Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Critical Care 71 (2022) 154021

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Clinical characteristics, respiratory management, and determinants of oxygenation in COVID-19 ARDS: A prospective cohort study

Elisa Estenssoro, MD [a,*], Cecilia I. Loudet, MD, MSc [a], Arnaldo Dubin, MD, PhD [b], Vanina S. Kanoore Edul, MD, PhD [c], Gustavo Plotnikow, RT [d], Macarena Andrian, MD [e], Ignacio Romero, MD [f], Judith Sagardía, MD [g], Marco Bezzi, RT [h], Verónica Mandich, MD [h], Carla Groer, MD [c], Sebastián Torres, MD [i], Cristina Orlandi, MD [j], Paolo N. Rubatto Birri, MD [b], María F. Valenti, MD [k], Eleonora Cunto, MD [l], María G. Sáenz, MD [a], Norberto Tiribelli, RT [m], Vanina Aphalo, MD [d], Lisandro Bettini, MD [n], Fernando G. Ríos [o], Rosa Reina, MD [p], on behalf of the SATI-COVID-19 Study Group [1]

[a] Hospital Interzonal de Agudos General San Martín, Buenos Aires, Argentina
[b] Sanatorio Otamendi, Buenos Aires, Argentina
[c] Hospital Juan A Fernández, Buenos Aires, Argentina
[d] Sanatorio Anchorena, Buenos Aires, Argentina
[e] Hospital Provincial Dr Castro Rendón, Neuquén, Argentina
[f] Sanatorio Güemes, Buenos Aires, Argentina
[g] Hospital A Posadas, Buenos Aires, Argentina
[h] Hospital Santojanni, Buenos Aires, Argentina
[i] Sanatorio Anchorena San Martín, Buenos Aires, Argentina
[j] Hospital Francisco López Lima, Río Negro, Argentina
[k] Sanatorio de Los Arcos, Buenos Aires, Argentina
[l] Hospital Dr. F J Muñiz, Buenos Aires, Argentina
[m] Complejo Médico de la Policía Federal Argentina Churruca Visca, Buenos Aires, Argentina
[n] Hospital Provincial del Centenario, Santa Fe, Argentina
[o] Sanatorio Las Lomas, Buenos Aires, Argentina
[p] Sociedad Argentina de Terapia Intensiva, Buenos Aires, Argentina.

ARTICLE INFO

Keywords:
COVID-19
ARDS
Mechanical ventilation
Ventilatory ratio
Obesity
BMI

ABSTRACT

Purpose: To identify determinants of oxygenation over time in patients with COVID-19 acute respiratory distress syndrome (ARDS); and to analyze their characteristics according to Berlin definition categories.
Materials and methods: Prospective cohort study including consecutive mechanically ventilated patients admitted between 3/20/2020–10/31/2020 with ARDS. Epidemiological and clinical data on admission; outcomes; ventilation, respiratory mechanics and oxygenation variables were registered on days 1, 3 and 7 for the entire population and for ARDS categories.
Results: 1525 patients aged 61 ± 13, 69% male, met ARDS criteria; most frequent comorbidities were obesity, hypertension, diabetes and respiratory disease. On admission, 331(21%), 849(56%) and 345(23%) patients had mild, moderate and severe ARDS; all received lung-protective ventilation (mean tidal volumes between 6.3 and 6.7 mL/kg PBW) and intermediate PEEP levels (10–11 cmH_2O). PaO_2/FiO_2, plateau pressure, static compliance, driving pressure, ventilation ratio, pH and D-dimer >2 mg/L remained significantly different among the ARDS categories over time. In-hospital mortality was, respectively, 55%, 58% and 70% ($p < 0.000$). Independent predictors of changes of PaO_2/FiO_2 over time were BMI; preexistent respiratory disease; D-dimer >2 mg/L; day 1-PEEP, and day 1-ventilatory ratio.
Conclusion: Hypoxemia in patients with COVID-19-related ARDS is associated with comorbidities, deadspace and activated coagulation markers, and disease severity—reflected by the PEEP level required.

Abbreviations: ARDS, acute respiratory distress PaO_2FiO_2 syndrome; COVID-19, coronavirus disease 2019; BMI, Body mass index; PBW, predicted body weight; PEEP, positive end-expiratory pressure; ICU, Intensive Care Unit; HFNC, high-flow nasal cannula; NIV, noninvasive mechanical ventilation; APACHE II, Acute Physiologic and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; Vt, tidal volume; CXR, Chest X-ray; CT scan, Computed Tomography scan; RASS, Richmond Agitation Sedation Scale; ACE inhibitors, Angiotensin converting enzyme inhibitors; LDH, lactate dehydrogenase; Vd/Vt, dead space fraction.

* Corresponding author at: Hospital Interzonal de Agudos General San Martín, 42 No. 577, 1900 La Plata, Buenos Aires, Argentina.
E-mail address: estenssoro.elisa@gmail.com (E. Estenssoro).

[1] The complete list of investigators of the SATI-COVID-19 Study Group is included in Online Data Supplement.

https://doi.org/10.1016/j.jcrc.2022.154021
0883-9441/

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused more than 378 million infections and over 5,600,000 deaths worldwide [1]. About 5% to 20% of patients hospitalized with coronavirus disease 2019 (COVID-19) require admission to the intensive care unit (ICU) for diffuse lung infiltrates and severe hypoxemia; rates of invasive mechanical ventilation among this group may vary from 30% to 90% [2,3].

Many patients with COVID-19 admitted to the ICU and requiring mechanical ventilation patients develop acute respiratory distress syndrome (ARDS), the most severe form of acute respiratory failure. Thus, the characterization of ARDS pathophysiology is of utmost relevance to apply appropriate mechanical ventilation strategies without generating ventilation-induced lung injury. Some researchers have reported that, in some patients, ARDS secondary to COVID-19 might have atypical characteristics when compared to the usual causes of ARDS, such as exhibiting deep oxygenation compromise in the presence of preserved respiratory-system compliance while another subgroup of patients has the typical ARDS behavior of hypoxemia and low respiratory-system compliance [4]. However, other authors have not recorded such uncommon features [5,6].

Recently, we described the clinical characteristics, outcomes and prognostic variables in a prospective observational study which included 1909 patients with COVID-19 on mechanical ventilation in Argentina [7]. In the present study, we analyze the subgroup of patients with ARDS of that cohort. Our main objective was to identify the independent determinants of oxygenation, as measured as PaO_2/FiO_2, over days 1, 3 and 7 from ICU admission. A secondary objective was to analyze the differences among the three categories of severity of the Berlin definition of ARDS, exploring physiological parameters and ventilation management over time, as well as their final outcomes. An additional objective was to confirm a binary distribution of respiratory-system compliance and oxygenation phenotypes.

2. Materials and methods

This is a prospective, multicenter, cohort study organized by the Argentine Society of Intensive Care Medicine (SATI). It enrolled 1909 consecutive adult patients ≥18 with confirmed COVID-19 admitted to hospitals in Argentina between 3/20/2020–10/31/2020, who required invasive mechanical ventilation. Description of study planning and procedures are published elsewhere [7].

