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Increased respiratory dead space could associate with coagulation activation and poor outcomes in COVID-19 ARDS

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ABSTRACT

Purpose: To determine whether VDPhys/VT is associated with coagulation activation and outcomes.
Materials and methods: We enrolled patients with COVID-19 pneumonia who were supported by invasive mechanical ventilation and were monitored using volumetric capnography. Measurements were performed during the first 24 h of mechanical ventilation. The primary endpoint was the likelihood of being discharge alive on day 28.
Results: Sixty patients were enrolled, of which 25 (42%) had high VDPhys/VT (>57%). Patients with high vs. low VDPhys/VT had higher APACHE II (10[8-13] vs. 8[6-9] points, $p = 0.002$), lower static compliance of the respiratory system (35[24–46] mL/cmH_2O vs. 42[37–45] mL/cmH_2O, $p = 0.005$), and higher D-dimer levels (1246 [1050–1594] ng FEU/mL vs. 792[538–1159] ng FEU/mL, $p = 0.001$), without differences in P/F ratio (157 [112–226] vs. 168[136–226], $p = 0.719$). Additionally, D-dimer levels correlated with VDPhys/VT ($r = 0.530$, $p < 0.001$), but not with the P/F ratio ($r = -0.103$, $p = 0.433$). Patients with high VDPhys/VT were less likely to be discharged alive on day 28 (32% vs. 71%, aHR = 3.393[1.161–9.915], $p = 0.026$).
Conclusions: In critically ill COVID-19 patients, increased VDPhys/VT was associated with high D-dimer levels and a lower likelihood of being discharged alive. Dichotomic VDPhys/VT could help identify a high-risk subgroup of patients neglected by the P/F ratio.
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1. Background

Since the outbreak of the novel coronavirus disease (COVID-19) at the end of 2019 in Wuhan, China [1], cases have been reported in five continents, and the World Health Organization declared COVID-19 a pandemic [2]. In the most serious cases, the clinical picture of COVID-19 is characterized by lung opacities on chest imaging and hypoxemic respiratory failure with intensive care unit (ICU) admission and the need for respiratory support [3-5]. Indeed, the development of acute respiratory distress syndrome (ARDS) is one of the hallmarks of severe COVID-19, and mechanical ventilation is the cornerstone of ICU support in COVID-19-related ARDS [6]. However, an atypical presentation of ARDS has been described in COVID-19 patients, with severe gas exchange impairment and discordantly preserved respiratory system mechanics [6]. Some authors have proposed other pathophysiological mechanisms to explain gas exchange impairment, different from shunt or ventilation/perfusion (V/Q) mismatch [6,7]. Increased respiratory dead space has been suggested as a relevant mechanism in these patients [7]. This idea is supported by data from deceased COVID-19 patients showing viral infection of endothelial cells with inflammatory infiltration and microthrombosis in the lungs and other organs [8]. Similarly, some cohorts have described coagulation activation and increased D-dimer [3,5]. Moreover, in a Chinese cohort, a D-dimer level > 1000 ng FEU/mL was independently associated with mortality [9]. Therefore, vascular pulmonary disease has been proposed as a relevant trait in patients with COVID-19 [6]. However, data regarding the association between respiratory and coagulation activation parameters are lacking. Of special interest is the respiratory dead space because it is the portion of tidal volume that does not participate in gas exchange such as when alveolar perfusion is close to zero (i.e., pulmonary embolism) [10]. The physiological dead space (VDPhys/VT) is composed of airway dead space and alveolar dead space [10]. In a mechanically ventilated patient, the airway dead space is the sum of the anatomical dead space (conducting airways) and apparatus dead space [10]. An alveolar

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, Acute respiratory distress syndrome; aHR, Adjusted hazard ratio; COVID-19, Coronavirus disease 2019; ICU, Intensive care unit; IMV, Invasive mechanical ventilation; P/F ratio, arterial to inspired oxygen ratio; $PECO_2$, mean expiratory carbon dioxide pressure; SOFA, Sequential Organ Failure Assessment; VDPhys/VT, Physiological respiratory dead space; V/Q, Ventilation/perfusion; VR, Ventilatory ratio.

