from the University of Chicago was analyzed to validate the results. In the study conducted on the population from the ARDS network, the odds ratio (OR) for the simplified Vd/Vt was found to be 1.05, with a 95% confidence interval (CI) ranging from 1.00 to 1.10 and a *p*-value of 0.024, indicating a statistically significant association. Similarly, data from the University of Chicago presented an OR of 1.02, with a 95% CI between 1.01 and 1.09 and a p-value of 0.003, also suggesting a significant relationship. These findings highlight the relevance of Vd/Vt measurements in these populations and their potential implications in understanding outcomes in acute respiratory distress syndrome (ARDS).
Graf et al[25] 2022 (N=60)	Chile - one center	*******	Prospective cohort	-Volumetric capnography Servo I (Maquet™, Solna, Sweden), $NICO_2$ monitor (Respironics™, Carlsbad, CA, USA) -Bohr-Enghoff equation -Measurements on the first day of ARDS diagnosis	-Vt = 5.95 [5.40-6.30] mL/kg IBW. -PEEP 13 [12-14] cm H_2O -Position: prone position in approximately half of the patients -Sedation used: neuromuscular blockade	-COVID-19 -Mild and moderate ARDS -APACHE II = 9 (6-11)	A statistically significant difference of Vd/Vt values was shown among survivors and non survivors (or hospitalized patients within 28 days); 0.51 [0.44-0,58] *vs.* 0.58 [0.51-0.65] (*p*=0.015), AUC=0.684 [0.543-0.824], *p*=0.015 cut off Vd/Vt=0.566 (sensitivity = 70.4% και specificity = 75.8%). High levels of Vd/Vt are associated with a higher APACHE II score, worse respiratory mechanical properties (higher Pplat and lower Crs) and high d-Dimers values, while no correlation with oxygenation was noted.

IBW, Ideal Body Weight; ARDS, Acute Respiratory Distress Syndrome; Vd/Vt, Dead Space Fraction; Vt, Tidal Volume, PEEP, Positive End-Expiratory Pressure; ALI, Acute Lung Injury; SAPS II, Simplified Acute Physiology Score II; OR, Odds Ratio; APACHE II, Acute Physiology And Chronic Health Evaluation II; ICU, Intensive Care Unit; VAE/Vt, alveolar exhaled CO_2 to Tidal Volume; AUC, Area Under the Curve; Pplat, plateau pressure; PCO_2, partial pressure of CO_2; ROC, Receiver Operating Characteristic Curve; $EtCO_2$, End-Tidal CO_2; RR, Respiratory Rate; CI, Confidence Interval; PaO_2, Partial Pressure of Arterial Oxygen; $PetCO_2$, partial pressure of end-tidal CO_2; Crs, Respiratory System Compliance. COVID-19, Coronavirus disease 2019; Pplat: Plateau Pressure, Crs: Respiratory System Compliance. VD/VT: Equation of Frankenfield et al[3] = 0.320 + 0.0106 ($PaCO_2$-$EtCO_2$) + 0.003 (RR) + 0.0015 (age). Each asterisk (*) represents one grading point in the NOS scale.

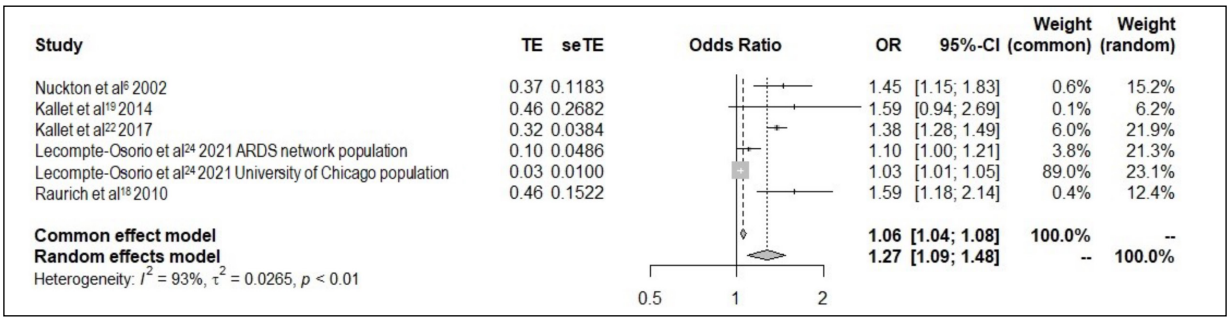

Figure 2. Odds ratio forest plot.