For the present study, we included patients who on day 1 of mechanical ventilation in the ICU met the criteria of ARDS according to the three categories of the Berlin definition [9]. We registered date of hospital and ICU admission, type of hospital, age, gender, body mass index (BMI, kg/m^2), obesity (BMI ≥30 kg/m^2) comorbidities, use of medications, previous utilization of high-flow nasal cannula (HFNC) and noninvasive mechanical ventilation (NIV) and their duration, APACHE II, Sequential Organ Failure Assessment (SOFA) scores, vasopressor utilization, and laboratory variables.

Physiological respiratory and mechanical ventilation variables were collected on days 1, 3 and 7; they are presented for the entire population and for mild, moderate and severe ARDS categories [8]: blood gas analysis, percentage of patients with infiltrates involving 3–4 quadrants on CXR, PaO_2/FiO_2, tidal volume (Vt, mL/kg of predicted body weight [PBW], Richmond Agitation-Sedation Scale (RASS), FiO_2, respiratory rate, PEEP level (cmH_2O), plateau pressure (cmH_2O), respiratory-system compliance (Vt/(plateau pressure-PEEP)), and driving pressure (plateau pressure-PEEP). To evaluate ARDS phenotypes described in COVID-19, compliance was dichotomized to <40 and ≥ 40 mL/cmH_2O [9]. Ventilatory ratio was estimated as Vt x RR x $PaCO_2$/PBW [kg] x 100 × 37.5; values >1 correlate with increased deadspace [10].

Local investigators collected worst daily values for each variable.

We recorded utilization of prone positioning, and number and duration of sessions, acute kidney failure and requirement of renal replacement therapy, septic shock, bacteremia, ventilation-associated pneumonia, use of corticosteroids, and length of mechanical ventilation and of ICU and hospital stay. All patients included were followed until death in the hospital or hospital discharge, whichever occurred first.

The main outcome was the identification of the determinants of oxygenation, and the patterns of change in physiological respiratory and mechanical ventilation variables for the entire ARDS group and for mild, moderate and severe categories on days 1, 3 and 7.

Variables are reported as absolute numbers and percentages, and medians [25th–75th] percentiles. Differences between the three ARDS categories were analyzed with multiple chi-square test, one-way ANOVA and Kruskall-Wallis tests, as appropriate. A P value <0.05 was considered statistically significant. Bonferroni correction was applied for multiple comparisons.

Generalized estimating equations were used to account for correlations between physiological respiratory and mechanical ventilation variables in the entire group over 1, 3 and 7 days. P values for time-effect for the entire group and for time-subgroup (ARDS categories) interactions were calculated. A model was constructed with oxygenation (PaO_2/FiO_2) over time (days 1, 3 and 7) as the outcome variable. An unstructured correlation matrix was selected. Variables that differed between ARDS categories (P value <0.10) in univariate analysis were entered into the model to explore their effect on oxygenation over time.

Kaplan-Meier survival curves until Day 90 were plotted, and differences analyzed with log-rank test.

Data were analyzed with Stata 14.0 (StataCorp LP, College Station, TX).

Definitions of comorbidities, variables and other relevant data are shown in the Additional Files section.

The study was approved by Ethics Committee of the Sociedad Argentina de Terapia Intensiva (SATI); by the Comisión Conjunta de Investigación en Salud de la Provincia de Buenos Aires—CCIS, and by each study each institutional review board, which defined the requirement for informed consent.

3. Results

3.1. Epidemiological and clinical variables

ARDS was present in 1525 patients on mechanical ventilation on day 1 of ICU admission, constituting 79.9% of the entire SATICOVID cohort. The flow diagram of the study is presented in Fig. 1. Patients were predominantly male (69%), aged 61 ± 13 years, and had a BMI of 32 ± 6 kg/m^2. Obesity (49%), arterial hypertension (47%), diabetes (30%) and previous respiratory disease (14%) were the most frequent comorbidities. Before ICU admission, 4% had received noninvasive ventilation for 1 [1,2] days, or high-flow nasal cannula (8%) for 24[7–48] hours; 21% underwent endotracheal intubation outside the ICU. On admission, patients had an arterial O_2 saturation of 88 ± 8%, a lactate of 1.7[1.3–2.1] mmol/L, and 40% required vasopressors (Table 1).

Mild, moderate and severe ARDS was reported in 331 (21%), 849 (56%) and 345 (23%) patients, respectively. Compared to the other categories, patients with severe ARDS exhibited significant differences: higher BMI, higher incidence of obesity and of previous use of NIV, lower incidence of cardiovascular and renal pre-existent conditions, and lower utilization of antihypertensive drugs and β-blockers. Notably, there were no differences in age nor in the severity of the acute disease or of organ failures among the 3 categories on admission, as measured by APACHE II and SOFA scores. Additionally, pre-intubation PaO_2/FiO_2 was lower, and LDH and d-dimer were significantly higher in severe ARDS than in mild to moderate.

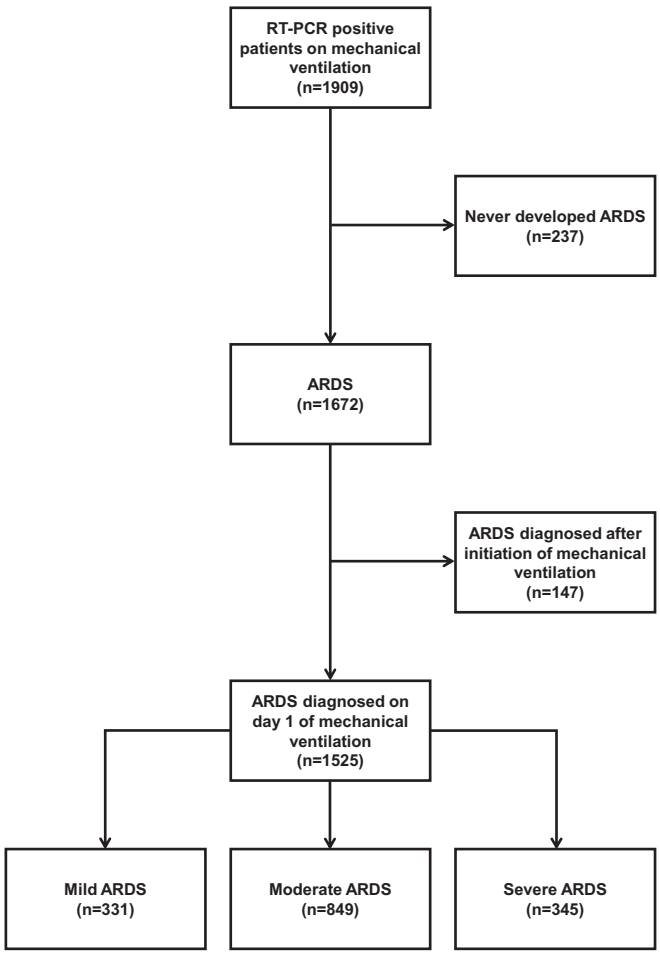

Fig. 1. Title: Flow-diagram of the study.