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dead space is a construct that takes into account the remnant tidal volume that does not participate in gas exchange [10]. In normal healthy subjects, the alveolar dead space is expected to be negligible, whereas in pulmonary arterial thrombosis or pulmonary microcirculatory thrombosis, an increased alveolar dead-space is expected [10]. As VDPhys/VT includes alveolar dead-space changes, it may be useful for monitoring lung microcirculatory changes. Interestingly, in mechanically ventilated patients and monitored with volumetric capnography, VDPhys/VT assessment is a feasible bedside parameter [10]. In COVID patients, two retrospective studies reported an increased VDPhys/VT, which was determined by an indirect method based on Harris-Benedict's formula or surrogates [11,12]. In these studies, VDPhys/VT was not independently associated with outcome and the association between VDPhys/VT and coagulation activation was not explored. We hypothesize that in patients with ARDS related to COVID-19, respiratory dead space determined by volumetric capnography is increased and, associated with coagulation activation (as D-dimer) and patient outcomes.

2. Methods

2.1. Study design and patients

This observational analytical study was conducted during the first wave of the COVID-19 pandemic in Chile (March 3–August 31, 2020). The cohort is part of a prospectively obtained database by the project "Registro de pacientes graves ingresados en la Unidad de Cuidados Intensivos adultos" (RUCI) of Clínica Alemana de Santiago approved by our local IRB (#00011516). Data were collected as part of routine clinical practice, and all data were used in a de-identified manner; therefore, the need for informed consent was waived by the IRB as it was deemed unnecessary according to national regulations waiving for informed consent. Demographic, clinical, and laboratory data were obtained from a dedicated database. Inclusion criteria for participation in this study were as follows: age > 18 years, patients with a diagnosis of COVID-19 suspected on clinical-tomographic grounds and confirmed by polymerase chain reaction, patients admitted to the intensive care unit and supported with invasive mechanical ventilation, monitored with volumetric capnography, and mechanical ventilation setting in volume control and under neuromuscular blockade. Exclusion criteria were: pulmonary embolism or other thromboses, bleeding, chronic anticoagulant treatment, patients with indication for anticoagulant therapy, pregnancy, and dying patient. Demographic, clinical, and laboratory data were obtained from a dedicated database.

2.2. Variables of interest

- Critically ill scores: Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA).
- Oxygenation variable: arterial to inspired oxygen ratio (P/F ratio).
- Carbon dioxide clearance impairment: physiological respiratory dead space (VDPhys/VT) by volumetric capnography and ventilatory ratio (VR).
- Respiratory support setting: Positive end-expiratory pressure (PEEP) and tidal volume indexed by ideal body weight.
- Respiratory mechanics: Plateau pressure and static compliance of the respiratory system.
- Coagulation activation: We focused on D-dimer because it is the only laboratory parameter independently associated with worse outcomes [9,13]. D-dimer level determination was performed on the same day as the respiratory dead-space assessment.

2.3. Physiological respiratory dead space measurement

All patients were ventilated in volume control mode and treated with neuromuscular blockade at the time of measurement. The ventilator parameters were unchanged for at least 1 h before the dead space measurement. Respiratory dead space was evaluated as physiological respiratory dead space (VDPhys/VT). VDPhys/VT was calculated as follows [13,14]:

$$\frac{VDPhys}{VT} = \frac{PaCO2 - PECO2}{PaCO2}$$

where $PaCO_2$ is the arterial partial pressure of carbon dioxide, and $PECO_2$ is the mean expiratory pressure of carbon dioxide.

For this equation, $PECO_2$was obtained from volumetric capnography using the mechanical ventilation (Servo I ventilator, Maquet™, Solna, Sweden) or $NICO_2$ monitor (Respironics™, Carlsbad, CA, USA). Simultaneously, $PaCO_2$ was obtained from a sample of arterial blood using point of care blood analyzer (RAPID Point™ 500 Blood Gas Analyzer, Siemens Healthineers, USA). Additionally, ventilatory ratio (VR), a surrogate of VDPhys/VT, was obtained [10].

2.4. Outcomes

Primary outcome was the cumulative proportion of patients discharged alive from hospital on day 28.