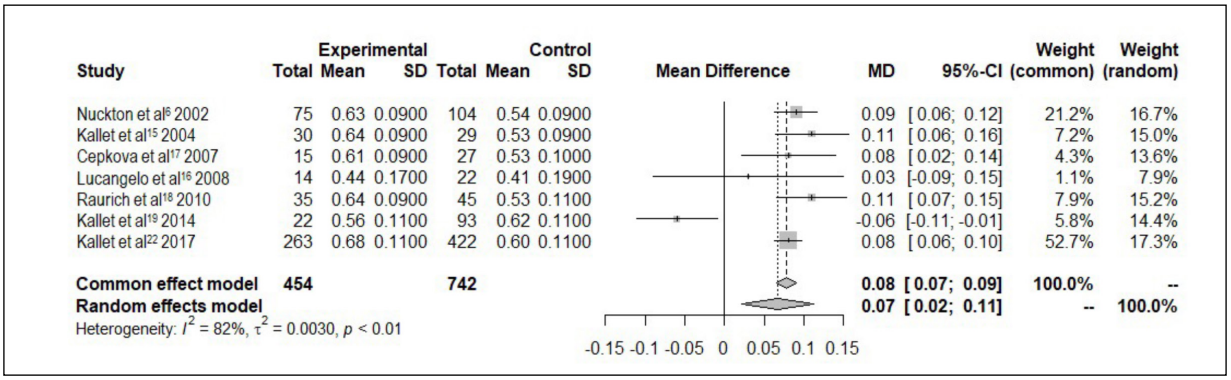

Figure 3. Mean difference plot.

meta-analysis was performed for both effect measures (MD, OR) used in our meta-analysis. In the OR effect measure group, the sequential omission of each study led to the variation of the OR estimate from 1.23 [95% CI (1.05, 1.44), I^2=94%, p<0.01] to 1.34 [95% CI (1.15, 1.56), I^2=77%, p<0.01]. In addition, regarding the mean difference effect measure, the leave-one-out meta-analysis showcased MDs varying from 0.06 [95% CI (0.01, 0.12), I^2=85%, p=0.03] to 0.09 [95% CI (0.07, 0.1), I^2=0, p<0.01] (Tables II and III).

Reporting Biases (Publication Bias)

Publication bias was evaluated with the use of funnel plots together with the aid of the trim and fill method. In the group in which odds ratio was used as an effect measure the visual inspection of the funnel plot together with the trim-and-fill method raises high suspicion of publication bias as 3 missing studies are calculated (Figure 4). In the mean difference group, low suspicion of publication bias is suspected (Figure 5).

Table II. Leave-one-out meta-analysis (odds ratio).

Study omitted	Odds ratio (OR)	95% CI	*p*-value	τ^2	τ	I^2
Nuckton et al[6] 2002	1.24	(1.05, 1.48)	0.01	0.0284	0.1685	94
Kallet et al[19] 2014	1.25	(1.07, 1.47)	<0.01	0.0270	0.1642	94
Kallet et al[22] 2017	1.25	(1.04, 1.51)	0.02	0.0321	0.1793	80
Lecompte-Osorio et al[24] 2021 ARDS network population	1.33	(1.11, 1.59)	<0.01	0.0304	0.1745	94
Lecompte-Osorio et al[24] 2021 University of Chicago population	1.34	(1.15, 1,56)	<0.01	0.01785	0.1324	77
Raurich et al[18] 2010	1.23	(1.05, 1.44)	<0.01	0.0236	0.1537	94

CI, Confidence Interval.

Table III. Leave-one-out meta-analysis (mean difference).

Study omitted	Mean difference (MD)	95% Confidence interval (CI)	*p*-value	τ^2	τ	I^2
Nuckton et al[6] 2002	0.06	(0.01, 0.12)	0.03	0.0037	0.0608	85
Kallet et al[15] 2004	0.06	(0.01, 0.11)	0.03	0.0033	0.0578	84
Cepkova et al[17] 2007	0.06	(0.01, 0.12)	0.02	0.0037	0.0608	85
Lucangelo et al[16] 2008	0.07	(0.02, 0.12)	<0.01	0.0033	0.0576	85
Raurich et al[18] 2010	0.06	(0.01, 0.11)	0.03	0.0033	0.0578	84
Kallet et al[19] 2014	0.09	(0.07, 0.1)	<0.01	0	0	0
Kallet et al[22] 2017	0.06	(0.01, 0.12)	0.02	0.0038	0.0619	85

Table IV. GRADE approach.