3.2. Oxygenation, mechanical ventilation and acid-base variables

In accordance with the study design, PaO_2/FiO_2 decreased significantly between ARDS categories of increasing severity; this occurred from days 1 to 7. Within each category, PaO_2/FiO_2 increased over time in moderate and severe ARDS and decreased in mild ARDS. The three categories were mechanically ventilated with equally protective tidal volumes. PEEP utilized values were intermediate, with slight decreases over time in the three categories. At all-time points, the severity of ARDS category corresponded to higher FiO_2 utilization. (Fig. 2, panels A-D).

On days 1, 3 and 7, plateau and driving pressures were higher and respiratory-system compliance was lower, according to the severity of ARDS category (between-group comparisons). Within each category, plateau pressure and respiratory-system compliance showed slight but statistically significant improvements while driving pressure remained unchanged (Fig. 2, panels *E*-G). Respiratory-system compliance had a unimodal distribution over the 3 days of the study (Fig. 3); it was lower than 40 mL/cmH_2O in 60% of patients on day 1.

Arterial PCO_2 values were consistently higher than normal in the three ARDS categories over time; the worst values corresponded to severe ARDS. On days 1 and 3, PCO_2 was different between categories. Arterial pH was lower in severe ARDS compared to the other categories on day 1; but increased progressively over time, together with bicarbonate. (Fig. 2, panels H-J).

In the three time points, ventilatory ratio was higher in severe ARDS compared to mild and moderate ARDS. Within each category, ventilatory ratio gradually increased in moderate and severe ARDS and did not change in mild ARDS (Fig. 2, panel K). The correlation between ventilatory ratio and PaO_2/FiO_2 is shown in Fig. 4.

Lymphopenia, and elevated LDH, ferritine and D-Dimer occurred across all degrees of ARDS severity.

All the values of laboratory, respiratory, and acid-base variables are shown in the Supplementary material, Tables S1 and S2.

3.3. Treatments, evolution and outcomes

Prone positioning was utilized in 73% of patients ($n = 1108$), with increasing frequency according to severity categories, but number and duration of sessions was similar. Dexamethasone was administered in 875 patients of 1328 (66%) without differences across categories (Table 2).

The proportion of patients in each category of severity changed over time (Fig. 5). By day 7, 374 of 1211 (31%) surviving patients had mild ARDS, 628 (52%) had moderate and 102 (8%) had severe; 106 patients had $PaO_2/FiO_2 > 300$ (9%). Hospital mortality for the entire group was 60%; a decision to withdraw life-supporting treatments had been made in 4.8% of the deceased patients. Mortality for mild, moderate and severe ARDS it was respectively 55%, 58% and 70%. Kaplan-Meier curves are shown in Fig. 6. Other outcomes are shown in Table 2.

3.4. Determinants of oxygenation

In the model constructed, time, and PEEP on day 1 were positively correlated with PaO_2/FiO_2 on days 1, 3 and 7; however, BMI, preexistent respiratory disease, d-dimer >2 mg/L, and ventilatory ratio on day 1 negatively affected oxygenation (Table 3).

4. Discussion

In this large, multicenter cohort study carried out in 1525 patients on mechanical ventilation with ARDS secondary to COVID-19, our main findings were that factors independently associated with changes of oxygenation over time were preexistent conditions, such as previous respiratory diseases and BMI; and also variables reflecting the severity of the disease, as the level of PEEP required, the increased ventilatory ratio—a surrogate of Vd/Vt—and the concentration of D-Dimer, a marker of widespread activation of coagulation and likely of thrombosis of lung vessels. To our knowledge, this is the first study that integrates determinants of hypoxemia in ARDS in a model.

As in most studies of COVID-19 and non-COVID-19 ARDS, patients were old, predominantly male and exhibited frequent underlying diseases. Obesity, arterial hypertension, diabetes and pre-existent respiratory disease were the most frequent comorbidities, similar to other studies about COVID-19 ARDS [6,11]; but different from the largest study about ARDS, the LUNG-SAFE study, in which COPD, diabetes and immunoincompetence prevailed [12].

As in most studies, moderate ARDS was the most frequent ARDS category on admission [5-13]. This remained as such over the first week but there was also a tendency toward improved oxygenation, reflected by the increase of patients with mild ARDS and even of patients with $PaO_2/FiO_2 > 300$, probably reflecting evolution of the disease, and utilization of PEEP and other adjunctive therapies that might increase oxygenation [14-16]. As in the LUNG-SAFE study, mild, moderate and severe ARDS were associated with increasing mortality.

The three ARDS categories were managed with low Vt and intermediate PEEP levels and followed the standard recommendations for lung protective ventilation [17]. In comparison with the LUNG-SAFE study, in which mean applied Vt was 7.6 mL/kg PBW for the entire population [12], we report herein a Vt of 6.4 mL/kg PBW on day 1, similar to the COVID-19 French and Italian cohorts [5,6]. In contrast to the LUNG-SAFE study, in which Vt decreased with increasing severity of ARDS (7.8, 7.6 and 7.5 mL/kg PBW, for mild, moderate and severe ARDS respectively, $P < 0.02$) [12], the Vt applied in the categories of increasing

Table 1
Epidemiological variables, risk factors and clinical status on ICU admission in COVID-19 ARDS patients.