2.5. Statistical analysis

Initial demographic, severity, and physiological descriptive analyses were performed. Categorical and continuous variables are presented as N (%) and median [IQR], respectively. Associations among categorical variables were analyzed using correlations, and Pearson's coefficients were obtained. In agreement with a previous report [15], our cohort was dichotomized according to the VDPhys/VT value as high VDPhys/VT (>57%) or low VDPhys/VT (<57%). Additionally, receiver operating characteristic curve for VDPhys/VT and outcome was obtained. Distributions of continuous variables were explored using the Kolmogorov-Smirnov test, and differences were analyzed using the Mann-Whitney *U* test. Differences in categorical variables were analyzed using Fisher's exact test or chi-square test. Univariate analysis was performed to identify variables associated with outcome achievement. Cox regression was used to analyze the cumulative proportion of patients whom were discharged alive at 28 days, and adjusted hazard ratios were obtained. In this analysis, patients who die and patients who remain into the hospital were considered as unfavorable outcome while only patients discharged alive to the their homes were considered as favorable outcome or outcome achieved. Finally, the curves for the cumulative proportions of outcome achievement were compared using the log-rank test. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using the SPSS software (version 20.0; SPSS, Chicago, IL, USA).

3. Results

3.1. Patients

A total of 60 individuals were identified (See Fig. 1). The patients were mainly male (83%) and 61 [54–69] years old. All the patients received volume-controlled ventilation and were treated with neuromuscular blockade. Their APACHE II and SOFA scores were 9 [6-11] and 5 [3-6] points, respectively. Similar to previous reports, our patients had a low lymphocyte count (670 [474–952] per mm^3) and high biomarkers of inflammation in addition to increased D-dimer levels (1066 [695–1420] ngFEU/mL). We observed moderate hypoxemia with a P/F ratio of 164 [134–226]. Protective ventilation was provided with a tidal volume of 5.95 [5.40–6.30] mL/kg of predicted body weight. Overall, moderate PEEP was provided 13 [12-14] cmH_2O. Carbon dioxide clearance was impaired with a VDPhys/VT of 56% [45–61] and VR 1.688 [1.399–1.960]. All patients were treated with prophylactic doses of low molecular weight heparin and with methylprednisolone

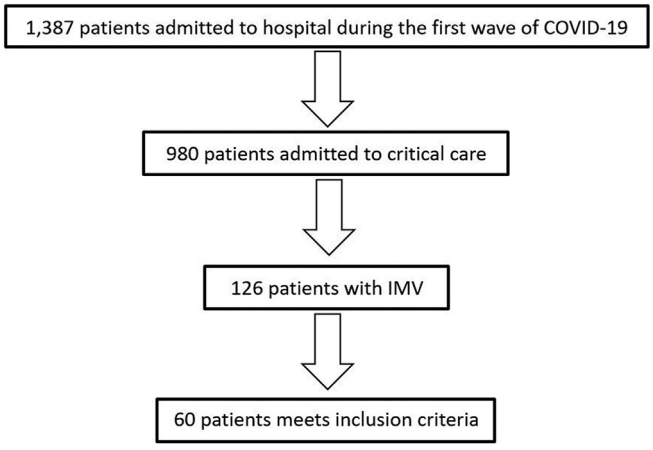

Fig. 1. Study flow chart, where IMV is invasive mechanical ventilation.

40 mg twice daily for five days and followed by 40 mg once daily for five days in agreement with our protocol for COVID-19 ARDS. A detailed description of the patients is summarized in Table 1.

3.2. Characteristics of patients with high respiratory dead space

25 patients (41.6%) had VDPhys/VT >57%; these patients, were the old and had higher severity scores at admission. Regarding the inflammatory response, in patients with high VDPhys/VT, we found increased levels of C-reactive protein and procalcitonin. Additionally, these patients had increased D-dimer levels. Interestingly, oxygenation assessed by the P/F ratio was not different among the groups (157[112–226] versus 168[136–226]). While PEEP and tidal volume were not different, respiratory system mechanics was more impaired in patients with high VDPhys/VT. In fact, these patients had higher plateau pressures (24 [22-26] cmH_2O versus 22[21-24] cmH_2O, $p = 0.024$) and lower static compliance of respiratory system (35[24-46] mL/cmH_2O versus 42 [37–45] mL/cmH_2O, p = 0,005). We found an increased VR in patients with high vs low VDPhys/VT (1.952 [1.322–2.582] vs. 1.476 [1.016–1.396], respectively; $p < 0.001$). Additionally, we saw a correlation between VR and VDPhys/VT ($r = 0.508$, $p < 0.001$). A detailed description of the patients according to dichotomous VDPhys/VT approach is presented in Table 2.

Table 1
Overall description, where APACHE II is Acute Physiology and Chronic Health Evaluation II, SOFA is Sequential Organ Failure Assessment score, P/F ratio is arterial to inspired oxygen pressure, TV is tidal volume, Cst is static compliance of respiratory system, VD_{Phys}/VT is physiological respiratory dead space, and VR is ventilatory ratio.