Subgroup	Patients number	τ^2	Effect measure	95% CI	95% PI	Quality of evidence
Odds ratio (OR)	1,477	0.0265	OR=1.27	(1.09, 1.48)	(0.77, 2.1)	⊕○○○ ***Very Low***
Mean difference	1,196	0.003	MD=0.07	(0.02, 0.11)	(-0.09, 022)	⊕⊕○○ ***Low***
Comparison	**Study limitations**	**Directness**	**Consistency**	**Precision**	**Publication bias**	
Odds ratio	Moderate	Direct	Inconsistent	Precise	High	
Mean difference	Moderate	Direct	Inconsistent	Precise	Low	

CI, Confidence Interval; PI, Prediction Interval.

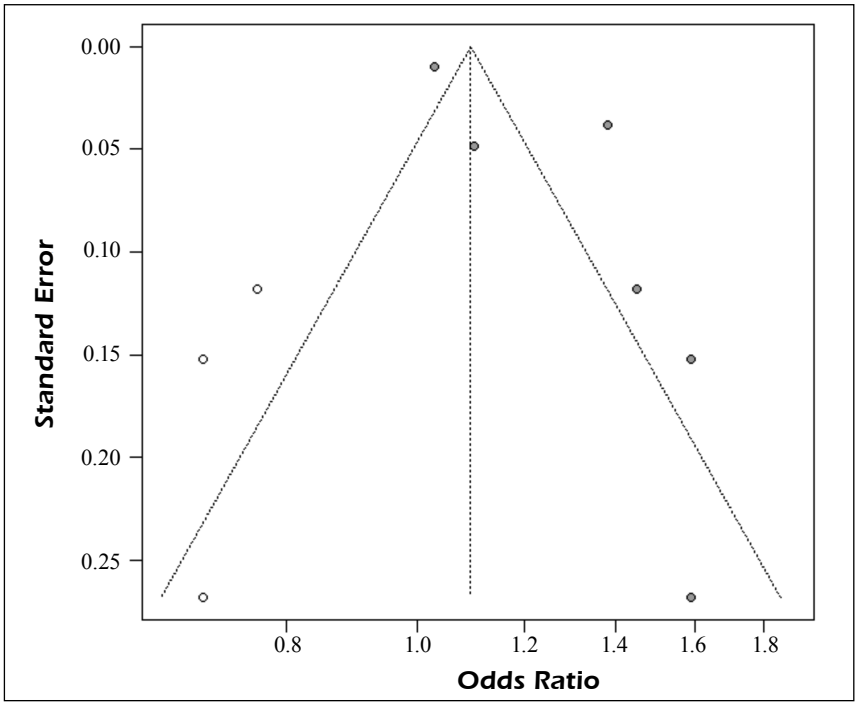

Figure 4. Funnel plot - odds ratios. Grey points represent the included studies, while white points represent calculating missing studies.