	All patients $n = 1525$ (100)	Mild ARDS $n = 331$ (21)	Moderate ARDS $n = 849$ (56)	Severe ARDS $n = 345$ (23)	P value*
Age	61 ± 13	62 ± 14	61 ± 13	59 ± 14	0.033
Male sex	1046 (69)	232 (70)	589 (69)	225 (65)	0.277
BMI (kg/m^2)	32 ± 8	30 ± 6	31 ± 7	34 ± 9	0.000
Comorbidities					
Obesity (BMI ≥30)	739 (49)	138 (42)	406 (48)	195 (57)	0.001
Arterial hypertension	720 (47)	157 (48)	406 (48)	157 (46)	0.753
Diabetes	463 (30)	110 (33)	252 (30)	101 (29)	0.420
Respiratory disease	210 (14)	36 (11)	116 (14)	58 (17)	0.080
Chronic kidney disease	77 (5)	24 (7)	45 (5)	8 (2)	0.012
Immunosuppression	69 (5)	10 (3)	48 (6)	11 (3)	0.059
Chronic heart failure	68 (4)	24 (7)	27 (3)	17 (5)	0.009
Ischemic heart disease	96 (6)	30 (9)	52 (6)	14 (4)	0.026
Chemotherapy (previous 6 months)	40 (3)	11 (3)	22 (3)	7 (2)	0.568
Chronic liver disease	26 (2)	3 (1)	19 (2)	4 (1)	0.191
Solid organ transplantation	10 (1)	1 (0)	8 (1)	1 (0)	0.299
Charlson comorbidity score	1 [1–2]	1 [1–3]	1 [1–2]	1 [1–2]	0.382
Absence of any comorbidity	114 (7)	30 (9)	62 (7)	22 (6)	0.391
Habits and drug utilization					
Utilization of ACE inhibitors or AII receptor blockers	290 (19)	79 (24)	156 (18)	55 (16)	0.023
Current smoker	215 (14)	52 (16)	112 (13)	51 (15)	0.487
Utilization of beta-blockers	106 (7)	38 (12)	55 (6)	13 (4)	0.000
Utilization of statins	110 (7)	37 (11)	64 (8)	9 (3)	0.000
Respiratory Management before ICU admission					
Prior utilization of non-invasive mechanical ventilation	66 (4)	9 (3)	33 (4)	24 (7)	0.017†
Duration of non-invasive mechanical ventilation (days)	1 [1–2]	1 [1–1]	1 [1–2]	1 [1–2]	0.207
Prior utilization of high flow nasal cannula	129 (8)	32 (10)	60 (7)	37 (11)	0.08
Duration of high flow nasal cannula use (hours)	24 [7–48]	25 [8–48]	24 [8–72]	24 [6–48]	0.488
Pre-intubation respiratory rate	32 ± 6	33 ± 6	32 ± 6	32 ± 6	0.881
Pre-intubation PaO_2/FiO_2	84 [66–116]	88 [68–134]	86 [69–119]	75 [58–102]	0.000
Number of quadrants of extension of lung infiltrates on CXR or on CT scan	4 ± 1	4 ± 1	4 ± 1	4 ± 1	0.383
Endotracheal intubation in the ICU	1196 (79)	265 (81)	654 (78)	277 (81)	0.460
Variables of severity of disease, first 24 h in the ICU					
Oxygen saturation by pulse oximetry at admission	88 ± 8	90 ± 6	89 ± 8	87 ± 9	<0.0001
APACHE II	15 ± 7	15 ± 7	15 ± 7	16 ± 7	0.393
$SOFA_{24\text{-}h}$	6 ± 3	5 ± 3	6 ± 3	6 ± 3	0.147
Maximum body temperature (°C)	38.2 ± 0.9	38.2 ± 0.8	38.2 ± 0.9	38.2 ± 0.8	0.91
Requirement of vasopressors	723 (47)	169 (51)	398 (47)	156 (45)	0.265
Arterial lactate, mmol/L	1.7 [1.3–2.2]]	1.8 [1.4–2.2]]	1.7 [1.3–2.2]]	1.7 [1.3–2.2]]	0.733
Fluid balance in the first day, mL	700 [−150;1665]	708 [−200;1600]	700 [−135;1680]	650 [−137;1680]	0.613

Variables are presented as n(%), mean ± standard deviation, or median [25–75%] percentiles.
% were calculated according to the data recorded for each variable.
Abbreviations: BMI, body mass index; ACE, angiotensin-converting enzyme; AII, angiotensin II; ICU, Intensive Care Unit; APACHE II, Acute Physiological and Chronic Health Evaluation II; SOFA, Sequential Organ-Failure Assessment.
* Corresponds to between-group (category of ARDS severity) comparisons. Within-group comparisons (changes over time in each group) are shown in Fig. 2, panels A-K.
† $P > 0.05$ after Bonferroni correction.

severity in the two studies mentioned and in ours remained stable, denoting a worldwide adoption of lung protective strategy during the COVID-19 pandemic [5,6,11].

In the mentioned ARDS-COVID-19 studies and in ours, PEEP levels utilized were intermediate (11–12 cmH_2O) and similar across severity categories [6,11,13]. This could be reflecting recent findings which associate high PEEP levels with increased mortality compared to a low Vt-low PEEP strategy [18]. In the LUNG-SAFE study, PEEP values were lower (7.4–10.1 cmH_2O), significantly increasing with hypoxemia severity [12].

According to the increasing degree of pulmonary compromise from mild to severe ARDS, lung mechanics and oxygenation were progressively more affected: plateau pressure, respiratory-system compliance, driving pressure and ventilatory ratio differed significantly at all time points among the three ARDS categories, with values similar to other studies of COVID-19 ARDS [6,11].

At the beginning of the pandemic, it was hypothesized that there were two phenotypes in COVID-19 ARDS: a "classical" ARDS, with deep hypoxemia and low respiratory-system compliance, and a subgroup with hypoxemia but, paradoxically, high compliance. Alterations in pulmonary blood flow distribution would account for altered oxygenation in the high-compliance subgroup [4,9]. We, as well as other authors, found a unimodal distribution of respiratory system-compliance [5,6]. Moreover, in patients with the largest compromise in oxygenation (severe ARDS), respiratory-system compliance was the lowest, as expected; and patients with mild ARDS exhibited the highest compliance values. These findings suggest that COVID-19 induced ARDS is most similar to classical ARDS in terms of respiratory-system compliance and oxygenation. Contrary to the suggestion that high and low respiratory-system compliance might represent increasingly severe stages of the disease, compliance improved over time in ARDS subgroups—except for severe ARDS. Low compliance in the three ARDS categories occurred over the study period, reflecting the loss of aeration—a main feature of ARDS.