Demographic and epidemiological variables	*Value*
Male, N (%)	50 (83)
Age	61 [54–69]
Body mass index, Kg/m^2	29.4 [27. 3-34.7]
Severity variables	
APACHE II score, points	9 [6-11]
SOFA score, points	5 [3-6]
Respiratory variables	
P/F ratio, dimensionless	164 [13 4-225]
TV, mL/Kg PBW	6.0 [5.4–6.3]
PEEP, cmH_2O	13 [12-14]
Plateau pressure, cmH_2O	23 [22-24]
Cst, mL/cmH_2O	39 [32-45]
VD_{Phys}/VT, %	56 [45–61]
VR, dimensionless	1.688 [1.399–1.960]
Hemostasis parameters	
D-dimer, ngFEU/mL	1066 [695–1420]
Fibrinogen, mg/dL	644 [48 3-718]
Platelets, $10^3/mm^3$	280 [216–365]
Biochemical parameter	
Lactate dehydrogenase, U/L	398 [327–507]
Inflammatory parameters	
Ferritin, ng/mL	1926 [954–3654]
C reactive protein, mg/dL	13.9 [7.3–23.6]
Procalcitonin, ng/mL	0.22 [0. 14-0.47]
Outcomes	
ICU mortality	6 (10)
Mortality at 28 days	6 (10)
Mortality at 90 days	7 (11.7)
Discharged alive at day 28, N (%)	33 (55)

3.3. Respiratory dead space and coagulation activation

We found a moderate and significant positive correlation between VDPhys/VT and D-dimer levels ($r = 0.530$, $p < 0.001$, Fig. 2A); however, we failed to find a correlation between VDPhys/VT and other variables of hemostasis, such as platelet count or fibrinogen level. Similarly, patients with high VDPhys/VT had higher D-dimer levels than those with low VDPhys/VT (1246[1050–1594] vs 792[538–1159], respectively, $p = 0.001$). We failed to find a correlation between coagulation variables and oxygenation (Fig. 2B). Additionally, we saw a lack of correlation between VR and D-dimer levels ($r = 0.127$, $p = 0.332$).

3.4. Outcome

Overall, seven patients died while 33 (55%) patients were discharged alive home on day 28. Of all variables studied, only age,

Table 2
Description of patients according to dichotomous VD_{Phys}/VT, where APACHE II is Acute Physiology and Chronic Health Evaluation II, SOFA is Sequential Organ Failure Assessment score, P/F ratio is arterial to inspired oxygen pressure, TV is tidal volume, Cst is static compliance of respiratory system, VD_{Phys}/VT is physiological respiratory dead space, and VR is ventilatory ratio.

Variables	*High VD/VTPhys N = 25*	*Low VD/VTPhys N = 35*	*Significance*
Male, N (%)	19 (76)	31 (89)	0.174
Age	64 [57–74]	58 [51–64]	0.022
Body mass index, Kg/m^2	29.4 [26. 6-32.3]	30.5 [27. 3-35.9]	0.409
Severity variables			
APACHE II score, points	10 [8-13]	8 [6-9]	0.002
SOFA score, points	5 [4-7]	5 [3-6]	0.094
Respiratory variables			
P/F ratio, dimensionless	157 [11 2-226]	168 [136–226]	0.719
TV, mL/Kg PBW	5.7 [5.2–6.2]	6.0 [5. 5-6.6]	0.318
PEEP, cmH_2O	12 [11-15]	13 [12-14]	0.466
Plateau pressure, cmH_2O	24 [22-26]	22 [21-24]	0.024
Cst, mL/cmH_2O	35 [24-46]	42 [37–45]	0.005
VD_{Phys}/VT, %	62 [59–67]	47 [43–53]	0.015
VR, dimensionless	1.952 [1.322–2.582]	1.476 [1.016–1.396]	<0.001
Hemostasis parameters			
D-dimer, ngFEU/mL	1246 [1050–1594]	792 [53 8-1159]	0.001
Fibrinogen, mg/dL	629 [594–743]	656 [437–711]	0.398
Platelets, $10^3/mm^3$	283 [223–365]	264 [21 2-377]	0.647
Biochemical parameter			
Lactate dehydrogenase, U/L	441 [364–515]	371 [323–481]	0.153
Inflammatory parameters			
Ferritin, ng/mL	1865 [700–3379]	1942 [1193–3721]	0.354
C reactive protein, mg/dL	17.6 [9.8–32.1]	8.5 [5.2–17.8]	0.002
Procalcitonin, ng/mL	0.43 [0. 17-1.28]	0.20 [0. 10-0.36]	0.011
Outcome			
Discharged alive at day 28, N (%)	8 (32)	25 (71)	0.003