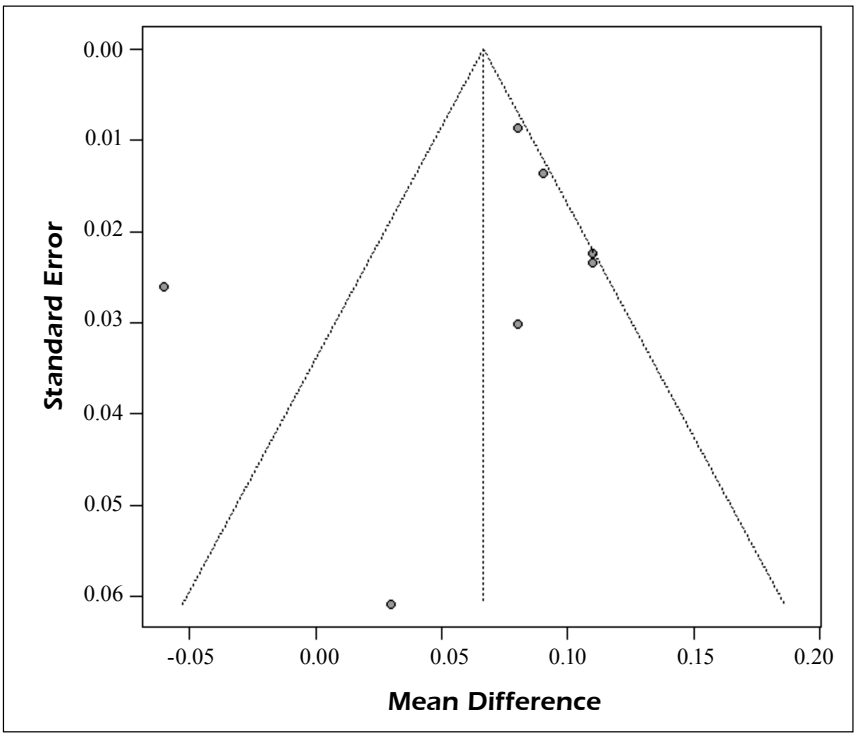

Figure 5. Funnel plot - mean differences.

Certainty of Evidence

The GRADE approach is presented in Table IV. Specifically, high publication bias was suspected in the odds ratio group as missing studies were calculated. In addition, inconsistency occurred due to the high inter-study heterogeneity calculated in both groups. Study limitations in both groups were moderate according to NOS evaluation, as seen in **Supplementary Table II**, and due to the cohort study design of the included studies. Finally, there were no major concerns with the directness and precision domains in all outcomes. In conclusion, certainty of evidence was low in the mean difference group and very low in the odds ratio group.

Discussion

Acute respiratory distress syndrome remains a destructive disease with high morbidity and mortality worldwide. Multiple pathophysiological mechanisms have been implicated in the development and progression of this syndrome, and increased dead space is a key mechanism.

The purpose of this systematic review and meta-analysis was to summarize and assess the current literature on the prognostic value of the Vd/Vt ratio in the mortality of ARDS. Patients with elevated values of Vd/Vt in early ARDS are more likely to have a worse outcome. Following a systematic literature search, twelve studies[6,15-25] were identified and included in the study, with a total of more than 1,700 patients. All studies showed that non-survivors had increased dead space mainly in the first 24 hours.

After evaluating the included studies, certain points of interest should be mentioned.

The study of Nuckton et al[6] showed a clear difference between those who survived and those who died. It is worth noting the fact that a respiratory volume greater than 8 ml/kg of ideal body weight (IBW) was used, which may confuse the outcomes, and also that a weak relation between PEEP and Vd/Vt ratio was displayed. Specifically, only 31 out of 179 patients received Vt 6 ml/kg. In addition, this study included patients with a P/F less than or equal to 200.

In four studies, the lead author is Richard H Kallet from San Francisco General Hospital[15,19,22,23], who was also part of the research team of Nuckton et al[6]. In 2014, this team[19] presented a Vd/Vt difference between survivors and those who died, which grew from day 1 to day 2. This difference with the progress of time also reflects the pathophysiological progression of the disease.

Moreover, in 2017[22], this team, in a large study of 685 patients, showed the superiority of this index over others, such as the oxygenation index, driving pressure, and age. They also showed no association with mortality in mild ARDS (according to the Berlin criteria); however, this study is limited by its retrospective nature.

Zhang et al[21] calculated the dead space fraction through the equation of Frankenfield et al[3] (VD/VT) and through volumetric capnography. Comparatively, the index of FrankenfIeld et al[3] constitutes a better prognostic tool.

In a retrospective study, Lecompte-Osorio et al[24] suggest a practical evaluation of dead space. They modified the initial equation of Enghoff by replacing the mean expired CO_2 with $EtCO_2$, a modification that can introduce bias. They also displayed that this simple and practical index is associated with mortality. We can draw the conclusion that even simple estimates of dead space give us evidence on mortality. Literature that employs these estimates is relatively new; however, they lack robust design and do not qualify as prospective studies. As a result, this conclusion remains uncertain. It is also necessary to compare the long-established measurement of Vd/Vt with the modified estimates, such as the replacement of mean expired CO_2 with end-expiratory CO_2, as the classic formula is believed to be a better estimate of dead space than an alveolar shunt. In a quick review of the literature on this topic, it appears that the studies using these practical indicators concern pediatric populations[26].