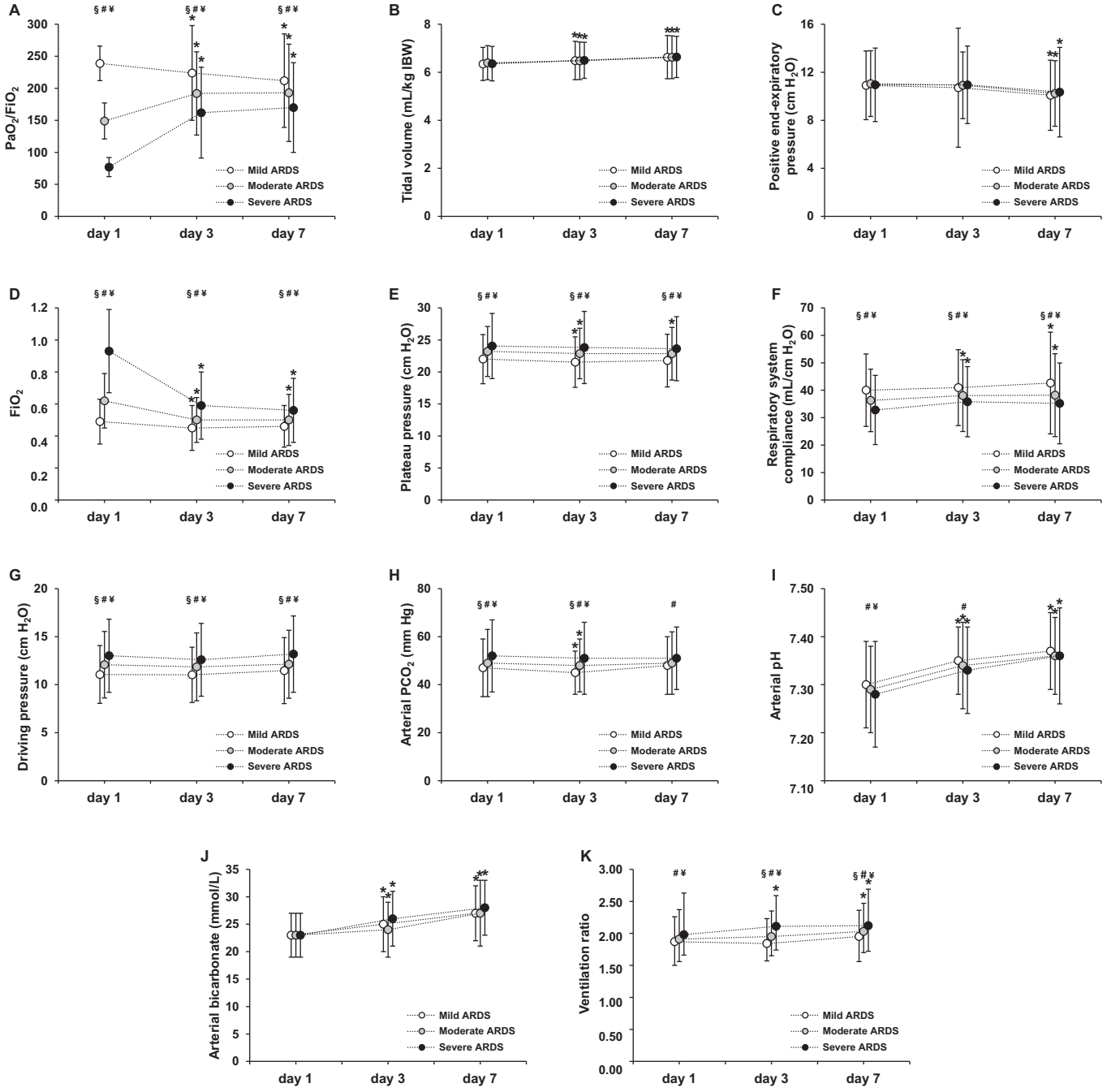

Fig. 2. Evolution of different physiological and mechanical ventilation variables over time.
Of note, all three categories were ventilated with protective ventilation and intermediate PEEP levels, without differences among over time. Lung mechanics and blood gases, however, greatly differed among mild, moderate and severe ARDS.
In between-group (ARDS categories) analysis, § corresponds to $P < 0.05$ for the comparison of mild vs. moderate ARDS; # corresponds to $P < 0.05$ for mild vs. severe ARDS; and ¥ $P < 0.05$ for moderate vs. severe ARDS.
For within-group comparisons (changes within each ARDS category over time), *corresponds to $P < 0.05$ vs. day 1. Absolute values are shown in Table A1.

As mentioned, the variables that affect the evolution of PaO_2/FiO_2 on days 1, 3 and 7 were patients' pre-existent risk factors, such as previous respiratory disease and increasing BMI; a procoagulant status represented by a D-dimer >2 mg/L; ventilatory ratio on day 1, a marker of deadspace and, as such, of altered V/Q inequality; and, expectedly, PEEP utilization.

In a meta-analysis including 37 studies, which examined the adjusted risks of COVID-19-related hospitalizations, ICU-admissions, and mortality in patients with chronic respiratory disease, COPD was identified as a risk factor for the three mentioned outcomes [19,20]. COPD patient susceptibility to COVID-19 might be associated to an increased expression of angiotensin-converting enzyme 2 (ACE-2) which would facilitate SARS-CoV-2 entry into lung cells [21].

Obesity was the most frequent comorbidity in this cohort. BMI increased significantly across ARDS severity categories and had a negative association with oxygenation in the model. Excessive load on the respiratory muscles, tendency toward atelectasis, and alterations in respiratory drive make obese patients prone to severe respiratory

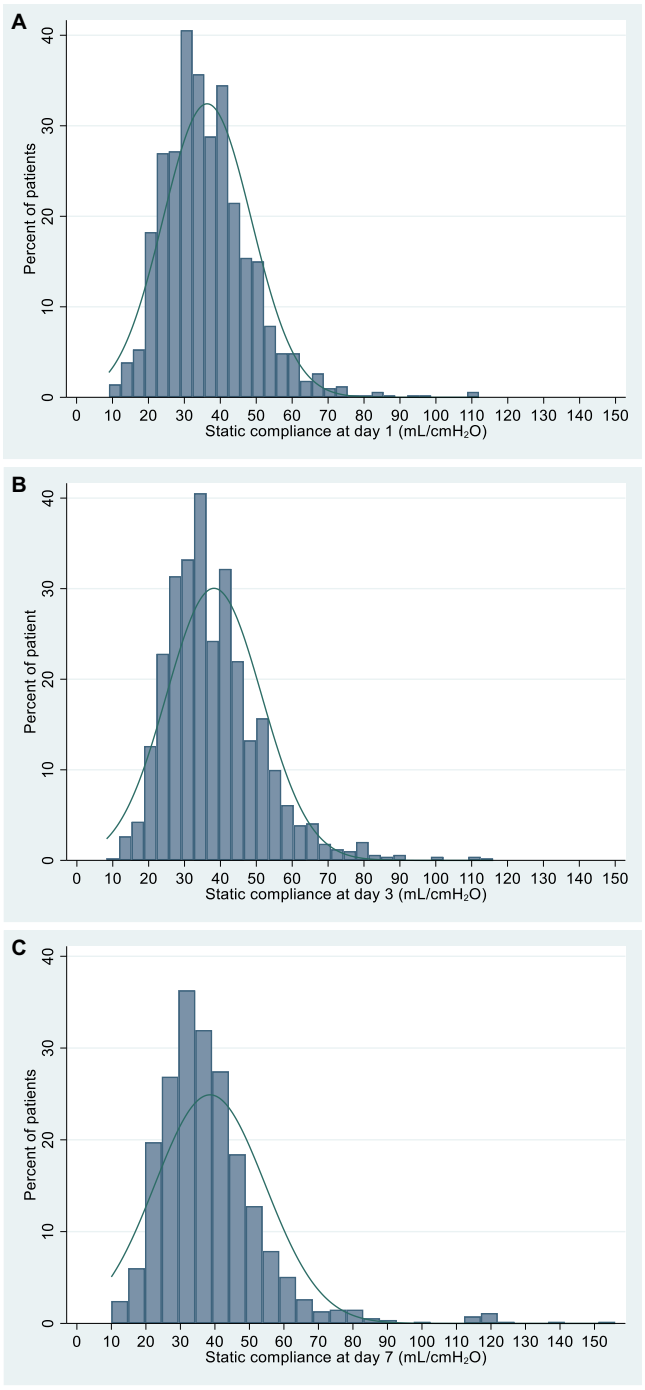

Fig. 3. Histogram of the distribution of compliance values on days 1, 3 and 7.
There is a unimodal distribution of compliance on the 3 days. The curves are close to the normal distribution.