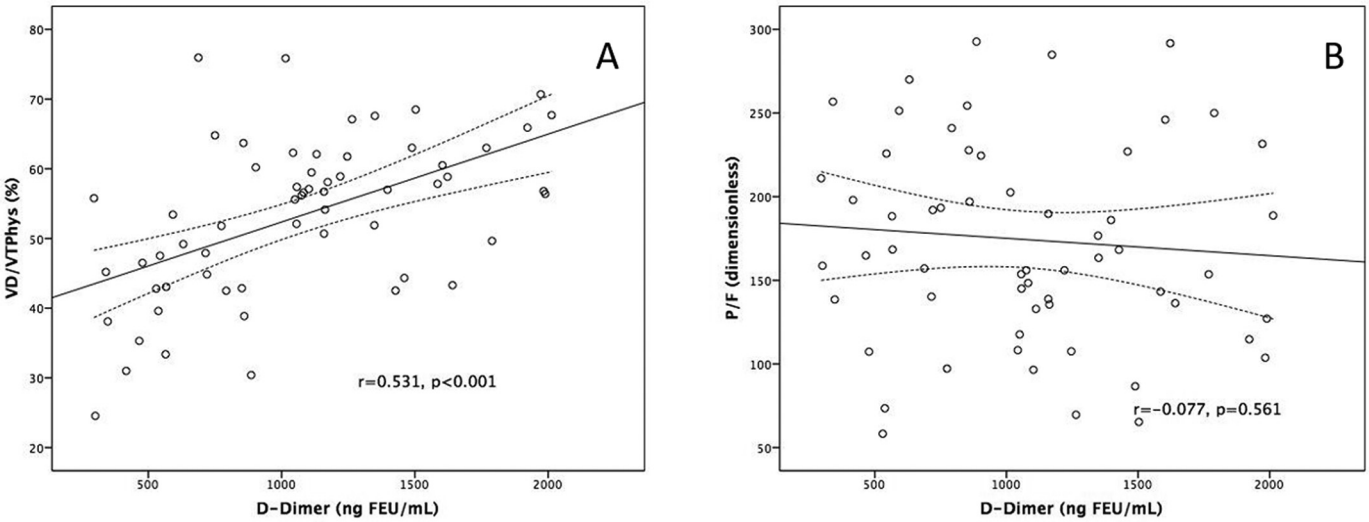

Fig. 2. A: VDPhys/VT versus D-dimer. B: P/F ratio versus D-dimer.

APACHE II, SOFA, static compliance of the respiratory system and VDPhys/VT (as a continuous or dichotomous variable) were different between patients discharged alive at 28 days and those who did not (Table 3). Patients with high VDPhys/VT had a lower cumulative proportion of outcome achievement than those with low VDPhys/VT (32% versus 71%, respectively, $p = 0.03$). We performed the Cox proportional hazards model considering the following variables: APACHE II, SOFA, static compliance of the respiratory system, P/F ratio, prone positioning, D-dimer level (>1000 ngFEU/mL), and dichotomous VDPhys/VT, which was defined a priori. In this model dichotomous VDPhys/VT was associated with the likelihood of outcome achievement on day 28 with an aHR of 3.393 [1.161–9.915], $p = 0.026$. The adjusted curves are shown in Fig. 3. When we replace VDPhys/VT for VR, we failed to found an association between VR and outcome (aHR of 0.889 [0.486–1.628], $p = 0.704$).

3.5. Discrimination analysis for association between VDPhys/VT and outcome

We performed a discrimination assessment using ROC curves analysis (Fig. 4). An area under the curve (AUC) of 0.684 [0.543–0.824] was obtained ($p = 0.015$). Based on *Youden* index, a VDPhys/VT of 56.66% was identified as better cut-off for outcome discrimination with sensitivity of 70.4% and specificity of 75.8%.