Finally, Graf et al[25] paper is the sole study that includes COVID-19 cases as well as direct Vd/Vt measurement. As we mentioned above, the etiology of ARDS is not ultimately related to the use of Vd/Vt as a prognostic indicator.

However, unlike the other studies, its exclusion criteria do not allow for the inclusion of patients with chronic obstructive pulmonary disease (COPD). The fact that there is no obvious relationship between P/F and Vd/Vt is surprising since, as we mentioned above, the severity of ARDS is directly related to Vd/Vt. At the same time, however, it advocates for the view that P/F should not be the absolute decision-making indicator, as it is considered unsafe in many aspects. Graf et al[25] suggest the use of Vd/Vt to classify high-risk patients with satisfactory P/F. At this point, it is worth noting that certain studies that were carried out prior to the introduction of the Berlin criteria refer to ARDS and acute lung injury (ALI) as two discreet clinical conditions. Indeed, in the studies of Nuckton et al[6], Kallet et al[15], Raurich et al[18], the patients included had a P/F less than or equal to 200. It is therefore necessary to conduct further and larger studies that will compare P/F with Vd/Vt in terms of disease severity.

In an effort to quantify the results mentioned above, we performed a meta-analysis of the studies providing data regarding the odds ratio and mean differences between survivors and non-survivors of ARDS. Indeed, non-survivors had higher levels of Vd/Vt than non-survivors with an MD=0.07 [95% CI (0.02, 0.11), I^2=82%, p<0.01]. In addition, non-survivors were more likely to have a higher level of Vd/Vt than survivors with and OR=1.27 [95% CI (1.09, 1.48), I^2=93%, p<0.01]. At this point, it is important to note that we defined early ARDS within the first 48 hours. Moreover, we examined the effect of each individual study on the overall outcome through leave-one-out meta-analysis and therefore lowered the inter-study heterogeneity in the group using mean difference as an effect measure to 0. More specifically, when Kallet et al[19] was omitted from the overall analysis, heterogeneity was nonexistent, probably due to the fact that this study's population is from the only randomized control trial included. In addition, publication bias was suspected to be high in the group using the odds ratio, and missing studies were calculated. One reason why this could be happening is because more studies were giving data about mean differences, and fewer were giving data about odds ratios, resulting in missing data. For the reasons mentioned above, in the leave-one-out meta-analysis regarding odds ratio as an effect measure, even if the same study[19] is omitted, heterogeneity could not be significantly lowered due to high suspicion of publication bias. Last but not least, the certainty of the evidence was calculated as low due to the inter-study heterogeneity and due to issues raised with publication bias in one group.

The above data allow us to draw certain safe conclusions. Initially, we are given the impression that in the past few years, studies have become increasingly complex. One possible explanation would be that the measurement of Vd/Vt is not considered reliable and practical, and thus, although there is general approval as to the predictive value, an effort is made to develop an easier estimation method of the dead space. Certain studies display satisfactory data on the sensitivity and specificity of the index; however, they are few and include a very small number of patients (N<80). In addition, the application of the index is

restricted in diseases with increased dead space, such as chronically hypercapnic patients, pulmonary hypertension, and thromboembolic disease, is limited. The studies that we included in the review exclude these types of patients, except for Graf et al[25] study, which only excludes patients with thromboembolic disease. It is understood that the early measurement of Vd/Vt is a good mortality indicator. The groups that showed no differences in the first 24 hours had a small number of patients (N<50). Also, all the studies we cited occurred after the ARMA trial[27] and thus, in all studies, except for the population of Nuckton et al[6], protective mechanical ventilation was used. In ARDS, the appropriate settings in mechanical ventilation pose a great challenge. In recent years, protective ventilation with Vt 6-8 ml/kg IBW, moderate/high PEEP values, and muscle relaxation has been used. All of the above can affect exhaled volume by providing false information about Vd/Vt. This is confirmed in two[20,21] studies, since the Vd/Vt index is presented as a superior prognostic tool since it corrects this type of bias. Finally, in ARDS, PEEP can decrease Vd/Vt as more respiratory units are recruited, but sometimes alveolar overdistention is caused by a subsequent increase. The effect of PEEP is difficult to predict, as both phenomena may occur simultaneously. In certain studies we included in the review, increased PEEP[21,28] was not associated with the Vd/Vt ratio. One study[6] showed a small correlation.