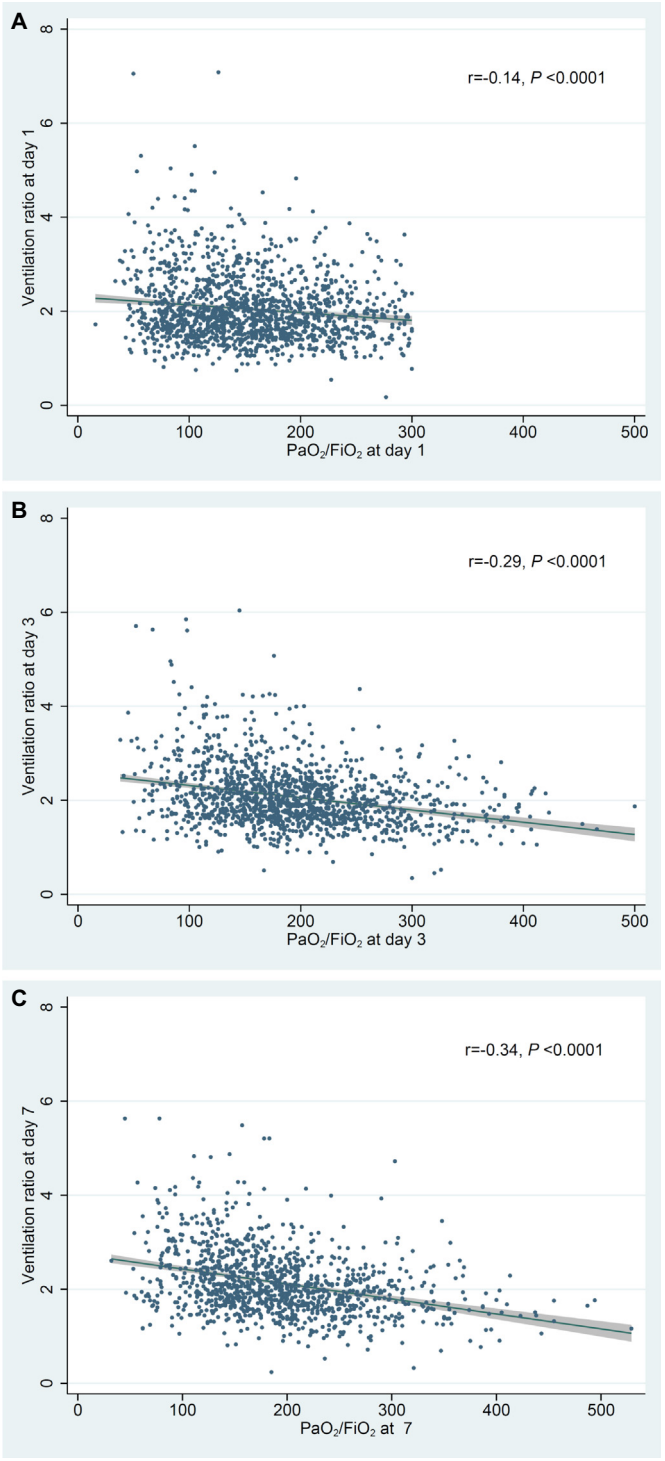

Fig. 4. Correlation between ventilatory ratio and PaO_2/FiO_2 on days 1 (top), 3 (middle) and 7 (bottom).
The significance of the correlation was significantly increased over time. Dark blue horizontal bar shows median value, and upper and lower horizontal light black bars show 90th and 10th percentiles.

failure, as evidenced during the 2009 H1N1 influenza pandemic [22,23]. Obesity might affect COVID-19 via other mechanisms: low-grade chronic inflammatory state, dysregulated immune response, endothelial dysfunction, coagulopathy, and risk of hypertension, diabetes and cardiovascular disease [24,25]. A recent meta-analysis confirmed the association of obesity with severity of disease in COVID-19 [26].

Ventilatory ratio, a simple bedside marker of ventilation efficiency, has good correlation to physiological deadspace fraction (Vd/Vt) in patients with ARDS [10]. Increases in Vd/Vt are reflected by an increase of hypercapnia but also of hypoxemia [10,27,28]. Moreover, high ventilatory ratio has been associated with increased mortality in COVID-19, mirroring the impact of Vd/Vt on classical ARDS prognosis [28,29].

We found that the increase in ventilatory ratio was consistently and negatively associated with increasing hypoxemia in the three ARDS categories over time, except between mild and moderate ARDS on day 1.

Table 2
Complications, outcomes and selected treatments.

Variables	All patients $n = 1525$ (100%)	Mild ARDS $n = 331$ (21%)	Moderate ARDS $n = 849$ (56%)	Severe ARDS $n = 345$ (23%)	*P* value*
Utilization of prone position (n, %)	1108 (73)	221 (67)	621 (73)	266 (77)	0.011
Number of prone sessions	2 [2–4]	2 [1–4]	2 [2–4]	2 [2–4]	0.626
Duration of prone sessions (hours)	24 [22–36]	24 [20–36]	24 [20–36]	24 [24–36]	0.138
Use of dexamethasone	1328 (88)	283 (86)	741 (87)	304 (89)	0.408
Use of vasopressors	1250 (82)	275 (83)	687 (81)	288 (83)	0.481
Acute kidney injury	832 (55)	184 (56)	465 (55)	183 (53)	0.766
Renal replacement therapy	308 (20)	67 (20)	180 (21)	61 (18)	0.384
Ventilator-associated pneumonia	535 (35)	111 (34)	306 (36)	118 (34)	0.642
Pulmonary embolism	174 (6)	45 (7)	87 (5)	42 (6)	0.265
In-hospital mortality	919 (60)	182 (55)	496 (58)	241 (70)	0.0001
Refractory hypoxemia as main cause of death	420 (47)	78 (44)	217 (45)	125 (53)	0.000
Length of mechanical ventilation (days)	13 [7–23]	14 [7–23]	14 [8–24]	12 [6–20]	0.006
Length of ICU stay (days)	17 [10–28]	17 [11–28]	17 [11–29]	14 [8–24]	0.0001
Length of hospital stay (days)	22 [14–35]	23 [15–36]	23 [14–37]	18 [11−32]	0.0001

* Corresponds to between-group (category of ARDS severity) comparisons.

Hypercapnia also increased over time in mild and moderate ARDS, and remained elevated in severe ARDS over the entire study period.

Widespread activation of coagulation, reflected by an increased D-dimer levels was early reported in COVID-19 [30,31]. Lung autopsy findings in patients with COVID-19 ARDS included severe endothelial injury (endothelialitis) and disseminated microthrombosis [32,33]. While macrovascular and microvascular thrombosis were described in classical ARDS anatomopathological descriptions [34], microthrombosis was 9 times more frequent in autopsies of patients dying from COVID-19 pneumonia than in those dying from 2009 H1N1 pandemic influenza [32]. Microthrombosis can explain the increased physiological Vd/Vt and hypoxemia. As such, we found that a D-dimer higher than 2.0 mg/L on admission was an independent determinant of oxygenation. A similar value of D-Dimer (1880 ng/mL) correlated with disseminated areas of hypoperfusion in perfusion scans in patients with COVID-19 ARDS [5]. Our study, in agreement with others, suggests that microthrombosis might be crucial for causing hypoxemia by increased Vd/Vt in COVID-19 ARDS [5].