4. Discussion

To the best of our knowledge, this is the first study to explore the association between respiratory dead space by volumetric capnography, outcome, and coagulation activation in critically ill COVID-19 patients. The main finding was an increased respiratory dead space, which was correlated with coagulation activation (as D-dimer) and associated with a lower probability of being discharged alive at 28 days. We failed to find any association between oxygenation (P/F ratio) and respiratory dead space or coagulation activation. Additionally, we found a cut-off value for VDPhys/VT and outcome discrimination of 56.66%, similar to previous report (57%).

Our findings regarding respiratory dead space are in agreement with those of previous reports. This is a physiological parameter that synthetize carbon dioxide clearance impairment and has been independently associated with mortality in ARDS [15]. This observation is true in the early and intermediate phases of ARDS [16] and in patients with ARDS, according to the Berlin definition under lung-protective ventilation [17]. In a dichotomous approach, a respiratory dead space >57% was independently associated with an increased mortality rate [15]. Respiratory clearance of carbon dioxide has been explored in COVID-19 patients. *Vasques* et al. found increased respiratory dead space in 213

Table 3
Description of patients according to outcome, where APACHE II is Acute Physiology and Chronic Health Evaluation II, SOFA is Sequential Organ Failure Assessment score, P/F ratio is arterial to inspired oxygen pressure, TV is tidal volume, Cst is static compliance of respiratory system, VD_{Phys}/VT is physiological respiratory dead space, and VR is ventilatory ratio.

Variables	*Discharged alive on day 28, YES N = 33*	*Discharged alive on day 28, NO N = 27*	*Significance*
Male, N (%)	29 (88)	21 (78)	0.243
Age	56 [50–62]	70 [64–76]	<0.001
Body mass index, Kg/m^2	29.6 [25. 3-33.9]	29.3 [26. 2-32.4]	0.271
Severity variables			
APACHE II score, points	7 [5-9]	11 [9-13]	<0.001
SOFA score, points	4 [2-6]	6 [5-8]	0.006
Respiratory variables			
P/F ratio, dimensionless	173 [138–208]	149 [98–200]	0.082
TV, mL/Kg PBW	6.1 [5. 6-6.7]	5,8 [5. 2-6.4]	0.121
PEEP, cmH_2O	13 [12-14]	12 [11-13]	0.173
Plateau pressure, cmH_2O	23 [22-25]	23 [21-25]	0.970
Cst, mL/cmH_2O	43 [38–49]	37 [30-44]	0.041
VD_{Phys}/VT, %	51 [44–58]	58 [51–65]	0.015
VD_{Phys}/VT > 57%, N (%)	8 (24)	17 (63)	0.003
VR, dimensionless	1.586 [1.12 6-2.046]	1.708 [1.058–2.358]	0.453
Prone Position, N (%)	14 (56)	18 (51.4)	0.466
Hemostasis parameters			
D-dimer, ngFEU/mL	1029 [670–1388]	1145 [736–1554]	0.082
D-dimer >1000 ngFEU/mL, N (%)	17 (52)	18 (67)	0.179
Fibrinogen, mg/dL	664 [619–709]	594 [47 7-711]	0.177
Platelets, $10^3/mm^3$	247 [184–311]	272 [209–336]	0.970
Biochemical parameter			
Lactate dehydrogenase, U/L	454 [370–539]	378 [295–461]	0.444
Inflammatory parameters			
Ferritin, ng/mL	1942 [585–3299]	1975 [231–3720]	1.000
C reactive protein, mg/dL	13.9 [8.6–19.2]	17.6 [5.7–29.5]	0.139
Procalcitonin, ng/mL	0.20 [0. 15-0.45]	0.32 [0.05–0.69]	0.357