As dead space is the volume of air that is not being perfused, it can be influenced by various factors. The first factor of influence is alterations in pulmonary blood flow, including conditions such as pulmonary embolism or hemodynamic instability. Prone positioning can impact the distribution of ventilation and perfusion, to an extent could influence Vd/Vt. Higher levels of tidal volumes cause overdistention, and levels of PEEP can cause either overdistention if they are high or respiratory unit de-recruitment if they are low[29]. As shown in the current systematic review and meta-analysis ARDS can cause alterations both in lung compliance and pulmonary blood flow. The research on the prognostic significance of Vd/Vt trending in ARDS requires that certain factors that influence its values remain the same. Therefore, we recommend the measurement of Vd/Vt in patients with protective mechanical ventilation settings with a stable tidal volume after the optimal PEEP has been applied. The patient's position should remain the same, either prone or supine, when dead space is measured. It would be of great interest for a correlation to be found between lung compliance and Vd/Vt in order to help the differential diagnosis, for instance, between ARDS worsening and pulmonary embolism.

We note that the outcomes and conclusions of the clinical studies we referenced were quite informative. However, it is important to interpret results with caution due to the high heterogeneity and publication bias in some analyses. Different methods of calculating dead space were used. The majority of the studies included in the review utilize the Enghoff modification for calculating Vd/Vt. This modification replaces alveolar PO_2 with arterial PO_2, assuming their difference is insignificant. There exists a divergence of opinions regarding the use of this modification because of the Alveolar-arterial difference (A-a gradient). In ARDS, due to alveolar-capillary dysfunction, the A-a gradient is expected to be greater. In addition, the method of substituting the mean exhaled CO_2 with $EtCO_2$, as proposed by Lecompte-Osorio et al[24] is an easier approach. However, it is not fully consistent with Bohr's definition. Furthermore, the data of most included studies relied upon a small number of patients. All the above could be contributing factors to the high heterogeneity in our study. It is worth mentioning that the study design among the included studies was heterogeneous. A study that compares the different methods of calculating dead space is necessary.

Strong Points and Limitations

In the studies we included, it seems that an increased Vd/Vt index (but also VD/VT index of FrankenfIeld et al[3]) is associated with greater mortality. The majority of the studies we included scored well in quality assessment and in addition, they concern studies in the era of protective mechanical ventilation and VILI avoidance.

This systematic review included observational studies, including two retrospective studies[22,24]. Non-English studies were not retrieved. Furthermore, many of the studies had a small number of patients. Different dead space calculation equations were used, and the impact on Vd/Vt values was not emphasized. In the quantitative analysis, the certainty of the evidence was low, and many studies did not report quantitative data and, therefore, could not be included in the meta-analysis. Publication bias evaluation should be examined with caution as the trim and fill method could be highly heterogenous.

Conclusions

ARDS is a systemic disease with a variety of pathophysiological mechanisms, including an increase in dead space. The high mortality and morbidity of the syndrome create a need to highlight prognostic indicators that will help in making medical decisions. The assessment of dead space through the Vd/Vt ratio is a prognostic indicator, and indeed, early elevated Vd/Vt values are associated with higher mortality, as we have displayed in this study. However, the interpretation of our results requires caution due to the noted limitations. Almost ten years after the Berlin definition, new studies should focus on other gravity indicators than the P/F ratio.

Ethics Approval and Informed Consent

Not applicable due to the study's design as a systematic review.

Availability of Data and Materials

No new data were created in this study. Any further inquiries should be directed to the corresponding author.

Conflict of Interest

All authors declare no conflict of interest.

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Authors' Contributions

Vasileios Issaris: conceptualization, investigation, methodology, project administration, supervision, validation, visualization, writing-original draft, and writing-review and editing. Gerasimos Panagiotis Milas: conceptualization, formal analysis, methodology, validation, visualization. Christos Georgios Dragonas: conceptualization, methodology, project administration, visualization. Georgios Poupouzas: writing-review and editing. Nektarios Anagnostopoulos: conceptualization, methodology, project administration, visualization. Rovina Nikoletta: conceptualization, methodology, project administration, supervision, roles/writing-original draft, and writing-review and editing.

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