As expected, PEEP produced a strong, independent impact on oxygenation over time, resembling the effect reported in classical ARDS as it decreases severe shunt, secondary to improved ventilation of dorsal lung areas and to reduced cardiac output [34]. Additionally, PEEP impairs ventral perfusion thereby decreasing ventral Vd/Vt [35]. The effect of PEEP on oxygenation in COVID-19 ARDS might be independent of recruitability since the response to a single-breath derecruitment maneuver has been highly heterogeneous [36].

In this cohort, mortality was higher than that reported in other studies which only included ARDS patients with COVID-19 carried out in high-income countries (HICs) [6,11]. High prevalence of vasopressor utilization at some point of the disease course (in 82% of patients) and of acute kidney injury (in 55%) might, to some extent, account for the increased mortality. Nevertheless, mortality was lower in reference to two studies also conducted, as ours, in low and middle-income countries (LMICs) [37,38]. Differences between HICs and LMICs in ARDS and in sepsis outcomes have been described, and occur secondary to complex economic and organizational factors in LMICs, as shown in the ICON and LUNG SAFE studies [39,40].

This study has limitations. First, we only studied patients on days 1, 3 and 7 after initiation of mechanical ventilation, representing very precise time points so there is a certain possibility that gas-exchange and lung mechanical characteristics might have varied over time. Second, ventilation management was not standardized, therefore this could

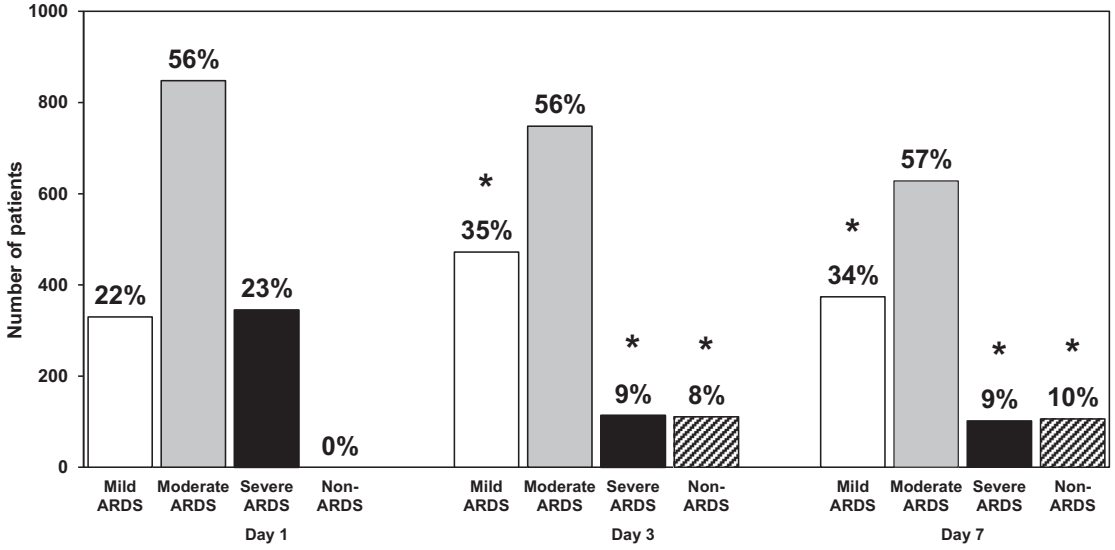

Fig. 5. Frequency of each of the categories of severity of ARDS over time.
Remarkably, the proportion of patients with moderate ARDS remains stable, and patient improvement becomes evident on day 3, when $PaO_2/FiO_2 > 300$ (Non-ARDS) begin to appear.
*Refers to $P < 0.05$ in comparison with day 1 of each category of severity.

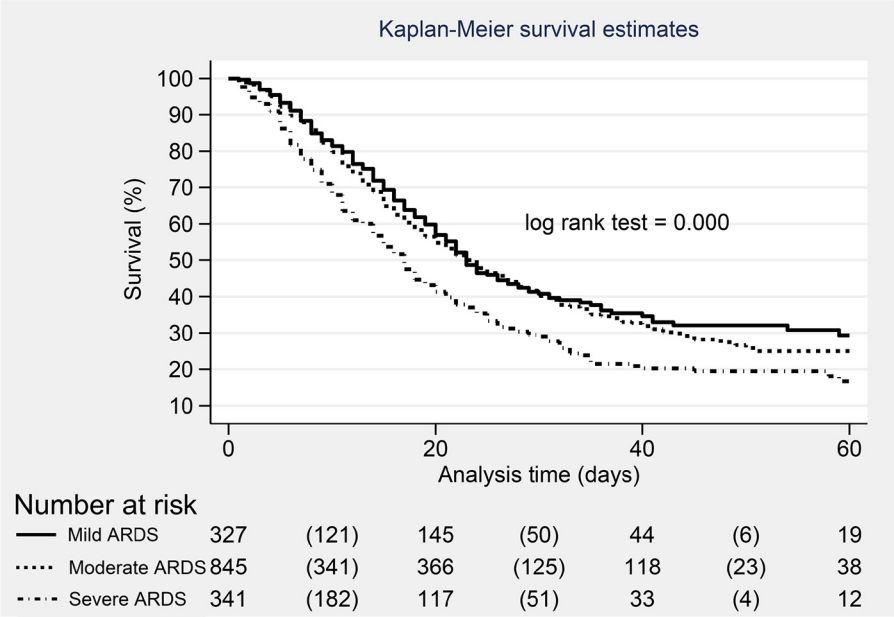

Fig. 6. Kaplan-Meier survival curves for mild, moderate and severe ARDS.
The curve for severe ARDS clearly differentiates from the other two from the very beginning.

Table 3
Model including factors associated with evolution of oxygenation over 1, 3 and 7 days.

PaO_2/FiO_2	Coef.	Std. Err.	z	$P > \|z\|$	[95% Conf. Interval]
Time	3.87	0.48	8.08	0.000	[2.93–4.80]
Body mass Index (kg/m^2)	−1.08	0.22	−4.93	0.000	[−1.51, −0.65]
Preexistent respiratory disease	−15.33	4.41	−3.47	0.001	[−23.98, −6.68]
D-dimer >2 mg/L	−12.19	3.24	−3.76	0.0001	[−18.54, −5.84]
Respiratory-system compliance (ml/kg)	0.65	0.12	5.417	0.0001	[0.41, 0.89]
PEEP on day 1 (cmH_2O)	1.57	0.57	2.77	0.006	[0.46, 2.69]
Ventilation ratio on day 1	−11.97	2.43	−4.92	0.0001	[−16.74, −7.20]
-cons	188.66	10.41	18.12	0.0001	[164.26, 209.06]

have added further variability to the data. Third, there was no direct measurement of Vd/Vt or shunt fraction, which would have provided a better panorama of COVID-19 ARDS pathophysiology. Finally, we were not able to compare these COVID-19 ARDS patients with concurrent non-COVID 19 ARDS; we could only refer to the LUNG-SAFE study.