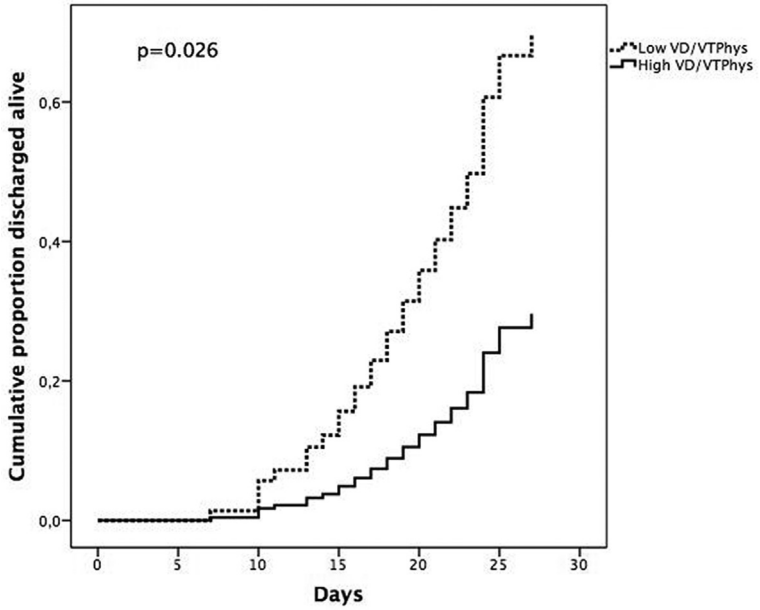

Fig. 3. Cumulative proportion of patients discharged alive on day 28. Curves were adjusted by APACHE II, SOFA, static compliance of the respiratory system, P/F ratio, prone position and D-dimer level (>1000 ngFEU/mL).

COVID-19 patients [11]. In a large retrospective cohort of COVID-19 patients, *Morales-Quinteros* et al. reported significant impairment in respiratory CO_2 clearance [12]. However, in both studies, respiratory dead space was obtained without volumetric capnography; therefore, only indirect approaches to respiratory dead space have been used. Remarkably, our findings using volumetric capnography support these previous reports and confirm that respiratory dead space is increased in COVID-19 patients. Moreover, our study adds to previous reports the novel association between respiratory dead space and coagulation activation.

Regarding ventilatory ratio, we saw a weak correlation with respiratory dead space. This is in agreement with a previous report of our group [14]. As expected, VR was increased in patients with high respiratory dead space. However, we failed to found an association between VR at beginning of invasive mechanical ventilation and outcome. Similar finding has been previously reported in COVID ARDS [12]. As surrogate of VDPhys/VT, VR do not take into account carbon dioxide output, therefore, this difference could explain our findings.

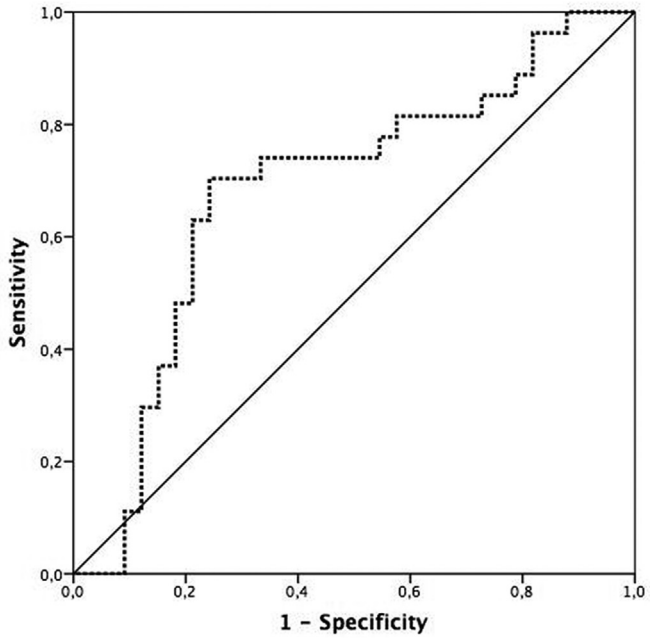

Fig. 4. ROC curve for VDPhys/VT and outcome.

We focused on D-dimer because it is a simple laboratory parameter of coagulation activation with reported prognostic value [9,13]. The most typical finding in patients with COVID-19 and coagulopathy is increased D-dimer concentration [18]. In a series of 1099 patients with COVID-19 from China [3], a D-dimer level higher than >0.5 mg/L was found in 260 of 560 patients. In another Chinese observational cohort [13] of 183 patients with COVID-19, mean D-dimer concentration in those who did not survive was significantly higher than that in the survivors. A third study [1] found that patients who were admitted to the ICU had a significantly higher D-dimer concentration (2.4 [0.6–14.4] mg/L) than those who did not require ICU admission (0.5 [0.3–0.8] mg/L). Finally, D-dimer levels >1 mg/L at admission, resulted in an 18-times increased risk of death [9].

In COVID-19 patients, both D-dimer and respiratory dead space could be linked by microthrombosis formation in the pulmonary circulation. In fact, viral infections may initiate a complex systemic inflammatory response as part of innate immunity. The activation of host defense systems leads to coagulation activation and thrombin generation as critical communication components among humoral and cellular amplification pathways, a term called thromboinflammation or immunothrombosis [19]. As in our patients, significant inflammation is present in patients with SARS-CoV-2 infection, based on elevated levels of interleukin-6, C-reactive protein, and fibrinogen at presentation [20]. Given the tropism of the virus for angiotensin-converting enzyme type 2 (ACE2) receptors, endothelial cell activation and damage followed by disruption of the natural antithrombotic state are expected [21]. This inflammation associated with COVID-19 and coagulation activation may explain the elevated D-dimer levels, as increased levels have been associated with many conditions other than thromboembolism, with infection being an important etiology [22-24]. Additionally, direct endothelial damage appear to contribute to the pathophysiology of microcirculatory alterations in SARS-CoV-2 infections [25,26]. The viral receptor for cell adhesion is ACE2, which is expressed in endothelial cells [26]. An early report demonstrated viral inclusions within endothelial cells and sequestered mononuclear and polymorphonuclear cellular

infiltration, with evidence of endothelial apoptosis and microvascular prothrombotic effects postmortem of SARS-CoV-2 infection [8]. As a result, microcirculatory dysfunction may contribute to clinical expression of COVID-19. From a clinical perspective, in addition to the systemic hypercoagulability and potential for thromboembolic complications, microvascular endothelial injury with microcirculatory clot formation noted in postmortem evaluation is consistent with thrombotic microangiopathy that may occur in patients [8]. Therefore, this endotheliopathy could explain the increasing number of reports of both micro- and macrocirculatory thromboembolic complications [8,22,27].

In cardiac surgery, intraoperative coagulation activation with increased alveolar dead space has been reported [28]. Moreover, in this study, preoperative heparin infusion reduced coagulation activation and blunted dead space increase [28]. In patients with ARDS, coagulation intervention using activated protein C reduced the respiratory dead space but did not improve outcomes [29]. These reports show the relationship between coagulation activation and respiratory dead space. As mentioned above, the interplay between inflammation and hemostasis has been well described, and on this basis, in ARDS patients treated with corticosteroids, a reduction in respiratory dead space has been reported [30]. Therefore, our finding of an association between increased respiratory dead space and D-dimer supports the hypothesis that vascular pulmonary disease is a relevant issue in critically ill COVID-19 patients. Moreover, treatment focused on inflammatory response (i.e.: corticoids) and/or on coagulation activation (i.e.: "optimized" prophylactic doses of heparins) also could be supported from our findings. Currently, COVID-19 lack globally accepted standard therapy and some medical societies suggest anticoagulant therapy for high-risk patients [31]. Our data could help optimize patient stratification for an anticoagulant therapy approach.

This work is a hypothesis-generator study, and our findings should be interpreted with caution. First, statistical association should not be assumed as causative association; therefore, whether higher respiratory dead space is due to coagulation activation and microthrombosis remains an unproven hypothesis; however, our approach has a strong pathophysiological basis, is widely available, and is less invasive than histological. Second, the gold standard for respiratory dead space is the Multiple Inert Gas Elimination Technique (MIGET) [32]. However, this advanced technique for gas exchange studies is clinically unavailable. The dead space approach reported by *Tusman* et al. [33] has been contrasted with MIGET; however, the availability of software for this capnogram analysis is lower than that of simple volumetric capnography for $PECO_2$ determination. For VDPhys/VT, only volumetric capnography is required. Third, overt pulmonary embolism is classically characterized by increased D-dimer and VDPhys/VT, but D-dimer levels associated with tomographically proven pulmonary embolism in patients with COVID-19 pneumonia are higher (>2660 ng/mL) [34] than in our cohort (<2020 ng/mL). Finally, the small sample size precludes definitive conclusions, and these findings need to be confirmed in a larger cohort. In view of its strong physiological rationale, VDPhys/VT measurement should be considered a valuable tool for severity assessment and follow-up of COVID-19 patients with ARDS.

5. Conclusions

Critically ill patients with ARDS related to COVID-19 had an increased respiratory dead space, which was associated with D-dimer levels and a lower probability of being discharged alive at 28 days. A VDPhys/VT >57% could identify a high-risk subgroup of patients neglected by oxygenation as assessed by the P/F ratio.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board "Comite Ético-Científico, Clínica Alemana de Santiago, Universidad del Desarrollo" (# 2020–25).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author statement

Jerónimo Graf: conception, data analysis and interpretation, writing of the manuscript; **Rodrigo Pérez**: data acquisition, writing of the manuscript; **René López**: conception, study design, data analysis, writing of the manuscript.

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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