5. Conclusions

This study provides evidence that hypoxemia in patients with COVID-19-related ARDS is associated to risk factors, such as BMI and previous respiratory disease, aside from markers of severity of disease — expressed as increased deadspace, activated coagulation, and levels of PEEP required.

Author's contributions

EE, GP, RR and VSKE conceived and designed the study. EE, CIL and AD analyzed the data. FGR, GP and VSKE were in charge of the project administration. AD designed the figs. EE, AD and CIL verified the data. EE, GP, RR, FGR, VSKE, CIL, AD, MA, IR, JS, MB, VM, CG, ST, CO, PNRB, MFV, EC, MGS, NT, LB and VA contributed to the acquisition and interpretation of the data.

Funding

This research did not receive any specific grant for funding agencies in the public, commercial or not-for-profit sectors.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154021.

References

[1] Hopkins Johns. Coronavirus Resource Center. COVID-19 Dashboard. Available at. https://coronavirus.jhu.edu/map.html; 2022. Accessed February 1, 2022.
[2] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
[3] Wunsch H. Mechanical ventilation in COVID-19. Interpreting the current epidemiology. Am J Respir Crit Care Med. 2020;202:1–4.
[4] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46:1099–02.

[5] Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8:1201–8.
[6] COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day 90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47:60–73.
[7] Estenssoro E, Loudet CI, Ríos FG, Kanoore Edul VS, Plotnikow G, Andrian M, et al. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): a prospective, multicentre cohort study. Lancet Respir Med. 2021;9:989–98.
[8] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33.
[9] Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care. 2020;24:154.
[10] Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2019;199:333–41.
[11] Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, Hernández M, Gea A, Arruti E, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020;46:2200–11.
[12] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315:788–800.
[13] Camporota L, Sanderson B, Dixon A, Vasques F, Jones A, Shankar-Hari M, et al. Outcomes in mechanically ventilated patients with hypoxaemic respiratory failure caused by COVID-19. Br J Anaesth. 2020;125:e480–3.
[14] Estenssoro E, Dubin A, Laffaire E, Canales HS, Sáenz G, Moseinco M, et al. Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome. Intensive Care Med. 2003;29:1936–42.
[15] Camporota L, Sanderson B, Chiumello D, Terzi N, Argaud L, Rimmelé T, et al. Prone position in coronavirus disease 2019 and noncoronavirus disease 2019 acute respiratory distress syndrome: an international multicenter observational comparative study. Crit Care Med. 2021 Sep 24. https://doi.org/10.1097/CCM.0000000000005354.
[16] Langer T, Brioni M, Guzzardella A, Carlesso E, Cabrini L, Castelli G, et al. Prone position in intubated, mechanically ventilated patients with COVID-19: a multi-centric study of more than 1000 patients. Crit Care. 2021;25:128.
[17] Fan E, Del Sorbo L, Goligher E, Hodgson C, Munshi M, Walkey A, et al. An official american thoracic society/european society of intensive care medicine/society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253–63.
[18] Biasi Cavalcanti A, Suzumura EN, Laranjeira LN, Paisani DN, Damiani LP, Guimarães HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2017;318:1335–45.
[19] Pardhan S, Wood S, Vaughan M, Trott M. The risk of COVID-19 related Hospitalisations, intensive care unit admission and mortality in people with underlying asthma or COPD: a systematic review and Meta-analysis. Front Med (Lausanne). 2021;8:668808.
[20] Lee SC, Son KJ, Han CH, Park SC, Jung JY. Impact of COPD on COVID-19 prognosis: a nationwide population-based study in South Korea. Sci Rep. 2021;11:3735–43.
[21] Leung JM, Yang CX, Tam A, Shaipanich T, Hackett T-L, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J. 2020;55:2000688.
[22] Malhotra A, Hillman D. Obesity and the lung: 3 obesity, respiration and intensive care. Thorax. 2008;63:925–31.
[23] Estenssoro E, Ríos FG, Apezteguía C, Reina R, Neira J, Ceraso DH, et al. Pandemic 2009 influenza a in Argentina: a study of 337 patients on mechanical ventilation. Am J Respir Crit Care Med. 2010;182:41–8.
[24] Luzi L, Radaelli M. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. Acta Diabetol. 2020;57:759–64.
[25] Dana R, Bannay A, Bourst P, Ziegler C, Losser M, Gibot S, et al. Obesity and mortality in critically ill COVID-19 patients with respiratory failure. Int J Obes (Lond). 2021;45:2028–37.
[26] Cai Z, Yang Y, Zhang J. Obesity is associated with severe disease and mortality in patients with coronavirus disease 2019 (COVID-19): a meta-analysis. BMC Public Health. 2021;21:1505.
[27] Liu X, Liu X, Xu Y, Huang Y, Chen S, et al. Ventilatory ratio in Hypercapnic mechanically ventilated patients with COVID-19–associated acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201:1297–9.
[28] Vasques F, Sanderson S, Formenti F, Shankar-Hari M, Camporota L. Physiological deadspace ventilation, disease severity and outcome in ventilated patients with hypoxaemic respiratory failure due to coronavirus disease 2019. Intensive Care Med. 2020;7:1–2.
[29] Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002;346:1281–6.
[30] Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med. 2020;173:268–77.
[31] Piazza G, Morrow DA. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19. JAMA. 2020;324:2548–9.
[32] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383:120–8.
[33] Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 2020;4:1–4.
[34] Tomashefski JF, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. Am J Pathol. 1983;112:112–26.
[35] Perier F, Tuffet S, Maraffi T, Alcala G, Victor M, Haudebourg AF, et al. Effect of positive end-expiratory pressure and Proning on ventilation and perfusion in COVID-19 acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;202:1713–7.
[36] Grieco D, Bongiovanni F, Chen L, Menga L, Cutuli S, Pintaudi G, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit Care. 2020;24:529.
[37] Ñamendys-Silva SA, Gutiérrez-Villaseñor A, Romero-González JP. Hospital mortality in mechanically ventilated COVID-19 patients in Mexico. Intensive Care Med. 2020;46:2086–8.
[38] Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir Med. 2021:407–18.
[39] Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med. 2014;2:380–6.
[40] Laffey JG, Madotto F, Bellani G, Pham T, Fan E, Brochard L, et al. Geo-economic variations in epidemiology, patterns of care, and outcomes in patients with acute respiratory distress syndrome: insights from the LUNG SAFE prospective cohort study. Lancet Respir Med. 2017;5:627–38.